Analysis of Ventricular Activation Using Surface
Electrocardiography to Predict Left Ventricular Reverse
Volumetric Remodeling During Cardiac
Resynchronization Therapy

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Background—Cardiac resynchronization therapy for heart failure with left bundle branch block reduces left ventricular (LV) conduction delay, contraction asynchrony, and LV end-systolic volume (“reverse remodeling”). Up to one third of patients do not improve, and the electric requirements for reverse remodeling are unclear. We hypothesized that reverse remodeling is predicted by the left bundle branch block ventricular activation sequence, the paced activation sequence, and interactions between these 2 conditions.

Methods and Results—Twelve-lead ECGs during left bundle branch block and cardiac resynchronization therapy were analyzed in 202 consecutive patients (New York Heart Association class III to IV heart failure, ejection fraction ≤35%) for predictors of reverse remodeling (≥10% reduction in end-systolic volume) at 6 months. Greater longest baseline LV activation time predicted increased odds of reverse remodeling (odds ratio [confidence interval] = 1.30 [1.11, 1.52] per 10-ms increase), whereas higher QRS scores for LV scar predicted reduced reverse remodeling (odds ratio [confidence interval] = 0.49 [0.27, 0.88] for each 1-point increase from 0 to 4; 0.92 [0.83, 1.01] for each 1-point increase ≥4). After cardiac resynchronization therapy, increasing R amplitudes in leads V1 through V2 (odds ratio [confidence interval] = 2.76 [1.01, 7.51] for each 1 increase over [baseline R = 4.5]) and left→right frontal axis shift (odds ratio [confidence interval] = 2.00 [0.99, 4.02]), indicators of ventricular activation wavefront fusion, were positive predictors of reverse remodeling. Predicted probability of reverse remodeling ranged from <20% for patients with adverse predictors to 99% for those with positive predictors.

Conclusions—Ventricular activation with the use of the ECG accurately predicts LV reverse remodeling during cardiac resynchronization therapy. Greater longest baseline LV activation time and smaller scar volume combined with wavefront fusion on the paced ECG, anticipate higher probability of reverse remodeling. (Circulation. 2010;121:626-634.)

Key Words: bundle-branch block ■ implantable cardioverter-defibrillator ■ heart failure ■ pacing

Left ventricular (LV) conduction delay due to left bundle branch block (LBBB) causes regional heterogeneity in contraction and stretch (asynchrony), which reduces pump function and stimulates negative LV remodeling. The conceptual basis of cardiac resynchronization therapy (CRT) is to minimize LV conduction delay, which reduces contractile asynchrony and instantaneously improves LV mechanics. Resynchronization of electromechanical activation induces “reverse” remodeling (LV volume reductions) and improved pump function (increased LV ejection fraction [LVEF]).

We hypothesized that the volumetric reverse remodeling response to CRT can be predicted by the baseline LBBB ventricular activation sequence, the paced ventricular activation sequence, and the interaction between these 2 conditions.

Methods

We developed a predictive model to test the hypothesis that the probability of reverse volumetric remodeling could be accurately characterized by the ventricular activation pattern on the 12-lead surface ECG before and after CRT.

Study Sample

The study sample consisted of 202 consecutive patients with New York Heart Association class III to IV heart failure despite medical therapy, LVEF ≤35%, and LBBB (QRS duration [QSRd] ≥120 ms; delayed intrinsicoid deflection in leads I, V5, V6 ≥50 ms; broad
slurred R waves in I, aVL, V₅, and V₆; rS or QS waves in V₇ through V₁₂; ST-T wave vectors opposite the major QRS vector). Patients with right bundle branch block (RBBB), right ventricular (RV) pacing, or myocardial infarction ≤3 months previously were excluded. Simultaneous biventricular pacing was applied without exception for the first 6 months.

**Echocardiography and ECG**

Standard supine 12-lead ECGs (filter range, 0.15 to 100 Hz; AC filter, 60 Hz, 25 mm/s, 10 mm/mV) were obtained at baseline and before discharge. Echocardiograms were performed at baseline and after 6 months of CRT. Patients were imaged in the left lateral decubitus position with a commercially available system (Vingmed System Seven, General Electric–Vingmed, Milwaukee, Wis) with a 3.5-MHz transducer at a depth of 16 cm in conventional parasternal and apical views. Standard 2-dimensional and color Doppler data triggered to the QRS complex were saved in cine-loop format. LV end-systolic volume (ESV) and end-diastolic volume (EDV) were measured at the apical 2- and 4-chamber views; LVEF was calculated with the use of the biplane Simpson method. Interobserver and intraobserver reproducibility for LV volume measures were 90% and 96%, respectively.³

**ECG Analysis of Ventricular Activation**

ECGs were analyzed blind to echocardiographic results. All measurements were made with the use of digital calipers at 200% magnification calibrated for paper speed 25 mm/s. Normal frontal plane axis was +90° to +30°, left axis deviation (LADEV) ≥−30° to −60°, right axis deviation (RADEV) ≥−90° to +90°. Right superior axis (RSA) was >180° to 90°; right inferior axis (RIA) >90° to 180°. “Incompletely” right superior axis (IRSA) was extreme LADEV (−60° to −90°) with rS or QS complexes in the inferior leads and equiphasic QR in I (see below for QRS hieroglyphic framework). Axis quadrant shift was displacement of LBBB frontal plane axis by ≥1 quadrant during CRT (eg, normal→LADEV, normal→RSA).

**QRS Hieroglyphic Framework for Ventricular Activation Pattern Comparisons**

The QRS complex in each lead before and after CRT was deconstructed into 4 possible waveform elements (R, S, Q, QS). Absolute amplitudes (mV) and durations (ms) of all elements of each QRS complex were used to characterize specific activation patterns (eg, R and S present, R=S amplitude, pattern=Rs). Ventricular activation in each lead was characterized by 9 possible patterns or QRS hieroglyphs, as follows: (1) R; (2) RS (R=S and both >1 mm, or both <1 mm; equiphasic); (3) Rs (R >s); (4) rS (S >r); (5) QS; (6) QR (Q <R); (7) Qr (Q >R >1 mm, or both <1 mm; equiphasic); (8) Qr (Q >r); and (9) QRS (all 3 waveforms present).

**Characterization of Ventricular Activation During LBBB**

Typical LBBB activation is registered as right (R)→left (L) (frontal plane), anterior (A)→posterior (P) (horizontal plane), and variable axis. This yields a QRS hieroglyphic signature with dominant positive forces in I, aVL (R, Rs); negative forces in aVR (QS); variable forces in II, III, AVF (R, Rs, S, QS); dominant negative forces in V₁ through V₃ (QS, Q); transition V₃ through V₄ (rS→Rs, R); and dominant positive forces in V₄ through V₆ (R, Rs).

**QRS Notching**

LBBB is characterized by sequential ventricular activation (RV→LV)⁴,⁵ and registered as fragmented QRS complexes with RSR' configuration (“notch”). QRS notching was defined as ≥1 notch in the R or S wave present in ≥2 adjacent anterior, lateral, or inferior leads.⁶

**RV and LV Activation Time**

Because multiple notches in the R and S wave during LBBB may occur because of myocardial scar,⁶ the first notch was assumed to indicate the transition between RV and LV depolarization. Notching in the first 40 ms of the S wave in V₁ through V₂ was excluded because this indicates scar in the QRS score. RV activation time (RVAT) was measured as time (ms) between QRS onset and first notch in any of ≥2 adjacent leads. LV activation time (LVAT) was QRSd−RVAT (ms).

For modeling purposes, the longest LVAT (LVATₘₐₓ) recorded in any lead and region was used. A numeric relationship between QRSd and LVATₘₐₓ was derived with the use of linear regression (LVATₘₐₓ [ms]=−35.839+0.763×QRSd [ms]+0.000619×QRSd [ms]²), permitting estimation of LVATₘₐₓ in the absence of QRS notching (40 patients).

**Quantification of LV Scar**

Myocardial scar has been linked to reduced CRT response.³ ECG quantification of LV scar volume was calculated with the use of the Selvester QRS score for LBBB.²,³ The effects of scar on LBBB surface registration translate as specific QRS hieroglyphic signatures, manifest as unopposed rightward electric forces by infarct region: QR, QR, rS in I, aVL (anterior-superior); QR, QR, rS in I, V₁ through V₃ (apical); QR, QR, rS in II, aVF (inferior); QS→rS, RS, or Rs in V₁ through V₃ (anterior-septal). Notching on the ascending limb of the S wave in V₁ through V₂ indicates posterolateral infarct.

**Evidence for Ventricular Activation Fusion During Biventricular Pacing**

Experimental models of LBBB demonstrate maximum improvement in LV pump function occurs when intra-LV electric asynchrony is minimized by wavefront fusion.¹ Wavefront opposition and reversal during biventricular pacing should yield ECG evidence of fusion, as follows: (1) expected change in frontal plane electric axis: normal or LADEV→RADEV; (2) expected changes in QRS hieroglyphic signatures: rightward forces emerge in leads with dominant lateral forces (R in I, aVL→rQ, QR, QS); anterior forces emerge in leads with dominant posterior forces (eg, QS in V₁→rS, RS, Rs; QS or rS in V₁→RS, Rs, R; or Rs or QS in V₁→Rs, Rs; Rs or RS in V₁→Rs or Rs; R); (3) an alternate way of characterizing evidence for ventricular fusion is using regional or global measures of CHange in R wave amplitude in the expected direction in Lateral (I, aVL) and Precordial leads (V₁-V₆) (CHRLP) before and after CRT.

Although LV pacing yields specific ventricular activation patterns generally in accordance with stimulation site, nearly identical ECG activation sequences may be registered at widely spaced sites,⁹ and electric resynchronization during CRT correlates unpredictably with stimulation site because of conduction blocks.³ For these reasons, LV lead position was not relevant to this analysis.

**End Points**

The primary end point was LV reverse volumetric remodeling, defined as ≥10% reduction in ESV at 6 months.³ Supplemental reverse remodeling end points, chosen to provide additional insights into the predictive model, were ≥10% reduction in EDV (mechanistically similar measure of reverse remodeling) and ≥30% reduction in ESV (“superresponse”).²

**Statistical Analysis**

For descriptive summaries, categorical variables are presented as n (percent) and continuous variables as median (25th, 75th percentile).

Indices of change in R amplitude were generated by calculating, for each patient, the change in R amplitude for each lead from baseline to post-CRT, as a proportion of the baseline value. The postimplantation value was used in cases in which an R was absent at baseline and post implantation; a value of 1 was used in cases in which an R was present at baseline and absent postimplantation; and a value of 0 was used in cases in which both were absent. Change values were set to positive if the change was in the expected direction (decrease in I, aVL, and V₄ through V₆; increase in V₁ through V₃) and were negative otherwise. Leads II, III, and aVF had no expected direction and retained their calculated sign. These change values were then averaged across relevant leads for each
patient. Four summaries were created: (1) mean of I and aVL; (2) mean of V₁ and V₂; (3) mean of all leads except aVR; and (4) mean of I, aVL, and V₁ through V₆ (CHRLP).

Candidate predictors for multivariable modeling were selected with the use of the aforementioned framework, including variables that characterize LBBB (LVAT, LV scar volume, QRS hieroglyphs) and expected evidence of ventricular fusion (axis change, change in R amplitudes, and changes in QRS hieroglyphic signatures). In cases in which several related measures were available (eg, regional LVAT versus LVAT_max), univariate tests were used to determine which measure had the strongest relationship with the end point. Continuous variables were checked for linearity of their relationship with the outcome, and revised versions (usually truncations) were created where necessary; categorical variables related to each other were determined to check whether a combination of the variables would be a better predictor than the individual variables.

After this screening process, 13 variables were selected as candidates for the primary end point logistic regression model (6 baseline, 7 post-CRT). Baseline variables were as follows: QRSd, LVAT_max, QRS score, QS hieroglyph in aVR, R hieroglyph in V₆, and R >5 mV in V₁ or V₆. Post-CRT variables were as follows: LADEV → RADEV, R → Q, qR, QR, or QS in I and aVL, new R waves >5 mV in both V₁ and V₂, and mean change in R amplitude in the expected direction in I and aVL in V₁ and V₂, and in all leads except aVR. For the 2 supplemental models, the same set of predictors was used, with minor modifications.

For each end point, all candidate predictors were entered into a logistic regression model, and stepwise selection was then used to identify the set of significant independent predictors. Relative risk is expressed as odds ratio (OR) (95% confidence interval [CI]). Predicted probabilities of the primary end point were generated from the final logistic regression model. In cases in which model variables are not specifically displayed in a plot, median or mode values were used in generating predictions (QRS points, change in R amplitude, LVAT → RADEV → no). For characterizing tiers of response, patients were divided into low, middle, and high responders, with predicted probability of response 0% to 49%, 50% to 74%, and 75% to 100%, respectively, and patterns among their predictor values were examined.

Results

The median (25th, 75th percentile) age was 67 (60, 75) years. Overall, 73% were male, and 53% had an ischemic cardiomyopathy. LVAT_max was ≈67% QRSd and was most frequently found in the inferior leads. On average, ≈20% of the LV volume was scar. CRT resulted in a slight reduction in median QRSd, overall rightward frontal plane axis shift, modest reductions in ESV and EDV, and modest increases in LVEF (Table 1).

QRS Hieroglyphs by Pivotal Leads: Baseline and After CRT

The preliminary screening process for candidate predictors of ≈10% reduction in ESV indicated that the expected changes in local and regional QRS hieroglyphic signatures were most pronounced in I, aVL, and V₁ and V₂, designated pivotal leads. During LBBB, a dominant R → L, A → P activation pattern was observed in ≈95% of patients (Table 2). Less than 5% of patients had L → R and/or P → A activation because of dominant Q or S waves in I and aVL and R waves in V₁ through V₂, caused by scar.

During CRT, rightward forces emerged in I and aVL and anterior forces in leads V₁ through V₂. These effects were greatest in I and V₁ and were observed in 74% and 53% of patients, respectively. Reciprocally, evidence of persistent leftward and posterior activation was recorded in 26% (I) and 47% (V₁).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>Post-CRT</th>
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<tbody>
<tr>
<td>Echocardiographic measurements</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESV, mL</td>
<td>157 (116, 199)</td>
<td>124 (88, 167)</td>
</tr>
<tr>
<td>EDV, mL</td>
<td>207 (163, 252)</td>
<td>183 (140, 230)</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>25 (19, 30)</td>
<td>32 (26, 38)</td>
</tr>
<tr>
<td>ECG measurements</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation, n (%)</td>
<td>23 (11)</td>
<td>14 (7)</td>
</tr>
<tr>
<td>QRSd, ms</td>
<td>165 (148, 176)</td>
<td>158 (142, 174)</td>
</tr>
<tr>
<td>Frontal plane axis, °</td>
<td>−31 (−51, −8)</td>
<td>−99 (−121, −76)</td>
</tr>
<tr>
<td>LADEV, n (%)</td>
<td>98 (49)</td>
<td>35 (17)</td>
</tr>
</tbody>
</table>

Evidence for Ventricular Activation Fusion During CRT

A rightward axis emerged in 67% of patients. However, a RSA was observed in only 58% and RIA in 9%. In contrast, 20% had LADEV or normal axis during CRT, and 12% had IRSA. Therefore, nearly one third of patients did not have evidence of ventricular fusion by frontal plane axis during CRT. Similarly, although ≈90% had an axis quadrant shift, a RSA or RIA was achieved in only three fourths of these patients. The remaining one fourth had primarily a leftward (LADEV or IRSA) axis quadrant shift (Table 3).

Evidence for ventricular fusion with the use of QRS hieroglyphs was recorded in all 4 pivotal leads, with greatest frequency in I and V₁. Evidence of wavefront collision (Q and S emergence, R regression) was observed in I for 71% of patients. However, total (QS) or near-total (Qr) reversal of activation in I was observed in only 55%. Similarly, total reversal of activation in V₁ (dominant R emergence) was observed in only 50%. Evidence for activation reversal was ≈50% less evident in aVL and V₂.
A ≥50% reduction in R-wave amplitude in I and aVL, reflecting L→R wavefront fusion in the horizontal plane, was observed in 60% of patients. Reciprocally, a ≥50% increase in R-wave amplitude in V1 and V2, due to A→P wavefront fusion, was observed in only 62%.

Predictors of ≥10% Reduction in ESV at 6 Months
A multivariable model identified 2 baseline and 2 post-CRT independent predictors of ≥10% reduction in ESV at 6 months (Table 4). Increasing LVATmax was associated with a greater probability of ≥10% reduction in ESV (OR [CI] = 1.30 [1.11, 1.52] per 10-ms increase) up to 125 ms; for longer LVATmax, there was no further increase in probability of response (Figure 1). Patients with values in the lowest quartile (≤80 ms) had a 51% response rate compared with 73% response in patients with values of >125 ms. Although QRSd was weakly associated with reverse remodeling probability in preliminary univariate comparisons, this relationship was replaced by LVATmax in the multivariable model.

Increasing QRS scores were negatively associated with reverse remodeling (OR [CI] = 0.49 [0.27, 0.88] for each 1-point increase from 0 to 4; 0.92 [0.83, 1.01] for each 1-point increase >4). Patients with QRS scores in the lowest quartile (0 to 3) had a response rate of 78% compared with patients with scores in the highest quartile (>9), whose response rate was 45%.

After CRT, increasing R amplitudes in V1 through V2, indicating ventricular fusion, were associated with increased probability of reverse remodeling. This effect was not observed until the mean change in R amplitude was ≥4.5 times the baseline value (OR [CI] = 2.76 [1.01, 7.51] for each 1× increase ≥4.5×). Although only 25 patients fell in this upper range, the response rate was 84% versus 60% in patients with mean change V1 through V2 R ≥4.5 times baseline. A second measure of ventricular fusion, LADEV3RADEV, was associated with increased probability of reverse remodeling (OR [CI] = 2.00 [0.99, 4.02]). Patients showing this axis quadrant shift had a response rate of 70% compared with 60% in patients without.

Visual evidence for the effect of LVATmax and the other independent predictors of reverse remodeling is provided in Figure 1. Predicted probability of reverse remodeling is greatest for longer baseline LVATmax in the presence of post-CRT ventricular fusion, indicated by larger changes in R amplitude in leads V1 through V2 (top right) and LADEV→RADEV axis quadrant shift (lower left). In contrast, the positive effects of increasing LVATmax are offset by higher QRS scores such that longer LVATmax in the presence of a high QRS score has lower predicted probability of reverse remodeling than very short LVATmax in the presence of a low QRS score (lower right).

Predicting Reverse Remodeling Using a Global Measure of Ventricular Fusion
As for most of the R-wave amplitude directional change variables, there was no change in probability of reverse remodeling and the other independent predictors of reverse remodeling was provided in Figure 1. Predicted probability of reverse remodeling is greatest for longer baseline LVATmax in the presence of post-CRT ventricular fusion, indicated by larger changes in R amplitude in leads V1 through V2 (top right) and LADEV→RADEV axis quadrant shift (lower left). In contrast, the positive effects of increasing LVATmax are offset by higher QRS scores such that longer LVATmax in the presence of a high QRS score has lower predicted probability of reverse remodeling than very short LVATmax in the presence of a low QRS score (lower right).
Low responders had a predictive model showed good discrimination (c-index 0.74). Response tiers are shown in Table 5. The multivariable Tiers of Reverse Remodeling Response:

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI) for ESV Reduction</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVATmax</td>
<td>1.30 (1.11, 1.52) for each 10-ms increase up to 125</td>
<td>0.0010</td>
</tr>
<tr>
<td>QRS score</td>
<td>0.49 (0.27, 0.88) for each 1-point increase from 0 to 4</td>
<td>0.0022*</td>
</tr>
<tr>
<td>Post-CRT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean change in R amplitude in V1 and V2 in expected direction</td>
<td>2.76 (1.01, 7.51) for each 1-mV increase &gt;4.5</td>
<td>0.048</td>
</tr>
<tr>
<td>LADEV to RADEV</td>
<td>2.00 (0.99, 4.02)</td>
<td>0.052</td>
</tr>
</tbody>
</table>

Model c-index=0.74.
*Overall test.

LVATmax (48 to 62 ms) occurred only in this group, with no QRS scores 0 to 2. These patients also had limited or absent fusion evidence after CRT (Figure 3).

High responders had ≥1 favorable predictor (ie, QRS score <3 or change in R amplitude >5) or a combination of favorable predictors (ie, QRS score 3 and LVATmax >110 ms, or QRS score 4 to 9 and LVATmax >110 ms and quadrant shift). Alternately, high responders had fair values for 1 predictor that were offset by very favorable values for others (ie, smaller change in R amplitude but LVATmax >130 ms). There were no QRS scores >12, whereas all changes in R amplitude >5 occurred in the high responders (Figure 3).

Middle-range responders had intermediate values for predictors (ie, QRS score 90 to 110 ms, QRS score 6 to 11, quadrant shift, midrange change in R amplitude) or an offsetting combination of very favorable and midrange predictor values (ie, long LVATmax but high QRS score and small change in R amplitude).

### Predictors of Supplemental Reverse Remodeling End Points

Multivariable models for supplemental reverse remodeling end points yielded predictors similar to those in the ≥10% ESV reduction model (Table 6). The ≥30% ESV reduction end point was met by 59 patients (29.2%). Each 10-ms increase in LVATmax was associated with increased probability of ≥30% ESV reduction, slightly less versus the ≥10% ESV model (OR=1.23 versus 1.30). The relationship of QRS score, for its entire range, to a ≥30% reduction in ESV was similar to the relationship of QRS score ≥4 to a ≥10% reduction in ESV (OR=0.91 versus 0.92 for each 1-point increase). Ventricular fusion (V2 R amplitude change from <1 to >5 mm) also predicted ≥30% ESV reduction (OR=2.90). Axis quadrant shift was not significant, possibly because of the lower event rate.

The ≥10% EDV reduction end point was met by 45.5% of patients (92/202). Greater LVATmax was directly associated with EDV reduction (OR=1.92 for each 10-ms increase up to 95), whereas higher QRS scores were inversely related.
Ventricular fusion (V1 R amplitude change from 1 to 5 mm) also predicted EDV reduction (OR=3.03); axis quadrant shift did not.

Discussion

This study demonstrates that the probability of reverse volumetric LV remodeling during CRT in patients with asynchronous heart failure and LBBB can be accurately predicted by characterization of the ventricular activation sequence before and after CRT with the use of the standard 12-lead ECG. The main findings are as follows: (1) The translational mechanism for volumetric reverse remodeling is activation wavefront fusion, which is evident on the paced ECG; and (2) the probability of reverse remodeling is

Figure 1. Probability of reverse remodeling by baseline and post-CRT predictors. Top left, Increasing probability of response with greater LVATmax. Line represents predicted probability of response for each value of LVATmax. Diamonds represent actual response rates among LVATmax quartiles. Top right, Increasing probability of response with greater LVATmax and post-CRT evidence of ventricular fusion (P→A activation reversal). Bottom left, Increasing probability of response with greater LVATmax and post-CRT evidence of ventricular fusion (L→R activation reversal). Bottom right, Increases in QRS score reduce response probability for any value of LVATmax.

Figure 2. Predicting reverse remodeling using a global measure of ventricular fusion. Greater changes in R-wave amplitudes after CRT, indicative of wavefront fusion, predict higher probability of response. The points along the line are individual predicted values.
positively influenced by LV conduction delay (LVAT\textsubscript{max}) and negatively influenced by LV scar volume (QRS score) on the baseline ECG.

Uncertainty about the physiology of ventricular resynchronization is reflected in significant heterogeneity in clinical response to CRT. A CRT responder feels better, has less heart failure morbidity, and demonstrates evidence of reverse remodeling; a nonresponder exhibits none of these. Up to one third of CRT patients are nonresponders. The reasons for this are complex and incompletely characterized but most likely relate to poorly understood interactions between substrate conditions and pacing-induced changes in ventricular activation.

We evaluated reverse volumetric remodeling as an end point because (1) experimental models have demonstrated a direct linkage between LV electric activation, mechanics, and reverse remodeling\textsuperscript{1,10}; (2) reverse remodeling is associated with reduced heart failure morbidity and mortality\textsuperscript{2}; and (3) it is the least subjective element of CRT response.

At baseline, longer LVAT\textsubscript{max} was significantly associated with ESV reduction, indicating that greater LV conduction delay is associated with higher probability of reverse remodeling, if it is assumed that delay is sufficiently corrected by CRT. In contrast, each QRS score point (indicative of 3% LV scar volume) was associated with a reduction in the probability of reverse remodeling, with the greatest effect in the lower points range (0 to 4). Higher LV scar volume is associated with lower probability of reverse remodeling. After CRT, larger changes in R-wave amplitude in pivotal leads V\textsubscript{1} through V\textsubscript{2}, indicating P\textright\rightarrow A activation reversal, and LADEV\rightarrow RADEV frontal plane axis quadrant shift, indicating L\rightarrow R activation reversal, were associated with an increased probability of reverse remodeling. Higher CHRLP scores, a global measure of change in ventricular activation during CRT, also predicted ESV reduction. Therefore, paced ventricular activation wavefront fusion increases the probability of reverse remodeling. These results provide evidence that interactions between myocardial substrate (scar volume), baseline LV conduction delay, and paced-activation wave-
Table 6. Multivariable Predictors of Supplemental Reverse Remodeling End Points

<table>
<thead>
<tr>
<th>Variable</th>
<th>Reverse Remodeling End Point</th>
<th>$P$</th>
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<tbody>
<tr>
<td></td>
<td>ESV, OR (95% CI) for</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$\geq 30%$ reduction*</td>
<td>0.0004</td>
</tr>
<tr>
<td>Baseline</td>
<td>LVAT$_{\text{max}}$</td>
<td>1.23</td>
</tr>
<tr>
<td></td>
<td>10-ms increase</td>
<td></td>
</tr>
<tr>
<td>Post-CRT</td>
<td>QRS score</td>
<td>0.91</td>
</tr>
<tr>
<td></td>
<td>1-point increase</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>LVAT$_{\text{max}}$</td>
<td>1.92</td>
</tr>
<tr>
<td></td>
<td>10-ms increase up to 95</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>QRS score</td>
<td>0.87</td>
</tr>
<tr>
<td></td>
<td>1-point increase</td>
<td></td>
</tr>
<tr>
<td>Baseline V$_1$ R $&lt;$1 $\rightarrow$ post V$_2$ R $&gt;$5</td>
<td>2.90</td>
<td>0.0090</td>
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<tr>
<td>Baseline V$_2$ R $&lt;$1 $\rightarrow$ post V$_2$ R $&gt;$5</td>
<td>3.03</td>
<td>0.022</td>
</tr>
</tbody>
</table>

*Model c-index 0.70 for both ESV and EDV.

Conclusions

Fronts (fusion response) anticipate the probability of reverse remodeling. These results were duplicated in multivariable models for supplemental reverse remodeling end points ($\geq 30\%$ reduction in ESV and $\geq 10\%$ reduction in EDV).

This study provides a framework for understanding the heterogeneous clinical response to CRT. The interaction between substrate conditions, post-CRT evidence of ventricular fusion, and the probability of reverse remodeling are evident in the characterization of low-, middle-, and high-probability responders. Patients with small LVAT$_{\text{max}}$ and large LV scar volume are unlikely to remodel even when paced fusion is present (“volumetric nonresponders”). “Volumetric superresponders” are characterized by large conduction delays, small scar volumes, and the most robust evidence of paced fusion. Several other observations on the interaction between substrate conditions and post-CRT evidence of ventricular fusion are evident in Figure 1. At very high values of LVAT$_{\text{max}}$, the probability of reverse remodeling was still at least 40% to 50% even for weak or absent paced ECG evidence for ventricular fusion (ie, no LADEV $\rightarrow$ RADEV axis quadrant shift or low-range increases in V$_1$ through V$_2$ R amplitudes). Reciprocally, for very low values of LVAT$_{\text{max}}$, the probability of reverse remodeling may still reach 80% if there is strong paced ECG evidence for ventricular fusion (ie, highest range increases in V$_1$ through V$_2$ R amplitudes).

Only two thirds of patients had paced ECG evidence of ventricular fusion. This implies that failure to correct LV conduction delay, despite biventricular pacing, contributes significantly to volumetric nonresponse. Nearly 20% of patients had axis quadrant shift to LADEV or IRSA (extreme LADEV), and 10% had a normal axis during CRT. In some of these patients, failure to generate ECG evidence of fusion during simultaneous biventricular pacing was likely due to LV capture latency, conduction delay, or blocks, with a common consequence of different bidirectional paced activation times favoring persistent R $\rightarrow$ L, A $\rightarrow$ P conduction. Sequential biventricular pacing might improve the fusion response in some of these patients, especially the subset with IRSA. It is also likely that fusion failure in some patients was due to stimulation from a site incapable of reversing LV activation.

On the other hand, the probability of volumetric reverse remodeling was reasonably high in some patients even without paced ECG evidence of ventricular fusion. Global ventricular activation patterns are represented by the 12-lead ECG, whereas local activation patterns may be concealed. Reduction of local conduction delay sufficient to improve regional LV mechanics may be concealed within the surface registration of the paced ECG; alternately, concealed local activation patterns may prevent LV electric resynchronization. Because the translation of cardiac electric activation to the surface ECG is incompletely understood, interpretation of ventricular activation with the use of any surface method may be unpredictably incorrect.

This study supports the concept that asynchronous heart failure is fundamentally an electric disorder that can be resolved at the level of ventricular conduction. A close linkage between electric and mechanical asynchrony has been demonstrated in animal models and preliminarily in humans. The greater the LV conduction delay, the greater are the potential gains in reverse remodeling when conduction delay is sufficiently corrected, if it is assumed that LV scar volume is not prohibitive. Targeting LV pacing sites with the use of real-time ECGs to evaluate evidence of activation wavefront fusion and reversal, rather than rigid adherence to anatomic targets, may improve CRT response.

Limitations

Echocardiographic measures of LV volumes may be less accurate than other methods. The surface ECG may not accurately reflect important changes in LV activation. QRS score is modestly less accurate than newer imaging methods for calculating scar volume. We did not evaluate other forms of ventricular conduction delay.

Disclosures

Dr Sweeney is a consultant to and has received honoraria for speaking from Medtronic Inc. Dr Schalij has received grants from Biotronik, Medtronic Inc, and Boston Scientific. Dr Bax has received grants from Biotronik, Medtronic Inc, Boston Scientific, BMS Medical Imaging, St Jude Medical, Edwards Life Sciences, and GE Healthcare. The remaining authors report no conflicts.

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**CLINICAL PERSPECTIVE**

Ventricular conduction delay due to left bundle branch block alters the left ventricular (LV) electric activation sequence. The resulting electric asynchrony is manifest in prolonged QRS durations due to slow myocardial conduction. This causes regional heterogeneity in contraction and stretch (mechanical asynchrony) that reduces pump function and stimulates negative LV reverse remodeling, indicated by increased LV volumes. The conceptual basis of cardiac resynchronization therapy (CRT) for asynchronous heart failure is to minimize LV conduction delay, which reduces contractile asynchrony and instantaneously improves LV mechanics. Sustained resynchronization of electromechanical activation induces “reverse” remodeling (LV volume reductions) and improved pump function (increased LV ejection fraction). Reverse LV remodeling is associated with reduced heart failure morbidity and mortality. Up to one third of CRT patients do not improve. The reasons for this are complex and incompletely characterized but can be explained by interactions between substrate conditions and pacing-induced changes in ventricular activation derived from analysis of the standard 12-lead ECG before and after CRT. Longer LV activation time and smaller LV scar volume during left bundle branch block on the baseline ECG predict higher probability of reverse remodeling. Evidence for activation wavefront fusion on the CRT-paced ECG, indicating conduction defect reversal, also predicts reverse remodeling and provides the translational mechanism for volumetric reverse remodeling. Knowledgeable application of the standard 12-lead ECG can be used to accurately predict the probability of a reverse remodeling response to CRT.

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Analysis of Ventricular Activation Using Surface Electrocardiography to Predict Left Ventricular Reverse Volumetric Remodeling During Cardiac Resynchronization Therapy
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