Late best response to cardiac resynchronization therapy is associated with better survival of patients with congestive heart failure

Soldatova AM, Kuznetsov VA, Krinochkin DV, Enina TN, Gorodniuk IG

Soldatova AM, Kuznetsov VA, Krinochkin DV, et al. Late best response to cardiac resynchronization therapy is associated with better survival of patients with congestive heart failure. Curr Res Cardiol 2017;4(4):58-60.

AIM: The aim was to evaluate clinical, morphological, functional features and mortality in patients with congestive heart failure (CHF) and different time of the best response to cardiac resynchronization therapy (CRT).

MATERIALS AND METHODS: 122 patients (82.8% men) with NYHA functional class III-IV (mean age 54.8 ± 9.6 years) were enrolled. At baseline, 1, 3 months and each 6 months after implantation we evaluated clinical and echocardiographic parameters. In 28 patients the best decrease of left ventricular end-systolic volume (LVESV) was achieved up to 3 months (1.1 ± 0.9 months, I group–early response) and in 94 patients–after 3 months (22.6 ± 14.9 months, II group–late response).

RESULTS: At baseline groups did not differ in main clinical characteristics, the proportion of atrial fibrillation, the presence of left bundle-branch block (LBBB), width of the QRS complex and parameters of mechanical dyssynchrony. Level of left ventricular ejection fraction (LVEF) and left ventricular volumes were comparable between groups. In the II group responders (decrease in LVESV ≥ 15%) were identified more frequently (90.4% vs. 60.7%; p=0.001), all patients with decrease of LVESV ≥ 30% (super responders) had late response.

During follow-up period (33.2 ± 16.7 months) increase in LVEF and decrease in LVESV were more evident in patients with late response.

In Kaplan-Meier analysis mortality in II group was significantly lower (3.2% vs 28.6%; p=0.001). Cox regression showed that LVESV (HR 1.012; 95% CI 1.004–1.021; P=0.005) and the time of response (HR 0.131; 95% CI 0.032–0.530; P=0.004) were associated with long-term mortality.

CONCLUSION: Patients with early response to CRT show significantly lower improvement in LVEF and LVESV compared to patients with late CRT response. Super respone to CRT in associated with late functional improvement. Early response and greater LVESV are associated with higher mortality rate.

Key Words: *Cardiac resynchronization therapy; Congestive heart failure; Response*

Cardiac resynchronization therapy (CRT) is an effective treatment option for patients with congestive heart failure (CHF). Several large multicentre clinical trials have confirmed that CRT improves heart function, exercise capacity, and quality of life, reduces mortality and hospitalization, and can improve the prognosis of patients with CHF (1). Accumulated experience of implanting CRT devices suggests that the response to CRT and the timing of the response vary between individual patients. Some patients show an early response to CRT with significant improvements in clinical and functional parameters within the first 3 months after device implantation (2). By contrast, other patients show later responses (3). According to Prinzen et al. an early response to CRT is associated with improved long-term cardiac remodelling (4). However, there is little information about the relationship between the timing of the response to CRT and survival in patients with CHF.

AIM

The aim of the study was to evaluate the clinical, morphological, and functional features, and the mortality rate in patients with CHF according to the timing of their response to CRT.

MATERIALS AND METHODS

The study enrolled 122 patients (82.8% men) with CHF corresponding to New York Heart Association (NYHA) functional class II–IV. Enrollment began in January 2005 and ended in December 2012. Their mean ± standard deviation (SD) age was 54.8 ± 9.6 years. The main criteria for CRT were: 1. NYHA functional class II–IV; 2. Left ventricular ejection fraction (LVEF) <35%; 3. Interventricular and/or intraventricular dyssynchrony on echocardiography. QRS complex width >120 ms, or QRS<120 ms + 3 parameters of mechanical dyssynchrony (5). All of the patients received medical treatment in accordance with current guidelines (5,6). The mean ± SD duration of follow-up was 33.2 ± 16.7 months. We evaluated the patients' clinical and echocardiographic parameters at baseline, and at 1 month, 3 months, and every 6 months after implantation. We carried out electrocardiography and assessed NYHA functional class in a 6-min walk test. Standard echocardiography, including tissue Doppler imaging (TDI), was performed using a commercially available system (Philips IE 33; Philips, USA). Patients with QRS<120 ms were required to meet at least three additional criteria of mechanical dyssynchrony: septal to posterior wall motion delay (SPWMD) >130 ms, left-ventricular pre-ejection period (LVPEP) >140 ms, interventricular mechanical delay (IVMD)>40 ms, intraventricular delay assessed by TDI>60 ms, interventricular delay by TDI >102 ms (7,8).

Patients were classified according to the change in left ventricular end-systolic volume (LVESV) as responders (reduction in LVESV of >15%) or super-responders (reduction in LVESV of >30%) (9,10). The best response (greatest recorded reduction) in LVESV was observed within 3 months after CRT in 28 patients (early best response group; mean ± SD: 1.1 ± 0.9 months) and more than 3 months after CRT in 94 patients (late best response group; mean ± SD: 22.6 ± 14.9 months).

Statistical analyses were performed using SPSS for Windows version 21.0 (SPSS Inc., Chicago, IL, USA). Results are expressed as the mean ± SD. Continuous variables were compared using Student's t test for normally distributed variables or the Mann–Whitney test for non-normally distributed variables. The χ^2 or Fisher's exact test were used to compare categorical variables. Differences in continuous variables between the baseline and follow-up visits were compared using paired t tests. The Kaplan–Meier method was used to estimate event-free survival and differences between the curves were compared using the log-rank test. Variables with P<0.05 in the univariate analysis were incorporated into a multivariable Cox proportional hazards model to determine predictors of survival with the hazard ratio (HR) and 95% confidence interval (CI). Values of P<0.05 were considered statistically significant.

Tyumen Cardiology Research Center, Tomsk National Research Medical Center, Russian Academy of Science, Tomsk, Russia

Correspondence: Dr Anna Soldatova, Tyumen Cardiology Research Center, Tomsk National Research Medical Center, Russian Academy of Science; Melnikaite 111, Russia, Telephone 8-922-267-77-78, email amsoldatova@mail.ru

Received: August 22, 2017, Accepted: November 01, 2017, Published: November 03, 2017

RESULTS

At baseline, both groups were similar in terms of their clinical characteristics, the proportion of patients with atrial fibrillation (AF), LVEF, width of the QRS complex, and the presence of left bundle-branch block (LBBB) (Table 1).

TABLE 1

Baseline clinical and functional characteristics of study participants (n=122)

Parameter	Group I (n=28)	Group II (n=94)	p I-II
Age, (years)	54.4 ± 13.0	54.9 ± 8.4	NS
Men, (%)	92.9	79.8	NS
Coronary artery disease, (%)	46.4	61.7	NS
NYHA functional class	2.9 ± 0.6	2.7 ± 0.7	NS
6-minute walk distance test, (м)	277.9 ± 93.6	307.1 ± 101.9	NS
Left bundle branch block, (%)	60.7	59.6	NS
Atrial fibrillation, (%)	35.7	37.2	NS
Miocardial infarction, (%)	35.7	37.2	NS
LVEDV, (ml)	252.6 ± 76.7	230.5 ± 48.7	NS
LVESV, (ml)	180.1 ± 63.5	160.2 ± 42.7	NS
LVEF, (%)	29.5 ± 4.7	31.1 ± 5.7	NS
QRS, (ms)	141.7 ± 38.6	142.3 ± 38.9	NS
CRT-D, (%)	60.7	66	NS
Responders/non-responders, (%)	60.7/39.3	90.4/9.6	0,001
Super-responders, (%)	0	56.4	<0,001
Mortality, (%)	28.6	3.2	<0,001
Time of the best response, (months)	1.1 ± 0.9	22.6 ± 14.9	<0,001
Septal to lateral wall delay (M-mode, ms)	100.8 ± 50.7	131.9 ± 75.9	NS
Left ventricular pre-ejection period, (ms)	133.5 ± 22.8	143.9 ± 40.8	NS
Interventricular mechanical delay, (ms)	36.5 ± 22.8	52.2 ± 33.8	NS
Intraventricular delay by TDI, (ms)	57.6 ± 31.7	77.1 ± 57.9	NS
Interventricular delay by TDI, (ms)	76.8 ± 35.7	87.2 ± 49.8	NS

M ± SD: Mean Standard Deviation; NYHA: New York Heart Association; LVEF: Left Ventricular Ejection Fraction; LVESV: Left Ventricular End-systolic Volume; LVEDV: Left Ventricular End-diastolic Volume; CRT-D: Cardiac Resynchronization Therapy Defibrillator; TDI: Tissue Doppler Imaging; NS: Non-significant.

The proportion of responders (i.e. patients with a decrease in LVESV ≥ 15%) was significantly greater in the late reduction group than in the early best response group (90.4% vs. 60.7%; P=0.001). All patients classified as super-responders (i.e. reduction in LVESV of ≥ 30%) were in the late best response group (Table 1).

During the follow-up period, both groups experienced a significant reduction in LVESV and an increase in LVEF. However, these changes were significantly greater in the late best response group (Table 2).

TABLE 2

Functional parameters at follow-up (n=122)

Parameter	Group I (n=28)	Group II (n=94)	p I-II
6 MVD, (m)	375.1 ± 72.4	371.2 ± 81.3	NS
▲ LVEF, (%)	22.7 ± 14.6	39.5 ± 27.6	0.003
▲ LVESV, (%)	19.3 ± 11.4	34.3 ± 15.9	<0.001
LVEDV, (ml)	224.5 ± 72.8	181.9 ± 47.7	<0.001
LVESV, (ml)	146.2 ± 56.3	105.6 ± 39.3	<0.001
LVEF, (%)	36.0 ± 5.9	42.8 ± 8.9	<0.001

M ± SD: Mean Standard Deviation; 6 MVD: 6 Minute Walk Distance; LVEF: Left Ventricular Ejection Fraction; LVESV: Left Ventricular End-systolic Volume; LVEDV: Left Ventricular End-diastolic Volume

The survival rates in the early and late best response groups were 74.1% and 96.8%, respectively (log-rank test P < 0.001). The Kaplan–Meier plots are shown in Figure 1.

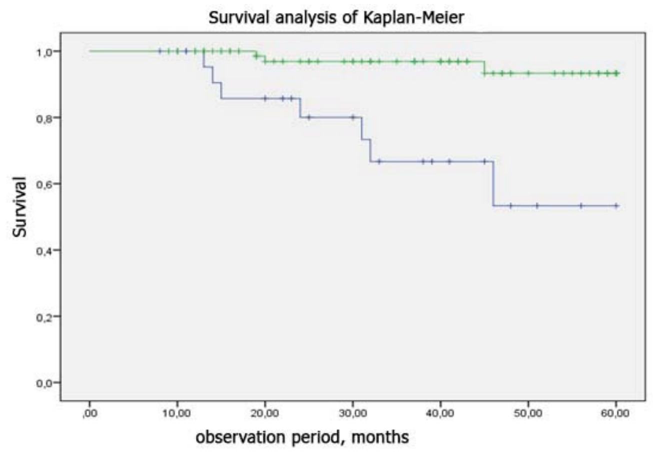

Figure 1) *Survival in patients with early and late best response to CRT*

Multivariable Cox regression showed that LVESV (HR 1.012; 95% CI 1.004–1.021; P=0.005) and the timing of the best response (HR 0.131; 95% CI 0.032–0.530; P=0.004) were significantly and independently associated with long-term mortality.

DISCUSSION

CRT was recently introduced as a new treatment modality for patients with major CHF. Randomized controlled trials have demonstrated that CRT is associated with reductions in CHF symptoms, CHF-related hospitalization, and all-cause mortality (1,5). The impact of CRT on cardiac remodelling varies among patients and the underlying mechanism is unclear. According to some authors, one of the fundamental mechanisms involves elimination of electrical dyssynchrony (i.e. the QRS complex) (11). In the current guidelines, the width of the QRS complex and the presence of LBBB are criteria for CRT implantation (1,6,12). Prior studies showed that patients with a wide QRS complex and LBBB had better clinical and functional parameters and a greater increase in LVEF than in patients with a narrow QRS complex and patients without LBBB (11). Other studies have shown that the positive effects of CRT are related to the elimination of mechanical dyssynchrony, as assessed by echocardiography and that mechanical dyssynchrony parameters can be used to select candidate patients for CRT (12,13). Recent studies have shown that there is a high prevalence of left ventricular mechanidcal dyssynchrony in patient with narrow QRS and few trials have shown the benefit of CRT in these patients (14,15). Published in 2005 results of Care-HF study have shown that CRT is an effective therapy for patients with cardiac dyssynchrony and QRS width 120-149 ms (16). Meta-analysis on effects of CRT in patients with narrow QRS and baseline mechanical asynchrony published by Jeevanantham et al. in 2008 demonstrated significant reduction in NYHA class, improvement in LVEF during follow-up (17). In our study, the two groups of patients divided according to the timing of their best response to CRT were similar in terms of the width of the QRS complex, the presence of LBBB, and mechanical dyssynchrony parameters. Considering these findings, we suspect that several different mechanisms might mediate the positive effect of CRT, and that the mechanism might differ between clinically similar groups.

Long-term experience of CRT implantation suggests that approximately one-third of patients do not benefit from this treatment. These patients, termed non-responders, have worse prognosis than responders and super-responders. Our study yielded similar results. The late best response group, which included significantly greater proportions of responders and super-responders, showed better improvements in LVEF and LVESV, and had a higher survival rate than the early best response group. According to the CARE-HF study, the greater reduction in mortality rate in patients with a late response is only apparent more than 12 months after CRT (18), and this was also demonstrated in our study. At the end of the observation period, the mortality rate was significantly lower in patients with a late best response. Cox regression showed that LVESV and the timing of the best response were associated with long-term mortality.

A reduction in LVESV of ≥ 15% is a standardized criterion for assessing the response to CRT. However, there is no consensus regarding the timing of evaluating the response in the observation period. Most studies assessed the echocardiographic changes within 12 months after implantation (8,9,13). In two-thirds of patients in our study, the best improvements in LVESV and

LVEF were observed more than 3 months after CRT, and these changes were significantly greater than those in patients whose best response was observed within 3 months after CRT. It should be noted that 60% of patients with good CRT response (decrease of LVESV ≥ 15%) who demonstrated late best response did not experience improvements in LVESV or LVEF within the first 12 months after CRT.

The psychological aspect of our results is very important. Physicians and patients usually expect for a quick initial response to CRT and functional improvements, even during the first days. It seems that these rapid effects are associated with better responses and better survival to CRT. But in recent studies Cleland et al. reported that clinical outcome and clinical response to CRT are not the same (19,20). The effects of CRT, in terms of the clinical and functional improvements, are not always associated with a survival benefit (19). Our study demonstrated that long-term survival was associated with the timing of the best response and with reverse remodelling after CRT. It is important to note that the early best response group was associated with smaller clinical and functional improvements and with worse long-term survival than the late best response group. Thus, early clinical and functional improvement should not be used as a marker for the efficacy of CRT in terms of long-term mortality.

LIMITATIONS

The limitation of our study is that we enrolled patients with QRS complex width >120 ms, or QRS≤120 ms + 3 parameters of mechanical dyssynchrony. The enrolment began in January 2005 and ended in December 2010 and in that period QRS>120 ms was one of the mail criteria for CRT implantation (5). As recent studies have shown that there is a high prevalence of left ventricular mechanidcal dyssynchrony in patient with narrow QRS and few trials have shown the benefit of CRT in these patients (14-17). It should be mentioned that from 2005 till the last update of clinical recommendations in 2013 in our clinic we used St. Mary's Hospital and Imperial College (London) protocol for CRT implantation which included parameters of mechanical dyssynchrony assessed by TDI (20,21).

CONCLUSION

Patients with a late best response to CRT were characterized by higher rates of responders and super-responders and better improvements in LVESV, LVEDV, and LVEF compared with patients with an early best response. Early best response and greater LVESV are associated with higher long-term mortality rates. The timing of the best response to CRT and survival during the observation period were not associated with the width of the QRS complex, the presence of LBBB, and mechanical dyssynchrony.

CLINICAL IMPLICATION

In real clinical practice early clinical and functional improvement should not be used as a marker for the efficacy of CRT in terms of long-term mortality. In patients with early response without further improvement of functional parameters the clinical course should be carefully observed. Absence of functional improvement during the first year after implantation necessitate careful monitoring and optimization of AV- and VV- delays of CRT-system to achieve better results.

DISCLOSURE

The authors have nothing to disclose.

REFERENCES

1. Priori SG, Blomström-Lundqvist C, Mazzanti A, et al. ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC) Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). Europace 2015;17(11):1601-87.
2. Kuznetsov VA, Melnikov NN, Krinochkin DV, et al. Acute hemodynamic effect of cardiac resynchronization therapy in patients with chronic heart failure. Vestnik Aritmologii 2013;74:50-4.
3. Van der Heijden AC, Hoke U, Thijssen J, et al. Long-term echocardiographic outcome in super-responders to cardiac resynchronization therapy and the association with mortality and defibrillator therapy. Am J Cardiol. 2016;118(8):1217-24.
4. Prinzen FW, Auricchio A. The "missing" link between acute hemodynamic effect and clinical response. J Cardiovasc Transl Res. 2012;5(2):188-95.
5. Belenkov YN, Vasyuk YA, Galjavich AS, et al. National recommendations of Chronic Heart Failure Society, Russian Society of Cardiology and Russian Scientific Medical Society of Physicians for diagnosis and treatment of Chronic Heart failure (second revision). Zhurnal Serdechnaya Nedostatochnost'. 2007;8(1):4-41.
6. El-Missiri AM. Echocardiographic assessment of left ventricular mechanical dyssynchrony–A practical approach. The Egypt Heart Journal. 2014;66(3):217-25.
7. Cazeau SJ, Daubert J, Tavazzi L, et al. Responders to cardiac resynchronisation therapy with narrow or intermediate QRS complexes identified by simple echocardiographic indices of dyssynchrony: The DESIRE study. Eur J Heart fail 2008;10:273-80.
8. Reant P, Zaroui A, Donal E, et al. Identification and characterization of super-responders after cardiac resynchronization therapy. Am J Cardiol 2010;105:1327-35.
9. Zhang Q, Zhou Y, Yu CM. Incidence, definition, diagnosis, and management of the cardiac resynchronization therapy nonresponder. Curr Opin Cardiol. 2015;30(1):40-9.
10. Steffel J, Ruschitzka F. Superresponse to cardiac resynchronization therapy. Circulation. 2014;130(1):87-90.
11. Mascioli G, Padelett L, Sassone B, et al. Electrocardiographic criteria of true left bundle branch block: A simple sign to predict a better clinical and instrumental response to CRT. PACE. 2012;35:927-34.
12. Ponikowski P, Voors AA, Anker SD, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016;37:2129-200.
13. Maréchaux S, Guiot A, Castel AL, et al. Relationship between two-dimensional speckle-tracking septal strain and response to cardiac resynchronization therapy in patients with left ventricular dysfunction and left bundle branch block: A prospective pilot study. J Am Soc Echocardiogr. 2014;27(5):501-11.
14. Yu CM, Chan YS, Zhang Q, et al. Benefits of cardiac resynchronization therapy for heart failure patients with narrow QRS complexes and coexisting systolic asynchrony by echocardiography. J Am Coll Cardiol. 2006;48:2251-7.
15. Bleeker GB, Holman ER, Steendijk P, et al. Cardiac resynchronization therapy in patients with a narrow QRS complex. J Am Coll Cardiol. 2006;48:2243-50.
16. Cleland JG, Daubert JC, Erdmann E, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. (CARE-HF). N Engl J Med. 2005;352:1539-49.
17. Jeevanantham V, Zareba W, Navaneethan S, et al. Meta-analysis on effects of cardiac resynchronization therapy in heart failure patients with narrow QRS complex. Cardiol J 2008;15(3):230-6.
18. Cleland JG, Freemantle N, Erdmann E, et al. Long-term mortality with cardiac resynchronization therapy in the Cardiac Resynchronization-Heart Failure (CARE-HF) trial. Eur J Heart Fail. 2012;14(6):628-34.
19. Cleland JGF, Ghio S. The determinants of clinical outcome and clinical response to CRT are not the same. Heart Failure Reviews. 2012;17(6):755-66.
20. Cleland JGF. How to assess new treatments for the management of heart failure: Composite scoring systems to assess the patients' clinical journey. Eur J Heart Fail. 2002;4(3):243-7.
21. Whinnett ZI, Davies JE, Lane RE, et al. Echocardiographic methods for selecting patients suitable for biventricular pacing therapy. Minerva Cardioangiol. 2005;53(3):211-20.