Original article

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RESYNCHRONIZATION THERAPY IN PATIENTS WITH HEART FAILURE

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Prognosis in heart failure (HF) is poor and mortality widely ranges - 15-60% per year. Cardiac resynchronization therapy (CRT) is a therapeutic concept for patients who have NYHA III or IV class, LVEF ≤ 35%, left bundle branch block with wide QRS ≥ 120ms and ventricular dyssynchrony on optimal medical therapy.

The aim of the study was to determine the effects of resynchronization therapy in patients with moderate to severe HF.

In our study, 140 patients with HF were treated with different modalities of therapy in the Clinical Centre Niš. The first group of patients received CRT, and the second, control group were HF patients without echo criteria for CRT. In the control group, 36 patients received an implantable cardioverter-defibrillator (ICD).

Results of the study showed that resynchronization therapy in patients with HF improves different parameters: clinical symptoms, echocardiographic parameters, decreases QRS duration, increases 6-minute walk test distance and decreases mortality rate.

The benefit of cardiac resynchronization therapy in combination with optimal medical therapy is proven to be beneficial in patients with HF and asynchrony. CRT improved clinical symptoms of heart failure and had influence on disease progression. *Acta Medica Medianae 2013;52(2):10-14.*

Key words: *heart failure, resynchronization therapy, mortality*

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Introduction

Heart failure is a clinical syndrome which is caused by a large number of cardiac diseases and it is characterized by inability of the heart to pump the adequate amount of blood that could satisfy the body's needs for oxygen in proportion to physical activity (at rest and effort), provided that the venous blood flow to the heart is normal. Mortality from heart failure is high and ranges from 15% -60%, and the economic impact of morbidity is important (1). Prognosis of heart failure is poor and mortality in different groups of patients ranges from 15%-60% per year. Prognosis depends on the cardiac status. Left ventricular ejection fraction (LVEF), left ventricular volumes at the end of systole and diastole, and strain (stress) of the left ventricle were good predictors of mortality and survival. Thus, the mortality of patients after myocardial infarction with ejection fraction below 25% was 50% during one year, while in patients with LVEF around 55% was less than 10% during one year, which indicates that the prognosis depends on the amount of saved (intact) heart muscle (2).

Treatment of heart failure is diverse and it includes (3):

- Non-pharmacological therapy (general instructions and safety, controlled physical activity and training);
- Drug therapy (ACE inhibitors, diuretics, B-blockers, digitalis, vasodilators, anticoagulation, antiarrhythmic drugs);
- Surgical treatment and medical devices (resynchronization therapy, CABG, etc.).

Resynchronization therapy (CRT) is recommended to patients with advanced heart failure (NYHA functional class III-IV), LVEF ≤35%, with left bundle branch block (QRS≥120 ms) and echocardiographicaly proven asynchrony who are on optimal medical therapy for one year minimum (4). CRT has been approved by the U.S. FDA in 2001. Large multicenter, randomized studies have shown that the procedure is safe and effective method of treatment and that leads to improvement in clinical symptoms, functional status and exercise tolerance (4).

There are four levels of cardiac asynchrony in patients with heart failure - atrioventricular, interventricular, intraventricular and intramural. CRT improves asynchrony of heart contractions at all four levels.

Duration of the QRS complex is used to assess ventricular asynchrony ant thus for the selection of patients for CRT. It is also used to assess the effectiveness of therapy after a narrowing of the QRS complex using the biventricular pacemaker which simultaneously activates both ventricles and helps to achieve resynchronization on ventricular level (5).

Aim

The aim of the study was to investigate the effects of CRT therapy in patients with heart failure.

Material and methods

This study included 140 patients with heart failure treated at the Clinic for Cardiovascular Diseases Niš in the period from September 2008 to October 2010. The study group (n=56) comprised patients with heart failure and CRT therapy (NYHA functional class III-IV; LVEF ≤35%; QRS ≥120 ms, dilated left ventricle >55mm) (6), on the optimal medicament therapy for heart failure with echocardiographic criteria that met criteria for response to CRT therapy (preejection interval of the left ventricle greater than 140 msec, difference between preejection intervals of left and right ventricle greater than 40 msec, SPWMD-systolic posterior wall motion delay >135msec) (7). Control group (n=84) comprised patients with heart failure (NYHA III-IV, LVEF ≤35%, QRS ≤120 ms, on the optimal medical therapy) who did not fulfill echo-cardiographic criteria for CRT – the so-called "non-responders". Within the control group, 36 patients received ICD since they met criteria for its implantation (primary prevention after myocardial infarction, minimum 40 days after the event with left ventricular dysfunction or LVEF ≤35%; patients who survived ventricular fibrillation-VF or hemodynamically unstable ventricular tachycardia-VT; patients with non-ischemic dilated cardio-myopathy and significant left ventricular dysfunction with sustained VT, and the life expectancy of at least one year) (8). In the control group, there were 44 patients with heart failure on the optimal medical therapy alone: B-blocker, ACE inhibitor, diuretic, digitalis, anti-arrhythmic drugs (patients who refused ICD implantation in the primary prevention). In all patients prior to CRT implantation we performed a 12-lead ECG, echocardiography, 6-minute walk test using a pedometer, physical examination and detailed medical history including used medication. One year after the device implantation, we performed ECG, echocardiography, 6-minute walk test, physical examination and determined the number of hospitalizations due to heart failure symptoms.

Results

In the group of patients with CRT we found statistically significantly lower values of all parameters after implantation of a CRT-P(D) pacemaker compared to the same parameters before installation (QRS: 149.23ms vs. 125.33ms; LVEF: 24.63% vs. 36.27%; 6-minute walking distance: 220.83m vs. 296m; end diastolic volume-EDV: 283.87ml vs. 167.43ml; end systolic volume-ESV: 185.5ml vs. 112.8ml, p<0.001) (Table 1). In the group of patients with implanted cardioverter defibrillator (ICD) there was a statistically significant increase of end-systolic volume-ESV, from 93.68 to 98.05 (t=4.340, p<0.001) and an increase in left ventricle pre-ejection period (LVPEP), from 125.89 to 128.95 (t=3.550, p=0.002). Patients with heart failure who were on medical therapy alone showed a significant reduction in parameters: LVEF (31.82 vs. 30.41; t=2.663, p=0.015), 6 minute walk distance (215.14 vs. 202.27; t=3.199, p=0.004). In the same group there was an increase in end-systolic volume (91.59 ml vs. 96.41 ml; t=2.704, p=0.013) and LVPEP (123.64 vs. 127.45; t=2.489, p=0.021).

Discussion

During the early application of CRT, some authors have argued that CRT was accepted without having the necessary data from randomized clinical trials which would support this new therapy. However, most would agree that any lack of data has now been overcome. Today, more than 4.000 patients are included in randomized clinical trials with CRT.

Prolongation of life and reduction in hospitalizations after CRT were compared with other pharmacological and non-pharmacological approaches in patients with advanced heart failure. CRT showed significant improvements in above-mentioned parameters and consequently gave a favourable cost-effectiveness ratio. A preliminary economic analysis of the COMPANION study leads to the conclusion that this procedure is both effective and cost beneficial. Slightly higher price of CRT device implantation is mitigated by a significant reduction in the number of hospitalizations in the first year after its use (9).

PATH-CHF trial was a randomized, controlled trial designed in order to assess the acute haemodynamic effects and long-term evaluation of the clinical benefits of RV, LV and biventricular pacing in patients with moderate to severe heart failure and intra-ventricular conduction block (10). The obtained results were encouraging, with a slight improvement in all primary and secondary endpoints during pacing.

Table 1. Comparative analysis of the parameters (QRS width, EF, 6-minute walk test, EDV, ESV, PEPLV, PEPRV, SPWMD) in patients with heart failure who underwent different treatments of heart failure

	CRT-P(D)		ICD		Drug therapy	
	Before $\bar{x}$ (sd)	After $\bar{x}$ (sd)	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)*	113.16(5.58)	113.95(5.91)^{ns}	103.86(9.37)	104.32(8.90)^{ns}
EF(%)	24.63(5.08)	36.27(8.37)*	27.16(6.59)	27.00(5.89)^{ns}	31.82(6.26)	30.41(5.75)‡
6min(m)	220.83(38.53)	296.00(67.63)*	209.89(28.18)	213.11(32.62)^{s}	215.14(28.73)	202.27(30.22)†
EDV(ml)	283.87(55.81)	167.43(44.38)*	166.37(24.40)	164.11(23.97)^{ns}	156.36(33.13)	157.45(34.03)^{ns}
ESV(ml)	185.50(50.63)	112.80(22.33)*	93.68(21.19)	98.05(21.43)*	91.59(14.61)	96.41(18.67) ‡

MUSTIC study was also a randomized evaluation of CRT which included 67 patients (11). The primary endpoint was a change in 6-minute walk distance, but it also included secondary goals such as achieved changes in the quality of life, NYHA class, peak Vo2, hospital re-admissions, worsening of heart failure symptoms and overall mortality. In patients with CRT they found a significant improvement of both primary and secondary endpoints. In our study we observed that 6-minute walk distance before applying CRT (D) pacemaker was 220.83m, and after the follow-up period of one year it significantly increased to approximately 296m ($p<0.001$).

MIRACLE study was designed to evaluate the results of previous studies with CRT and for additional assessment of therapeutic efficacy and mechanisms of benefit from CRT (12). MIRACLE trial began in 1998 and was completed in 2000. Patients were randomly subjected to CRT, and compared with the control group they showed a significant improvement in the quality of life indicating an overall improvement in clinical status. In addition, in relation to the number of patients in the control group, fewer patients with the CRT required hospitalization (8% vs. 15%) and intravenous drug therapy (7% vs. 15%) in the treatment of heart failure deterioration (both $p<.05$). Patients in CRT group, compared with the patients in control group, had a lesser number of hospitalizations by 50%, and therefore a significant reduction of in-hospital stay, which resulted in a decrease of the total number of days spent in the hospital by 77% during six months.

Aims of the MIRACLE-ICD study were almost identical to the goals of MIRACLE trial (13). MIRACLE-ICD was a prospective, multicenter, randomized double-blind study whose objective was to assess the safety and clinical efficacy of combined ICD with CRT system in patients with dilated cardiomyopathy. The included 369 patients were randomly assigned to ICD and CRT off ($n=182$) or on ICD and CRT activated ($n=187$) groups. Patients with activated CRT showed a significant improvement in quality of life, NYHA functional class, exercise testing and clinical response compared to control subjects. The scope of improvement could be compared with the improvement that showed MIRACLE trial, suggesting that patients with heart failure with an indication for ICD have as much benefit from CRT as well as patients without ICD indication. Of importance is that the efficiency of biventricular anti-tachycardia pacing is significantly higher than with single ventricular (RV) configuration. This observation suggests another potential benefit of a combination of ICD with CRT in these patients. Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial was a clinical trial that was conducted to compare the optimal pharmacological therapy alone or with CRT in patients with dilated cardiomyopathy, intraventricular conduction delay (IVCD) in NYHA III-IV functional class (14). Over a period of 12-16 months, the overall mortality or hospitalization for any reason, the use of any of the "device" therapy was reduced by around 20% compared to the use of a pharmacological therapy alone. In addition, "pacing only" cardiac resynchronization device reduced the risk of death from any cause by 24%, and cardiac resynchronization device with ICD-TV reduced the risk by 36% ($p=0.003$). The reason for the implementation of the ICD to CRT device is based on the assumption that the prevention of sudden cardiac death in patients with heart failure can reduce mortality more effectively than the CRT alone.

Conclusion

Resynchronization therapy in patients with heart failure leads to improvement of clinical parameters: it reduces clinical symptoms (lower NYHA class) and width of the QRS complex, improves echocardiographic parameters (LVEF increase, systolic and end-diastolic volumes and diameters decrease, the preejection intervals shortens, mitral regurgitation is lesser), increases the 6-minute walk distance, diminishes the number of hospitalizations due to heart failure symptoms and reduces mortality in patients with heart failure. The benefit of CRT in combination with optimal medical therapy is proven and indisputable in patients with heart failure and asynchrony. CRT showed a considerable symptomatic improvement in patients as well as strong positive effects on disease progression. It is likely that in the future indications for this therapy will expand since the selection of patients and methods are in advance in order to achieve a better and more adequate therapeutic response.

QRS duration remains the most practical and the most valid parameter for patient selection. The predictive value of QRS duration comes from its strong correlation with the mechanical asynchrony. However, echocardiography is now unavoidable in the assessment of mechanical asynchrony. The biggest problem remains the choice of echocardiographic parameters which could predict clinical benefit in patients with the CRT and which will distinguish the group of patients in whom the success cannot overcome the risks and complications of the implantation.

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RESINHRONIZACIONA TERAPIJA KOD GRUPA BOLESNIKA SA SRČANOM INSUFICIJENCIJOM

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Prognoza srčane insuficijencije je loša. Mortalitet se u različitim grupama bolesnika kreće od 15%-60% za godinu dana. Resinhronizaciona terapija (CRT) srčane insuficijencije podrazumeva lečenje uznapredovale srčane slabosti bolesnika koji pripadaju NYHA III-IV grupi, EF ≤ 35%, sa blokom leve grane (QRS kompleks ≥ 120ms) i ehokardiografski dokazanom asinhronijom, koji su unazad godinu dana na optimalnoj medikamentoznoj terapiji. Cilj istraživanja bio je ispitivanje efekata resinhronizacione terapije kod bolesnika sa srčanom insuficijencijom. U ispitivanju je učestvovalo 140 bolesnika sa srčanom insuficijencijom lečenih na Klinici za kardiovaskularne bolesti u Nišu u periodu od septembra 2008. do oktobra 2010. godine. Ispitivanu grupu (n=56) činili su bolesnici sa srčanom insuficijencijom i sa CRT terapijom. Kontrolnu grupu (n=84) činili su bolesnici sa srčanom insuficijencijom koji ne ispunjavaju ehokardiografske kriterijume za CRT, tzv. eho-kardiografski non-responderi. Unutar kontrolne grupe, 36 bolesnika je dobilo ICD terapiju na osnovu ispunjenih kriterijuma za ugradnju ICD. Rezultati su pokazali da resinhronizaciona terapija kod bolesnika sa srčanom insuficijencijom dovodi do poboljšanja kliničkih parametara: dovodi do poboljšanja kliničkih simptoma, smanjuje širinu QRS kompleksa, do poboljšanja ehokardiografskih parametara, povećava distancu pri šetanju u trajanju od 6 minuta, smanjuje broj hospitalizacija usled simptoma srčane insuficijencije, smanjuje mortalitet bolesnika sa srčanom insuficijencijom.

Korist srčane resinhronizacione terapije, uz optimalnu medikamentoznu terapiju, dokazana je i nesporna kod bolesnika sa srčanom insuficijencijom i asinhronijom. CRT je pokazala velika simptomatska poboljšanja kao i uticaj na progresiju bolesti. *Acta Medica Medianae 2013;52(2):10-14.*

Ključne reči: *srčana insuficijencija, resinhronizaciona terapija, mortalitet*

