Slow and Discontinuous Conduction Conspire in Brugada Syndrome
A Right Ventricular Mapping and Stimulation Study

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Background—Brugada syndrome (BrS) is associated with lethal arrhythmias, which are linked to specific ST-segment changes (type-1 BrS-ECG) and the right ventricle (RV). The pathophysiological basis of the arrhythmias and type-1 BrS-ECG is unresolved. We studied the electrophysiological characteristics of the RV endocardium in BrS.

Methods and Results—RV endocardial electroanatomical mapping and stimulation studies were performed in controls (n=1100512) and BrS patients with a type-1 (BrS-1, n=10) or type-2 BrS-ECG (BrS-2, n=12) during the studies. BrS-1 patients had prominent impairment of RV endocardial impulse propagation when compared with controls, as represented by: (1) prolonged activation-duration during sinus rhythm (86±4 versus 65±3 ms), (2) increased electrogram fractionation (1.36±0.04 versus 1.15±0.01 deflections per electrogram), (3) longer electrogram duration (83±3 versus 63±2 ms), (4) activation delays on premature stimulation (longitudinal: 160±26 versus 86±9 ms; transversal: 112±5 versus 58±6 ms), and (5) abnormal transversal conduction velocity restitution (42±8 versus 18±2 ms increase in delay at shortest coupling intervals). Wider and more fractionated electrograms were also found in BrS-2 patients. Repolarization was not different between groups.

Conclusions—BrS-1 and BrS-2 patients are characterized by wide and fractionated electrograms at the RV endocardium. BrS-1 patients display additional conduction slowing during sinus rhythm and premature stimulation along with abnormal transversal conduction velocity restitution. These patients may thus exhibit a substrate for slow and discontinuous conduction caused by abnormal active membrane processes and electric coupling. Our findings support the emerging notion that BrS is not solely attributable to abnormal electrophysiological properties but requires the conspiring effects of conduction slowing and tissue discontinuities. (Circ Arrhythmia Electrophysiol. 2008;1:379-386.)

Key Words: arrhythmia ■ electrophysiology ■ mapping ■ Brugada syndrome ■ sudden cardiac death

Brugada syndrome (BrS) is an inheritable syndrome associated with sudden cardiac death (SCD) by ventricular tachycardia or fibrillation (VT/VF).1 It predominantly affects the right ventricle (RV), as ECG abnormalities are found in right precordial leads, and VT/VF mostly arises in the RV.1 The signature ECG-change, which is required for the diagnosis and linked to VT/VF, is a coved-type ST elevation in V1-V3 (type-1 BrS-ECG) and may occur spontaneously. Also, drug challenge with sodium channel blocking drugs (eg, ajmaline) may lead to the diagnosis when it causes conversion of a normal or type-2 ECG into a type-1 BrS-ECG.1

BrS has been regarded a primary electric disease because gross structural abnormalities are undetectable by clinical imaging. However, the pathophysiological basis of the type-1 BrS-ECG and VT/VF is unresolved. There are 2 leading hypotheses (reviewed in Ref. 2): the depolarization disorder hypothesis, ie, RV conduction delay,3,4 and the repolarization disorder hypothesis, ie, transmural dispersion of RV action potential morphology.5 Up to 30% of BrS patients carry loss-of-function mutations in SCN5a1,6 the gene which encodes the cardiac sodium channel α-subunit that drives impulse conduction. Recently, RV interstitial derangements (myocarditis, cardiomyocyte vacuolization, fibrofatty infiltration) were found in endomyocardial biopsies of BrS patients.7 These derangements, even when undetectable by clinical imaging, may result in increased electric coupling resistance that impairs impulse propagation and act as arrhythmogenic
substrate. Accordingly, in the explanted heart of a SCN5a-mutation carrying BrS patient,8 we found RV fibrosis, fatty infiltration, conduction slowing, and reentrant arrhythmias. The adverse electrophysiological manifestations linked to these interstitial changes were particularly evident by analysis of conduction velocity (CV) restitution.5–11 This analysis revealed abnormally strong conduction slowing on premature stimulation. Thus, CV-restitution analysis may uncover how conduction slowing and increased coupling resistance or tissue discontinuities interact in the pathophysiology of BrS.

The aim of the present study was to further investigate the electrophysiological characteristics of RV endocardium in BrS patients. We hypothesized that the type-1 BrS-ECG and associated arrhythmias are based on impaired impulse propagation, which may be linked to increased coupling resistance. Furthermore, BrS patients may have a different arrhythmogenic substrate at the time when they have a type-1 BrS-ECG than at periods when they do not. Accordingly, we conducted electrophysiological studies in BrS patients when they had a type-1 BrS-ECG or when they had a type-2 BrS-ECG, and in controls, to assess RV electrogram characteristics during sinus rhythm (endocardial mapping) and during premature stimulation (CV-restitution).

Methods

Patients

In this prospective single-center study, 34 patients were included: 22 BrS patients and 12 controls. The diagnosis BrS was made according to the consensus criteria1 and required documentation of a type-1 BrS-ECG, either spontaneously present or provoked by sodium channel blocking drugs in conjunction with either: documented VT/VF, family history of SCD, either spontaneously present or provoked by sodium channel blocking drugs in conjunction with either: documented VT/VF, family history of SCD, or documented or suspected VTs (syncope or multiple near-syncope not otherwise explained). Controls needed a normal VT/VF, family history of SCD, or documented or suspected VTs (syncope or multiple near-syncope not otherwise explained). Controls needed a normal tissue discontinuities interact in the pathophysiology of BrS.

Because of the variable nature of the BrS-ECG,1 BrS patients were classified according to their ECG at the time of the studies. Consequently, 3 patient groups were studied: (1) “BrS-1 patients”: BrS patients with a type-1 BrS-ECG during the studies (n=10); (2) “BrS-2 patients”: BrS patients with a type-2 BrS-ECG during the studies (n=12); and (3) “controls” (n=12) (Table 1).

Table 1. Group Characteristics

<table>
<thead>
<tr>
<th></th>
<th>BrS-1 (n=10)</th>
<th>BrS-2 (n=12)</th>
<th>Control (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>46±3</td>
<td>50±3</td>
<td>53±3</td>
</tr>
<tr>
<td>Male</td>
<td>10 (100%)</td>
<td>10 (83%)</td>
<td>8 (67%)</td>
</tr>
<tr>
<td>Syncope/aborted SCD</td>
<td>3 (30%)</td>
<td>6 (50%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Nonsustained ventricular tachycardia</td>
<td>1 (10%)</td>
<td>1 (8%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Multiple episodes near-syncope</td>
<td>4 (40%)</td>
<td>4 (33%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Nocturnal agonal respiration</td>
<td>1 (10%)</td>
<td>2 (17%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Palpitations</td>
<td>2 (20%)</td>
<td>2 (17%)</td>
<td>12 (100%)</td>
</tr>
<tr>
<td>Family history BrS/SCD</td>
<td>5 (50%)</td>
<td>7 (58%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>SCN5a mutation</td>
<td>6 (60%)</td>
<td>2 (17%)</td>
<td>NA</td>
</tr>
</tbody>
</table>

Data are mean±SE or No. (% of patients).

BrS indicates Brugada syndrome; NA, not analyzed; SCD, sudden cardiac death.

Were performed first because the stimulation studies carried with them the risk of VT/VF induction.

Cardiac MRI, including delayed gadolinium-enhanced imaging, was performed in all but 4 BrS patients. MRI was not available before implantable cardioverter defibrillator-implantation/catheterization in 3 BrS patients and was refused by 1 BrS patient. Echocardiography was performed in these BrS patients and also in all controls. Molecular genetic analysis of SCN5a was performed in all BrS patients. Patients were not sedated, and all antiarrhythmic drugs were discontinued for at least 5 half-lives. Studies in controls were performed after successful radiofrequency ablation.

CARTO Mapping

Electroanatomical mapping of the complete endocardial RV was performed during sinus rhythm with CARTO (Biosense-Webster) and a locatable mapping catheter (Navistar 4 mm/8F, Biosense-Webster). Care was taken to perform endocardial mapping at random throughout the RV.

A reference locator pad under the patient’s back was used for spatial reference, and ECG lead II as time reference. Signals were analyzed off-line by at least 2 investigators using specially developed software12 on Matlab R2006b (MathWorks). The investigators were blinded to catheter location, and consensus was required for each electrogram. Only sinus node driven beats were included. Electrograms were excluded if their technical quality was insufficient or if catheter-induced right bundle branch block or extrasystoles occurred. We obtained 3 groups of RV electrogram properties: (1) activation, (2) fractionation and duration, and (3) repolarization. Three-dimensional reconstructions of these measurements, using the spatial information enclosed within CARTO, were studied. For this purpose, 4 regions within the RV were defined: RV-outflow tract (RVOT, upper 25% of RV), RV-apex (lower 25% of RV), RV-free wall, and RV-septum.

To study activation, we assessed activation time (AT), defined as the interval (milliseconds) from onset of QRS in lead II to the steepest negative dV/dt (≤−0.04 V/s) of the intrinsic deflection in the endocardial unipolar electrogram.13 To avoid selection of remote unipolar components, the timing of the steepest negative dV/dt in the unipolar electrogram had to correspond with a positive or negative deflection in the bipolar electrogram (Figure 1). Activation-duration was defined as the interval (milliseconds) between the earliest AT of any electrogram (activation-start) and the latest AT of any electrogram (activation-end). In the 3-dimensional model of activation (Figure 2), we assessed the presence of conduction block.

Fractionation of electrograms was defined as the presence of ≥2 intrinsic deflections with a dV/dt≤−0.04 V/s, separated by ≥10 ms, in the unipolar signal with corresponding deflections in the bipolar electrogram (Figure 1). Fractionation was expressed as mean number of intrinsic deflections per electrogram. Thus, fractionation index index =1 denotes no fractionation in any complex. Electrogram duration was
measured in the bipolar signal as the interval between the first and last deflection, and expressed as mean bipolar electrogram duration (milliseconds). The spatial distribution of these parameters was studied in the 3-dimensional reconstructions.

To study repolarization, we assessed local activation recovery interval (ARI) and repolarization time (RT). ARI, a measure of action potential duration, was defined as the interval (milliseconds) between AT and the end of recovery; the latter was determined in the unipolar signal as the largest positive dV/dt of the T-wave (Figure 1). RT was defined as AT + ARI (milliseconds). Electrograms with flat or distorted T-waves were excluded from repolarization analysis. Mean values of ARI and RT in each patient were used to compare global differences in ARI and RT. Standard deviations of ARI and RT were used to compare dispersion in ARI and RT.

Stimulation Studies
CV-restitution was assessed with the use of a quadrupolar pacing catheter (Evaluator, 6F, St Jude Medical), a decapolar mapping catheter (MarinCIS, 7F, Medtronic; 5 electrode pairs separated by 2 mm, with 5 mm spacing between pairs), and the Prucka-Cardiolab (GE Medical Systems). To account for possible anisotropy in propagation at shorter coupling intervals (CI), we studied CV-restitution in 2 directions, which we estimated to be either parallel or perpendicular to the general RV endocardial fiber orientation and activation front (longitudinal and transversal CV-restitution, respectively). Longitudinal CV-restitution was assessed by positioning the mapping catheter longitudinally over the RV-free wall with the tip pointing toward the RVOT and stimulating with the pacing catheter from the RV-apex (Figure 3). We assessed transversal CV-restitution by positioning the mapping catheter circumferentially in the mid-RV free wall (Figure 3) and stimulating from its distal electrode pair. We paced at twice diastolic threshold using a drive train of 8 stimuli (S1) at a basic cycle length (BCL) of 500 ms, followed by a single premature stimulus (S2). The CI of S2 was reduced in steps of 10 ms from 400 to 200 ms or until the ventricular effective refractory period. Bipolar electrograms from the 5 electrode pairs were assessed for paced-AT, defined as the interval (milliseconds) from the stimulus to the intrinsic deflection (Figure 4). Paced-ATs were assessed off-line by at least 2 investigators, and consensus was required for each electrogram. Electrograms were excluded if their technical quality was insufficient or if fusion beats or spontaneous ventricular extrasystoles interfered with the drive train.

Each endocardial CV-restitution curve was described by 4 parameters (Figure 4): (1) paced-AT at BCL; (2) onset paced-AT increase (milliseconds), ie, the longest CI at which paced-AT exceeded paced-AT at BCL by 5 ms and continued to increase; (3) mean paced-AT increase (milliseconds), ie, the mean difference for all electrode pairs between paced-AT at BCL and the maximal paced-AT; (4) ventricular effective refractory period (milliseconds). The representation of CV-restitution at the body surface was described by 3 comparable parameters for paced-QRS duration in lead II: (1) paced-QRS at BCL (milliseconds); (2) onset paced-QRS increase (milliseconds), ie, the mean difference for all electrode pairs between paced-QRS at BCL and the maximal paced-QRS; (3) ventricular effective refractory period (milliseconds). The representation of CV-restitution at the body surface was described by 3 comparable parameters for paced-QRS duration in lead II: (1) paced-QRS at BCL (milliseconds); (2) onset paced-QRS increase (milliseconds), ie, the longest CI at which paced-QRS duration exceeded paced-QRS duration at BCL by 5 ms and continued to increase; (3) paced-QRS increase (milliseconds), ie, the difference between paced-QRS duration at BCL and the maximal paced-QRS duration.

Statistical Analysis
Statistical analyses were performed in SPSS 15.0. Variables were compared by 1-way ANOVA using a Tukey-HSD or Games-Howell multiple comparisons post hoc test depending on equality of vari-

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**Figure 1.** Electrogram analysis. Typical electrograms obtained simultaneously during CARTO mapping of a BrS-1 patient. A, ECG lead V1. B, Endocardial unipolar electrogram. C, Endocardial bipolar electrogram. Solid squares indicates moment of local activation; open circles, additional intrinsic deflections (fractionation index = 3); solid triangle, recovery; ARI, activation recovery interval; AT, activation time; ED, electrogram duration; RT, repolarization time; BrS, Brugada syndrome.

**Figure 2.** CARTO mapping. Typical 3-dimensional reconstructions in antero-posterior view of activation, fractionation, and electrogram duration of a BrS-1 patient (panels A, C, and E), and a control (panels B, D, and F). There is pronounced conduction slowing and increased electrogram fractionation and width in the BrS-1 patient. BrS indicates Brugada syndrome.
ances (Levene test). Categorical variables were compared by a Fisher exact or \( \chi^2 \) test when appropriate. The presence of a linear relationship between endocardial and body surface (ECG) CV-restitution curves was estimated with linear regression and Pearson correlations. A 2-sided significance level of 5% defined a statistically significant difference between groups. Continuous variables are presented as mean±SE. The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

Baseline Characteristics

Age and gender distributions were similar between groups. BrS-1 and BrS-2 patients had similar histories (Table 1). Cardiac imaging detected no gross structural abnormality in any patient. The proportion of patients with a SCN5A-mutation was larger among BrS-1 patients than among BrS-2 patients, but this difference was not statistically significant. Three BrS-1 patients had a SCN5A frameshift mutation leading to a truncated protein, whereas 3 other BrS-1 patients had a missense mutation. One BrS-2 patient had a frameshift mutation leading to a truncated protein whereas another had a missense mutation.

Sinus Rhythm: Activation

CARTO maps contained 81±6 mapping positions on an average, and ajmaline was used in 2 BrS-1 patients. In all patients, activation started in the lower septum/apex and subsequently diverged toward the tricuspid annulus and RVOT (Figure 2A and 2B). No apparent conduction block was observed in any patient. Yet, activation-duration was significantly longer in BrS-1 patients compared with controls (86 versus 65 ms) and activation-end was delayed (117 versus 81 ms; Table 2). In contrast, BrS-2 patients and controls had similar activation-durations and activation-ends. In the 2 BrS-1 patients in whom activation mapping was performed before and after a type-1 BrS-ECG was induced by ajmaline infusion, activation-duration increased by 20 ms on an
Sinus Rhythm: Repolarization

Neither mean heart rate, mean ARI or mean RT, nor dispersion of ARI or RT differed between BrS patients and controls (Table 2). In both patients who received ajmaline, conversion of their type-2 BrS-ECG to a type-1 BrS-ECG was associated with reductions in mean ARI (24 ms) and RT (10 ms) on an average, but no change in ARI or RT dispersion (−0.6 ms and +3.7 ms, respectively).

RV Stimulation: Conduction and CV-Restitution

Stimulation thresholds were within normal limits (<1 V) in all patients. Delivering premature stimuli at increasingly shorter CIs evoked an increase in paced-AT and paced-QRS at shortest CIs. A typical CV-restituation pattern of a BrS-1 patient is shown in Figure 4C and 4D. Endocardial and ECG CV-restitution curves were clearly related in all patients (Figure 4E and 4F). This relation was as follows for longitudinal propagation: mean slope=0.92±0.06, range Pearson-R=0.825 to 0.977. For transversal propagation: mean slope=1.19±0.15, range Pearson-R=0.44 to 0.95.

In line with the observations during sinus rhythm, stimulation at BCL evoked more conduction slowing in BrS-1 patients than in BrS-2 patients or controls, as evidenced by longer paced-AT during both longitudinal and transversal propagation (Table 3; 160 and 112 ms for BrS-1 versus 86 and 58 ms for controls, respectively). Accordingly, paced-QRS at BCL was longer in BrS-1 patients than in controls during both longitudinal and transversal propagation (224 and 230 ms for BrS-1 versus 159 and 152 ms for controls, respectively). Similar differences in paced-QRS at BCL, albeit smaller, were observed between BrS-2 patients and controls (184 and 188 ms for BrS-2, respectively). BrS-1 patients had abnormal CV-restitution with significantly larger increases in paced-AT than controls during transversal propagation at shortest CIs (42 versus 18 ms). In contrast, there were no differences between groups with respect to ventricular effective refractory period, increase in paced-AT for longitudinal propagation, or the onset of paced-AT increase for either longitudinal or transversal propagation. During RV-apex stimulation for longitudinal CV-restitution analysis, VF was induced in 1 BrS-2 patient.

Table 2. CARTO Mapping

<table>
<thead>
<tr>
<th></th>
<th>BrS-1 (n=9)</th>
<th>BrS-2 (n=10)</th>
<th>Control (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activation-duration</td>
<td>86±4*†</td>
<td>65±4</td>
<td>65±3</td>
</tr>
<tr>
<td>Activation-start</td>
<td>31±5</td>
<td>20±3</td>
<td>17±2</td>
</tr>
<tr>
<td>Activation-end</td>
<td>117±8*†</td>
<td>85±4</td>
<td>81±2</td>
</tr>
<tr>
<td>Fractionation index</td>
<td>1.36±0.04*</td>
<td>1.38±0.06‡</td>
<td>1.15±0.01</td>
</tr>
<tr>
<td>Mean bipolar electrogram duration</td>
<td>83±3*</td>
<td>76±2‡</td>
<td>63±2</td>
</tr>
</tbody>
</table>

Data are mean±SE. ANOVA post hoc test: *P<0.05 for BrS-1 vs control; †P<0.05 for BrS-1 vs BrS-2; ‡P<0.05 for BrS-2 vs control.

ARI indicates activation recovery interval; BrS, Brugada syndrome; RT, repolarization time.

average when their type-2 BrS-ECG turned into a type-1 BrS-ECG.

Table 3. Stimulation Studies

<table>
<thead>
<tr>
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<th>BrS-1 (n=5)</th>
<th>BrS-2 (n=9)</th>
<th>Control (n=5)</th>
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<tbody>
<tr>
<td>Longitudinal</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Paced-AT BCL</td>
<td>160±26*</td>
<td>106±14</td>
<td>86±9</td>
</tr>
<tr>
<td>Onset paced-AT increase</td>
<td>260±10</td>
<td>243±15</td>
<td>258±10</td>
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<tr>
<td>Mean paced-AT increase</td>
<td>30±4</td>
<td>26±5</td>
<td>33±8</td>
</tr>
<tr>
<td>Ventricular effective refractory period</td>
<td>220±10</td>
<td>230±10</td>
<td>214±5</td>
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<tr>
<td>Paced-QRS BCL</td>
<td>224±21*†</td>
<td>184±5‡</td>
<td>159±6</td>
</tr>
<tr>
<td>Onset paced-QRS increase</td>
<td>255±5</td>
<td>253±14</td>
<td>244±2</td>
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<tr>
<td>Paced-QRS increase</td>
<td>35±8</td>
<td>33±5</td>
<td>24±5</td>
</tr>
<tr>
<td>Transversal</td>
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<tr>
<td>Paced-AT BCL</td>
<td>112±5*†</td>
<td>72±5</td>
<td>58±6</td>
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<tr>
<td>Onset paced-AT increase</td>
<td>260±23</td>
<td>238±8</td>
<td>257±15</td>
</tr>
<tr>
<td>Mean paced-AT increase</td>
<td>42±8*†</td>
<td>16±3</td>
<td>18±2</td>
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<tr>
<td>Ventricular effective refractory period</td>
<td>203±6</td>
<td>219±5</td>
<td>220±6</td>
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<tr>
<td>Paced-QRS BCL</td>
<td>230±11*†</td>
<td>188±7‡</td>
<td>152±5</td>
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<tr>
<td>Onset paced-QRS increase</td>
<td>247±15</td>
<td>245±4</td>
<td>247±12</td>
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<tr>
<td>Paced-QRS increase</td>
<td>34±9</td>
<td>21±4</td>
<td>17±6</td>
</tr>
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</table>

Data are mean±SE. ANOVA post hoc test: *P<0.05 for BrS-1 vs control; †P<0.05 for BrS-1 vs BrS-2; ‡P<0.05 for BrS-2 vs control.

AT indicates activation time; BCL, basic cycle length; BrS, Brugada syndrome.
Discussion

This study shows that BrS is associated with wider and more intensively fractionated electrograms at the RV endocardium as evidenced in BrS patients with either a type-1 or type-2 BrS-ECG. Furthermore, the type-1 BrS-ECG is associated with slow impulse propagation during sinus rhythm and premature stimulation along with abnormal transversal CV-restitution. In contrast, repolarization characteristics were not different between groups.

Impairment of impulse propagation in BrS appears to reside particularly in slowing of cell-to-cell transmission between myocardial cells, rather than propagation slowing in the specialized conduction system. This is suggested by more severe delays during RV stimulation (specialized conduction system not involved) than during sinus rhythm (specialized conduction system involved) (Tables 2 and 3). Activation delays almost doubled in BrS-1 patients during stimulation. These endocardial changes were faithfully reflected on the ECG by increases in the paced QRS-complex duration. A near doubling of activation delay on stimulation in BrS-1 patients is in accordance with studies in transgenic mice that lack 1 *SCN5a* allele.18 Of interest, BrS-2 patients also had wider QRS-complexes on premature stimulation suggesting a reduced safety factor for conduction,19 although they had normal activation-duration during sinus rhythm. In a recent study,20 BrS patients with inducible VF were noted to have wider paced QRS-complexes than BrS patients without inducible VF. Such a relation was not notable in the present study,20 BrS patients with inducible VF were noted to have wider paced QRS-complexes than BrS patients without inducible VF. Such a relation was not notable in the present study. However, in that study the patients with wider paced QRS-complexes tended to have more ST-elevation.20

Impulse propagation is determined by both active and passive membrane properties.21 Abnormal membrane excitability that causes conduction slowing in BrS may follow from reduced sodium current because of reduced sarcolemmal sodium channel density or changes in sodium channel function.6 For instance, delayed recovery from slow inactivation reduces sodium channel availability and reduces sodium current at short CIs.6 In addition, increased coupling resistance between cells or changes in fiber orientation may also reduce CV.21 In uniformly anisotropic cardiac tissue, the resistance to current flow is higher in the direction perpendicular to fiber orientation and is lower parallel to it.21 Although histological confirmation was lacking in the present study, we did not find functional changes to support the possibility that RV endocardial fiber orientation was grossly different in BrS, because the pattern of activation during sinus rhythm was normal17 in all patients (although activation was on average ~30% slower in BrS-1 patients). Consequently, passive membrane properties that cause impairment of propagation in BrS may be caused by increased coupling resistance, eg, fibrosis7,8 or loss of connexins.22 Such findings suggest overlap between BrS and ARVC,8,23,24 Of interest, fibrosis and reduced connexin expression may also result from reduced sodium current.7,8,18,22

Wide and fractionated electrograms are a common manifestation of increased coupling resistance after separation of myocardial fibers by fibrosis or fat and indicate that the electric impulse travels discontinuously.13,21,25 Accordingly, we found ~19% more electrogram fractionation and ~12 to 20 ms wider electrograms on an average in BrS patients. Still, discontinuous conduction can also be caused by functional derangements, eg, functional block and current-to-load mismatch.10,11,26 In the present study, this was illustrated by an increase in electrogram duration and fractionation with a decrease of sodium channel availability induced by ajmaline administration. Thus, wider and fractionated electrograms in BrS patients may be caused by both structural changes and derangements in active membrane properties. Of note, electrograms were rarely as severely fractionated or wide as may be found in the diseased area in myocardial infarction21 or ARVC.25 However, the mean electrogram duration in BrS-1 and BrS-2 patients was similar to previously reported electrograms in the affected area in ARVC.25 Interestingly, there was no correlation between the width or the degree of electrogram fractionation and the presence/absence of a *SCN5a* mutation.

Our previous electrophysiological and histological study of the heart of a BrS patient6 indicated that impaired active membrane properties and interstitial changes may be probed by CV-restitution analysis. In that patient, the *SCN5a* mutation caused enhanced slow inactivation although interstitial fibrosis and fatty infiltration were also found. These changes resulted in abnormal CV-restitution. Abnormal CV-restitution with a large increase in activation delay at short CIs, as found in the BrS-1 patients, is thought to represent the capacity of the myocardium to support slow conduction and act as an arrhythmic substrate that renders patients susceptible to reentrant arrhythmias.11 CV-restitution is dependent on the recovery rate of sodium channels and always exists in cardiac tissue at short diastolic intervals.27 Yet, structural changes cause abnormal CV-restitution and are associated with increased coupling resistance and fractionated electrograms.9,11 In addition, structural changes may be a prerequisite for abnormal CV-restitution, as shown in a study of transgenic mice that lack 1 *SCN5a* allele and had profound conduction slowing at a young age but no electrogram fractionation, structurally normal hearts, and normal CV-restitution at that time.18 Conversely, conduction slowing does appear to play a role in abnormal CV-restitution in BrS, as BrS-1 and BrS-2 patients had similar electrogram fractionation but only the added presence of sufficient conduction slowing in BrS-1 patients resulted in abnormal CV-restitution. Thus, unless diastolic intervals are abbreviated because of delay in repolarization,28 abnormal CV-restitution results from the interplay between conduction slowing and tissue discontinuities. Of note, we did not find an early onset of increase in activation delay (ie, at long CIs), as typically found in structurally severely disrupted tissue.9,11 Accordingly, a modest increase in electrogram fractionation and duration and the lack of gross structural abnormalities in BrS patients, as evidenced by cardiac MRI and echocardiography findings, support a relatively mild interstitial derangement in these patients.

Abnormal CV-restitution in BrS-1 patients was detected during transverse but not longitudinal propagation. With the placement of the catheters during the stimulation studies based on previous anatomic findings,15,16 activation data,17 and normal activation patterns as shown with CARTO,
CV-restitution was studied approximately parallel to the RV endocardial fiber orientation (longitudinal CV-restitution) and perpendicular to the fiber orientation (transversal CV-restitution). Although we lack histological confirmation, the finding that only transversal CV-restitution was abnormal suggests that increased coupling resistance/tissue discontinuities more strongly affect impulse propagation perpendicular to the myocardial fiber orientation than propagation parallel to it. This may be explained by smaller sarcolemmal expression of connexins (which are required for cell-to-cell impulse transmission) or more interstitial fibrosis at the long axis of the myocytes than at their short axis as shown previously in dogs and mice.22,29 The resulting reduction in conduction capacity may render transversal conduction more likely to slow or fail. Another explanation why we did not observe abnormal longitudinal CV-restitution may relate to the profound conduction slowing observed in BrS-1 patients, particularly at short CIs. A beat evoked by a premature stimulus at a short CI will arrive with great delay at a site distant from where it was evoked, and paradoxically increase the CI of this beat at the distant site. This effect is more likely to occur during RV-apex stimulation (long distance stimulus electrodes) than during transversal stimulation (short distance stimulus electrodes). Regardless of the underlying mechanisms, the disparate effects of premature stimulation on longitudinal and transversal propagation will further increase anisotropy, thereby facilitating reentrant excitation and arrhythmias.

In summary, our findings support the emerging notion7,8 that BrS is not solely attributable to abnormal electrophysiological properties, but requires the concerted effects of slow and discontinuous conduction in relation to impaired active membrane processes and increased coupling resistance. The observation that most BrS patients only develop arrhythmias after the third decade of their life1 may be explained by the requirement of interstitial changes to evolve over time.22 When this occurs, the effects of reduction in wave length attributable to conduction slowing are exacerbated by augmented anisotropy and discontinuous conduction due to interstitial changes. This will promote conduction block, reentry, and wavebreak and may be the elements to cause VT/VF in BrS. In this concept, tissue discontinuities are required and may already be relevant when relatively mild, because they conspire with functional impairments, eg, loss-of-function SCN5a mutations with or without mutations in modifying genes6 or environmental stressors such as sodium channel blocking drugs,1 vagal stimulation,9 or fever.30

Conclusions

BrS-1 and BrS-2 patients are characterized by wider and more fractionated electrograms at the RV endocardium when compared with controls. BrS-1 patients display additional RV endocardial conduction slowing during sinus rhythm and premature stimulation, along with abnormal CV restitution. This suggests that these patients exhibit a substrate for slow and discontinuous conduction caused by impairment of active membrane processes and electric coupling between cells. Our findings support the emerging notion that BrS is not solely attributable to abnormal electrophysiological properties but requires the conspiring effects of conduction slowing and tissue discontinuities.

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Disclosures

None.

References


Slow and Discontinuous Conduction Conspire in Brugada Syndrome: A Right Ventricular Mapping and Stimulation Study


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