Characterization of Left Ventricular Activation in Patients With Heart Failure and Left Bundle-Branch Block

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Background—Conventional activation mapping in the dilated human left ventricle (LV) with left bundle-branch block (LBBB) morphology is incomplete given the limited number of recording sites that may be collected in a reasonable time and given the lack of precision in marking specific anatomic locations.

Methods and Results—We studied LV activation sequences in 24 patients with heart failure and LBBB QRS morphology with simultaneous application of 3D contact and noncontact mapping during intrinsic rhythm and asynchronous pacing. Approximately one third of the patients with typical LBBB QRS morphology had normal transseptal activation time and a slightly prolonged or near-normal LV endocardial activation time. A “U-shaped” activation wave front was present in 23 patients because of a line of block that was located anteriorly (n=12), laterally (n=8), and inferiorly (n=3). Patients with a lateral line of block had significantly shorter QRS (P<0.003) and transseptal durations (P<0.001) and a longer distance from the LV breakthrough site to line of block (P<0.03). Functional behavior of the line of block was demonstrated by a change in its location during asynchronous ventricular pacing at different sites and cycle lengths.

Conclusions—A U-shaped conduction pattern is imposed on the LV activation sequence by a transmural functional line of block located between the LV septum and the lateral wall with a prolonged activation time. Assessment of functional block is facilitated by noncontact mapping, which may be useful for identifying and targeting specific locations that are optimal for successful cardiac resynchronization therapy. (Circulation. 2004;109:1133-1139.)

Key Words: bundle-branch block ■ heart failure ■ mapping

Cardiac resynchronization therapy, a recent nonpharmacological therapy for patients with heart failure (HF) and ventricular conduction delay, has revived interest in the ventricular activation sequence related to the morphology of left bundle-branch block (LBBB).

Conventional activation mapping in the dilated human left ventricle (LV) with LBBB morphology achieves only a gross estimate of the electrical activation sequence and the LV chamber anatomy, given the limited number of recording sites that may be collected in a reasonable time and given the lack of precision in marking specific anatomic locations.

Recently, catheter-based 3D nonfluoroscopic contact and noncontact mapping techniques have been introduced that permit in vivo reconstruction of the cardiac anatomy and assessment of the activation sequence with high spatial resolution.

Contact mapping usually records bipolar signals that represent local changes in electrical events, with an associated higher sensitivity to rapidly changing events and a lower sensitivity to slowly changing events. In contrast, unipolar signals, as recorded by noncontact mapping, retain electrical information across the whole transmural thickness, with equal sensitivity to fast and slow conduction. These attributes of both unipolar and bipolar recordings may facilitate a more complete characterization and localization of electrical events.

We sought to assess the LV activation sequence in patients with HF and LBBB undergoing cardiac resynchronization therapy by use of simultaneous application of 3D nonfluoroscopic contact and noncontact mapping.

Methods

Patients
Twenty-four consecutive patients with moderate to severe HF, LV ejection fraction < 35%, and dilated cardiomyopathy of any cause referred to the Division of Cardiology, University Hospital, Magdeburg, for nonpharmacological treatment of HF were prospectively enrolled in this study. All patients were on stable drug therapy (≥3 months) with maximally tolerated doses of ACE inhibitors or angiotensin-1 receptor blockers (100%), diuretics (100%), digitalis (67%), aldosterone antagonists (20%), and β-blockers (87%). Antiarrhythmic drugs, if any, were stopped before the procedure for at least 5 half-lives. In 3 patients, amiodarone was given for preventing atrial fibrillation and was continued during the study. All patients provided oral and written informed consent, and the studies were performed according to institutional ethics guidelines.

Received September 23, 2003; revision received November 18, 2003; accepted November 20, 2003.

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Circulation is available at http://www.circulationaha.org

DOI: 10.1161/01.CIR.0000118502.91105.F6

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Mapping Procedure

In addition to standard electrophysiological catheters deployed in the right atrium and right ventricle (RV), 16-pole or alternatively 8-pole microcatheters (Pathfinder 16 or 8, Cardima) were placed into the anterior and the lateral or posterior cardiac veins, and a reference catheter (Ref-Star, Cordis-Webster) was placed on the back of the patient.

Both the noncontact mapping system (EnSite 3000; Endocardial Solutions, Inc) and the contact system (CARTO, Biosense) as well as the navigation and mapping method have been described previously. The 64-electrode, noncontact array and a conventional 7F deflectable-tip mapping catheter (Navi-Star, Cordis-Webster) were deployed in the LV via the retrograde aortic approach from both femoral arteries. Furthermore, to reduce electrical and geometric interpolation by the contact system, the filling threshold was set at 10 mm during the acquisition process.

Definitions

The QRS duration was automatically calculated by a commercially available ECG recording system (Hewlett-Packard Pagewriter XIi). QRS duration was also measured manually from the beginning to the end of the QRS complex with simultaneous 12-lead ECG signals (maximum QRS) acquired on the digital electrophysiology recording system (Quinton Electrophysiology Corp) at a paper speed of 200 mm/s.

The LV endocardial breakthrough site was defined as the earliest location identified on the 3D color map from which activation consistently spread away to all parts of the LV. With noncontact mapping, the time of this event was marked within the initial 10% decrease in amplitude during the rapid downstroke of the associated virtual electrogram. In this way, far-field potentials from the RV and near-field potentials from the interventricular septum were separated.

The transseptal activation time was defined from the onset of the earliest QRS complex to the time of detected LV endocardial breakthrough.

The duration of LV endocardial activation was defined as the time from endocardial breakthrough to the site of latest endocardial activation. Using noncontact mapping, this site was defined as the latest location of peak negative amplitude for the associated virtual electrogram.

With noncontact mapping, lines of block were interpreted from both the patterns of activation observed in isopotential maps and the associated morphological features of electrograms (Figure 1). The line-of-block length was measured by use of a standard distance-
measuring feature built into the noncontact mapping system. Local split potentials were always present in the region of conduction block both on reconstructed and contact electrograms recorded from the LV mapping catheter (endocardially) and on the Cardima catheters (epicardially). The location of the middle one third of the line of block was projected onto 4 predefined quadrants of a left anterior oblique 45° schematic projection of the LV (Figure 2). The distance from the LV breakthrough site to the middle one third of the line of block was measured.

**Statistics**

The statistical significance of electrophysiological characteristics among and between groups of patients with different breakthrough sites was evaluated by 1-way ANOVA for repeated measurements. A probability value of 0.05 was considered statistically significant. Two-tailed unpaired t tests were used for comparing patients with different timing of the LV breakthrough as well as patients with an anterior to a lateral line of block. Automatic and manual QRS durations were compared by linear regression. Average data are shown as mean ± SD.

**Results**

Table 1 summarizes demographic and baseline ECG data of the patient population. Pathogenesis and ejection fraction were assessed in all patients by coronary artery angiography and left ventriculography at the end of the mapping procedure. During the mapping procedure, an average of 177 ± 67 equally distributed contact points for LV mapping were acquired. The estimated LV volume by the contact mapping

<table>
<thead>
<tr>
<th>TABLE 1. Characteristics of the 24 Evaluated Patients</th>
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<tbody>
<tr>
<td>Male gender, n (%)</td>
</tr>
<tr>
<td>Age, y</td>
</tr>
<tr>
<td>Pathogenesis: coronary artery disease, n (%)</td>
</tr>
<tr>
<td>NYHA functional class, n (%)</td>
</tr>
<tr>
<td>III</td>
</tr>
<tr>
<td>IV</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
</tr>
<tr>
<td>Peak oxygen consumption, mL·kg⁻¹·min⁻¹</td>
</tr>
<tr>
<td>Sinus rhythm, n (%)</td>
</tr>
<tr>
<td>Left bundle-branch block, n (%)</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
</tr>
<tr>
<td>PR interval, ms</td>
</tr>
<tr>
<td>QRS duration, ms</td>
</tr>
</tbody>
</table>
system was $315 \pm 110$ mL, which correlated with the LV volume calculated by nuclear magnetic resonance ($r=0.85, P<0.0001$).

Although automatically measured QRS durations showed a good correlation with the longest QRS duration ($r=0.87, P<0.0001$), some discrepancies were noted in patients with QRS durations $>150$ ms. One patient showed diffuse ventricular conduction delay (QRS 135 ms), and the remaining patients had LBBB QRS morphology.

**LV Activation Pattern During Intrinsic Rhythm**

A single LV septal endocardial breakthrough was identified in 22 patients: middle in 4, basal in 4, and apical in 14 (Table 2). A single anterior endocardial breakthrough was identified in 2 patients (Table 2). The transseptal time and the total LV endocardial activation time measured with both mapping systems were similar and demonstrated a large individual variability (Figure 3). Patients with coronary artery disease had a significantly longer total LV endocardial activation time ($121 \pm 17$ versus $99 \pm 17$ ms, $P<0.02$) but a similar transeptal time ($39 \pm 34$ versus $45 \pm 33$ ms, $P=0.724$).

Noncontact mapping showed that from the site of earliest LV breakthrough, activation spread both superiorly and inferiorly. However, in all but 1 patient, the activation wave front could not cross directly to the lateral wall from the anterior region. Instead, this wave front reached the lateral or posterolateral regions by propagating inferiorly around the apex and across the inferior wall (Figure 1); LV activation ultimately ended at the basal region near the mitral valve annulus. This “U-shaped” pattern of activation was observed in all but 1 patient.

Isocronal contour lines obtained from unipolar recording converged at the same location at which the wave front was unable to cross over, indicating a line of block (Figure 1). In contrast, isocronal contour lines obtained from bipolar recording did not demonstrate a line of block; however, close inspection of the contour lines revealed a narrower separation of isochrones and, thus, a lower propagation velocity in the same region in which noncontact mapping detected the line of block (Figure 1).

Visual inspection of local electrograms confirmed the presence of fragmented, double, or multiphasic components (Figures 1 and 2). The conduction block was best represented by a line in 21 patients and by a large area in the remaining 2 patients. The line of block generally paralleled the septum, was directed from the base toward the apex, and usually terminated near the apex (Figures 1 and 2). The location of the line of block was anterior in 12 patients, lateral in 8, and inferior in 3.

The combination of LV breakthrough site and transeptal time was the major determinant of both the distance from the LV breakthrough site to line of block and the QRS duration. Patients with a septoapical LV breakthrough showed the longest QRS duration, the longest transeptal time, but the shortest distance from the LV breakthrough site to line of block (Table 2).

A binary distribution of the transeptal time was evident, being the border zone between 20 and 40 ms (Figure 3); patients with a value >40 ms had a statistically longer QRS duration, had a shorter distance from the LV breakthrough site to line of block; had a mean LV transseptal length of $20 \pm 3$ mm; and had a significantly shorter time to LV breakthrough ($18 \pm 7$ versus $28 \pm 9$ ms, $P<0.0001$).

**Table 2. Distribution of Location of LV Breakthrough Site and Related Electrophysiological Findings**

<table>
<thead>
<tr>
<th>Location of LV Breakthrough Site</th>
<th>Site of Line of Block</th>
<th>Pathogenesis: DCM/CAD</th>
<th>QRS Duration Automatic, ms</th>
<th>Time to LV Breakthrough NCM, ms</th>
<th>Time of Total LV Activation NCM, ms</th>
<th>Distance From LV Breakthrough Site to Line of Block NCM, mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior (n=2)</td>
<td>None</td>
<td></td>
<td></td>
<td>11±3</td>
<td>86±20</td>
<td>98±6</td>
</tr>
<tr>
<td>Septal (n=22)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal (n=4)</td>
<td>Ant</td>
<td>DCM/CAD</td>
<td>149±20</td>
<td>16±25</td>
<td>107±20</td>
<td>92±35†</td>
</tr>
<tr>
<td>Middle (n=4)</td>
<td>Lat</td>
<td>CAD</td>
<td>149±35</td>
<td>38±25</td>
<td>82±20</td>
<td>63±15</td>
</tr>
<tr>
<td>Apical (n=14)</td>
<td>Inf</td>
<td>DCM</td>
<td>168±24</td>
<td>59±25*</td>
<td>101±20</td>
<td>63±10†</td>
</tr>
<tr>
<td>P</td>
<td>0.681</td>
<td></td>
<td>0.03</td>
<td>0.010</td>
<td>0.346</td>
<td>0.009</td>
</tr>
</tbody>
</table>

Ant indicates anterior; Lat, lateral; Inf, inferior; DCM, idiopathic dilated cardiomyopathy; CM, contact mapping; and NCM, noncontact mapping.

†Statistical difference between septal-basal and septal-apical at the level of significance $P<0.05$.

Figure 3. Distribution of LV transseptal and LV endocardial activation times as measured by both mapping systems. Shaded area marks border zone for binary distribution of transseptal time.
There was a statistically significant difference between patients with anterior and lateral line of blocks. Patients with a lateral line of block had the shortest QRS duration and transseptal time but the longest distance from the LV breakthrough site to line of block (Table 4).

The 3 patients on amiodarone showed activation sequences and activation times similar to those of the other patients.

**LV Activation Pattern During Asynchronous Ventricular Pacing**

Pacing at any cycle length (600 and 400 ms) from any attempted site within the coronary veins or from the apex of the RV was able to shift the line of block identified during intrinsic rhythm (Figure 4), indicating a functional behavior of this line. A large individual variability in both length and location of the line of block during pacing was noted. Accordingly, the fragmented local electrograms recorded during intrinsic rhythm along the line of block were no longer present during pacing (Figure 2), and there was an immediate reversibility of the electrogram morphology at the end of pacing. Occasionally, the line of block was no longer detectable during asynchronous pacing (Figure 4).
Discussion
We have demonstrated that patients with LBBB morphology have a specific “U-shaped” activation sequence that turns around the apex and inferior wall of the LV. This activation pattern is generated by a functional line of block that is oriented from the base toward the apex of the LV. The location and length of the line of block are highly variable but related to the site and time of LV breakthrough. Patients with QRS duration <150 ms demonstrate a line of block more frequently located in the lateral region of the LV.

Left Bundle-Branch Block
Our data show that surface ECG recordings are unable to precisely characterize the location and extent of specific ventricular delays. Consistent with previous data,1-3 our observations substantiate that LBBB is a rather complex electrical disease resulting from conduction delay located at several anatomic levels of the activation sequence. Prolongation of transseptal time in patients with LBBB has been described consistently1-3; we found that approximately one third of the patients with an LBBB QRS morphology had normal transseptal time and slightly prolonged or near-normal LV endocardial activation times. Therefore, the LBBB morphology emerged primarily from a prolongation of the intramural activation time.

Whereas the QRS duration demonstrated a continuous distribution, the transseptal time demonstrated a binary distribution with a border zone between 20 and 40 ms. The abrupt change in the transseptal time was correlated to a change in the LV breakthrough site, which suggests that LV breakthrough presenting at anterior or septobasal locations may proceed through one or more septal branches of the His-Purkinje system. In contrast, patients with a significantly prolonged transseptal time showed a midseptal or septoapical LV breakthrough site, which may indicate a cell-to-cell activation sequence from right ventricle to LV.

Usefulness of Unipolar and Bipolar Recording
The difference in physical meaning for unipolar and bipolar recording is particularly useful for more precisely evaluating whether an electrophysiological phenomenon occurs in the subendocardium or has an intramural origin. A similarly prolonged LV endocardial activation time was demonstrated in patients with different anatomic locations of the line of block identified with unipolar signals, which contrasted with the lack of a line of block with bipolar signals. This may suggest that the largest conduction delay is located more intramurally than subendocardially. Supportive evidence is provided by (1) a consistent reduction of the activation velocity in regions with fragmented, low-amplitude, bipolar potentials and (2) a high visual morphological correlation between virtual electrograms and unipolar signals recorded by both the LV endocardial mapping catheter and the epicardially placed Cardima catheters, suggesting that the virtual unipolar signal may retain and reveal intramural activation.

Therefore, we hypothesize that a functional line of block emerges in these cases from anisotropic conduction given by variation in alignment of subendocardial and myocardial layers of tissue, each with potentially different characteristics of conduction. Apparently, the entry site of both spontaneous and paced activation is capable of “unmasking” regional changes in layer alignment or local electrophysiological properties, thus showing new lines of functional block.

Site of LV Breakthrough Predicts the Location of Line of Block
Patients with an anterior or septobasal LV breakthrough site showed the shortest transseptal time and longest distance from the LV breakthrough site to line of block; both of these measures resembled those occurring in patients with healthy ventricle without ventricular conduction delay.1 Therefore, patients with HF, dilated cardiomyopathy, and abnormal QRS morphology and duration who exhibit an anterior or septobasal LV breakthrough site present with a lesser degree of electrical disarrangements between the 2 ventricles and within the LV. Although we did not measure conduction velocity, the fact that these patients had a significantly shorter, yet abnormal QRS duration and a significantly longer distance from the LV breakthrough site to line of block suggested that the conduction velocity in those patients is slightly prolonged.

The turning point of the U-shaped activation front was near the apex in all patients, even though the LV breakthrough site and distance from the LV breakthrough site to line of block varied significantly across the anterior and apical regions. This suggests that the anterior and the anterolateral regions of the LV may be more prone to anisotropy than any other region.

Functional Line of Block in LBBB
Unlike fixed anatomic obstacles, the ability to change the location and length of the line of block during asynchronous pacing from regions both adjacent to and remote from the line strongly supports a functional basis for these lines of block, which is further substantiated by the facts that (1) two thirds of the patients had idiopathic cardiomyopathy, thus lacking the presence of ischemic myocardial scar associated with morphologically based conduction delay and block, and presented the same patterns as patients with coronary artery disease; (2) both local electrograms recorded with both mapping techniques demonstrated fractionation, considered to be markers for anisotropic conduction, that disappeared when pacing was applied; and (3) the near-normal amplitude of both unipolar and bipolar electrograms in the region surrounding the line of block noted in the contact mapping further excludes the presence of myocardial scar.

Clinical Implications for Cardiac Resynchronization Therapy
Previous hemodynamic acute data showed that patients with QRS duration <150 ms had less acute benefit than patients with a QRS duration ≥150 ms. For the first time, our data provide evidence of a more homogeneous electrical activation process, especially in patients with QRS complex <150 ms, as indicated by a shorter transseptal time and a longer distance from the LV breakthrough site to line of block. That may result in the reported lower likelihood of improving LV ventricular function during acute resynchronization therapy.10,11 The finding that patients with LBBB QRS morphology, independent of the duration of the QRS complex, may have an anterior, lateral, or inferior line of block substantiated the
remarkable heterogeneity of LBBB and correlated well with recent echocardiographic observations of variable regions of mechanical delay in patients selected for cardiac resynchronization therapy.\textsuperscript{12,13} Notably, approximately two thirds of the patients with QRS duration $<150$ ms showed a laterally located line of block, suggesting that pacing should be located in a more basal site (ie, close to the takeoff of the vein from the coronary sinus). Unlike noninvasive imaging techniques, 3D mapping may be particularly helpful in locating and assessing the most effective pacing site in patients with QRS durations $<150$ ms by obtaining the best match between anatomic course of the coronary veins and the recorded electrical delay.

Limitations
Apart from electrical data, no physically independent morphological or structural information was collected in the LV. All measurements presented refer to electrical activation and not to any mechanical effect of abnormal conduction delay. However, it is very likely that the electromechanical uncoupling may further amplify regional and global asynchrony generated by electrical abnormalities.

Conclusions
Three-dimensional mapping is effective in the precise characterization of LV activation in terms of the global activation sequence as well as regional duration, velocity, and functional behavior in patients with HF, dilated cardiomyopathy, and LBBB morphology. Routine clinical application of 3D mapping may be warranted in such patients before implantation of cardiac resynchronization therapy devices. Because of the highly functional nature of the line of block, “blind” selection of pacing sites may unintentionally shift the dyssynchrony to a different location, thus potentially worsening the clinical condition. Unipolar mapping, such as applied in a noncontact mapping system, may be more effective than bipolar mapping for individualized identification and assessment of optimal pacing sites for cardiac resynchronization therapy.

References
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*Circulation*. 2004;109;1133-1139; originally published online March 1, 2004;
doi: 10.1161/01.CIR.0000118502.91105.F6
*Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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http://circ.ahajournals.org/content/109/9/1133

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