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PROCEEDINGS OF THE LATVIAN ACADEMY OF SCIENCES. Section B,
Vol. 72 (2018), No. 6 (717), pp. 313–321.

DOI: 10.2478/prolas-2018-0049

ASSESSMENT OF CARDIAC RESYNCHRONISATION THERAPY EFFICACY DETERMINING FACTORS FOR PATIENTS WITH MODERATE AND SEVERE HEART FAILURE IN THE POPULATION OF LATVIA IN A 12 AND 24 MONTH STUDY

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The aim of this study was to evaluate treatment of patients with moderate and severe heart failure (HF) who were resistant to pharmacotherapy in Latvia and to assess the cardiac resynchronisation therapy (CRT) by exploring the predisposing factors which provides CRT efficacy. We accomplished prospective analysis of left ventricle ejection fraction (LVEF) and other parameter changes 12 and 24 months after CRT device implantation, dividing the population into two groups: responders — to whom LVEF improvement was ≥10% and non-responders where ≥ 10% LVEF improvement was not achieved. The study included 50 chronic HF patients with preserved sinus rhythm, who underwent CRT device implantation in Latvia at the Pauls Stradiņš Clinical University Hospital from June 2009 to March 2012. In the group of patients where 12 and 24 months after CRT device implantation LVEF improvement ≥10% was achieved, there were statistically significantly more patients with left bundle branch block (LBBB) QRS morphology, wider QRS complex, nonischemic genesis of HF, and normal systolic blood pressure. Patients with LVEF improvement had more pronounced ventricular dyssynchrony measured by Echo before CRT device implantation and, accordingly, the CRT mode was programmed as left ventricle paced before right ventricle and close to 100% biventricular pacing was achieved and the patient was female.

Key words: *cardiac resynchronisation therapy, heart failure.*

INTRODUCTION

Heart failure (HF) is characterised as a pathophysiological condition, where due to abnormality of cardiac function, the heart fails to pump and eject blood at a rate commensurate with the requirements of the metabolising tissuses. Clinical manifestations of HF include progressing fatigue and weakness, exertional and/or rest dyspnea, pulmonary congestion, hepatomegaly, and ankle swelling. All listed symptoms notably affect quality of life. These patients have a markedly increased risk of life-threatening arrhythmias and the cause of death most frequently is HF progression and/or ventricular arrhythmias.

HF development can involve electrical dyssynchrony between right and left ventricle contractions. In an electrocardiogram (ECG) it is seen as interventricular conduction abnormalities, mostly as left bundle branch block (LBBB) or right bundle branch block (RBBB). Electrical and mechanical dyssynchrony results in a deterioration of contractile function of the heart and dilatation of ventricles.

For patients with moderate and severe HF pharmacotherpy is frequently ineffective, because it cannot prevent uncoordinated contractions of ventricles. For more than ten years, pharmacotherpy has been complemented with cardiac resynchronisation devices all over the world. Cardiac resyn-

chronisation therapy (CRT) restores adequate coordination between atria and ventricles, provides coordinated contraction of both ventricles and prevents cardiac dyssynchrony, which is one of the main reasons for poor prognosis to HF patients.

Selection of HF patients for CRT is based on three criteria — HF functional class according to NYHA (New York Heart Association), QRS complex duration (QRS ≥120 ms on ECG) and Echo parameters — left ventricle ejection fraction (LVEF) < 35% and left ventricle end diastolic diameter (EDD) > 55 mm. Approximately 25–30% of patients with CRT do not reach the expected effect on HF symptom reduction and preventing progression (McMurray *et al*., 2012; Dickstein *et al*., 2008).

CRT has been used for HF patient treatment since 2002. The first implantation of a CRT device in Latvia was performed in 2006 (J. Ansabergs, N. Nesterovics, M. Blumbergs). Over the last years, the patient population with CRT devices in Latvia has been rapidly growing, but the amount of implanted devices is still not sufficient (Fig. 1). Comparison of data from Latvia with data from other European countries shows that we are far from the leaders. On average in Eastern Europe there are 50–150 implantations per 1 million a year, compared to 150–220 CRT device implantations in Western Europe (Vardas *et al*., 2012; Arribas *et al*., 2014). In Latvia there were 56 CRT device implantations performed per 1 million population in 2016.

There have been no prospective or retrospective studies in Latvia to analyse the efficacy of CRT. In randomised multicenter trials the lack of CRT expected effectiveness is associated with improper patient selection, suboptimal location of left ventricle lead, inappropriate choise of medications as well as with unwarranted CRT device programming.

The aim of this study was to evaluate the course of treatment of patients with moderate and severe HF who are resistant to pharmacotherapy in Latvia and to assess factors that are related to CRT efficacy.

MATERIALS AND METHODS

The study included chronic HF patients with preserved sinus rhythm, who underwent CRT device implantation in Latvia at Pauls Stradiņš Clinical University Hospital from June 2009 to March 2012. During the study, evaluation of treatment course of patients with moderate and severe HF resistant to pharmacotherapy was accomplished by examining factors related to CRT efficacy. This clinical, longitudinal, prospective study was approved by the Latvian University Research Institute of Cardiology clinical-physiological research, drug and pharmaceutical clinical research Ethics Committee.

CRT device implantations were performed according to the European Society of Cardiology guidelines for HF therapy (and updates), i.e. for patients with severe HF (NYHA functional class III and ambulatory class IV HF) on optimal

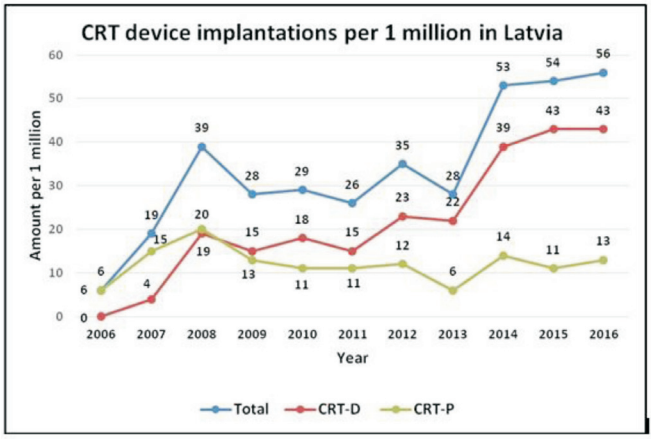

Fig. 1. Cardiac resynchronisation device implantations at Pauls Stradiņš Clinical University Hospital from 2006 to 2016. CRT-D, cardiac resynchronisation device with defibrilation function; CRT-P, cardiac resynchronisation device without defibrilation function.

pharmacological therapy (OPT), with QRS duration > 120 ms and LVEF < 35% and for patients with moderately severe HF (NYHA functional class II) if patient is on OPT, is in sinus rhythm, with LVEF ≤ 35% and QRS duration ≥150 ms.

All patients included in the study were in sinus rhythm and for all patients, a CRT device with three leads was implanted — one lead located in the right atrium, one in the right ventricle, and one through the CS was directed to the left ventricle. Consequently, all patients were provided with pacing, both for atrium and ventricles. A Chest X-ray after CRT device implantation is shown in Figure 2.

All patients were on OPT for HF treatment, which included fixed doses of angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB), beta-blockers (BB) and mineralocorticoid receptor antagonists (MRA).

The criteria of exclusion were permanent atrial fibrillation where restoration and preservation of sinus rhythm was impossible or sinus rhythm was not stable, radiofrequency catheter ablation of the atrioventricular junction due to paroxysmal or persistent atrial fibrillation, death of the patient, transplantation of the heart and application of a ventricular assist device (VAD).

There were 50 patients included and the follow-up visits were arranged 0, 3, 6, 12, and 24 months after CRT device implantation. From the excluded patients one had underwent radiofrequency catheter ablation of the atrioventricular junction (3 months after the inclusion visit) and two patients died during the study (5 and 16 months after the inclusion visit).

A database was created using Microsoft Office Excel. The records contained information about gender and age, the date of the CRT device implantation, HF (NYHA) functional class, 6-minute walking distance, hypertension and smoking, diabetes, dyslipidemia and anemia, body mass in-

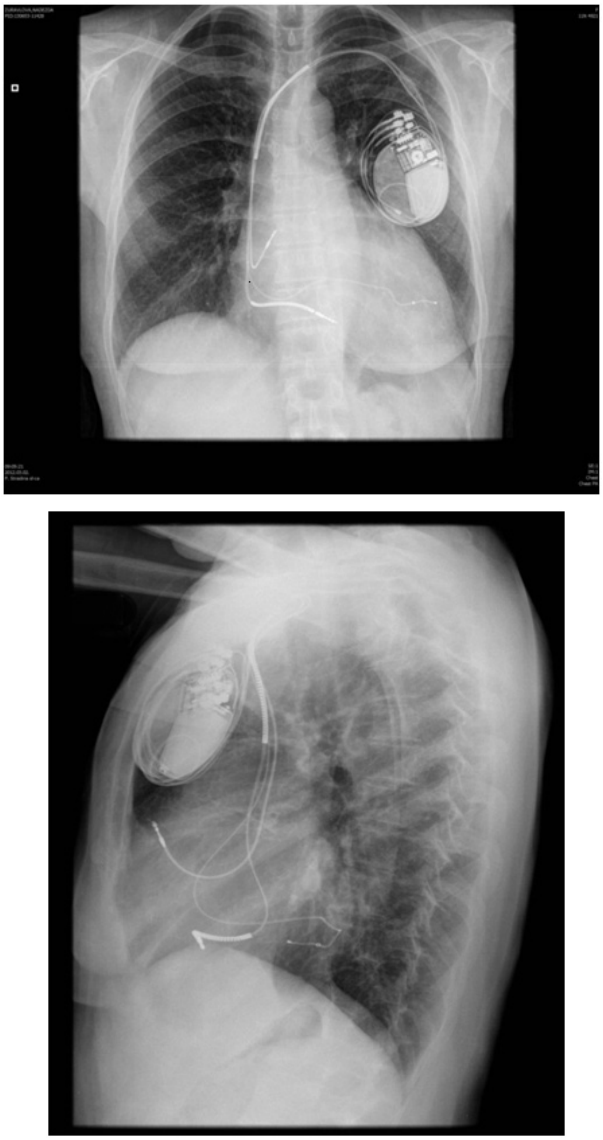

Fig. 2. Chest X-ray after CRT device implantation in anterior-posterior and lateral projections (images from Pauls Stradiņš Clinical University Hospital database, CRT implantation was performed by MD Nikolajs Ņesterovičs).

dex (BMI), C reactive protein (CRP), glomerular filtration rate (GFR), B-type Natriuretic Peptide (BNP), heart rate, QRS morphology and duration, etiology of HF, location of CS lead (based on X-ray analysis), Echo parameters (EDD, ESD, LAVI, LVEF, MR and interventricular dyssynchrony), pharmacological therapy, and presence of supraventricular and ventricular arrhythmias, and atrioventricular conduction.

The average values of parameters and measurements of the study population before CRT implantation are summarised in Tables 1 and 2. Statistical analysis was made using SPSS (Statistical Package for the Social Sciences for Windows), version 19.0. Generally accepted methods of descriptive statistics were used for characterisation of the population. Quantitative variables were described using mean arithmetic and standard deviation (SD), but in cases when the distribution of data did not complete criteria for normal distribution, the median and the quartiles were used. The

Table 1

AVERAGE VALUES OF PARAMETERS OF THE STUDY POPULATION BEFORE CRT IMPLANTATION

Age, years	64.6 ± 9.4
Males, %	66.7% (n = 32)
Body mass index, kg/m^2	29.56 ± 5.0
Diabetes, %	18.8 % (n = 9)
GFR < 60 ml/min/1.73m2, %	47.9 (n = 23)
BNP, pg/ml	1274 ± 151.80
NYHA class III / IV, %	85.41 (n=41)
6-minute walking distance, m	344.65 ± 123.83
History of hypertension, %	62.5 (n = 30)
History of smoking, %	72.9 (n = 35)
Hemoglobin, g/dl	13.91 ± 1.51
Nonischemic genesis of cardiomyopathy, %	43.8 (n = 21)
Ischemic genesis of cardiomyopathy, %	56.3 (n = 27)
LBBB, %	77.1 (n = 37)
EDD, mm	69.35 ± 0.84
LVEF, %	32 ± 0.73

CRT, cardiac resynchronisation therapy; GFR, glomerular filtration rate; BNP, B-type Natriuretic Peptide; NYHA, New York Heart Association; LBBB, left bundle branch block; EDD, end diastolic diameter; LVEF, left ventricle ejection fraction

Table 2

PHARMACOLOGICAL THERAPY OF STUDY POPULATION BEFORE CRT IMPLANTATION

BB (%)	95.8
ACEI/ARB (%)	89.5
Spironolactone (%)	85.4
Loop diuretics (%)	100
Digoxin (%)	2
Ivabradin (%)	20.8
Amiodaron (%)	20.8
Statins (%)	72.9

BB, beta-blockers; ACEI/ARB, angiotensin-converting enzyme inhibitors/ angiotensin receptor blockers

distribution of data was checked using the Kolmogorov–Smirnov test. Due to the insufficient number of patients (< 30) two independent groups were compared using the Mann–Whitney U-test. In compliance with a generally accepted principle in medical statistics, the level of significance was $p < 0.05$.

RESULTS

All patients underwent CRT device implantation and objective and subjective parameters were measured before and 3, 6, 12, and 24 months after the implantation. The population was divided into two groups (A and B) according to prospective evaluation of LVEF improvement measured by Echo:

Group A (responders) included patients showing improvement of LVEF ≥10%, 12 and 24 months after CRT device implantation;

Group B (non-responders) included patients showing improvement of LVEF ≤10%, 12 and 24 months after CRT device implantation.

Significant differences between group A and B patients were tested for 53 parameters: age and gender of patients, HF functional class, 6-minute walking distance, history of hypertension, smoking and diabetes, renal function, haemoglobin, CRP, dyslipidemia, BMI, BNP, heart rate, QRS duration and morphology, Echo parameters (VV dyssynchrony, EDD, ESD, LVEF, LAVI, MR grade), and etiology of HF. According to group of medications used for HF treatment the differences between both groups were summarised and patient answers on questions about quality of life were evaluated. CRT device programming data were used to determine differences in atrioventricular conduction disturbances between groups A and B. Assessment of the incidence of paroxysmal supraventricular and ventricular arrhythmias, presence of ventricular dyssynchrony and percentage of ventricular pacing after CRT implantation was carried out.

Statistically significant differences between groups A and B were found for five of the tested parameters and very significant differences were found for four parameters (p = 0.05–0.1), 12 months after CRT device implantation. Correlation analysis confirmed that systolic blood pressure, QRS morphology, type of myocardial injury, interventricular (V-V) dyssynchrony, CRT device dyssynchrony mode were associated with clinical benefit. However, strong differences after 12 months were found for history of smoking, total cholesterol, QRS duration and etiology of HF, and it is likely that these parameters were involved in improvement in patients in groups A and B. The results are summarised in Table 3.

Twenty-four months after CRT implantation, statistically significant differences between group A and B were found for eight parameters and strong differences were found for four parameters. Correlation analysis confirmed that clinical benefit is associated with systolic blood pressure, QRS morphology, type of myocardial injury, HF etiology, myocardial revascularisation, interventricular (VV) dyssynchrony, total cholesterol, and CRT device dyssynchrony mode. However, gender of patient, QRS duration, left ventricle end systolic diameter (ESD) and statin therapy may be involved in improvement. The results are summarised in Table 4.

DISCUSSION

Pharmacotherapy is the main tool for treatment of HF, but there are cases when the contractile function of the heart is restricted and positive effect of the pharmacotherapy cannot be reached. In cases where a contributing factor of HF is electrical dyssynchrony of ventricles and pharmacotherapy does not provide the effect which is expected, CRT can be used as an additional option for treatment of HF. This is the first study conducted in Latvia carried out to gain better understanding of the existing situation by estimating CRT efficacy. The first implantation of a CRT device in Latvia was performed in 2006 and the period of study (2009–2012) occurred during a rising rate of implantations.

Generally, CRT devices are used for patients with preserved sinus rhythm, but 25–35% of HF patients with electrical dyssynchrony have a permanent form of atrial fibrillation (Arribas *et al*., 2014). In contrast to patients in sinus rhythm, this group of patients has atrioventricular dyssynchrony, irregular and often rapid ventricular rate and the development of cardiomyopathy may be associated with fast ventricular rate instead of ventricular dyssynchrony; in addition these patients frequently have more adverse reactions. Therefore, patients with CRT who are in sinus rhythm cannot be compared to patients with CRT in atrial fibrillation. The condition in Latvia is similar: approximately 1/3 of CRT implantations are performed to patients in atrial fibrillation, to whom radiofrequency catheter ablation of the atrioventricular junction is done to provide 100% biventricular pacing and to avoid a fast ventricular rate. In this study only patients in sinus rhythm were included, which restricted the number of patients.

In the currently available literature, no precise definition of positive response to CRT effect is given. For HF patients with NYHA class II, a positive CRT effect often is predicted prolongation of life expectancy, while for HF patients with NYHA class III and IV, positive effects are reduction of severe HF symptoms, improvement of quality of life, reduced hospitalisation rate and even a small clinical improvement due to CR

In earlier studies the selected primary endpoints were set mortality and hopitalisation due to HF decompensation. Significant reduction of mortality was observed in COMPANION (Bristow *et al.,* 2004) and CARE-HF (Cleland *et al.,* 2005) trials that included HF patients with NYHA class III and IV. But the data from later trials like MADIT-CRT (Zareba *et al.,* 2011) and REVERSE (Daubert *et al.,* 2009), which included patients with mild and moderate HF and where the effect of CRT with ICD function was compared to ICD alone, showed that mortality was very low in both groups. Therefore, mortality is not an applicable criteria for CRT efficacy evaluation for all HF patients, because the group of patients with mild and moderate HF cannot be compared to the group of patients with clinically severe HF. In this study, which was conducted in Latvia, the reduction of mortality could not be estimated, because during the two-year period there were only two deaths and 24 months is not a sufficient time period to estimate mortality reduction. However, reduced hospitalisation was observed in both groups of patients with implanted CRT.

The cardinal clinical symptom of HF is exertional dyspnea. Accordingly, for assessment of CRT efficacy, the patient

Table 3

SUMMARY OF THE PARAMETERS ANALYSED 12 MONTHS AFTER CRT DEVICE IMPLANTATION

Parameters	Group A 48.9% (n = 23)	Group B 51.1% (n = 24)	*p* value
Age, years	64.8 ± 9.5	64.4 ± 9.5	0.893
Gender females (%) males (%)	 43.5 (n = 10) 56.5 (n = 13)	 25 (n = 6) 75 (n = 18)	0.181
HF functional class NYHA II (%) NYHA III (%) NYHA IV (%)	 13 (n = 3) 78.3 (n = 18) 8.7 (n = 2)	 16 (n = 4) 60 (n = 14) 24 (n = 6)	0.311
6-minute walking distance, m	356.8 ± 119.6	333.4 ± 128.9	0.642
Systolic blood pressure, mm Hg	131.1 ± 14.5	119.8 ± 15.8	0.015
History of hypertension, %	69.6 (n = 16)	56 (n = 14)	0.332
History of smoking, %	60.9 (n = 14)	84.0 (n = 21)	0.072
Diabetes, %	26.1 (n = 6)	12.0 (n = 3)	0.279
BMI, kg/m^2	29.91 (±4.7)	29.24 (±5.3)	0.583
CRP, mg/l	4.13 (±5.5)	4.0 (±4.1)	0.722
Reduced GFR, %	39.1 (n = 9)	56.0 (n = 14)	0.243
BNP, pg/ml	1172.6 (±723.0)	1367(±1291.4)	0.869
Hemoglobin, g/l	13.84 ± 1.82	13.81 ± 1.35	0.439
Total cholesterol, mmol/l	5.03 ± 1.32	4.32 ± 1.4	0.055
Statin therapy, %	69.6 (n = 16)	76.0 (n = 19)	0.616
Heart rate, x/min	72.81 (±11.27)	70.50 (±8.90)	0.385
QRS morphology: LBBB, % non-LBBB, %	 91.3 (n = 21) 8.7(n = 2)	 64.0 (n = 16) 36.0 (n = 9)	0.025
QRS duration, ms	176.17 (±21.05)	163.44 (±22.54)	0.071
Etiology of heart failure: ischemic, % nonischemic, %	 43.5 (n = 10) 56.5 (n = 13)	 68 (n = 17) 32.0 (n = 8)	0.087
Myocardial injury: scar of LV after myocardial infarction, % no scars or diffuse hypokinesia, %	 30.4 (n = 7) 69.6 (n = 16)	 64.0 (n = 16) 36.0 (n = 9)	0.036
Revascularisation is done, % not done, %	 47.8 (n = 11) 52.2 (12)	 62.5 (15) 37.5 (9)	0.492
Position of CS lead: lateral, posterolateral, posterior wall, % anterolateral wall, %	 100 (n = 23) 0.0 (n = 0)	 88.0 (n = 23) 12.0 (n = 3)	0.366
Echo parameters: EDD, mm ESS, mm interventricular dyssynchrony, ms LAVI, ml/ m^2 LVEF, %	 69.96 ± 5.41 57.16 ± 7.52 50.04 ± 22.23 51.43 ± 12.31 24.48 ± 5.03	 68.80 ± 6.28 57.1 ± 7.28 34.42 ± 18.18 48.84 ± 14.58 25.02 ± 5.06	 0.678 0.432 0.014 0.273 0.461
CRT dyssynchrony LVąRV, % BiVV& RVąLV, %	 65.2 (n = 15) 34.8 (n = 8)	 36.0 (n = 9) 64.0 (n = 16)	0.043

CRP, C reactive protein; LV, left ventricle; LAVI, left atrial volume index

Table 4

SUMMARY OF THE PARAMETERS ANALYSED 24 MONTHS AFTER CRT DEVICE IMPLANTATION

Parameter	Group A 56.25% (n = 27)	Group B 43.75% (n = 22)	*p* value
Age, years	63.4 ± 9.8	66.5 ± 8.7	0.256
Gender females, % males, %	 44.4 (n = 12) 55.6 (n = 15)	 19.0 (n = 4) 81.0 (n = 17)	0.064
HF functional class NYHA II, % NYHA III, % NYHA IV, %	 11.1 (n = 3) 77.8 (n = 21) 11.1 (n = 3)	 18.2 (n = 4) 59.1 (n = 13) 22.7 (n = 5)	0.361
6-minute walking distance, m	354.0 ± 113.1	332.0 ± 136.0	0.594
Systolic blood pressure, mm Hg	131.8 ± 14.7	117.5 ±14.1	0.002
History of hypertension, %	66.7 (n = 18)	33.3 (n = 9)	0.584
History of smoking, %	63.0 (n = 17)	81.8 (n = 18)	0.146
Diabetes, %	22.2 (n = 6)	18.2 (n = 4)	1.00
BMI, kg/m^2	29.6 (±5.2)	29.43 (±4.8)	0.950
CRP, mg/l	4.4 (±5.9)	5.0 (±7.6)	0.737
Reduced GFR, %	40.7 (n = 11)	54.5 (n = 12)	0.336
BNP, pg/ml	1249.0 (±151.2)	1293.2 (±153.2)	0.833
Hemoglobin, g/l	14.16 ± 1.76	13.68± 1.23	0.687
Total cholesterol, mmol/l	4.98(± 1.28)	4.16(±1.08)	0.020
Statin therapy, %	63.0 (n = 17)	86.4 (n = 19)	0.065
Heart rate, x/min	72.48 (±10.59)	70.76 (±10.08)	0.468
QRS morphology: LBBB, % non-LBBB, %	 96.3 (n = 26) 3.7 (n = 1)	 54.5 (n = 12) 45.5 (n = 10)	0.001
QRS duration, ms	175.15 (±20.29)	162.82(±23.25)	0.099
Etiology of heart failure: ischemic, % nonischemic, %	 40.7 (n = 11) 59.3 (n = 16)	 77.3 (n = 17) 22.7 (n = 5)	0.001
Myocardial injury: scar of LV after myocardial infarction, % no scars or diffuse hypokinesia, %	29.9 (n = 7) 74.1 (n = 20)	77.3 (n = 17) 22.7 (n= 5)	0.001
Revascularisation is done, % not done, %	 40.7 (n = 11) 59.3 (16)	 76.2 (n = 16) 23.8 (5)	0.014
Position of CS lead: lateral, posterolateral, posterior wall, % anterolateral wall, %	 96.3 (n = 26) 3.7 (n = 1)	 90.9 (n = 20) 9.1 (n = 2)	0.859

can evaluate reduction of exertional dyspnea and weakness. Clinical trials have established that CRT reduces symptoms only to patients with severe heart failure; furthermore, the REVERSE (Daubert *et al.,* 2009) trial confirmed that there was no improvement of symptoms to NYHA I and II class HF patients. Consequently, in estimation of isolated clinical symptoms there are approximately 20–30% non-responders among NYHA class III and IV HF patients, but among

NYHA class I and II there would almost zero non-responders.

In multiple trials as the most significant criteria of CRT efficacy is considered to be changes of LVEF (Daubert *et al.,* 2009; Zareba *et al.,* 2011; Yu *et al.,* 2005). It has been established that reduction of left ventricle volume and increase of LVEF are correlated with reduction of clinical symptoms and mortality in the CRT group. For patients with 10% left ventricle end-systolic volume reduction after CRT device implantation three-year survival reaches 90% compared to 50% patients who do not achieve 10% left ventricle end-systolic volume reduction (Yu *et al.,* 2005).

In our study 48.9% patients achieved ≥10% of LVEF improvement in 12 months. But during the 24-month period, the results were 56.25%. It can be assumed that only slightly more than a half of the patients achieves Echo positive improvement of HF, but the study showed that the effect of CRT depends not only on LVEF and positive remodelation of the left ventricle. Improvement of subjective symptoms, improvement of NYHA class, reduction of hospitalisation rate and delay of development of arrhythmias was also often achieved in the group of patients where LVEF improvement was 5–10%.

A statistically significant difference between groups A and B was found for systolic blood pressure (SBP). Correlation analysis showed that change in SBP is associated with improvement in both groups. The study also confirmed that SBP was lower in the group of non-responders. It can be concluded that lowering SBP 120 mmHg is not recommended, but this is hard to achieve because optimal pharmacotherapy includes several antihypertensive medications (ACEI/ ARB, BB, diuretics) and patients with severe HF already are hypotensive. Moreover, profound hypotension may lead to hypoperfusion of organs and cause decrease of CRT efficacy.

At the beginnig of the CRT "era", one of the leading criteria of CRT efficacy was considered to be QRS duration, but currently, QRS morphology also is analysed as an efficacy contributing factor.

In the largest CRT trial MADIT-CRT (n = 1820) where HF patients in NYHA class I and II were included (Moss *et al.,* 2009; Zareba *et al.,* 2011), reduction of mortality and hospitalisation in a CRT-D group was compared to an ICD group. It was estimated that reduction of relative risk in the CRT group was 34% ($p < 0.001$), compared to 57% ($p < 0.001$) in a subgroup that consisted of patients with LBBB. In the more notable MADIT-CRT report, which determined CRT long-term efficacy, seven-year data analysis of patients showed moderate clinical symptoms and significantly reduced systolic function of the left vetricle (published in 2014). In the group with CRT and LBBB, mortality was 18% in comparison to 29% ($p = 0.002$) in the ICD group. This suggests that nine patients should be treated with CRT-D to save one life in a seven-year period (Goldenberg *et al.,* 2014).

In our study comparative analysis 24 months after CRT implantation, LBBB was shown in 96.3% (n = 26) of group A and 54.5% (n = 12) of group B patients. There was a moderate correlation between improvement and QRS morphology ($r_s = 0.498$, $p < 0.001$) and in a longer the period there was more pronounced improvement for patients with LBBB.

LBBB is determinative criteria for CRT efficacy. This could be explained with more pronounced negative remodelation of left ventricle in patients of this group causing greater improvement due to CRT, as shown in international studies and in the present study. Studies also have established less improvement of NYHA class for patients with RBBB (Leong *et al*., 2012), which may be associated with inferior CRT efficacy.

In most trials where etiological factors of HF are explored, patients are divided into two large groups — a group of patients with ischemic genesis of HF to whom the underlying cause of HF is CAD and a group of patients with nonischemic genesis of HF to whom cause of dilated cardiomyopathy is not related to CAD. Clinical efficacy of CRT in both groups was evaluated in a subanalysis of the MADIT — CRT trial (Barsheshet *et al*., 2011; Zareba *et al*., 2011). There were 1046 patients with ischemic cardiomyopathy and 774 patients with nonischemic cardiomyopathy included in analysis; the follow-up was 2.4 years. Patients with ischemic cardiomyopathy achieved 34% ($p < 0.001$) reduction of mortality and HF decompensation by comparison of a CRT — D group to an ICD group, but patients with nonischemic cardiomyopathy achieved 44% ($p < 0.002$) reduction of mortality and HF decompensation in the CRT — D group, compared to the ICD group.

In our study patients were also divided by etiological factor of HF.

The percentage of patients with ischemic and nonischemic cardiomyopathy in our study was 56.3% (n = 27) and 43.8% (n = 21), respectively. Differences between groups A and B were observed already after 12 months, but the most evident differences were observed after 24 months, in group A 40.7% (n = 11) of patients and in group B 77.3% (n = 17) of patients had ischemic cardiomyopathy, however, percentage of nonischemic cardiomyopathy in group A and B was 59.3% (n = 16) and 22.7% (n = 5), respectively ($p = 0.01$). Multicenter trials and also this study established that patients with nonischemic genesis of HF gain more benefit from CRT when compared to patients with ischemic genesis of HF. This can explained by the anatomical structure of the left ventricle. After myocardial infarction hypokinetic and akinetic scars are involved in the development of HF and maintain the progression of HF, but in patients with nonischemic genesis of HF ventricles are diffusely enlarged and better comply with pacing and, therefore, even conduction of impulse can be provided.

Patients were divided into groups based on evaluation of echocardiographic localisation of myocardial injury. One group included patients with echocardiographically identi-

fied scars in one of the walls of left ventricle and the second group included patients to whom local scars were not found or diffuse hypokinesia was identified, which usually indicates nonischemic genesis of HF. Twenty-four months after CRT implantation in group A 29.9% (n = 7) of patients had myocardial scar and 74.1% (n = 20) had diffuse hypokinesia. However, in group B 77.3% (n = 17) of patients had localised injury of left ventricle and only 22.7% (n = 5) of patients had diffuse hypokinesia ($p < 0.001$). This indicates that patients with ischemic genesis of HF are less favourable candidates for high efficacy of CRT.

In our study we also analysed the revascularisation of myocardium, if it was performed before CRT device implantation. In group A 24 months after CRT implantation 40.7% (n = 11) of patients had underwent revascularisation, However, in group B there were 76.2% (n = 16) revascularised patients ($p = 0.014$). This also confirms that patients with ischemic genesis of cardiomyopathy are more likely to be nonresponders.

CRT is an effective method of treatment for HF patients with widened QRS complex. Studies and meta-analyses show that patients with significantly widened QRS complex gain the greatest benefit from CRT (Sipahi *et al*., 2011; Stavrakis *et al*., 2012). In our study the analysis of QRS duration before CRT implantation showed a statistically strong difference ($p = 0.099$) between group A and B 24 months after implantation. A wider QRS complex before CRT device implantation was associated with better effect of CRT.

In most CRT studies females are in the minority (24% of CRT candidates in European population); therefore, it may be concluded that in the general population the proportion of males with severe systolic dysfunction and wide QRS complex is greater (Zabarovskaja *et al*., 2012; Yi-Zhou *et al*., 2012). However, several studies that included patients with moderate and severe HF, reduced LVEF and wide QRS showed less improvement in mortality and hospitalisations after CRT implantation for males when compared to females (Yi-Zhou *et al*., 2012). In our study of 50 patients, 17 were females and 33 were males. In group A 24 months after CRT implantation, 55.6% (n = 15) of patients were males and 44.4% (n = 12) were females ($p = 0.064$). Correlation analysis showed a weak correlation between gender and improvement, but statistical significance was not achieved ($r_s = –0.267$, $p = 0.064$) due to the small number of patients. It is likely that a study with a greater number of patients would show that females are better candidates for CRT.

In our study 56.2% of patients had ischemic genesis of HF; therefore, one of the parameters evaluated was total cholesterol (TC) levels. In group A, 24 months after CRT device implantation, TC was 4.98 (±1.28) mmol/l, compared to 4.16 (±1.08) mol/l ($r_s = –0.335$, p = 0.020) in group B. It should be noted that the lower TC level in group B could be explained by a greater proportion of patients with ischemic genesis of HF, as patients with CAD were prescribed group medications for correction of dyslipidemia more often.

In group A, 24 months after CRT device implantation, 63.0% (n = 17) of patients were using statins, compared to 86.4% (n = 19) ($p = 0.065$) in group B. The explanation of such results could be similar to that given above.

It has been established that reduction of left ventricle volume and increase of LVEF is correlated with reduction of clinical symptoms and mortality in patients with CRT (Brignole *et al*., 2013). In our study, change of left ventricle end-systolic diameter (ESD) and end-diastolic diameter (EDD) were followed throughout the course of research. The difference in left ventricle ESD between group A and B 24 months after CRT implantation was slightly below the level of statistical significance ($p = 0.064$). However, after 24 months, a significant difference between group A and B was observed in V-V dyssynchrony: 51.37 (±19.45) ms in group A and 29.14 (±17.41) ms ($p < 0.001$) in group B. There was a weak correlation (rs = –0.361, $p = 0.013$) between V-V dyssynchrony and improvement. Consequently, the data showed that better the effect of CRT may be expected with more pronounced V-V dyssynchrony before the CRT implantation.

Two groups with different dyssynchrony prevention modes were analysed. The first group included patients to whom left ventricle was paced before the right ventricle (LV→ RV) and the second group included patients with other possible modes — synchronous pacing of both ventricles and right ventricle pacing before left ventricle (BiVV& RV→ LV). In both groups (A and B) a significant difference ($p = 0.042$) was observed in CRT dyssynchrony after 24 months between LV→RV group and combined BiVV& RV→ LV group. Twenty-four months data analysis showed that in group A there were more patients with LV→ RV pacing mode (65.2% (n = 15) and 63.0% (n = 17), respectively). Accordingly, patients with LBBB, where CRT mode is LV→ RV, can be considered as better candidates for effective CRT if compared to BiVV& RV→ LV.

CONCLUSIONS

The study showed that better effect of CRT may be expected in HF patients who have LBBB QRS morphology, wider QRS complex, nonischemic genesis of HF, normosystolic blood pressure, left ventricular lead positioned in lateral or posterolateral CS vein, severe ventricular dyssynchrony and CRT mode which provides left ventricle pacing before right ventricle and near 100% biventricular pacing, and for female patients.

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Received 3 January 2018
Accepted in the final form 6 June 2018

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SIRDS RESINHRONIZĀCIJAS TERAPIJAS EFEKTIVITĀTI NOTEICOŠO FAKTORU IZVĒRTĒJUMS PACIENTU ĀRSTĒŠANĀ AR MĒRENU UN SMAGU SIRDS MAZSPĒJU LATVIJAS POPULĀCIJĀ 12 UN 24 MĒNEŠU PĒTĪJUMĀ

Pētījuma mērķis bija analizēt ārstēšanas norisi hroniskas sirds mazspējas (HSM) pacientiem Latvijā ar vidēji smagu un smagu klīnisko gaitu, rezistenci pret farmakoterapiju, ar implantētām sirds resinhronizācijas iekārtām, pētot predisponējošos faktorus sirds resinhronizācijas terapijas (*cardiac resynchronisation therapy, CRT*) efektivitātes nodrošināšanā. Prospektīvi tika analizēti kreisā kambara izsviedes frakcijas (*ejection fraction, EF*) mērījumi un citi parametri 12 un 24 mēnešus pēc *CRT* ierīces implantācijas, pacientus dalot grupā, kur tika panākta ≥10% EF uzlabošanās (*responderi*) un grupā, kur netika panākta ≥10% EF uzlabošanās (*neresponderi*). Pētījumā analizēti 50 hroniskas sirds mazspējas pacienti ar saglabātu sinusa ritmu, kuriem veikta *CRT* implantācija Latvijā, Paula Stradiņa Klīniskajā universitātes slimnīcā, laika posmā no 2009. gada jūnija līdz 2012. gada martam. Divpadsmit un 24 mēnešus pēc *CRT* ierīces implantācijas, pacientu grupā, kur tika panākta Eho KG ≥10% *EF* uzlabošanās, bija statistiski ticami vairāk pacientu ar Hisa kūlīša kreisā zara pilnas blokādes morfoloģiju, platāku QRS kompleksu, neišēmiskas ģenēzes sirds mazspēju, normosistolisku asinsspiedienu. Pacientiem ar *EF* uzlabošanos bija izteiktāka kambaru disinhronija Eho KG mērījumos pirms *CRT* implantācijas, attiecīgi *CRT* ierīcē tika ieprogrammēti kambaru disinhroniju likvidējošie parametri, lai kreisais kambaris tiek stimulēts pirms labā kambara, tika nodrošināta tuvu 100% biventrikulāra stimulācija, un pacients bija sieviete.