Noninvasive Electrocardiographic Mapping to Improve Patient Selection for Cardiac Resynchronization Therapy

Beyond QRS Duration and Left Bundle Branch Block Morphology

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Objectives
This study sought to investigate whether noninvasive electrocardiographic activation mapping is a useful method for predicting response to cardiac resynchronization therapy (CRT).

Background
One third of the patients appear not to respond to CRT when they are selected according to QRS duration.

Methods
We performed electrocardiographic activation mapping in 33 consecutive CRT candidates (QRS duration >120 ms). In 18 patients, the 12-lead electrocardiographic morphology was left bundle branch block (LBBB), and in 15, it was nonspecific intraventricular conduction disturbance (NICD). Three indexes of electrical dyssynchrony were derived from intrinsic maps: right and left ventricular total activation times and ventricular electrical uncoupling (VEU) (difference between the left ventricular [LV] and right ventricular mean activation times). We assessed the ability of these parameters to predict response, measured using a clinical composite score, after 6 months of CRT.

Results
Electrocardiographic maps revealed homogeneous patterns of activation and consistently greater VEU and LV total activation time (LVTAT) in patients with LBBB compared with heterogeneous activation sequences and shorter VEU and LVTAT in NICD patients (VEU: 75 ± 12 ms vs. 40 ± 22 ms; p < 0.001; LVTAT: 115 ± 21 ms vs. 91 ± 34 ms; p = 0.03). LBBB and NICD patients had similar right ventricular total activation times (62 ± 30 ms vs. 58 ± 26 ms; p = 0.7). The area under the receiver-operating characteristic curve indicated that VEU (area under the curve [AUC]: 0.88) was significantly superior to QRS duration (AUC: 0.73) and LVTAT (AUC: 0.72) for predicting CRT response (p < 0.05). With a 50-ms cutoff value, VEU identified CRT responders with 90% sensitivity and 82% specificity whether LBBB was present or not.

Conclusions
Ventricular electrical uncoupling measured by electrocardiographic mapping predicted clinical CRT response better than QRS duration or the presence of LBBB. (J Am Coll Cardiol 2013;61:2435–43) © 2013 by the American College of Cardiology Foundation

When 12-lead electrocardiography (ECG) is used to identify electrical dyssynchrony, approximately one third of the patients undergoing cardiac resynchronization therapy (CRT)
appear not to obtain a substantial clinical response. Numerous efforts have been made to reduce the rate of nonresponse by improving patient selection using different nonelectrical measures of mechanical dyssynchrony and ventricular scar. However, despite showing early promise, none have as yet proved to be superior to the 12-lead ECG when tested in prospective, randomized studies. As a result, the international guidelines for CRT implantation continue to recommend the use of the 12-lead ECG when assessing potential CRT candidates (1–4).

The advantage of 12-lead ECG over nonelectrical methods is that it allows an assessment of the electrical substrate; CRT is, after all, an electrical therapy. Recent findings suggest that the degree and pattern of conduction disease are important in determining response to CRT. Patients with a narrow or moderately prolonged QRS duration do not appear to experience decreases in adverse clinical events when treated with CRT (5,6). Patients with left bundle branch block (LBBB) are likely to respond, while those with right bundle-branch block or nonspecific intraventricular conduction disturbance (NICD) are unlikely to respond (7,8).

A disadvantage of 12-lead ECG is that it provides only a general overview of ventricular electrical activation abnormalities. In this study, we hypothesized that by making a more detailed assessment of electrical activation, it is possible to predict response to CRT more reliably than by using 12-lead ECG.

Electrocardiographic mapping (ECM) is a noninvasive mapping technique developed to provide detailed patient-specific information on epicardial electrical activation (9). Using this high-resolution mapping technique, we sought to: 1) characterize the ventricular activation sequence of patients with 12-lead ECG morphology of LBBB and compare it with the activation sequence observed in patients with prolonged QRS duration but without typical LBBB morphology (NICD group); and 2) explore the ability of different ECM-derived parameters of electrical dyssynchrony to predict long-term clinical response to CRT.

### Methods

The execution of the study conformed to the principles outlined in the Declaration of Helsinki on research in human subjects. All patients gave written approval to participate in the study, which was approved by the institutional ethics committee.

**Patient population.** The study population consisted of a cohort of 33 consecutive patients scheduled for CRT-device implantation based on the following criteria: 1) New York Heart Association (NYHA) functional class II, III, or IV despite optimal medical therapy; 2) left ventricular (LV) ejection fraction ≤35% during sinus rhythm; and 3) intrinsic QRS duration ≥120 ms on 12-lead ECG. Heart failure etiology was considered ischemic in the presence of significant coronary artery disease (≥50% stenosis in ≥1 of the major epicardial coronary arteries) and/or a history of myocardial infarction or revascularization.

The mean age was 65 ± 9 years; 28 patients (85%) were male, 14 (42%) had an ischemic cardiomyopathy, 7 (21%) were NYHA functional class II, 25 (76%) were functional class III, and 1 (3%) was functional class IV. Mean LV ejection fraction was 27 ± 4%, and QRS duration as derived from 12-lead surface ECG was 152 ± 22 ms. Intraventricular conduction disturbances were defined according to the most recent American Heart Association/American College of Cardiology Foundation/Heart Rhythm Society criteria (10). Patients with right bundle branch block were excluded.

**Device implantation and follow-up.** All patients underwent implantation of a CRT defibrillator. Although the right ventricular (RV) lead was systematically implanted at the RV apex, the position of the LV lead was not pre-specified. The final position was determined by coronary venous anatomy with good stability, an acceptable pacing threshold, and no phrenic nerve capture.

All patients were clinically assessed by physicians who were blinded to the ECM data. The clinical assessment included estimation of NYHA functional class and acquisition of a 12-lead electrocardiogram (10 mm/mV; 25 mm/s) at 3 time points (i.e., before implantation and 3 and 6 months after implantation of their CRT device). Heart failure medications were adjusted as required, and adverse events (hospitalization or death) were recorded.

To assess CRT response, we used a clinical composite score that combined changes in clinical status (NYHA functional class) with the occurrence of major clinical events (hospitalization or death) (11). This score was previously used in studies evaluating the efficacy of CRT (12,13). Patients were considered as clinical responders if, during 6 months of follow-up, they remained alive, did not experience hospitalization for heart failure, and demonstrated an improvement of at least 1 NYHA functional class.

**Noninvasive mapping of electrical activation.** Ventricular epicardial activation maps were acquired during intrinsic sinus rhythm using a noninvasive, high-resolution ECM system (ECVUE, CardioInsight Technologies Inc., Cleveland, Ohio). As previously described in detail, body surface potentials were recorded from 252 sites around the entire surface of the torso (14). A thoracic computed tomography scan was performed with the electrodes attached to the torso.
patient. The body surface potentials and computed tomography images were then combined and processed to reconstruct 1,500 epicardial unipolar electrograms. Ventricular activation times were calculated from the onset of the QRS duration to the maximal negative slope of each unipolar electrogram. An epicardial breakthrough site was defined as the earliest location identified on the isochrone map. A line of slow conduction was recorded if the activation times of adjacent points on either side of this line differed by >50 ms.

The following electrical dyssynchrony indexes were derived from intrinsic activation maps: the RV total activation time (RVTAT), defined as the duration (in milliseconds) from the earliest to the latest site of RV activation during intrinsic rhythm; the LV total activation time (LVTAT), defined as the duration (in milliseconds) from the earliest to the latest site of left ventricular activation during intrinsic rhythm; and ventricular electrical uncoupling (VEU), defined as the difference between the mean LV and RV activation times during spontaneous rhythm (in milliseconds). A positive value reflects LV uncoupling (from the right ventricle), whereas a negative value reflects RV uncoupling (from the left ventricle).

We tested whether these ECM-derived parameters were associated with clinical response to CRT. In addition, we investigated how these parameters related to the LBBB morphology and the QRS duration derived from 12-lead surface ECG. To test reproducibility of the electrical dyssynchrony indexes, the activation maps of 13 randomly selected patients were analyzed by 2 operators who were blinded to patient characteristics and outcome.

Statistical analysis. Categorical variables were expressed as absolute numbers (percentages) and compared using the chi-square test or the Fisher exact test, as appropriate. Continuous variables were expressed as mean ± SD or median (interquartile range) and tested for normality using skewness, kurtosis, and omnibus tests. They were compared using either the Student t test or the Mann-Whitney U test, as appropriate. Interobserver variability of LVTAT, RVTAT, and VEU was assessed by an intraclass correlation coefficient. Receiver–operating characteristic (ROC) curves were generated, and areas under the curve (AUCs) were formed using SPSS software, version 18.0 (SPSS Inc., Chicago, Illinois) and the NCSS software 2007 (NCSS LLC, Kaysville, Utah). Statistical significance was assumed at p < 0.05.

Results

Electrical properties. Based on 12-lead ECG, 18 patients had an LBBB and 15 had an NICD. Compared with the NICD group, LBBB patients had a longer QRS duration (164 ± 16 ms vs. 137 ± 20 ms; p < 0.001), a longer LVTAT (115 ± 21 ms vs. 91 ± 34 ms; p < 0.03), and greater VEU (75 ± 12 ms vs. 40 ± 22 ms; p < 0.001). There were no significant differences between the 2 groups in terms of sex (males: 14 [78%] vs. 14 [93%]; p = 0.3), age (68 ± 9 years vs. 63 ± 9 years; p = 0.1), LV ejection fraction (26 ± 4% vs. 27 ± 5%; p = 0.7), or the presence of ischemic cardiomyopathy (6 [33%] vs. 8 [53%]; p = 0.3). Intraclass correlation coefficients were 0.92, 0.97, and 0.99 for LVTAT, RVTAT, and VEU, respectively. Baseline electrical characteristics of the 2 groups are summarized in Table 1.

Electrocardiographic activation maps in 18 LBBB patients. All LBBB patients had a single anterior (11 [61%]) or lateral (7 [39%]) RV breakthrough site. Epicardial breakthrough was apparent 24 ± 8 ms after the QRS onset. RV epicardial activation propagated centrifugally from the breakthrough site to activate the entire RV epicardium within 61 ± 28 ms (Figs. 1 and 2). The base was the latest RV segment to be activated in 13 patients (72%). There was no epicardial breakthrough in the left ventricle, which was activated passively from the right ventricle via the septum (Figs. 1 and 2). The spread of the activation front was consistently impaired (both anteriorly and posteriorly) by lines of slow conduction (crowded isochrones). These lines were typically oriented in a base-to-apex direction and appeared on the anteroseptal, anterolateral, posterolateral, and posteroseptal surfaces. These lines of slow conduction usually extended for more than two thirds of the distance from base to apex and were multiple (median: 2 [interquartile range: 2 to 3]). They were responsible for the observed prolonged LVTAT and VEU. The latest site of LV activation was basolateral for the majority of patients (16 [89%]). We observed no association between the etiology of ventricular impairment and RVAT (52 ± 18 ms vs. 67 ± 34 ms ischemic vs.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Baseline Electrical Characteristics of the Patients by QRS Morphology</th>
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<tbody>
<tr>
<td>Parameter</td>
<td>LBBB (n = 18)</td>
</tr>
<tr>
<td>QRS duration, ms</td>
<td>164 ± 16</td>
</tr>
<tr>
<td>RVTAT, ms</td>
<td>62 ± 30</td>
</tr>
<tr>
<td>LVTAT, ms</td>
<td>115 ± 21</td>
</tr>
<tr>
<td>VEU, ms</td>
<td>75 ± 12</td>
</tr>
</tbody>
</table>

Values are mean ± SD. QRS duration was measured with 12-lead electrocardiography. RVTAT, LVTAT, and VEU were calculated using the epicardial activation maps.

LBBB = left bundle branch block; NICD = nonspecific intraventricular conduction disturbance; RVAT = right ventricular total activation time; LVTAT = left ventricular total activation time; VEU = ventricular electrical uncoupling.
The right ventricular breakthrough is anterior or lateral. There is no left ventricular breakthrough. The left ventricle (LV) is activated by anterior and posterior wave fronts originating from the right ventricle (RV). One to 4 lines of slow conduction with a base-to-apex orientation markedly delay the left ventricular epicardial activation and confine the end of activation to the lateral base. Star indicates right ventricular breakthrough; arrows indicate the direction of the activation wave fronts. 1 = anteroseptal line; 2 = anterolateral line; 3 = posterolateral line; 4 = posteroseptal line; LBBD = left bundle branch block.

Electrocardiographic activation maps in 15 patients with nonspecific intraventricular conduction disturbance. Most (11 [73%]) of the NICD patients had a single RV breakthrough site, whereas 4 had additional sites of breakthrough in the left ventricle. In contrast to the LBBB group, activation sequences were heterogeneous among NICD patients. Breakthrough occurred a mean 27 ± 12 ms after QRS onset (p = 0.4 vs. LBBB). The RVTAT was similar to that measured in LBBB patients (58 ± 26 ms; p = 0.9 vs. LBBB), and the latest activated region of the right ventricle was usually basolateral. LV lines of slow conduction were present in 13 of the 15 patients. However, compared with the LBBB group, fewer lines of block were observed (median: 1 [interquartile range: 1 to 2]; p = 0.002 vs. LBBB), and when present, they were shorter (extending less than two thirds of the LV long axis) and their orientation was more variable (Figs. 3 and 4). As a consequence, LVTAT and VEU in NICD patients were shorter than in the LBBB group. Furthermore, we observed considerable variation in the location of the latest activated LV site: 4 anterobasal, 5 laterobasal, 3 posterobasal, 2 midlateral, and 1 apical. Ischemic patients displayed similar LVTATs (93 ± 39 ms vs. 89 ± 32 ms nonischemic group; p = 0.8) and VEU (45 ± 26 ms vs. 35 ± 18 ms nonischemic group; p = 0.4) compared with nonischemic patients. There was a trend toward higher RVTAT in the nonischemic group (48 ± 25 ms vs. 71 ± 24 ms nonischemic group; p = 0.09). The number of lines of slow conduction and the location of the latest activated area did not differ according to heart failure etiology.

Response to CRT. Of 33 patients, 21 (64%) met the clinical composite endpoint at 6 months and were identified as clinical responders. One patient experienced LV lead displacement after 3 months and was not further evaluated. During follow-up, 2 patients (6%) died and 3 (9%) were hospitalized due to worsening heart failure. The baseline characteristics of the responders and nonresponders are presented in Table 2. Responders had a longer baseline QRS duration (157 ± 19 ms vs. 139 ± 24 ms; p < 0.05), LVTAT (112 ± 29 ms vs. 89 ± 29 ms; p < 0.04), and VEU (72 ± 16 ms vs. 38 ± 23 ms; p < 0.001) than the nonresponders. LBBB was more prevalent in the responders compared with nonresponders (76% vs. 18%; p = 0.003).

Electrical parameters and prediction of response. In ROC analyses, QRS duration (AUC: 0.73 [interquartile range: 0.48 to 0.87]; p = 0.034), LVTAT (AUC: 0.72 [interquartile range: 0.48 to 0.87]; p = 0.033), and VEU (AUC: 0.88 [interquartile range: 0.65 to 0.96]; p = 0.004) showed a significant AUC when tested for their ability to predict a positive CRT response. RVTAT was not useful in predicting response to CRT (AUC: 0.51 [interquartile range: 0.48 to 0.87]; p = 0.034) compared with nonischemic patients. There was a trend significantly between QRS duration and LVTAT (p = 0.031, respectively), whereas AUC did not differ significantly between QRS duration and LVTAT (p = 0.92). The optimal cutoff value of VEU to predict CRT response derived from the ROC analysis was 7.1 ms, which corresponded to a cutoff value of 50 ms for VEU. By using a cutoff level of 50 ms to define the presence of ventricular uncoupling, it was possible to predict response with sensitivity, specificity, and positive and negative predictive values of 90%, 82%, 90%, and 82%, respectively.

The best cutoff values for QRS duration, LVTAT, and VEU were determined using ROC analysis (145 ms, 101 ms, and 50 ms, respectively). These values were then used to binarize these parameters and run logistic regressions. Significant relationships obtained for these 3 binarized predictors and for native discrete parameters (LBBB morphology, sex, and ischemic etiology) are displayed in Table 3. VEU >50 ms was associated with a 42-fold increase in the likelihood of being a responder (p < 0.001).

In all LBBB patients (n = 18), VEU was >50 ms, whereas 3 NICD patients (20%) achieved this VEU cutoff. These 3 NICD patients were clinical responders.
Figure 2 Electrocardiographic Activation Map of a Clinical Responder to CRT With a 12-Lead Surface ECG Exhibiting a Typical LBBB Activation Pattern

Epicardial ventricular surfaces of both ventricles are displayed in 3 views: anteroposterior (AP), left anterior oblique (LAO), and left lateral (LL). The left anterior descending artery is depicted as a white dotted line. The 12-lead electrocardiogram (ECG) shows a typical left bundle branch block (LBBB) morphology. The right ventricular lateral breakthrough is followed by a fast activation of this ventricle. The wave front spread to the left, with a first base-to-apex line of slow conduction at the level of the septum and a second one limited to the first two thirds of the anterolateral area (crowding of isochrones). Left ventricular activation ends at the lateral base. QRS duration: 155 ms; ventricular electrical uncoupling: 74 ms. CRT = cardiac resynchronization therapy.

Figure 3 Electrocardiographic Activation Map of a Clinical Nonresponder to CRT With a 12-Lead Surface ECG Exhibiting a NICD Activation Pattern

Epicardial surfaces of both ventricles are displayed in 3 views: AP, LAO, and LL. The left anterior descending artery is depicted as a white dotted line. On the 12-lead ECG, the QR pattern in leads I and aVL and the absence of a broad notched R-wave in V5 and V6 are criteria against the diagnosis of LBBB. There is a septobasal breakthrough with an eccentric activation followed by a heterogeneous and abnormally slow activation of the RV with delayed activated midlateral area. Left ventricular activation is slowed by an incomplete anterolateral line of slow conduction. The latest site of activation is the lateral base. QRS duration: 166 ms; ventricular electrical uncoupling: 35 ms. NICD = nonspecific intraventricular conduction disturbance; other abbreviations as in Figures 1 and 2.
Discussion

In this study, we show that noninvasive 3-dimensional activation mapping is useful in predicting which patients will respond to CRT. Prolongation of VEU was strongly associated with clinical CRT response and appeared to be a more powerful predictor than 12-lead ECG parameters. Such mapping also showed relatively consistent patterns of activation in patients with LBBB and pronounced VEU. In contrast, prolonged QRS duration without typical bundle branch block morphology (NICD) appears to represent a heterogeneous group of conduction defects. In the majority of cases, these defects do not appear amenable to treatment with conventional CRT. However, ECM identified pronounced prolongation of VEU in a subset of patients with NICD (20%), and these patients did appear to experience a clinical response after CRT.

**LBBB versus NICD electrocardiographic activation maps.** LEFT BUNDLE BRANCH BLOCK. Detailed analysis of the ventricular activation pattern in patients with LBBB on 12-lead ECG revealed the following major features: 1) RV breakthrough gave rise to a rapid and centrifugal spread of activation across the RV free wall; 2) there was no LV breakthrough; 3) 1 to 4 LV lines of slow conduction oriented in base-to-apex direction prevented rapid LV conduction; and 4) the site of latest activation occurred usually at the base of the lateral wall of the left ventricle.

### Table 2 Baseline Characteristics of Responders and Nonresponders to CRT

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Responders (n = 21)</th>
<th>Nonresponders (n = 11)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>65 ± 8</td>
<td>67 ± 11</td>
<td>0.5</td>
</tr>
<tr>
<td>Male</td>
<td>17 (81)</td>
<td>11 (100)</td>
<td>0.3</td>
</tr>
<tr>
<td>Ischemic cardiomyopathy</td>
<td>8 (38)</td>
<td>6 (55)</td>
<td>0.5</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>26 ± 4</td>
<td>26 ± 4</td>
<td>0.9</td>
</tr>
<tr>
<td>QRS duration, ms</td>
<td>157 ± 19</td>
<td>139 ± 24</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>LBBB pattern</td>
<td>16 (76)</td>
<td>2 (18)</td>
<td>0.003</td>
</tr>
<tr>
<td>RVTAT, ms</td>
<td>60 ± 30</td>
<td>59 ± 25</td>
<td>0.9</td>
</tr>
<tr>
<td>LVTAT, ms</td>
<td>112 ± 29</td>
<td>89 ± 29</td>
<td>0.04</td>
</tr>
<tr>
<td>VEU, ms</td>
<td>72 ± 16</td>
<td>38 ± 23</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are mean ± SD or number (%) of observations. QRS duration was measured with 12-lead echocardiography. RVTAT, LVTAT, and VEU were calculated using the epicardial activation maps. CRT = cardiac resynchronization therapy; other abbreviations as in Table 1.

### Table 3 Association Between Electrical Parameters and CRT Response: Univariate Analysis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>OR (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>QRS duration, ms*</td>
<td>7.4 (1.4–38.4)</td>
<td>0.017</td>
</tr>
<tr>
<td>LBBB</td>
<td>14.4 (2.3–89.9)</td>
<td>0.004</td>
</tr>
<tr>
<td>LVVTAT</td>
<td>5.3 (1.1–26.6)</td>
<td>0.04</td>
</tr>
<tr>
<td>VEU</td>
<td>42.8 (5.2–354.1)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Right ventricular total activation time, LVTAT, and VEU were calculated using the epicardial activation maps. QRS duration was measured with 12-lead electrocardiography. *QRS duration using a 145-ms cutoff. †Using a 101-ms cutoff. ‡Using a 50-ms cutoff.

OR – odds ratio; CI – confidence interval; other abbreviations as in Tables 1 and 2.
Relatively few human data are available with regard to the epicardial activation sequence in patients with LBBB. Wyndham et al. (15) performed epicardial contact mapping (with a handheld probe) in 5 patients with LBBB during surgery. Using 54 to 70 acquisition points per patient, they described a normal RV activation sequence, the consistent absence of LV breakthrough, and the phenomenon of lines of slow conduction over the anterior and posterior septal regions. Jia et al. (14) used ECM in 6 patients with LBBB. They confirmed that the RV activation pattern was consistent with that observed in the normal heart and detected lines of slow conduction, mainly on the anterior LV surface.

In the present study, we provide a more systematic description of the lines of slow conduction, which vary in length and number but appear consistently at a few typical anatomic locations (Fig. 1). We found these lines to be more prominent at the base, which may account for the finding that the basal region is typically the latest area to be activated.

**NICD.** In contrast, NICD patients demonstrated heterogeneous patterns of activation: 1) breakthrough could also occur on the LV surface; 2) lines of slow conduction were fewer (or even absent) and smaller and varied in geometric location; 3) the site of latest activation was highly variable. To the best of our knowledge, we present the first human data on the epicardial activation sequences in patients with NICD. In contrast to patients with LBBB displaying a “typical” activation pattern, the activation sequences in NICD are highly variable. Therefore, this group of patients particularly benefited from the innovative ECM assessment of the underlying electrical conduction abnormality.

**Electrical dysynchrony and CRT response.** It is now accepted that sufficient ventricular electrical conduction delay needs to be present for CRT to produce improvements in cardiac pump function. Twelve-lead ECG is the most frequently used and best validated technique for measuring this conduction delay. No reduction in heart failure events post-CRT was observed in patients with a QRS duration <150 ms in a subgroup analysis of the MADIT-CRT (Multicenter Automatic Defibrillator Implantation With Cardiac Resynchronization Therapy) trial (16). This finding was confirmed in a meta-analysis of 5 randomized, controlled trials that included >5,800 patients (6). The pattern of conduction disturbance also appears to be critical in determining a response to CRT. A further subgroup analysis of the MADIT-CRT trial showed that only patients with LBBB derived substantial clinical benefit from CRT (7). Again, this result was subsequently supported by the results of a meta-analysis (8). As a result of these findings, the 2012 European Society of Cardiology guidelines for the management of heart failure have been revised to recommend CRT only in the patients with LBBB (Class I, Level of Evidence: A) or a QRS duration ≥150 ms (Class IIa, Level of Evidence: A) (4). In patients with NYHA functional class I or II heart failure, the U.S. Food and Drug Administration allows CRT only in patients who are in sinus rhythm with LBBB (17). These guideline modifications have been made in response to the reports of high rates of nonresponders to CRT. They are aimed at improving the specificity of the selection process, but inevitably result in a reduced sensitivity. As a result, CRT device implantation is currently discouraged in patients with NICD with a QRS duration <150 ms. However, there is evidence that a proportion of patients with NICD respond to treatment with CRT (18,19). In the aforementioned meta-analysis, the authors acknowledged that the neutral effect of CRT in patients with moderately prolonged QRS duration may be actually due to a subset of patients at increased risk of hospitalizations and death. The same assumption may apply to the NICD patients, as evidenced by the high prevalence of ischemic cardiomyopathy in this group, a factor known to adversely affect the prognosis (4,18,19). Given the high proportion of patients presenting with NICD (approximately one third of the recent RAFT [Resynchronization–Defibrillation for Ambulatory Heart Failure Trial] and REVERSE [Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction] trials) and/or QRS duration <150 ms (40% of the European CRT survey) as well as the demonstrated clinical and survival benefits of CRT, additional selection criteria are clearly needed for identifying potential responders (13,20,21).

Studies investigating the electrical substrate beyond QRS duration or LBBB morphology are scarce. Sweeney et al. (22) carefully inspected standard 12-lead electrocardiograms of patients with LBBB who received CRT. The LV transition was measured between a notch occurring 40 ms after the QRS onset (which was assumed to be the RV-LV transition) and the end of the QRS complex. Increasing LV transition was associated with a greater probability of remodeling up to a plateau value of 125 ms. This estimate of LV transition, however, is only applicable to some LBBB patients who exhibit a clear notch in the QRS complex. The LV transition has also been estimated inversely by calculating the delay between QRS onset and LV activation measured from the LV lead. Varma (23) observed that this LV electrical delay exceeded 100 ms in 87% of LBBB patients compared with only 45% in those with RBBB. Singh et al. (24) corrected this delay for QRS duration and found that patients with a reduced baseline LV lead electrical delay (<50% of the QRS duration) had a worse clinical outcome at 12 months. Clearly, this parameter is dependent on LV lead position, which is not necessarily positioned in the latest activated region. Using LV noncontact endocardial mapping, Fung et al. (25) observed that patients with lines of slow conduction had a more favorable response to CRT than those without these lines. Auricchio et al. (26) first reported that 23 of 24 LBBB patients (96%) showed LV lines of slow conduction. Besides confirming the presence of these lines in patients with LBBB, we also found that the prevalence of lines of slow conduction was significantly lower in NICD patients.
The latter finding may explain why the presence of lines of slow conduction has previously been found to be associated with CRT response (25).

In the present study, we measured RVTAT as well as LVTAT by using >1,000 reconstructed electrograms. This allowed us to clearly define the area of latest activation. We observed that VEU was a stronger predictor of CRT response than LVTAT. In our study, LVTAT was not superior to QRS duration for predicting clinical response. Our finding that VEU > 50 ms is predictive of a positive CRT response suggests that electrical uncoupling of the left ventricle from the right ventricle is a fundamental component of the electrical substrate, which is amenable to treatment with CRT. VEU can be prolonged by 2 main mechanisms. First, because of a delay in the onset of LV activation relative to RV activation, this is determined mainly by the transeptal activation time. Second, because of an intraventricular-conduction delay, slowing of LV conduction by lines of slow conduction increases VEU, whereas slowing of RV activation can mitigate it. It is likely that a delay in LV activation relative to RV activation is responsible for dynamic alterations in transeptal pressure differences and presystolic shortening of septal muscle fibers, both resulting in a loss of septal contribution to the LV ejection fraction. Preserved RV activation also appears to be important. The presence of an RV conduction delay reduces VEU. This finding may explain why RV dysfunction has been negatively associated with CRT response (27). LV electrical uncoupling was found in all LBBB patients, which may account for the high rate of response to CRT in this subgroup. Interestingly, LV electrical uncoupling was also observed in some patients with NICD and appeared to be useful in identifying responders to CRT in this group.

VEU, therefore, has the potential to be a useful measure for selecting patients who may benefit from CRT, particularly patients who have prolonged QRS duration on surface ECG, but who do not display typical LBBB morphology.

**Study limitations.** The number of patients included in this study is modest; however, this is the largest study to date of detailed mapping of electrical activation abnormalities in patients undergoing CRT. Larger, randomized, and blinded studies are required to confirm these results. Patient selection is undoubtedly a major issue for CRT response. Optimization of the therapy delivery is also of major importance. In this regard, lead placement under real-time ECM assistance would be an interesting field of investigation.

**Conclusions**

Patients with LBBB have uniform patterns of activation when measured using detailed electrocardiographic maps, whereas in patients with NICD, conduction patterns are highly variable. This noninvasive 3-dimensional mapping tool derives a novel electrical dysynchrony parameter called VEU, which is significantly associated with a clinical response to CRT. VEU, which is consistently elevated in all LBBB but in only a few NICD patients, properly identifies clinical CRT responders in both of these subgroups. Thus, with substantial advantage over standard 12-lead ECG in identifying clinical responders to CRT, ECM can potentially improve prospective decision-making on candidacy for CRT.

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