CHAPTER 26

Comparison of time course of response to cardiac resynchronization therapy in patients with ischemic versus nonischemic cardiomyopathy

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ABSTRACT

Objectives: Time course of the effects of cardiac resynchronization therapy (CRT) on left ventricular (LV) systolic function and reverse remodeling is still unknown and was the subject of this study. In particular, whether the acute benefit of CRT translates in late response was explored. Furthermore, the time course of response was compared between ischemic and non-ischemic patients.

Methods: A total of 222 consecutive heart failure patients (135 ischemic) scheduled for CRT, were included. Standard echocardiography was performed before, immediately after CRT and at 6 months follow-up (6MFU) to measure LV end-systolic (ESV) and end-diastolic (EDV) volume, and ejection fraction (EF).

Results: Immediately after CRT, a significant improvement in LVEF (from 25±8% to 31±9%, p <0.001) and LVESV (from 163±68ml to 149±63ml, p <0.001) was observed, followed by an additional improvement at 6MFU (to 34±9% and 132±62ml respectively, both p <0.001). Significant reduction in LVEDV was observed only at 6MFU (from 217±73ml to 194±72ml, p <0.001). An acute reduction in LVESV of 6% could predict response to CRT at 6MFU (defined as a reduction ≥15% in LVESV) with a sensitivity and specificity of 79% and 75%. Time course of response to CRT was similar in ischemic and non-ischemic patients, but reduction in LVESV and LVEDV was significantly greater in non-ischemic patients (p <0.001).

Conclusions: The beneficial effect of CRT on LV systolic function occurs immediately after CRT, with additional improvement at 6MFU. The acute reduction in LVESV can predict response to CRT at 6MFU. Non-ischemic patients show a significantly greater LV reverse remodeling compared to ischemic patients.
INTRODUCTION

The precise time course of improvement in left ventricular (LV) function and reduction in LV volumes after cardiac resynchronization therapy (CRT) is currently unknown and was subject of the current study. For this purpose, 230 patients underwent sequential echocardiography before, 1 day and 6 months after CRT implantation. Moreover, the current study explored whether it could be possible that an acute improvement in systolic function predicts reverse remodeling at late follow-up. Finally, the time course of improvement in systolic function and reverse remodeling may be different between patients with ischemic and non-ischemic cardiomyopathy and this was also evaluated in the current study.

METHODS

A total of 230 consecutive heart failure patients, scheduled for implantation of a CRT device, were included. Traditional selection criteria for CRT were applied, including: New York Heart Association (NYHA) functional class III or IV, despite optimal medical therapy; LV ejection fraction (EF) ≤35% and QRS duration ≥120 ms. Patients with a recent myocardial infarction (<3 months) or decompensated heart failure were excluded. Clinical status, including assessment of NYHA class, Minnesota quality-of-life score and 6-minute walk test, was assessed before pacemaker implantation and at 6-months follow-up. QRS duration was measured at baseline, immediately after CRT and at 6 months follow-up from the surface ECG using the widest QRS complex from the leads II, V1 and V6. Moreover, 2D echocardiography was performed before and immediately after pacemaker implantation and repeated at 6 months follow-up to evaluate LV volumes and LVEF.

Patients were imaged in the left lateral decubitus position using a commercially available system (Vingmed Vivid Seven, General Electric Healthcare, Horten, Norway). Images were obtained using a 3.5-MHz transducer, at a depth of 16 cm in the standard apical views. All images were recorded digitally in cine-loop format and analyzed offline with commercial software Echopac 7.0.0 (GE Healthcare). LV end-systolic volume (ESV) and LV end-diastolic volume (EDV) were determined from the conventional apical 2- and 4-chamber views and LVEF was calculated using the biplane Simpson's technique. Inter- and intra-observer agreement for assessment of LV function and volumes were 90% and 96% respectively.

Echocardiographic response was defined as an improvement ≥15% in LVESV. Response was determined acutely after CRT implantation and at 6 months follow-up.

The LV pacing lead was inserted transvenously via the subclavian route. First, a coronary sinus venogram was obtained using a balloon catheter. Next, the LV pacing lead was inserted through the coronary sinus, using an 8Fr-guiding catheter, and positioned as far as possible in the venous system, preferably in the (postero-) lateral vein. The right atrial and ventricular
leads were positioned conventionally. When an indication for an internal defibrillator existed, a combined device was implanted (Contak CD or Renewal, Guidant Corp.; Insync III-CD or Marquis, Medtronic Inc.). In all patients the implantation was successful without major complications. Two types of LV leads were used (Easytrak 4512-80, Guidant Corp., or Attain-SD 4194, Medtronic Inc.). For each patient, the AV interval was adjusted to maximize mitral inflow duration with pulsed-wave Doppler echocardiography.

Continuous data are presented as mean±standard deviation; dichotomous data are presented as numbers and percentage. Comparison of data was performed using the paired or unpaired Student t test or χ² test when appropriate. For the LVESV and LVEDV, that were not normally distributed, a log-transformation has been performed. Sequential data measurements, in the total population and in the groups of patients with and without ischemic cardiomyopathy, were analyzed by repeated measures analysis of variance (ANOVA). A two-way ANOVA analysis was performed for comparison of time trends between patients with and without ischemic cardiomyopathy. To determine the relationship between immediate changes in LVESV after CRT and response to CRT at late follow-up (defined as a reduction ≥15% in LVESV), multivariable logistic regression analysis was applied including patient’s clinical and echocardiographic characteristics at baseline (odds ratios with their corresponding 95% confidence intervals [CI] are reported). Receiver operating characteristic (ROC) curve analysis was also applied to obtain a cut-off value for the acute percentage change in LVESV (acute delta LVESV) that can be used in clinical practice to predict echocardiographic response to CRT at late follow-up. The ‘optimal’ threshold was defined as the value for which the sum of sensitivity and specificity to distinguish between echocardiographic responders/non-responders was maximized. Statistical significance was set a two tailed p-value <0.05. A statistical software program SPSS 12.0 (SPSS Inc, Chicago, II, USA) was used for statistical analysis.

RESULTS

A total of 8 (3.5%) patients died before the 6-month follow-up was completed. Baseline characteristics of the remaining 222 patients (180 men, mean age 66±10 years) are summarized in Table 1. Most patients (94%) were in NYHA class III. Echocardiographic evaluation revealed LV dilatation with depressed LVEF.

A significant improvement in clinical status was observed at 6 months follow-up. In particular, NYHA class improved significantly from 3.1±0.3 to 1.9±0.7 (p <0.01). A total of 71% of patients exhibited a reduction in NYHA class of 1 score or more. Furthermore, the Minnesota quality-of-life score improved from 33±19 to 24±19 (p <0.01) and the 6-minute walking distance increased from 324±106 m to 392±108 m (p <0.01). QRS duration at baseline was
153±26 ms and decreased to 136±26 ms (p <0.01) immediately after CRT implantation, which remained unchanged at 6 months follow-up (136±28 ms).

Acutely after CRT implantation, a significant reduction in LVESV was observed (from 163±68 ml to 149±63 ml, p <0.001), with a significant improvement in LVEF (from 25±8% to 31±9%, p <0.001). LVEDV remained unchanged (217±77 ml at baseline vs. 216±76 ml after CRT implantation, p = NS).

At 6 months follow-up, a further reduction in LVESV to 132±62 ml (p <0.001 vs. baseline and immediate follow-up) was noted, with an additional improvement in LVEF to 34±9% (p <0.001 vs. baseline and immediate follow-up). LVEDV also showed a significant reduction to 194±72 ml (p <0.001 vs. baseline and immediate follow-up) at 6 months follow-up.

When a reduction in LV end-systolic volume ≥15% was used to define response to CRT, 40% of patients exhibited an immediate response to CRT, with an additional 23% of patients showing response at 6 months follow-up, resulting in a total of 63% echocardiographic responders to CRT.

Table 2 shows the results of the multivariable logistic regression analysis applied to identify whether the acute changes in LVESV after CRT and the baseline clinical and echocardiographic variables were related to response to CRT at late follow-up. After correction for the covariates, the only variables that remained significantly correlated with late response to CRT were the etiology of cardiomyopathy (OR = 0.28, 95%CI 0.13–0.63, p = 0.002) and the acute percentage
change in LVESV (acute delta LVESV, OR = 1.21, 95% CI 1.14-1.26, p <0.001). Furthermore, ROC curve analysis revealed that a cut-off value of 6% for acute delta LVESV yielded a sensitivity of 79% with a specificity of 75% to predict echocardiographic response to CRT (area under the curve = 0.85, p <0.001) (Figure 1).

Of the 222 patients included, 135 (61%) patients had ischemic cardiomyopathy and 87 (39%) had non-ischemic cardiomyopathy. No significant differences in the baseline characteristics were noted between the 2 groups (Table 3). The immediate changes after CRT in LV volumes and LVEF in patients with ischemic cardiomyopathy are shown in Figure 2 (panels A to C). Immediately after CRT implantation, a significant reduction in LVESV (from 163±65 ml to 150±61 ml, p <0.001) and an improvement in LVEF (from 25±8% to 31±9%, p <0.001) were observed. LVEDV remained unchanged (217±74 ml vs. 217±73 ml, p = NS).

At 6 months follow-up, a further reduction in LVESV to 139±59 ml (p <0.001 vs. baseline and immediate follow-up) was detected (Figure 2, panel A). Similarly, a further improvement

Table 2. Multivariable logistic regression analysis: estimates of correlation between the baseline clinical and echocardiographic characteristics (including the acute changes in left ventricular end-systolic volume) and response to cardiac resynchronization therapy, defined as a reduction ≥15% of left ventricular end-systolic volume at 6 month follow-up.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Odds ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.99 [0.95-1.03]</td>
<td>0.74</td>
</tr>
<tr>
<td>Male gender</td>
<td>1.28 [0.48-3.41]</td>
<td>0.62</td>
</tr>
<tr>
<td>6-minute walk test</td>
<td>1.00 [0.99-1.00]</td>
<td>0.95</td>
</tr>
<tr>
<td>QRS duration</td>
<td>0.98 [0.97-1.01]</td>
<td>0.075</td>
</tr>
<tr>
<td>Ischemic etiology</td>
<td>0.28 [0.13-0.63]</td>
<td>0.005</td>
</tr>
<tr>
<td>Left ventricular ejection fraction</td>
<td>0.99 [0.94-1.04]</td>
<td>0.75</td>
</tr>
<tr>
<td>Left ventricular end-diastolic volume</td>
<td>0.99 [0.99-1.00]</td>
<td>0.56</td>
</tr>
<tr>
<td>Acute delta left ventricular end-systolic volume</td>
<td>1.21 [1.14-1.26]</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

![Figure 1](image1.png)

**Figure 1.** Optimal cut-off value of the percentage change in left ventricular end-systolic volume immediately after CRT (acute delta LVESV = [(LVESV at baseline – LVESV acutely after CRT)/LVESV at baseline] x 100) to predict echocardiographic response to CRT at late follow-up, determined by ROC curve analysis. AUC = area under the curve.
Time course of response to CRT in ischemic and non-ischemic patients

In LVEF to 33±10% (p <0.001 vs. baseline and immediate follow-up) was noted (Figure 2, panel B). In addition, a reduction in LVEDV to 202±68 ml was observed (p <0.001 vs. baseline and immediate follow-up) (see Figure 2, panel C).

In 32% of patients with ischemic cardiomyopathy, an acute reduction in LVESV ≥15% was noted; at 6 months follow-up, an additional 22% showed a significant reduction in LVESV, resulting in a total of 54% echocardiographic responders to CRT out of 135 patients with ischemic cardiomyopathy.

The immediate changes after CRT in LV volumes and LVEF in patients with non-ischemic cardiomyopathy are displayed in Figure 2 (panels A to C). Immediately after CRT implantation, a significant improvement in LVESV (from 163±74 ml to 146±68 ml, p <0.001) and LVEF (from 25±8% to 32±8%, p <0.001) were observed. LVEDV remained unchanged (217±74 ml vs. 215±81 ml, p = NS).

At 6 months follow-up, a further reduction in LVESV to 122±64 ml (p <0.001 vs. baseline and immediate follow-up) was detected (Figure 2, panel A). Similarly, a further improvement in LVEF to 35±8% (p <0.001 vs. baseline and immediate follow-up) was noted (Figure 2, panel B). In addition, a reduction in LVEDV to 184±78 ml was observed (p <0.001 vs. baseline and immediate follow-up) (Figure 2, panel C).

In 53% of patients with non-ischemic cardiomyopathy an acute reduction in LVESV ≥15% was noted (p <0.05 vs. 32% of acute responders with ischemic cardiomyopathy); at 6 months follow-up, an additional 25% of patients showed a significant reduction in LVESV, resulting in a total of 78% echocardiographic responders to CRT out of 87 patients with non-ischemic cardiomyopathy (p <0.05 vs. 54% of late responders with ischemic cardiomyopathy).

A significant difference in time course after CRT implantation between ischemic and non-ischemic patients was observed for LVESV and LVEDV (Figure 2): the improvement over time of these parameters was more outspoken in patients with non-ischemic cardiomyopathy, particularly at late follow-up (two-way ANOVA p <0.001). No significant difference was found for the changes over time of LVEF between the 2 groups (Figure 2).

<table>
<thead>
<tr>
<th>Table 3. Baseline characteristics of patients with ischemic cardiomyopathy and non-ischemic cardiomyopathy.</th>
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</thead>
<tbody>
<tr>
<td>Variable</td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Male/Female</td>
</tr>
<tr>
<td>QRS duration (ms)</td>
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<tr>
<td>NYHA class II/IV (n)</td>
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<tr>
<td>Left ventricular ejection fraction (%)</td>
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<tr>
<td>Left ventricular end-diastolic volume (ml)</td>
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<td>Left ventricular end-systolic volume (ml)</td>
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**DISCUSSION**

Thus far, most of the studies addressed the effects of CRT on LV systolic function and LV reverse remodeling at mid- or long-term follow-up. Both an absolute increase >5% in LVEF and a reduction ≥15% in LVESV have been used to define a favorable response to CRT. Few studies focused on the acute effects of CRT. Breithardt et al. demonstrated a significant increase in dP/dt\textsubscript{max} immediately after CRT, while Dohi and coworkers defined acute response to CRT as an increase ≥15% in LV stroke volume. Other studies applied a definition...
of acute response as a reduction $\geq 15\%$ in LVESV \textsuperscript{12,13}, but did not include information on long-term follow-up.

Accordingly, the precise time course of response to CRT is currently unknown. It is unclear whether improvement of LV systolic function after CRT implantation is a gradual process or whether this improvement occurs immediately and then remains unchanged, or whether some patients may not respond acutely, but do respond at later stage.

The current study evaluated the precise time course of response to CRT, systematically looking at parameters of LV systolic function (LVEF, LVESV) and LV remodeling (LVEDV, LVESV). Acutely after implantation, a significant increase in LVEF and a decrease in LVESV were observed, followed by an additional improvement in these parameters at 6 months follow-up. Of note, significant reduction in LVEDV only occurred at late follow-up. The acute improvement after CRT implantation probably indicates a pure effect of CRT on cardiac systolic performance, reflected in the changes in LVEF and LVESV (but not in LVEDV). Conversely, late improvement is the result of significant LV reverse remodeling (with a reduction in both LVEDV and LVESV) with a further improvement in LV systolic function. Indeed, the beneficial effect of CRT on LV remodeling (with changes in cardiac structure and geometry) needs more time to occur.

In clinical practice, it is important to identify whether a patient responds to CRT or not, particularly in terms of LV systolic function. In fact, an improvement in LV systolic function is most likely the base for a clinical improvement and it has been demonstrated to be the best predictor of improved survival after CRT \textsuperscript{14}. Furthermore, the possibility to predict a significant improvement in LV systolic function (i.e. response to CRT) at long-term follow-up through the evaluation of the acute effects of CRT may be of great interest, with important implications for patient management. In the current study, the acute percentage change in LVESV was found to be an independent predictor of response to CRT at long-term follow-up, defined as a reduction $\geq 15\%$ in LVESV. In particular, a reduction of 6% in LVESV immediately after implantation could predict response to CRT at late follow-up with a sensitivity of 79% and specificity of 75%.

The difference in response to CRT between patients with ischemic and non-ischemic cardiomyopathy has been a matter of debate. Additional analyses from the MUSTIC and MIRACLE \textsuperscript{15,16} trials revealed that at mid- and long-term follow-up after CRT, the improvement in LV systolic function and LV reverse remodeling are significantly greater in patients with non-ischemic cardiomyopathy as compared to patients with ischemic cardiomyopathy.

In the present study, the time course of response to CRT was evaluated in patients with ischemic and non-ischemic cardiomyopathy. Both groups showed a similar trend over time with an immediate improvement in LVESV and LVEF, followed by an additional improvement at late follow-up, and a reduction of LVEDV only at late follow-up. However, the reduction in LVESV and LVEDV was significantly greater in patients with non-ischemic cardiomyopathy as compared to patients with ischemic cardiomyopathy, particularly at late follow-up. This
finding is probably related to the presence of more myocardial scar tissue in patients with ischemic cardiomyopathy that may limit the extent of LV reverse remodeling 17–19.

According to the abovementioned definition of response to CRT, patients with non-ischemic cardiomyopathy also showed a significantly higher percentage of responders both at acute (53% vs. 32%) and late (78% vs. 54%) follow-up. Furthermore, etiology of cardiomyopathy was found to be an independent predictor of response to CRT at long-term follow-up at the multivariable logistic regression analysis.

In the current study, the acute and late effects of CRT on LV diastolic function and on right ventricular remodeling and function were not analyzed. Furthermore, the results on LV volumes and function need to be confirmed in larger multi-center studies and eventually in comparison with a control group.
REFERENCES


