Effect of Posterolateral Scar Tissue on Clinical and Echocardiographic Improvement After Cardiac Resynchronization Therapy

Gabe B. Bleeker, MD; Theodorus A.M. Kaandorp, MD; Hildo J. Lamb, MD, PhD; Eric Boersma, PhD; Paul Steendijk, PhD; Albert de Roos, MD, PhD; Ernst E. van der Wall, MD, PhD; Martin J. Schalij, MD, PhD; Jeroen J. Bax, MD, PhD

Background—Currently, one third of patients treated with cardiac resynchronization therapy (CRT) do not respond. Nonresponse to CRT may be explained by the presence of scar tissue in the posterolateral left ventricular (LV) segments, which may result in ineffective LV pacing and inadequate LV resynchronization. In the present study, the relationship between transmural posterolateral scar tissue and response to CRT was evaluated.

Methods and Results—Forty consecutive patients with end-stage heart failure (NYHA class III/IV), LV ejection fraction ≤35%, QRS duration >120 ms, left bundle-branch block, and chronic coronary artery disease were included. The localization and transmurality of scar tissue were evaluated with contrast-enhanced MRI. Next, LV dyssynchrony was assessed at baseline and immediately after implantation with tissue Doppler imaging. Clinical parameters, LV volumes, and LV ejection fraction were assessed at baseline and at a 6-month follow-up. Fourteen patients (35%) had a transmural (>50% of LV wall thickness) posterolateral scar. In contrast to patients without posterolateral scar tissue, these patients showed a low response rate (14% versus 81%; P<0.05) and did not show improvement in clinical or echocardiographic parameters. In addition, LV dyssynchrony remained unchanged after CRT implantation (84±46 versus 78±41 ms; P=NS). Patients without posterolateral scar tissue and severe baseline dyssynchrony (≥65 ms) showed an excellent response rate of 95% compared with patients with a posterolateral scar and/or absent LV dyssynchrony (11%).

Conclusions—CRT does not reduce LV dyssynchrony in patients with transmural scar tissue in the posterolateral LV segments, resulting in clinical and echocardiographic nonresponse to CRT. (Circulation. 2006;113:969-976.)

Key Words: cardiac resynchronization therapy ■ heart failure ■ left ventricular dyssynchrony ■ magnetic resonance imaging ■ ultrasonics

Cardiac resynchronization therapy (CRT) is a rapidly evolving treatment option for patients with drug-refractory heart failure. Large clinical trials have reported the sustained benefit of CRT in patients with severe heart failure (NYHA class III or IV), impaired left ventricular (LV) ejection fraction (EF) (≤35%), and a wide QRS complex (>120 ms).1–3 Beneficial effects of CRT include improvement in heart failure symptoms, quality of life, exercise capacity, and LV systolic performance.1–4 Simultaneously, however, it was noted that 20% to 30% of patients did not respond to CRT, emphasizing the need for better selection criteria.2,5–8 In the search for new selection criteria, it was demonstrated that the predominant mechanism determining the response to CRT is the resynchronization of preexistent LV dyssynchrony.5–8

Recently, new echocardiographic techniques, for example, tissue Doppler imaging (TDI), have shown that QRS duration, which is traditionally considered a marker of LV dyssynchrony, does not correlate well with LV dyssynchrony, thus explaining the low predictive value of the QRS duration for response to CRT.9,10 Additional studies have indeed demonstrated that assessment of LV dyssynchrony with TDI was superior over ECG-assessed QRS duration for predicting response to CRT.7,8 However, LV dyssynchrony may not be the only determinant of response to CRT because some patients with LV dyssynchrony do not respond to CRT. Another potential reason for nonresponse to CRT (in patients with ischemic cardiomyopathy) may be the presence of...
extensive scar tissue in the region of the tip of the LV pacing lead (usually the posterolateral LV region). Pacing the left ventricle in nonviable or scarred myocardium may result in less effective or even ineffective LV pacing and, as a consequence, failure of LV resynchronization and no response to CRT. Accordingly, the aim of the present study was to evaluate the response to CRT in relation to LV dyssynchrony on the one hand and scar tissue in the posterolateral wall on the other hand. To determine precisely the spatial and transmural extent of scar tissue, contrast-enhanced MRI was used.

Methods

Patients and Study Protocol
Forty consecutive patients with severe heart failure and chronic coronary artery disease (ischemic cardiomyopathy) who were scheduled for the implantation of a CRT device were prospectively included. Patients were selected according to the traditional selection criteria for CRT: severe heart failure (NYHA class III or IV), severely depressed LVEF (≤35%), and a QRS complex exhibiting left bundle-branch block with a duration >120 ms. Chronic coronary artery disease was defined as angiographically proven stenosis of >50% in ≥1 major epicardial coronary artery. Patients with a recent myocardial infarction (<3 months), decompensated heart failure, a previous cardiac pacemaker, or intracranial aneurysm clips were excluded.

The study protocol was as follows. Before pacemaker implantation, contrast-enhanced MRI was performed to determine the extent and transmurality of infarcted myocardial tissue. Next, clinical status was assessed, and resting 2D transthoracic echocardiography was performed to measure LV volumes and LVEF. Also, TDI was performed to assess the extent of LV dyssynchrony. LV dyssynchrony was reassessed on the day after implantation to assess the extent of resynchronization. Clinical status, LV volumes, and LVEF were reassessed at a 6-month follow-up.

Magnetic Resonance Imaging

Data Acquisition
A clinical 1.5-T Gyroscan ACS-NT MRI scanner (Philips Medical Systems) equipped with Powertrack 6000 gradients, release 9.1 of the scanner software, and a 5-element cardiac synergy coil was used. Patients were positioned in the supine position. Images were acquired during breathholds of ~15 seconds with vector ECG gating. The heart was imaged from apex to base with 20 to 24 imaging levels (depending on the heart size) in short-axis views. Contrast-enhanced images were acquired ~15 minutes after bolus injection of gadopentetate dimeglumine 0.15 mmol/kg (gadolinium-diethylenetriamine pentacetic acid, Magnevist, Schering AG/Berlex Laboratories) with an inversion-recovery gradient echocardiographic sequence; the inversion time was determined with a Look-Locker sequence. Typical parameters were a field of view of 400×400 mm², a matrix size of 256×256, a slice thickness of 5 mm, a slice gap of ~5 mm, a flip angle of 15°, an echo time of 1.36 ms, and a repetition time of 4.53 ms.

Data Analysis
The contrast-enhanced images were scored visually by 2 experienced observers who were blinded to other MRI, echocardiographic, and clinical data using a 17-segment model. Each segment was graded on a 5-point scale (segmental scar score): 0 = absence of hyperenhancement, 1 = hyperenhancement of 1% to 25% of the LV wall thickness, 2 = hyperenhancement extending to 26% to 50%, 3 = hyperenhancement extending to 51% to 75%, and 4 = hyperenhancement extending to 76% to 100% of the LV wall thickness. A transmural scar in the posterolateral region was defined as a segmental scar score of 3 or 4 (hyperenhancement extending to 51% to 100% of LV wall thickness) in ≥1 of the following LV segments: basal posterior, mid posterior, basal posterolateral, and mid posterolateral.

Clinical Evaluation
Evaluation of clinical status included assessment of NYHA functional class, quality-of-life score (using the Minnesota quality-of-life questionnaire), and 6-minute hall-walk test. NYHA functional class was scored by an independent physician who was blinded to all other patient data. Patients with an improvement of ≥1 NYHA functional class and an improvement ≥25% in 6-minute walking distance were classified as responders. In addition, patients who died of progressive heart failure before the 6-month follow-up assessment were classified as nonresponders. In all patients, QRS duration was measured from the surface ECG using the widest QRS complex from the leads II, V₅, and V₆. In addition, the QRS axis in the frontal plane was measured from the surface ECG immediately after implantation. The ECGs were recorded at a speed of 25 mm/s and were evaluated by 2 independent observers without knowledge of the clinical status of the patient.

Echocardiography
Patients were imaged in the left lateral decubitus position with a commercially available system (Vingmed System Seven, General Electric—Vingmed). Images were obtained with a 3.5-MHz transducer at a depth of 16 cm in the parasternal and apical views (standard long-axis and 2- and 4-chamber images). Standard 2D and color Doppler data triggered to the QRS complex were saved in cine-loop format. LV end-systolic and end-diastolic volumes and LVEF were calculated from the conventional apical 2- and 4-chamber views with the biplane Simpson technique.

Assessment of Mitral Regurgitation
The severity of mitral regurgitation was graded semiquantitatively from color-flow Doppler images. For quantification of mitral regurgitation, the apical 4-chamber images were used. Mitral regurgitation was classified as follows: mild = 1+ (jet area/left atrial area < 10%), moderate = 2+ (jet area/left atrial area, 10% to 20%), moderately severe = 3+ (jet area/left atrial area, 20% to 45%), and severe = 4+ (jet area/left atrial area > 45%).

TDI to Assess LV Dyssynchrony
In addition to the conventional echocardiographic examination, TDI was performed to assess LV dyssynchrony. For TDI, color Doppler frame rates varied between 80 and 115 frames per second, depending on the sector width of the range of interest; pulse repetition frequencies were between 500 Hz and 1 kHz, resulting in aliasing velocities between 16 and 32 cm/s. TDI parameters were measured from color images of 3 consecutive heartbeats by offline analysis. Data were analyzed with commercial software (Echopac 6.1, General Electric—Vingmed). To determine LV dyssynchrony, the sample volume was placed in the basal portions of the septum and the LV lateral wall; peak systolic velocities and time-to-peak systolic velocities were obtained, and the delay in peak velocity between the septum and the LV lateral wall was calculated as an indicator of LV dyssynchrony (referred to as the septal-to-lateral delay). From previous observations, a septal-to-lateral delay ≥ 65 ms was considered to represent severe LV dyssynchrony. Interobserver agreement and intraobserver agreement for assessment of the septal-to-lateral delay were 90% and 96%, respectively.

Pacemaker Implantation
The LV pacing lead was inserted transvenously via the subclavian route. First, a coronary sinus venogram was obtained during occlusion of the coronary sinus with a balloon catheter. Next, the LV pacing lead was inserted into the coronary sinus with the help of an 8F guiding catheter and positioned as far as possible in the venous system, preferably in the (posterolateral) lateral vein. The right atrial and right ventricular leads were positioned conventionally. When a conventional indication for an internal defibrillator existed, a combined device was implanted. At implantation, both the sensing and pacing thresholds (at pulse duration of 0.5 ms) of the LV pacing lead
we used \( P \) tests with Yates’ correction (dichotomous data) and Mann-Whitney tests (continuous variables). Differences in baseline characteristics and results of comparison between CRT responders and nonresponders were measured. For each patient, the AV interval was adjusted to maximize the mitral inflow duration with pulsed-wave Doppler echocardiography. No adjustments were made to the V-V interval during the first 6 months of CRT. The final position of the LV pacing lead was assessed with cine fluoroscopy.

**Statistical Analysis**

Continuous data are presented as mean±SD; dichotomous data are presented as numbers and percentages. Data within patient groups (to compare the effect of CRT) were compared by use of paired Student \( t \) tests (continuous variables) and Wilcoxon signed-ranks tests (NYHA classification). Differences in baseline characteristics and 6-month follow-up between independent patient groups were evaluated with unpaired Student \( t \) tests (continuous variables) and Mann-Whitney tests (NYHA classification).

Multivariable linear regression analyses were applied to evaluate the relation between clinical and echocardiographic variables (quality-of-life score, 6-minute walking distance, LVEF, LV end-diastolic and end-systolic volumes) at the 6-month follow-up and the presence of posterolateral scar tissue and/or LV dyssynchrony at baseline. We included a posterolateral scar–by–LV dyssynchrony interaction term to study the extent to which these variables modify each other’s relationship with improvement at the 6-month follow-up.

Finally, to compare response rate to CRT in different patient groups, we used \( \chi^2 \) tests with Yates’ correction (dichotomous variables). All tests are 2 sided, and a value of \( P<0.05 \) was considered statistically significant.

The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.

**Results**

Forty consecutive patients were included in this study (35 men; mean age, \( 67\pm10 \) years). Baseline patient characteristics are summarized in Table 1.

**Pacemaker Implantation**

CRT device and lead implantation was successful in all patients without major complications (Contak TR or CD, Guidant, and Insync III or CD, Medtronic Inc). Two types of LV leads were used: Easytrack 4512–80 (Guidant) or Attain-SD 4189 (Medtronic Inc).

The LV pacing lead was positioned in the mid lateral region in 20 patients (50%) and in the posterolateral region in 20 patients (50%).

**Postimplantation Results**

After CRT implantation, QRS duration decreased from \( 160\pm29 \) to \( 149\pm24 \) ms \( (P<0.05) \). TDI demonstrated a reduction in LV dyssynchrony immediately after implantation of the CRT device from \( 90\pm43 \) to \( 47\pm39 \) ms \( (P<0.001) \).

**Clinical and Echocardiographic Improvement After CRT**

One patient died at 4 months after CRT implantation as a result of worsening heart failure. Accordingly, this patient did not have a clinical follow-up assessment at 6 months.

In the remaining 39 patients, 23 showed a significant improvement in NYHA class: 5 patients showed an improvement of 2 NYHA classes, 18 patients improved by 1 NYHA class, 14 patients did not improve, and 2 patients showed a worsening in NYHA class. In addition, the quality-of-life score decreased from \( 39\pm15 \) to \( 23\pm20 \) \( (P<0.001) \) and the 6-minute walking distance increased from \( 290\pm99 \) to \( 357\pm169 \) m \( (P<0.01) \).

On the basis of a lack of improvement in NYHA class at 6 months or a lack of improvement ≥25% in 6-minute walking distance, 16 patients (40%) were classified as nonresponders. The patient who died before the 6-month follow-up showed a gradual decline in his clinical situation after CRT implantation and therefore was also classified as a nonresponder.

A modest improvement in LVEF from \( 23\pm7\% \) to \( 29\pm11\% \) \( (P<0.01) \) was observed. Significant reverse remodeling occurred after 6 months of CRT. The LV end-systolic volume decreased from \( 191\pm77 \) mL at baseline to \( 157\pm54 \) mL after 6 months of CRT \( (P<0.05) \). Similarly, LV end-diastolic volume decreased from \( 245\pm82 \) mL at baseline to \( 226\pm77 \) mL at the 6-month follow-up \( (P<0.05) \).

**Posterolateral Scar Tissue**

Of the 680 segments evaluated, 314 segments (46%) revealed hyperenhancement on MRI. In particular, 102 (15%) showed minimal hyperenhancement (score 1), 86 (13%) had hyperenhancement score 2, 82 (12%) had score 3, and 44 (6%) had score 4.

Fourteen patients (35%) had a transmural scar (hyperenhancement score 3 or 4) in the posterolateral region (basal posterior, mid posterior, basal posterolateral, and/or mid posterolateral segments). An example of a patient with a transmural scar in the posterolateral region is shown in Figure 1.

Baseline characteristics between patients with \( (n=14) \) and without \( (n=26) \) posterolateral scar tissue were comparable; in particular, QRS duration was similar \( (158\pm42 \) versus \( 164\pm26 \) ms, respectively; \( P=NS) \). At implantation, both the LV sensing threshold \( (14.3\pm8.6 \) versus \( 13.6\pm9.9 \) mV, re-
Posterolateral Scar Tissue and Response After CRT

Baseline values of both clinical (NYHA class, 6-minute walking distance, and quality-of-life score) and echocardiographic (LVEF, LV end-systolic volume, LV end-diastolic volume) parameters were comparable between patients with (n=14) and without (n=26) posterolateral scar tissue (Table 2). Of the patients without transmural posterolateral scar tissue (n=26), 21 patients (81%) were classified as responders.

In these patients, there was an immediate reduction in LV dyssynchrony after CRT implantation (from 93±41 to 31±27 ms; P<0.05), indicating resynchronization of LV contraction. At the 6-month follow-up, there was a significant improvement in NYHA class, 6-minute walking distance, and quality-of-life score. In addition, LVEF improved significantly (from 24±7% to 32±10%; P<0.05), and significant LV reverse remodeling was observed (Table 2).

In the patients with a transmural scar in the posterolateral region (n=14), only 2 patients (14%) were classified as a responder at the 6-month follow-up (P<0.05 versus patients without scar tissue).

Baseline LV dyssynchrony in these patients was not statistically different compared with that in patients without a transmural posterolateral scar (84±46 versus 93±41 ms, respectively; P=NS). However, in patients with a transmural posterolateral scar, LV dyssynchrony remained unchanged after implantation of the CRT device (84±46 versus 78±41 ms; P=NS), indicating an absence of LV resynchronization.

At the 6-month follow-up, no improvement was observed in NYHA class, 6-minute walking distance, and quality-of-life score. Also, LVEF failed to improve (from 22±7% to 23±10%; P=NS), and LV reverse remodeling was not observed.

LV Dyssynchrony and Response After CRT

Mean LV dyssynchrony in all patients was 90±43 ms (range, 5 to 182 ms) before CRT. Thirty-three patients (83%) showed severe baseline LV dyssynchrony (≥65 ms). The site of latest activation was the posterolateral region in all patients. No differences were observed in baseline clinical and echocardiographic parameters between patients with (n=33) and patients without (n=7) severe baseline LV dyssynchrony (Table 3).

In the patients with severe baseline LV dyssynchrony (≥65 ms, n=33), 23 patients (70%) were classified as responders at the 6-month follow-up. In these patients, LV dyssynchrony decreased from 103±32 to 50±41 ms after implantation (P<0.05). At the 6-month follow-up, a significant improvement in both clinical and echocardiographic parameters was observed. NYHA class improved significantly, the 6-minute walking distance improved from 288±97 to 383±164 m (P<0.05), and the quality-of-life score improved from 39±13 to 19±18 (P<0.05). LVEF showed an increase from 23±6% to 31±11% (P<0.05), with significant LV reverse remodeling (Table 3).

None of the 7 patients without severe baseline LV dyssynchrony (<65 ms), showed response to CRT at the 6-month follow-up.
follow-up (*P* < 0.05 versus patients with LV dyssynchrony). No change was observed in LV dyssynchrony immediately after implantation (from 24 ± 17 to 32 ± 27 ms; *P* = NS).

Quality-of-life, LVEF, and LV end-diastolic volume remained unchanged, and a significant deterioration was observed in the 6-minute walking distance (from 304 ± 121 to 239 ± 147 m; *P* < 0.05) and LV end-systolic volume at the 6-month follow-up (from 171 ± 95 to 197 ± 70 mL; *P* < 0.05).

**Posterolateral Scar Tissue and LV Dyssynchrony Versus Response to CRT**

Figure 2 shows the percentage of responders to CRT for 4 different patient categories based on the presence/absence of transmural posterolateral scar tissue in combination with the presence or absence of severe baseline LV dyssynchrony (≥65 ms).

Only the patients with severe baseline LV dyssynchrony and without a transmural posterolateral scar (n = 22) showed an excellent response rate (95%). Of interest, the nonresponding patient in this category had a nontransmural scar in the posterolateral region (hyperenhancement score 2). In contrast, all other patients showed a low response rate after CRT. Patients with severe LV dyssynchrony and a transmural posterolateral scar (n = 11) had a response rate of 18%. Patients without severe LV dyssynchrony at baseline had a response rate of 0%, regardless of the presence (n = 4) or absence (n = 3) of posterolateral scar tissue. The baseline clinical and echocardiographic parameters of the 22 patients with severe baseline LV dyssynchrony and without posterolateral scar tissue were comparable to the baseline parameters of the other patients (Table 4).

The patients with severe baseline LV dyssynchrony and without a transmural posterolateral scar (n = 22) showed a significant reduction in LV dyssynchrony (from 105 ± 31 to 30 ± 28 ms; *P* < 0.05) and an excellent improvement in both clinical and echocardiographic parameters at the 6-month follow-up.

The patients without baseline LV dyssynchrony and/or transmural posterolateral scar tissue (n = 18) failed to show a significant reduction in LV dyssynchrony (from 71 ± 48 to 68 ± 42 ms; *P* = NS), and there was no improvement in clinical and echocardiographic parameters.

**Multivariable Linear Regression Analysis**

Table 5 demonstrates that the presence of posterolateral scar tissue and LV dyssynchrony at baseline is independently associated with an improvement in clinical (quality-of-life score and 6-minute walking distance) and echocardiographic (LVEF, LV end-diastolic and end-systolic volumes) variables at the 6-month follow-up. In addition, a significant posterolateral scar–by–LV dyssynchrony interaction was observed for improvement in quality-of-life score, 6-minute walking distance, and LVEF at the 6-month follow-up. We found that in patients with posterolateral scar tissue, LV dyssynchrony did not influence improvement in quality-of-life score (regression coefficient, −31.0 + 31.9 = 0.9; Table 5), 6-minute walking distance (regression coefficient, 205 – 217 = 12), and LVEF (regression coefficient, 11.1 – 10.8 = 0.3) at the 6-month follow-up. This supports the finding that patients with posterolateral scar tissue are unlikely to improve after CRT regardless of baseline LV dyssynchrony. No interaction

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**TABLE 3. Patients With (n=33) and Without (n=7) Baseline LV Dyssynchrony: Clinical and Echocardiographic Variables Before and After 6 Months of CRT**

|                      | Dyssynchrony (n=33)* | No Dyssynchrony (n=7) | *P*
|----------------------|----------------------|----------------------|-----
| NYHA class, III/IV   |                      |                      |     
| Baseline             | 0/0/29/4             | 0/0/7/0              | NS  
| Follow-up            | 3/20/6/3†            | 0/0/7/0              | <0.05 
| 6 min Walk test, m   |                      |                      |     
| Baseline             | 288±97               | 304±121              | NS  
| Follow-up            | 383±164†             | 239±147†             | <0.05 
| QOL score            |                      |                      |     
| Baseline             | 39±13                | 36±23                | NS  
| Follow-up            | 19±18†               | 39±20                | <0.05 
| LVEF, %              |                      |                      |     
| Baseline             | 23±6                 | 24±8                 | NS  
| Follow-up            | 31±11†               | 19±4                 | <0.05 
| LVEDV, mL            |                      |                      |     
| Baseline             | 249±79               | 221±103              | NS  
| Follow-up            | 222±71†              | 242±111              | NS  
| LVESV, mL            |                      |                      |     
| Baseline             | 194±74               | 171±95               | NS  
| Follow-up            | 150±48†              | 197±70†              | <0.05 

Abbreviations as in Table 2.

*One patient died before the 6-month follow-up.
†*P* < 0.05, follow-up vs baseline.

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**Figure 2.** Percentages of responders to CRT for 4 different patient categories based on the presence or absence of transmural posterolateral scar tissue (Scar+/Scar−) in combination with the presence or absence of baseline LV dyssynchrony (≥65 ms) (Dys+/Dys−).
was observed for improvement in LV end-diastolic and end-systolic volumes at the 6-month follow-up.

**Discussion**

The findings in the present study demonstrate that patients with transmural scar tissue in the posterolateral wall do not respond to CRT, even if extensive LV dyssynchrony exists. The combined assessment of scar tissue and LV dyssynchrony is needed to optimize prediction of response to CRT. Integration of these parameters resulted in a 95% response rate to CRT.

CRT, introduced in the early 1990s, is considered an important breakthrough in the treatment of patients with dilated cardiomyopathy and end-stage heart failure. Traditional patient selection for CRT includes severe heart failure (NYHA class III or IV), depressed LVEF ($\leq$35%), and a widened QRS complex (>120 ms) with left bundle-branch block configuration. Using these criteria, various studies have demonstrated the immediate benefit of CRT on hemodynamics and systolic performance of the left ventricle. Moreover, large clinical trials have shown that these immediate effects were accompanied by an improvement in heart failure symptoms, exercise capacity, and LVEF at midterm follow-up. However, it has simultaneously become clear that 20% to 30% of patients do not respond to CRT. Therefore, better understanding of the mechanism underlying response (and failure to respond) is needed to allow better selection of patients who will benefit from CRT. Recent data have shown that baseline LV dyssynchrony is an important factor in the response to CRT. Indeed, patients with extensive LV dyssynchrony showed good response to CRT, whereas patients without dyssynchrony did not respond. For example, Yu et al. have evaluated 30 patients undergoing CRT and showed a significant improvement in clinical parameters (NYHA class, 6-minute walking distance) and echocardiographic variables (LVEF, LV reverse remodeling). The same authors have also demonstrated that TDI is the optimal approach to assess LV dyssynchrony.

**TABLE 4. Patients With Baseline LV Dyssynchrony ($\geq$65 ms) Without Posterolateral Scar Tissue (n=22) Versus Patients Without Baseline LV Dyssynchrony and/or Posterolateral Scar Tissue (n=18): Clinical and Echocardiographic Variables Before and After 6 Months of CRT**

<table>
<thead>
<tr>
<th>Independent Variable</th>
<th>Dyssynchrony, No Scar (n=22)</th>
<th>Other (n=18)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA class, I/II/III/IV</td>
<td>22</td>
<td>12</td>
<td>NS</td>
</tr>
<tr>
<td>Baseline</td>
<td>0/0/19/3</td>
<td>0/0/17/</td>
<td>NS</td>
</tr>
<tr>
<td>Follow-up</td>
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<td>2/0/13/2</td>
<td>&lt;0.05</td>
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<tr>
<td>6-min Walk test, m</td>
<td>Baseline</td>
<td>277±97</td>
<td>309±104</td>
</tr>
<tr>
<td>Follow-up</td>
<td>432±118†</td>
<td>259±178</td>
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<tr>
<td>QOL score</td>
<td>Baseline</td>
<td>38±13</td>
<td>40±18</td>
</tr>
<tr>
<td>Follow-up</td>
<td>12±10†</td>
<td>38±20</td>
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<tr>
<td>LVEF, %</td>
<td>Baseline</td>
<td>24±7</td>
<td>23±7</td>
</tr>
<tr>
<td>Follow-up</td>
<td>34±9†</td>
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<td>LVEDV, mL</td>
<td>Baseline</td>
<td>253±80</td>
<td>235±92</td>
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<td>Follow-up</td>
<td>211±67†</td>
<td>245±84</td>
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<td>LVESV, mL</td>
<td>Baseline</td>
<td>197±75</td>
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<td>Follow-up</td>
<td>138±32†</td>
<td>191±59</td>
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**TABLE 5. Multivariable Linear Regression Models**

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<th>Model With Interaction Term</th>
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<td>LV dyssynchrony†</td>
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<tr>
<td>Interaction</td>
<td>...</td>
<td>31.9</td>
</tr>
<tr>
<td>6-min Walk test, post</td>
<td>Intercept -44.3</td>
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<td>LV dyssynchrony†</td>
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<tr>
<td>Interaction</td>
<td>...</td>
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<tr>
<td>LVEF, post</td>
<td>Intercept 12.2</td>
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<td>LV dyssynchrony†</td>
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<td>&lt;0.001</td>
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<tr>
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<td>LVEDV, post</td>
<td>Intercept 66.8</td>
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<tr>
<td>Interaction</td>
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<tr>
<td>LVESV, post</td>
<td>Intercept 56.0</td>
<td>57.3</td>
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<tr>
<td>LV dyssynchrony†</td>
<td>-38.5</td>
<td>0.025</td>
</tr>
<tr>
<td>Interaction</td>
<td>...</td>
<td>6.6</td>
</tr>
</tbody>
</table>

**Abbreviations as in Table 2.**
*One 1 patient died before 6 months follow-up. †P<0.05, follow-up vs baseline.
Similar results were obtained in the present study; the patients with a delay ≥65 ms showed an immediate resynchronization after initiation of CRT, accompanied by an improvement in NYHA class, 6-minute walking distance, and quality-of-life score at 6 months of CRT. In addition, an improvement in LVEF and a reduction in LV volumes were observed after 6 months of CRT. In contrast, these beneficial effects were not observed in patients with a delay <65 ms. Still, on an individual basis, only 71% of the patients with LV dyssynchrony responded to CRT, indicating that other factors are important.

In the present study, only patients with ischemic cardiomyopathy were included. These patients frequently have a history of myocardial infarction and may have large areas of scar tissue. It is currently unclear whether LV pacing in a scarred region will be beneficial and was evaluated in the present study. The location and transmurality of scar tissue in the left ventricle were assessed with contrast-enhanced MRI, which currently has the highest spatial resolution and highest accuracy to assess scar tissue noninvasively.22 It appeared that patients with transmural scar tissue in the posterolateral wall did not improve in clinical or echocardiographic parameters, not even the patients with LV dyssynchrony at baseline. This observation suggests that transmural scar tissue in the target region (for LV pacing) prohibits response to CRT; this hypothesis is further supported by the fact that patients with LV dyssynchrony did not exhibit resynchronization after CRT.

The patients with the highest likelihood of improvement after CRT (95% response rate) were the patients without transmural scar tissue in the posterolateral wall with severe baseline LV dyssynchrony. This observation underscores that assessment of LV dyssynchrony in patients with ischemic cardiomyopathy should be combined with preimplantation evaluation of scar tissue to verify whether the region that will be targeted for LV pacing does not contain transmural scar tissue.

Study Limitations
In the present study, all patients had ischemic cardiomyopathy. In these patients, extensive scar tissue can be present and may interfere with response to CRT. In patients with idiopathic dilated cardiomyopathy, localized scar tissue may be a lesser issue. Still, recent observations with contrast-enhanced MRI in patients with idiopathic dilated cardiomyopathy have also demonstrated areas of fibrosis. The effect of fibrosis in dilated cardiomyopathy on response to CRT needs further evaluation.

The posterolateral region was the site of latest activation in all patients with LV dyssynchrony in the present study. It is anticipated that the negative impact of scar tissue will also apply to other regions with late activation, but this needs further study.

The presence of contractile reserve (using provocative tests such as dobutamine stress echocardiography or MRI) and its relation to response to CRT were not evaluated in the present study and need further study. Furthermore, the differentiation between passive myocardial movement or active contraction of scarred LV segments, as is possible with strain or strain rate imaging, needs further study.

In the present study, no adjustments were made to the V-V interval of the CRT device. However, V-V optimization may be of additional benefit in patients with posterolateral scar tissue. When the V-V interval is optimized, the negative effects of a delayed activation of the LV lateral wall through the scarred LV myocardium may be corrected, and this issue remains to be evaluated.

Conclusions
In the present study, CRT does not reduce LV dyssynchrony in patients with transmural scar tissue in the posterolateral LV segments, resulting in clinical and echocardiographic nonresponse to CRT, regardless of baseline LV dyssynchrony. Patients without transmural scar tissue in the posterolateral LV segments and with severe baseline LV dyssynchrony (≥65 ms), on the other hand, have an excellent response rate of 95% after CRT implantation.

Despite the observation that CRT has a low success rate in patients with posterolateral scar tissue, the number of patients in the present study is relatively small, and the results of the present study need to be confirmed in future larger studies.

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Disclosures
Dr Bax received speaker fees from Guidant, Medtronic, and GE. Dr Schalij received speaker fees from Guidant and serves as a consultant in the advisory board of Guidant Europe. The other authors report no conflicts.

References
At present, cardiac resynchronization therapy (CRT) is considered a major breakthrough in the treatment of patients with drug-refractory heart failure. Recent large randomized trials have convincingly shown that CRT has beneficial effects on heart failure symptoms and LV function. Simultaneously, however, it was noted that 20% to 30% of patients did not respond to CRT, emphasizing the need for better selection criteria. In the search for better selection criteria, it was demonstrated that the predominant mechanism determining response to CRT is the resynchronization of preexisting LV dyssynchrony. However, the presence of LV dyssynchrony may not be the only determinant of response to CRT because some patients with LV dyssynchrony still do not respond to CRT. A potential explanation for nonresponse to CRT in patients with baseline LV dyssynchrony may be the presence of extensive scar tissue in the region of the LV pacing lead (usually the posterolateral LV region), resulting in ineffective LV stimulation. The present study is the first to evaluate response to CRT in relation to LV dyssynchrony on the one hand and scar tissue in the posterolateral wall on the other hand. Our results indicate that pacing the left ventricle in nonviable or scarred myocardium may result in less effective or even ineffective LV pacing and, as a consequence, failure of LV resynchronization and nonresponse to CRT. These results suggest that in patients with ischemic cardiomyopathy and history of previous myocardial infarction, assessment of scar tissue in the region targeted for LV stimulation should be considered before CRT implantation.
Effect of Posterolateral Scar Tissue on Clinical and Echocardiographic Improvement After Cardiac Resynchronization Therapy

Gabe B. Bleeker, Theodorus A.M. Kaandorp, Hildo J. Lamb, Eric Boersma, Paul Steendijk, Albert de Roos, Ernst E. van der Wall, Martin J. Schalij and Jeroen J. Bax

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