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Chapter 6

Characteristics of heart failure patients associated with good and poor response to cardiac resynchronization therapy: a PROSPECT (Predictors of Response to CRT) sub-analysis

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ABSTRACT

Background: Predictors of Response to Cardiac Resynchronization Therapy (CRT) (PROSPECT) was the first large-scale, multicenter clinical trial that evaluated the ability of several echocardiographic measures of mechanical dyssynchrony to predict response to CRT. Since response to CRT may be defined as a spectrum and likely influenced by many factors, this sub-analysis aimed to investigate the relationship between baseline characteristics and measures of response to CRT.

Methods: A total of 286 patients were grouped according to relative reduction in left ventricular end-systolic volume (LVESV) after 6 months of CRT: super-responders (reduction in LVESV ≥30%), responders (reduction in LVESV 15% to 29%), non-responders (reduction in LVESV 0% to 14%) and negative-responders (increase in LVESV). Additionally, 3 sub-groups were formed according to clinical and/or echocardiographic response: +/+ responders (clinical improvement and a reduction in LVESV ≥15%), +/- responders (clinical improvement or a reduction in LVESV ≥15%), and -/- responders (no clinical improvement and no reduction in LVESV ≥15%). Differences in clinical and echocardiographic baseline characteristics between these sub-groups were analyzed.

Results: Super-responders were more frequently females, had non-ischemic heart failure, had a wider QRS complex and more extensive mechanical dyssynchrony at baseline. Conversely, negative-responders were more frequently in NYHA class IV and had a history of ventricular tachycardia (VT). Combined positive responders after CRT (+/+ responders) had more non-ischemic etiology, more extensive mechanical dyssynchrony at baseline and no history of VT.

Conclusions: Sub-analysis of data from PROSPECT showed that gender, etiology of heart failure, QRS duration, severity of heart failure, a history of VT and presence of baseline mechanical dyssynchrony influence clinical and/or LV reverse remodeling after CRT. Although integration of information about these characteristics would improve patient selection and counseling for CRT, further randomized controlled trials are necessary prior to changing the current guidelines regarding patient selection for CRT.

INTRODUCTION

Cardiac resynchronization therapy (CRT) improves left ventricular (LV) systolic function, heart failure (HF) symptoms, quality of life, and prognosis in patients with moderate or severe heart failure, depressed systolic function, and a wide QRS complex.[1-3] Although results of large clinical trials support the role of CRT as an important therapeutic option in HF, 30% of individual patients do not improve clinically after CRT. In an effort to enhance patient selection criteria and improve response to CRT, single center studies have used echocardiography to detect mechanical dyssynchrony,[4-8] predicated on the assumptions that correction of dyssynchrony underlies the major mechanism of CRT and that echocardiography is superior to electrocardiography in detecting dyssynchrony.

PROSPECT (Predictors of Response to Cardiac Resynchronization Therapy) was the first large-scale, multicenter clinical trial that evaluated the ability of several echocardiographic measures of mechanical ventricular dyssynchrony to predict response to CRT in an observational blinded setting.[9] Although various markers of dyssynchrony contributed significantly to prediction of clinical outcome and reverse remodeling at 6 months follow-up, the sensitivity and specificity of these markers were modest.

Several explanations for the results of PROSPECT have been proposed, including high variability of tissue Doppler (TDI) measurements, and the need for better methods to assess dyssynchrony such as 2D strain imaging or real-time 3-dimensional echocardiography.[10-12] Heart failure however, is a complex syndrome and various pathophysiological issues contribute to the development of heart failure, including age, gender, etiology of heart failure, extent of scar tissue, LV size, etc. It may well be that response to CRT is determined by the combination of these factors[13, 14] rather than dyssynchrony alone. This sub-analysis aimed to investigate the relationship between multiple baseline characteristics (including dyssynchrony measurements) and measures of response to CRT. Response to CRT was defined in two ways:

1) Extent of LV reverse remodeling at 6 months follow-up; and

2) A combination of both clinical and echocardiographic improvement after CRT.

The principal aim of this study was to better characterize the interplay between several key baseline clinical and echocardiographic parameters and measures of response in the PROSPECT population.

METHODS

Complete methods for PROSPECT have been described previously.[15] In brief, 426 patients indicated for CRT (left ventricular ejection fraction [LVEF] ≤35%, New York Heart Association [NYHA] functional class III or IV, and QRS duration ≥130 ms)[16] were enrolled, followed up and analyzed in the final report. Several echocardiographic measures of dyssynchrony were tested as possible predictors of response to CRT defined in 2 ways (clinical composite score and LV end-systolic volume [LVESV] reduction ≥15% at 6 months follow-up). In this sub-analysis, patients were grouped according to the extent of LV reverse remodeling after 6 months of CRT, or to the combined presence/absence of clinical and echocardiographic improvement (definitions see below, "definition of response").

Echocardiography

Left ventricular end-diastolic volume (LVEDV) and LVESV were obtained from the apical 2- and 4-chamber views, and LVEF was calculated using the biplane Simpson's technique.[17]
Three echocardiographic measures of dyssynchrony were evaluated:

1. left ventricular filling ratio (defined as left ventricular filling time [LVFT] in relation to cardiac cycle length [RR] as measured by transmitral Doppler echo [LVFT/RR])[8],
2. inter ventricular mechanical delay (defined as the difference between left and right ventricular pre-ejection intervals [IVMD])[8] and finally,
3. septal to lateral delay (Ts-[lateral-septal]), defined as the delay between time to peak systolic velocity at basal septal and basal lateral segments.[18]

Definition of response

Echocardiographic response

Patients were divided into echocardiographic response sub-groups according to the extent of LV reverse remodeling at 6 months follow-up (Table 1). These sub-groups were defined as follows:

1. super-responders: patients with a reduction in LVESV ≥30%,
2. responders: patients with a reduction in LVESV of 15% to 29%,
3. non-responders: patients with a reduction in LVESV ranging from 0% to 14% and,
4. negative-responders: patients with an increase in LVESV at 6 months follow-up.

Table 1. Definitions of sub-groups according to CRT response at 6 months follow-up: extent of LV reverse remodeling, and combined clinical and echocardiographic response

LV reverse remodeling	
↓ LVESV ≥30%	super-responders
↓ LVESV 15-29%	responders
↓ LVESV 0-14%	non-responders
↑ LVESV	negative-responders
Combined clinical and echocardiographic response	
Improved CCS *AND* ↓ LVESV ≥15%	+/+ responders
Improved CCS *OR* ↓ LVESV ≥15%	+/- responders
NO improved CCS *AND NO* ↓ LVESV ≥15%	-/- responders

CCS = Clinical Composite Score; LVESV = left ventricular end-systolic volume

Combined clinical and echocardiographic response

Improvement in clinical status was measured with the use of the Clinical Composite Score (CCS)[19] at 6 months. Positive clinical response was defined as: the patient survived and was not hospitalized for HF, demonstrated improvement in NYHA class at last observation carried forward or had moderate or marked improvement in patient global assessment score at last observation carried forward. Using both clinical and echocardiographic data, 3 sub-groups were formed according to clinical and/or echocardiographic response;

1.+/+ responders: improved CCS *and* a reduction in LVESV ≥15%,

2.+/- responders: improved CCS *or* a reduction in LVESV ≥15% and,

3.-/- responders: no improvement in CCS *and* no reduction in LVESV ≥15% (Table 1).

For both end-points, extensive analysis of baseline characteristics between the 3 sub-groups was performed.

Statistical analysis

Continuous data are presented as mean±SD, and dichotomous data are presented as numbers and percentages. Comparison of continuous data between 2 patient groups was performed using the independent-samples t test. For comparison between more than 2 groups, least squares regression or analysis of variance (ANOVA) was used, when appropriate. Fisher's exact tests were used to compare dichotomous data between 2 patients groups. For comparison between more than 2 groups, Cochran-Mantel-Haenszel tests for trend were used.[20] All analyses were performed with SAS software (version 9, SAS Inc., Cary, NC). All statistical tests were 2-sided. A p-value <0.05 was considered statistically significant.

RESULTS

Patient characteristics

From the original 426 patients analyzed in PROSPECT, 63 were excluded because of incomplete echocardiographic baseline data. During follow-up, 15 patients died and 18 patients did not have the 6-month follow-up visit. Finally, 44 patients had incomplete data from the 6-month follow-up visit; accordingly, the current study population consisted of 286 patients. These were the patients with complete clinical assessment and complete, paired (baseline and 6 months follow-up) LVESV measurements. Baseline characteristics of the study population are displayed in Table 2. Most patients were male (71%) and underlying etiology of cardiomyopathy was ischemic in 53% of patients. Nineteen percent of patients had a history of either paroxysmal or persistent atrial fibrillation (AF), and a history of ventricular tachycardia (VT) was reported in 80 patients (28%). Patients had severely depressed LV function (mean LVEF 23±7%, mean LVEDV 233±99 ml and mean LVESV 170±88 ml). Medication included diuretics in 86%, angiotensin converting enzyme inhibitors in 91% and beta-blockers in 84% of patients.

Table 2. Baseline characteristics (n = 286)

Age (years)	68 ± 11
Gender (male)	202 (71%)
NYHA functional class III	275 (96%)
Ischemic etiology	151 (53%)
History of myocardial infarction	128 (45%)
Diabetes	81 (28%)
History of AF	53 (19%)
History of VT	80 (28%)
QRS duration (ms)	164 ± 23
LVEF (%)	23 ± 7
LVEDV (ml)	233 ± 99
LVESV (ml)	170 ± 88
LVFT/RR (%)	44 ± 9
IVMD (ms)	43 ± 37
Ts-(lateral-septal) (ms)	56 ± 41

AF = atrial fibrillation; IVMD = inter ventricular mechanical delay; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; LVFT/RR = left ventricular filling ratio; NYHA = New York Heart Association; Ts = time to peak systolic velocity; VT = ventricular tachycardia

Sub-group analysis according to extent of LV reverse remodeling

A mean reduction in LVESV of 19.7±27.3% was observed in the total study population at 6 months follow-up. One hundred and eight patients (37.8%) were classified as super-responders, defined as a relative reduction in LVESV ≥30%. A reduction in LVESV of 15% to 29% was reported in 53 patients (18.5%) and accordingly, these patients were classified as responders. Sixty-seven patients (23.4%) did not show a significant reduction in LVESV (0% to 14%) and were considered non-responders. Finally, 58 patients (20.3%) demonstrated an increase in LVESV (indicating deterioration of LV function) and were classified as negative-responders (Figure 1, Panel A).

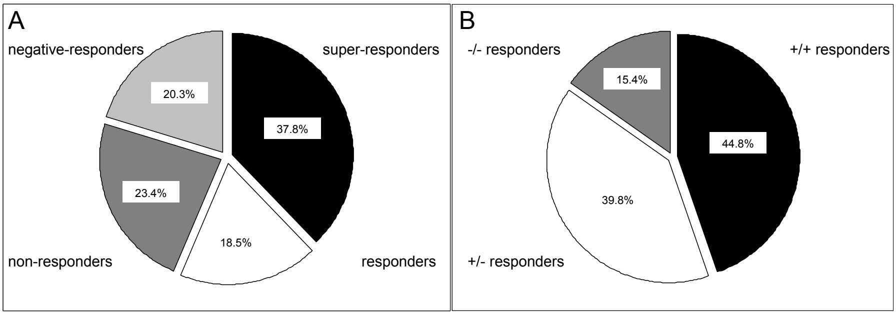

Figure 1. Percentage of responders according to the extent of reduction in LVESV (Panel A) and the combination of clinical response and a reduction in LVESV ≥15% (Panel B).

Several baseline characteristics differed significantly between the 4 sub-groups (Table 3). Echocardiographic response was better among females ($p = 0.0026$). Accordingly, super-response was more frequently observed in females, with 45 women (53.6%) demonstrating super-response vs. 63 men (31.2%, $p = 0.0005$). Secondly, NYHA functional class IV was associated with less reduction in LVESV ($p = 0.016$). Moreover, a larger reduction in LVESV was observed in patients with non-ischemic etiology of heart failure ($p = 0.023$) and super-response was noted in 44.4% of patients with non-ischemic heart failure vs. 31.8% in patients with ischemic heart failure ($p = 0.029$). Additionally, a wider QRS complex was associated with greater reduction in LVESV at follow-up ($p = 0.033$) and a history of VT was significantly related to less LVESV reduction ($p = 0.0005$). For the 3 measures of dyssynchrony, a trend towards better response was observed for lower LVFT/RR ($p = 0.051$) and both larger IVMD and larger Ts-(lateral-septal) were strongly associated with a larger reduction in LVESV at 6 months follow-up ($p = 0.0002$ for IVMD and $p = 0.0022$ for Ts-[lateral-septal]).

To further evaluate differences between patients who demonstrated a marked improvement in LV volume at 6 months follow-up, and patients who deteriorated, comparison of baseline characteristics between the 2 extreme sub-groups (super-responders and negative-responders) was performed. Super-responders were more frequently females (p = 0.0034), were less often in NHYA functional class IV (p = 0.02) and less frequently reported history of VT (p = 0.0026) as compared to negative-responders (Figure 2, Panels A-C). Additionally, super-responders had a wider QRS complex (p = 0.039), and more evidence of mechanical dyssynchrony with a larger IVMD (p<0.0001) and a larger Ts-(lateral-septal) (p = 0.0066) in comparison to negative-responders (Figure 2, Panels D-F).

Table 3. Differences in baseline characteristics between super-responders (SUPER), responders (RESP), non-responders (NON) and negative responders (NEG)

	SUPER (n = 108)	**RESP (n = 53)**	**NON (n = 67)**	**NEG (n = 58)**	p-value
Age (years)	68 ± 10	67 ± 10	68 ± 11	66 ± 13	0.37
Gender (male)	63 (58%)	43 (81%)	49 (73%)	47 (81%)	**0.0026**
NYHA class IV	1 (1%)	2 (4%)	3 (4%)	5 (9%)	**0.016**
Non ischemic etiology	60 (56%)	25 (47%)	27 (40%)	23 (40%)	**0.023**
Diabetes	27 (25%)	16 (30%)	22 (33%)	16 (28%)	0.52
History of AF	21 (19%)	11 (21%)	10 (15%)	11 (19%)	0.71
History of VT	19 (18%)	13 (25%)	25 (37%)	23 (40%)	**0.0005**
QRS duration (ms)	166 ± 20	168 ± 26	163 ± 23	158 ± 24	**0.033**
LVEF (%)	30 ± 9	27 ± 8	29 ± 11	29 ± 10	0.73
LVESV (ml)	161 ± 88	196 ± 81	168 ± 90	167 ± 89	0.77
LVEDV (ml)	223 ± 102	261 ± 93	230 ± 97	229 ± 100	0.83
LVFT/RR (%)	43 ± 9	43 ± 8	46 ± 8	45 ± 10	0.051
IVMD (ms)	50 ± 35	47 ± 34	44 ± 38	25 ± 39	**0.0002**
Ts-(lateral-septal) (ms)	68 ± 44	50 ± 38	49 ± 38	44 ± 35	**0.0022**

Abbreviations as in Table 2

Provided p-values are for trend between sub-groups, Cochran-Mantel-Haenszel test for categorical variables and least squares regression for continuous variables

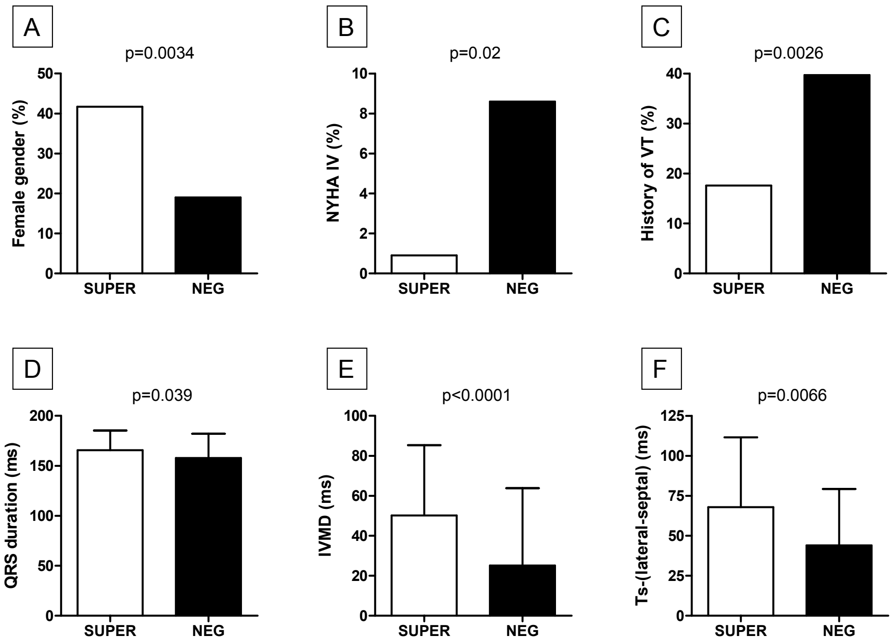

Figure 2. Differences in clinical (Panels A-D) and echocardiographic (Panels E-F) baseline characteristics between LVESV super-responders (SUPER) and negative-responders (NEG). Panels D-F show mean and 1 standard deviation. IVMD = inter ventricular mechanical delay; NYHA = New York Heart Association; Ts = time to peak systolic velocity; VT = ventricular tachycardia.

Sub-group analysis according to combined echocardiographic and clinical response

A positive clinical response at 6 months follow-up was observed in 209 patients (73%). After combining this clinical improvement with the echocardiographic response (reduction in LVESV ≥15%), 128 patients (45%) demonstrated both clinical and echocardiographic response and were classified as +/+ responders. Either clinical response or LVESV response was reported in 114 patients (40%) and accordingly, these patients were classified as +/- responders. Of note, 81 patients had clinical response without LV reverse remodeling ≥15% and a reduction in LVESV ≥15% without clinical improvement was noted in 33 patients. Finally, 44 patients (15%) did not improve in clinical status nor had a reduction in LVESV ≥15%. These patients were classified as -/- responders (Figure 1, Panel B).

Differences in baseline characteristics between the 3 combined sub-groups are summarized in Table 4. For combined positive response after CRT (+/+ responders), there was a strong association with non-ischemic etiology of heart failure ($p = 0.021$). Moreover, history of VT was most frequently observed in -/- responders ($p = 0.0030$). Finally, +/+ responders had a lower LVFT/RR ($p = 0.013$) and a higher IVMD ($p = 0.028$).

Table 4. Differences in baseline characteristics between 3 combined sub-groups according to clinical and echocardiographic response

	+/+ response (n = 128)	**+/- response (n = 114)**	**-/- response (n = 44)**	p-value
Age (years)	68 ± 10	69 ± 11	65 ± 12	0.086
Gender (male)	45 (35%)	28 (25%)	11 (25%)	0.16
NYHA class IV	2 (2%)	6 (5%)	3 (7%)	0.11
Non ischemic etiology	72 (56%)	45 (39%)	18 (41%)	**0.021**
Diabetes	35 (27%)	36 (32%)	10 (23%)	0.54
History of AF	25 (20%)	17 (15%)	11 (25%)	0.31
History of VT	24 (19%)	37 (32%)	19 (43%)	**0.0030**
QRS duration (ms)	166 ± 21	164 ± 23	158 ± 24	0.18
LVEF (%)	29 ± 9	29 ± 10	29 ± 10	0.86
LVESV (ml)	171 ± 89	167 ± 82	178 ± 99	0.80
LVEDV (ml)	235 ± 102	228 ± 91	241 ± 110	0.73
LVFT/RR (%)	42 ± 9	45 ± 8	46 ± 9	**0.013**
IVMD (ms)	49 ± 34	40 ± 38	34 ± 41	**0.028**
Ts-(lateral-septal) (ms)	63 ± 43	51 ± 36	48 ± 45	0.12

Abbreviations as in Table 2

Provided p-values are for differences between sub-groups, Cochran-Mantel-Haenszel test for categorical variables and analysis of variance (ANOVA) for continuous variables

DISCUSSION

In this sub-analysis of the PROSPECT study, we explored the relationship between baseline characteristics and CRT outcomes, defined on a reverse remodeling spectrum as well as combinations of clinical and volume responses. We showed that patients manifesting different responses in these terms have distinguishable baseline profiles.

Defining CRT outcomes

Are there more clinically relevant ways of defining CRT outcomes than dichotomous LV volume changes or clinical status alone? Perhaps the most important measure of outcome is mortality. There is evidence that CRT under the existing indications improves survival.[3] However to further refine the patient sub-populations that are likely to manifest mortality reductions with CRT would require expensive studies that will face enrollment difficulties. For example, do patients with wide QRS, LVEF ≤35%, symptomatic HF and only ischemic etiology derive a mortality benefit with CRT? Do women with HF gain a survival advantage with CRT? In recognition of the barriers to performing such studies, as well as the fact that non-vital outcomes reflecting quality of life are often more important to patients, clinical status measured in various different ways and changes in LV volumes have emerged as surrogate measures of outcomes after CRT.

Whether measured as clinical composite score, NYHA status, 6-minute walk test, or quality of life, clinical status is clearly important to the patient. However, clinical improvement would ideally be accompanied by a survival advantage. Further it would be important to know if clinical improvement might come at a cost of possibly shortened life expectancy. Conversely, one might accept worsened clinical status if a therapy might prolong life. Certainly it would be important to know if both measures are expected to worsen with CRT. It appears that non-ischemic patients with echocardiographic evidence of mechanical dyssynchrony and no history of VT are more likely to improve both clinically and by LV volume.

LV reverse remodeling has been demonstrated to correlate well with survival in HF trials of medical interventions[21] and may be a credible surrogate end-point for mortality. More specifically, LV reverse remodeling after CRT has proven to be an important prognostic factor for long-term outcome (more important than clinical response).[22, 23] Yu and colleagues determined a relationship between the extent of LVESV reduction and long-term clinical outcomes.[22] These authors reported that patients with a reduction in LVESV ≥10% after CRT, had significantly better survival compared to patients with LVESV reduction <10%. A more recent study by Ypenburg et al also related long-term prognosis to the extent of LV reverse remodeling at mid-term follow-up.[23] A total of 302 heart failure patients treated with CRT were divided into 4 sub-groups according to the extent of LV reverse remodeling at 6 months follow-up (similar to the sub-groups in the present study). Patients with an increase in LVESV ("negative-responders") showed a high mortality rate (>60% at 36 months follow-up), while in the group with a decrease in LVESV ≥30% ("super-responders"), only 1 patient (1.6%) died. These prognostic data from previous CRT studies emphasize the importance of LV reverse remodeling. Redefining LVESV changes after an intervention allows for more in-depth, clinically relevant understanding of the changes that might occur after CRT.

Effect of baseline characteristics on LV volume change after CRT

Do certain baseline characteristics, such as QRS duration, echocardiographically measured dyssynchrony, etiology of heart failure, gender, NYHA class or history of VT, serve as determinants of CRT outcomes?

The predictive value of QRS duration remains controversial. Several studies have shown no added value of a wider QRS complex in patients who were pre-selected on the basis of a QRS duration >120 ms.[24, 25] Conversely, there are also reports of greater response after CRT in patients with a wider QRS complex.[3] In the current report, a significant correlation was noted between longer QRS duration and greater reduction in LVESV at 6 months follow-up.

Evidence of pre-implantation mechanical dyssynchrony assessed with echocardiography seemed a step forward compared with QRS duration, and accordingly, many single-center studies have reported strong relationships between such measures and outcomes after CRT.[4-8] PROSPECT demonstrated that several measures of mechanical dyssynchrony were statistically different between responders and non-responders to CRT, but with modest sensitivity and specificity.[9] However, with further refining of the outcome definitions, hypothesis generating observations can be made. Three of the dyssynchrony parameters tested in PROSPECT were associated with extent of reverse remodeling or the combination end-point after CRT: LVFT/RR, IVMD and Ts-(lateral-septal). These measures were selected as they represent 3 different levels of cardiac dyssynchrony: atrioventricular dyssynchrony (LVFT/RR), inter-ventricular dyssynchrony (IVMD) and intraventricular dyssynchrony (Ts-[lateral-septal]). Other studied measures of mechanical dyssynchrony were not evaluated in this study for 1 or more of the following reasons: 1) not statistically different between responders and non-responders in PROSPECT (standard deviation of time from QRS to peak systolic velocity in ejection phase for 12 left ventricular segments [Ts-SD]), 2) had high variability (e.g. septal-posterior wall motion delay [SPWMD]), and 3) pathophysiologically redundant (left ventricular preejection interval [LPEI] is included in IVMD). All 3 studied dyssynchrony parameters were significantly associated (borderline significance for LVFT/RR) with the extent of LV reverse remodeling at 6 months follow-up. Super-response was more frequently observed in patients with more extensive dyssynchrony, suggesting that pre-implantation echocardiographic assessment of cardiac mechanical dyssynchrony may serve to help determine likelihood of LVESV reduction.

Etiology of HF may affect outcome after CRT. It has been observed in multiple studies, including PROSPECT, that non-ischemic HF patients are more likely to improve. In the current analysis, a larger decrease in LVESV in patients with non-ischemic heart failure was noted. This observation is consistent with previous work of Ajmone et al,[26] and recent data from CARE-HF.[27] However, also in CARE-HF, similar reduction in mortality was observed in ischemic vs. non-ischemic patients so that until present it remains unclear what the relative merits of CRT are in ischemic and non-ischemic heart failure patients.[27, 28] Nonetheless, it has been demonstrated that the presence of transmural scar tissue in the region of the LV lead has a negative influence on response to CRT.[29]

A greater reduction in post CRT LVESV has been described in women vs. men. A large observational study by Lilli et al showed not only greater changes in LV volumes in women, but also a higher percentage (76.1% in women vs. 59.3% in men, $p<0.05$) that demonstrated significant LV reverse remodeling, defined as a reduction in LVESV ≥10% at 12 month follow-up.[30]

Patients in NYHA functional class IV did poorly with CRT in the current study. In fact, 5 of the 11 (45%) such patients demonstrated an increase in LVESV at 6 month follow-up. Although a small observational study by Herweg et al reported a significant decrease in LVESV from 174±65 ml to 150±78 ml ($p<0.01$) after initiation of CRT in 10 inotrope-dependent, NYHA class IV heart failure patients,[31] use of CRT with or without defibrillator backup, in end-stage, NYHA class IV patients remains difficult.

An interesting finding in the present study is the relationship between a history of VT and extent of LV reverse remodeling. Patients with negative response were twice as likely to have a history of VT as compared to super-responders. In addition, correlations between less VT and greater LV volume reduction[32] and clinical improvement (NYHA class)[33] have also been reported previously.

Clinical implications

Rather than attempting to predict narrowly defined responses to CRT in individual patients, the current study evaluated factors that contribute to post CRT clinical course, comprising of structural and clinical definitions. Therefore, consideration of the relevant baseline characteristics (gender, NYHA class, etiology, dyssynchrony, history of VT) may help place the patient in the appropriate part of the spectrum of responses and aid in pre-implantation counseling and setting of expectations.

Limitations

A limitation of the current study is that no long-term outcome data are available with regard to morbidity and mortality after the 6 months follow-up. However, as previously indicated, LV reverse remodeling after CRT is an important prognostic factor for long-term outcome. Furthermore, the current definitions of CRT response do not take into account disease progression. Patients with no changes in clinical or structural measures might seem to be "non-responders" but in some cases may in fact represent a positive outcome, as disease progression may be attenuated compared with natural history.[34, 35] However, this can not be confirmed from the current data, due to the absence of a control group. Finally, other issues that could also be related to response to CRT, such as optimal LV pacing lead position, percentage of biventricular pacing and extent of myocardial scar, were not addressed in this study. Future studies are warranted to further elucidate the effect of these additional characteristics on outcome after CRT.

Conclusions

Sub-analysis of data from PROSPECT showed that gender, etiology of heart failure, QRS duration, severity of heart failure symptoms, a history of VT and the presence of baseline mechanical dyssynchrony influence response to CRT. Integrating information regarding these characteristics would improve patient selection and counseling for CRT. However, further randomized controlled trials to study the effect of CRT in these groups are necessary prior to changing the current guidelines regarding patient selection for CRT.

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