Relative Merits of Left Ventricular Dyssynchrony, Left Ventricular Lead Position, and Myocardial Scar to Predict Long-Term Survival of Ischemic Heart Failure Patients Undergoing Cardiac Resynchronization Therapy

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Background—The relative merits of left ventricular (LV) dyssynchrony, LV lead position, and myocardial scar to predict long-term outcome after cardiac resynchronization therapy remain unknown and were evaluated in the present study.

Methods and Results—In 397 ischemic heart failure patients, 2-dimensional speckle tracking imaging was performed, with comprehensive assessment of LV radial dyssynchrony, identification of the segment with latest mechanical activation, and detection of myocardial scar in the segment where the LV lead was positioned. For LV dyssynchrony, a cutoff value of 130 milliseconds was used. Segments with <16.5% radial strain in the region of the LV pacing lead were considered to have extensive myocardial scar (>50% transmurality, validated in a subgroup with contrast-enhanced magnetic resonance imaging). The LV lead position was derived from chest x-ray. Long-term follow-up included all-cause mortality and hospitalizations for heart failure. Mean baseline LV radial dyssynchrony was 133±98 milliseconds. In 271 patients (68%), the LV lead was placed at the latest activated segment (concordant LV lead position), and the mean value of peak radial strain at the targeted segment was 18.9±12.6%. Larger LV radial dyssynchrony at baseline was an independent predictor of superior long-term survival (hazard ratio, 0.995; P=0.001), whereas a discordant LV lead position (hazard ratio, 2.086; P=0.001) and myocardial scar in the segment targeted by the LV lead (hazard ratio, 2.913; P<0.001) were independent predictors of worse outcome. Addition of these 3 parameters yielded incremental prognostic value over the combination of clinical parameters.

Conclusions—Baseline LV radial dyssynchrony, discordant LV lead position, and myocardial scar in the region of the LV pacing lead were independent determinants of long-term prognosis in ischemic heart failure patients treated with cardiac resynchronization therapy. Larger baseline LV dyssynchrony predicted superior long-term survival, whereas discordant LV lead position and myocardial scar predicted worse outcome. (Circulation. 2011;123:70-78.)

Key Words: defibrillation • heart failure • medical imaging

Randomized controlled trials have demonstrated that cardiac resynchronization therapy (CRT) improves the clinical outcome of advanced heart failure patients with depressed left ventricular (LV) ejection fraction (<35%) and wide QRS complex (>120 milliseconds).1,2 However, after application of the current selection criteria, a substantial percentage of patients do not benefit from CRT, particularly patients with ischemic heart failure.3-6 Consequently, extensive research has been conducted in multiple single-center studies to identify predictors of favorable midterm outcome, defined as improvement in New York Heart Association (NYHA) functional class or reduction in LV end-systolic volume and improvement in LV ejection fraction at the 6-month follow-up.7 Baseline LV dyssynchrony, optimal LV lead position (in the latest mechanically activated region), and extent and location of myocardial scar have been proposed as determinants of midterm outcome after CRT.8-11 Only a few studies, however, have evaluated the determinants of long-term survival and morbidity reduction.12,13 Baseline LV dyssynchrony and optimal LV lead position appear to be important determinants of superior long-term outcome.12,13 In contrast, little is known about the impact of myocardial scar tissue on long-term outcome. More important, the relative merits of these 3 parameters (baseline LV dyssynchrony, LV...
50% stenosis in 1 or more of the major coronary artery disease, define ischemic heart failure were the presence of significant QRS duration on the surface ECG fraction (≥35%), together with NYHA functional class III or IV and selected for CRT according to the presence of depressed LV ejection fraction (by guest on July 25, 2017 http://circ.ahajournals.org/ Downloaded from

Between June 2000 and July 2008, a total of 397 patients with ischemic heart failure who received CRT at the Leiden University Medical Center were included in the present study. Patients were

Patient Population

Currently, 2-dimensional speckle tracking echocardiography can provide useful information on the presence of LV dyssynchrony, the location of the latest mechanically activated segment, and the presence and extent of scar tissue. Accordingly, this imaging technique may be ideal to use for a comprehensive analysis (with focus on these three parameters) in advanced heart failure patients who are considered for CRT. The aim of the present study was to evaluate the relative merits of LV dyssynchrony, optimal LV lead position (in the latest activated segment), and presence of myocardial scar in the region where the LV pacing lead is placed to predict long-term outcome of patients with ischemic heart failure treated with CRT. Baseline LV dyssynchrony, latest activated segment, and presence of myocardial scar were determined with a comprehensive 2-dimensional speckle tracking analysis.

Methods

Figure 1. Assessment of LV radial dyssynchrony and latest mechanical activated segment by 2-dimensional speckle tracking radial strain imaging. The midventricular short-axis view of the left ventricle is divided into 6 segments, and the time–radial strain curves are displayed. LV dyssynchrony is calculated as the time difference in peak radial strain between the anteroseptal and posterior segments. In addition, the latest activated segment is identified (posterior segment in this example; arrow).

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Echocardiographic Data

Patients were imaged in the left lateral decubitus position with a commercially available ultrasound system (Vivid-7, General Electric-Vingmed, Milwaukee, WI) equipped with a 3.5-MHz transducer. Standard 2-dimensional gray-scale and color-Doppler images triggered to the ECG were acquired in cine-loop format and transferred to a workstation for offline analysis (EchoPac 7.0.0, GE Medical Systems, Horten, Norway). LV end-diastolic and end-systolic volumes were assessed from the LV apical 2- and 4-chamber views. LV ejection fraction was derived according to the biplane Simpson method. Clinically important data were prospectively collected, including the assessment of LV dyssynchrony and the identification of the latest activated segment and the segmental value of radial strain.

LV Dyssynchrony and Latest Activated Segment

Midventricular short-axis LV images were selected to assess LV dyssynchrony and the latest activated segment. Standard 2-dimensional gray-scale images were acquired at an optimal frame rate to ensure reliable operation of the software (EchoPac 7.0.0). By applying speckle tracking radial strain analysis, we obtained time–radial strain curves of the 6 segments into which the LV is divided (anteroseptal, anterior, lateral, posterior, inferior, and septal). Time to peak radial strain was calculated for each segment, and the latest activated segment was identified. A time delay between the anteroseptal and posterior segments ≥130 milliseconds defined the presence of substantial LV dyssynchrony (Figure 1).
Myocardial Scar

Two-dimensional speckle tracking radial strain analysis was additionally used to assess myocardial scar. From midventricular short-axis images of the LV, peak radial strain was calculated for each of the 6 segments (Figure 2). Myocardial segments with a peak radial strain value $\leq 16.5\%$ were considered to be scar segments, as previously validated. To further validate this cutoff value in the present study population, contrast-enhanced magnetic resonance imaging (MRI) data were analyzed and compared with 2-dimensional speckle tracking radial strain data. Forty-three patients who underwent contrast-enhanced MRI before CRT implantation were divided into 2 groups according to the percentage of hyperenhancement of the myocardial wall ($\leq 50\%$ or $>50\%$ of the wall). Transmural myocardial scar was defined by $>50\%$ hyperenhancement of the myocardial wall. Twenty-five patients (58%) showed $>50\%$ hyperenhancement in the area where the LV lead was placed, whereas the remaining 18 patients showed $\leq 50\%$ hyperenhancement. The mean radial strain value in segments with $>50\%$ hyperenhancement was significantly lower than in segments showing $\leq 50\%$ hyperenhancement ($11.7\% \pm 1.3\%$ versus $21.3\% \pm 2.4\%$; $P<0.001$). With receiver-operating characteristic curve analysis, a cutoff value of 16.5% radial strain identified transmural myocardial scar on contrast-enhanced MRI, yielding an area under the curve of 0.83.

**Figure 2.** Assessment of segmental peak radial strain by 2-dimensional speckle tracking imaging. From the time–radial strain curves, peak radial strain can be quantified for each segment in which the left ventricle is divided. A pre-established cutoff value of 16.5% defines the presence of transmural myocardial scar.17 A, An example of a patient with myocardial scar in the latest activated segments (lateral and posterior segments; peak radial strain $<16.5\%$; arrows). B, In contrast, an example of a patient without myocardial scar in the latest activated segments (peak radial strain $\geq 16.5\%$; arrows).

### CRT Device Implantation

To insert the LV lead, first a coronary sinus venogram was obtained with the use of a balloon catheter. Thereafter, an 8F guiding catheter was used to place the LV lead (Easytrak, Guidant Corp, St. Paul, MN; Attain, Medtronic Inc, Minneapolis, MN; or Corox, Biotronik, Berlin, Germany) in the coronary sinus. The right atrial and ventricular leads were positioned conventionally. Finally, all leads were connected to a dual-chamber biventricular CRT device (Contak Renewal, Guidant Corp; Insync III or Insync Sentry, Medtronic Inc; or Lumax, Biotronik). The preferred position was a lateral or a posterolateral vein; the operator was blinded to echocardiographic information on the site of latest mechanical activation.

### Assessment of LV Lead Position

After CRT device implantation, the LV lead position was confirmed from the chest x-ray as previously described. Using the lateral views, we scored LV lead positions as anterior, lateral, posterior, or inferior. Using the frontal views, we scored the LV lead position as basal, mid, or apical. The agreement between the site of latest mechanical activation assessed by 2-dimensional speckle tracking radial strain analysis and the LV lead position derived from chest x-ray was prospectively analyzed. The LV leads positioned at the latest activated segment were classified as concordant. In contrast, LV lead positions
outside the latest activated segment were classified as discordant. LV leads located at the apical regions were excluded from further analysis. The interobserver and intraobserver agreement for the assessment of LV lead position was excellent ($\kappa=0.88$ for both).15

**Outcome Data at Long-Term Follow-Up**

After CRT implantation, all patients were followed up at 3- to 6-month intervals until July 2009 at the heart failure outpatient clinic of the CRT implantation center. All-cause mortality, heart transplantation, and hospital admission for decompensated heart failure were recorded as events. The primary end point was the combination of hospitalization for heart failure and all-cause mortality.

**Statistical Analysis**

Continuous variables are expressed as mean±SD unless otherwise indicated. Categorical data are expressed as frequencies and percentages. Continuous variables were compared by use of the Student $t$ test for unpaired and paired data. Categorical variables were compared by use of the $\chi^2$ test. Cumulative event rates for LV radial dysynchrony, LV lead position (discordant/discardant), and myocardial scar in the targeted segment were obtained by the Kaplan-Meier method using all-cause mortality and the combined end point (all-cause mortality and hospitalization for heart failure). Cox proportional hazards analysis was used to determine the value of LV radial dysynchrony, LV lead position, and myocardial scar in the targeted segment to predict long-term survival. First, univariable analysis of baseline clinical and echocardiographic characteristics, LV radial dysynchrony, LV lead position, and myocardial scar in the targeted segment was performed using all-cause mortality as an end point. For each variable, the hazard ratio and 95% confidence intervals were calculated. In the multivariable analysis, the predictive values of LV radial dysynchrony, LV lead position, and myocardial scar in the targeted segment were corrected by those variables with a value of $P<0.05$ in the univariable analysis. Finally, the relative merits of LV radial dysynchrony, LV lead position, and myocardial scar in the targeted segment over baseline clinical characteristics were assessed by calculating the Harrell C-concordance statistic and the global $\chi^2$. All statistical analyses were performed with SPSS software (version 15.0, SPSS Inc, Chicago, IL) and STATA software (version 10.1, Stata Corp, College Station, TX). A value of $P<0.05$ was considered statistically significant.

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

**Results**

**Patient Population**

The baseline characteristics of the 397 patients with chronic ischemic heart failure (341 men [86%]; mean age, 67±10 years) are presented in Table 1. All patients had depressed LV ejection fraction (25±7%), symptomatic advanced heart failure (mean NYHA functional class 3.0±0.3), and a wide QRS complex (155±33 milliseconds). All patients had optimized medical therapy, including angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, $\beta$-blockers, and diuretics at maximum tolerated dosages.

**Two-Dimensional Speckle Tracking Radial Strain Analysis**

The assessment of LV radial dysynchrony by 2-dimensional speckle tracking radial strain analysis was feasible in 389 patients (98%); mean LV radial dysynchrony was 133±98 milliseconds (Table 1). Significant LV dysynchrony ($\geq 130$ milliseconds) at baseline was observed in 44% of the patients (Table 1; see also the online-only Data Supplement). The most frequent site of latest mechanical activation was the posterior segment (155 [39%]), followed by the lateral segment (140 [33%]), inferior segment (28 [7%]), and anteroseptal segment (33 [8%]).

The LV lead was positioned at the midventricular region in the majority of the patients (351 [88%]). This was the posterior region in 178 patients (45%), the lateral region in 182 (46%), and the anterior region in 37 (9%). In 271 patients (68%), the LV lead was placed at the latest activated segment as determined by 2-dimensional speckle tracking radial strain imaging (Table 1). These patients formed the concordant LV lead position group. The remaining 126 patients (32%), in whom the LV lead position did not coincide with the latest activated segment formed the discordant LV lead position group (see the online-only Data Supplement).

Finally, the mean value of peak radial strain was 18.9±12.6% in the segment where the LV lead was positioned. The mean peak radial strain values at the posterior, lateral, and anterior segments were 19.3±13.7%, 18.3±12.6%, and 15.1±10.1%, respectively. Myocardial scar (defined as strain $<16.5\%$ based on validation with contrast-enhanced MRI) in the segment targeted by the LV pacing lead was observed in 51% of the patients (Table 1; see also the online-only Data Supplement).

**Clinical and Echocardiographic Follow-Up After 6 Months of CRT**

After 6 months of CRT, a significant improvement in clinical parameters was observed: 259 patients (66%) showed an improvement of at least 1 NYHA functional class; the 6-minute walking distance increased from 306±112 to 371±121 m.

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**Table 1. Baseline Characteristics**

<table>
<thead>
<tr>
<th>Clinical variables</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>67±10</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>341 (86)</td>
</tr>
<tr>
<td>QRS duration, ms</td>
<td>155±33</td>
</tr>
<tr>
<td>Sinus rhythm, %</td>
<td>321 (81)</td>
</tr>
<tr>
<td>NYHA functional class</td>
<td>3.0±0.3</td>
</tr>
<tr>
<td>Quality-of-life score</td>
<td>36±19</td>
</tr>
<tr>
<td>6-min walking distance, m</td>
<td>301±115</td>
</tr>
<tr>
<td>Medical therapy, %</td>
<td></td>
</tr>
<tr>
<td>$\beta$-blockers</td>
<td>280 (71)</td>
</tr>
<tr>
<td>ACEI/ARB-II</td>
<td>353 (89)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>328 (83)</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>180 (45)</td>
</tr>
<tr>
<td>Statins</td>
<td>304 (77)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Echocardiographic variables</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV end-diastolic volume, mL</td>
<td>216±78</td>
</tr>
<tr>
<td>LV end-systolic volume, mL</td>
<td>161±67</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>25±7</td>
</tr>
<tr>
<td>LV radial dysynchrony, ms</td>
<td>133±98</td>
</tr>
<tr>
<td>LV radial dysynchrony $\geq$ 130 ms, %</td>
<td>44</td>
</tr>
<tr>
<td>Discordant LV lead position, %</td>
<td>32</td>
</tr>
<tr>
<td>Radial strain in the targeted segment, %</td>
<td>19.1±12.6</td>
</tr>
<tr>
<td>Myocardial scar in the targeted segment, %</td>
<td>51</td>
</tr>
</tbody>
</table>

ACEI/ARB-II indicates angiotensin-converting enzyme inhibitor/angiotensin receptor blockers II. Continuous variables are expressed as mean±SD.
and the quality-of-life score improved from 35±19 to 24±19 (P<0.001). In addition, there was a significant reduction in LV end-diastolic volume (from 216±78 to 181±69 mL; P<0.001) and end-systolic volume (from 161±67 to 136±58 mL; P<0.001), together with a significant improvement in LV ejection fraction (from 25±7% to 31±9%; P<0.001). At the 6-month follow-up, 231 patients (58%) showed significant LV reverse remodeling, with a reduction in LV end-systolic volume ≥15%. The remaining 166 (42%) did not show significant LV reverse remodeling and were considered nonresponders.

LV Radial Dyssynchrony, LV Lead Position, and Myocardial Scar in the Targeted Segment Compared With Long-Term Outcome

Long-term follow-up started after CRT implantation. During a median follow-up of 21 months (range, 1 to 90 months), there were 88 hospitalizations for heart failure in 39 patients (10%), and 88 patients (22%) died. During follow-up, none of the patients underwent heart transplantation.

After 3 years of CRT, the survival rate of patients with LV radial dyssynchrony (≥130 milliseconds) was 82% compared with 65% for patients without substantial dyssynchrony (<130 milliseconds; log-rank P=0.001; Figure 3A). Similarly, at the 3-year follow-up, patients with LV radial dyssynchrony showed a superior survival free of the combined end point compared with patients without LV radial dyssynchrony (75% versus 63%; log-rank P=0.003; Figure 3B).

The 3-year survival rate of patients with an LV lead placed at the site of latest mechanical activation (concordant LV lead position) was significantly higher compared with patients with discordant LV lead position (80% versus 54%; log-rank P<0.001; Figure 3C). In addition, after 3 years of CRT, the
survival free of the combined end point was significantly higher in patients with a discordant LV lead position than in patients with a discordant LV lead position (75% versus 54%; log-rank \( P < 0.001 \); Figure 3D).

Finally, the presence of myocardial scar in the targeted segment had a strong influence on survival rates (Figure 3E and 3F). At the 3-year follow-up, patients without myocardial scar in the segment where the LV lead was placed (peak radial strain \( \geq 16.5\% \) ) showed higher survival rates than patients with myocardial scar in the targeted segment (peak radial strain \( < 16.5\% \); 87% versus 58%; log-rank \( P < 0.001 \)). Similarly, the 3-year survival free of the combined end point was significantly higher in patients without myocardial scar in the segment targeted by the LV lead compared with patients with myocardial scar (81% versus 57%; log-rank \( P < 0.001 \); Figure 3F).

**Predictors of Long-Term Survival in Ischemic Heart Failure Patients After CRT**

The predictive value of LV radial dyssynchrony, LV lead position, and myocardial scar in the targeted segment on all-cause mortality was analyzed by Cox proportional hazards analysis. The independent predictors of all-cause mortality were age, plasma levels of creatinine, LV radial dyssynchrony, discordant LV lead position, and myocardial scar in the targeted segment (Table 2). To evaluate the relative merits of LV radial dyssynchrony, discordant LV lead position, and myocardial scar in the targeted segment over the clinical variables to predict long-term outcome, analysis of the discrimination indexes was performed, and the global \( \chi^2 \) scores were calculated. Table 3 shows the Harrell C-concordance statistic index for each model. The accuracy of the Cox proportional hazards model to predict long-term outcome progressively increased by adding LV dyssynchrony, discordant LV lead position, and myocardial scar in the segment where the LV lead was positioned. In addition, Figure 4 shows that LV dyssynchrony had an incremental prognostic value over clinical variables (age and creatinine plasma levels). The addition of discordant LV lead position had an incremental prognostic value over the combination of clinical variables and LV dyssynchrony. Finally, the addition of myocardial scar on top of LV radial dyssynchrony and discordant LV lead position resulted in a further improvement of the prognostic stratification of these patients (Figure 4).

**Discussion**

The findings of the present study demonstrated that the presence of substantial LV dyssynchrony, appropriate location of the LV pacing lead, and absence of myocardial scar in the segment targeted by the LV lead were independent determinants of long-term prognosis in ischemic heart failure patients treated with CRT. Furthermore, the combination of these 3 parameters had an incremental prognostic value over clinical parameters.

**Table 2. Cox Univariable and Multivariable Regression Analyses to Identify Predictors of All-Cause Mortality**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Univariable HR (95% CI)</th>
<th>Univariable P</th>
<th>Multivariable HR (95% CI)</th>
<th>Multivariable P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per 1 y)</td>
<td>1.028 (1.005–1.052)</td>
<td>0.017</td>
<td>1.027 (1.003–1.051)</td>
<td>0.028</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.060 (0.547–2.052)</td>
<td>0.863</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYHA functional class</td>
<td>1.953 (1.129–3.376)</td>
<td>0.017</td>
<td>1.447 (0.819–2.558)</td>
<td>0.204</td>
</tr>
<tr>
<td>QRS duration (( \geq 150) ms)</td>
<td>1.008 (0.651–1.559)</td>
<td>0.973</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma levels of creatinine (per 1 mmol/mL)</td>
<td>1.003 (1.002–1.004)</td>
<td>&lt;0.001</td>
<td>1.004 (1.002–1.007)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.566 (0.982–2.497)</td>
<td>0.060</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV end-diastolic volume (per 1 mL)</td>
<td>1.001 (0.998–1.004)</td>
<td>0.506</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV ejection fraction (&lt;25%)</td>
<td>1.568 (1.020–2.409)</td>
<td>0.040</td>
<td>1.316 (0.831–2.085)</td>
<td>0.242</td>
</tr>
<tr>
<td>LV radial dyssynchrony (per 1 ms)</td>
<td>0.995 (0.992–0.998)</td>
<td>&lt;0.001</td>
<td>0.995 (0.992–0.998)</td>
<td>0.001</td>
</tr>
<tr>
<td>Discordant LV lead position</td>
<td>3.095 (2.033–4.717)</td>
<td>&lt;0.001</td>
<td>2.086 (1.336–3.258)</td>
<td>0.001</td>
</tr>
<tr>
<td>Myocardial scar in the targeted segment (radial strain &lt;16.5%)</td>
<td>3.367 (2.075–5.435)</td>
<td>&lt;0.001</td>
<td>2.913 (1.740–4.877)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

HR indicates hazard ratio; CI, confidence interval.

**Table 3. Incremental Prognostic Value of LV Dyssynchrony, Discordant LV Lead Position, and Myocardial Scar: Discrimination Index Analysis**

<table>
<thead>
<tr>
<th>Model</th>
<th>Clinical parameters</th>
<th>Clinical parameters + LV dyssynchrony</th>
<th>Clinical parameters + LV dyssynchrony + discordant LV lead position</th>
<th>Clinical parameters + LV dyssynchrony + discordant LV lead position + Myocardial scar</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>0.659</td>
<td>0.703</td>
<td>0.732</td>
<td>0.751</td>
</tr>
</tbody>
</table>

Harrell C-Concordance Statistic Index
Figure 4. Relative merits of LV radial dyssynchrony, discordant LV lead position, and myocardial scar in the targeted segment. The bar graph shows the $\chi^2$ value for the 3 models predicting all-cause mortality. The smallest model (model 1) includes clinical variables (age and plasma levels of creatinine) and is nested in models 2, 3, and 4. The addition of LV dyssynchrony (model 2) provides incremental prognostic information over baseline clinical variables. Further addition of discordant LV lead position (model 3) provides incremental prognostic information over baseline clinical variables and LV dyssynchrony. Finally, the addition of myocardial scar in the segment targeted by the LV lead (radial strain value <16.5%; model 4) results in further incremental prognostic value on top of clinical characteristics, LV dyssynchrony, and LV lead position. Model 1, clinical variables (age, plasma levels of creatinine). Model 2, model 1 plus LV dyssynchrony. Model 3, model 2 plus discordant LV lead position. Model 4, model 3 plus myocardial scar in the targeted segment.

In addition, the location and extent of myocardial scar tissue are determinants of CRT response. Patients with transmural scar in the area where the LV lead is placed or patients with large areas of myocardial scar tissue showed a lower response rate to CRT compared with patients with minimal scar tissue. However, the prognostic predictive value of myocardial scar tissue in ischemic heart failure patients treated with CRT has not been yet established. Delayed contrast-enhanced MRI and nuclear imaging are considered the gold standard for evaluating myocardial scar tissue. Recently, the role of 2-dimensional speckle tracking radial strain imaging to evaluate myocardial scar tissue has also been demonstrated. In the present study, the presence of myocardial scar in the segment where the LV lead was placed was evaluated with this imaging technique, and the results indicated that patients with myocardial scar tissue in the targeted segment (peak radial strain <16.5%) had lower long-term survival rates than patients without myocardial scar (peak radial strain ≥16.5%). More important, the presence of myocardial scar in the segment paced by the LV lead had incremental prognostic value over clinical characteristics, LV reverse remodeling, LV dyssynchrony, and optimal LV lead position ($\chi^2=105.2; P<0.001$; see Figure 4).

Therefore, comprehensive assessment of LV dyssynchrony, latest activated segment, and myocardial scar tissue appears crucial for selecting ischemic heart failure patients who will benefit most from CRT. Two-dimensional speckle tracking radial strain imaging may be of value to assess all these issues before CRT implantation.

Study Limitations

The present study included ischemic heart failure patients. Low radial strain can also be observed in patients with nonischemic heart failure and remodeled LVs without myocardial scar. Nevertheless, the cutoff value of radial strain used in the present study was validated with contrast-
enhanced magnetic resonance in a subgroup of ischemic heart failure patients. Additional studies including nonischemic heart failure patients are needed to elucidate the role of radial strain speckle tracking imaging to predict long-term prognosis in these subpopulations.

Clinical Implications

Several pathophysiological factors may determine prognosis after CRT. The importance of baseline LV dyssynchrony assessment and optimal LV lead position to predict long-term outcome after CRT has been demonstrated in several studies. However, as indicated previously, positioning the LV pacing lead in a scar segment may limit the improvement in clinical and echocardiographic parameters. The present study extends these results and demonstrates the relative merits of baseline LV dyssynchrony, LV lead position, and myocardial scar tissue in the targeted segment. The combination of these 3 parameters had a strong influence on the long-term outcome of ischemic heart failure patients treated with CRT. Despite substantial LV dyssynchrony or optimal LV lead position at the latest activated segment, the effect of CRT on long-term prognosis may be reduced by the presence of myocardial scar in the region where the LV pacing lead has been placed. In addition, these 3 pathophysiological factors had incremental prognostic value over clinical variables. The implementation of an integrated approach that includes assessment of LV dyssynchrony and the latest activated segment together with characterization of myocardial scar may improve patient selection and survival after CRT. Two-dimensional speckle tracking radial strain imaging may provide this comprehensive evaluation of candidates for CRT.

Conclusions

Long-term outcome of ischemic heart failure patients after CRT implantation is determined independently by baseline LV dyssynchrony, LV lead position, and myocardial scar in the region where the LV pacing lead was placed. Larger baseline LV dyssynchrony predicted superior long-term survival, whereas discordant LV lead position and myocardial scar predicted worse outcome. These 3 parameters provided incremental prognostic value over clinical variables. Two-dimensional speckle tracking radial strain allowed an integrated evaluation of ischemic heart failure patients who are candidates for CRT by evaluating these 3 parameters.

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Disclosures

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**CLINICAL PERSPECTIVE**

The beneficial effects of cardiac resynchronization therapy on long-term survival are influenced by several pathophysiological factors. The present study demonstrated the relative merits of left ventricular (LV) dyssynchrony, LV lead position, and myocardial scar to predict long-term outcome of ischemic heart failure patients treated with cardiac resynchronization therapy. With speckle tracking radial strain analysis, the extent of LV dyssynchrony, site of latest mechanical activation, and presence of myocardial scar at the LV segment where the LV pacing lead is placed were evaluated. In addition, the LV lead position was derived from chest x-ray and was defined as concordant when the LV pacing lead coincided with the site of latest mechanical activation. Mean baseline LV radial dyssynchrony was 133±98 milliseconds. A discordant LV lead position was reported in 271 patients (68%), and the mean value of peak radial strain at the targeted segment was 18.9±12.6%. During a median follow-up of 21 months, 88 patients (22%) died. Larger LV radial dyssynchrony at baseline was an independent predictor of superior long-term survival (hazard ratio, 0.995 per 1-millisecond increment; P=0.001), whereas a discordant LV lead position (hazard ratio, 2.086; P=0.001) and myocardial scar in the segment targeted by the LV lead (hazard ratio, 2.913; P<0.001) were independent predictors of worse outcome. Addition of these 3 parameters yielded incremental prognostic value over the combination of clinical parameters. These data underscore the need for integrated evaluation that includes assessment of these 3 parameters to further improve patient selection and survival after cardiac resynchronization therapy.
Relative Merits of Left Ventricular Dyssynchrony, Left Ventricular Lead Position, and Myocardial Scar to Predict Long-Term Survival of Ischemic Heart Failure Patients Undergoing Cardiac Resynchronization Therapy
Victoria Delgado, Rutger J. van Bommel, Matteo Bertini, C. Jan Willem Borleffs, Nina Ajmone Marsan, Arnold C.T. Ng, Gaetano Nucifora, Nico R.L. van de Veire, Claudia Ypenburg, Eric Boersma, Eduard R. Holman, Martin J. Schalij and Jeroen J. Bax

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Table 1 (supplemental file). Baseline clinical and echocardiographic characteristics of the study population based on the presence of significant LV dyssynchrony, concordant/discordant LV lead position and presence of myocardial scar.

<table>
<thead>
<tr>
<th>Clinical variables</th>
<th>LV dyssynchrony</th>
<th>LV lead position</th>
<th>Myocardial scar</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≥130 ms (n=172)</td>
<td>&lt;130 ms (n=217)</td>
<td>Concordant (n=271)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>66±9</td>
<td>68±10*</td>
<td>67±10</td>
</tr>
<tr>
<td>Gender (male, %)</td>
<td>145 (84)</td>
<td>189 (87)</td>
<td>232 (85)</td>
</tr>
<tr>
<td>QRS duration (ms)</td>
<td>155±32</td>
<td>148±33*</td>
<td>152±33</td>
</tr>
<tr>
<td>Sinus rhythm (%)</td>
<td>141 (82)</td>
<td>172 (79)</td>
<td>221 (81)</td>
</tr>
<tr>
<td>NYHA functional class</td>
<td>3.0 ± 0.3</td>
<td>3.0 ± 0.3</td>
<td>3.0 ± 0.3</td>
</tr>
<tr>
<td>Quality of life score</td>
<td>35±19</td>
<td>37±19</td>
<td>35±18</td>
</tr>
<tr>
<td>6-minute walking distance (m)</td>
<td>304±114</td>
<td>297±117</td>
<td>305±113</td>
</tr>
<tr>
<td>Medical therapy (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B-blockers</td>
<td>129 (75)</td>
<td>145 (67)</td>
<td>194 (72)</td>
</tr>
<tr>
<td>ACEI/ARB-II</td>
<td>152 (88)</td>
<td>194 (89)</td>
<td>239 (88)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>146 (84)</td>
<td>176 (81)</td>
<td>215 (79)</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>71 (41)</td>
<td>104 (48)</td>
<td>115 (42)</td>
</tr>
<tr>
<td>Statins</td>
<td>141 (82)</td>
<td>155 (71)*</td>
<td>205 (76)</td>
</tr>
<tr>
<td>Echocardiographic variables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV end-diastolic volume (ml)</td>
<td>230±85</td>
<td>206±69*</td>
<td>218±79</td>
</tr>
<tr>
<td>LV end-systolic volume (ml)</td>
<td>173±73</td>
<td>154±61*</td>
<td>164±70</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>25±7</td>
<td>25±7</td>
<td>25±7</td>
</tr>
<tr>
<td>LV radial dyssynchrony (ms)</td>
<td>221±77</td>
<td>63±42*</td>
<td>142±103</td>
</tr>
<tr>
<td>Radial strain in the targeted segment (%)</td>
<td>18.8±11.0</td>
<td>19.4±13.8</td>
<td>20.3±12.7</td>
</tr>
</tbody>
</table>

*p<0.05.

Abbreviations: ACEI/ARB-II = angiotensin converting-enzyme inhibitor/angiotensin receptor blockers-II; LV=left ventricular; NYHA=New York Heart Association.

LV dyssynchrony assessment with 2-dimensional speckle tracking was feasible in 98% of patients (n=389)
하혈성심부전에서 심실재통기화치료 효과의 결정인자:
좌심실 dyssynchrony vs. 좌심실 lead 위치 vs. 심근반흔

김용진 교수 서울대학교병원 순환기내과

Summary

배경
하혈성심부전 환자에서 심실재통기화치료(cardiac resynchronization therapy)의 장기예후를 결정하는 인자로서 좌심실 dyssynchrony, 좌심실 lead 위치, 심근반흔 각각의 중요성을 비교한 연구는 아직 없었다.

방법 및 결과
397명의 하혈성심부전 환자에서 2D speckle 추적 심초음파검사를 시행하여 좌심실의 radial dyssynchrony를 측정하고, 가장 높게 수축하는 부위를 확인하였으며, 좌심실 lead가 있는 부위에서 심근반흔의 존재 여부를 평가하였다. 130msec를 기준으로 좌심실 dyssynchrony를 전단하였다. 좌심실 lead가 위치한 부위의 radial strain이 16.5% 미만이면 심근반흔(50% 이상의 transmurality)을 전단하였다. 장기 추적관찰을 통해 총 사망률과 심부전 악화에 의한 입원을 기록하였다. 환자의 평균 좌심실 radial dyssynchrony는 133±98msec였다. 271명(68%)의 환자에서 좌심실 lead는 가장 높게 수축하는 부위에 위치하였고, 목표 부위의 평균 최대 radial strain은 18.9±12.6%였다. 증가된 기저 좌심실 radial dyssynchrony가 장기 생존율의 독립적인 예측인자였고(HR, 0.995; P=0.001), 반면에 가장 높게 수축하는 부위에 lead가 위치하지 않은 discordant lead position(HR 2.086; P=0.001)와 좌심실 lead가 위치한 부위의 심근반흔(HR 2.913; P<0.001)이 병명예후를 예측하는 독립적인 위험인자였다. 이러한 세 가지 변수를 포함하였을 때, 임상변수를 종합한 것보다 추가적인 예후 예측력을 보였다.

결론
좌심실의 radial dyssynchrony, 좌심실의 discordant lead position, 좌심실 pacing lead 부위의 심근반흔은 하혈성심부전 환자에서 심실재통기화치료의 장기예후를 결정하는 독립적 인자이다. Radial dyssynchrony의 증가는 좋은 예후, discordant lead position과 심근반흔은 불량한 예후의 예측인자이다.
Commentary

2002년 MIRACLE 연구에서 심실과등기화지표의 높은 효과가 처음 보고된 이후, 심실과등기화지표는 대규모 임상연구를 통해 좌심실구형률이 저하된<35% QRS duration이 높아진(>120msec) 진행성 심부전 환자에서 예후를 개선하는 효과가 증명되어 널리 사용되고 있다. 지난 8년간 많은 임상실험이 발효하고 연구가 진행되었지만, 여전히 1/3 정도의 환자는 아직 치료 효과를 관찰할 수 없으며, 특히 혈력심부전 환자에서 높았다. 이는 심실과등기화지표의 높은 비용과 부작용을 고려할 때 큰 문제가 아닐 수 없다. 따라서, 심실과등기화지표의 효과를 예측할 수 있는 보다 나은 방법을 개발하여, 치료의 적응증으로 활용할 수 있는 방법이 필요하며, 많은 연구가 이에 대한 연구를 진행하고 있다. 하지만 아직 심실과등기화지표의 정기적 예측자의 관련 연구는 거의 없다. 이러한 점에서 본 연구의 임상적 중요성이 있다고 하겠다.

본 연구의 결과를 요약하면, 좌심실의 dyssynchrony가 높을 때, 좌심실 lead의 위치가 적절할 때 (수축이 가장 높아지는 부위에 위치할 때), 그리고 좌심실 lead가 위치한 곳에 심근약화이 없을 때 심실과등기화지표의 정기적 예후가 좋다는 것이다. 이러한 세 가지 인자를 종합하면 기존의 임상적 연구에 더해 추가적인 예후 예측력이 관찰되었다.

좌심실의 dyssynchrony가 심실수축의 비효율성을 증가시키고 임상적으로 심실기능을 악화시킨다는 것을 알게 되었다. 하지만, 대부분의 심실과등기화지표 임상연구가 좌심실의 mechanical dyssynchrony가 아닌 심실로 주변의 QRS widening을 기준으로 하고 있어서 심실과등기화지표의 지표로서 좌심실의 dyssynchrony에 대해서는 여전히 논란이 있다. Mechanical dyssynchrony에 대한 대표적인 심장스캐너 연구결과는 PROSPECT 연구와 RetinQ 연구이다. PROSPECT 연구에서 심초음파 검사로 측정하는 dyssynchrony가 심실과등기화지표의 효과를 예측할 수 없었으며, 측정 방법의 낮은 재현성이 가장 큰 문제로 지적되었다. 정상적인 QRS duration을 보이지만, 심초음파상 좌심실 dyssynchrony를 나타내는 환자를 대상으로 심실과등기화지표 효과를 분석한 RetinQ 연구에서도 dyssynchrony는 기저 효과를 예측하는 데 도움이 되지 못했다. 하지만, 최근 보고된 연구에서 심초음파의 최신 기술인 speckle tracking 방법으로 radial strain을 측정하여 정확한 dyssynchrony는 심실과등기화지표의 효과를 예측할 수 있다고 알려져 있고 있다(Figure 1). 이 방법은 검사의 재현성 역시 높일 수 있는 장점이 있어 앞으로 대규모 임상학 연구를 통한 분석이 필요하다.
기대된다.
심근반응이 많을수록 심실재동기화치료의 효과가 떨어지는 것은 '|'명연한 결과라고 할 수 있다. 본 연구에서는
gold standard로 사용되던 심장 MRI 대신에 심초음파
로 심근반응을 진단하였다는 점이 기존 연구와 다르며,
특히 좌심실 lead가 위치한 곳에 심근반응이 있는지를
평가하였다는 점에서 차별성이 있다. Speckle tracking
으로 측정한 radial strain이 16.5% 미만인 경우 심근반
응으로 진단하였는데 radial strain의 저하가 심근반응에
의해서만 나타나는 것이 아니라라는 제한점을 고려할 필
요가 있다. 또한, 심근반응이 없으면 그 자체가 speckle
tracking의 정확성에 영향을 줄 수 있다는 점도 고려해
야 한다. 이는 이 부분에 대해서 추가적인 연구가 필요
한 이유라고 하겠다.
심실재동기화치료에 반응하지 않는 환자군을 찾는 것은
필요 없는 시술에 따른 부작용과 비용을 줄이는데
서 매우 중요하다. 현재 가이드라인에서 제시하고 있는
심실재동기화치료의 적용증, 즉 좌심실구혈률 <35%, 심
전도 상 QRS duration >120msec는 많은 임상연구 결과
를 토대로 결정된 것이지만, 여전히 많은 환자에서의 치
료 효과가 관찰되지 않는다. 특히 혈압성심부전 환자는
심근반응이 많고, 관상동맥관련 사건은 심실재동기화치
료와 직접적인 관련이 있어서 치료 효과가 더욱 떨어지
는 것이 사실이다. 본 논문에서 제시된 세 가지 결정인자
는 항후 치료 효과를 예측하는 데 있어 더욱 중요한 역
할을 할 것으로 생각되며, 대규모 전향적 임상연구를 통
해 확인될 필요가 있다.