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DIFFERENT RESPONSE CRITERIA TO CARDIAC RESYNCHRONIZATION THERAPY IN PATIENTS WITH CONGESTIVE HEART FAILURE

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Aim. To investigate the agreement among different response criteria to cardiac resynchronization therapy (CRT) and long-term mortality in patients with congestive heart failure (CHF).

Methods. The study enrolled 141 patients (men 77.3%; women 22.7%) with CHF (65.2% ischemic and 34.8% non-ischemic etiology). Mean age was 58.6 [53.0;66.0] years. All patients had NYHA II-IV, left ventricular ejection fraction (LVEF) ≤35%; QRS ≥130 мs and/or left bundle branch block. Mean follow-up period was 45.0±34.2 months. Response to CRT was defined according to dynamics of NYHA functional class, LVEF, and left-ventricular end-systolic volume (LVESV).

Results. Moderate agreement was found among LVEF and LVESV (Cohen's k coefficient 0.591±0.068) while we did not find the agreement among echocardiographic criteria and NYHA. Long-term mortality had moderate negative correlation with LVESV (r=-0.486; p<0.001), weak negative correlation with LVEF (r=-0.297; p<0.001), no significant correlation with NYHA functional class was found (r=-0.102; p=0.298). The correlation among long-term mortality and LVESV was significantly stronger when compared with long-term mortality and NYHA correlation (p<0.001), and no significant differences were found when compared with long-term-mortality and LVEF correlation (p=0.086).

Conclusion. Agreement between different criteria to define response to CRT is poor. The strongest correlation with long-term mortality was found for LVESV. This inconsistency among different response criteria severely limits the ability to generalize results over multiple CRT studies.

Key words: survival; mortality; response criteria; cardiac resynchronization therapy; congestive heart failure; echocardiography

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Cardiac resynchronization therapy (CRT) is an effective treatment for patients with congestive heart failure (CHF) with reduced ejection fraction and prolonged QRS duration. Large multi-center clinical trials have confirmed that CRT can improve cardiac function, exercise capacity and quality of life in patients with CHF. CRT reduces mortality and hospitalization and can also improve the prognosis in CHF patients [1, 2]. About 30% patients do not respond adequately to CRT and search of new selection criteria and respond predictors is one of the most important questions of CRT implantation [3-7]. In most trials, prognostic models for CRT response were based on baseline clinical and functional parameters. Meanwhile, there is a lack of consensus on the definition of response to CRT and in what period after implantation it should be assessed. clinical and echocardiographic response criteria were used [8, 9].

A joint position statement from the Heart Failure Association (HFA), European Heart Rhythm Association (EHRA), and European Association of Cardiovascular Imaging (EACVI) of the European Society of Cardiology (ESC) calls to stop the current binary approach of CRT response and calls for the response to be individualized for every patient [10]**.** Thus, it worth to compare the agreement of different response criteria to CRT in real clinical practice, and to analyze the relationship between different response criteria and long-term mortality.

Aim. To investigate the agreement among different response criteria to CRT and long-term mortality in patients with CHF.

MATERIAL AND METHODS

This study enrolled 141 patients from local database of implanted CRT devices (mean age 58.6 [53.0;66.0] years, 77.3% men) with CHF (92 patients with ischemic and 49 with non-ischemic etiology) [11]. Main criteria for CRT implantation were New York heart association (NYHA) functional class II-IV, reduced left ventricular ejection fraction (LVEF) <35%, QRS ≥ 130 ms, and left bundle branch block. Combined devices with defibrillator function (CRT-D) were implanted in 64.5% of patients. The device implantation was effective in all patients and occurred without complications. All patients received medical treatment according to the current guidelines [1].Clinical characteristics of the study participants are shown in Table 1.

At baseline, after 1 month, 3 months, and every 6 months after implantation we evaluated clinical, electrocardiographic, and echocardiographic parameters. Standard echocardiography was performed using a commercially available system Philips IE 33.

The study was conducted in accordance with the ethical standards of the Local Institutional Review Board and with the 1964 Helsinki declaration and its later amendments. This project was approved by the Local Bioethics Committee. All patients gave their written informed consent before the study.

Mean follow-up period was 45.0±34.2 months. Response to CRT was evaluated retrospectively according to the best dynamics of NYHA functional class, LVEF, left ventricle end-systolic volume (LVESV). According to dynamics of these parameters patients were divided in 4 groups: non-responders (increase of NYHA functional class, decrease of LVEF, increase of LVESV); non-progressors (no changes of NYHA, increase of LVEF <5%, decrease of LVESV <15%); responders (1 grade decrease of NYHA, increase of LVEF 5-9%, decrease of LVESV 15-29%); superresponders (2 grade decrease of NYHA, increase of LVEF ≥10%, decrease of LVESV ≥30%)

Statistical analysis was performed using SPSS for Windows version 23.0 (SPSS Inc., Chicago, IL, USA). In case of normal distribution results were expressed as the mean value ± standard deviation (mean±SD), in case of not normal distribution as median and interquartile range (Me [25%;75%])]). The χ^2 or Fisher's exact test were used to compare categorical variables. Continuous variables were compared using Student's t test for normally distributed variables or the Mann–Whitney test for non-normally distributed variables. The Cohen κ-coefficient was used to assess agreement between the different response criteria. Cohen κ-coefficient <0.2 was defined as the absence of agreement, from 0.21 to 0.39 as minimal agreement, 0.40 – 0.59 – poor agreement, from 0.6 to 0.79 – moderate, from 0.8 to 0.9 – strong agreement, > 0.9 – almost ideal agreement [13]. To assess the relationship between the response to CRT and all-cause mortality a correlation analysis was performed with the calculation of the Kendall correlation coefficient. P<0.05 was significant.

RESULTS

According to dynamics of NYHA functional class 67 patients (47.5%) were responders, 15 patients (10.6%) - superresponders, 56 patients (39.7%) were non-progressors, and 3 patients (2.1%) – non-responders. According to dynamics of LVEF 57 patients (40.4%) were identified as superresponders, 33 patients (23.4%) were responders, 36 (25.5%) and 15 (10.6%) patients were identified as non-progressors and non-responders. When assessing the response to CRT according to dynamics of LVESV 55 patients (35.5%) were superresponders, 28 patients (19.9%) responders. 49 patients (34.8%) demonstrated decrease of LVESV 0-15% and were identified as non-progressors, in 14 patients (9.9%) LVESV increased when compared to baseline values (Fig. 1).

The lowest percentage of non-responders (2.1%) and at the same time the lowest percentage of superresponders (10.6%) were identified when assessing the response according to the dynamics of NYHA, and the largest percentage of superresponders (40.4%) when assessing response based on LVEF dynamics.

Fifty-five patients (39%) died during the observation period. The percentage of CRT-D devices did not

Table 1.

Clinical characteristics of the study participants (n=141)

Parameters	N (%)
Number of patients, n	141
Mean age, years	58.6 [53.0;66.0]
Male/female, n (%)	109 (77.3)/32 (22.7)
Non-ischemic etiology, n (%)	49 (34.8%)
Ischemic etiology, n (%)	92 (65.2 %)
Diabetes, n (%)	25 (17.7%)
Myocardial infarction, n (%)	64 (45.4%)
Atrial fibrillation, n (%)	34 (24.1%)
Radiofrequency ablation, n (%)	15 (10.6%)
Arterial hypertension, n (%)	102 (72.3%)
Left bundle branch block, %	111 (78.7%)
QRS, ms	172.87±26.3
QRS ≥150 ms	112 (79.4%)
QRS 130-149 ms	29 (20.6%)
LVEF, %	31 [27;33]
LVESV, ml	168.6 [142.0;207.1]
Left ventricular end-diastolic volume, ml	239.0 [209.0;289.0]
NYHA II, n (%)	59 (41.8%)
NYHA III, n (%)	62 (44.0%)
NYHA IV, n (%)	20 (14.2%)
ACEI/ARB (%)	136 (96.5%)
β-blocker, n (%)	128 (90.8%)
Diuretic, n (%)	119 (84.4%)
Statins, n (%)	84 (59.6%)
Digoxin, n (%)	39 (27.7%)
Spironolactone, n (%)	120 (85.1%)
Warfarin, n (%)	43 (30.5%)
Platelet inhibitor, n (%)	88 (62.4%)
Antiarrhythmic drugs, n (%)	24 (17.0%)
Targeted vein, n (%)	115 (81.6%)

Note thereafter: LVEF - left ventricular ejection fraction; LVESV - left ventricular end-systolic volume NYHA - New York Heart Association; ACEI - angiotensin-converting enzyme inhibitors; ARB - angiotensin II receptor blockers differ between died and survived patients (56.4% vs 69.8% respectively: p=0.105). The rate of implantation of a left ventricular lead into the target vein also did not differ between deceased and survived patients (75% vs 86%; p=0.118). Among the deceased patients, the number of responders+superresponders was 16 (29.1%) when assessing by the decrease of LVESV, 29 (51.8%) when assessing by the decrease of NYHA class and 28 patients (50%) on LVEF assessment. Among the surviving patients, there was not a single non-responder when assessing the response according to the dynamics of LVESV and NYHA functional class. Kaplan-Meier curves are shown in Fig. 2.

Of 141patients, 118 (83.7%) showed a positive response according to at least 1 criteria, whereas 93 patients (66%) were classified as a non-responder by at least 1 criteria. Similarly, 48 patients (34.0%) showed a positive response by 3 criteria, whereas only 36 patients (25.5%) showed a positive response by 3 criteria and were alive during follow-up period.

The Cohen κ-coefficient demonstrated the absence of agreement between echocardiographic criteria and NYHA (κ-coefficient <0.2), and poor agreement between response defined by LVESV and LVEF (κ-coefficient 0.5) (Table 2).

Correlation analysis showed a significant moderate negative correlation of all-cause mortality with the response assessed by the dynamics of LVESV and a poor negative correlation with the response assessed by the dynamics of LVEF (Table 3).

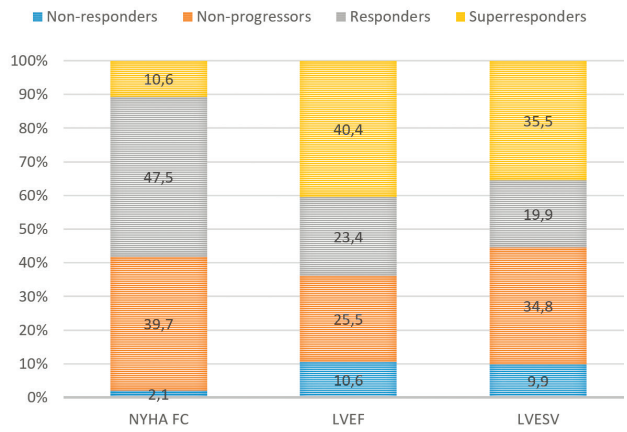

Fig. 1. Distribution of response to CRT using different criteria: dynamics of NYHA, LVEF, and LVESV.

Comparison of correlation coefficients showed a significant difference in the strength of the relationship between mortality and LVESV and NYHA (p<0.001), and no significant differences in the correlation coefficients of NYHA - LVEF (p=0.057) and LVEF - LVESV (p=0.086).

DISCUSSION

The definition of response to CRT varies across clinical trials. Numerous variables including clinical and functional parameters, event-based, imaging, or composite outcomes have been used to describe response to CRT. Results of MIRACLE, MUSTIC SR, and MIRACLE ICD trials demonstrated that CRT could improve exercise capacity, quality of life, NYHA class and these criteria were used to evaluate the efficacy of CRT [14-16]. In other studies, echocardiographic parameters of reverse remodeling` (LVESV, LVEF) were used to define the response [17]. In several large multicenter studies hospitalization for CHF, total mortality, and cardiovascular mortality were used as a measure of the effect of CRT [18,19].

However, the agreement between echocardiographic and clinical criteria for defining a response to CRT is low. When 11 pairs of most cited response criteria were evaluated the agreement between response criteria was strong in only 7.6% of response criteria pairs [8, 9]. Yu C.M. et all did not find the agreement between the decrease of LVESV, improvement of NYHA class, increase in exercise tolerance, and improvement in the quality of life after CRT [20]. In a recent study by Bleeker et al. authors compared a decline in NYHA class (clinical response) with a 15% decrease in LVESV echo response) and concluded that the agreement of 76% [21]. In the MIRACLE trial, correlation between the change in left ventricular end-diastolic volume and change in NYHA class after 6 months of CRT was weak (r=0.13), and the correlation between the change in distance walked in 6 minutes and change in LVEF was weak (r=0.15) [14]. In addition, patients with reduction in LVESV 0-14% demonstrate improvement in clinical status and LVEF and survival rates compared to subjects with reduction in LVESV 15-30% [6]. The main conclusion that should be drawn from our study is similar: the agreement between echocardiographic and clinical criteria for defin-

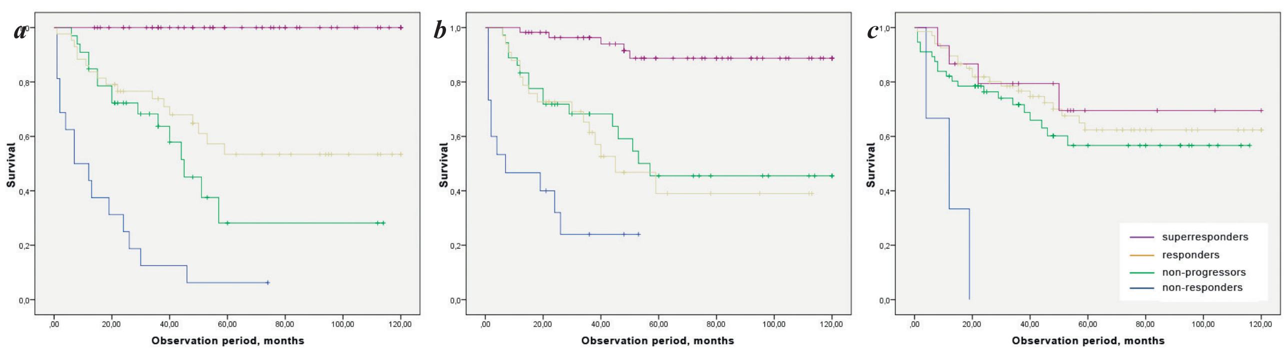

Fig. 2. Kaplan-Meier curves for groups with different response to CRT defined by: a - LVESV: Log Rank test: non-responders vs all groups p<0.001; non-progressors vs responders p=0.167; superresponders vs all groups p<0.001. b - LVEF: Log Rank test: non-responders vs all groups p<0.05; non-progressors vs responders p=0.280; superresponders vs all groups p<0.001. c - NYHA: Log Rank test: non-responders vs all groups p<0.05; non-progressors vs responders p=0.386; superresponders vs non-progressors p=0.381; superresponders vs responders p=0.748.

ing a positive response to CRT is only slightly better than that expected by chance alone.

Previous studies have reported different rates of CRT response when different definitions of response were used within the same population. For example, the PROSPECT study reported that 56% of patients were echocardiographic responders (decrease of LVESV ≥15%), whereas 69% of patients were clinical responders (improvement in the clinical composite score) [17]. Thus, different measures of CRT response can lead to incorrect management of patients in clinical practice and inadequate interpretation of the results of studies aimed at finding predictors of response to CRT.

We found a comparable percentage of patients with a positive response to CRT (responders+superresponders) using different criteria, however, according to our data, there was poor or no agreement between the criteria. The number of superresponders when assessing by echocardiographic criteria was significantly higher in comparison with the assessment of NYHA, and the lowest percentage of non-responders was found when we used dynamics of NYHA as a response criterion.

Whether death should be considered a nonresponse to CRT is an area in which there is inconsistency. There are at least 3 different methods that authors have used to incorporate death into response criteria: cardiovascular death, death due to worsening of CHF, and death due to any cause. Although inclusion of all-cause mortality as a criteria for nonresponse may not be appropriate, a patient who dies of worsening of CHF should, objectively, be classified as a non-responder. Regardless, there is no consistent method for incorporating mortality into the definition of response to CRT, and this needs to be standardized.

We considered all-cause mortality as an endpoint. None of the survived patients was non-responders when using NYHA class or LVESV as a response criteria. At the same time, about half of the deceased patients were responders or superresponsors when assessing the dynamics of LVEF (50%) and NYHA (51.8%). In recent studies with a large population of heart failure patients treated with CRT the reduction in LVESV demonstrated to be a better predictor of long-term survival than improvement in the clinical status [22-25], that was confirmed in our study. Nakai T. et al concluded that the functional response definition (NYHA) is associated with a higher response rate and better clinical outcomes than that of the echocardiographic response definition, and therefore it is reasonable to use the functional definition to assess CRT response [26]. Potentially this result may be explained by high percentage (70%) of patients who had NYHA III at baseline in the study of Nakai T. el al, while only 14% of patients had NYHA II. In our study, 42% of patients had NYHA II, that means they had less severity of CHF. In addition, the follow up period in the study of Nakai T. et al was 6 months. Previously CRT has been shown to have early effect during first year on clinical response (NYHA), but long-term effect on reverse remodeling [6, 27].

In our study combined CRT-D devices were implanted in 64.5% of patients and 35.5% of patients received CRT-P. Some recent large observational studies highlighted the importance of CHF etiology in the assessment of potential benefits of CRT-D over CRT-P. CRT-D was associated with a significant risk reduction in all-cause mortality compared with CRT-P in patients with ischemic cardiomyopathy [28]. Data from the DANISH trial illustrate that a strategy for routine implantation of CRT-D versus CRT-P for patients with a non-ischemic etiology does not improve overall long-term survival [29]. Recent CRT guidelines indicate the addition of cardioverter-defibrillator to CRT should be considered, especially in younger patients with a good survival prognosis, ischemic etiology, and a favorable comorbidity profile or presence of myocardial fibrosis. Moreover, the benefit of the implantable cardioverter-defibrillator is governed by the balance between the risk of sudden cardiac death and the risk of death from other causes, as well as comorbidities [1, 2, 30]. A joint position statement from the HFA, EHRA, and EACVI of the ESC indicates that a process of shared decision-making should guide the choice between CRT-P and CRT-D between patients and clinicians, considering both medical facts and patient values [10]. It should be noted that most part of CRT-P devices was implanted before 2012. Subsequently, CRT-D devices were implanted for all CHF patients, except for isolated cases. More than 80% of CRT-P devices were implanted in patients with non-ischemic etiology of CHF with NYHA III/IV.

CRT is one of the most effective therapies for CHF resulting in improved quality of life, beneficial reverse remodeling and reductions in heart failure hospitalization rates and all-cause mortality. Mechanisms of the positive effect of CRT may differ among cases that limits the ability to compare the results of different studies and makes difficulties in real clinical practice. Numerous variables including functional, event-based, imaging, or composite outcomes have been used to describe response to CRT. The importance of certain metrics might differ according to the stakeholders, such as patients, doctors, payers, or industry. Indeed, the size and shape of the ventricle is irrelevant for patients complaining of exercise intolerance. For a patient with CHF and NYHA II the most significant effect will be a slowdown in the progression of CHF, and such a patient will not experience a significant improvement in NYHA. For a patient with coronary artery disease and prior myocardial infarction an improvement in prognosis will be much more important measure than a decrease in LVESV.

Table 2.

Agreement among the response criteria

Criteria for assessment of CRT response	LVEF	NYHA
LVESV	0.591±0.068*	0.192±0.083
LVEF	-	0.168±0.083

Table 3.

Agreement among response criteria and all-cause mortality

Criteria for assessment of CRT response	LVESV	LVEF	NYHA
Total mortality	r=-0,486 p<0,001	r=-0,297 p<0,001	r=-0,102 p=0,298

The aim of CRT may also differ among cases. No consensus exists on how or when to measure response to CRT. It is still not clear what magnitude of change constitutes response «predictors of response». Most of predictors are based on results of observational studies, and due to a lack of control data, cannot determine the relation between the clinical and functional effect of CRT and outcome benefit (risk reduction). On the other hand, according to Cleland J.G. et al. for many doctors and patients' acute improvement in quality of live and improvement of exercise tolerance is more clear and measurable effect rather than the disease outcome [31].

Thus, due to the individual clinical and hemodynamic characteristics of CRT response and due to the low agreement between different response criteria the need for an integrated approach to assessing the effectiveness of CRT becomes obvious. In real clinical practice, the effect of CRT should be evaluated by one isolated criteria.

STUDY LIMITATIONS

The study had a retrospective design, and the number of patients was relatively low. A significant limitation of the study is that the evaluation of the response to CRT was carried out not at a fixed specific time after implantation, but during the whole observation period for each individual patient that could significantly affect the results obtained.

We did not analyze the intra- and interobserver variability of echocardiographic criteria, and therefore the limitation of the study is the probable errors in the evaluation of echocardiographic criteria.

Only the most used criteria for evaluating response to CRT were evaluated in the study. It was previously shown that the levels of inflammatory mediators and markers of myocardial fibrosis have a significant relationship with the effects of CRT, as well as speckle tracking echocardiography with an assessment of two- and three-dimensional strain can also be used to predict the response to CRT [32, 33]. However, in the current study the levels of biochemical markers, parameters of speckle-tracking echocardiography were not evaluated. Additionally, we did not assess the severity of the functional and clinical response to CRT in groups with different etiology of CHF.

CONCLUSION

Agreement between different criteria to define response to CRT is poor. The strongest correlation with long-term mortality was found for LVESV. This inconsistency among different response criteria severely limits the ability to generalize results over multiple CRT studies.

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