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ASSESSMENT OF FACTORS
DETERMINING EFFICACY OF CARDIAC
RESYNCHRONISATION THERAPY
FOR PATIENTS WITH HEART FAILURE
IN THE POPULATION OF LATVIA

Summary of the Doctoral Thesis
for obtaining the degree of a Doctor of Medicine

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Abbreviations used in the paper

ACC	American College of Cardiology
ACEI	angiotensin-converting enzyme inhibitor/s
AHA	American Heart Association
ARB	angiotensin receptor blocker/s
AV	atrioventricular
BAB	beta-adrenergic blocking agent/s
BiVV	biventricular
BMI	body mass index (kg/m^2)
BNP	brain natriuretic peptide
CaCB	calcium channel blockers
CHD	coronary heart disease
CHF	chronic heart failure
cm	centimetres
CMP	cardiomyopathy
CRO	C-reactive protein
CRT	cardiac resynchronisation therapy/device
CRT-D	implantable device, which combines functions of resynchronisation therapy and an implantable cardioverter defibrillator
CRT-P	implantable device, which combines functions of resynchronisation therapy and a cardiac pacemaker
CS	coronary sinus
CV	cardiovascular
EchoCG	echocardiogram
ECG	electrocardiogram
EDD	left ventricular end diastolic diameter

EF	ejection fraction
ESD	left ventricular end systolic diameter
FC	funcional class
GFR	glomerular filtration rate
g/dl	grams per decalitre
Hb	haemoglobin
HF	heart failure
ICD	an implantable cardioverter defibrillator
IVMD	interventricular mechanic dyssynchrony
IQR	interquartile range
kg/m ²	kilograms per cubic meter
LAO	left anterior oblique
LAVI	left atrial volume index
LBBB	left His bundle branch block
LVH	left ventricular hypertrophy
LV → RV	left ventricle before right ventricle
ml	millilitres
mm	millimetres
mm Hg	millimetres of mercury
Mon	month
MR	mitral regurgitation
MRA	mineralocorticoid receptor antagonist/s
ms	milliseconds
NASPE	North American Society of Pacing and Electrophysiology
NT-proBNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
ODT	optimal drug therapy

QRS	QRS complex in an electrocardiogram
p	5 % statistical error probability
pg/ml	picograms per millilitre
RAO	right anterior oblique
RBBB	right His bundle branch block
RV → LV	right ventricle before left ventricle
SBP	systolic blood pressure
SD	standard deviation
SE	standard error
TC	total cholesterol
VAD	ventricular assist devices
vs.	against (<i>versus</i>)
VV	interventricular
x/min	beats per minute
X-ray	X-ray image/X-ray examination
P, P-R, Q, q, QRS, RR	markings of teeth and intervals in an electrocardiographic image

INTRODUCTION

Topicality of the paper

Heart failure (HF) is a pathophysiological condition when disturbance of cardiac functions lead to failure of the heart to pump and to eject blood in accordance with requirements of metabolising tissues (McMurray et al., 2012). The disease is associated with reduced ability of heart to ensure an adequate blood supply throughout the body; thus, leading to the progression of exhaustion, weakness, increase of shortness of breath, formation of congestive symptoms in lungs in a case of minor or low strain and/or in a state of rest, development of hepatomegaly, and swelling of legs. The listed symptoms affect quality of life. Such patients have a significantly increased risk of life-threatening arrhythmias, and a cause of death usually is progression of heart failure and/or ventricular arrhythmias (ventricular tachycardia and ventricular fibrillation) (McMurray et al., 2012).

In some patients, development of heart failure is caused by electric dyssynchrony between right and left ventricular contractions (uncoordinated contraction of both ventricles). In ECGs it appears in a form of intraventricular conduction disorders through His's bundle main branches, in case of forming of full left His bundle branch block (LBBB) or full right His bundle branch block (RBBB). Electrical and mechanic dyssynchronies result in cardiac contractile dysfunction, ventricular cavity dilation, and decline of cardiac contractile function (Mann, 2011; McMurray et al., 2012).

In patients with moderate to severe HF, pharmacological therapy is often ineffective because it fails to prevent the resulting uncoordinated ventricular contraction. For over a decade drug therapy in the world is accompanied by cardiac resynchronisation devices. Cardiac resynchronisation therapy (CRT) helps restore proper coordination between atria and ventricles of the heart,

ensures agreed contractions of both ventricles, preventing a patient from ventricular electrical dyssynchrony, which is one of the indicators of unfavourable prognosis of HF (Dickstein et.al., 2008).

Selection of patients for implantation of a CRT device is based on three selection criteria – HF class in line with NYHA (New York Heart Association), width of QRS complex ($QRS \geq 120$ ms according to electrocardiographic data), and Echo cardiographic (EchoCG) parameters – left ventricular ejection fraction (EF) ≤ 35 % and left ventricular end diastolic diameter (EDD) ≥ 55 mm measurements. Regardless of the above, approximately in 25–30 % of patients cardiac resynchronisation devices do not ensure the desired effect in reduction of HF and delay of the progression (McMurray et al., 2012; Dickstein et al., 2008).

In the world, CRT method has been used in treatment of patients with heart failure since 2002 (ACC/AHA /NASPE Guidelines, 2002). In Latvia, the first CRT device was implanted in 2006 (*J. Ansabergs N. Nesterovičs, M. Blumbergs*). In recent years, the number of patients with implanted CRT devices has grown in Latvia (until 2012 CRT implantations were performed only in P. Stradins Clinical University Hospital), but it is still insufficient. In 2011 in Latvia, the total of 55 CRT devices were implanted, of which only half of the patients still have a preserved sinus rhythm, in 2012 – 73 CRT devices and in 2013 – 63 CRT devices were implanted (see Figure 1). When comparing data of Latvia with the data of other European countries, we do not certainly rank among the leaders. On average, 50–150 CRTs per 1 million population per year are being implanted in patients in Eastern Europe, while in Western Europe the number reaches 150–220 of CRT devices per 1 million of population per year (Arribas et al., 2014). In 2013 in Latvia, 28 CRT devices were implanted per 1 million of population.

Until now, no prospective or retrospective analysis of efficiency of CRT devices have been carried out assessing CRT-induced improvements in treatment of patients with HF. Lack of the expected CRT efficiency in randomised multicentre trials is associated with improper selection of patients, sub-optimal positioning of left ventricular electrode, inadequate choice of medications, as well as unjustified programming of the CRT device. CRT clinical efficiency and inefficiency criteria have not been evaluated also in Latvia. There are still many patients in Latvia for whom the CRT implantation could reduce clinical manifestations of HF, improve their quality of life, as well as reduce mortality. This would reduce the work load of medical emergency service providers, duration of hospital stays and bed-day costs, as well as high cost-burden of treatment of acute heart failure to society.

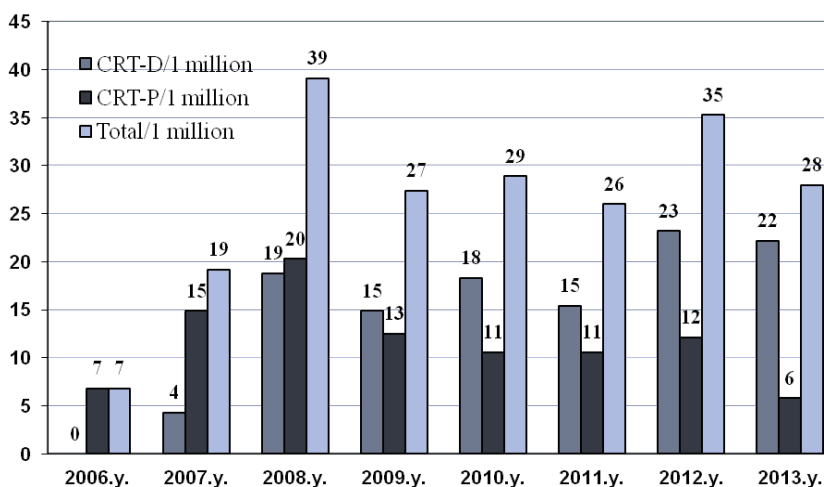


Figure 1 Implantations of cardiac resynchronisation devices in Latvia per 1 million of population in the period from 2006 to 2013
 CRT-D – cardiac resynchronisation devices with defibrillation function
 CRT-P – cardiac resynchronisation devices without defibrillator function

Novelty and practical importance of the paper

A study in assessment of efficiency of CRT devices in patients with HF with preserved sinus rhythm assessing the CRT-driven improvement of treatment was carried out for the first time in Latvia.

CRT efficiency-determining parameters for mitigation of ventricular interventricular dyssynchrony, its prevention and therefore positive remodelling of the heart and further stabilisation of clinical course of HF were assessed. Localisation of left ventricular electrode in coronary sinus branches was analysed. A set of CRT device programming parameters was analysed developing recommendations for programming after implantation of a CRT device.

The study allows assessment and specification of indications for application of CRT in patients with HF with interventricular dyssynchrony.

In Latvia the method is used by a number of certified technicians who have actively participated in the study and improved their skills and knowledge during its course. The developed recommendations for selection of patients with HF and improvement of further course of treatment after implantation of CRT will help refine selection of patients and avoid the relatively high number of non-responders in Latvia.

Structure of the Thesis

The Doctoral Thesis has been written in Latvian, in length of 130 pages. The Paper contains one appendix. The Paper follows a traditional design, including abstracts in Latvian and English, introduction, topicality, novelty and practical importance of the study, aim of the study, tasks, hypothesis, literature review, materials and methods, results, discussion, conclusions, list of articles

and reports, as well as bibliography consisting of 82 sources. The thesis contains 57 tables and 38 figures.

Aim of the research

The study aims to analyse progression of treatment and factors affecting its efficacy in HF patients with moderate and severe clinical course using implantable cardiac resynchronisation therapy devices.

Tasks of the study

1. To evaluate the efficiency of CRT device implantation in patients with moderate and severe HF within a two-year period.
2. To evaluate change in subjective and objective efficiency criteria of HF patients and longitudinal safety of a CRT device.
3. To evaluate differences between groups of CRT responders and non-responders by comparing data to the initial clinical parameters.
4. To determine differences in visualised EchoCG parameters in high and low CRT efficiency groups.
5. To evaluate differences between groups of CRT responders and non-responders by analysing EchoCG visualised parameters and laboratory values.
6. To study the impact of CRT implantation technique and programmed parameters on CRT efficiency.
7. To identify dominant factors of longitudinal CRT efficiency, according to study data prior to the implantation of a CRT device.

Hypothesis

In application of cardiac resynchronisation devices for patients with moderate and severe heart failure, correlation of diagnostic imaging, enhanced laboratory examinations, localisation of ventricular electrodes, and programming of a cardiac resynchronisation device plays an important role in assessment of selection criteria and efficiency of the complex therapy.

1 MATERIALS AND METHODS

1.1 Selection of patients

The study included 50 patients with heart failure who had undergone implantation of cardiac resynchronisation device (CRT) at Pauls Stradins Clinical University Hospital in the period between June 2009 to March 2012.

The study analysed course of treatment for HF patients with moderate and severe clinical course, resistance to pharmacotherapy, exploring predisposing factors for effective cardiac resynchronisation therapy.

This clinical, longitudinal, prospective, two-arm study has received approval from the Ethics Committee for clinical and physiological studies, clinical research of medicinal and pharmaceutical products of the Research Institute of Cardiology of the University of Latvia.

1.2 Inclusion and exclusion criteria

CRT implantation was performed in patients on the basis of heart failure treatment guidelines and amendments thereto published by the European Society of Cardiology in 2008 and 2010. Namely, in patients with severe heart failure (with NYHA Class III and outpatiently with NYHA Class IV), with optimal medication therapy (OMT), $QRS \geq 120$ ms and $EF \leq 35$ % and moderate heart failure (with NYHA Class II), if patients receiving OMT, had sinus rhythm, $EF \leq 35$ % and $QRS \geq 150$ ms (Dickstein et al., 2008; Dickstein et al., 2010).

All patients were informed on tactics and possible complications of CRT implantation, as well as on further programming of a CRT device, development of a plan for assessment of health status and subsequent treatment recommendations. In case of agreement, patients signed a special CRT

implantation consent form, which is approved for the use in Pauls Stradins Clinical University Hospital.

All patients enrolled in the study had preserved sinus rhythm, and all of them underwent implantation of a CRT device with three electrodes. Thus, all patients were provided with both atrial and ventricular pacing. All patients received OMT for treatment of heart failure.

The study did not include CRT patients with permanent atrial fibrillation to whom sinus rhythm restoration and maintenance was impossible or did not give stable results. Further analysis of the study excluded those patients who underwent atrioventricular connection radio frequency catheter ablation, heart transplantation or a surgery of a ventricular assist device (VAD).

1.3 Statistical analysis of the research data

The statistical analysis of the data was performed using the SPSS programme (IBM SPSS Statistics Version 23, SPSS inc., USA). The test results $p < 0.05$ were found to be statistically significant. Quantitative variables were defined through the arithmetic mean and standard deviation (SD). In cases of significant standard error (SE), if the data did not meet normal distribution – interquartile range (IQR) and median were assessed. Assessment of qualitative differences of patient groups was determined in %. Proportional data compliance with normal distribution was determined using *Mann-Whitney U-test*, and differences between the two varied quantitative data using *Wilcoxon signed ranks* test. Comparison of normal deviation quantitative variables was performed using *Independent samples t-test* and differences between the two quantitative variables was performed using *Paired samples t-test*. Link between quantitative variables was determined by the *Spearman* and *Pearson* rank-order correlation coefficient tests, in compliance with the test application procedures. Correlation

between the two variables was analysed using the logistic regression method. Categorical variables were compared using Pearson's chi-square (χ^2) indicator or Fisher's exact test in compliance with the test application procedures.

2 RESULTS AND ANALYSIS

2.1 General characteristics of the study population

The research includes 50 patients who meet the inclusion and exclusion criteria, of which 48 comply with the protocol of the study, the data of which have been used for further study of the research results. Two patients were excluded from the further study due to one having had atrioventricular connection radio frequency catheter ablation due to frequent atrial fibrillation paroxysms and the other patient had undergone a surgery of VAD device.

Demographics, risk factors, cardiovascular anamnesis, hemodynamics, objective parameters and prehospitalisation therapy of the entire study cohort (n = 48) have been represented in Table 2.1. Prior to implantation of a CRT device, ACEI/ARB was not used by 5 (10.4 %) patients due to low arterial blood pressure, BAB was not used by 2 (4.2 %) patients due to low heart rate, aldosterone receptor antagonists were not used by 7 (14.6 %) patients due to low arterial blood pressure and GFA.

Table 2.1

Phenotypic characterisation of patient population

Parameters	
Age (years), mean \pm SD	64.85 \pm 9.49
Gender – male, n (%)	33 (68.8)
BMI (kg / m ²), mean \pm SD	29.52 \pm 4.92
Adiposity (BMI \geq 30kg / m ²), n (%)	21 (43.8)
History of smoking, n (%)	34 (70.8)
Diabetes, n (%)	9 (18.8)
Arterial hypertension, n (%)	18 (37.5)
SBP (mm Hg), mean \pm DS	125.96 \pm 15.77
DBP (mm Hg), mean \pm DS	75.52 \pm 8.33
SBP >140 (mm Hg), n (%)	15 (31.3)

Parameters	
Chronic heart failure, n (%)	
II NYHA	7 (14.6)
III NYHA	34 (70.8)
IV NYHA	7 (14.6)
Chronic kidney disease, n (%)	23 (47.9)
Ischemic Genesis CMP, n (%)	28 (58.3)
Revascularisation, n (%)	
CABG	5 (10.4)
PCI	21 (43.8)
CABG + PCI	1 (2.1)
SV arrhythmia, n (%)	14 (97.9)
Accelerated AV control, n (%)	34 (70.8)
VT/VF anamnesis, n (%)	34 (7.8)
HR (beats/min), mean \pm DS	71.44 \pm 10.07
6-min walking test (m), mean \pm DS	349.23 \pm 118.55
Prehospitalisation therapy, n (%)	
Loop diuretics	45 (93.8)
ARA	41 (85.4)
BAB	46 (95.8)
ACEI/A2RB	43 (89.6)
CaCB	7 (14.6)
Cardiac glycosides	1 (2.1)
IKB	10 (20.8)
Potassium channel blocker	10 (20.8)
Statins	36 (75.0)
Antiagregants, n (%)	
ASA	26 (54.2)
ASA + P2Y12	8 (16.7)
Anticoagulants, n (%)	
Combined antithrombotic therapy (ASA + OAK)	4 (8.3)

SD – standard deviation, BMI – body mass index, SBP – systolic blood pressure, DBP diastolic blood pressure, NYHA – New York Heart Association, CMP – cardiomyopathy, PCI – percutaneous coronary intervention, CABG – coronary artery bypass grafting, SV – supraventricular, AV – atrioventricular, VT/VF – ventricular tachycardia/fibrillation, HR – heart rate, ARA – aldosterone receptor antagonists; BAB – beta-adrenergic blocking agents; ACEI – angiotensin-converting enzyme inhibitors; ARB – angiotensin receptor blockers; CaCB – calcium channel blockers; IKB – If channel blockers; ASA – acetylsalicylic acid; OAK – oral anticoagulants.

2.2 Efficacy and safety of cardiac resynchronisation therapy

Initial left ventricular ejection fraction (EF) of the study population, according to the EchoCG data was on average 24.81 ± 5.23 %; after CRT implantation. EF showed statistically significant development (Figure 2.1).

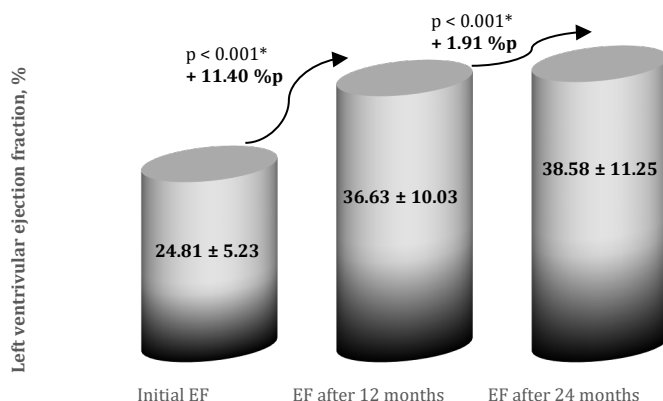


Figure 2.1 **Left ventricular ejection fraction before and after CRT implantation**

** Paired samples t-test was used for data calculations*

EF – ejection fraction. CRT – cardiac resynchronisation therapy

High cardiac resynchronisation therapy efficiency (Δ EF improvement ≥ 10 %) after 12 months was observed in 23 (48.9 %) patients and after 24 months in 27 (60.0 %) patients, defined as group A or CRT responders (Figure 2.2). Patients not conforming to the therapeutic effects (Δ EF improvement < 10 %) were defined as group B or CRT non-responders.

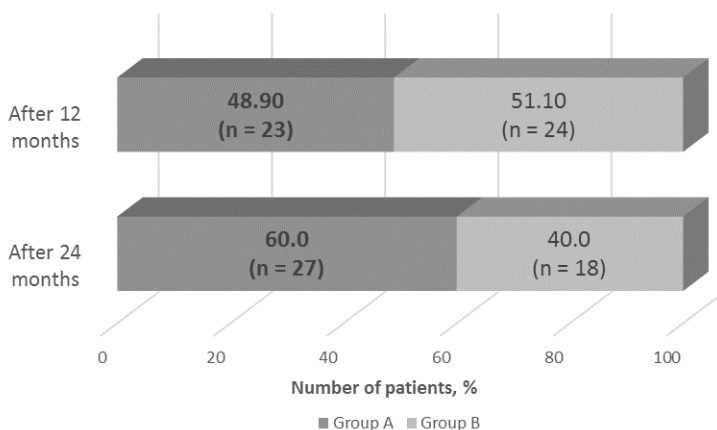


Figure 2.2 Evaluation of cardiac resynchronisation therapy efficiency (ΔEF improvement $\geq 10\%$) during patient testing
 ΔEF – changes in ejection fraction

Cardiovascular death due to CHF decompensation occurred in three patients: for one patient (2.1 %) in three months, for two patients (4.2 %) in 24 months; thus, the number of patient data analysed within the 12-month visitation was 47, and within 24 months – 45 patients. Device-related complications and bleeding was not observed. Post-CRT device implantation patients were statistically significantly less frequently admitted to hospital (Figure 2.3).

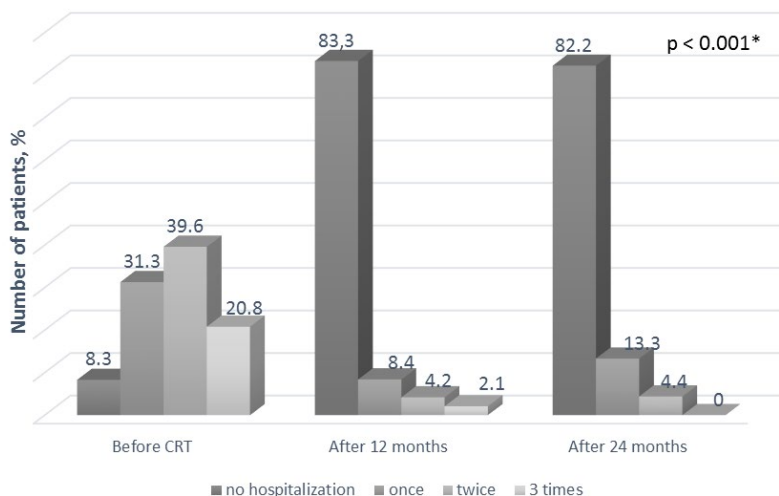


Figure 2.3 **Frequency of hospitalisation before and after CRT implantation**

* *Wilcoxon signed ranks* test was used for data calculations

CRT – cardiac resynchronisation therapy

After CRT implantation, according to NYHA classification, patients' functional class (FC) improved statistically significantly. Upon hospital admission, FC IV was observed in 7 (14.6 %), in 12 months – 2 (4.3 %), 24 months later in 1 (2.2 %) patient; $p < 0.001$ (Figure 2.4).

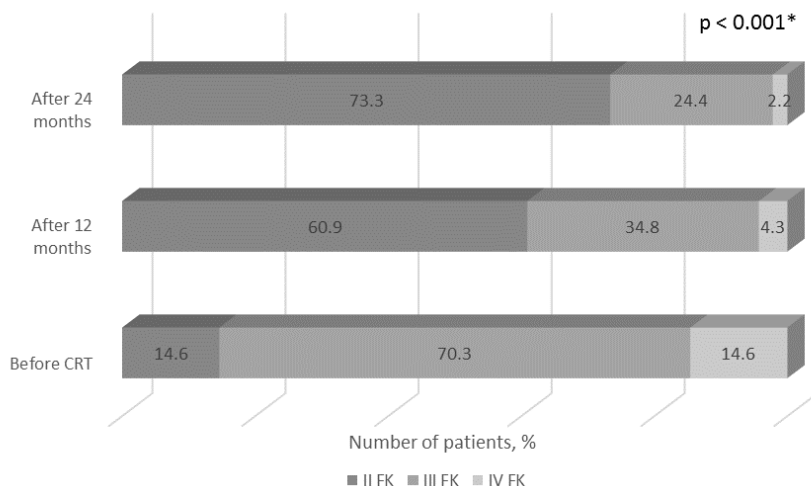


Figure 2.4 NYHA functional class before and after CRT implantation

* *Wilcoxon signed ranks* test was used for data calculations

NYHA – New York Heart Association, CRT – cardiac resynchronisation therapy

A year after cardiac resynchronisation therapy device implantation ($n = 47$), 6-minute walking test statistically significantly improved by 113.85 metres; $p < 0.001$; however, after 24 months ($n = 44$) it improved by 147.25 metres; $p < 0.001$.

After CRT implantation, mean BNP median statistically significantly decreased from 939.00 pg/ml [517.50; 1769.25] to 320.00 pg/ml [148.00; 653.00] after 12 months ($p < 0.001$) and 189.00 pg/ml [100.50; 518.50] after 24 months ($p < 0.001$) (Figure 2.5).

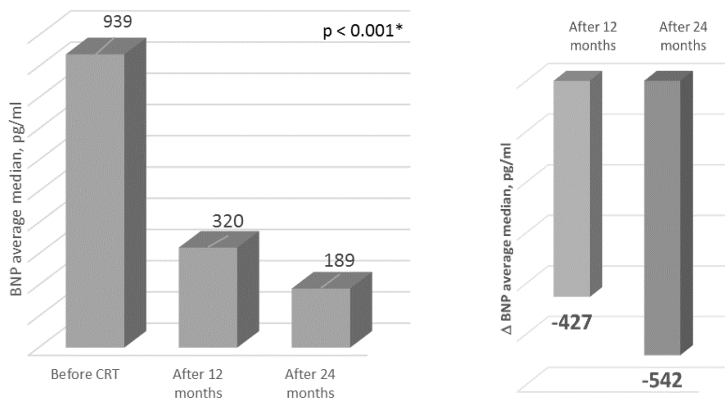


Figure 2.5 BNP and its changes before and after CRT implantation

* *Wilcoxon signed ranks* test was used for data calculations

BNP – brain natriuretic peptide, CRT – cardiac resynchronisation therapy, Δ – changes

Immediately after cardiac resynchronisation therapy device implantation, the mean QRS width significantly decreased by -15.50 ms; $p < 0.001$, after 12 months the mean QRS width significantly decreased by -18.75 ms; $p < 0.001$; however, after 24 months by -17.31 ms; $p < 0.001$ (*Paired samples t-test* was used for data calculations).

EchoCG parameters decreased statistically significantly 12 months after CTR implantation – left ventricular end diastolic diameter (EDD) by -4.89 mm ($p = 0.006$) and after 24 months by -8.00 mm ($p < 0.001$), correspondingly left ventricular end systolic diameter (ESD) by -8.47 mm ($p < 0.001$) and -10.65 mm ($p < 0.001$), left atrial volume index (LAVI) decreased by -4.07 ml/m² ($p = 0.138$) and -6.39 ml/m² ($p = 0.009$) (Figure 2.6). Interventricular mechanic dyssynchrony (IVMD) decreased statistically significantly after 12 months by -26.33 ms ($p < 0.001$) and -23.84 ms ($p < 0.001$) after 24 months of CRT implantation.

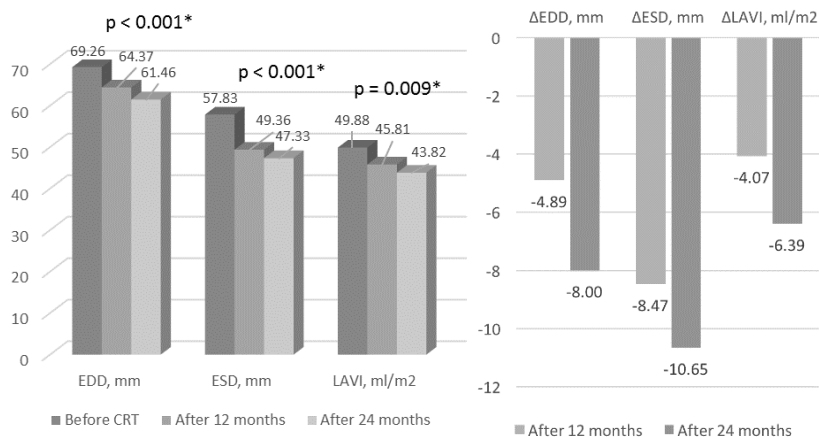


Figure 2.6 EchoCG parameters and their changes before and after CRT implantation

* Paired samples t-test was used in data calculations

EchoCG – echocardiogram, CRT – cardiac resynchronisation therapy, EDD – left ventricular end diastolic diameter, ESD – left ventricular end systolic diameter, LAVI – left atrial volume index, Δ – changes

After CRT implantation, degree of wet regurgitation in patients improved statistically significantly; respectively, upon joining the hospital degree III was indicated in 7 (14.6 %), after 12 months in 3 (6.4 %), and after 24 months in 2 (4.4 %) patients; $p < 0.001$.

2.3 Effect of clinical factors on cardiac resynchronisation therapy

Efficiency of cardiac resynchronisation therapy after two years, based on phenotypic characteristics of the study population has been represented in Table 2.2. The studied phenotypic characteristics had no significant deviation from the one-year cardiac resynchronisation therapy efficiency groups.

Considering individual demographic and anamnesis factors, significantly different trends were observed in CRT responders and non-responders groups. In 12 months, cardiac resynchronisation therapy was statistically significantly

more prevalent in females (n = 15) compared to males (n = 32), respectively 11 (73.3 %) vs. 12 (37.5 %; p = 0.030); a similar trend was observed in 24 months as well (Figure 2.7). After 12 months, smokers (n = 34) exhibited the trend to less frequently end up in CRT responders group compared to non-smokers (n = 13), respectively 14 (41.2 %) vs. 9 (69.2 %; p = 0.111; *Chi-square* test was used for data calculations).

Table 2.2

Anamnesis and demographic data with $\Delta EF \geq 10$ % and $\Delta EF < 10$ % after 24 months

Parameter	Group A (n = 27)	Group B (n = 18)	p value*
Age (years), mean \pm SD	63.41 \pm 9.85	65.00 \pm 8.22	0.560**
BMI (kg / m ²), mean \pm SD	29.72 \pm 5.12	29.47 \pm 4.69	0.866**
Adiposity (BMI \geq 30kg / m ²), n (%)	13 (48.1)	7 (38.9)	.0,540
Parameter	Group A (n = 27)	Group B (n = 18)	p value*
Diabetes, n (%)	6 (22.2)	1 (5.6)	0.215
Arterial hypertension, n (%)	18 (66.7)	9 (50.0)	0.264
Heart Failure Class, n (%)			
NYHA II	3 (11.1)	4 (22.2)	0.466
NYHA III	21 (77.8)	11 (61.1)	
NYHA IV	3 (11.1)	3 (16.7)	
Chronic kidney disease, n (%)	11 (40.7)	10 (55.6)	0.329
Revascularisation, n (%)			
CABG	2 (7.4)	1 (5.9)	
PCI	9 (33.3)	11 (64.7)	0.078
CABG + PCI	0	1 (5.9)	
SV arrhythmia, n (%)	19 (70.4)	12 (66.7)	0.793
Accelerated AV control, n (%)	9 (33.3)	5 (27.8)	0.693
VT/VF anamnesis, n (%)	23 (85.2)	15 (83.3)	0.867

* *Chi-square* test and ***Independent samples t*-test were used for data calculations.

ΔEF – changes in ejection fraction, group A – ΔEF improvement ≥ 10 %, group B – ΔEF improvement < 10 %, BMI – body mass index, NYHA – New York Heart Association, PCI – percutaneous coronary intervention, CABG – coronary artery bypass grafting, SV – supraventricular, AV – atrioventricular, VT – ventricular tachycardia, VF – ventricular fibrillation, SD – standard deviation.

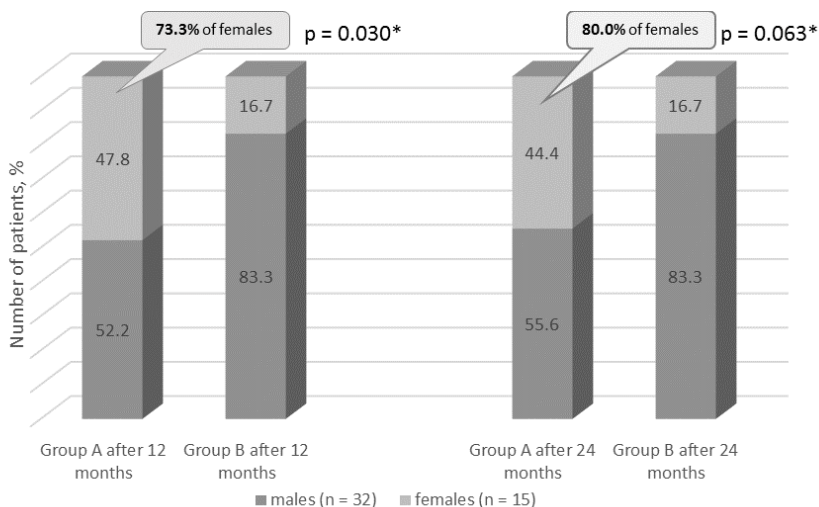


Figure 2.7 Gender impact on efficiency of cardiac resynchronisation therapy after 12 and 24 months

* *Chi-square* test was used in data calculations

Group A – Δ EF improvement ≥ 10 %, group B – Δ EF improvement < 10 %

Based on the obtained long-term data (24 months), CRT efficacy was statistically significantly more frequently observed in patients (n = 20) with non-ischemic genesis CMP 16 (66.7 %) compared to ischemic CMP (n = 25) patients 11 (44.0 %; p = 0.018) (Figure 2.8). Patients (n = 20) without identified revascularisation, after 24 months presented similar data – statistically significantly more frequently resulting in CRT responders group compared to patients with prior revascularisation, respectively 16 (80.0 %) vs. 11 (42.3 %; p = 0.030; *Chi-square* test was used in data calculations).

Correlation between phenotypic and objective data using cardiac resynchronisation therapy has been represented in Table 2.3.

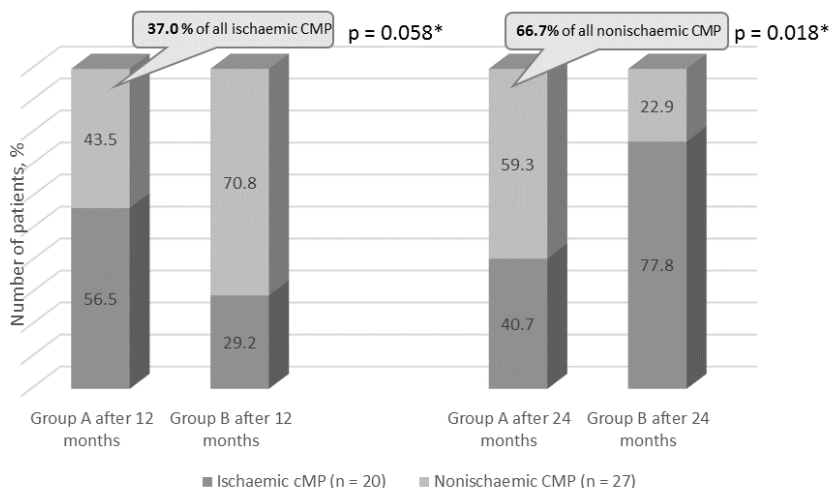


Figure 2.8 Effect of cardiomyopathy genesis on effect of cardiac resynchronisation therapy after 12 and 24 months

* *Chi-square* test was used in data calculations

Group A – Δ EF improvement $\geq 10\%$, group B – Δ EF improvement $< 10\%$,

CMP – cardiomyopathy

Table 2.3

Relationship between subjective and objective parameters with Δ EF $\geq 10\%$ and Δ EF $< 10\%$

Parameter	r factor after 12 months (n = 47)	p value*	r factor after 24 months (n = 45)	p value*
HR (beats/min), mean \pm DS	0.131	0.381	0.183	0.230
SBP (mm Hg), mean \pm DS	0.307	0.036	0.436	0.003
DBP (mm Hg), mean \pm DS	0.129	0.387	0.016	0.916
6-min walking test (m), mean \pm DS	0.058	0.700	0.029	0.849
CHF, NYHA FC, n (%)	-0.078	0.602**	0.053	0.731**
BMI (kg / m ²), vid \pm SD	0.166	0.263	0.112	0.463
Re-hospitalisation, n (%)	-0.259	0.078**	0.294	0.050**

* *Pearson* and ***Spearman* correlation tests were used in data calculations.

Δ EF – ejection fraction change, HR – heart rate, SBP – systolic blood pressure, DBP – diastolic blood pressure, BMI – body mass index, CHF – chronic heart failure, NYHA – New York Heart Association, FC – functional class.

After 12 months, statistically significantly higher systolic blood pressure was observed in patients (n = 23) with improved $\Delta EF \geq 10\%$, 130.70 ± 14.14 mm Hg compared to patients (n = 24) with $\Delta EF < 10\%$, 121.06 ± 16.28 mm Hg; p = 0.036; statistically significant differences remained after 24 months as well, respectively 131.89 ± 14.73 vs. 117.78 ± 14.37 mm Hg; p = 0.003 (Figure 2.9)

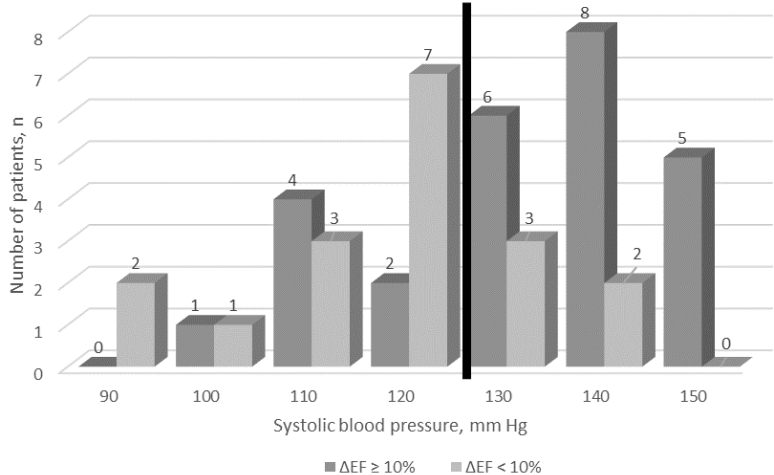


Figure 2.9 Systolic blood pressure based on cardiac resynchronisation therapy efficacy after 24 months

** Independent samples t- test was used for data calculations*
 ΔEF – changes in ejection fraction

CRT efficacy after two years dependant on subjective and objective data characterisation of the other patient population has been represented in Table 2.4. The analysed phenotypic data showed little discrepancy with the one-year cardiac resynchronisation therapy efficacy in groups.

Table 2.4

**Difference in objective parameters $\Delta EF \geq 10\%$ and $\Delta EF < 10\%$ in groups
after 24 months**

Parameter	Group A (n = 27)	Group B (n = 18)	p value
HR (beats/min), mean \pm SD	72.81 \pm 11.27	69.06 \pm 8.13	0.201*
SBP (mm Hg), mean \pm SD	131.89 \pm 14.73	117.78 \pm 14.37	0.003*
DBP (mm Hg), mean \pm SD	75.56 \pm 8.47	75.28 \pm 8.82	0.917*
HR > 70 beats/min, n (%)	15 (55.6)	9 (50.0)	0.714**
6-min walking test (m), mean \pm SD	354,04 \pm 112,10	346 \pm 137,91	0,856*
Hospitalisation prior to CRT implantation, n (%)	24 (88.9)	17 (94.4)	0.640**

* *Independent samplest*-test, ***Chi-square* test were used in data calculations.

ΔEF – changes in ejection fraction, group A – ΔEF improvement $\geq 10\%$, group B – ΔEF improvement $< 10\%$, HR – heart rate, SBP – systolic blood pressure, DBP – diastolic blood pressure, CRT - cardiac resynchronisation therapy, SD – standard deviation.

Patients (n = 23) with a trend for a lower systolic blood pressure (SBP < 130 mm Hg) upon hospitalisation resulted in CRT responders group much less frequently compared to patients (n = 24) with SBP ≥ 130 mm Hg, respectively 8 (34.8 %) vs. 15 (62.5 %; p = 0.057) after 12 months and 8 (31.1 %) vs. 19 (79.2 %; p = 0.005) after 24 months (Figure 2.10).

Patients less frequently admitted to hospital due to HF decompensation prior to CRT implantation statistically more frequently resulted in CRT responders group after 12 months, respectively 3 (75.0 %) – without prior hospitalisation (n = 4) vs. 8 (53.3 %) – once hospitalised (n = 15) vs. 10 (55.6 %) – twice hospitalised (n = 18) vs. 2 (20.0 %) – thrice hospitalised (n = 10); however, statistical significance was not reached p = 0.191. A similar trend was observed also after 24 months, respectively 3 (75.0 %) – without prior hospitalisation (n = 4) vs. 10 (71.4 %) – once hospitalised (n = 14) vs. 11 (64.7%) – twice hospitalised (n = 17) vs. 3 (30 %) – thrice hospitalised (n = 10); p = 0.169.

CRT efficacy dependant on prehospitalised medicine did not reach statistical reliability.

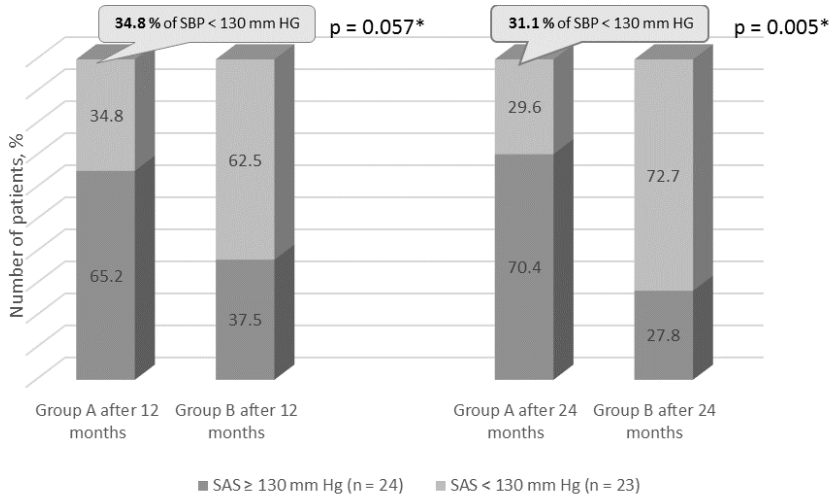


Figure 2.10 **Impact of systolic blood pressure on cardiac resynchronisation therapy after 12 and 24 months**

* *Chi-square* test was used in data collections. Group A – Δ EF improvement $\geq 10\%$, group B – Δ EF improvement $< 10\%$, SBP – systolic blood pressure

2.4 Effect of ECG on cardiac resynchronisation therapy

Analysing the impact of the initial mean QRS width on CRT efficiency, a statistically significant moderate positive correlation was observed after 12 months ($r = 0.322$; $p = 0.027$) and after 24 months ($r = 0.297$; $p = 0.048$), which indicates on a better response to CRT treatment in patients with a wider QRS (*Pearson* correlation test was used in data collections).

In patients ($n = 23$) with improved Δ EF $\geq 10\%$ after 12 months a statistically significant wider mean QRS 177.04 ± 21.20 ms was observed compared to patients ($n = 24$) with Δ EF $< 10\%$, 162.54 ± 22.38 ms; $p = 0.027$;

statistically significant differences were observed also after 24 months, respectively 175.15 ± 20.29 vs. 161.22 ± 25.40 ms; $p = 0.048$ (Figure 2.11).

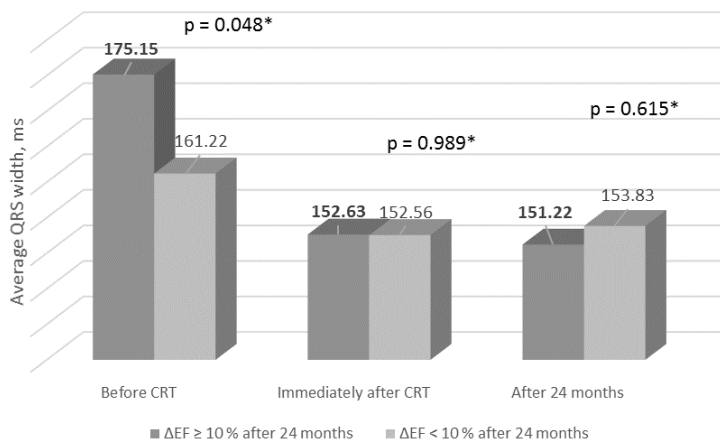


Figure 2.11 QRS width before and after CRT implantation

* *Independent samples t-test* was used in data collections

ΔEF – changes in ejection fraction, CRT – cardiac resynchronisation therapy

After 12 months, patients with LBBB after ECG ($n = 36$) showed improved cardiac resynchronisation therapy statistically significantly more frequently compared to patients with RBBB with His bundle or incomplete LBB ($n = 9$) or dissynchrony of echocardiography without wide QRS ($n = 2$), respectively 22 (61.1 %) vs. 1 (11.1 %) vs. 0 (0 %); $p = 0.030$; after 24 months a similar trend was observed, respectively 26 (74.3 %) vs. 1 (12.5 %) vs. 0 (0 %; $p = 0.001$) (Figure 2.12).

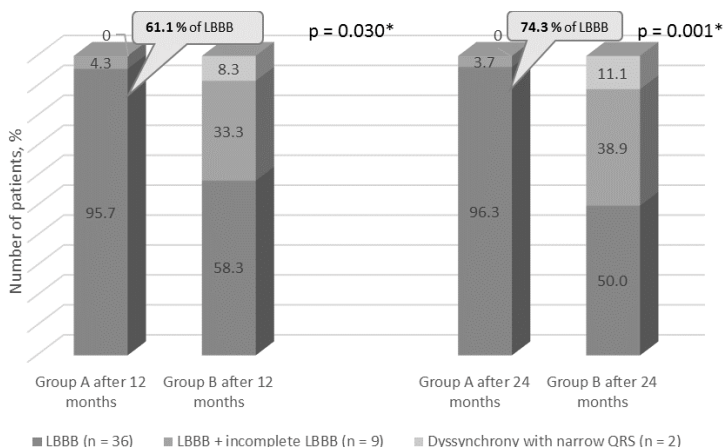


Figure 2.12 **Impact of QRS morphology on cardiac resynchronization therapy after 12 and 24 months**

* *Chi-square* test was used in data calculations

Group A – Δ EF improvement $\geq 10\%$, group B – Δ EF improvement $< 10\%$,
 LBBB – left His bundle branch block, RBBB – right His bundle branch block,
 EchoCG – echocardiogram

2.5 Effect of EchoCG on cardiac resynchronization therapy

Correlation of echocardiogram parameters and cardiac resynchronization therapy has been represented in Table 2.5. Analysing the initial IVMD impact on CRT, a statistically significant moderate positive correlation was observed after 12 months ($r = 0.427$ $p = 0.003$) and a strong correlation after 24 months ($r = 0.560$ $p < 0.001$). Patients ($n = 24$) with a scar in the left ventricle wall resulted in the group of cardiac resynchronization therapy statistically significantly less frequently 6 (26.1 %) compared to patients ($n = 24$) without a scar 17 (73.9 %; $p = 0.002$) after 12 months and 7 (25.9 %) vs. 20 (74.1 %; $p = 0.001$) after 24 months (*Chi-square* test was used in data calculations). Efficiency of cardiac resynchronization therapy dependant on myocardial contractility has been respresented in Figure 2.13.

Table 2.5

Correlation of echocardiogram parameters with $\Delta EF \geq 10\%$ and $\Delta EF < 10\%$

Parameter	r coefficient after 12 months (n = 47)	p value	r coefficient after 24 months (n = 45)	p value
EDD (mm), mean \pm DS	0.074	0.620	0.113	0.462
ESD (mm), mean \pm DS	0.174	0.243	0.241	0.111
LAVI (ml/m ²), mean \pm DS	0.142	0.341	0.124	0.140
MR degree, n (%)	0.088	0.556**	-0.018	0.908**
IVMD (ms), mean \pm DS	0.427	0.003	0.560	< 0.001

* *Pearson* and ***Spearman* correlation tests were used in data calculations.

ΔEF – changes in ejection fraction, CRT – cardiac resynchronisation therapy, IVMD – interventricular mechanical dyssynchrony, EDD – left ventricular end diastolic diameter, ESD – left ventricular end systolic diameter, LAVI – left atrial volume index, MR – mitral regurgitation.

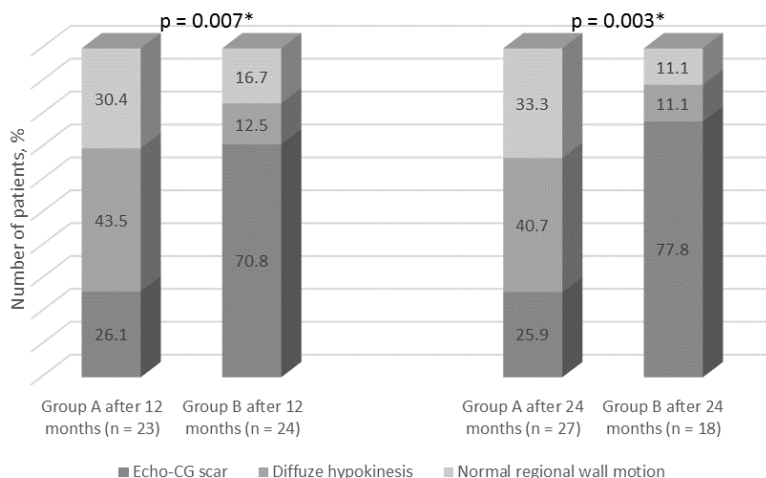


Figure 2.13 Impact of myocardial contractility on cardiac resynchronisation therapy after 12 and 24 months

* *Chi-square* test was used in data calculations

Group A – ΔEF improvement $\geq 10\%$, group B – ΔEF improvement $< 10\%$,
EchoCG – echocardiogram

Efficiency of cardiac resynchronisation therapy dependant on echocardiographic characteristics of the patient population within a year and two has been represented in Tables 2.6 and 2.7.

Table 2.6

Echocardiogram data with $\Delta EF \geq 10\%$ and $\Delta EF < 10\%$ after 12 months

Parameter	Group A (n = 23)	Group B (n = 24)	p value
MI scars, n (%)	6 (26.1)	17 (70.8)	0.002*
MI scar localisation, n (%)			
Anterior wall	3 (50.0)	4 (23.5)	0.019*
Top	1 (16.7)	4 (23.5)	
Wide anterior wall	0 (0)	9 (52.9)	
Prosterior wall	2 (33.3)	0 (0)	0.620**
EDD (mm), mean \pm DS	69.70 \pm 5.70	68.83 \pm 6.13	
EDD after 12 mon. (mm), mean \pm DS	60.31 \pm 14.22	68.25 \pm 7.34	0.020**
ESD (mm), mean \pm DS	59.13 \pm 6.82	56.58 \pm 7.87	0.243**
ESD after 12 mon. (mm), mean \pm DS	42.17 \pm 10.91	56.25 \pm 10.24	< 0.001**
LAVI (ml/m ²), mean \pm DS	51.83 \pm 12.24	48.02 \pm 14.72	0.341**
LAVI after 12 mon. (ml/m ²), mean \pm DS	38.48 \pm 9.41	52.83 \pm 20.83	0.004**
MR degree, n (%)			0.467*
I	5 (21.7)	6 (25.0)	0.027*
II	15 (65.2)	12 (50.0)	
III	3 (13.0)	4 (16.7)	
MR degree after 12 mon., n (%)			
I	16 (69.6)	8 (33.3)	0.524*
II	7 (30.4)	10 (41.7)	
III	0	3 (12.7)	
EF < 30 %, n (%)	19 (82.6)	18 (75.0)	0.003**
IVMD (ms), mean \pm DS	50.48 \pm 22.39	32.43 \pm 16.21	0.032**
IVMD after 12 mon. (ms), mean \pm DS	19.61 \pm 16.30	11.38 \pm 8.03	

* *Chi-square* and ** *Independent samplest-test* were used in data calculations.

Group A – ΔEF improvement $\geq 10\%$, group B – ΔEF improvement $< 10\%$,
EF – ejection fraction, ΔEF – changes in ejection fraction, IVMD – interventricular
mechanic dyssynchrony, EDD – left ventricular end diastolic diameter, ESD – left
ventricular end systolic diameter, LAVI – left atrial volume index, MR – mitral
regurgitation.

Table 2.7

Echocardiogram data with $\Delta EF \geq 10\%$ and $\Delta EF < 10\%$ 24 months after CRT implantation

Parameter	Group A (n = 27)	Group B (n = 18)	p value
MI scars, n (%)	7 (25.9)	14 (77.8)	0.001*
MI scar localisation, n (%)			
Anterior wall	4 (57.1)	3 (21.4)	0.125*
Apex	1 (14.3)	4 (28.6)	
Wide anterior wall	1 (14.3)	7 (50.0)	
Posterior wall	1 (14.3)	0 (0)	
EDD (mm), mean \pm DS	70.00 \pm 5.67	68.67 \pm 6.23	0.462**
EDD after 24 mon. (mm), mean \pm DS	57.18 \pm 12.87	67.89 \pm 7.36	0.003**
ESD (mm), mean \pm DS	59.44 \pm 7.62	55.78 \pm 7.03	0.111**
ESD after 24 mon. (mm), mean \pm DS	41.99 \pm 11.31	55.33 \pm 11.03	< 0.001**
LAVI (ml/m ²), mean \pm DS	51.59 \pm 13.26	48.14 \pm 14.59	0.415**
LAVI after 24 mon. (ml/m ²), mean \pm DS	37.59 \pm 7.45	53.17 \pm 18.63	0.003**
MR degree, n (%)			
I	5 (18.5)	5 (27.8)	0.615*
II	16 (59.3)	10 (55.6)	
III	4 (14.8)	3 (16.7)	
MR degree after 24 mon., n (%)			
I	22 (81.5)	5 (27.8)	0.001*
II	3 (11.1)	10 (55.6)	
III	0	2 (11.1)	
EF < 30 %	22 (81.5)	13 (72.2)	0.464*
IVMD (ms), mean \pm DS	51.37 \pm 19.45	27.65 \pm 13.5	< 0.001**
IVMD after 24 mon. (ms), mean \pm DS	18.74 \pm 21.09	17.56 \pm 10.43	0.804**

* Chi-square and ** Independent samplest-test were used in data calculations.

Group A – ΔEF improvement $\geq 10\%$, group B – ΔEF improvement $< 10\%$, EF – ejection fraction, ΔEF – changes in ejection fraction, IVMD – interventricular mechanic dyssynchrony, EDD – left ventricular end diastolic diameter, ESD – left ventricular end systolic diameter, LAVI – left atrial volume index, MR – mitral regurgitation.

2.6 Effect of clinical factors on cardiac resynchronisation therapy

Clinical parameters did not differ statistically significantly when compared A and B groups before and after CRT implantation (Table 2.8). Analysing effects of total cholesterol on CRT, a statistically significant moderately positive correlation was observed 12 months after CRT implantation ($r = 0.375$; $p = 0.009$) and after 24 months ($r = 0.326$; $p = 0.029$), which indicated on the better response to CRT treatment in patients without identified statin therapy for coronary heart disease.

Table 2.8

Difference in clinical data in $\Delta EF \geq 10\%$ and $\Delta EF < 10\%$ groups 24 months after CRT implantation

Parameter	Group A* (n = 27)	Group B* (n = 18)	p value
BNP (pg/ml)	890.00 [650.00; 1541.00]	992.50 [376.75; 1870.25]	0.844***
TC (mmol/l)	4.99 ± 1.28	4.17 ± 1.03	0.029**
LDLC (mmol/l)	2.84 ± 1.08	2.49 ± 0.91	0.269**
HDLC (mmol/l)	1.22 ± 0.44	1.09 ± 0.33	0.301**
TG (mmol/l)	1.40 [0.80; 1.70]	1.00 [0.700; 1.40]	0.231***
Hb (g/dl),	13.84 ± 1.82	14.10 ± 1.06	0.556**
Glucose (mmol/l)	6.29 ± 2.35	6.01 ± 1.24	0.637**
CRO (mg/l)	2.70 [1.65; 5.60]	2.1 [1.45; 5.55]	0.497***

* Median and interquartile interval, ** *Independent samples t-test* and *Mann-Whitney U* test were used in data calculations. Group A – ΔEF improvement $\geq 10\%$, group B – ΔEF improvement $< 10\%$, ΔEF – changes in ejection fraction, BNP – brain natriuretic peptide, TC – total cholesterol, HDLC – high density lipoprotein cholesterol, LDLC – low density lipoprotein cholesterol, TG – triglycerides, Hb – haemoglobin, CRO – C-reactive protein.

2.7 Effect of cardiac resynchronisation devices on cardiac resynchronisation therapy

Localisation of *lateral and posterior-lateral* electrodes for stimulating left ventricular in coronary sinus was identified in 40 (85.1 %) patients, of which CRT efficacy after 12 months was observed in 21 (52.5 %) compared to other localisations of electrodes – 2 (28.6 %); however, statistical significance was not reached ($p = 0.416$) and 24 months after CRT – 24 (63.2 %) vs. 3 (42.9 %; $p = 0.412$; *Chi-square* test was used in data calculations).

Left ventricle before right ventricle (LV→ RV) was stimulated in 23 (47.9 %) patients. Patients with LV → RV pacing statistically significantly more frequently resulted in CRT efficiency group compared to patients with a different pacing sequence, respectively 16 (69.6 %) vs. 7 (30.4 %) 12 months after CRT ($p = 0.006$) and 17 (63.0 %) vs. 10 (37.0 %) after 24 months ($p = 0.021$). Comparison of CRT programmed pacing types have been represented in Figure 2.14.

Effective biventricular pacing (≥ 95 %) was reached by 43 (91.5 %) patients 12 months after CRT and 43 (95.6 %) after 24 months. Patients ($n = 43$) with effective biventricular pacing statistically more frequently resulted in CRT efficiency group 23 (100 %) compared to patients ($n = 4$) without effective biventricular pacing 0 (0 %; $p = 0.109$) after 12 months and 27 (100 %) vs. 0 (0 %; $p = 0.155$) after 24 months (*Chi-square* test was used in data calculations).

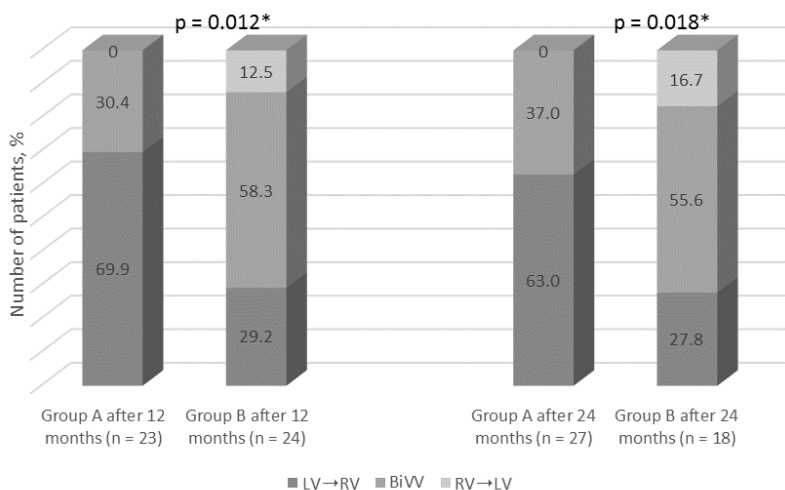


Figure 2.14 **Influence of interventricular pacing type on cardiac resynchronisation therapy after 12 and 24 months**

* *Chi-square* test was used in data calculations

Group A – Δ EF improvement $\geq 10\%$, group B – Δ EF improvement $< 10\%$,

RV → LV – left ventricle before right ventricle, BiVV – biventricular,

RV → LV – right ventricle before left ventricle

2.8. Prognostic parameters of effective cardiac resynchronisation therapy

Multivariate analysis (MVA), as prognostic clinical and objective parameter, indicated the impact of LBBB on efficacy of CRT devices after 12 and 24 months, statistically significant IVMD, higher SBP (Tables 2.9 and 2.10).

Table 2.9

Influencing factors of efficiency of cardiac resynchronisation therapy after 12 months

Parameter	Exp B	p value*
Gender – female, n (%)	0.271	0.051
LBBB, n (%)	0.283	0.056
QRS width, mm	0.242	0.088

*Multiple linear regression backward method was used for data analysis.

LBBB – left His bundle branch block.

Table 2.10

Influencing factors of efficiency of cardiac resynchronisation therapy after 12 months

Parameter	Exp B	p value*
SBP, mm Hg	0.235	0.040
LBBB, n (%)	0.394	0.001
IVMD, mm	0.419	< 0.001

* Multiple linear regression backward method was used for data analysis.

SBP – systolic blood pressure, LBBB – left His bundle branch block,

IVMD – interventricular mechanic dyssynchrony.

3 DISCUSSION

Heart failure is a complex clinical syndrome, which occurs due to abnormality of cardiac structure or function leading to worsening of ventricular activity, failure of the heart to provide adequate blood circulation and tissue metabolism. Undoubtedly, the use of pharmacotherapy plays the key role in the treatment of HF; however, there are cases when contractile cardiac functions are limited, and positive effect of the pharmacotherapy cannot be reached. In cases where a contributing factor of HF is electrical dyssynchrony of both ventricles and pharmacological therapy does not give the expected results, the treatment of HF requires an additional use of a cardiac resynchronisation device (CRT). At present, CRT has become a significant component of treatment of heart failure for patients resistant to drug therapy.

This is the first study conducted in Latvia which is carried out with application of CRT for better understanding of the situation in this field in the country and to assess CRT efficacy, as well as to define and evaluate factors predisposing inefficiency of CRT. CRT device implantations in Latvia have been performed since 2006. This study was conducted during the period when more intense rate of implantations of CRT devices was initiated in Latvia (2009 to 2012).

In general, the clinical, longitudinal, prospective, two-arm study included 50 CRT patients with preserved sinus rhythm. All patients underwent CRT device implantation, and the subjective and objective feelings of the patients were evaluated prior to implantation, 12 and 24 months after CRT. Two patients were excluded from the further study, one of which underwent ablation of the radio frequency catheter of the atrioventricular joint, and the other had artificial ventricle implanted. Cardiovascular death due to CHF decompensation was observed in three patients – 1 (2.1 %) patient in three months and 2 (4.2 %) patients

in 24 months. Therefore, the number of patients included in the study at the 12 months visitation was 47 patients and at the 24 months visitation – 45 patients.

Based on the above, after prospective evaluation of EchoCG-measured improvement of the left ventricular ejection fraction (EF) $\geq 10\%$, the population of this study was divided into two main groups (group A and B):

- **Group A (responders)** included patients who 12 and 24 months after a CRT device implantation reached improvement of left ventricular ejection fraction (EF) $\geq 10\%$;
- **Group B (non-responders)** included patients who 12 and 24 months after implantation of a CRT device failed to reach improvement of left ventricular EF $\geq 10\%$.

The initial left ventricular ejection fraction (EF) of the study population, according to the EchoCG data, on average was $24.81 \pm 5.23\%$; after cardiac resynchronisation device implantation, EF statistically significantly increased compared to the initial EF, respectively by $11.40 \pm 9.31\%$ after 12 months, $p < 0.001$ and $13.67 \pm 10.84\%$ after 24 months, $p < 0.001$. High cardiac resynchronisation efficiency (Δ EF improvement $\geq 10\%$) after 12 months was observed in 23 (48.9 %) patients and after 24 months – 27 (60.0 %) patients defined as group A or CRT responders.

It could be assumed that only slightly more than a half of patients achieved EchoCG positive improvement of HF; however, the study showed that CRT efficiency depends not only on EF and positive remodelling of left ventricle. Often improvement of subjective symptoms as well as reduction in hospital admittances was also achieved in the group of patients where EchoCG-measured EF improvement was 5–10 %.

The main task of the study was to analyse differences of groups A and B evaluating 53 different possible factors affecting treatment 12 and 24 months

after CRT implantation. Correlation analysis was applied for identification of the links between the variables.

Subjective and objective parameters

The study showed distinct prevalence of male participants (68.8 %). Nevertheless, compared to males, statistical reliability was observed in females 12 months after CRT, respectively 73.3 % vs. 37.5 %; $p = 0.030$, after 24 months a similar trend was maintained, respectively 80.0 % vs. 50.0 %, which was close to statistical significance ($p = 0.063$). This leads to the conclusion that following gender-based analysis, females are better candidates for CRT implantation.

Assessment of systolic blood pressure (SBP) on CRT efficiency showed statistically significant moderately strong positive correlation ($r = 0.436$; $p = 0.003$) after 24 months, which indicates on a better response to CRT in patients with higher SBP (divide of SBP – 130 mm HG). It can be explained that lowered SBP may enhance hypoperfusion of vital organs and cause the drop of CRT efficiency.

SBP may not be treated as a prognostic factor to estimate pre-treatment indications by analysing blood pressure figures before CRT implantation. However, in view of indications for CRT implantation, numerical values of blood pressure must be considered, thus ensuring ODT to avoid medication hypotension in patients.

The study did not include active smokers; therefore, this factor was evaluated based on prior length and amount of smoking in the study population. 34 (70.8 %) patients were anamnestic smokers. The study concluded that long-term smokers at least 20 cigarettes a day for ten years ($n = 34$) after 12 months of CRT resulted in CRT responders group less frequently compared to non-smokers ($n = 13$), respectively 14 (41.2 %) vs. 9 (69.2 %; $p = 0.111$), after

24 months a similar trend was observed, respectively 17 (53.1 %) vs. 10 (76.9 %), although statistical significance was not reached $p = 0.188$.

Assessment of heart failure functional class before CRT implantation showed the dominance of patients with HF III NYHA functional class 70.8 %. At 12-months control visit, HF III NYHA was observed in 34.8 % patients and at 24-months control visit – 24.4 % patients. HF II NYHA respectively – 14.6 %; 60.9 % and 73.3 % ($p < 0.001$). However, assessment of statistical differences linked to HF functional class, in groups A and B neither after 12 nor 24 months statistically significant correlation was observed ($p = 0.466$ after 24 months).

Prior to resynchronisation device implantation, frequent and repeated hospital admissions of patients due to CHF decompensation occurred. However, after CRT device implantation, admissions to hospitals happened less frequently. Respectively, 12 months after CRT four patients were hospitalised once, two patients twice and one patient three times ($p < 0.001$), and after 24 months – six patients were hospitalised once and two patients twice ($p < 0.001$). Statistically significant moderate negative correlation was observed between the repeated hospitalisations due to CHF decompensation and CRT efficiency ($r = -0.294$; $p = 0.050$), which indicates on a better response to the therapy in patients with fewer hospitalisations before CRT implantation (12 mon. – $r = -0.259$; $p = 0.078$).

Patients with re-hospitalisation more than two times due to CHF decompensation before CRT device implantation comparatively less frequently resulted in CRT responders group after 12 months compared to patients with 1 – 2 times hospitalisation occurrences, respectively 20.0 % vs. 54.5 %, which was close to statistical significance ($p = 0.076$), a similar trend was observed after 24 months, respectively 30.0 % vs. 67.7 %; $p = 0.063$.

Evaluating HF etiology, the study patients are typically divided into two large groups – ischemic genesis HF patients, heart failure factor of which is coronary heart disease (CHD) and non-ischemic genesis HF patients, where dilated cardiomyopathy (CMP) is not connected with CHD.

Clinical efficacy of CRT in both groups was assessed in subanalysis of MADIT-CRT trial (Zareba et al., 2011; Barsheshet et al., 2011). The study included 1046 patients with ischemic CMP and 774 patients with non-ischemic CMP, the follow-up took 2.4 years. Patients with ischemic CMP reached 34 % reduction of mortality and clinical deterioration of heart failure if compared CRT-D group with the group of patients with ICD, while patients with non-ischemic CMP reached 44% reduction of mortality or deterioration of heart failure in CRT-D group compared to the ICD group.

HF development causes of the current study varied; however, ischemic genesis CMP were observed in 28 (58.3 %) patients and non-ischemic genesis CPM in 20 (41.7 %) patients. Longitudinal (24 months) study data indicate that statistically significant frequency of CRT efficiency was observed in non-ischemic genesis CPM patients (66.7 %) compared to ischemic genesis CMP patients (44.0 %; $p = 0.018$).

Multi-centre trials and this study show that patients with non-ischemic origin of HF benefit more from CRT when compared to patients with ischemic genesis HF. This could be explained by the anatomical structure of left ventricle. In patients after myocardial infarction, HF development mechanism involves hypokinetic or akinetic scars that maintain the HF progression mechanism, while in patients with HF of non-ischemic genesis ventricles are diffusely enlarged and better submit to ventricular pacing, providing smoother conduction of impulses into ventricles.

Thus, based on HF genesis and etiological factors of HF development, it can be concluded that patients having suffered heart attack are poorer responders

to CRT efficiency. Comparing data of the study in groups A and B, myocardial revascularisation has been traced if such treatment has been conducted before CRT implantation. Patients without identified revascularisation 24 months after CRT statistically significantly more frequently resulted in CRT responders group compared to patients with performed revascularisation, respectively 16 (80.0 %) vs. 11 (42.3 %), $p = 0.030$. The changes can be linked to CMP genesis, and thus claimed that patients with ischemic CMP have a bigger chance of ending up in CRT non-responders group (B) and patients with non-ischemic genesis – in responders group (A).

Statistically significant influence between types of revascularisation and cardiac resynchronisation therapy was not observed.

Before CRT implantation, all patients were ensured OMT. It was limited to several patients due to hypotension, bradycardia, significant kidney damage. CRT efficiency did not differ statistically significantly 12 and 24 months after CRT in patients who received optimal medication therapy (ACEI/ARB, BAB, un ARB) in maximally tolerable doses, according to ESC CHF Guidelines, compared to patients who did not tolerate optimal medication therapy.

Differences in groups A and B were observed in dyslipidemia therapy group. Patients ($n = 12$) without identified statin therapy 24 months after CRT showed a more frequent prevalence resulting in CRT responders group compared to patients ($n = 33$) who used statins, respectively 10 (83.3 % vs. 17 (51.5 %), which was close to statistical significance $p = 0.086$. This again proved that patients with ischemic CMP, identified with statins after myocardial infarction, more frequently resulted in the non-responders group.

ECG visualisation parameters

CRT is an effective method in reduction of clinical symptoms of HF in patients with heart failure and widened QRS interval. Studies and meta-analysis

show that patients with significantly widened QRS interval derive the greatest benefits from CRT (Sipahi et al., 2011; Stavrakis et al., 2012).

The width of QRS complex before CRT implantation for the study patients was 169.71 ± 22.54 ms. Immediately after CRT implantation the mean width of QRS decreased significantly by -15.50 ± 21.12 ms; $p < 0.001$. 12 months after CRT, the mean QRS width decreased statistically significantly by -18.75 ± 24.71 ms; $p < 0.001$; however, after 24 months by -17.31 ± 22.34 ms; $p < 0.001$. Assessing the impact of initial mean QRS width on CRT efficiency, a statistically significant moderate positive correlation was observed 12 months after CRT ($r = 0.322$; $p = 0.027$) and after 24 ($r = 0.297$; $p = 0.048$), which indicates on a better response to CRT therapy in patients with a wider QRS.

After CRT implantation, statistically significant QRS width correlation with $\Delta EF \geq 10\%$ improvement was not observed.

At the beginning of CRT “era”, width of QRS complex was considered as one of leading criteria of CRT efficacy, but over the years morphology of QRS complex has also been analysed as a factor contributing to the efficiency. In the MADIT-CRT ($n = 1820$) (Moss et al., 2009; Zareba et al., 2011) study, reduction of mortality and hospital admittances in CRT-D group compared to ICD group was 34 %, while in the subgroup which consisted of patients with LBBB – 57 %. More pronounced efficacy of CRT, which established long-term efficacy of CRT, is MADIT-CRT (published in 2014) 7-year data analysis of HF patients with moderate course of the disease and markedly reduced systolic left ventricular dysfunction. In the patient group with LBBB, all types of mortality in the CRT-D group was 18 % compared to the ICD group, where mortality over the 7-year observation was 29 %. This suggests that nine HF patients should be treated with CRT to save one life in the 7-year period (Goldenberg et al., 2014).

In the current study, there were 37 (77.1 %) patients with LBBB before CRT implantation. 12 months after CRT, patients with LBBB ($n = 36$) showed

CRT efficiency statistically significantly more frequently compared to patients with RBBB (n = 9) or without EchoCG dyssynchrony without wide QRS (n = 2), respectively 22 (61.1 %) vs. 1 (11.1 %) vs. 0 (0 %; p = 0.030), 24 months after CRT a similar trend was maintained, respectively 26 (74.3 %) vs. 1 (12.5 %) vs. 0 (0 %; p = 0.001). Assessment of correlation proved that moderately close link exists between improvement and QRS complex morphology. The longer the period since patient randomisation in the study, the better improvement for the patients with LBBB.

Left His bundle branch full block is a decisive criterion of CRT efficiency. This could be explained by more pronounced adverse remodelling of left ventricle in this patient population. Consequently, the CRT therapy may give greater improvement. This is shown in international studies, and a convincing confirmation is also this study carried out in Latvia. Research data also confirm improvement of lower HF functional class in patients with RBBB (Leong et al., 2012) which could probably correlate with inferior CRT efficiency.

EchoCG parameters

Numerous international studies (Daubert et. al., 2009; Zareba et. al., 2011; Tang et. al., 2010) compare patients with identified scars in left ventricle with patients with much rarer EchoCG identified scars or possessing diffuse hypokinesia of left ventricle.

The study included 24 (50.0 %) patients with post-infarction scar, according to EchoCG data, 13 (27.1 %) patients possessing diffuse hypokinesia of left ventricle; however, 11 (22.9 %) patients had no disturbed myocardial contractility. Patients (n = 23) detected with a scar in one of the walls of left ventricle statistically less frequently resulted in CRT efficiency group; 6 (26.1 %) compared to patients (n = 24) without post-infarction scar 17 (73.9 %; p = 0.002) 12 months after CRT and 7 (25.9 %) vs. 20 (74.1 %; p = 0.001) after

24 months. The groups differed, and the data, similarly to HF CMP genesis, indicated on HF patients with ischemic genesis as weaker candidates to CRT efficiency.

The study revealed statistically significant decrease in size of cavity of left ventricle after CRT (EDD by -4.89 ± 11.60 mm; $p = 0.006$ after 12 months and -8.00 ± 13.16 mm; $p < 0.001$ after 24 months; ESD by -8.47 ± 13.01 mm; $p < 0.001$ and -10.65 ± 14.19 mm; $p < 0.001$; LAVI by -4.07 ± 18.51 mm; $p = 0.138$ and -6.39 ± 15.78 mm; $p = 0.009$). Statistically significant decrease was observed in IVMD 12 months after CRT; by -26.33 ± 21.26 ms; $p < 0.001$ and by -23.84 ± 24.33 ms; $p < 0.001$. Moreover, after CRT implantation statistically significant improvement was observed in degree of patient mitral regurgitation, respectively upon hospitalisation degree III was observed in 7 (14.6 %), after 12 months – 3 (6.4 %), 24 months later – 2 (4.4 %) patients; $p < 0.001$.

Assessing initial IVMD impact on CRT efficiency, statistically significant moderate positive correlation was observed after 12 months ($r = 0.427$ $p = 0.003$) and strong correlation after 24 months ($r = 0.560$, $p < 0.001$), which indicates on a better response to CRT in patients with a more distinct IVMD before CRT implantation.

Most significant clinical parameters

One of the objectives of the research was to trace HF biomarker BMP changes while in action. After CRT implantation, mean BNP median statistically significantly decreased from 939.00 pg/ml [517.50; 1769.25] to 320.00 pg/ml [148.00; 653.00] after 12 months ($p < 0.001$) and 189.00 pg/ml [100.50; 518.50] after 24 months ($p < 0.001$). The data, similarly to the data by EchoCG on heart cavity decrease, indicate on longitudinal positive CRT efficiency.

Evaluating total cholesterol impact on CRT efficacy, statistically significant moderate positive correlation was observed both 12 months after CRT ($r = 0.375$; $p = 0.009$), and 24 months after CRT ($r = 0.326$; $p = 0.029$), which indicates on a better response to CRT in patients without identified statin therapy due to coronary heart disease.

Ventricular dyssynchrony programmed parameters for CRT device

Contemporary CRT devices allow very variable programming of right and left ventricle contraction time, and it is labelled as VV interval. The ventricular pacing parameters are programmed into CRT device to prevent dyssynchrony, according to CRT ventricular VV dyssynchrony severity and direction (which ventricle contracts first). The study patients with programmed left ventricle pacing before the right one statistically significantly more frequently resulted in CRT efficiency group compared to patients with a different pacing sequence, respectively 16 (69.6 %) vs. 7 (30.4 %) 12 months after CRT ($p = 0.006$) and 17 (63.0 %) vs. 10 (37.0 %) after 24 months ($p = 0.021$).

Therefore, it can be concluded that patients with LBBB, whose right ventricle contracts first and the left ventricles contraction is delayed, and CRT mode is LV → RV can be considered as better candidates for effective CRT.

The study analyses ratio of pacing of ventricles, by optimising atrioventricular (AV) and interventricular (VV) conduction during the process of CRT device programming, by assessing differences in CRT responders and non-responders groups.

CRT efficiency is based on close to 100 % provision of pacing of both ventricles. Percentage decrease of biventricular pacing causes decrease in positive efficiency of resynchronisation therapy. To prevent such occurrence, patients were carefully monitored during the study, adjusting both ventricular pacing parameters of CRT and assessing the need for pharmacological treatment

of tachyarrhythmia due to frequent extrasystoles or atrial fibrillation. One patient was excluded from further analysis of the study and underwent atrioventricular connection catheter ablation due to constantly recurrent, medically refractory atrial fibrillation. In this study, all patients were provided the best possible biventricular pacing to achieve better efficiency of CRT. Biventricular pacing was lower than 95 % in only 4 patients and all these patients ended up in the non-responders group of the therapy.

One of the objectives of the research was to assess localisation of left ventricular electrode of a CRT device in coronary sinus branches, radiographically evaluating correlation between positioning of an electrode and efficiency of CRT.

International, multi-centre studies show that localisation of an electrode for left ventricular pacing in the coronary sinus is important in ensuring effectiveness of CRT. At present, *lateral* and *posterolateral* CS vein is regarded as the best site for localisation of the electrode, while the results of *anterior* and apical pacing of CS vein are worse. The analysis of MADIT-CRT study compared position of CS apical pacing with pacing positions of the rest of the left ventricle. Apical left ventricular pacing is associated with poorer efficiency of CRT (Singh et al., 2011).

In this, first time in Latvia, study targeted at CRT efficacy, it was important to assess sites of localisation of left ventricular electrodes, because it is one of the most important criteria for positive efficiency of CRT. Coronary sinus localisation of an electrode in *lateral* wall was identified in 45.8 % patients, *posterolateral* wall in 39.6 %, *anterolateral* wall in 6.3 % and *posterior* wall in 8.3 % patients. Localisation of left ventricular electrodes in *posterior* and *posterolateral* wall were identified in 40 (85.1 %) patients, of which CRT efficacy after 12 months was observed in 21 (52.5 %) compared to other localisations of electrodes 2 (28.6 %); however, statistical significance was not

reached ($p = 0.416$) and after 24 months 24 (63.2 %) vs. 3 (42.9 %; $p = 0.412$). Thus, it can be concluded that in case of 7 patients, localisation of CS electrode for pacing of left ventricle was not the most favourable positioning, and five of the patients belonged to the group of patients with $EF \geq 10$ % improvement reached after 12 months.

4 CONCLUSIONS

1. High CRT efficiency within two years was reached by nearly two thirds of the study population with the total growth of left ventricle ejection fraction by approximately 14 %p.
2. CRT implantation is a safe and efficient HF treatment method. CRT statistically significantly improves patient life quality by significantly reducing the amount of hospital admissions, improving cardio load tolerance and decreasing remodelling of left ventricle. Device-related complications or adverse cardiovascular events were not observed during the study.
3. Patients with non-ischemic cardiomyopathy, systolic blood pressure above 130 mm Hg and those with fewer hospital admissions due to HF decompensation showed statistically significantly larger CRT efficiency over a longer period of time.
4. Patients with a wider QRS complex (> 170 ms) and morphologic left His bundle branch block before CRT implantation were more responsive to CRT.
5. Patients with post-infarction scar, according to EchoCG data, showed poorer CRT results compared to patients with diffuse hypokinesia or without disturbed myocardial contractility. Patients with significantly larger interventricular mechanic dyssynchrony (> 50 ms) before CRT implantation reached a better longitudinal CRT efficiency. Impact of clinical indicators on CRT efficiency was not observed.

6. Patients with programmed left ventricle pacing before the right one statistically significantly more frequently reached higher CRT efficiency compared to patients with a different pacing sequence. Impact of other device-related factors on CRT efficiency was not observed.
7. Dominant parameters affecting longitudinal CRT efficiency are initially LBBB, interventricular mechanic dyssynchrony > 50 ms and SBP above 130 mm HG.

5 PRACTICAL RECOMMENDATIONS

Patient selection and objective assessment of implantation criteria before CRT implantation is significant in the further course of disease and clinical outcomes. CRT implantation criteria is a set of objectivisable data, which may provide data on the prospective efficiency of the implantable device.

The created recommended CRT prospective efficiency and patient selection table may serve as a practical tool for selecting patients for cardiac resynchronisation device implantations, as well as prognosticating their performance efficiency (Table 5.1).

Table 5.1

CRT prospective efficiency patient selection

CRT efficiency determining factor	Good candidates for CRT	Moderate candidates for CRT	Poor candidates for CRT
QRS width	≥ 150 ms	$\leftarrow \diamond \rightarrow$	< 120 ms
QRS morphology	LBBB	$\leftarrow \diamond \rightarrow$	LBBB or interventricular mechanic dyssynchrony without wide QRS
Left ventricular cavities	Bigger	$\leftarrow \diamond \rightarrow$	Smaller
Ventricular dyssynchrony	Yes	$\leftarrow \diamond \rightarrow$	No
Localisations of CS electrode	<i>Lateral and posterolateral CS vein</i>	$\leftarrow \diamond \rightarrow$	<i>Anterior and apical CS vein</i>
Gender	Female	$\leftarrow \diamond \rightarrow$	Male
Systolic Blood Pressure	Above 130 mm Hg	$\leftarrow \diamond \rightarrow$	Below 130 mm HG
Functional class of heart failure	NYHA II	$\leftarrow \diamond \rightarrow$	NYHA IV
Genesis of heart failure	Non-ischemic	$\leftarrow \diamond \rightarrow$	Ischemic
Ratio of pacing of both ventricles	Close to 100 % biventricular pacing	$\leftarrow \diamond \rightarrow$	Less than 90 % biventricular pacing
Co-existent illnesses	No	$\leftarrow \diamond \rightarrow$	Yes
Re-hospitalisation	Rarer	$\leftarrow \diamond \rightarrow$	More frequent

LBBB – left His bundle branch block, RBBB – right His bundle branch block, CS – coronary sinus, NYHA – New York Heart Association.

Articles on the subject of the study

Publications (scientific articles) on the subject of the study

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