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CARDIAC RESYNCHRONIZATION THERAPY WITH OR WITHOUT AN IMPLANTABLE CARDIOVERTER DEFIBRILLATOR IN DIFFERENT GROUPS OF HEART FAILURE PATIENTS

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Aim. Patients with heart failure have poor prognosis and mortality rate is between 15–60% per year. Implantable cardioverter-defibrillators and cardiac resynchronization therapy have been shown to improve survival, decrease hospital readmissions and mortality, and improve functional status and quality of life in patients with heart failure and left ventricular systolic dysfunction. Aim of the study was to examine the effects of different CRT devices in carefully selected heart failure patients during 1 year.

Material and methods. We included 98 heart failure patients. First group (n=60) received CRT-P, while in second group (n=38) were patients with CRT-D pacemaker (with an additional cardioverter-defibrillator option).

Results. Data gathered in our the study showed that both CRT-P and CRT-D in adequately selected heart failure patients improve different clinical parameters: symptoms, echocardiographic parameters, decrease QRS duration, increase 6 min walk test distance, decrease mortality rate.

Conclusion. Patients with both CRT-P and CRT-D showed improvement in heart failure symptoms and CRT had significant influence on disease prognosis during 1 year of follow up. Nevertheless we do not have the perfect criteria for selection of patients and their follow up after the device implantation. In patients with the rhythm disturbances CRT-D option is the right choice only if the patient has the indications for resynchronization therapy as well. This choice however depends on clinical judgment of the operator more than on strict protocols and guidelines which are necessary but we need more clinical trials to support current hypothesis.

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Key words: chronic heart failure, pacemaker, prognosis.

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CRT — cardiac resynchronization therapy, CRT-P — cardiac resynchronization therapy pacemaker, CRT-D — cardiac resynchronization therapy pacemaker with an ICD, COMPANION — Comparison of Medical Therapy, Pacing, and Defibrillation in Chronic Heart Failure study, CARE-HF — Cardiac Resynchronization–Heart Failure study, EDD — end-diastolic diameter, EDV — end-diastolic volume of left ventricle, ESV — end-systolic volume of left ventricle, ICD — Implantable cardioverter defibrillator, IVCD — inter-ventricular conduction delay, LV — left ventricle, LVEF — left ventricle ejection fraction, MIRACLE — Multicenter InSync randomized Clinical evaluation study, MUSTIC-SR — MUltisite STimulation In Cardiomyopathies in Sinus Rhythm study, NYHA — New York Heart Association, PEP LV — pre-ejection interval of left ventricle, PEP RV — pre ejection interval of right ventricle, RV — right ventricle, Six (6) MWD — six minute walking distance, SPWMD — septal-posterior wall motion delay, VT — ventricular tachycardia, VF — ventricular fibrillation.

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СЕРДЕЧНАЯ РЕСИНХРОНИЗИРУЮЩАЯ ТЕРАПИЯ С ИЛИ БЕЗ ИМПЛАНТИРУЕМОГО КАРДИОВЕРТЕР-ДЕФИБРИЛЛЯТОРА В РАЗЛИЧНЫХ ГРУППАХ ПАЦИЕНТОВ С СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТЬЮ

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Цель. Пациенты с сердечной недостаточностью (СН) имеют плохой прогноз, а уровень смертности между 15–60% в год. Имплантируемые кардиовертеры-дефибрилляторы и сердечная ресинхронизирующая терапия показали улучшение выживаемости, снижение повторных госпитализаций и смертности, а также улучшение функционального статуса и качества жизни больных с СН и систолической дисфункции левого желудочка. Цель исследования состояла в изучении влияния различных СРТ-устройств на тщательно отобранных пациентов, страдающих СН в течение 1 года.

Материал и методы. Мы включили в исследование 98 пациентов с СН. Первая группа (n=60) получила РСТ-Р, в то время, вторую группу (n=38) составляли пациенты с CRT-D кардиостимуляторами (вариант с дополнительным кардиовертер-дефибриллятором).

Результаты. Данные, полученные в нашем исследовании показали, что и РСТ-Р и РСТ-D у надлежащим образом выбранного пациента с СН способны улучшить различные клинические параметры — симптомы, эхокардиографические параметры, уменьшение длительности комплекса QRS, увеличение теста 6 мин ходьбы, снижение смертности.

Вывод. Пациенты с РСТ-Р и РСТ-D показали улучшение симптомов СН, и СРТ имела значительное влияние на прогноз заболевания в течение 1 года наблюдения. Тем не менее, мы не имеем идеальные критерии для отбора пациентов и их последующего ведения после имплантации устройства. У пациентов с нарушениями ритма РСТ-D вариант является правильным выбором, только если пациент имеет показания для ресинхронизирующей терапии. Однако этот выбор зависит от клинического решения лечащего врача больше, чем от строгих протоколов и рекомендаций, которые являются необходимыми, но мы нуждаемся в дополнительных клинических испытаниях для поддержки существующей гипотезы.

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Ключевые слова: хроническая сердечная недостаточность, наличие кардиостимулятора, прогноз.

Introduction

Prognosis is poor in heart failure patients and mortality rate is 15–60% in different population groups. It mainly depends on cardiac status which important indicators are left ventricular ejection fraction (LVEF), end-systolic and end-diastolic volumes of left ventricle (EDS, EDV), and left ventricular wall stress. The major cause of heart failure in developed countries is myocardial infarction [1]. It has been shown that mortality rate in patients after myocardial infarction and LVEF<25% was about 50% after one year,

while in those with LVEF around 55% it was <10%. Therefore, prognosis depends on preserved myocardial tissue after myocardial infarction [2]. It should be emphasized that mentioned correlation is not linear but exponential. If LVEF is lower than so called "critical value" of 30% mortality rapidly increases.

Ventricular arrhythmias and ventricular extrasystoles are common in patients with chronic heart failure and they are independent factors of worse prognosis. Patients with mild forms of chronic heart failure die of sudden cardiac death while those with advanced forms die of worsening heart failure.

Implantable cardioverter-defibrillators and cardiac resynchronization therapy have been shown to improve survival, decrease hospital readmissions and mortality, and improve functional status and quality of life in patients with heart failure and left ventricular systolic dysfunction. Implantable cardioverter-defibrillators are 99% effective in stopping life-threatening arrhythmias and are the most successful therapy to treat ventricular fibrillation, the major cause of sudden cardiac arrest. The use of these devices to prevent sudden cardiac arrest is supported by published guidelines. However, challenging patient cases exist that do not meet guideline requirements but due to recently published data, may benefit from cardiac resynchronization therapy pacemaker or cardiac resynchronization defibrillator therapy [3].

Current evidence-based guidelines recommend an implantable cardioverter-defibrillator for the primary prevention of sudden cardiac death in selected patients with impaired left ventricular function, and cardiac resynchronization therapy for improvement of symptoms and survival in selected patients with impaired left ventricular function and abnormal ventricular conduction. Many patients may be eligible for both treatments, but it does not necessarily follow that such patients would obtain additional benefit from the combined treatment over one treatment alone. A simple pragmatic approach would be to use resynchronisation therapy, in order to reduce symptoms and extend life in patients with New York Heart Association (NYHA) class 3 or 4 heart failure, with the addition of an implantable cardioverter-defibrillator left to clinical judgment on an individual basis when additional indications exist. When such an addition is contemplated the hypothesized incremental benefits in survival would need to be balanced by the possible increase in morbidity owing to, for example, inappropriate shocks [4].

Matherial and methods

Patient selection. We included in our study 98 patients with heart failure treated in Clinic for Cardiovascular diseases Nis during 2009 — January 2012. The first examined group consisted of 60 patients with CRT pace-maker – CRT-P (NYHA class 3/4, LVEF≤35%, QRS≥120ms, with dilated left ventricle (LV>55mm), on optimal drug therapy of heart failure and with fulfilled echocardiographic criteria for CRT therapy response (pre-ejection period of left ventricle >140msec, difference between left and right pre-ejection period >40msec, septal-posterior wall motion delay — SPWMD >135msec)) [5]. In the second examined group (n=38) we included patients with heart failure and CRT pace-maker with additional cardioverter-defibrillator option- CRT-D (NYHA class 3/4, LVEF≤35%, QRS ≥120ms, with dilated left ventricle (LV>55mm), on optimal drug therapy of heart failure and with fulfilled echocardiographic criteria for CRT therapy response and with heart rhythm disturbances as ventricular arrhythmias detected on 24-hour Holter ECG, patients who survived ventricular fibrillation (VF) or hemodynamically unstable ventricular tachycardia (VT), patients with non-ischemic dilated cardiomyopathy and significant left ventricular dysfunction with sustained VT and life expectancy longer than 1 year) [5].

All patients were on optimal drug therapy that included beta blocker, ACE inhibitor, aldosterone antagonist, diuretic, digitalis and antiarrhytmic agent as needed.

Parameters of interest and follow-up. In all patients before CRT implantation we performed 12 channels ECG, echocardiography, we measured 6 minute walking distance (6MWD), and determined subjective health status and drug compliance. After 1 year (at average) of CRT implantation we determined: NYHA functional class, QRS complex duration, echocardiographic parameters (LVEF; end-diastolic and end-systolic diameter of left ventricle — EDD, EDS; end-diastolic and end-systolic volumes of left ventricle — EDV, ESV; pre-ejection intervals of left and right ventricle — PEPLV, PEPRV; SPWMD), 6MWD and mortality rate. We also compared the number of hospitalizations due to worsening heart failure between observed groups.

In ***statistical analysis*** continuous variables are provided as means ±SD, and categorical variables are shown as percentages. Comparisons between groups for continuous variables were performed using Student *t* test or Wilcoxon's rank-sum test, as appropriate. Comparisons for categorical variables were performed using the chi-squared test. Multivariable logistic regression was used for the composite end point of death or re-hospitalization.

Results

Parameters at CRT-P and CRT-D implantation were not different in observed groups of patients (Table 1). The average age in patients with resynchronization therapy alone — CRT-P was 61,77±9,81 years while in those with CRT-D the average age was 58,11±13,24 with no significant difference (F=0,972, p=0,384). In the observed groups of patients there were more male patients: 44 (73,3%) with CRT-P and 34 (89,5%) with CRT-D pacemaker implanted. We did not find statistical difference in gender structure between groups (p>0,05). We found no significant difference in heart failure aetiology between observed groups of patients (Table 2). Dilated

Table 1

Parameters at CRT-P and CRT-D pacemaker implantation

	CRT-P (n= 60)	CRT-D (n= 38)
Pacing threshold A (volt, 0.5msec±SD)	1,16±0,76	0,9±0,45
Pacing threshold RV (volt, 0.5msec±SD)	0,75±0,85	0, 8±0,3
Pacing threshold LV (volt, 0.5msec±SD)	1,75±0,9	1,75±1,1
Sensing A (mv±SD) Sensing RV (mv±SD) Sensing LV (mv±SD)	2±0,76 9±4,7 11±3,8	1,8±0,65 12±3,6 12±4,4
Duration of the procedure (min)	70±12,8	87±14,3
Duration of the radiation (min) per procedure	9,6±5,3	10,8±0,3
Received dose of radiation (μGy/m^2) per procedure	1786±141,3	1911±95
Complications haematoma pneumothorax infection extracardiac stimulation	5 0 0 3	3 0 0 1

cardiomyopathy was a cause of heart failure in the majority of our patients.

After 1 year of follow-up only 26 (43,3%) patients with CRT-P pacemaker and 15 (39,4%) patients with CRT-D pacemaker were not hospitalized due to worsening of heart failure. Only 4 patients (6,7%) with CRT-P and 3 patients with (7,9%) pacemaker had 3 or more hospitalizations during 1 year after implantation (Table 3). There was not direct correlation between group of patients (type of CRT implanted) and number of hospitalizations (p>0,05). In the group of patients with CRT-P pacemaker before device implantation 40 patients (66,7%) were in NYHA 3 class, and 20 patients (33,3%) were in NYHA 4 class. One year after pacemaker implantation 30 patients (50%) were in NYHA 2 class. In the group of patients with CRT-D pacemaker before device implantation 26 patients (68,4%) were in NYHA 3 class and 12 patients (31,6%) were in NYHA 4 class. One year after device implantation there was no patients in NYHA 4 class. In the CRT-D pacemaker group 18 patients (47,4%) were in NYHA 2 class after follow up. After pacemaker implantation in both groups of patients

Table 2

Aetiology of heart failure in different groups of patients

	CRT-P		CRT-D	
	N	%	N	%
non-ischemic	42	70	25	65,8
ischemic	18	30	13	34,2
Total	60	100,0	38	100,0

Table 3

Number of hospitalizations in patients with different heart failure therapy

		CRT-P		CRT-D	
		N	%	N	%
No. hospitaliz.	0	26	43,3	15	39,4
	1	22	36,7	14	36,8
	2	8	13,3	6	15,7
	3	4	6,7	2	5,2
	4	0	0,0	1	2,6
	5	0	0,0	0	0,0
Total		60	100,0	38	100,0

n.s. p>0,05

Table 4

Comparative analysis of investigated parameters in heart failure patients with different types of therapy

	CRT-P		CRT-D	
	Before $\bar{x}$ (sd)	After $\bar{x}$ (sd)	Before $\bar{x}$ (sd)	After $\bar{x}$ (sd)
QRS (ms)	149,23 (10,30)	125,33 (10,66)	153,16 (5,58)	124,95 (5,91)
LVEF (%)	24,63 (5,08)	36,27 (8,37)	27,16 (6,59)	34,00 (5,89)
6MWD (m)	220,83 (38,53)	296,00 (67,63)	209,89 (28,18)	273,11 (32,62)
EDV (ml)	283,87 (55,81)	167,43 (44,38)	266,37 (24,40)	164,11 (23,97)
EDS (ml)	185,50 (50,63)	112,80 (22,33)	173,68 (21,19)	108,05 (21,43)
PEP LV	180,77 (17,58)	146,17 (8,57)	175,89 (6,93)	138,95 (5,13)
PEP RV	115,10 (20,41)	94,73 (17,31)	113,68 (13,76)	92,58 (12,79)
SPWMD	193,90 (44,27)	140,67 (22,44)	187,11 (11,43)	135,00 (10,57)

Abbreviations: LVEF — left ventricle ejection fraction, 6MWD — six minute walking distance, EDV — end-diastolic volume of left ventricle, ESV — end-systolic volume of left ventricle, PEP LV — pre-ejection interval of left ventricle, PEP RV — pre ejection interval of right ventricle, SPWMD — septal-posterior wall motion delay.

Table 5

Comparative analysis of parameters (end-diastolic and end-systolic diameters of left ventricle in heart failure patients with different types of therapy

	CRT-P		CRT-D	
	Before $\bar{x}$ (sd)	After $\bar{x}$ (sd)	Before $\bar{x}$ (sd)	After $\bar{x}$ (sd)
EDD	71,60 (6,00)	64,67 (4,95)	73,58 (4,78)	66,05 (3,88)
ESD	61,77 (5,91)	57,17 (4,31)	62,95 (2,69)	58,53 (1,77)

Abbreviations: EDD — end-diastolic diameter of left ventricle, ESD — end-systolic diameter of left ventricle.

significant improvement in NYHA functional class was observed.

Analysis of the parameters presented in Table 4 showed that all echocardiographic parameters and indicators of life quality improved. LVEF and 6MWD were significantly increased, while other parameters of interest were significantly lower after CRT-P and CRT-D pacemaker implantation, p<0,001. Between observed groups we found no significant difference between observed parameters.

Significant decrease of end-diastolic and end-systolic diameters of left ventricle (EDD, ESD) was observed in both groups of patients, p<0,001 (Table 5). We found no significant difference between those parameters before and after the CRT pacemaker implantation in both groups. Not only functional but structural improvement of left ventricle was determined.

In the group of patients with CRT-P pacemaker 4 patients (6,7%) died during the period of 1 year of follow-up. In patients with CRT-D pacemaker implanted 2 patients (5,3%) died during the same period, however no statistical difference in mortality rate was observed in 2 examined groups. Patients with CRT-P had longer survival period (389,4 days) than those in CRT-D group (349,5 days), but with no statistical difference (Figure 1).

Discussion

In the early period of use of resynchronization therapy some authors claimed that this therapy was accepted without necessary randomized clinical trials which could show its benefit. However, nowadays we have more than 4000 patients included in trials of CRT.

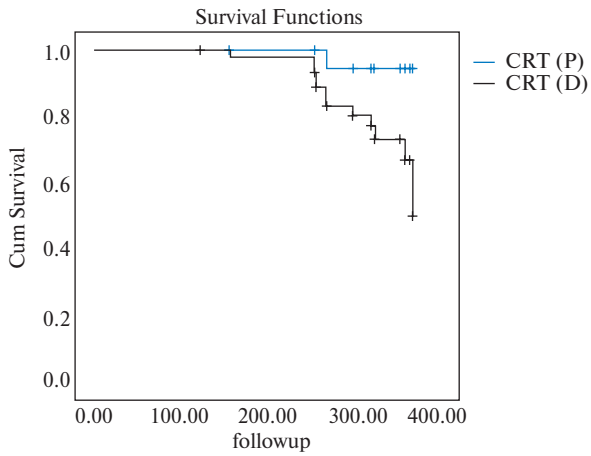

Figure 1. Kaplan Meier survival curve in patients with different therapy modalities.

Inclusion criteria for clinical CRT studies are relatively strict such as having NYHA class 3/4, long duration of QRS complex, sinus rhythm and bi-ventricular pacing configuration.

Since CRT-D devices became widely available, patients with ICD labelled devices are included in trials and era of examinations of safety and efficiency of CRT-D and effects of CRT on development of potentially malignant ventricular arrhythmias started.

The design of the MIRACLE-ICD study was nearly identical to that of the MIRACLE trial. MIRACLE-ICD was a prospective, multicenter, randomized, double blind clinical trial intended to assess the safety and clinical efficacy of another combined ICD and cardiac resynchronization system in patients with dilated cardiomyopathy (LVEF<35%, LV EDD>55 mm), NYHA class 3 or 4, inter-ventricular conduction delay (IVCD) (QRS>130 ms), and an indication for an ICD. Primary and secondary efficacy measures were essentially the same as those evaluated in the MIRACLE trial but also included measures of ICD function (including the efficacy of antitachycardia therapy with biventricular pacing). In a cohort of 369 patients randomly assigned to ICD on and CRT off (n=182), or ICD on and CRT activated (n=187), those with the CRT activated showed significant improvements in quality of life, NYHA class, exercise capacity and composite clinical response compared with control subjects. The magnitude of improvement was comparable to that seen in the MIRACLE trial, suggesting that heart failure patients with an ICD indication benefit as much from CRT as those patients without an indication for an ICD [6]. Of interest, the efficacy of biventricular anti-tachycardia pacing was significantly greater than that seen in the univentricular (RV) configuration. This observation suggests another potential benefit of a combined ICD plus resynchronization device in such patients. In our study benefit and efficiency of CRT-D was clearly demonstrated ant it was comparable with that achieved in the CRT-P group.

The COMPANION trial was a multicenter, prospective, randomized, controlled trial that assessed optimal pharmacological therapy alone or with CRT using a pacemaker or a combination pacemaker-defibrillator in patients with dilated cardiomyopathy, IVCD, NYHA 3 or 4

functional class, and no indication for a device. The trial design called for random assignment of 2200 patients into one of three treatment groups: I (440 patients) receiving optimal medical care only, group II (880 patients) receiving optimal medical care and biventricular pacing alone, and group III (880 patients) receiving optimal medical care and CRT-ICD device. The trial was terminated prematurely after assignment of 1520 patients at the recommendation of an independent data and safety monitoring board. Over 12–16 months, the primary composite end-point of all-cause death or any hospitalization was decreased by approximately 20% with use of either device therapy compared with pharmacologic therapy alone. Further, a pacing only resynchronization device reduced the risk of death from any cause by 24% (p=0,06) and a resynchronization device with ICD reduced the risk by 36% (p=0,003) [7]. In our study mortality rate was lower in CRT-D group (not significantly, though).

Five randomized controlled trials met the inclusion criteria, recruiting a total of 3434 participants. Four studies compared CRT-P with Optimal Pharmacologic Therapy (OPT), two studies compared CRT-D with OPT and one study compared CRT-P with CRT-D. In all trials, patients with an indication for an ICD were excluded. Studies were of good to moderate quality. Two trials reported that allocation to treatment group had been concealed (CARE-HF and MIRACLE), blinding occurred in three trials (CONTAK-CD, MUSTIC-SR and MIRACLE) and intention-to-treat was used in four analyses (CARE-HF, COMPANION, MIRACLE and MUSTIC-SR) [8–11]. In our study only patients who fulfilled criteria for an ICD also got the CRT-D pacemaker according to the guidelines of European Society of Cardiology [12].

Conclusion

Meta-analyses showed that both CRT-P and CRT-D devices significantly reduced the mortality and level of heart failure hospitalisations. They also improved health-related quality of life in people with New York Heart Association (NYHA) class 3 and 4 heart failure and evidence of dyssynchrony (QRS interval >120 ms) who were also receiving optimal drug treatment. A single direct comparison (COMPANION) indicated that the effects of the CRT-P and CRT-D were similar, with the exception of an additional reduction in sudden cardiac death, associated with CRT-D [7]. On average, implanting a CRT device in 13 people would result in the saving of one additional life over a 3-year period, compared with optimal drug treatment [13].

After use of resynchronization therapy as CRT-P or CRT-D option we noticed significant improvement in echocardiographic parameters (increase in LVEF, decrease in end-diastolic and end-systolic diameters of left ventricle, pre-ejection intervals of left and right ventricles) decrease in NYHA functional class. There was no significant difference in those parameters between two observed groups of patients including the number of re-hospitalizations and mortality rate.

Cardiac resynchronization therapy rapidly advanced as a result of data gained through clinical trials. Clinical studies resulted in general acceptance of CRT for patients with standard criteria. The benefit of CRT alongside with the optimal drug therapy is clearly demonstrated in patients with heart failure and asynchrony. CRT showed paramount improvements in clinical symptoms and disease progression. Nevertheless we do not have the perfect criteria for selection of patients and their follow up after the device implantation. In patients with the rhythm disturbances CRT-D option is the right choice only if the patient has the indications for resynchronization therapy as well. This choice nowadays depends on clinical judgment of the operator more than on strict protocols and guidelines.

It is certain that in the future we will have wider indication area for this type of therapy and more sophisticated selection criteria for patients in order to gain better and adequate therapeutic response.

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