Chapter 5

Prevalence and characteristics of patients with clinical improvement but not significant left ventricular reverse remodeling after cardiac resynchronization therapy

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ABSTRACT

Background: Although most patients who improve in clinical status after cardiac resynchronization therapy (CRT) also show a significant left ventricular (LV) reverse remodeling, some patients do not show echocardiographic improvement. The aim of the present study was to evaluate the degree of agreement between clinical and echocardiographic response to CRT in a large cohort of heart failure patients, and to evaluate the characteristics of patients with clinical response but without echocardiographic response.

Methods: In 440 consecutive heart failure patients (mean age 66±11 years, 81% men) treated with CRT, agreement between clinical and echocardiographic responses at 6 months of follow-up were evaluated. The combined clinical response was defined as: ≥1-point New York Heart Association functional class improvement or ≥15% increase in 6-minute walk test. Echocardiographic response was defined by a reduction in LV end-systolic volume (LVESV) ≥15%.

Results: At 6 months of follow-up, clinical response was observed in 84% (n = 370) of the patients. Significant reduction in LVESV was noted in 63% (n = 276). The majority of patients who improved clinically did show LV reverse remodeling (72%, n = 268). Importantly, 28% (n = 102) of patients who improved clinically did not show significant LV reverse remodeling. The patients with clinical response but without echocardiographic response had more often ischemic heart failure as compared topatients with positive clinical and echocardiographic response (69.6% vs. 57.5%; p = 0.021). Moreover, patients with such discordant responses had more narrow QRS complex (148±31 vs. 159±31 ms; p = 0.004), and showed less LV dyssynchrony than patients with concordant positive responses (90±77 vs. 171±105 ms; p<0.001).

Conclusions: Although there is a good concordance between echocardiographic and clinical response to CRT, up to 28% of the population experienced clinical response without significant LV reverse remodeling. Subjects with such discrepant responses have more frequently ischemic heart failure and show more narrow QRS complex and less LV dyssynchrony than patients with both clinical and echocardiographic response.

INTRODUCTION

Beyond demonstrated improvements in heart failure symptoms and morbidity and mortality, cardiac resynchronization therapy (CRT) has shown to prevent progression of heart failure by inducing left ventricular (LV) reverse remodeling.[1-4] In addition, a significant reduction in LV end-systolic volume (LVESV) after CRT has shown to be independently related to improved clinical outcome.[5,6] Nevertheless, definition of response to CRT remains still controversial and several trials have included either clinical or echocardiographic end-points to define response to CRT.[2,7-11] Whether clinical and echocardiographic responses to CRT coincide always has not been extensively explored.[12,13]

Few studies have addressed the frequency of patients who show clinical improvement but not LV reverse remodeling and vice versa.[12,14] Particularly, better knowledge of the amount of patients with discordant clinical and echocardiographic response to CRT in the daily clinical practice may yield a more realistic overview of the "non-response rate" issue and may help to plan different strategies to improve the response rate. In addition, evaluation of the baseline characteristics of patients who do not show a concordant clinical and echocardiographic response to CRT may provide new insight into the pathophysiological effects of CRT. Thus, the present study aimed to evaluate the concordance and discordance between clinical and echocardiographic responses to CRT in a large cohort of advanced heart failure patients. Specifically, differences in baseline characteristics of patients who experience clinical improvement but do not show evidence of significant LV reverse remodeling after CRT were evaluated and further compared to the characteristics of patients with both clinical and echocardiographic improvement.

METHODS

Patient population

A total of 440 heart failure patients who were treated with CRT, according to the current guidelines, and who completed a 6-month follow-up period were enrolled in the present evaluation.[15] Patients with recent myocardial infarction (≤3 months) or decompensated heart failure were excluded. Heart failure etiology was considered ischemic when the patient had previous myocardial infarction or revascularization, or was known for significant angiographic coronary disease (≥50% stenosis in ≥1 major epicardial artery). Clinical evaluations were performed before CRT implantation and at 6 months of follow-up. In addition, all the patients underwent 2-dimensional echocardiography at baseline to evaluate LV volumes, LV ejection fraction (LVEF) and LV dyssynchrony. At 6 months of follow-up, the echocardiography was repeated for LV volumes and LVEF evaluation. All baseline and follow-up clinical and echocardiographic analyses were performed by independent blinded observers.

Clinical evaluation

The clinical evaluation consisted of New York Heart Association (NYHA) functional class assessment, coupled to quality of life (QoL) score (Minnesota Living with Heart Failure Questionnaire) and exercise capacity (6-minute walk test [6MWT]).[16,17] Clinical response to CRT was defined as: ≥1-point NYHA functional class improvement,[18] ≥10-point decrease in QoL score and ≥15% increase in the 6MWT. The combined clinical end-point was the presence of ≥1-point NYHA functional class gain or ≥15% increase in the 6MWT.

Two-dimensional echocardiography

Echocardiographic data were obtained at rest in the left lateral decubitus position using a commercially available system (Vingmed System 7, GE-Vingmed Ultrasound AS, Horten, Norway) with a 3.5-MHz transducer at a 16-cm depth in the standard parasternal long-axis, parasternal short-axis, and apical views. Two-dimensional and color Doppler data were collected. Apical 2- and 4-chamber views were used to calculate LV end-diastolic volume (LVEDV) and LVESV and to derive LVEF according to the Simpson's method.[19] Mitral regurgitation severity was graded semi-quantitatively on a 4-point scale using color Doppler imaging in the apical 4-chamber view according to current guidelines.[20] Echocardiographic response to CRT was defined by a ≥15% reduction in LVESV (reverse remodeling).[21]

Left ventricular dyssynchrony was assessed with 2-dimensional speckle-tracking radial strain analysis (EchoPac 108.1.5, General Electric/Vingmed Ultrasound, Horten, Norway). As previously described, from the mid LV short-axis view (level of the papillary muscles) the endocardial border is manually traced at an end-systolic frame.[22] Subsequently, 2 concentric regions of interest are automatically provided by the software and further adjusted for optimal tracking of the myocardial wall. Finally, the mid LV short-axis view is divided in 6 segments and the time-strain tracings are provided for each segment. The time difference between the peak radial strain of the anteroseptal and the posterior segments is calculated to define LV dyssynchrony. An established cut-off value of ≥130 ms indicates significant LV dyssynchrony, as previously described.[22]

CRT device implantation

CRT device implantation was performed through the subclavian vein. First, a coronary sinus venogram was obtained using a balloon catheter. Thereafter, an 8F guiding catheter was used to place the LV lead (Easytrak, Guidant Corp, St Paul, MN; Attain, Medtronic Inc, Minneapolis, MN; or Corox, Biotronik, Berlin, Germany) in the coronary sinus, preferably in the posterolateral vein.[23] The right atrial lead was positioned in the atrial appendage and right ventricular lead was positioned in the ventricular apex. A defibrillator was combined to CRT when recommended by current guidelines.[24] Finally, all leads were connected to a dual chamber biventricular CRT-device (Contak Renewal, Guidant Corp; Insync III or Insync Sentry, Medtronic Inc; or Lumax, Biotronik).

Statistical analysis

Continuous variables are presented as mean±SD and were compared with Student t-test for paired and unpaired data. Categorical variables are presented as number and percentage and were compared with $\chi 2$ test. A p-value <0.05 was considered statistically significant. Data were analyzed with SSPS 17.0 (SSPS Inc, Chicago, IL).

RESULTS

Patient characteristics

Baseline characteristics of the patient population are summarized in Table 1. Of the 440 patients with heart failure included in the study (mean age 66±11 years, 81% men), 62% (n = 274) had ischemic etiology. Most of the patients were in NYHA functional class III (95%) and mean LVEF was 26±8%. In addition, mean QRS duration was 156±32 ms. Mean LV dyssynchrony was 149±103 ms. All patients were treated according to current guidelines,[25] including diuretics, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers and β-blockers at maximal tolerable dosages.

Clinical response

At 6 months of follow-up, in the overall population there was a significant improvement in NYHA functional class (from 3.0±0.2 to 2.0±0.7, p<0.001), QoL score (from 35±18 to 22±18,

Table 1. Baseline characteristics (n = 440)

Age (years)	65 ± 11
Men / Women	356 / 84
Ischemic cardiomyopathy	274 (62%)
QRS duration (ms)	156 ± 32
Sinus rhythm	347 (79%)
NYHA class	
III	418 (95%)
IV	22 (5%)
6MWT (m)	308 ± 112
QoL	35 ± 12
Medication	
B-blockers	309 (70%)
ACE-inhibitors / ARB	400 (91%)
Diuretics / Spironolactone	370 (84%)
LVEDV (ml)	224 ± 80
LVESV (ml)	169 ± 70
LVEF (%)	26 ± 8
Radial LV dyssynchrony (ms)	149 ± 103
Mitral regurgitation grade 3-4	77 (18%)

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker

p<0.001) and in 6MWT (from 308±112 m to 384±121 m, p<0.001). When a ≥1-point NYHA functional class improvement was applied as definition of response to CRT, 80% (n = 351) of the patients were classified as responders (Table 2). A ≥15% increase in the 6MWT was noted in 62% (n = 271) of the patients. A ≥10-point improvement in the QoL score was observed in only 52% (n = 230) of the patients. Finally, the combined clinical response (≥1 NYHA functional class improvement or ≥15% increase in the 6MWT distance) was recorded in 84% of patients (n = 370).

Table 2. Frequencies of responder and non-responders at 6 months of follow-up according to pre-specified definitions

n = 440	Yes	No
Clinical definitions		
NYHA improvement ≥1 functional class	351 (80%)	89 (20%)
6MWT increase ≥15%	271 (62%)	169 (38%)
QoL score decrease ≥10 points	230 (52%)	210 (48%)
Combined clinical end-point	370 (84%)	70 (16%)
Echocardiographic definition		
LVESV decrease ≥15%	276 (63%)	164 (37%)

Echocardiographic response

At 6 months of follow-up, a significant reduction in LV volumes was observed (LVEDV: from 224±80 to 198±74 ml, $p<0.001$; LVESV: from 169±70 to 137±65 ml, $p<0.001$) together with a significant improvement in LVEF (from 26±8% to 33±10%, $p<0.001$). Based on echocardiographic definition of CRT response, the percentage of responders was 63% (n = 276) (Table 2).

Clinical vs. echocardiographic response

The concordance between the different definitions of CRT response was evaluated by using as reference a combined clinical response (improvement in NYHA ≥1-point or ≥15% increase in the 6MWT). According to this definition, 84% of patients (n = 370) were clinical responders to CRT and 16% (n = 70) were non-responders. This criterion provided the highest proportion of favorable response to CRT. Therefore, the patient population was divided in clinical responders and clinical non-responders according to the improvement in the combined clinical outcome (clinical+ and clinical−, respectively). Concordance between the clinical and echocardiographic definitions of response is shown in Figure 1. Most of the patients who showed an improvement in the clinical end-point also exhibited significant LV reverse remodeling (72%, n = 268). In addition, most of the patients who did not improve in the clinical end-point did not show a significant decrease in LVESV (89%, n = 64).

The disagreement between clinical response and echocardiographic response ranged between 11% and 28% (see Figure 1). A disagreement of only 11% was recorded amongst non-responders. The disagreement between positive clinical and echocardiographic definitions arises from the fact that 28% (n = 102) of patients who improved clinically did not show LV reverse remodeling.

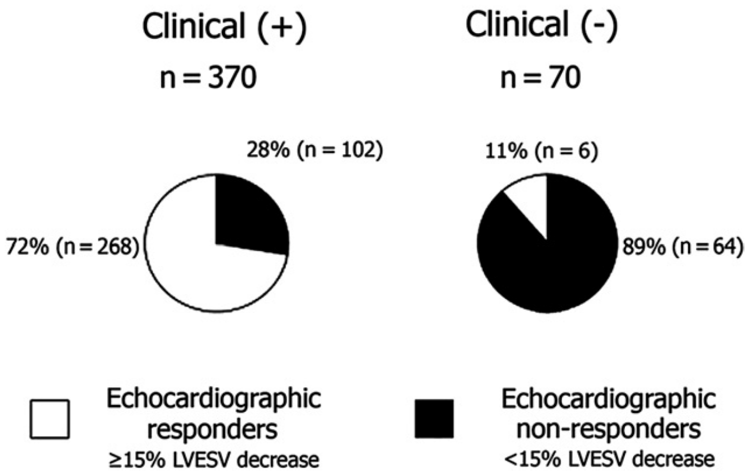

Figure 1. Concordance between different definitions of response to CRT. The pie charts show the percentages of patients with concomitant clinical response, as defined by an increase of ≥1 NYHA functional class or an increase of ≥15% in the 6MWT, and echocardiographic response, as defined by LV reverse remodeling ≥15% at 6 months of follow-up. Among patients who showed a positive clinical response (n = 370), 72% showed also a significant LV remodeling and 28% did not exhibit such a reduction in LVESV.

Characteristics of patients with clinical response but absence of echocardiographic response

Patients with concomitant positive clinical and echocardiographic responses were compared to patients with positive clinical response but no significant LV remodeling. Among the patients with clinical but without echocardiographic response (n = 102), 44% showed <15% reduction in LVESV at 6 months of follow-up, whereas the remaining 56% showed progression of heart failure with LV dilatation. Table 3 summarizes the differences between patients with both positive clinical and echocardiographic responses and patients with clinical response but without echocardiographic response. The most remarkable differences between the 2 groups were the proportion of patients with ischemic etiology and the extent of LV dyssynchrony. A significantly larger proportion of ischemic heart failure patients was noted in the group of patients with positive clinical response but no echocardiographic response (69.6% vs. 59.5%; $p = 0.021$). Furthermore, patients with positive clinical response but without echocardiographic response had more narrow QRS complex (148±31 vs. 159±31 ms; $p = 0.004$). Finally, the patients with positive clinical response but without echocardiographic response had less LV radial dyssynchrony than patients with concordant positive responses (90±77 vs. 171±105 ms; $p<0.001$). In contrast, LV volumes and function were comparable between the 2 groups.

Table 3. Baseline characteristics of patients with clinical and echocardiographic favorable responses [Clinical (+) and Echo (+)] vs. patients with positive clinical response but no echocardiographic response [Clinical (+) and Echo (−)]

Variable	Clinical (+) and Echo (+) (n = 268)	Clinical (+) and Echo (-) (n = 102)	p-value
Age (years)	66 ± 18	65 ± 13	0.697
Male sex	214 (79.9%)	88 (86.3%)	0.099
Ischemic cardiomyopathy	154 (57.5%)	71 (69.6%)	**0.021**
NYHA class IV	11 (4.1%)	9 (8.8%)	0.404
6MWT (m)	318 ± 110	298 ± 125	0.159
QoL	34 ± 18	36 ± 19	0.249
Hemoglobin (g/dL)	8.37 ± 0.90	8.33 ± 0.99	0.671
Creatinine clearance (ml/min)	71 ± 28	70 ± 31	0.800
QRS duration (ms)	159 ± 31	148 ± 31	**0.004**
LBBB	156 (58.2%)	56 (54.9%)	0.323
RBBB	16 (6%)	9 (8.8%)	0.456
IVCD	52 (19.4%)	15 (14.7%)	0.370
LVEDV (ml)	230 ± 79	225 ± 85	0.580
LVESV (ml)	173 ± 70	170 ± 74	0.660
LVEF (%)	26 ± 8	25 ± 8	0.742
Radial LV dyssynchrony (ms)	43 (16%)	22 (21.6%)	0.137
Mitral regurgitation grade 3-4	171 ± 105	90 ± 77	**<0.001**

IVCD = interventricular conduction delay; LBBB = left bundle branch block; RBBB = right bundle branch block

DISCUSSION

The present study confirms that most patients treated with CRT will experience favorable clinical and echocardiographic responses. However, in a sub-group of patients the improvement in clinical status is not accompanied by prevention of heart failure progression. Of interest, patients with clinical and but no echocardiographic responses have significantly more ischemic heart failure than patients with both positive responses. Furthermore, these patients show more narrow QRS complex, and significantly less LV mechanical dyssynchrony as assessed with 2-dimensional radial strain speckle-tracking imaging than patients with both clinical and echocardiographic response.

Therapeutic targets in heart failure therapy

Improvement in clinical status, as assessed with NYHA functional class, QoL or 6MWT, and reduction in LV volumes and improvement in LVEF are surrogate end-points extensively used in landmark CRT trials.[26] Some of these surrogate end-points have been related to long-term survival, established true end-point of any heart failure therapy.[27] There is conflicting evidence relating an improvement in NYHA functional class, QoL, or 6MWT to long-term survival.[28-30] Changes in NYHA functional class may not be sensitive enough to detect important changes in exercise capacity and changes in 6MWT have not been demonstrated to predict long-term survival.[29] In contrast, the occurrence and the amount of LV reverse remodeling have been shown to be independent determinants of long-term survival.[5,6] In 141 heart failure patients undergoing CRT device implantation, Yu et al[5] demonstrated that a reduction in LVESV ≥10% at 6 months of follow-up predicted accurately long-term all-cause and cardiovascular mortality. Those patients showing such amount of LV reverse remodeling had superior long-term outcome than patients with a reduction in LVESV <10% (log-rank $p = 0.003$). In addition, LV reverse remodeling was the strongest independent predictor of all-cause mortality ($\beta = 1.048$, $p = 0.001$) and cardiovascular mortality ($\beta = 1.072$, $p<0.001$).[5] These results were confirmed and extended in a series of 302 heart failure patients treated with CRT.[6] The study showed that the extent of LV reverse remodeling varied among heart failure patients treated with CRT. A significant percentage of patients showed a reduction in LVESV ≥30%, the so-called super-responders.[6] This sub-group of patients showed the highest survival rates. More importantly, the study demonstrated that long-term survival after CRT device was independently determined by the extent of LV reverse remodeling.[6] According to those data, LV reverse remodeling may be a more appropriate surrogate end-point to evaluate the efficacy of CRT as heart failure therapy than subjective clinical parameters.[27] Whether combination of both responses (clinical and echocardiographic) may better predict or not long-term survival needs additional studies.

Agreement between clinical and echocardiographic response to CRT

The agreement between clinical and echocardiographic response to CRT has not been extensively explored.[12,14] Most studies have shown that, based on clinical improvement (as defined by an increment ≥1 NYHA functional class), the CRT response rate at 6 months of follow-up is around 67%.[31] In contrast, when the CRT response is based on the occurrence of LV reverse remodeling, the response rate decreases to 57%.[31] Although improvement in NYHA functional class and extent in LV reverse remodeling are closely related,[12] the agreement between the 2 responses is not perfect. In the present study, 28% of patients with clinical improvement did not experience LV reverse remodeling. These results confirm previous studies.[12,14] For example, in a series of 144 heart failure patients undergoing CRT device implantation, 27% of the patients who improved clinically did not show LV reverse remodeling at 6 months of follow-up.[12] In addition, a sub-analysis of the PROSPECT trial including 286 heart failure patients treated with CRT demonstrated that 28% of the patients exhibited a clinical improvement but not LV reverse remodeling.[14] These observations were further confirmed in a recent pooled analysis of CRT studies by Fornwalt et al[11] showing that the agreement between multiple different clinical and echocardiographic responses is suboptimal, with a higher symptomatic response rate as compared to echocardiographic response rate. These results indicate that, despite improvements in functional status, CRT does not reverse LV remodeling in a sub-group of patients and suggest that a placebo effect may be present as well. Whether this specific group of patients has improved long-term survival was not addressed in the present study. However, it may be interesting to better understand the clinical characteristics of these patients and how CRT exerts its effects on LV performance in order to elucidate the reasons for these discrepant CRT responses.

Baseline characteristics of patients with clinical response but absence of LV reverse remodeling

The current in-depth analysis provided further insight in the definition of response to CRT by analyzing the baseline characteristics of patients with positive clinical response but no LV reverse remodeling 6 months after CRT.

First, ischemic heart failure was identified more frequently in patients with clinical but without echocardiographic response as compared to patients with both favorable responses. Different pathophysiological mechanisms have been proposed to explain these findings. The presence of scar, especially at the site of LV lead implantation may limit the benefits of CRT in these patients.[32] Furthermore, patients with ischemic heart failure have shown complex patterns of electrical and mechanical activation that may not be correctable by CRT.

Second, patients with clinical response but without LV reverse remodeling had more narrow QRS complex and less extensive LV mechanical dyssynchrony than the patients with both positive responses. This observation strengthens the idea that patients without baseline LV dyssynchrony may not show LV reverse remodeling after CRT. However, a significant improvement in NYHA functional class could still be noted. Indeed, a previous sub-study from the CONTAK-CD and MIRACLE trials demonstrated that heart failure patients with right bundle branch block showed a significant improvement in NYHA functional class but not in LVEF.[33] Despite wide QRS complex (>120 ms), patients with right bundle branch block may not show a pronounced LV mechanical dyssynchrony. In this sub-group of patients, CRT may exert different effects including a potential mechanical desynchronization of the left ventricle. This potential effect may prevent LV reverse remodeling although improvement in clinical status may still occur. Therefore, considering that LV resynchronization is mandatory for echocardiographic response after CRT,[34] patients without significant baseline LV mechanical dyssynchrony may not experience significant LV reverse remodeling after CRT. However, it remains unclear why these patients still exhibit an improvement in NYHA functional class. Moreover, additional studies are needed to elucidate whether this specific sub-group of patients (presence of clinical response without LV reverse remodeling) will have different long-term survival as compared to patients with concordant response.

Conclusion

CRT induces clinical and echocardiographic response in the vast majority of patients. However, in as much as 28% of the patients, this favorable clinical response is not accompanied by LV reverse remodeling. Subjects with such discrepant responses have more frequently ischemic heart failure, have more narrow QRS complex and less extensive LV dyssynchrony than patients with both positive clinical and echocardiographic response. Whether these patients (with discrepant response) have worse long-term outcome remains to be determined.

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