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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Aims
Predictors of Response to Cardiac Resynchronization Therapy (CRT) (PROSPECT) was the first large-scale, multi-centre 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 and results
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 15–29%), non-responders (reduction in LVESV 0–14%), and negative responders (increase in LVESV). In addition, three 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 subgroups were analysed. Super-responders were more frequently females, had non-ischaemic heart failure (HF), and had a wider QRS complex and more extensive mechanical dyssynchrony at baseline. Conversely, negative responders were more frequently in New York Heart Association class IV and had a history of ventricular tachycardia (VT). Combined positive responders after CRT (+/+ responders) had more non-ischaemic aetiology, more extensive mechanical dyssynchrony at baseline, and no history of VT.

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

Keywords
Cardiac resynchronization therapy • Heart failure • Echocardiography • Clinical trial • Reverse remodelling

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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 HF, 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-centre 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, multicentre 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 the prediction of clinical outcome and reverse remodelling at 6-month 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 3D echocardiography. 10–12 Heart failure, however, is a complex syndrome, and various pathophysiological issues contribute to the development of HF, including age, gender, aetiology of HF, extent of scar tissue, LV size, and so on. 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:

(i) extent of LV reverse remodelling at 6-month follow-up; and
(ii) 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 [LV 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 analysed in the final report. Several echocardiographic measures of dyssynchrony were tested as possible predictors of response to CRT defined in two ways [clinical composite score (CCS) and LV end-systolic volume (LVESV) reduction ≥ 15% at 6-month follow-up]. In this sub-analysis, patients were grouped according to the extent of LV reverse remodelling after 6 months of CRT, or to the combined presence/absence of clinical and echocardiographic improvement (for definitions, see section ‘Definition of response’).

Echocardiography

Left ventricular end-diastolic volume (LVEDV) and LVESV were obtained from the apical two- and four-chamber views, and LVEF was calculated using the biplane Simpson’s technique. 17

Three echocardiographic measures of dyssynchrony were evaluated:

(i) LV filling ratio [defined as LV filling time (LVFT) in relation to cardiac cycle length (RR) as measured by transmural Doppler echo (LVFT/RR)];
(ii) inter-ventricular mechanical delay [defined as the difference between left and right ventricular pre-ejection intervals (IVMD)]; and finally,
(iii) 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 subgroups according to the extent of LV reverse remodelling at 6-month follow-up (Table 1). These subgroups were defined as follows:

(i) super-responders: patients with a reduction in LVESV ≥ 30%;
(ii) responders: patients with a reduction in LVESV of 15–29%;
(iii) non-responders: patients with a reduction in LVESV ranging 0–14%; and
(iv) negative responders: patients with an increase in LVESV at 6-month follow-up.

Combined clinical and echocardiographic response

Improvement in clinical status was measured with the use of the 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, three subgroups were formed according to clinical and/or echocardiographic response;

(i) +/+ responders: improved CCS and a reduction in LVESV ≥ 15%;

Table 1 Definitions of subgroups according to cardiac resynchronization therapy response at 6-month follow-up: extent of left ventricular reverse remodelling, and combined clinical and echocardiographic response

<table>
<thead>
<tr>
<th>LV reverse remodelling</th>
<th>Combination</th>
<th>CCS, clinical composite score; LVESV, left ventricular end-systolic volume.</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ LVESV ≥ 30%</td>
<td>Super-responders</td>
<td></td>
</tr>
<tr>
<td>↓ LVESV 15–29%</td>
<td>Responders</td>
<td></td>
</tr>
<tr>
<td>↓ LVESV 0–14%</td>
<td>Non-responders</td>
<td></td>
</tr>
<tr>
<td>↑ LVESV</td>
<td>Negative responders</td>
<td></td>
</tr>
<tr>
<td>Combined clinical and echocardiographic response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improved CCS and ↓ LVESV ≥ 15%</td>
<td>+/+ Responders</td>
<td></td>
</tr>
<tr>
<td>Improved CCS or ↓ LVESV ≥ 15%</td>
<td>+/- Responders</td>
<td></td>
</tr>
<tr>
<td>No improved CCS and no ↓ LVESV ≥ 15%</td>
<td>+/- Responders</td>
<td></td>
</tr>
</tbody>
</table>
were two-sided. A software (version 9, SAS Inc., Cary, NC, USA). All statistical tests for trend were used. For comparison between more than two groups, Cochran–Mantel–Haenszel tests for trend were used. All analyses were performed with SAS software (version 9, SAS Inc., Cary, NC, USA). All statistical tests were two-sided. A $P$-value $< 0.05$ was considered statistically significant.

### Results

#### Patient characteristics

From the original 426 patients analysed 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-month follow-up) LVESV measurements. Baseline characteristics of the study population are given in Table 2. Most patients were male (71%), and underlying aetiology of cardiomyopathy was ischaemic 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 $23 \pm 7\%$, mean LVEDV $233 \pm 99$ mL and mean LVESV $170 \pm 88$ mL). Medication included diuretics in 86%, angiotensin-converting enzyme-inhibitors in 91%, and beta-blockers in 84% of patients.

#### Subgroup analysis according to extent of left ventricular reverse remodelling

A mean reduction in LVESV of $19.7 \pm 27.3\%$ was observed in the total study population at 6-month follow-up. One hundred and eight patients (37.8%) were classified as super-responders, defined as a relative reduction in LVESV $\geq 30\%$. A reduction in LVESV of 15–29% 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 (0–14%) 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 1A).

Several baseline characteristics differed significantly between the four subgroups (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%, $P = 0.0005$). Second, 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-ischaemic aetiology of HF ($P = 0.023$), and super-response was noted in 44.4% of patients with non-ischaemic HF vs. 31.8% in patients with ischaemic HF ($P = 0.029$). In addition, 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 three 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-month 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-month follow-up, and patients who deteriorated, comparison of baseline characteristics between the two extreme subgroups (super-responders and negative responders) was performed. Super-responders were more frequently females ($P = 0.0034$), were less often in NYHA functional class IV ($P = 0.02$), and less frequently reported history of VT ($P = 0.0026$) compared with negative responders (Figure 2A–C). In addition, 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 with negative responders (Figure 2D–F).

#### Subgroup analysis according to combined echocardiographic and clinical response

A positive clinical response at 6-month 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 +/2 responders. Of note, 81 patients had clinical response without LV reverse remodelling ≥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 2/2 responders (Figure 1B).

Differences in baseline characteristics between the three combined subgroups are summarized in Table 4. For combined positive response after CRT (+/+- responders), there was a strong association with non-ischaemic aetiology of HF (P = 0.021). Moreover, history of VT was most frequently observed in -/- responders (P = 0.0003). Finally, +/- responders had a lower LVFT/RR (P = 0.013) and a larger IVMD (P = 0.028).

**Discussion**

In this sub-analysis of the PROSPECT study, we explored the relationship between baseline characteristics and CRT outcomes, defined on a reverse remodelling 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 cardiac resynchronization therapy 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. However, to further refine the patient sub-populations that are likely to manifest mortality reductions with CRT would require expensive studies that will face enrolment difficulties. For example, do patients with wide QRS, LVEF ≤35%, symptomatic HF, and only ischaemic aetiology derive a mortality benefit with CRT? Do women with HF gain a survival advantage with CRT?

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

Table 4 Differences in baseline characteristics between three combined subgroups according to clinical and echocardiographic response

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

Abbreviations as in Table 2.
Provided P-values are for differences between subgroups. Cochran–Mantel–Haenszel test for categorical variables and ANOVA for continuous variables.
Significant P-values in boldface.
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 CCS, NYHA status, 6 min 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 whether 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 whether both measures are expected to worsen with CRT. It appears that non-ischaemic 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 remodelling has been demonstrated to correlate well with survival in HF trials of medical interventions and may be a credible surrogate endpoint for mortality. More specifically, LV reverse remodelling after CRT has proved to be an important prognostic factor for long-term outcome (more important than clinical response). Yu et al. determined a relationship between the extent of LVESV reduction and long-term clinical outcomes. These authors reported that patients with a reduction in LVESV ≥10% after CRT had significantly better survival compared with patients with LVESV reduction <10%. A more recent study by Ypenburg et al. also related long-term prognosis to the extent of LV reverse remodelling at mid-term follow-up. A total of 302 HF patients treated with CRT were divided into four subgroups according to the extent of LV reverse remodelling at 6-month follow-up (similar to the subgroups in the present study). Patients with an increase in LVESV (negative responders) showed a high mortality rate (>60% at 36-month follow-up), whereas in the group with a decrease in LVESV ≥30% (super-responders), only one patient (1.6%) died. These prognostic data from previous CRT studies emphasize the importance of LV reverse remodelling. 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 left ventricular volume change after cardiac resynchronization therapy**

Do certain baseline characteristics, such as QRS duration, echocardiographically measured dyssynchrony, aetiology of HF, 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. Conversely, there are also reports of greater response after CRT in patients with a wider QRS complex. In the current report, a significant correlation was noted between longer QRS duration and greater reduction in LVESV at 6-month follow-up.

Evidence of pre-implantation mechanical dyssynchrony assessed with echocardiography seemed a step forward compared with QRS duration, and accordingly, many single-centre studies have reported strong relationships between such measures and outcomes after CRT. PROSPECT demonstrated that several measures of mechanical dyssynchrony were statistically different between responders and non-responders to CRT, but with modest sensitivity and specificity. 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 the extent of reverse remodelling or the combination endpoint after CRT: LVFT/RR, IVMD, and Ts-(lateral-septal). These measures were selected as they represent three 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 one or more of the following reasons: (i) not statistically different between responders and non-responders in PROSPECT (standard deviation of time from QRS peak to systolic velocity in ejection phase for 12 LV segments [Ts-SD]), (ii) had high variability [e.g. septal-posterior wall motion delay (SPWMD)], and (iii) pathophysiologically redundant (LV pre-ejection interval is included in IVMD). All three dyssynchrony parameters studied were significantly associated (borderline significance for LVFT/RR) with the extent of LV reverse remodelling at 6-month 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 the likelihood of LVESV reduction.

Aetiology of HF may affect the outcome after CRT. It has been observed in multiple studies, including PROSPECT, that non-ischaemic HF patients are more likely to improve. In the current analysis, a larger decrease in LVESV in patients with non-ischaemic HF was noted. This observation is consistent with the previous work of Marzan et al. and the recent data from CARE-HF. However, also in CARE-HF, similar reduction in mortality was observed in ischaemic vs. non-ischaemic patients so until present it remains unclear what the relative merits of CRT are in ischaemic and non-ischaemic HF patients. 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.

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 remodelling, defined as a reduction in LVESV ≥10% at 12-month follow-up. 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 to 150 ± 78 mL (P < 0.01) after the initiation of CRT in 10 inotrope-dependent, NYHA class IV HF patients, the 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 the extent of LV reverse remodelling. Patients with negative response were twice as likely to have a history of VT compared with super-responders. In addition, correlations between less VT and greater LV volume reduction and clinical improvement (NYHA class) 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 structural and clinical definitions. Therefore, consideration of the relevant baseline characteristics (gender, NYHA class, aetiology, dysynchrony, history of VT) may help place the patient in the appropriate part of the spectrum of responses and aid in pre-implantation counselling 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-month follow-up. However, as indicated previously, LV reverse remodelling 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. However, this cannot be confirmed from the current data because of 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 the 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, aetiology of HF, QRS duration, severity of HF symptoms, a history of VT, and the presence of baseline mechanical dysynchrony influence response to CRT. Integrating information regarding these characteristics would improve patient selection and counselling 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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Extent of response after CRT: results from PROSPECT


