Changes in global left ventricular function by multidirectional strain assessment in heart failure patients undergoing cardiac resynchronization therapy

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ABSTRACT

Aim: To evaluate the acute and late effects of cardiac resynchronization therapy (CRT) on multidirectional left ventricular (LV) strain assessed by 2-dimensional (2D) speckle tracking imaging and automated function imaging (AFI).

Methods and Results: Multidirectional LV strain (Global radial [GRS Avg], circumferential [GCS Avg] and longitudinal peak systolic strain [GLPSS Avg]) were measured in 141 heart failure patients before CRT implantation, immediately after and at 3 to 6 months of follow-up. Moreover, the acute effects on multidirectional LV strain were evaluated after interrupting CRT at follow-up. Response to CRT was defined as a decrease in LV end-systolic volume ≥15%. Responders (57%) and non-responders (43%) showed similar baseline values for GRS Avg, GCS Avg and GLPSS Avg. At follow-up, significant improvement in multidirectional LV strain, combined with significant reverse LV remodeling and improvement in LV ejection fraction, was only noted in responders. Importantly, no significant changes in multidirectional LV strain were observed immediately after CRT device implantation or after interruption of the device at follow-up.

Conclusions: Two-dimensional speckle tracking imaging and AFI enable the quantification of multidirectional LV mechanics. Improvement in LV strain in the 3 orthogonal directions after CRT appears to be a long-term effect and is related to the extent of reverse LV remodeling after CRT.
INTRODUCTION

It is well established that cardiac resynchronization therapy (CRT) is an effective treatment for advanced heart failure in selected patients. The beneficial effects include improvement in clinical parameters, such as symptoms, quality of life, and exercise distance as well as reduction in hospitalizations and mortality, but also include improvement in functional parameters, including improvement in global left ventricular (LV) function, LV reverse remodeling and reduction in mitral regurgitation.1-7 Nevertheless, a consistent proportion of patients do not respond to CRT.1,8,9 In order to understand the high prevalence of non-responders, several non-invasive imaging studies have been performed to study the exact mechanism underlying CRT.10,11 Two-dimensional (2D) speckle tracking imaging enables the angle-independent assessment of multidirectional LV strain and differentiates those myocardial segments with active contraction from those segments passively tethered. In addition, the novel algorithm automated function imaging (AFI) is a novel echocardiographic technique based on 2D strain imaging that enables quantification of regional and global LV longitudinal strain.12-15 In the present study, we used 2D speckle tracking imaging and AFI to study the effects of CRT on multidirectional LV strain. Echocardiography was performed at baseline, after CRT initiation, during follow-up and during interruption of biventricular pacing, in order to differentiate between acute and late effects.

METHODS

Study population and protocol
A total of 141 consecutive patients with chronic heart failure, scheduled for implantation of a CRT device, were included in the current study. The selection criteria for CRT included: advanced symptomatic heart failure (New York Heart Association functional class III or IV), LV ejection fraction ≤35% and QRS duration on surface electrocardiogram ≥120 ms.16 Patients with recent myocardial infarction (<3 months) or decompensated heart failure were excluded. Etiology was considered ischemic in the presence of significant coronary artery disease (≥50% stenosis in one or more of the major epicardial coronary arteries) and/or a history of myocardial infarction with electrocardiographic evidence or prior revascularization.

The study protocol included a comprehensive echocardiographic evaluation with assessment of multidirectional LV strain with 2D speckle tracking imaging at 4 different times of follow-up: before and within 24-48h after CRT device implantation, and after 3 to 6 months of CRT, with the device activated and after 5 minutes of CRT device interruption. In addition, LV volumes, ejection fraction and mitral regurgitation severity along with clinical parameters were evaluated at baseline and follow-up. Echocardiographic, clinical and LV lead position data were analyzed retrospectively, by two different observers blinded to the recorded data, respectively.
Echocardiographic evaluation

Patients were imaged in the left lateral decubitus position using a commercially available system (Vingmed Vivid-7, General Electric Vingmed, Milwaukee, Wisconsin). Data acquisition was performed with a 3.5-MHz transducer at a depth of 16 cm in the parasternal and apical views (standard apical long-axis, 2- and 4-chamber images). Standard 2D images were stored in cineloop format from 3 consecutive beats and were transferred to a workstation for further off-line analysis (EchoPac 6.1, GE Medical Systems, Horten, Norway).

LV end-diastolic and end-systolic volumes were derived and LV ejection fraction was calculated from apical 2- and 4-chamber views by Simpson’s rule. Mitral regurgitation was evaluated semi-quantitatively from color-flow Doppler images at the apical 4-chamber views. Mitral regurgitation was graded on a 3-point scale, according to current guidelines: mild (jet area/left atrial area <20%), moderate (jet area/left atrial area 20-45%) and severe (jet area/left atrial area >45%).

In addition, LV dyssynchrony was evaluated with tissue Doppler imaging (TDI) and with 2D speckle tracking radial strain imaging, as previously described. With TDI, the time difference between basal septal and basal lateral peak systolic velocities were calculated to define LV dyssynchrony. By applying 2D speckle tracking radial strain imaging to mid-ventricular parasternal short-axis images, LV dyssynchrony was evaluated measuring the time difference between the anteroseptal to (postero)lateral peak radial strain.

Patients who showed a decrease of ≥15% in LV end-systolic volume at follow-up were classified as echocardiographic responders to CRT.

Multidirectional LV strain assessment

Multidirectional analysis of LV strain (at radial, circumferential and longitudinal directions) was performed using 2D speckle tracking imaging and AFI. The speckles, natural acoustic markers equally distributed within the myocardium, can be detected and tracked on the standard grey-scale 2D images. Myocardial strain can be calculated by measuring the change of the position of the speckles within a myocardial segment along the cardiac cycle.

Two-dimensional speckle tracking imaging to assess global radial and circumferential strain

The assessment of global radial (GRS Avg) and circumferential strain (GCS Avg) was performed by applying 2D speckle tracking imaging to the parasternal short-axis views of the LV. Radial strain measures the thickening and thinning of the myocardium, whereas circumferential strain measures the shortening and lengthening along the curvature of the LV. The mid-ventricular short-axis of the LV is divided in 6 segments and the values of GRS Avg and GCS Avg are derived from the average of the 6 segmental peak systolic strain values. Conventionally, LV thickening is quantified with positive values and shortening with negative values. However, for the purpose of the present study, circumferential shortening was scored also in positive values.

Automated function imaging to assess global LV longitudinal strain

Global LV longitudinal strain was quantified using the novel AFI technique. For this purpose, one single cardiac frame is needed form each apical view (apical long-axis, 4- and 2-chamber views) us-
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ing a mean frame rate of 70 fps (range 40-100 fps). The method has been described elsewhere. In brief, the LV end-systolic frame is defined in the apical long-axis view and the closure of the aortic valve is marked. The time interval between the R-wave and aortic valve closure is used as a reference for the 4- and 2-chamber view loops. After defining the mitral annulus and the LV apex with 3 index points at the end-systolic frame in each apical view, the automated algorithm traces 3 concentric lines on the endocardial border, the mid-myocardial layer and epicardial border, including the entire myocardial wall. The LV is divided in 6 segments in each apical view and the tracking quality is validated for each segment. Then, the myocardial motion is analyzed and the automated algorithm, using a 17-segment model, provides the peak systolic longitudinal strain for each segment in a polar-map, with the average value of peak systolic longitudinal strain for each view and the averaged global longitudinal peak systolic strain (GLPSS Avg) for the complete LV (Figure 1). Generally, longitudinal strain values are presented as negative values, and a more negative value indicates larger longitudinal strain. However, for the purpose of the present study, the global strain values are presented as positive values.

Clinical evaluation

Clinical evaluation included evaluation of heart failure symptoms using New York Heart Association functional class, quality-of-life by the Minnesota Living with Heart Failure questionnaire, and exercise tolerance using 6-minute walking distance. QRS duration was measured in all patients from the surface electrocardiogram, using the widest QRS complex from the leads II, V1 and V6. The electrocardiograms were recorded at 25 mm/sec and were evaluated by two independent observers without knowledge of the clinical status of the patient.

Device implantation

The right atrial and right ventricular leads were positioned conventionally. To insert the LV lead, first a venogram from the coronary sinus was obtained using a guiding balloon catheter. Thereafter, an 8F guiding catheter was used to position the LV lead (Easytrak 4512-80, Guidant Corporation, St. Paul, Minnesota; or Attain-SD 4189, Medtronic Inc., Minneapolis, Minnesota) into the coronary sinus. All leads were connected to a dual-chamber biventricular ICD (Contak CD or TR, Guidant Corporation; or Insync III or CD, Medtronic Inc.). One day after implantation, LV lead position was defined from the chest-X-ray and scored as lateral, posterior or anterior, as previously described.

Statistical analysis

Continuous variables were presented as mean values ± SD and were compared with 2-tailed Student t test for paired and unpaired data. Categorical data were presented as number and percentage and compared with χ²-test and McNemar test, as appropriate. Differences in multidirectional LV strain over time between responders and non-responders were evaluated with analysis of the variance (ANOVA) for repeated measurements. In addition, for overall population and within the same group of patients, GRS Avg, GCS Avg and GLPSS Avg values were compared at 3 different stages: 1) baseline values (PRE) vs. values immediately after implant (ON), 2) PRE vs. follow-up data (F-UP) and 3) F-UP values vs. values after the interruption of the CRT device (OFF). To adjust for inflation of
Figure 1.
Changes in global LV longitudinal strain after CRT device implantation.

Example of a 17-segment “bull’s eye” display of the LV of a responder to CRT. A red color indicates normal strain values, whereas light-red and blue colors indicate lower strain values. From top to bottom are provided bull’s eye displays at baseline (PRE, top), immediately after CRT implantation (POST, middle) and at follow-up (F-UP, bottom). An improvement in global LV longitudinal strain (GLPSS Avg) is shown at follow-up, with an increase in the homogeneous red color-coded area.

Abbreviations: CRT: cardiac resynchronization therapy; F-UP: follow-up; GLPSS Avg: global longitudinal peak systolic strain; LV: left ventricular; POST: immediately after biventricular pacemaker implantation; PRE: baseline.
the type I error with multiple tests, we applied a posthoc Bonferroni correction; consequently, a p value < 0.017 was considered significant (0.05 divided by 3 different stages). Furthermore, relation between change in GLPSS Avg and change in LV volumes and ejection fraction was assessed by linear regression analysis. All statistical analyses were performed with SPSS software (version 12.0, SPSS Inc., Chicago, Illinois). A p value <0.05 was considered statistically significant.

RESULTS

Study population
Baseline characteristics of the 141 patients included (mean age 66±11 years, 82% men) are summarized in Table 1. Patients had severe heart failure (mean New York Heart Association class 3.0±0.4), with severe LV dysfunction (mean LV ejection fraction 25±7%) and wide QRS complex (mean 143±36 ms). Ischemic etiology of heart failure was present in 84 patients (60%). In addition, 55 (39%) patients had moderate to severe mitral regurgitation. All patients had optimized medical therapy, in-

<table>
<thead>
<tr>
<th>Table 1. Baseline characteristics</th>
<th>n = 141</th>
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<tbody>
<tr>
<td>Age (yrs)</td>
<td>66 ± 11</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>115 (82%)</td>
</tr>
<tr>
<td>Ischemic etiology (%)</td>
<td>84 (60%)</td>
</tr>
<tr>
<td>QRS duration (ms)</td>
<td>143 ± 36</td>
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<tr>
<td>Sinus rhythm (%)</td>
<td>121 (86%)</td>
</tr>
<tr>
<td>NYHA functional class</td>
<td>3.0 ± 0.4</td>
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<tr>
<td>Quality-of-life score</td>
<td>35 ± 18</td>
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<tr>
<td>6-minute walking distance (m)</td>
<td>313 ± 114</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>25 ± 7</td>
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<tr>
<td>LV end-systolic volume (ml)</td>
<td>156 ± 62</td>
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<tr>
<td>LV end-diastolic volume (ml)</td>
<td>207 ± 71</td>
</tr>
<tr>
<td>TDI LV dyssynchrony (ms)</td>
<td>74 ± 44</td>
</tr>
<tr>
<td>2D-speckle tracking LV dyssynchrony (ms)</td>
<td>179 ± 127</td>
</tr>
<tr>
<td>Mitral regurgitation</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>38 (27%)</td>
</tr>
<tr>
<td>Severe</td>
<td>17 (12%)</td>
</tr>
<tr>
<td>Medical therapy</td>
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<tr>
<td>ACE-inhibitors</td>
<td>121 (86%)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>126 (89%)</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>96 (68%)</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>35 (25%)</td>
</tr>
</tbody>
</table>

Abbreviations: 2D: Two-dimensional; ACE: angiotensin-converting enzyme; LV: left ventricular; NYHA: New York Heart Association; TDI: Tissue Doppler imaging
Including angiotensin-converting enzyme inhibitors, beta-blockers and diuretics, at maximum tolerated dosages. CRT implantation was successful in all patients and no complications were observed. The LV lead was positioned in a posterior vein in 63 (45%) patients, in a lateral vein in 67 (47%) and an anterior vein in 11 (8%) patients.

**Changes in clinical status after 6 months of CRT**
At follow-up, a significant improvement in all clinical parameters was observed in the overall population. Mean New York Heart Association class improved from 3.0±0.4 to 2.0±0.6 (p<0.001), the quality-of-life score improved from 35±18 to 22±20 (p<0.001) and the 6-minute walking distance increased from 313±114 m to 374±121 m (p<0.001).

**Changes in LV performance after initiation of CRT and at mid-term follow-up**
After 3 to 6 months of CRT, improvement in LV function and reverse remodeling was noted; LV end-systolic volume decreased from 156±62 ml to 125±60 ml (p<0.001), LV end-diastolic volume decreased from 207±71 ml to 181±69 ml (p<0.001) and LV ejection fraction increased from 25±7% to 33±10% (p<0.001). In addition, mitral regurgitation severity significantly improved at follow-up, with a significant reduction in mitral regurgitation (from 38/17 patients with moderate/severe mitral regurgitation to 13/10 patients respectively, p<0.001).

Changes in multidirectional LV strain for overall population are presented in Table 2. Immediately after CRT initiation no change in radial, circumferential or longitudinal strain were noted. However, at mid-term follow-up a significant improvement in all the 3 orthogonal directions of myocardial deformation was observed whereas interruption of CRT did not induce any change in multidirectional strain values.

**Table 2. Changes in multidirectional LV strain after CRT**

<table>
<thead>
<tr>
<th></th>
<th>PRE</th>
<th>POST</th>
<th>F-UP</th>
<th>OFF</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GRS Avg (%)</td>
<td>15.9 ± 9.4</td>
<td>16.6 ± 9.3</td>
<td>20.9 ± 12.8*</td>
<td>18.3 ± 10.2</td>
<td>0.002</td>
</tr>
<tr>
<td>GCS Avg (%)</td>
<td>8.2 ± 3.3</td>
<td>8.6 ± 3.7</td>
<td>10.5 ± 4.6*</td>
<td>9.8 ± 4.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GLPSS Avg (%)</td>
<td>7.8 ± 2.8</td>
<td>7.5 ± 3.1</td>
<td>8.5 ± 3.5†</td>
<td>8.9 ± 3.7</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*p <0.001 vs. PRE; †p = 0.010 vs. PRE

Abbreviations: F-UP = at 3- or 6-month follow-up; GCS Avg = averaged global circumferential strain; GLPSS Avg = averaged global longitudinal peak systolic strain; GRS Avg = averaged global radial strain; OFF = after 3- or 6-month follow-up with interruption of CRT device; POST = within 24-48 hours after implantation of CRT; PRE = baseline.

Figure 1 illustrates the example of a patient with improvement of GLPSS Avg at follow-up.

Finally, changes in LV longitudinal function as assessed with AFI were related to LV reverse remodeling after 3-6 months of CRT, demonstrating a direct relationship between both parameters (Figures 2 A-C).
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Responders vs. non-responders

Based on a reduction in LV end-systolic volume of ≥15% after CRT, 80 (57%) patients were classified as responders. There were no differences in baseline characteristics between responders and non-responders, except for significantly more male patients, more ischemic patients, shorter QRS duration and less LV dyssynchrony in the non-responders (Table 3).

Figure 2. Relation between change in global LV longitudinal strain and change in LV volumes and function after CRT.

Relation between absolute change in global LV longitudinal strain (GLPSS Avg) and the absolute change in LV ejection fraction (LVEF, panel A), the relative change in LV end-systolic volume (LVESV, panel B) and the relative change in LV end-diastolic volume (LVEDV, panel C) respectively. Responder patients are presented in black dots, whereas non-responders are presented in white dots.

Abbreviations: CRT: cardiac resynchronization therapy; GLPSS Avg: global longitudinal peak systolic strain; LV: left ventricular; LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; LVESV: left ventricular end-systolic volume

Responders vs. non-responders

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At follow-up, responders showed (by definition) significant LV reverse remodeling; LV end-systolic volume decreased from 157±63 ml to 101±52 ml and LV end-diastolic volume decreased from 209±74 ml to 160±67 ml (both p<0.001). As a consequence, a significant improvement in LV ejection fraction was observed (from 26±6% to 38±8%; p<0.001) (Figure 3).

In addition, responder patients showed a significant reduction in mitral regurgitation severity (from 27/9 patients with moderate/severe mitral regurgitation to 5/0 patients, respectively; p<0.001). In non-responders no significant changes in LV volumes, ejection fraction or mitral regurgitation severity were observed.

At baseline, multidirectional LV strain analysis showed similar values of radial, circumferential and longitudinal strain in responders and non-responders (Figure 4). In responders no acute change in multidirectional LV strain were noted, but a significant improvement in all the 3 orthogonal directions was demonstrated at follow-up. These values remained stable during interruption of biventricular pacing. Conversely, in non-responders, radial, circumferential and longitudinal myocardial strain remained unchanged at follow-up.

Table 3. Baseline characteristics in responders and non-responders

<table>
<thead>
<tr>
<th></th>
<th>Responders (n=80)</th>
<th>Non-responders (n=61)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>67 ± 9</td>
<td>64 ± 13</td>
<td>0.1</td>
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<tr>
<td>Male gender (%)</td>
<td>60 (75%)</td>
<td>55 (90%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Ischemic etiology (%)</td>
<td>40 (50%)</td>
<td>44 (72%)</td>
<td>0.01</td>
</tr>
<tr>
<td>QRS duration (ms)</td>
<td>150 ± 37</td>
<td>135 ± 33</td>
<td>0.01</td>
</tr>
<tr>
<td>Sinus rhythm (%)</td>
<td>67 (84%)</td>
<td>54 (88%)</td>
<td>0.7</td>
</tr>
<tr>
<td>NYHA functional class</td>
<td>3.0 ± 0.4</td>
<td>3.0 ± 0.4</td>
<td>0.3</td>
</tr>
<tr>
<td>Quality-of-life score</td>
<td>33 ± 16</td>
<td>37 ± 19</td>
<td>0.2</td>
</tr>
<tr>
<td>6-minute walking distance (m)</td>
<td>323 ± 108</td>
<td>300 ± 121</td>
<td>0.3</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>26 ± 7</td>
<td>25 ± 7</td>
<td>0.4</td>
</tr>
<tr>
<td>LV end-systolic volume (ml)</td>
<td>157 ± 63</td>
<td>155 ± 61</td>
<td>0.8</td>
</tr>
<tr>
<td>LV end-diastolic volume (ml)</td>
<td>209 ± 74</td>
<td>204 ± 68</td>
<td>0.6</td>
</tr>
<tr>
<td>TDI LV dyssynchrony (ms)</td>
<td>90 ± 40</td>
<td>51 ± 37</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2D-speckle tracking LV dyssynchrony (ms)</td>
<td>217 ± 129</td>
<td>129 ± 105</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1.

At follow-up, responders showed (by definition) significant LV reverse remodeling; LV end-systolic volume decreased from 157±63 ml to 101±52 ml and LV end-diastolic volume decreased from 209±74 ml to 160±67 ml (both p<0.001). As a consequence, a significant improvement in LV ejection fraction was observed (from 26±6% to 38±8%; p<0.001) (Figure 3).

In addition, responder patients showed a significant reduction in mitral regurgitation severity (from 27/9 patients with moderate/severe mitral regurgitation to 5/0 patients, respectively; p<0.001). In non-responders no significant changes in LV volumes, ejection fraction or mitral regurgitation severity were observed.

At baseline, multidirectional LV strain analysis showed similar values of radial, circumferential and longitudinal strain in responders and non-responders (Figure 4). In responders no acute change in multidirectional LV strain were noted, but a significant improvement in all the 3 orthogonal directions was demonstrated at follow-up. These values remained stable during interruption of biventricular pacing. Conversely, in non-responders, radial, circumferential and longitudinal myocardial strain remained unchanged at follow-up.

DISCUSSION

This study provides new insights on the effects of CRT on LV function using 2D speckle tracking imaging and the novel echocardiographic AFI technique. The main findings can be summarized as follows: 1) CRT initiation or withdrawal did not induce any acute changes in multidirectional LV strain, however
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a significant increase in radial, circumferential and longitudinal strain was noted at long-term follow-up, 2) changes in GLPSS Avg were related to the extent of LV reverse remodeling after CRT and consequently 3) improvement in multidirectional LV strain during follow-up was only noted in responder patients, whereas non-responders did not show any change in LV deformation pattern.

Changes in multidirectional LV function after CRT

Despite the dramatic improvement in LV function and reduction in LV volumes after CRT demonstrated in large studies, information regarding changes in multidirectional LV function is limited. To date, few studies have reported the changes in LV radial, circumferential or longitudinal strain after CRT.26;27 Zhang et al. evaluated in 39 patients changes in multidirectional LV strain after 3 months of CRT. 26 Applying 2D speckle tracking imaging to LV short-axis images, the authors demonstrated that responder patients showed a significant improvement in radial and circumferential strain at 3-month follow-up. However, in non-responder patients, radial and circumferential strain values remained unchanged.26 In addition, when 2D speckle tracking imaging was applied to LV apical views, GLPSS Avg value improved in responder patients (from 8.0 ± 2.9% to 9 ± 3.5, p = NS) whereas in non-responder patients, GLPSS Avg decreased (from 7.1 ± 3.8% to 6.2 ± 2.7%, p = NS).26 Similarly, Becker et al.27 studied 47 heart failure patients using 2D speckle tracking analysis applied to 4- and 2-chamber views and demonstrated a significant increase in global LV longitudinal strain after 3 months of CRT.27 The present study confirms those results and demonstrates in a larger population the beneficial effects of CRT on LV mechanics.

Relation between changes in multidirectional LV strain and LV reverse remodeling after CRT

The effects of CRT can be divided into acute and chronic effects.10 Studies evaluating the acute effects have demonstrated that CRT abruptly enhances LV systolic function by an increase in stroke
Figure 4. Changes in multidirectional LV strain after CRT according to response
Average global LV radial (GRS Avg), circumferential (GCS Avg) and longitudinal strain (GLPSS Avg) in responder and non-responder patients at baseline (PRE), at 24-48h after pacemaker implantation (POST) and at follow-up with the device turned on (F-UP) and turned off (OFF). (*paired t-test for comparisons within the same group (p<0.001).
Abbreviations: as in Figure 1 and OFF: at follow-up with the device turned off.
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volume, a reduction in LV end-systolic volume, and a rise in LV pressure.\textsuperscript{9,28,29} These beneficial hemodynamic effects are the result of the more coordinated (synchronized) contraction of the LV immediately after CRT initiation. Of note, these results are rapidly reversed when CRT is interrupted, and underscore that the acute effect of CRT is related to enhanced and more coordinated (synchronized) LV function.\textsuperscript{9} At 6-month follow-up however, the hemodynamic benefits are more related to structural reverse remodeling of the LV.\textsuperscript{6,30} Various echocardiographic studies have shown a reduction in LV volumes, associated with an increase in LV ejection fraction, and improvement in mitral regurgitation severity after long-term CRT.\textsuperscript{28,30,31} The present study confirms previous findings and, in terms of multidirectional LV strain, myocardial strain pattern has a similar time course: no significant changes were observed immediately after CRT initiation; however, at follow-up, a significant increase in myocardial strain in all the 3 orthogonal directions was observed and remained stable after CRT withdrawal at follow-up. These observations suggest that the increase in multidirectional LV strain is related to structural reverse remodeling, rather than to acute pacing effects, particularly since CRT withdrawal did not reduce myocardial strain. When patients were divided into responders and non-responders, this effect was only observed in responder patients, with a significant increase in multidirectional LV strain at follow-up, that remained unchanged when CRT was turned off.

**Study Limitations**

Multidirectional LV strain was evaluated at 4 time-points and no additional data were acquired between hospital discharge (24-48 hours after CRT implantation) and 3-6 months follow-up. Two-dimensional speckle tracking imaging is highly dependent on image quality and frame rate. In the present study, echocardiographic images were acquired at mean frame rate of 70 frames/s. However, in few studies, the frame rate was between 40-50 frames/s. Nevertheless, the strain-time curves obtained were reliable enough to be included in the study.

**CONCLUSIONS**

Two-dimensional speckle tracking imaging and the novel AFI algorithm enable quantification of LV systolic function and characterization of its changes after CRT. Improvement in multidirectional LV strain after CRT appears as a long-term effect and is related to the extent of reverse LV remodeling after CRT.

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