VILNIUS UNIVERSITY

VYTĖ VALERIJA MANEIKIENĖ

CARDIAC RESYNCHRONISATION THERAPY: EVALUATION AND PREDICTION OF EFFECTIVENESS

Summary of the Doctoral Dissertation

Biomedical Sciences, Medicine (06B)

Vilnius, 2015

The dissertation was prepared at the Clinic of Cardiovascular Disease, Faculty of Medicine, Vilnius University in the period of 2009 – 2014.

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VILNIAUS UNIVERSITETAS

VYTĖ VALERIJA MANEIKIENĖ

ŠIRDIES RESINCHRONIZUOJAMOJO GYDYMO EFEKTYVUMO ĮVERTINIMAS IR PROGNOZAVIMAS

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Abbreviations

ACEI – angiotensin-converting enzyme inhibitor

AoV – aortic valve

AF – atrial fibrillation

AVN – atrioventricular node

ARB – angiotensin receptor blocker

CABG – coronary artery by-pass operation

CI – confidence interval

CMP – cardiomyopathy

COPD – chronic obstructive pulmonary disease

CRT – cardiac resynchronization therapy

DM – diabetes mellitus

ESC – European Society of Cardiology

GFR – glomerular filtration rate

H-ACMP – hypertensive – arrhythmogenic cardiomyopathy

HF – heart failure

HR – hazard ratio

123I-MIGB - Iodine-123-metaiodobenzylguanidine

IVCD – intraventricular conduction delay

LBBB – left bundle branch block

LV – left ventricle

LV EF – left ventricle ejection fraction

MI – myocardial infarction

MVI – mitral valve insufficiency

PAD – peripheral artery disease

OMT – optimal medical treatment

RBBB – right bundle branch block

SR – sinus rhythm

VUH SK – Vilnius University Hospital Santariškių Klinikos

1. Relevance of the problem

Chronic heart failure (HF) is the main cause determining increasing morbidity and mortality of the patients suffering from cardiovascular diseases related to sudden death or progressive heart insufficiency. Implantation of re-synchronizing bi-ventricular pacemaker is one of the most modern methods of surgical treatment of heart failure. Heart failure causes changes of anatomical structure of the heart, dilatation of heart chambers and results in mechanical and electrical desynchronization of the heart. Simultaneous two-wire bi-ventricular stimulation of interventricular septum and the lateral wall of the left ventricle was named re-synchronizing therapy (cardiac resynchronization therapy – CRT). During re-synchronization, premature activation of the lateral wall of the left ventricle, simultaneously synchronizing contraction of the atria, acts like electrical by-pass and markedly improves contraction of the left ventricle (LV). At the Clinic of Cardiology and Angiology of Vilnius University Hospital Santariškių Klinikos, implantation of bi-ventricular heart pacemakers was started in 2002 and 386 patients underwent this method of treatment till the end of 2013. Long-term data of observation of the patients were collected, stored and analyzed, in order to evaluate the role of resynchronization in the process of the left ventricle recovery and re-modelling, decreasing all-cause morbidity and mortality, possibility to perform heart transplantation for some of these patients. Cardiac resynchronization therapy is a progressive, modern and very promising method of non-medicament treatment of heart failure; however, there are many unanswered questions requiring thorough studies and long-term observation, still. The benefits of CRT both in increasing survival rate and relieving clinical symptoms of heart failure in properly selected patients were definitely demonstrated in multicenter randomized double blind controlled clinical trials. Although large clinical trials provide basic guidelines for modern implementation of CRT in clinical practice, the cohorts of patients are being formed in these trials usually, and these patients undergo certain treatment that differs from circumstances existing in real world significantly.

2. Importance and novelty of the research

The Theses analyze data of the patients suffering from heart failure treated by means of CRT at the Clinic of Cardiology and Angiology of VUH Santariškių Klinikos since 2002 till 2013. The experience gained allowed to form sufficient samples in patient groups that were less analyzed in large multicenter researches or were presented as results of metaanalysis of subgroups. The analysis of long-lasting work became important, in order to improve selection of the patients for this method of treatment and to achieve long-term positive results of treatment of the patients suffering from advanced heart failure.

The attempt to use sophisticated nuclear radiology methods in order to improve patient selection was brand-new, also. For the first time in Lithuania, we used imaging of adrenergic innervation of the heart with 123 I-MIGB (Iodine-123-metaiodobenzyl-guanidine) to evaluate global and regional adrenergic innervation of the heart in patients with heart failure; the further clinical course of these patients was prospectively followed-up, while implementing different methods of treatment (optimal medical treatment [OMT] or CRT).

Comparative analysis of baseline characteristics and further clinical course of the patients of all these groups enables us to evaluate the significance of selection criteria for long-term positive results of the treatment better; it allows us to avoid application of expensive and time-exhausting treatment for the patients, who have no internal sources for improvement of their condition, also.

3. Tasks of the study

To evaluate statistical data of morbidity and survival in general and in different patient groups after CRT (taking into account type of the rhythm disturbances, type of conduction impairment, patient age, additional procedures performed, in order to increase efficacy of CRT, including modification of AV node, pacemaker upgrading):

A. To analyze values and interaction of clinical, ultrasound heart examination and biochemistry parameters in prediction of response to CRT and choosing further tactics of treatment;

B. To evaluate prognostic relevance of radionuclide imaging of adrenergic nervous system, while applying these data as selection criterion for CRT and choosing tactics of treatment.

4. Principal statements for defense:

1) The response to cardiac resynchronization therapy is statistically reliably related with recovery of electrical synchronicity – decrease of duration of QRS complex and results in improvement of the left ventricle's systolic function.
2) In patients suffering from atrial fibrillation, application of cardiac re-synchronization therapy is as effective as in patients with sinus rhythm, in event of maintenance of sufficient efficacy of biventricular stimulation (adequate medicament rate control or modification of atrioventricular node).
3) The efficacy of cardiac resynchronization therapy is comparable both in newly implanted and in upgraded pacemakers' groups; however, the higher number of complications is more characteristic of the latter group.
4) The application of cardiac resynchronization therapy in elderly (>70 years) patients is as effective and safe, as in younger patients.
5) The findings of imaging of global and regional cardiac adrenergic innervation, using 123I-MIBG, predict cardiac events of unfavorable course, cardiac death and response to the method of treatment chosen in patients suffering from severe, advanced heart failure.

This scientific study conforms to the principles of Helsinki declaration (www.wma.net/e/policy/pdf/17c.pdf).

The biomedical study was approved by the Committee of Biomedical Studies of Vilnius region.

Permission No. 158200-13-622-194, 2013-05-14.

5. Study subjects

The study analyzed the data of 386 patients, who were examined and treated at VUH SK Centre of Cardiology and Angiology and for whom heart failure of different etiology was

diagnosed; these patients underwent implantation of resynchronizing pacemakers, in accordance with current guidelines. The patients were interviewed at the Consultative Out-patient Department of VUH SK by the cardiologist of Sub-unit of Heart Failure during scheduled visits; the interview included information concerning demographic data, anamnesis of the disease, concomitant diseases, clinical condition of the patient, risk factors; during the visit, the data of physical and instrumental examination were evaluated, as well as tactics of medicament treatment considered. The records included into medicine documents of VUH SK were periodically analyzed, in order to evaluate morbidity of the patients, readmissions to the hospital and mortality. During the study, the patients were distributed into four homogenous groups in accordance with the type of rhythm disturbance:

1. The 1st group included the patients who had sinus rhythm (SR) at implantation of the pacemaker and afterwards, during the follow-up; these patients corresponded to class I (level of evidence A) of European Society of Cardiology (ESC) guidelines; the group consisted of 103 patients and was considered to be a control group.
2. The 2nd group included the patients who at implantation had SR, but later on, during the follow-up, developed atrial fibrillation (AF); these patients corresponded to class IIa (level of evidence B) of ESC guidelines; the group consisted of 71 patient.
3. The 3rd group included the patients who, at implantation of the device, had atrial fibrillation (tachy/brady syndrome or tachysystolic AF, unsuccessfully controlled by means of medicaments) with concomitant disorders of intraventricular conduction; these patients corresponded to class IIa (level of evidence B) of ESC guidelines; the group consisted of 126 patients;
4. The 4th group included patients who, at implantation of the device, had atrial fibrillation (tachy/brady syndrome or tachysystolic AF, unsuccessfully controlled by means of medicaments) and narrow QRS complexes, decreased inotropic LV function, expecting high percentage of ventricular stimulation or anticipating procedure of AV node modification; these patients corresponded to class IIa (level of evidence B) of ESC guidelines; the group consisted of 86 patients.

The sub-analysis of the whole sample of the study subjects (386 patients) was performed and the patients were distributed in accordance with:

- primary vs. upgraded cardiac stimulation – the group of patients form whom, in accordance with regular indications of permanent long-term stimulation of the heart, single-chamber pacemakers were implanted; during the follow-up, these patients developed worsening of the systolic function of the left ventricle and it was decided to replace the pacemaker with upgraded, biventricular resynchronizing one; this group included 78 patients, in comparison, the group of patients, for whom CRT devices were implanted primarily, included 308 patients.
- age – from all study subjects senior (≥ 70 years) patients were separated; this group included 145 patients; in comparison, the group of younger patients consisted of 241 study subject.
- different control of rate - the group of patients (n = 212), who suffered from atrial fibrillation underwent sub-analysis, also; two sub-groups were distributed; one of the sub-groups included patients with modification of atrioventricular node (n=91), the other one included patients with medicament control of heart rate (n=121).

The distinct prospective study group was formed during the course of the study; it included 67 patients, corresponding to the guidelines for implantation of resynchronizing pacemaker, who underwent examination of radionuclide imaging of cardiac adrenergic innervation using iodine-123 marked metaiodobenzylguanidine (123I MIBG); further evaluation of predictive significance of this examination for clinical outcomes of patients, for whom different methods of treatment were applied, including CRT and optimal medicament treatment, was performed. This scientific study conforms to the principles of Helsinki declaration (www.wma.net/e/policy/pdf/17c.pdf).

The biomedical study was approved by the Committee of Biomedical Studies of Vilnius region, Permission No. 158200-06-342-83.

6. Methods

6.1. Evaluation of electrocardiogram: ECG was evaluated before implantation of the pacemaker (rhythm, type of conduction disorder, including left or right BB block, non-specific impairment of intraventricular conduction) and, subsequently, in certain periods (to assess signs of electric asynchronism, i.e. width of QRS complex, efficacy of rhythm and rate control).

6.2. Evaluation of cardiac ultrasound examination data: these data were assessed prior implantation of CRT device and subsequently; the assessment included evaluation of function of the left ventricle (left ventricle ejection fraction – LV EF), end diastolic (LVEDD) and end systolic (LVESD) diameters of the left ventricle, size of the right ventricle, mitral valve insufficiency (grading from grade I to grade III), tricuspid valve insufficiency (grading from grade I to grade III), estimated systolic pulmonary artery pressure.

6.3. Evaluation of the results of cardiopulmonary test performed, if it is possible, prior and after implantation of the pacemaker; these tests enable us to evaluate the changes of exertion tolerance in CRT patients during the treatment.

6.4. In patients of prospective part of the study, who had disorders of intraventricular conduction and who underwent computed perfusion scintigraphy of myocardium and imaging of cardiac adrenergic innervation, and for whom, subsequently, implantation of resynchronizing pacemaker was performed or optimal medical therapy was continued, the results of the imaging were evaluated, as well as predictive significance of these findings in prognosticating of the further clinical course of the disease was assessed.

6.5. Evaluation of specific blood markers (B type natriuretic peptide – BNP) was performed prior implantation of the device and subsequently, in order to assess the severity of heart failure and evaluate efficacy of the treatment; evaluation of blood tests (general hematology, including hemoglobin level and platelet count; blood biochemistry, including creatinine and urine acid levels) prior the procedure and subsequently was performed, also.

Course and design of the study. The study was performed since January, 2010 till December, 2013. Demographic, clinical, ultrasound cardiac examination data and data of laboratory, instrumental tests were collected in retro-prospective manner, in accordance with the plan of the study established. The patients were observed during their hospitalizations at the Cardiology, Cardiac Surgery Departments of Clinic of Cardiovascular diseases VUH SK and, during their out-patient visits, at Heart Failure Sub-unit of Out-patient Consultation Clinic; the changes of clinical condition, admissions to the hospital and undesirable events (deaths) taking place during the treatment were recorded.

The data of CRT patients recorded till the period of the study were collected from information available on ELI (electronic case history) records. During the period when the study was performed, anamnesis and demographic data were collected while interviewing the patient.

The response to CRT during the follow-up was evaluated taking into account stability/improvement of the patient condition (the same or lower NYHA class) or worsening of the condition (higher NYHA class)/death of the patient. The combined clinical score (survival for 1 year with no heart failure hospitalizations, and improvement by ≥ 1 NYHA classes) was evaluated, also.

7. Statistical analysis

Statistical analysis was performed using SPSS 18 software. Mean (M) and standard deviation (SD) were used to describe quantitative characteristics of the research. Frequencies (n) and percents (%) were used for qualitative characteristics. Depending on applicable assumptions Student's t-test for independent samples was used to compare means of particular qualitative characteristic of different samples. Analysis of variance ANOVA was used to compare quantitative variables of more than two samples (when variances were unequal Welch test statistics was used). When hypothesis of the equality of means of two or more groups was discarded, pairwise comparison of this characteristic was additionally used. In that case Tukey HSD Post Hoc test was used.

Differences of qualitative characteristics of experimental groups were assessed using Chi square test.

For comparison of baseline and follow up data paired t test was applied. Correlations between different variables were measured using Pearson correlation coefficient. Survival free from death and hospitalization were analyzed by the Kaplan-Meier method. Receiver Operating Characteristic (ROC) curve analysis was performed to estimate cut-off values of different variables, predicting death or impairment of patients. Univariable Cox proportional hazard model were applied to select the clinical characteristics and treatments that correlated with death.

Selected level of significance p= .05.

8. Results

8.1. Baseline characteristics of the patients, regarding the type of electrical conduction disturbances and analysis of clinical outcomes, mean follow-up duration 27.9 months (±24.7).

The whole group of subjects studied included 386 patients for whom resynchronizing cardiac pacemakers were implanted since the beginning of 2002 till December 31, 2013. The examination of the patients, concerning baseline impairment of electrical conduction of the heart, showed that the majority of the patients had left His bundle branch block (n=257; 66.6%).

Table 1. Comparison of all baseline characteristics, regarding type of primary QRS (type of conduction impairment).

	Total (n=386)	Narrow QRS (n=86)	LBBB (n= 257)	RBBB (n=17)	IVCD (n=26)	p
Age, ± SD,y	65.45±11.59	63.93±10.85	65.69±11.82	68.53±11.85	66.17±11.46	0.411
LVEF, mean±SD, %	28.78±9.29	32.03±9.27	27.85±9.15	30.94±10.23	25.73±7.34	0.001
QRS, mean±SD, ms	162.37±38.76	101.44±14.74	182.47±22.12	161.82±13.81	167.12±16.64	<0.001
LVEDD, mean±SD, cm	6.62±0.96	6.22±0.84	6.74±0.97	6.55±0.73	6.73±1.04	<0.001
LVESD, mean±SD, cm	5.43±1.13	4.94±1.02	5.57±1.12	5.01±1.00	5.81±1.13	<0.001
MVI, mean±SD, grade	1.65±0.66	1.55±0.60	1.67±0.68	1.70±0.41	1,82±0.78	0.325
Gender, n (%)						
Female	106 (27.5%)	25 (29.1%)	75 (29.2%)	3 (17.6%)	3 (11.5%)	0.201
Male	280 (72.5%)	61 (70.9%)	182 (70.8%)	14 (82.4%)	23 (88.5%)	
NYHA Class n (%)						
2nd	8 (2.1%)	3 (3.5%)	5 (1.9%)	0 (0%)	0 (0%)	0.830
3rd	278 (72%)	62 (72.1%)	186 (72.4%)	13 (76.5%)	17 (65.4%)	
4th	100(25.9%)	21 (24.4%)	66 (25.7%)	4 (23.5%)	9 (34.6%)	
Ischemic CMP, n (%)	115 (29.8%)	23 (26.7%)	73 (28.4%)	5 (29.4%)	14 (53.8%)	0.009
Dilatative CMP,n(%)	85 (22%)	11 (12.8%)	66 (25.7%)	3 (17.6%)	5 (19.2%)	
H-ACMP, n (%)	140 (36.3%)	45 (52.3%)	84 (32.7%)	6 (35.3%)	5 (19.2%)	
Valvular CMP, n (%)	46 (11.9%)	7 (8.1%)	34 (13.2%)	3 (17.6%)	2 (7.7%)	
Prior MI, n (%)	95 (24.6%)	20 (23.3%)	58 (22.6%)	6 (35.3%)	11 (42,3%)	0.107
	53 (13.7%)	15 (28.3%)	29 (54.7%)	2 (3.8%)	7 (13.2%)	0.103
Prior AoV prosthesis, n (%)	43 (11.1%)	5 (5.8%)	32 (12.5%)	3 (17.6%)	3 (11.5%)	0.303

Prior stroke, n (%)	38 (9.8%)	6 (7.0%)	30 (11.7%)	0 (0%)	2 (7.7%)	0.289
Thyroid gl. pat., n (%)	57 (14.7%)	17 (19.8%)	37 (14.4%)	1 (5.9%)	2 (7.7%)	0.280
DM, n (%)	63 (16.3%)	21 (24.4%)	35 (13.6%)	1 (5.9%)	6 (23.1%)	0.052
Art. hypert.,n (%)	199 (51.5%)	50 (58.1%)	124 (48.2%)	11 (64.7%)	14 (53.8%)	0.278
COPD, n (%)	41 (10.6%)	7 (8.1%)	31 (12.1%)	0 (0%)	3 (11.5%)	0.367
PAD, n (%)	25 (6.5%)	7 (8.1%)	16 (6.2%)	0 (0%)	2 (7.7%)	0.646
AF,n (%)	212 (54.9%)	74 (86.0%)	117 (45.5%)	9 (52.9%)	12 (46.2%)	**<0.001**
Prior pacemaker impl., n (%)	78 (20.2%)	2 (2.3%)	76 (29.6%)	0 (0%)	0 (0%)	**<0.001**
AVN modif., n (%)	98 (25.4%)	37 (43.0%)	56 (21.8%)	4 (23.5%)	1 (3.8%)	**<0.001**
SR -> AF, n (%)	75 (19.4%)	7 (8.1%)	59 (23.0%)	5 (29.4%)	4 (15.4%)	**0.015**
Medications, n (%)						
Orfarin	284 (73.6%)	78 (90.7%)	175 (68.1%)	13 (76.5%)	18 (69.2%)	**0.001**
Aspir/Clopidogr	86 (22.3%)	6 (7.0%)	66 (25.7%)	6 (35.3%)	8 (30.8%)	**0.001**
Betablockers	326 (84.5%)	75 (87.2%)	213 (82.9%)	16 (94.1%)	22 (84.6%)	0.533
ACEI/ARB	256 (66.3%)	54 (62.8%)	174 (67.7%)	11 (64.7%)	17 (65.4%)	0.866
Loop diuretics	327 (84.7%)	73 (84.9%)	217 (84.4%)	14 (82.4%)	23 (88.5%)	0.946
MRA	218 (56.5%)	53 (61.6%)	142 (55.3%)	7 (41.2%)	16 (61.5%)	0.395
Digoxin	98 (25.4%)	34 (39.5%)	55 (21.4%)	3 (17.6%)	6 (23.1%)	**0.008**
Amiodarone	54 (14%)	8 (9.3%)	40 (15.6%)	2 (11.8%)	4 (15.4%)	0.530
Nitrates	26 (6.7%)	4 (4.7%)	16 (6.2%)	2 (11.8%)	4 (15.4%)	0.214
Statins	63 (16.3%)	7 (8.1%)	44 (17.1%)	5 (29.4%)	7 (26.9%)	**0.035**

Approximately one fifth of the study subjects consisted of patients with narrow QRS complexes (n=86; 22.3%); CRT devices were implanted for these patients, because high percentage of ventricular stimulation was expected in future, possibly diminishing almost decreased left ventricle ejection fraction in these patients. Other groups of patients with conduction disorders consisted of small number of patients with right bundle branch block (n=17; 4.4%) and non-specific intraventricular conduction delay (n=26; 6.7%).

Table 2. Clinical outcomes of all patients at the end of follow-up.

	1st year	2nd year	3rd year	Total, during the whole period of follow-up
One-year mortality n (%)	32 (8.3%)	17 (4.4%)	19 (4.9%)	80 (20.7%)
Summarized mortality n (%)	32 (8.3%)	49 (12.7%)	68 (1.6%)	80 (20.7%)
Admissions per year n (%)	95 (24.6%)	41 (10.6%)	21 (5.4%)	187 (48.4%)
Summarized admissions n (%)	95 (24.6%)	136 (35.2%)	157 (40.7%)	187 (48.4%)
Admissions and deaths per year n (%)	117 (30.3%)	49 (12.7%)	29 (7.5%)	225 (58.3%)
Summarized admissions or deaths n (%)	117 (30.3%)	166 (43.0%)	195 (50.5%)	225 (58.3%)

Mortality rate in whole study population was highest during the first year (n=32; 8.3%); both during the second and third year, 4.5% of patients had died a year, additionally. The mortality rate during the whole period of follow-up was 20.7% (n= 80). During this period, almost a half of the patients (48.4%) experienced the worsening of the course of heart failure, requiring treatment at the hospital. The evaluation of combined criterion of death and admission to the hospital because of worsening of heart failure, showed that almost 60 per cent (58.3%) of the patients had had these events during the whole period of follow-up; these findings substantiated proposals stating that the group of patients suffering from chronic heart failure required significant part of funds allocated for health care.

The evaluation of functional class changes during the first year showed that more than 40 per cent (n=155) of the patients had improvement in one NYHA class and only one per cent of the patients had improvement in two NYHA classes. During the same period, 146 (37.8%) patients remained in stable condition; therefore, total response to CRT rate was 78 per cent. Distribution between different groups of conduction disturbances, regarding functional NYHA classes or clinical course did not differ during the first year.

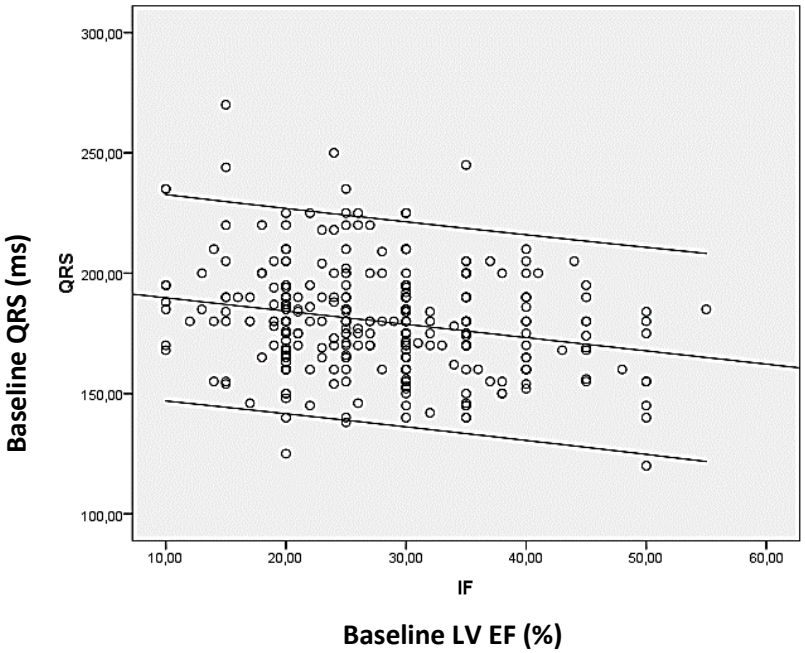
Clinical course of all patients during the follow-up was known; however, the data of control ultrasound heart examination were not available for some patients (approximately 70 % of the patients underwent echocardiography after 6 – 12 months after implantation of CRT device).

Table 3. Changes of QRS width and left ventricle ejection fraction during the treatment.

	Prior	After	p
QRS, ms	179.9±22.1	145.6±17.5	<0.001
LVEF, %	27.1±8.5	32.7±10.7	<0.001

Regardless clinical outcomes, electrical synchronization was reliably successful in patients who had wider QRS complex prior implantation of a pacemaker (patients with primarily narrow QRS complex were not included), as QRS width decreased from 179.9±22.1 to 145.6±17.5 ms ($p < 0.001$). At the same time, the ejection fraction of the left ventricle had increased reliably from 27.1±8.5 to 32.7±10.7% ($p < 0.001$).

Figure 1. Correlation between baseline QRS width and baseline left ventricle ejection fraction. The correlation is negative: the wider baseline QRS, the lower is the baseline LV EF (r=-0.227, p<0.001).

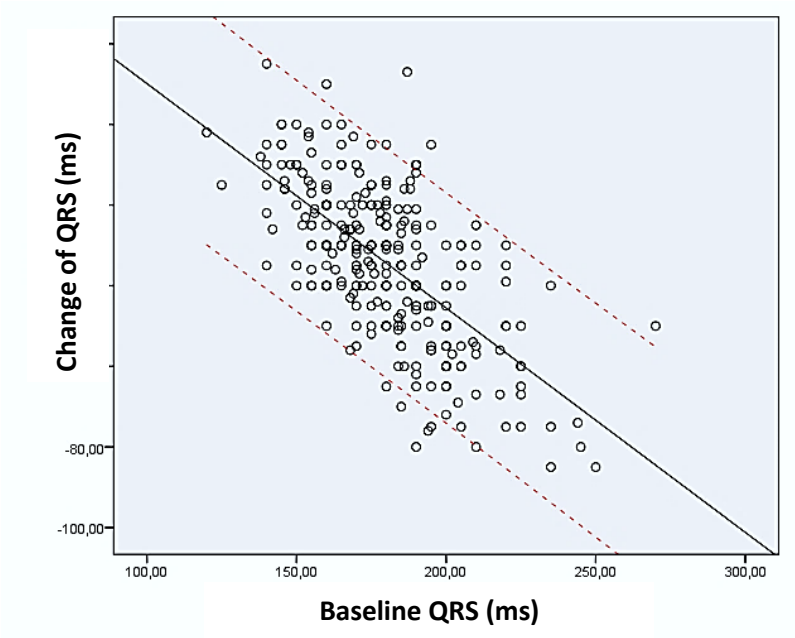


The reliable correlation between changes of QRS complex and changes of LV ejection fraction was not found out; however, analysis of homogenized group of patients showed weak positive trend: the greater narrowing of QRS is related to higher improvement of LV EF.

During the whole period of follow-up, the survival data in all four groups (the patients were distributed in accordance with baseline type of conduction disorder) did not differ significantly.

The evaluation of baseline characteristics analyzed, seems to demonstrate that only small part of these is significant in predicting mortality of the patients. So, age, gender, conduction disorder type and QRS width (< 150 and ≥ 150 ms) had no influence on patient survival during the first year and subsequent three years.

Figure 2. Correlation between baseline QRS width and changes of QRS width after implantation of CRT device. The correlation is negative: the wider baseline QRS undergoes greater narrowing after implantation of pacemaker (r=-0.649, p<0.001).



The etiology of cardiopathy was important for long-term survival (HR 1.95; 95% CI 1.2-3.2); p=0.009), it was also influenced by a history of myocardial infarction (one-year HR 2.8; 95% CI 1.4–5.6; p=0.005; three-year HR 2,6, 95%PI 1,6–6,3, p=0,005), stroke (three-year HR 2.4, 95% CI 1.3–4.4; p=0.007), history of coronary artery by-pass grafting (one-year HR 3.9; 95% CI 1.9–8.1; three-year HR 2.8, 95% CI 1.6– .9; p<0.001). No other pathology had an influence on survival.

Functional state of the patient at implantation was found to be important for a long-term mortality; NYHA functional class did not influence patient first year survival (showing correct selection of the patients even in poor clinical condition, as the procedure is justifiable, when predicted survival is at least 1 year after implantation of a pacemaker); however, during the late period the 4th NYHA functional class at operation became reliable predictive criterion. Among medications used, only beta-blockers and ACEI/ARB reliably predicted more favorable outcomes (beta-blockers both for early and long- term, ACEI/ARB – for long-term, only).

8.2. Baseline characteristics and analysis clinical course of control (the 1st) group of patients, mean follow-up duration 29.6 months (±25.3).

Table 4. Baseline characteristics.

Characteristic	*Baseline data (n=99)*
Age, mean ± SD, yrs	63.8 ± 12.8
Body surface area, mean ±SD, m2	1.9 ± 0.2
BMI	29.9 ± 6.4
BMI > 30 (obesity), n (%)	41 (44.1)
Gender, n (%)	
Female	24 (24.2)
Male	75 (75.8)
NYHA class, n (%)	
II	2 (2.0)
III	74 (74.7)
IV	23 (23.3)
Ischemic CMP, n (%)	37 (37.4)
Non-ischemic CMP, n (%)	62 (62.6)
Dilatative CMP, n (%)	41 (41.4)
H-A CMP, n (%)	12 (12.1)
Valvular CMP, n (%)	9 (9.1)
History of MI, n (%)	27 (27.3)
History of CABG, n (%)	18 (18.2)
AoV prosthesis, n (%)	10 (10.1)
History of stroke, n (%)	5 (5.1)
Pathology of thyroid gland, n (%)	8 (8.1)
DM, n (%)	16 (16.2)
Arterial hypertension, n (%)	48 (48.5)
COPD, n (%)	9 (9.1)
PAD, n (%)	6 (6.1)
Oncology, n (%)	7 (7.1)
Medications, n (%)	
Orfarin	35 (35.4)
Aspirin/Clopidogrel	45 (45.5)
Beta-blockers	84 (84.8)
ACEI/ARB	72 (72.7)
Loop diuretics	86 (86.9)
MRA	58 (58.6)
Digoxin	7 (7.1)
Amiodarone	10 (10.1)
Nitrates	6 (6.1)
Statins	23 (23.2)
Anti-depressants	8 (8.1)
Insulin	6 (6.1)
QRS ms, mean ± SD	177.9 ± 26.1

Data of ultrasound cardiac examination:	
LVEF, mean ± SD, %	26.2 ± 9.0
LVEDD, mean ± SD, cm	6.8 ± 0.9
LVESD, mean ± SD, cm	5.8 ± 1.1
MVI, mean ± SD, grade	1.6 ± 0.7
TVN, mean ± SD, grade	1.3 ± 0.6
RV width, cm	3.2 ± 0.6
Estimated systolic PA pressure, mean ± SD, mm Hg	40.9 ± 12.1
Laboratory findings:	
Haemoglobin, g/l, mean ± SD	139 ± 14.3
Anaemia, n (%)	19 (19.6)
Platelets x10e9/l, mean ± SD	203.0 ± 58.8
Decreased no. of platelets, n (%)	10 (10.4)
Creatinine mcmol/l, mean ± SD	95.9 ± 33
Increased creatinine level, n (%)	21 (21.6)
GFR , mL/min/1.73 m2, mean ± SD	71.1 ± 21.1
Normal renal function (GFR ≥ 60)	66 (68.0)
Renal insufficiency (GFR < 60)	31 (32.0)
Urine acid, mcmol/l, mean ± SD	373 ± 99
Increased level of urine acid, n (%)	14 (14.1)
BNP, pg/l, mean ± SD	866.1 ± 1675.2
Increased level of BNP, n (%)	54 (54.5)

Table 5. Analysis of mortality and morbidity during follow-up period.

	1st year	2nd year	3rd year	Total during the follow-up period
Mortality per year, n (%)	6 (6.1)	6 (6.1)	2 (2.0)	18 (18.2)
Summarized n (%)	6 (6.1)	12 (12.1)	14 (14.1)	18 (18.2)
Admissions per year, n (%)	16 (16.2)	4 (4.0)	5 (5.1)	34 (34.3)
Summarized, n (%)	16 (16.2)	20 (20.2)	25 (25.3)	34 (34.3)
Deaths or admissions per year n (%)	20 (20.2)	8 (8.1)	5 (5.1)	43 (43.4)
Summarized deaths or admissions, n (%)	20 (20.2)	28 (28.3)	33 (33.3)	43 (43.4)

In accordance with demographic data, male patients were at risk of death or admission to the hospital more frequently. During the follow-up period, there were no death among female patients in this group (n=24). During the first year, 6 (6.1%) male patients had died; during three years of follow-up 17 per cent of male patients (13 of 75 patients) had died, with

total mortality rate among male patients achieving 24 per cent (18 of 75 patients). The same trend is seen when evaluating the combined result, including deaths or admissions because of heart failure – the male patients were admitted to the hospital or died markedly more frequently (during the first year these findings were 25.3 vs 4.2%, during three years 41.3 vs 8.3%, with total result during the follow-up 52 vs 16.7% in male and female, respectively).

In whole group of these study subjects, during the first year death was reliably predicted by the following events, including history of myocardial infarction (14.8 vs 2.8%), CABG (22.2 vs 2.5%), peripheral artery disease (14.8 and 2.8%). However, these factors were not important, regarding long-term period. Chronic obstructive pulmonary disease (77.8 vs 40%) reliably increased death and admission risk during the long-term period; the presence of arterial hypertension was also important, as higher arterial pressure concomitant to heart failure was a sign of better prognosis (31.2 vs 55%). Concomitant cancer at the time of implantation of a device significantly increased long-term mortality. High number of concomitant diseases (2.3±2.2 vs 1.4±1.3) also reliably increased risk of death during early and long-term follow-up period.

In general, admissions and mortality during both early and long-term (three-year) follow-up periods were influenced by increase of creatinine level (105.8±41.6 and 88.3±22.0) and presence of marked renal insufficiency (24.9 and 19%).

8.3. Comparative analysis of the 2nd group of patients (sinus rhythm at the time of implantation of the device with development of atrial fibrillation during follow-up, mean follow-up duration 29.1 months (± 23.9).

The group included 75 patients; mean age of these patients was 66.8±11.8 years; almost one third of them were females (28%). Almost one third of the patients was suffering from advanced (NYHA IV functional class) HF (n=22; 29.3%). In more than a half of the patients (n=47; 62.2%) the cardiopathy was of non-ischemic etiology (i.e. dilative, hypertensive-arrhythmogenic, valvular). The remaining patients were suffering from coronary heart disease and 82% of them (23 patients of 28) had a history of myocardial infarction. A half of

the patients had concomitant essential arterial hypertension and approximately one fifth had pathology of thyroid gland. Approximately in one third of the patients (n=26; 35.1%) signs of anemia were present and almost a half of the patients (n=35; 47.3%) had markedly impaired kidney function (GFR < 60 ml/min/1,73m2).

After one year, among NYHA III class patients 17 (32.7%) experienced improvement (progressed in NYHA II class), 24 (46.1%) remained in the same condition and 11 (21.1%) descended to NYHA IV class (three of these patients had died). In the group of the patients of NYHA IV class, improvement was observed in 10 (45.4%), other 12 (54.6%) patients remained in the same class (five of them had died).

Table 6. Comparison of treatment efficacy between the 1st and the 2nd groups.

Parameter	Patients with stable sinus rhythm, 1st gr (n = 99)	Patients with sinus rhythm, who developed AF, 2nd gr. (n = 75)	p
Change in NYHA f. cl., n (%)			
• improved ≥ I f.cl.	41 (41.8)	30 (40.0)	0.759
• remained stable	44 (44.9)	32 (42.7)	
• worsened/death during the first year	13 (13.3)	13 (17.3)	
• Total deaths	18 (18.2)	17 (22.7)	0.294
Δ QRS	-33.8±23.1	-27.2±26.1	0.086
QRS index	-17.5±14.4	-14.0±17.3	0.151
LV EDD cm after 1 year	6.5±1.2	6.4±1.1	0.567
Δ LV EDD cm	-0.3±0.8	-0.3±0.6	0.918
LV ESD cm after 1 year	5.4±1.3	5.1±1.3	0.202
Δ LV ESD cm	-0.3±1.0	-0.3±1.2	0.939
KS IF % after 1 year	31.4±11.2	33.3±9.5	0.318
Δ KS IF %	5.1±9.5	4.8±8.8	0.823
MV insufficiency, grade, after 1 year	1.4±0.6	1.5±0.6	0.246
Δ MV insufficiency grade	-0.2±0.6	-0.1±0.6	0.215
TV insufficiency grade, after 1 year	1.2±0.5	1.3±0.6	0.442
Δ TV insufficiency grade	-0.1±0.5	0.02±0.5	0.230

RV width, cm, after 1 year	3.3±0.7	3.1±0.5	0.314
Δ RV width, cm	0.03±0.5	0.01±0.5	0.854
Estimated PA systolic pressure, mm Hg, after 1 year	40.8±12.2	41.2±13.0	0.874
Δ estimated PA systolic pressure, mm Hg	-0.9±10.1	-0.7±10.8	0.895

Both groups of study subjects did not differ, regarding clinical or ultrasound examination data over time; the results were superior in neither group, nor with stable rhythm, or those who developed atrial fibrillation later.

Table 7. Comparison of the 1st and 2nd group, regarding treatment outcomes including mortality/admissions and improvement in NYHA f. cl. (p).

Variables	Period					
	Death			Death/admission		
	One-year	Three - year	Total	One- year	Three-year	Total
1st group vs 2nd group	0.555	0.288	0.294	0.267	0.006 33-66 40-35	0.005 43-56 48-27

The impairment of sinus rhythm, developing during biventricular stimulation, had no influence on total, as well as early and long - term **mortality**.

The total and long-term results, regarding **combined clinical score (mortality and admissions regarding worsening HF)** in these groups are different. During three years, in sinus rhythm group (n = 99), 33 patients had events, in comparison with 40 patients in the 2nd group, that included 75 patients (33 vs 53.3%, respectively; p=0.006). During the whole period of observation, the events took place for 43 patients of the first group (n = 99), in comparison with 48 patients of the second group (n=75; 43.4 vs 64%, respectively; p=0.005).

No **differences between the 1st and 2nd group were found out** (p=0.417), regarding improvement in NYHA class (**effective – insufficiently effective response**).

8.4. Comparative analysis of the 3rd group patients (atrial fibrillation and impairment of intraventricular conduction, i.e. wide QRS complex), mean follow-up duration 28.1 month (± 25.2).

The group included 138 patients, their mean age was 67.2±10.6 years. Approximately one-fourth, 37 (26.8%), of the patients were females. Almost three-fourth were in NYHA III functional class at implantation of CRT device and remaining 37 patients (26.8%) were in critically severe condition because of cardiac insufficiency. Three-fourth of the patients suffered from cardiopathy of non-ischemic etiology (i.e., dilated, hypertensive-arrhythmogenic, valvular). Almost all of the patients of ischemic group (31 of 33 patients) had the history of myocardial infarction; for 14 of 33 of these patients CABG had been performed. Half of the patients (71 of 138; 51.4%) suffered from arterial hypertension, other concomitant pathologies were present in 10–15% of the patients.

In total, 36 (26.1%) patients had died; 14 (10.1%) of them died during the first year. Improvement was present in 31 (31%) of 99 NYHA III functional class patients, 43 (43%) patients remained in the same condition and worsening was present in 25 (25%) of these patients (12 patients had died; 12% of 99 NYHA III functional class patients). There were 37 patients in NYHA IV functional class; 20 (54%) of them progressed to NYHA III functional class and 17 remained in NYHA IV functional class (two of these patients had died in a year, it makes only 5.4% from total of the patients in IV functional class).

Table 8. Comparison of treatment efficacy between the 1st and 3rd study groups.

Parameter	Patients with sinus rhythm 1st group (n = 99)	AF with wide QRS 3rd group (n = 138)	p
Change in NYHA f. cl., N (%)			
- improved ≥ I f. cl.	41 (41.8)	53 (38.4)	0.308
- remained stable	44 (44.9)	56 (40.6)	
- worsened/died during the first year	13 (13.3)	29 (21.0)	
Total deaths	18 (18.2)	36 (26.1)	0.101
Δ QRS	-33.8±23.1	-33.1±19.7	0.794
QRS index	-17.5±14.4	-17.7±9.4	0.943
LVEDD cm after 1 year	6.5±1.2	6.5±1.0	0.678
Δ KS GDD cm	-0.3±0.8	-0.3±0.6	0.680
LVESD cm after 1 year	5.4±1.3	5.2±1.3	0.407
Δ LVESD cm	-0.3±1.0	-0.4±0.8	0.488
LVEF % after 1 year	31.4±11.2	33.0±11.1	0.372
Δ LVEF %	5.1±9.5	6.0±8.9	0.559
MV insufficiency grade after 1 year	1.4±0.6	1.6±0.6	0.058
Δ MV insufficiency grade	-0.2±0.6	-0.2±0.6	0.609
TV insufficiency grade after 1 year	1.2±0.5	1.5±0.7	0.008
Δ TV insufficiency grade	-0.1±0.5	-0.1±0.6	0.691
RV width cm after 1 year	3.3±0.7	3.5±0.6	0.029
Δ RV width cm	0.0±0.5	0.0±0.5	0.834
Estimated PA systolic pressure mm Hg after 1 year	40.8±12.2	43.7±13.5	0.164
Δ estimated PA systolic pressure mm Hg	-0.9±10.1	-2.3±10.8	0.416

Both groups did not differ, regarding clinical course; neither group (patients with stable sinus rhythm and patients with atrial fibrillation and wide QRS) was superior in accordance with improvement of functional condition or mortality rate.

The comparison of ultrasound heart examination data after implantation of CRT device in the 1st and 3rd groups showed reliable difference only in **tricuspid valve insufficiency** expressed in grades and right ventricle width both prior and after implantation of a pacemaker; the changes of right ventricle size during the treatment were similar in both groups.

Table 9. Comparison of the 1st. 2nd and 3rd groups, regarding outcomes of the treatment – mortality/admissions and improvement of NYHA (p).

Variables	Period						
	Death			Death or admission			NYHA
	One-year	Three-year	Total	One-year	Three-year	Total	Improvement
1st vs 3rd group	0.191	0.062	0.101	0.006 20-41 79-97	0.002 33-73 66-65	0.006 43-84 56-54	0.369
2nd vs 3rd group	0.280	0.281	0.353	0.304	0.533	0.383	0.542

The comparison of the group of patients with baseline sinus rhythm and subsequent development of AF (the 2nd group) and the group with baseline AF (the 3rd group), showed no significant differences, concerning mortality rate data or combined criterion (mortality and admissions) expression. The mortality data were similar and comparable with the first class of indications group (the 1st group) of stable sinus rhythm; however, the rate of **combined event** (admissions because of HF worsening or death) was different in these groups. The **patients with disturbed rhythm had markedly higher number** of events (due to admissions) during early (32.8 vs 44.9%; p=0.002), long-term – three years (33.8 vs 50.4%; p=0.002) periods and during the whole follow-up. The trends of efficient clinical response were similar in all three groups.

8.5. Comparative analysis of the 4th group patients (atrial fibrillation, including tachy/brady syndrome or unsuccessfully medicament controlled tachysystolic AF, with narrow QRS complexes), mean follow-up duration - 22,4 months (±20,1).

The group included 74 patients, their mean age was 63.0±10.9 years. One-third of the group were females (n=24; 32.4%). Almost one-fourth of the patients (n=18; 24.3%) suffered from critically severe heart failure. In three-fourth of the patients (n=57; 77%), the cardiopathy was of non-ischemic etiology (dilative, hypertensive – arrhythmogenic, valvular); the arrhythmogenic-hypertensive cardiopathy was prevailing in this group (n=42;

58.1). More than the half of the patients had arterial hypertension (n=43; 58.1%). In 20% of the cases diabetes mellitus or pathology of thyroid gland were diagnosed; other pathology was present in 10% of the patients. The QRS complex average was 100.5±15.0 ms (it was not higher than QRS duration indicated by the guidelines – 120 ms). The mean left ventricle ejection fraction was 32.7±8.8% and it was higher, in comparison with other groups.

After 1 year, in NYHA III class group 20 (37.8%) patients had improved, 31 patient (58.5%) remained stable and only 2 patients (3.8%) showed worsening of the condition (one of these patients did not survive). In NYHA IV functional class, 10 patients (55.5%) had improved and in other 8 patients (44.5%) there were no changes of functional class; 5 of these patients had died.

Table 10. Comparison of treatment between the 1st and 4th study groups.

Parameter	Patients with SR 1st group (n = 99)	Patients with AF and narrow QRD 4th group (n = 74)	p
Change in NYHA f. cl. N(%)			
- improved ≥ I f. cl.	41 (41.8)	31 (41,9)	0.878
- remained stable	44 (44.9)	35 (47,3)	
- worsened/died during the 1st year	13 (13.3)	8 (10,8)	
Total deaths	18 (18.2)	9 (12,2)	0.193
Δ QRS	-33.8±23.1	33.6±18.4	**<0.001**
QRS index	-17.5±14.4	35.4±20.1	**<0.001**
LVEDD cm after 1year	6.5±1.2	5.9±0.8	**0.003**
Δ LVEDD cm	-0.3±0.8	-0.2±0.5	0.220
LVESD cm after 1 year	5.4±1.3	4.5±1.0	**<0.001**
Δ LVESD cm	-0.3±1.0	-0.3±0.6	0.644
LVEF % after 1 year	31.4±11.2	36.7±10.5	**0.011**
Δ LVED %	5.1±9.5	4.4±7.2	0.622
MV insufficiency grade after 1 year	1.4±0.6	1.5±0.5	0.471
Δ MV insufficiency grade	-0.2±0.6	-0.04±0. 6	0.119
TV insufficiency grade after 1 year	1.2±0.5	1.4±0.6	**0.035**
Δ TV insufficiency grade	-0.1±0.5	-0.1±0.6	0.764
RV width cm after 1 year	3.3±0.7	3.2±0.5	0.436
Δ RV width cm	0.03±0.5	-0.10±0.5	0.201
Estimated PA systolic pressure mm Hg after 1 year	40.8±12.2	40.3±11.1	0.817
Δ estimated PA systolic pressure mm Hg	-0.9±0.1	0.4±10.2	0.493

Comparison of the groups of patients of stable sinus rhythm and patients with atrial fibrillation and narrow QRS complexes showed that clinical improvement in these groups was similar. Data of ultrasound heart examination, similarly to these before the treatment, remained better in the group with atrial fibrillation and narrow QRS; systolic and diastolic diameters were reliably lower, left ventricle ejection fraction was higher; however, the changes of these parameters in both groups had no positive differentiation, as QRS complex duration in the group of atrial fibrillation had reliably increased after implantation of CRT device (the average of Δ QRS was app. 33.6±18.4 ms, the max. enlarged QRS was 135.0±15,6 ms).

Table 11. Comparison of main patient groups (1st, 2nd, 3rd, 4th), concerning outcomes of the treatment – mortality/admissions and NYHA improvement (p).

Variables	Period						NYHA f. cl.
	Death			Death or admission			
	One-year	Three-year	Total	One-year	Three-year	Total	Improvement
1st vs 4th group	0.408	0.520	0.193	**<0.001** 20-34 79-40	**<0.001** 24-41 75-33	**0.017** 43-45 56-29	0.466
2nd vs 4th group	0.491	0.255	0.070	**0.007** 19-34 56-40	0.183	0.408	0.344
3rd vs 4th group	0.414	0.061	**0.012** 36-102 9-65	**0.014** 41-34 97-40	**0.013** 53-41 85-33	0.554	0.295

Total mortality rate was different only in groups of patients with atrial fibrillation and impairment of intraventricular conduction and without impairment, with narrow QRS complexes: 26.1 in the third and 12.2% in the fourth group; p=0.012. In comparison with other groups, mortality rate did not differ.

The evaluation of combined clinical score showed that the higher rate during the first year was present in the fourth group, in comparison with other groups; the same trend was

present in long-term period and in whole follow-up period, when comparing the patients with stable sinus rhythm and subjects with atrial fibrillation and narrow QRS complexes.

Neither of the group was superior in the point of view of clinical improvement in comparison with other.

8.6. Sub-analysis of the patients with atrial fibrillation and modification of atrioventricular node (91 patient) and patients with AF on medicament rate control (121 patient).

Table 12. Comparison of treatment response in patients with AF and medicament rate control and patients with AF after modification of AV node.

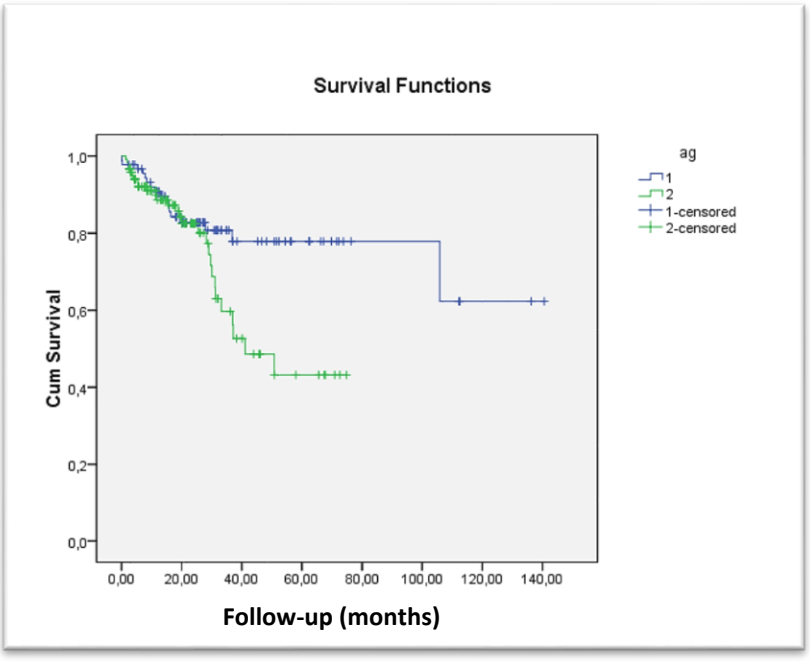
Parameter	Medicament rate control (n = 121)		AV node modification (n = 91)		p
Change of NYHA f. cl. n (%)					
- improved ≥ I f. cl.	41	33.1	44	48.4	0.077
- remained stable	57	47.1	34	37.4	
- worsened/died during the first year	23	19.8	13	14.3	
- total deaths	17	18.7	28	23.1	0.270
Δ QRS	-12.5±35.4		-6.0±39.4		0.219
QRS index	-1.5±27.4		4.2±30.9		0.151
LVEDD cm after 1 year	6.3±0.9		6.2±1.1		0.594
Δ LVEDD cm	-0.2±0.5		-0.3±0.6		0.366
LVESD cm after 1 year	5.0±1.2		5.0±1.3		0.834
Δ LVESD cm	-0.3±0.8		-0.4±0.8		0.466
LVEF % after 1 year	34.1±11.2		34.3±10.9		0.901
Δ LVEF %	5.2±7.8		5.7±9.1		0.692
MV insufficiency grade after 1 year	1.5±0.5		1.6±0.6		0.119
Δ MV insufficiency grade	-0.1±0.5		-0.13±0.6		0.921
TV insufficiency after 1 year	1.4±0.6		1.5±0.7		0.379
Δ TV insufficiency grade after 1 year	-0.1±0.5		-0.1±0.7		0.920
RV width cm after 1 year	3.4±0.6		3.3±0.6		0.461
Δ RV width cm	-0.0±0.4		-0.0±0.5		0.731
Estimated PA systolic pressure after 1 year	43.3±14.1		41.7±11.4		0.466
Δ estimated PA systolic pressure mm Hg	-2.0±11.2		-0.7±10.0		0.451

During the first year, clinical response, when comparing CRT groups on medicament control and after AV node ablation, no significant differences were found out, regarding improvement by more than one NYHA functional class (33.1 and 48.4%, respectively), and

number of patients without marked changes (47.1 and 37.4%, respectively). The findings of poor response (19.8 and 14.3%; p=0.077, respectively) and total mortality (18.7 and 23.1%, respectively) were similar, also. The comparison of the groups also showed, that one year after initiation of CRT, neither ultrasound heart examination data, nor changes of these data had significant differences in any parameter.

The comparison of efficient clinical response patients in both groups of AF control demonstrated, that only cardiopathy of non-ischemic etiology was prevailing in the group of efficient CRT in patients with AV node ablation. This can be explained by the difference of baseline characteristic, when the bigger number of the patients suffering from ischemic cardiopathy was included into the group of medicament rhythm control and later on entered the sub-group of efficient response, although nonischaemic CMP patients were prevailing there (70.7%).

Figure 3. Kaplan Meyer survival curves. Significant superiority of the group of patients with AV node modification (the 1st group; blue line) is demonstrated (p=0.033).



8.7. Sub-analysis of patient groups with primary CRT (308 patients) and CRT upgrade procedure (78 patients).

Analysis of clinical efficacy showed that there were no significant differences between the group of primary CRT and patients with pacemaker upgrading: improvement in one or more NYHA classes was present in 41.4 and 34.5% of the patients, respectively (p=0.605) and there was almost the same number of patients without marked change of condition (43 and 44.9%, respectively). During the whole period of follow-up, total mortality was almost the same, also (19.8 and 24.4%, respectively; p=0.230). The baseline QRS complex was reliably larger in the group of CRT upgrade; however, the complex became reliably and markedly narrower after upgrading, in comparison with the group of primary CRT (ΔQRS -43.0±24.5 vs -13.3±33.3 ms, QRS index -21.0±13.9 and -3.1±26.7%; p<0,001). The trends of baseline characteristics were similar to these of ultrasound heart examination data; only TV and RV width after one year were different; however, the changes of these parameters in these groups were comparable.

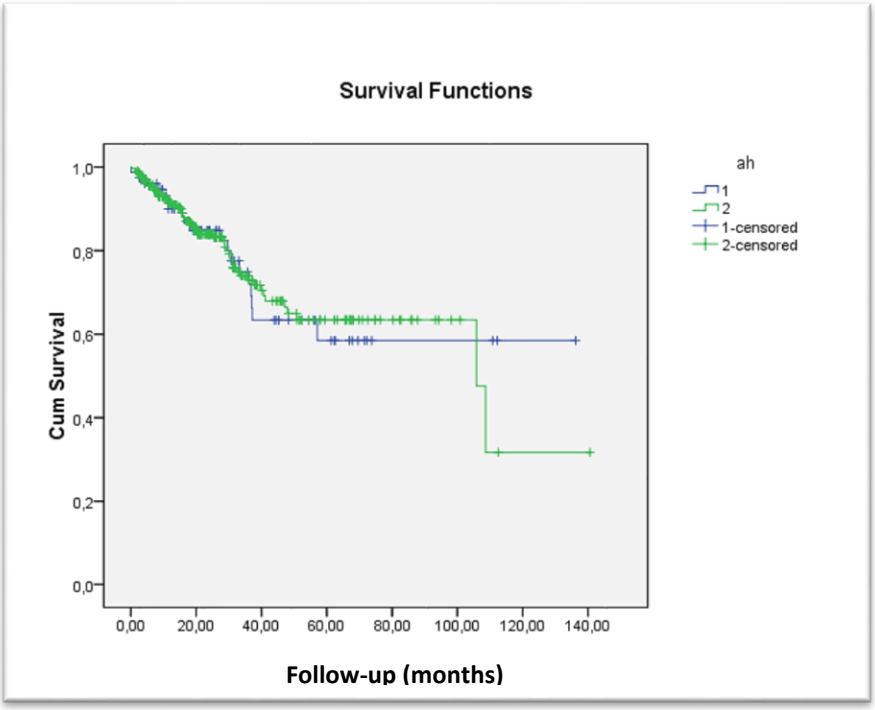
Table 13. Comparison of treatment response between primary CRT patients and patients with pacemaker upgrading.

Parameter	Primary CRT (n = 308)		Pacemaker upgrading (n = 78)		p
Change of NYHA f. cl. n (%)					
- improved ≥ I f. cl.	127	41.4	28	35.9	0.605
- remained stable	133	43.0	36	44.9	
- worsened/died during the first year	48	15.6	14	19.2	
- total deaths	61	19.8	19	24.4	0.230
Δ QRS	-13.3±33.3		-43.0±24.5		<0.001
QRS index	-3.1±26.4		-21.0±13.9		<0.001
LVEDD cm after 1 year.	6.4±1.1		6.4±1.1		0.836
Δ LVEDD cm	-0.3±0.7		-0.3±0.6		0.971
LVESD cm after 1 year	5.1±1.3		5.1±1.3		0.907
Δ LVESD cm	-0.3±1.0		-0.4±0.8		0.590
LVEF % after 1 year	33.0±10.8		34.5±10.7		0.329
Δ LVEF %	5.0±9.2		6.1±7.1		0.343

MV insufficiency grade after 1 year	1.5±0.6	1.6±0.6	0.665
Δ MV insufficiency grade	-0.12±0.6	-0.1±0.6	0.511
TV insufficiency after 1 year	1.3±0.6	1.5±0.7	**0.026**
Δ TV insufficiency grade	-0.1±0.6	-0.1±0.6	**0.794**
RV width cm after 1 year	3.2±0.6	3.5±0.6	**0.002**
Δ RV width cm	-0.0±0.5	0.0±0.4	0.598
Estimated PA systolic pressure mm Hg after 1 year	41.5±12.7	42.9±12.4	0.457
Δ estimated PA systolic pressure mm Hg	-1.2±11.0	-0.9±8.4	0.826

The comparison of patients with efficient response in both groups showed the same reliable differences, as in complete study groups (including the width of baseline QRS, delta QRA after treatment, changes of QRS index, baseline TV insufficiency, baseline RV width and RV width one year after).

Figure 4. *Kaplan-Meyer curve for comparison of survival in primary CRT and pacemaker upgrading groups. No difference between the groups is found (p=0.980).*



8.8. Sub-analysis of senior (≥70 years) and younger patient (<70 years) groups.

Table 14. Comparison of response to the treatment between the groups of younger and senior patients.

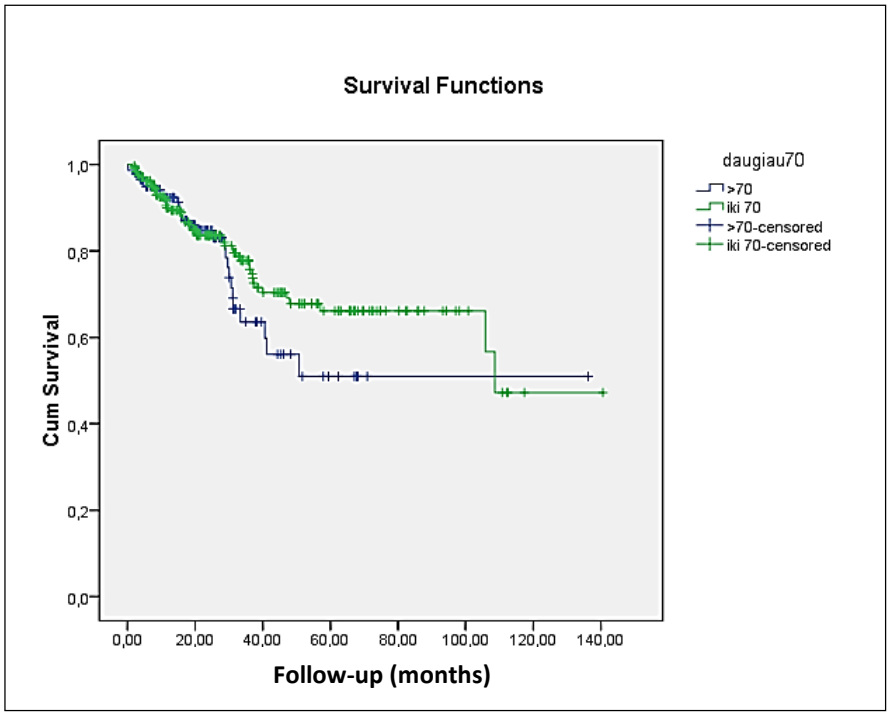
Parameter	≥ 70 years (n = 145)		< 70 years (n = 241)		p
Change of HYHA F. cl. n (%)					
- improved ≥ I f. cl.	43	29.7	112	46.7	0.004
- remained stable	73	50.3	94	39.2	
- worsened/died during the first year	29	20.0	34	14.2	
- total deaths	29	20.0	52	21.1	0.447
Δ QRS	-20.6±31.1		-18.5±35.41		0.568
QRS index	-8.4±23.7		-5.6±26.3		0.286
LVEDD cm after 1 year	6.0±0.9		6.6±1.1		<0.001
Δ LVEDD cm	-0.2±0,6		-0.3±0.6		0.253
LVESD cm after 1 year	4.8±1.1		5.3±1,3		0.004
Δ LVESD cm	-0.2±1.2		-0.4±0.8		0.109
LV EF % after 1 year	34.5±11.7		32.7±10.3		0.225
Δ LVEF %	4.4±10.5		5.7±7.7		0.303
MV insufficiency grade after 1 year	1.5±0.6		1.5±0.6		0.979
Δ MV insufficiency grade	-0.1±0.6		-0.1±0.6		0.889
TV insufficiency grade after 1 year	14±0.7		1.3±0.6		0.550
Δ TV insufficiency grade	-0.0±0.6		-0,1±0.5		0.370
RV width cm after 1 year	3.3±0.5		3.3±0.6		0.475
Δ RV width cm	0.0±0.5		-0.0±0.5		0.629
Estimated PA systolic pressure after 1 year mmHg	44.7±14.0		40.5± 1.8		0.023
Δ estimated PA systolic pressure mmHg	-0.9±13.8		-1.2±8.8		0.811

The comparison of the results in the groups of senior and younger patients showed, that survival during the first year and total survival did not differ, marked improvement for one and more NYHA functional classes was more common in younger patient group, in comparison with elderly ones (46.7 and 26.7%, respectively; p=0.004). The changes of QRS on CRT was even, QRS index did not differ, as well. As in baseline ultrasound heart

examination data of elderly patients the hearts were found to be less dilated (lower LV end-systolic and diastolic diameters), the same trend remained after a year of treatment, although the changes of these parameters were identical; one year after initiation of CRT, LVEF became the same in both groups. The difference between the groups in estimated systolic pulmonary artery pressure remained reliable, as it was at baseline; the pressure was higher in elderly patients (44.7±14.0 and 40.5±1.8 mm Hg; p=0.023).

The comparison of the groups of patients with good clinical response in accordance with patients' age, showed that ischemic cardiopathy was more common among the senior patients; however, this was observed in baseline comparison of the patient groups. One year after initiation of CRT, the results of ultrasound heart examination (left ventricle end-systolic and diastolic diameters) were better in the group of elderly patients; however, this trend was present at the baseline and the change of these parameters were similar in both age groups.

Figure 5. Kaplan-Meyer curves for comparison of survival in senior and younger patient groups; no difference was found out (p = 0.289).



8.9. Analysis of baseline characteristics and clinical course of prospective group of the study (67 patients).

In this group 67 heart failure patients were investigated with the New York Heart Association (NYHA) functional class II–IV, wide QRS complexes (>120 milliseconds), reduced left ventricular ejection fraction (LV EF) eligible for CRT. 123I-MIBG planar and single photon emission computed tomography (SPECT) scans were performed in a supine position with calculation of early and late heart-to-mediastinum (H/M) ratios, washout ratio (WR), summed defect scores and scores difference from SPECT acquisition. All patients were then divided in two groups according to their clinical status – 36 patients underwent implantation of CRT, and 31 patients were continued with OMT. Initial conventional heart failure markers and NYHA were assessed at the time of 123I-MIBG imaging and 6 months later. Comparisons of two groups were done applying the Student's t-test, and if samples were small, the Fisher's exact test was used. NYHA groups were compared applying the ANOVA single factor analysis. Receiver Operating Characteristic (ROC) curve analysis under optimal sensitivity and specificity of the relationship, was determined the critical values of different parameters in prediction of response.

Cardiac 123I-MIBG imaging data differed insignificantly, presenting a similar cardiac adrenergic innervation status in both groups. In the CRT group, NYHA and LV EF indicated more pronounced signs of HF. For all patients, NYHA IV patients had significantly larger LV diameter, smaller EF, larger BNP levels, lower late H/M values and larger denervation score difference. Clinically responders (as ones with decreasing or stabile NYHA functional class) to therapy in both groups had significantly higher early H/M ratio – 2.35 ± 0.41 than non-responders – 2.00±0.44 (p=0.004), and late H/M ratio – 2.11±0.44 for responders and 1.72±0.54 for non-responders (p=0.005). ROC curves of cardiac adrenergic innervation 123I-MIBG imaging data presents statistically significant cutoff value of early and late H/M ratios, separating patients groups to responders and non-responders: early H/M ratio – cutoff value of 2.00, area under the curve (95 % CI) 0.729 (0.583–0.874)with the sensitivity of 0.784 and

specificity of 0.687 (p=0.006); late H/M ratio – cutoff value of 1.77, area under the curve (95 % CI) 0.743 (0.586 – 0.900) with the sensitivity of 0.824 and specificity of 0.687 (p=0.004). There were no significant differences in regional cardiac 123I-MIBG data for responders and non-responders.

Conclusions. Cardiac 123I-MIBG imaging has valuable prognostic power predicting clinical outcomes of HF patients with wide QRS complexes, despite the chosen type of treatment, with better outcomes for patients with cut off value early H/M ratio above 2.00 and late H/M ratio above 1.77.

In order to use material resources in optimal way, we would like to recommend to perform evaluation of the patients with severe heart failure (NYHA IV class) more accurately, taking into account their prognosis of clinical course, in accordance with the results of sympathetic nervous system imaging.

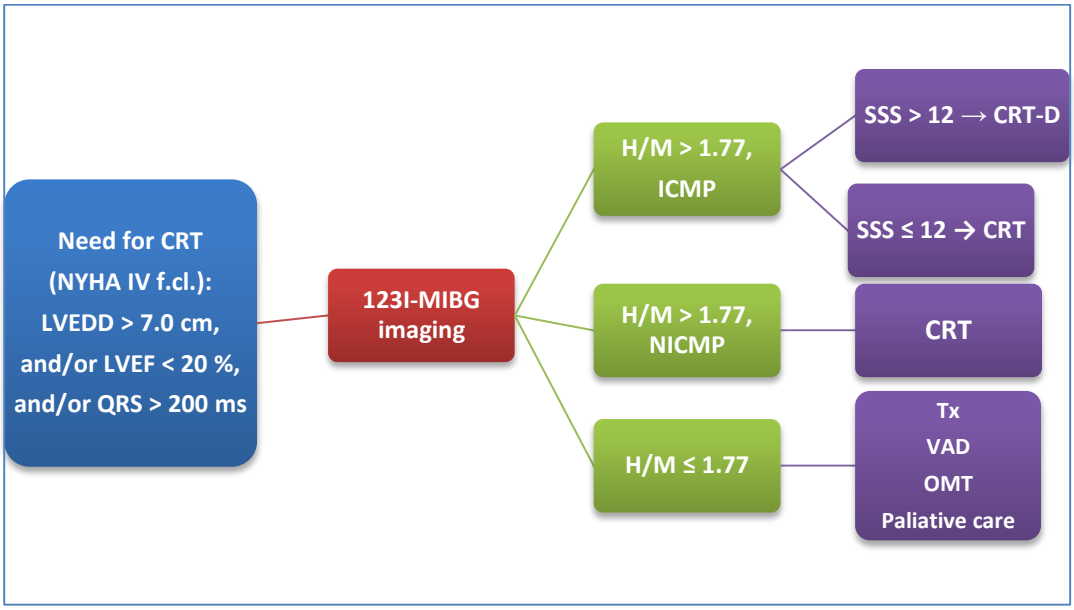
The comment of current CRT guidelines, concerning evaluation of patient's functional condition, states, that the procedure for patients, suffering from extremely severe heart failure (NYHA IV class), should not be performed during hospitalization because of worsening of HF; at first, it is recommended to stabilize patient's condition, discharge patient from the hospital for out-patient treatment and then perform planned implantation of a pacemaker. The results of our study also show, that NYHA functional class prior implantation is an independent marker of further clinical course. Baseline level of heart remodeling is another important factor influencing the course of the disease; the reversibility of the process is hardly believable, when certain degree of heart enlargement and increase of volumes is achieved. In 2011, researchers from Cleveland clinics published analysis of 471 patient data; the patients were distributed in accordance with enlargement of the diameter of the left ventricle. The hearts with LVEDD greater than 7.0 cm were considered to be highly enlarged. The study demonstrated that baseline diameter of LV negatively correlated with changes of LF ejection fraction after implantation of CRT device and was an independent mortality predicting factor (HR 1.25, 95 % ; CI 1.05-1.47; p=0.01)(1). In our study using MIGB, LVEDD

related to ineffective response, was also approximately the same (in the group of efficient response it was 6.6±1.1 vs 6.9±0.9 cm in the group of inefficient response, insufficiently reliable, p=0.6). The role of baseline LVEF in response to CRT is controversial. MADIT-CRT multicenter study, including 1809 patients, data, published in 2013, showed clinical efficacy of CRT to be independent of baseline LVEF (no advantage even when LVEF >30%); however, it was found out, that echocardiographic response had improved in line with better baseline LVEF, so it was concluded, that procedure was more beneficial for patients in whom systolic LVEF was less deteriorated (2). In our study, the critical values of LVEF in different patient groups distributing patients into response or non-response ones ranged from 20 to 25%. The increase of duration of QRS complex is related to both decrease of LVEF and increase of morbidity and mortality. Our study using MIBG, showed reliable distribution of QRS values in the groups of response and non-response CRT (174.5±30.6 vs 212.2±60.9; p=0.028).

So, while summarizing, we would like to recommend to perform scheduled imaging of adrenergic innervation of the heart in patients matching guidelines for implantation of CRT criteria and suffering from severe heart failure (ambulatory NYHA IV class) with LVEDD ≥7.0 cm and/or LV EF≤20% and/or QRS width ≥200 ms; the investigation should include estimation late heart-mediastinum (H/M) ratio from planar images. Cut-off value of H/M ratio for predicting response to CRT(adjusted for medium energy collimators used at our clinic) is 1.77; in event the findings are higher than critical value and the patient is suffering from ischemic cardiomyopathy, it is useful to perform myocardial perfusion scintigraphy and evaluate a summed stress score (SSS). In event H/M ratio is >1.77 and SSS >12, the patient is at a high risk of sudden death because of development of life-threatening rhythm disorders and implantation of CRT device with defibrillation function (CRT-D) should be considered. In event H/M >1.77 and SSS ≤12, implantation of CRT device should be performed. In event H/M ≤1.77, the probability of poor clinical prognosis is very high and potential of reversible remodeling is doubtful, so other options of treatment (if appropriate conditions are met) e.g., inclusion into recipient waiting list, implantation of ventricular assist device as a bridge to transplantation, should be considered; in event contraindications for heart transplantation

are present, optimal medication therapy should be continued and, if needed, supportive or palliation treatment performed.

Figure 6. Algorithm of clinical decisions for advanced heart failure patients.



LVEDD – left ventricle end-diastolic diameter; LVEF – left ventricle ejection fraction; MIBG – 123I metaiodobenzylguanidine imaging; H/M – heart/mediastinum ratio; ICMP – ischemic cardiomyopathy; NICMP - nonischaemic cardiomyopathy, SSS - summed stress score from myocardial perfusion scintigraphy; CRT-D – resynchronizing device with defibrillation function; Tx – heart transplantation, VAD – ventricular assist device, OMT – optimal medical therapy.

9. Conclusions

9.1. Implantation of CRT device reliably restores electric synchronicity and improves left ventricle ejection fraction in general sample of patients with different types of conduction disorders.

9.2. Ischemic etiology of heart failure, history of myocardial infarction and coronary artery by-pass grafting surgery, functional status (NYHA class) at the time of implantation of the device were independent prognostic early, as well as long-term markers of mortality.

9.3. More than one-third of the patients, for whom CRT devices were implanted, had atrial fibrillation with impaired ventricular conduction (wide QRS complex); their survival rate, clinical course and processes of recovery of the left ventricle did not differ from these of patients with stable sinus rhythm.

9.4. Some of the patients (over 40% of sinus rhythm patient at the time implantation in our study), during subsequent treatment after implantation of CRT device, developed rhythm disturbances (persistent or permanent atrial fibrillation). Mortality risk in these patients has not increased, however the need of admissions because of heart failure was reliably higher.

9.5. The patients with tachysystolic atrial fibrillation, narrow QRS and decreased left ventricle ejection fraction after implantation of CRT device showed similar improvement of clinical condition as the patients with wide QRS complexes. Mortality rate in these patients did not differ from this in sinus rhythm patients; however, the mortality rate was lower, in comparison with patients with atrial fibrillation and wide QRS complex.

9.6. During the first year, the clinical course of CRT patients with atrial fibrillation was influenced by medicament rate control or modification of atrioventricular node similarly; however, during the whole period of follow-up, electric isolation of the atria reliably significantly decreased mortality and the rate of admissions because of worsening of heart failure.

9.7. One-wired stimulation of the right ventricle impaired ventricular excitation markedly (reliably wider QRS complexes, in comparison with the cases of natural impairment of conduction). The substitution of one-wired ventricular pacemaker by cardiac resynchronizing device, as well as primary implantation of resynchronizing pacemaker, similarly influenced clinical course of the patients, their morbidity and mortality rate.

9.8. The results of resynchronizing treatment of elderly patients (≥70 years), concerning both one-year and general morbidity and mortality, were similar to

those of younger patients; however, the improvement of functional class was markedly better in younger ones. The over-time changes of ultrasound examination data in both groups were similar, also.

9.9. Global cardiac adrenergic innervation 123I-MIBG provides additional information about condition and prognosis of further clinical course of patients, suffering from heart failure.

10. Recommendations for practice

10.1. In order to achieve optimal results in heart failure out-patient care, it is recommended to perform complex evaluation of clinical condition of the patients, suitable for resynchronization and implant CRT devices as soon as appropriate (in 1-3 months), to avoid the development of deterioration of functional condition (higher NYHA class).

10.2. Adequate biventricular stimulation should be maintained in patients with atrial fibrillation; therefore, optimal medicament treatment to control heart rhythm should be administered. It is recommended to evaluate the efficacy of the treatment after one month after implantation of the device and, in event of failure of the treatment, to perform radiofrequency modification of AV node.

10.3. The patients with one-wired ventricular pacemakers and deteriorating left ventricle ejection fraction should undergo replacement of their pacemakers with CRT devices as soon as possible.

10.4. n order to improve the life quality and survival of elderly patients, CRT should be encouraged to be performed for these patients.

10.5. In order to optimize planning and distribution of material resources of non-medicament treatment of advanced heart failure in extremely ill patients of NYHA IV class, it is recommended to perform radionuclide imaging of cardiac adrenergic innervation and, in line with the results of this test, plan further tactics of treatment.

11. Literature

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12. List of publications

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- Marinskis G., Maneikienė V. Cardiac resynchronization therapy: problems and complications. 3rd Baltic Heart failure meeting, Tallinn, 6 October 2012 (poster).
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Methodic recommendation

- Donatas Vajauskas, Algirdas Edvardas Tamošiūnas, Kęstutis Ručinskas, Vytė Valerija Maneikienė „Širdies adrenerginės inervacijos vaizdinimas“, 2012, Vilnius.

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