Delay in Right Ventricular Activation Contributes to Brugada Syndrome

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Background—Although Brugada syndrome revolves around reduced net depolarizing force, the electrophysiological mechanisms of its defining features (right precordial ST-segment elevation and ventricular tachyarrhythmias) remain unresolved. Two proposed mechanisms are (1) right ventricular (RV) conduction delay and (2) selective and significant RV subepicardial action potential shortening. Both mechanisms must cause disparate contractile changes: delay in RV contraction and reduction of contractile force, respectively. We aimed to establish the electrophysiological mechanism of Brugada syndrome by studying the timing and force of RV contraction.

Methods and Results—Using tissue Doppler echocardiography, we studied how these contractile variables change on induction of the characteristic ST-segment changes of Brugada syndrome by flecainide challenge. Accordingly, we studied patients in whom flecainide induced these changes (inducible) and those in whom these changes were not induced (control). We found that (1) the occurrence of a positive response (coved-type ST elevation) after flecainide coincides with delay in the onset of contraction between the RV and left ventricle (LV); (2) the extent of contraction delay between RV and LV correlates with the magnitude of ST elevation; and (3) RV ejection time (duration of RV ejection phase) shortens as the Brugada ECG pattern emerges.

Conclusions—These results indicate that both proposed mechanisms of Brugada syndrome may be operative. (Circulation. 2004;109:1272-1277.)

Key Words: arrhythmia ■ Brugada syndrome ■ conduction ■ death, sudden ■ electrophysiology

Brugada syndrome is an inherited, autosomal dominant disorder characterized by sudden death from ventricular tachyarrhythmias, ECG right precordial ST-segment elevation, and conduction slowing.1,2 Although its pathophysiological mechanisms are unresolved, clinical observations place the right ventricle (RV) at the heart of this syndrome: ST-segment elevation is present only in right precordial leads, ventricular ectopy initiating tachyarrhythmias originates from the RV,3-6 ventricular arrhythmias are more easily induced from the RV (particularly the RV outflow tract, RVOT) than the left ventricle (LV),3,4 and body surface mapping shows RV conduction slowing.7

Some consider Brugada syndrome an RV cardiomyopathy.8-10 However, no structural anomalies are usually detected by routine imaging and endomyocardial biopsy.1,2,11 Thus, it was proposed that Brugada syndrome is a primary electrical disease. This hypothesis was greatly boosted by the discovery that 30% of patients have a mutation in SCN5A, the gene encoding the pore-forming α-subunit of the cardiac sodium (Na) channel.12 So far, SCN5A is the only gene with a proven involvement. The mutant Na channels conduct less Na current.13 Furthermore, the ECG abnormalities and tachyarrhythmias are exacerbated/provoked by Na channel blockers. Accordingly, the proposed electrophysiological mechanisms revolve around reduction of net depolarizing forces.14,15 Two hypotheses were raised. One hypothesis, supported by clinical7,16-21 and modeling studies,22 ascribes the ECG features and arrhythmias to conduction delay. Asynchronous activation of subendocardial and subepicardial cells creates voltage gradients between these cells, which drive electrotonic current, causing ST-segment elevations and arrhythmias based on transmural phase 2 reentry.14 The second hypothesis, equally strongly supported by clinical23 and experimental24 studies, ascribes reduction of net depolarizing forces to an imbalance between depolarizing and repolarizing currents. This hypothesis holds that during phase 1 of the subepicardial action potential, Na current reduction allows the transient outward current, Ito, to repolarize the membrane beyond the voltage range in which L-type calcium (Ca) channels are activated. Failure of L-type Ca channels to activate results in loss of the action potential plateau. Because Ito is not expressed in subendocardial cells, the action potential plateau is preserved here. The resulting disparity in action potential duration drives electrotonic current, ST-segment...
elevation, and tachyarrhythmias. In both hypotheses, the preferential involvement of the RV over the LV is less readily explained. It may follow from the fact that the subepicardium constitutes a larger proportion of the total mass in the RV than in the LV. Furthermore, \( I_n \) is more strongly expressed in RV subepicardium than in LV subepicardium.

Given that both proposed electrophysiological mechanisms must cause disparate contractile changes, analyzing these changes may aid in elucidating the electrophysiological basis of Brugada syndrome. Conduction slowing must delay the onset of contraction, whereas loss of action potential plateau must abolish contractions of subepicardial cells, because Ca-induced Ca release from the sarcoplasmic reticulum is absent. Accordingly, electron-beam CT scan studies found gross regional wall motion abnormalities in the RV, particularly the RVOT (but not the LV), that were exacerbated by Na channel blockers. However, these studies did not distinguish whether these wall motion abnormalities resulted from delayed activation causing asynchronous contraction, reduced contractile force, or both.

We aimed to explore both proposed electrophysiological mechanisms by establishing the timing and force of contraction of RV and LV using tissue Doppler echocardiography (TDE). We conducted TDE during flecainide challenge in patients in whom flecainide induced the characteristic ECG pattern and in those in whom flecainide did not evoke this pattern. We also conducted TDE in patients with this pattern at baseline. TDE performed through analysis of digitally stored raw data are well suited for this purpose, because the timing and force of contraction of multiple sites within the RV and LV can be analyzed synchronously at a high temporal and spatial resolution. Importantly, although TDE is noninvasive, it provides direct assessment of distinct intramural regions, and it can be linked to concurrent ECG recording. It complements previous modalities that have the inherent limitation of lacking information on contraction timing and velocity (CT scan) or being indirect (signal-average ECG, body surface mapping), invasive (catheterization), or incapable of assessing multiple sites synchronously.

### Methods

**Patients**

We studied 29 consecutive patients in one hospital (Academic Medical Center). There were 3 groups, as follows. (1) “Inducible” (n=10, 5 men, average age 44 years): those in whom flecainide challenge (2 mg/kg in 10 minutes) provoked a positive ECG response according to current criteria (type 1, coved-type). These patients were screened because Brugada syndrome was diagnosed in a relative by typical ECG features with sudden death and/or inducible ventricular tachyarrhythmias during electrophysiological testing. At baseline, 4 patients had type 2 ST segments, and 5 had type 3 ST segments. These types constitute a classification system for the severity and specificity of ST-segment aberrations in Brugada syndrome, where type 1 is the most severe form and type 3 the mildest. Six patients had a SCN5A mutation. (2) “Control” (n=13, 6 men, 41 years): those in whom flecainide challenge did not induce typical ECG changes. These patients were studied because history, family history, or ECG raised a suspicion of Brugada syndrome; one had a type 2 ECG and 12 a type 3 ECG at baseline. (3) “Baseline positive” (n=6, 6 men, 57 years): these patients had aborted sudden death and/or inducible ventricular tachyarrhythmias and typical ECG features at baseline (type 1); consequently, they did not receive flecainide. All patients had a normal 2D echocardiogram without regional RV/LV wall motion abnormalities, RV/LV dilation, hypertrophy, or more than minimal valve insufficiency. No patient took antiarrhythmic drugs.

**Tissue Doppler Echocardiography**

Imaging was performed with a 2.5-MHz phased array transducer. TDE images were acquired during end-expiratory apnea at baseline and at the maximal flecainide dose in control subjects (average dose 141±4.4 mg) or the dose that elicited a positive response in inducible patients (111±13.4 mg). In baseline positive patients, only baseline recordings were obtained. We used an apical view and optimized the alignment of the RV/LV free walls and interventricular septum (IVS) with the ultrasound beam. Sector angle and settings were adjusted to obtain frame rates exceeding 120 frames/s. A cine loop of 2 consecutive heartbeats was stored on magneto-optical discs.

### Main Electrocardiogram and Tissue Doppler Echocardiogram Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Inducible Baseline</th>
<th>Flecainide</th>
<th>Control Baseline</th>
<th>Flecainide</th>
<th>Baseline Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, ms</td>
<td>67 (4.6)</td>
<td>71 (3.2)</td>
<td>68 (2.2)</td>
<td>71 (1.7)</td>
<td>76 (8.7)</td>
</tr>
<tr>
<td>PR, ms</td>
<td>182 (8.7)*</td>
<td>203 (7.6)*</td>
<td>151 (6.6)</td>
<td>179 (5.3)</td>
<td>175 (11.4)</td>
</tr>
<tr>
<td>QRS, ms</td>
<td>108 (4.8)*</td>
<td>128 (5.6)</td>
<td>92 (3.0)</td>
<td>117 (3.0)</td>
<td>106 (5.5)</td>
</tr>
<tr>
<td>Shortest QT, ms</td>
<td>381 (16.4)</td>
<td>392 (8.7)</td>
<td>379 (7.4)</td>
<td>394 (8.5)</td>
<td>336 (19.9)</td>
</tr>
<tr>
<td>Longest QT, ms</td>
<td>411 (14.0)</td>
<td>437 (12.7)</td>
<td>402 (9.9)</td>
<td>418 (8.4)</td>
<td>391 (23.9)</td>
</tr>
<tr>
<td>QT dispersion, ms</td>
<td>30 (5.5)</td>
<td>45 (10.7)</td>
<td>23 (3.6)</td>
<td>32 (9.1)</td>
<td>55 (8.8)*</td>
</tr>
<tr>
<td>Maximal ST, mm</td>
<td>1.9 (0.5)</td>
<td>3.6 (0.5)*</td>
<td>1.0 (0.2)</td>
<td>1.2 (0.1)</td>
<td>4.4 (0.7)*</td>
</tr>
<tr>
<td>Delay in contraction onset between RV and LV, ms</td>
<td>19.5 (7.2)*</td>
<td>44.5 (4.0)*</td>
<td>1.9 (3.0)</td>
<td>2.7 (2.6)</td>
<td>40.5 (1.8)*</td>
</tr>
<tr>
<td>Reduction of RV peak systolic velocity, %</td>
<td>...</td>
<td>19.4 (7.2)</td>
<td>...</td>
<td>22.5 (5.7)</td>
<td>...</td>
</tr>
<tr>
<td>Reduction of LV peak systolic velocity, %</td>
<td>...</td>
<td>14.4 (6.1)</td>
<td>...</td>
<td>16.3 (6.4)</td>
<td>...</td>
</tr>
<tr>
<td>RV ejection time, ms</td>
<td>300 (9.3)</td>
<td>273 (11.2)*</td>
<td>306 (5.3)</td>
<td>302 (4.6)</td>
<td>257 (22.9)*</td>
</tr>
<tr>
<td>LV ejection time, ms</td>
<td>306 (11.1)</td>
<td>298 (7.1)</td>
<td>300 (5.6)</td>
<td>299 (2.8)</td>
<td>282 (26.4)</td>
</tr>
</tbody>
</table>

Values are mean (SEM). *P*<0.05 vs corresponding value in the control group for measurements at baseline according to Scheffé’s multiple comparison test and according to Student's t test for values after flecainide.
Images were analyzed offline at a PC workstation using custom software. TDE analysis was conducted concurrently by 2 investigators (R.T. and P.S.). Results from this analysis were accepted only if both investigators reached consensus. Of note, both investigators were blinded to the ECG. Three sample areas were positioned in the annular plane of the IVS, the RV free wall, and the LV free wall. Three sample areas were in the respective midventricular segments. Using tissue Doppler analysis, we measured (1) delay in onset of ventricular ejection (at the end of the isovolumetric ejection phase) between the RV and IVS regions and (2) peak systolic velocities. The time differences between pulmonary valve opening and closure and aortic valve opening and closure were measured by color M-mode through the tricuspid and mitral valves (RV and LV ejection times, respectively). Values were expressed as the mean of the measurements from 2 transferred beats.

Electrocardiography
Concurrent with echocardiography, we studied ECGs at baseline and after flecainide. A routine 12-lead ECG was recorded, with leads V₁ and V₂ positioned above the third intercostal space cranially from V₁ (V₁ICS) and V₂ (V₂ICS), respectively. ST-segment elevation was measured at the nadir of the ST segment if a positive flecainide response was elicited (type 127) or 80 ms past the J point if the flecainide test was negative. Maximal ST-segment elevation was the highest ST elevation among leads V₁, V₅, V₆, V₁ICS, and V₂ICS. QT durations were measured in all leads from the onset of QRS to the intersection of the tangent to the steepest terminal part of the T wave with the isoelectric line. The longest and shortest QT duration among the 12 leads were recorded; their difference was QT dispersion.

Statistical Analysis
Values are expressed as mean±SEM. Group differences at baseline were analyzed by 1-way ANOVA followed by Scheffé’s multiple comparison test. Group differences after flecainide were analyzed by 2-tailed Student’s t test. Statistical significance was defined as \( P < 0.05 \).

Results
Conduction Slowing
Inducible patients had longer PR and QRS intervals at baseline than control subjects, in accordance with reduced net depolarizing force. Because of its Na channel–blocking effect, flecainide caused overall conduction slowing in both groups, as evidenced by PR and QRS prolongation (Table). However, TDE revealed that conduction slowing was more severe in the RV than the LV in inducible patients. Figure 1 shows typical TDE findings at baseline and on flecainide.
challenge in a control (A and B) and an inducible (C and D) patient. On average, on development of the Brugada ECG pattern, systolic RV movement started 44.5 ms after LV (Table, Figure 2). A similar delay was found in patients with a baseline positive ECG (40.5 ms) but was absent from control subjects (1.9 ms). Although delay of RV contraction onset at baseline was, on average, longer in inducible patients (19.5 ms) than in control subjects (1.9 ms), there was too much overlap to correctly stratify individual patients into each group before flecainide testing. In contrast, after flecainide, a >20-ms delay between LV and RV contraction onset had 100% specificity and 100% sensitivity in separating patients from both groups. Providing further support for the hypothesis that RV activation slowing strongly contributes to the Brugada ECG pattern, delay in contraction onset between LV and RV correlated with the severity of ST-segment elevation on flecainide (Figure 3; correlation coefficient $r=0.80$, $P<0.0001$).

Reduction of Tissue Systolic Velocities
Flecainide reduced tissue systolic velocities to the same extent in the RV and LV in inducible patients and control subjects (Table). Similarly, delay in contraction onset between LV and RV did not correlate with reduction in RV peak systolic velocity in either group (correlation coefficient $=0.40$, $P=0.07$). These findings did not support the hypothesis that significant shortening of (RV subepicardial) action potentials causes Brugada syndrome. Also, ECG analysis provided no support, because flecainide changed QT variables equally (mild QT prolongation) in both groups (Table). However, support did arise from the observation that, after flecainide, ejection time (the duration of the ejection phase, which diminishes as action potential duration shortens$^{28}$) of RV, but not LV, was significantly shorter in inducible patients than control subjects (Table, Figure 4).

Discussion
RV Conduction Slowing
We found novel evidence to confirm that Brugada syndrome is associated with RV conduction slowing. Furthermore, the linear correlation between delay of RV contraction onset and ST elevation strongly supported the hypothesis that conduction slowing contributes to the Brugada ECG. The magnitude of delay in RV contraction (compared with LV contraction) on flecainide challenge in inducible patients was similar to RV contraction delay in patients with typical ST elevations at baseline (baseline positive). Interestingly, this delay was also similar to the timing of late potentials and delayed potentials from the RVOT subepicardium in Brugada patients, as reported previously,$^{18}$ suggesting that these potentials represent delayed RV activation. Our finding that conduction is more strongly impaired in RV than LV, both at baseline and after the occurrence of typical ST elevations on flecainide, corroborates previous direct and indirect observations on preferential RV involvement in Brugada syndrome. Of particular interest is a case report of 2 Brugada syndrome patients, which showed that the regions in which RV activation delay was found by endocardial monophasic action
potential recordings corresponded to the regions in which ST elevations were found (right precordial leads in one patient and inferior leads in the other). Additional published evidence for a pivotal role of conduction slowing includes the following. Clinically, late potentials are consistently found in signal-averaged ECGs. They have a higher prevalence in Brugada syndrome patients, are associated with malignant (coved-type) ST elevations, and are exacerbated by flecainide. They and other markers of slow conduction are associated with stronger inducibility of ventricular tachyarrhythmias. Also, body surface mapping indicates slow conduction in the RV. Finally, in modeling studies, Brugada syndrome ECGs and tachyarrhythmias are induced by conduction slowing.

**Action Potential Shortening**

We also explored the other major proposed electrophysiological mechanism of Brugada syndrome: selective and significant RV subepicardial action potential shortening. We found less unequivocal evidence to support this hypothesis. We did not find QT shortening when ST elevations occurred. Instead, we observed mild QT prolongation, in accordance with the known effects of flecainide, which was of the same magnitude in inducible patients and control subjects. More importantly, we did not detect stronger impairment of tissue systolic velocities (a derivative of contractile force) in RV than LV on development of ST elevation, arguing against selective RV action potential shortening. We did, however, find that ejection time of RV but not LV was significantly shorter after flecainide in inductive patients than control subjects. Shortening of RV ejection time cannot be explained by RV activation delay alone, because previous echocardiographic studies have established that RV ejection time is unaltered in subjects with idiopathic right bundle-branch block (ie, in the absence of heart disease). Given that ejection time is determined by preload, afterload, contractile force, and action potential duration, reduced RV (but not LV) ejection time may signify RV action potential shortening, because preload and afterload were unchanged and RV and LV systolic velocities were equally reduced. In further support of the concept that reduced ejection time may signify reduced Ca influx is an echocardiographic study of patients with inherited long-QT syndrome. Here, it was shown that prolongation of late systolic wall thickening (in comparison with control subjects) was reversed by L-type Ca channel blockers, thereby suggesting that this prolongation of ventricular ejection results from (excessive) Ca influx.

**Study Limitations**

Although TDE is a powerful tool to obtain qualitative insights into the electrophysiological basis of Brugada syndrome, it carries some limitations. First, the RVOT is not readily accessible to TDE and therefore was not included in this study. This may explain why the observed conduction delay, although clearly more prominent in RV than LV, was smaller than theory would require for the generation of the Brugada ECG. Given that the most significant alterations in Brugada syndrome (including wall motion abnormalities) are mapped to the RVOT, this region may harbor larger RV activation delay. It is thus likely that the observed conduction delay of the gross RV is an underestimation of RVOT conduction delay, which is ultimately responsible for Brugada syndrome. Second, the hypothesis that holds that Brugada syndrome is caused by loss of RV action potential plateau in subepicardium but not subendocardium cannot be readily tested, because TDE does not allow separate assessment of RV subepicardium and subendocardium. Still, indirect measures of action potential duration (LV/RV ejection times) did support this hypothesis. Taken together, it is likely that the limitations of present TDE technology have resulted in an underestimation of the differences between critical regions (RVOT, subepicardium) and the remainder of the heart and that alleviation of these limitations would serve to reveal the true magnitude of these differences and further strengthen our conclusions. It is conceivable that the baseline differences in delay of RV contraction between inducible patients and control subjects would prove to be significantly larger than in the present analysis and that the overlap between both groups would be strongly reduced or absent. In that case, TDE analysis at baseline may be sufficient to make the diagnosis of Brugada syndrome in individual patients without the need for flecainide challenge. At present, flecainide challenge is still required in this patient category.

**Conclusions**

We provided novel evidence that the ECG features of Brugada syndrome are caused largely by RV activation delay. The strongest evidence emanates from the observation that the magnitude of ST elevation correlates with the extent of RV activation delay. We also found support for a role of RV action potential shortening in Brugada syndrome in the novel finding that RV ejection time is reduced when typical ST elevations occur.

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