Electrophysiologic substrate and intraventricular left ventricular dyssynchrony in nonischemic heart failure patients undergoing cardiac resynchronization therapy

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BACKGROUND Electrocardiographic imaging (ECGI) is a method for noninvasive epicardial electrophysiologic mapping. ECGI previously has been used to characterize the electrophysiologic substrate and electrical synchrony in a very heterogeneous group of patients with varying degrees of coronary disease and ischemic cardiomyopathy.

OBJECTIVE The purpose of this study was to characterize the left ventricular electrophysiologic substrate and electrical dyssynchrony using ECGI in a homogeneous group of nonischemic cardiomyopathy patients who were previously implanted with a cardiac resynchronization therapy (CRT) device.

METHODS ECGI was performed during different rhythms in 25 patients by programming their devices to biventricular pacing, single-chamber (left ventricular or right ventricular) pacing, and native rhythm. The electrical dyssynchrony index (ED) was computed as the standard deviation of activation times at 500 sites on the LV epicardium.

RESULTS In all patients, native rhythm activation was characterized by lines of conduction block in a region with steep activation–recovery interval (ARI) gradients between the epicardial aspect of the septum and the LV lateral wall. A native QRS duration (QRSd) >130 ms was associated with high ED (>30 ms), whereas QRSd <130 ms was associated with minimal (25 ms) to large (40 ms) ED. CRT responders had very high dyssynchrony (ED = 35.5 ± 3.9 ms) in native rhythm, which was significantly lowered (ED = 23.2 ± 4.4 ms) during CRT. All four nonresponders in the study did not show significant difference in ED between native and CRT rhythms.

CONCLUSION The electrophysiologic substrate in nonischemic cardiomyopathy is consistent among all patients, with steep ARI gradients co-localizing with conduction block lines between the epicardial aspect of the septum and the LV lateral wall. QRSd wider than 130 ms is indicative of substantial LV electrical dyssynchrony; however, among patients with QRSd <130 ms, LV dyssynchrony may vary widely.

KEYWORDS Cardiac resynchronization therapy; Electrocardiography; Heart failure; Imaging

ABBREVIATIONS ARI = activation–recovery interval; CRT = cardiac resynchronization therapy; ECGI = electrocardiographic imaging; ED = electrical dyssynchrony index; LV = left ventricle; LV-P = left ventricular pacing; NYHA = New York Heart Association; QRSd = QRS duration; RT = total repolarization time (Heart Rhythm 2011;8:692–699) © 2011 Heart Rhythm Society. All rights reserved.

Introduction

Cardiac resynchronization therapy (CRT) using biventricular pacing is a relatively new treatment modality designed to restore synchrony with the objective of improving cardiac mechanical performance in congestive heart failure.1–4 CRT has been demonstrated to be clinically effective in 60% to 70% of patients, and its indication as therapy has increased exponentially over the last several years. A number of different echocardiographic measures have been used clinically to select potential CRT candidates. The recently concluded PROSPECT2 trial has shown that none of the echocardiographic measures provides a consistent basis for clinical decisions regarding CRT implants. The ECG QRS duration (QRSd) is deemed to be the most clinically relevant measure for CRT. Although CRT has been shown to benefit the majority of symptomatic patients with wide
QRSd >130 ms, reports on the usefulness of CRT in moderate ranges of QRSd (100–130 ms) are conflicting. The RethinQ trial\(^3\) showed that CRT is not beneficial for patients with narrow QRSd. However, another recent study\(^4\) demonstrated potential short-term improvement with CRT in patients with QRSd <120 ms. This indicates that there may be heart failure patients with QRSd in the range from 100 to 130 ms who may respond well to CRT, but the measures of dyssynchrony used in RethinQ could not identify this group. With the reliability of echocardiographic measures in question (PROSPECT), the quest for an alternative measure of dyssynchrony in the context of CRT continues.

Electrocardiographic imaging (ECGI)\(^5\)–\(^8\) is a novel imaging modality for cardiac electrophysiology, based on 250 body surface ECGs and an accurate, patient-specific heart–torso anatomy derived from an ECG-gated computed tomographic scan. It noninvasively generates electroanatomic maps of epicardial potentials (voltage maps), electrograms, and activation and repolarization sequences. A previous study using ECGI in eight heart failure patients with ischemic cardiomyopathy undergoing CRT showed that the electrophysiologic substrate is extremely heterogeneous among these patients and that the efficacy of CRT depends strongly on the patient-specific substrate and pacing electrode placement relative to this substrate.\(^8\) This was a study in a very heterogeneous group of patients with varying degrees of coronary disease and ischemic cardiomyopathy. The objective of the current study is to characterize the left ventricular (LV) electrophysiologic substrate and electrical dyssynchrony in a population of nonischemic cardiomyopathy patients previously implanted with a CRT device. A quantitative index for LV electrical dyssynchrony is defined and computed, and its relationship with QRSd is studied.

Methods
ECGI was performed in each patient in each of the following rhythms: (1) biventricular CRT pacing (CRT); (2) LV pacing (LV-P); (3) right ventricular (RV) pacing (RV-P); and (4) nonpaced native rhythm (NAT), if applicable. Two patients had optimized interventricular (V-V) delays different from the nominal value, and ECGI was performed with both optimal (CRT-OPT) and nominal (CRT-NOM) V-V delays. The nominal V-V delay is the standard “factory” setting (simultaneous biventricular pacing).

Custom algorithms\(^5,6\) developed in our laboratory are used to combine the multielectrode body surface potential data with the heart–torso geometry obtained from computed tomography to generate electroanatomic maps of potentials, electrograms, and activation and repolarization sequences on the epicardial surface. The activation time was determined from each reconstructed epicardial electrogram by the time of steepest negative slope of the electrogram. The LV epicardium was delineated from computed tomography, including the epicardial aspect of the septum, and digitized using 500 points. An intra-LV electrical dyssynchrony index (ED) was computed in blinded fashion from the ECGI activation maps as the standard deviation of activation times (determined as explained earlier) at 500 sites on the LV epicardium, including the epicardial aspect of the septum.

Activation isochronal lines on the epicardial surface are depicted in black. Line/region of conduction block is determined if the activation times on its opposite sides differ by more than 40 ms. Regions of slow conduction are identified by crowding of isochrones. Regions of late LV activation are defined by sites where activation time is later than 80th percentile of QRS duration during native rhythm. Percentage of LV area activating late is computed by dividing the number of late LV sites (nodes) by the total number of nodes used to digitize the LV epicardium for ECGI images. Activation–recovery intervals (ARIs) over the epicardial surface are computed from the epicardial electrograms as the difference between recovery time (time corresponding to maximum dV/dt during T wave) and activation time (steepest downward slope during QRS) and displayed in color-coded maps. Epicardial dispersion of repolarization is computed as the difference between the largest and smallest ARI on the entire (RV and LV) epicardial surface.

Control value of ED in a population of 22 young healthy subjects without heart failure was determined at 20 ± 4 ms. A value above the control mean plus twice the standard deviation was deemed as abnormal (ED >28 ms). Hence, LV is defined to be electrically asynchronous when ED ≥28 ms. All study protocols were reviewed and fully approved by the Human Research Protection Office at Washington University, and written informed consent was obtained from all patients and/or their legal guardians prior to the study.

Statistical analysis
Continuous variables are represented as mean ± SD with these measures taken over the total patient population. Relationship between ED and QRSd, and activation time and repolarization ARI are evaluated using Pearson correlation coefficient (r). Student’s t-test is used to assess the significance of correlation. P < .05 is considered significant.

Results
Study population
Between January 2007 and April 2010, 25 heart failure patients (age 51 ± 18 years, range 6–68 years) with a CRT implant and nonischemic dilated cardiomyopathy were recruited retrospectively for the study. Patients were selected from the database of patients who were implanted with a CRT/CRT-ICD device and were being seen at the heart failure clinic at Barnes Jewish Hospital and/or St. Louis Children’s Hospital. The following inclusion criteria were used for patient selection: patients without any documented evidence of ischemia until study date, implanted with a CRT or CRT-ICD device at least 6 months prior to study date. CRT implant criteria were symptoms of New York Heart Association (NYHA) functional class III/IV heart failure with poor ejection fraction (<30%), accompanied by wide QRSd >120 ms and/or asynchronous wall motion seen on echocardiography. Post-CRT echocardiography and/or clinical response data were not used in selecting patients. Ischemia was ruled out by the latest coronary angiography performed for clinical reasons before the study and no documented hospitalizations or clinic visits for myocardial infarction until the date of study. No evidence of frank scar or aneurysm was found during echocardiographic evaluation (no areas of akinesia). Three patients (no. 1, 10, and 14) had no underlying rhythm (no atrioventricular [A-V] conduction and no ventricular escape beats at the time of the study). These patients were upgraded to biventricular pacing from RV pacing. Pre-CRT NYHA class was III to IV.
Responders to CRT were identified by echocardiographic evidence of reverse LV remodeling,9 manifest as reduction in LV end-systolic volume by more than 10% and by functional NYHA class improvement ≥1. Pre-CRT (preimplant) echocardiographic data for evaluation of LV volume were chosen as close as possible to the biventricular device implant date. Pre-CRT QRS duration was determined from clinical ECG of the patient, recorded with a commercially available standard ECG machine. In addition, a 12-lead ECG with respect to the Wilson central terminal was recorded in each rhythm at the time of the study. Careful visual determinations of QRS width were made by plotting each ECG lead in Matlab software at high gain and expanded time scale (resolution 0.5 ms). The mean value of QRS duration over all leads was reported. The standard deviation of these measurements in all cases was less than 2 ms. Pre-CRT and post-CRT patient characteristics are listed in the patient summary table (Table 1). Based on the LV volume criterion, patients 4, 8, 20, and 22 were classified as nonresponders. All other patients were responders to CRT. All patients had their LV–RV delay set to 0 ms, except for patient 2 (LV early by 10 ms) and patient 4 (LV early by 15 ms). The optimal A-V delay was set at the time of implant by Ritter method10 and was 175 ± 28 ms. LV ejection fraction was 21.6% ± 4.97% before CRT and 34.2% ± 8.44% post-CRT.

**Electrophysiologic substrate: Activation and repolarization**

Figure 1 shows representative ECGI epicardial activation isochrone maps in a responder patient (no. 2). These maps are representative of the data from all responder patients. The ECGI maps for each rhythm are shown in the left anterior oblique (ANT) and inferior (INF) views. The ECG QRSd and the ED of LV activation for each condition are also listed. Locations of the pacing sites are marked by asterisks. The native activation in responders (NAT, Figure 1) is characterized by a line of conduction block (indicated by a thick black line) located between the epicardial aspect of the septum and the LV lateral wall, causing activation to turn around the apex (white arrow; “U-shaped activation”)11 and resulting in late activation (dark blue, NAT, Figure 1) of a large portion of the lateral and inferior wall. A substantially large percentage of the LV epicardium (48% ± 16%) in all responders activated later than the 80th percentile of the QRS duration compared to controls (13% ± 6%).

**Table 1** Patient characteristics

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age (years)/sex</th>
<th>Time from implant</th>
<th>PRE-CRT</th>
<th>POST-CRT</th>
</tr>
</thead>
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<tr>
<td></td>
<td></td>
<td></td>
<td>QRSd (ms)</td>
<td>LVESV (mL)</td>
</tr>
<tr>
<td>1</td>
<td>6/F</td>
<td>6 months</td>
<td>110</td>
<td>32</td>
</tr>
<tr>
<td>2</td>
<td>21/M</td>
<td>3 years</td>
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<td>512</td>
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<tr>
<td>3</td>
<td>66/F</td>
<td>4 years</td>
<td>160</td>
<td>278</td>
</tr>
<tr>
<td>4</td>
<td>17/M</td>
<td>2 years</td>
<td>126</td>
<td>137</td>
</tr>
<tr>
<td>5</td>
<td>55/F</td>
<td>3 years</td>
<td>150</td>
<td>86</td>
</tr>
<tr>
<td>6</td>
<td>63/M</td>
<td>1 year</td>
<td>118</td>
<td>321</td>
</tr>
<tr>
<td>7</td>
<td>50/M</td>
<td>3 years</td>
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<td>281</td>
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<tr>
<td>8</td>
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<td>2 years</td>
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<td>160</td>
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<tr>
<td>9</td>
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<td>2 years</td>
<td>140</td>
<td>142</td>
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<td>137</td>
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<td>11</td>
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<td>153</td>
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<td>195</td>
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<td>2 years</td>
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<td>135</td>
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<tr>
<td>14</td>
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<td>213</td>
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<tr>
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<td>1 year</td>
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<td>130</td>
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<tr>
<td>16</td>
<td>64/F</td>
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<td>210</td>
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<td>2 years</td>
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<td>198</td>
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<td>18</td>
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<td>78</td>
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<tr>
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<td>3 years</td>
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<td>167</td>
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<td>24</td>
<td>47/F</td>
<td>3 years</td>
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<td>188</td>
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<td>25</td>
<td>53/F</td>
<td>2 years</td>
<td>126</td>
<td>199</td>
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CRT = cardiac resynchronization therapy; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; QRSd = QRS duration.
The gradients between the epicardial aspect of the anterior septum and the LV lateral wall observed in the ARI map are not apparent in the RT map. This is because the lateral wall activates about 150 ms later than the epicardial aspect of the anterior septum. This long time delay masks the ARI dispersion between these two regions. However, regions that activate without conduction delay (e.g., anterior lateral RV and epicardial aspect of septum) show similar dispersion in both ARI and RT maps. Similar observations were made in patient 23. In patient 25, some of the dispersion in ARI maps is preserved in the RT maps, where the delay in activation is not enough to compensate for the ARI difference. In patients with narrow QRS (e.g., Figure 4, patient 12 whose native QRSd = 100 ms), the difference in activation...
times between spatially adjacent areas of the ventricle is at most 40 to 50 ms, and RTs and their dispersion are primarily determined by ARI and ARI dispersion. Patterns in RT maps closely follow the ARI patterns in such cases. ARIs reflect intrinsic repolarization properties and have been shown to correlate with the local action potential duration. As such, they reflect changes due to remodeling processes if present in the diseased myocardium. Abnormally steep ARI dispersion between the epicardial aspect of the septum and LV lateral wall is present in all patients in the native rhythm and is co-localized with a line of block. RT dispersion depends on both the local ARIs and the activation sequence, and in the presence of significant conduction delays does not always reflect ARI dispersion. Importantly, RT dispersion creates the conditions (substrate) for a functional conduction block of a following (premature) excitation wave.

Figure 5 shows another example of ECGI activation maps in a responder patient (no. 12). Although his native QRS duration is only 100 ms, the native activation pattern (NAT, Figure 5) is very dyssynchronous (ED = 32 ms), characterized by lines of block and delayed activation of extensive areas of the LV lateral and inferior wall (blue, NAT, Figure 5). CRT restores LV ED to normal value (20 ms).

Figure 6 shows representative ECGI activation isochrones in a nonresponder patient. The lines of conduction block and the U-shaped activation pattern between the epicardial septal aspect and the lateral wall, typical of the native activation of responder patients, were not observed in the nonresponder native rhythm. There was a small area of slow conduction (crowded isochrones) in the LV, but it affected only a small portion of the lateral wall (blue). LV activation was synchronized (ED = 25 ms) in native rhythm and did not change substantially with CRT (ED = 26 ms). Figure 7 demonstrates ECGI activation maps in another nonresponder patient (no. 22) in CRT and native (NAT) rhythms. The native activation showed an incomplete right bundle branch block pattern, with earliest LV activation (red) occurring 20 ms before earliest RV activation (light green), but the overall intra-LV ED was close to control values (24 ms). CRT pacing made LV activation more heterogeneous and did not improve ED, which increased to 29 ms.

**LV electrical dyssynchrony**

The scatter plots in Figure 8 demonstrate the relationship between QRSd and ED for different rhythms (CRT-P, LV-P, RV-P, and NAT), combining data from all patients. There is a weak positive correlation between QRSd and ED. A summary of the values of the ED index over the entire patient population is provided in Table 2. For patients with native QRSd >130 ms, the ED index was consistently high (≥30 ms). However, for QRSd <130 ms, the ED values ranged from 24 ms (synchronized LV activation) to 40 ms (dyssynchronous LV activation). Only two patients had native QRSd <120 ms. Their QRSd was 100 and 118 ms, and their native ED value was 32 and 34 ms, respectively. Both were CRT responders. Responders in general had their baseline CRT ED values significantly lowered (P < .05) compared to native ED values. QRSd of responders (n =...
in this study was 140 ± 28 ms preimplant and 107 ± 27 ms post-CRT. Mean reduction is 33 ms, which corresponds to a mean change in QRSd of 23%. Similar relative changes in QRSd were observed in CRT responders in a previous study. Four nonresponders did not show a significant difference in ED values between baseline CRT and native rhythms (P >.1). Native QRSd of all four nonresponders were in the range from 120–130 ms.

Discussion
LV electrophysiologic substrate
The native activation pattern in nonischemic cardiomyopathy is similar among patients, in contrast to the large variability observed in ischemic CRT patients by Jia et al. The activation pattern is characterized by lines of conduction block extending from base to apex and located between the epicardial aspect of the septum and the LV lateral wall. This results in U-shaped activation around the line of block and very delayed activation (later than 80th percentile of QRSd) of a large portion of the LV lateral and inferior wall. Similar lines of block were also reported by Auricchio et al in invasive endocardial activation mapping studies of dilated cardiomyopathy patients. Unlike previous observations in ischemic cardiomyopathy, where the locations and orientations of conduction block lines were variable, depending on the location and extent of the infarct, lines of conduction block in nonischemic cardiomyopathy are located in the general anatomic area between the septum and the LV lateral wall and are oriented roughly parallel to the long axis from base to apex. ARI maps (Figure 2) show that steep ARI gradients co-localize with regions of conduction block. Moreover, the block lines shift during pacing from RV or
LV leads. These observations suggest the possibility that these blocks are, at least in part, functional in nature. We observed abnormally long ARIs near the line of block, which reflect prolonged action potential durations. No significant inverse relationship was observed between activation time and ARI ($r = 0.12 \pm 0.27$). Although such inverse relationship was demonstrated in normal subjects, it has not been established in cardiomyopathy with conduction disorders such as left bundle branch block. A previous study measuring ventricular activation times and ARIs over the anteroseptal wall reported an inverse relationship between activation time and ARI in cardiomyopathy patients without a history of ventricular tachycardias and/or T-wave alternans. The discrepancy between the findings of that study and the current study may be due to the limited sampling of a specific region of the epicardium. Indeed, looking just at the anteroseptal region (Figure 2), the inverse relation between activation time and ARI is apparent. Areas that activate early (red, orange, or yellow on activation map, ANT view) in the epicardial aspect of the anterior septum have longer ARIs (red, orange, or yellow on corresponding regions of ARI maps). However, that relationship is not preserved when the entire epicardium is taken into account. It is well known that progression of heart failure alters the underlying electrophysiologic substrate. In addition, these patients have been paced with CRT for an extended period of time. Pacing in turn can cause further electrical remodeling, especially changes in repolarizing currents. The abnormal repolarization and steep ARI gradients observed in this study were not observed in earlier ECGI studies of repolarization in structurally normal hearts.

**LV electrical dyssynchrony**

The LV ED index showed a weak positive correlation with QRSd. This is expected because these two quantities are not synonymous. QRSd is an estimate of the duration of global ventricular activation as reflected on the body surface ECG. ED, by definition, is a measure of the spatial dispersion of activation times across the LV and depends on how much of the LV activates late relative to the rest of LV myocardium. For example, in patient 12, a major portion of the LV lateral and inferior wall (blue, NAT, Figure 5) activated later than the 80th percentile of QRSd, resulting in a relatively high value of native ED (32 ms), whereas in patient 8, only a very small portion of the LV lateral wall activated late (light blue, NAT, Figure 6), resulting in a more synchronized ED index (25 ms).

From Table 2, it is observed that LV electrical dyssynchrony is consistently high (ED $\geq 30$ ms) for native QRSd $>130$ ms. However, among patients with native QRSd $\leq 130$ ms, electrical dyssynchrony may vary widely (from minimal to large LV electrical dyssynchrony). Four patients with QRSd between 120 and 130 ms had synchronized LV activation (ED $<28$ ms), and all of them were nonresponders. Two patients with QRSd $<120$ ms had very dyssynchronous LV activation (ED = 32 and 34 ms) during native rhythm, and both of them responded to CRT. This suggests that for some heart failure patients with QRSd $<120$ ms, the native ED index may still be high, and such patients may be potential responders to CRT. By using

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**Figure 7** Baseline cardiac resynchronization therapy (CRT) and native activation (NAT) in another nonresponder patient (no. 22). Native activation shows earliest activation of the left ventricle (red) 20 ms before earliest right ventricular activation (light green) and electrical dyssynchrony (ED) close to normal value (24 ms). CRT pacing did not improve ED (29 ms).

**Figure 8** Scatter plots of electrical dyssynchrony (ED) versus QRS duration (QRSd) for (1) cardiac resynchronization rhythm (CRT); (2) left ventricular paced rhythm (LV-P); (3) right ventricular paced rhythm (RV-P); and (4) native sinus rhythm (NAT).
QRSd as a strict cutoff for CRT implant decisions, it is possible that these potential beneficiaries of CRT therapy will be missed. On the other hand, if implant decisions were based solely on QRSd >120 ms, it is possible that candidates with QRSd between 120 and 130 ms will be implanted despite having already synchronized native LV activation, which is not likely to improve further with CRT. Although QRSd is a valuable measure for CRT response, cardiac indexes such as ED may complement QRSd, especially when QRS width is moderate (100–130 ms). This study does not establish a measure for identifying potential responders and nonresponders to CRT. It only suggests the possibility that an additional nonechocardiographic cardiac measure (the electrical dyssynchrony index ED), obtained noninvasively, may be useful for identifying responders versus nonresponders in the range of moderately wide QRS duration (100–130 ms). This possibility should be examined in a randomized prospective study involving a larger population of patients with QRSd in this range.

Study limitations
This study does not include effects of parameters such as A-V delay, V-V delay, or location of resynchronization leads on ventricular activation and function. In this study, 24 of 25 patients had LV leads in the lateral wall. Only one patient (no. 2) had an anterior LV lead, and he was a CRT responder. However, this study was not designed to systematically address the effect of location of resynchronization leads on CRT response, and results from this study were not used to guide lead placement. In the future, ECGI may be used in real time in the electrophysiology catheterization laboratory during CRT implant to assess potential areas of lead placement and their effects on LV activation and electrical synchrony.

The study does not include preimplant data. ECGI maps provide electrical dyssynchrony of the epicardium only; no information is obtained about transmural and endocardial dyssynchrony. This is a limitation of ECGI methodology, although animal studies have shown that assessment of epicardial electrical synchrony provides adequate assessment of intramural synchrony as well.17

The number of patients in this study (n = 25) is small, and the focus is nonischemic patients. They are not representative of the entire CRT population, which includes both ischemic and nonischemic patients. Future prospective ECGI studies involving larger populations of CRT patients in both ischemic and nonischemic categories are required to derive statistical conclusions and establish new ECGI-based criteria for CRT.

Acknowledgments
We thank Timothy Sekarski for superb technical expertise in acquiring the echocardiographic images and Timothy Street for capable assistance in performing computed tomographic scans for this study.

References

Table 2 Summary of left ventricular electrical dyssynchrony index values

<table>
<thead>
<tr>
<th>Patients with QRSd ≤130 ms (n = 14)</th>
<th>Patients with QRSd &gt;130 ms (n = 8)</th>
<th>Responders (n = 18)</th>
<th>Nonresponders (n = 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Native ED = 32.1 ± 4.3 ms Max: 40 ms Min: 24 ms</td>
<td>Native ED = 36.8 ± 4.6 ms Max: 45 ms Min: 30 ms</td>
<td>Native ED = 35.5 ± 3.9 ms Baseline CRT ED = 23.2 ± 4.4 ms</td>
<td>Native ED = 26.3 ± 2.3 Baseline CRT ED = 27.0 ± 1.4</td>
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</table>

CRT = cardiac resynchronization therapy; ED = electrical dyssynchrony of left ventricular activation; Max = maximum; Min = minimum; QRSd = QRS duration.