ST-Segment Elevation and Fractionated Electrograms in Brugada Syndrome Patients Arise From the Same Structurally Abnormal Subepicardial RVOT Area but Have a Different Mechanism

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Background—Brugada syndrome (BrS) is characterized by a typical ECG pattern. We aimed to determine the pathophysiologic basis of the ST-segment in the BrS-ECG with data from various epicardial and endocardial right ventricular activation mapping procedures in 6 BrS patients and in 5 non-BrS controls.

Methods and Results—In 7 patients (2 BrS and 5 controls) with atrial fibrillation, an epicardial 8x6 electrode grid (interelectrode distance 1 mm) was placed epicardially on the right ventricular outflow tract (RVOT) before video-assisted thoracoscopic surgical pulmonary vein isolation. In 2 other BrS patients, endocardial, epicardial RV (CARTO), and body surface mapping was performed. In 2 additional BrS patients, we performed decremental preexcitation of the RVOT before endocardial RV mapping. During video-assisted thoracoscopic surgical pulmonary vein isolation and CARTO mapping, BrS patients (n=4) showed greater activation delay and more fractionated electrograms in the RVOT region than controls. Ajmaline administration increased the region with fractionated electrograms, as well as ST-segment elevation. Preexcitation of the RVOT (n=2) resulted in ECGs that supported the current-to-load mismatch hypothesis for ST-segment elevation. Body surface mapping showed that the area with ST-segment elevation anatomically correlated with the area of fractionated electrograms and activation delay at the RVOT epicardium.

Conclusions—ST-segment elevation and epicardial fractionation/conduction delay in BrS patients are most likely related to the same structural subepicardial abnormalities, but the mechanism is different. ST-segment elevation may be caused by current-to-load mismatch, whereas fractionated electrograms and conduction delay are expected to be caused by discontinuous conduction in the same area with abnormal myocardium. (Circ Arrhythm Electrophysiol. 2015;8:1382-1392. DOI: 10.1161/CIRCEP.115.003366.)

Key Words: activation delay  ■  Brugada syndrome  ■  electrophysiology  ■  mapping

Brugada syndrome (BrS) is associated with a familial occurrence of sudden cardiac death by ventricular tachycardia or ventricular fibrillation or both (VT/VF). BrS is diagnosed when the typical ECG pattern (BrS-ECG, ie, coved ST-segment elevation followed by a negative T wave) occurs in at least one right precordial lead positioned at the second, third, or fourth intercostal space either spontaneously or after provocation by intravenous administration of class I antiarrhythmic drugs. Occurrence of this BrS-ECG can wax and wane and often precedes onset of VT/VF. In ≈20% to 30% of patients, a mutation in the gene encoding the sodium channel, the L-type Ca2+ channel, or the channel carrying the transient outward current (Ito) is found. Despite earlier studies in which BrS has been described in patients with structurally normal hearts, there is now increasing evidence that subtle structural abnormalities exist in the right ventricle outflow tract (RVOT) of BrS patients and that these may impair impulse propagation and could act as an arrhythmogenic substrate. The pathophysiologic basis of BrS remains incompletely understood. Three hypotheses, each with a specific mechanistic basis, have been proposed to explain the BrS-ECG: (1) repolarization disorder hypothesis, based on

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WHAT IS KNOWN

- Subtle structural abnormalities exist in the right ventricle outflow tract of Brugada syndrome patients.
- They may impair impulse propagation and could act as an arrhythmogenic substrate.

WHAT THE STUDY ADDS

- Fractionated electrograms/activation delay and ST-segment elevation in Brugada syndrome patients may both arise from the same (structurally abnormal) subepicardium of the right ventricle/right ventricle outflow tract region.
- The ST-elevation can be modulated by sodium channel blockers like ajmaline or by preexcitation.

We, therefore, (1) recorded conduction delay and fractionated electrograms at the epicardial RV/RVOT of patients undergoing a video-assisted thoracoscopic surgical (VATS) procedure for atrial fibrillation (AF), (2) performed epicardial and endocardial mapping of the RV/RVOT and epicardial ablation of regions with marked fractionated electrograms, (3) administered the sodium channel blocker ajmaline to modulate ST-segment elevation, and (4) performed premature stimulation of the RV/RVOT at different intervals after onset QRS during sinus rhythm (SR) to shift ST-segment elevation. Because fractionation/conduction delay and ST-segment elevation presumably are caused by the same substrate, we further hypothesize that there is an anatomic correlation between the epicardial areas of delayed RV/RVOT activation or fractionated electrograms or both and ST-segment elevation on the body surface map.

Methods

This study was performed in accordance with the Declaration of Helsinki, and written informed consent was obtained from all patients. Three studies were performed.

Study 1: Multiple epicardial RVOT unipolar electrograms were simultaneously acquired to assess the presence of fractionated electrograms, their related pathways, and activation delay in BrS patients and control patients who underwent VATS-pulmonary vein isolation (PVI; proposal 1, 3, and 4).

Study 2: Endocardial and epicardial mapping and RVOT ablation was performed in 2 BrS patients to evaluate the effect of ablation of epicardial areas with fractionated electrograms on ST-segment elevation and to correlate epicardial fractionation with ST-segment elevation before and after infusion of ajmaline (proposal 2–5).

Study 3: Premature stimulation of the RVOT at different times after onset of QRS during SR was performed in 2 other BrS patients in the course of diagnostic electrophysiological evaluation. With this method, we advanced the ST-segment elevation, allowing us to distinguish between the electrotonic current hypothesis and repolarization disorder hypothesis for ST-segment elevation (proposal 3–5).

Procedures

BrS was diagnosed using the consensus criteria. Controls were non-BrS who underwent VATS-PVI for AF. Signals were analyzed using a custom-made program based on MATLAB (The MathWorks, Inc, Natick, MA) or CARTO 3 Navigation System (Biosense Webster Inc, Diamond Bar, CA). Unipolar electrograms of poor quality (noise, movement artifacts) were excluded. Cardiac magnetic resonance was performed in all BrS patients without implantable cardioverter defibrillator (ICD) or computerized tomography scan in those with ICD.

Study 1: Epicardial RVOT Mapping During VATS-PVI

VATS-PVI was performed under general anesthesia. Before PVI, and after introduction of the various trocars, a custom-made 8x6 electrode grid (interelectrode distance 1 mm) was placed under visual guidance on the RVOT to obtain epicardial unipolar electrograms. A 256-channel mapping system (BioSemi, ActiveTwo, Amsterdam, The Netherlands; 24-bit dynamic range, 122.07 nV LSB, total noise 0.5 μV) was used with a sampling frequency of 2048 Hz (bandwidth DC, 400 Hz [−3 dB]). An indifferent reference electrode was inserted in the skin at one of the incision sites. Activation time was defined as the point of maximal negative dV/dt (≤−0.1 V/s) of the initial deflection of the unipolar electrogram. Total activation duration (TAD) of the myocardium underlying the grid was defined as the interval between the earliest and latest activation in milliseconds. To distinguish local from remote deflections, the timing of the maximal negative dV/dt of each deflection was compared with the Laplacian transformation.
at that same time. An electrogram was considered to be fractionated if multiple deflections with $dV/dt \leq -0.01$ V/s corresponded to Laplacian deflections. Every local electrogram was manually investigated for fractionation. Fractionation was quantified as the mean number of deflections per electrode per grid. Fractionation duration was measured as the interval between the first and last deflection in milliseconds of a fractionated complex.

**Study 2: CARTO Mapping of Endocardial and Epicardial Right Ventricle for Epicardial Ablation**

Antiarrhythmic drugs were withheld for at least 5 half-lives before the electrophysiology study. Before the invasive procedure, body surface mapping using a 64-electrode system was obtained and a computerized tomography scan was made to obtain a 3D heart–thorax reconstruction. Electro-anatomic endocardial and epicardial mapping of the RV was obtained during SR with CARTO 3 and a 3.5-mm tip quadripolar ThermoCool SmartTouch mapping catheter (Biosense Webster Inc) as described earlier. The same activation and fractionation criteria were applied as in study 1. Repolarization time was defined as the point of maximal positive $dV/dt$ in the T wave of the unipolar electrogram.30,31 The activation recovery interval, a surrogate for action potential duration, was the interval between activation time and repolarization time. To avoid interference by remote signals, bipolar signals obtained from the mapping catheter (signal at the tip—signal from the first ring electrode) were also analyzed. First, endocardial mapping was performed. Thereafter, pericardial puncture was performed according to Sosa et al., and baseline epicardial mapping was performed. Sites displaying fractionated electrograms were marked on the CARTO map. Subsequently, ajmaline was administered intravenously and epicardial mapping was repeated. Guided by the location of fractionated electrograms, radiofrequency ablation of these sites was performed. Radiofrequency ablations were performed at a power from 30 to 40 W, with the maximum temperature set at 43°C. After ablation of abnormal (fractionated) sites, the epicardial RV was remapped, and the absence of abnormal electrograms was used as end point for the ablation.

**Study 3: Endocardial CARTO 3 Mapping of RV and Stimulation of RV/RVOT**

In 2 patients undergoing diagnostic electrophysiological assessment for risk stratification for sudden cardiac death in BrS, a programmed electric stimulation protocol was performed, including premature stimulation of the endocardial RV/RVOT region. A decapolar catheter was placed in the coronary sinus for atrial stimulation. The mapping catheter was placed in the RVOT for ventricular stimulation and was performed at different intervals after the onset of the QRS complex during SR. Following a drive train of 8 atrial stimuli at a cycle length of 800 ms, a single ventricular extrastimulus—initially timed at the end of the last atrially stimulated and atroventricular conducted QRS complex—was delivered. The ventricular coupling interval was decreased in subsequent sequences with 10 ms intervals, allowing progressive preexcitation of the RVOT. This was repeated until fusion between atroventricular conducted ventricular activation and RVOT-paced ventricular activation was no longer present and the last QRS complex was fully paced from the ventricular myocardium.

**Results**

Eleven individuals were studied (Table 1): 6 BrS patients and 5 controls. Age at time of studies was 45±16 years in BrS patients and 57±9 years in control patients. Five of the 6 BrS patients were symptomatic, including 2 with an ICD for secondary prevention (documented VT/VF). Noninvasive cardiac imaging of the BrS patients (cardiac magnetic resonance $n=4$, computed tomography scan $n=2$) revealed no overt structural abnormalities, in particular, no signs of myocardial fibrosis on cardiac magnetic resonance. In 2 patients, a mutation in SCN5A was identified (c.2635T>C and c.3228+2delT).

**Table 1. Patient Characteristics**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, y</th>
<th>Sex</th>
<th>Procedure</th>
<th>Diagnosis BrS</th>
<th>Mutation</th>
</tr>
</thead>
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<tr>
<td>1.</td>
<td>56</td>
<td>M</td>
<td>Epicardial RV mapping during VATS-PVI</td>
<td>OHCA, Spontaneous type I ECG</td>
<td>No</td>
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<tr>
<td>2.</td>
<td>56</td>
<td>M</td>
<td>Epicardial RV mapping during VATS-PVI</td>
<td>Asymptomatic, Drug induced BrS</td>
<td>No</td>
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<tr>
<td>3.</td>
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<td>M</td>
<td>Endocardial and epicardial RV mapping</td>
<td>IHCA, Spontaneous type I ECG</td>
<td>Yes</td>
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<tr>
<td>4.</td>
<td>57</td>
<td>M</td>
<td>Endocardial and epicardial RV mapping</td>
<td>Syncope, polymorphic VT, Drug induced BrS</td>
<td>No</td>
</tr>
<tr>
<td>5.</td>
<td>36</td>
<td>M</td>
<td>Endocardial mapping and RV stimulation</td>
<td>Syncope, Spontaneous type I ECG</td>
<td>Yes</td>
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<tr>
<td>6.</td>
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<td>M</td>
<td>Endocardial mapping and RV stimulation</td>
<td>Syncope, Drug induced BrS</td>
<td>No</td>
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<tr>
<td>7.</td>
<td>58</td>
<td>M</td>
<td>Epicardial RV mapping during VATS-PVI</td>
<td>Control</td>
<td>NP</td>
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<tr>
<td>8.</td>
<td>68</td>
<td>M</td>
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<td>Control</td>
<td>NP</td>
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<tr>
<td>9.</td>
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<td>10.</td>
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<td>11.</td>
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<td>F</td>
<td>Epicardial RV mapping during VATS-PVI</td>
<td>Control</td>
<td>NP</td>
</tr>
</tbody>
</table>

BrS indicates Brugada syndrome; F, female; IHCA, in-hospital cardiac arrest; M, male; NP, no mutation analysis performed; OHCA, out-of-hospital cardiac arrest; RV, right ventricle; and VATS-PVI, video-assisted thoracic surgical pulmonary vein isolation.
Riology study was performed under general anesthesia with rocuronium, propofol, and sufentanil. The effects of ajmaline administration and epicardial ablation on ST-segment elevation were less prominent than those in patient 3. There was a moderate increase in ST-segment elevation with ajmaline, and ST-elevation was slightly lower after ablation. The endocardial unipolar electrograms of the RVOT showed no fractionated signals (data not shown). Epicardial mapping showed fractionated electrograms at the superior, mid, and posterior site of the RVOT. Activation recovery intervals were 310±18 ms on average at the epicardial RVOT and 405±9 ms at the epicardial RV free wall. After ajmaline administration, the area with abnormal electrograms expanded toward the anterior and inferior RVOT. This area was additionally marked and successfully ablated. After epicardial ablation of the fractionated signals, late potentials and fractionation diminished (Figure 4A). After the procedure, the patient remained free of ventricular arrhythmias during 12 months of follow-up. Ultimate fractionated electrograms were 270 and 220 ms (patient 3 and 4, respectively) after onset QRS, and occurred far before ST-segment elevation ended.

To reveal changes in V1 caused by ajmaline, we subtracted the ECG during baseline from the ECG during peak ajmaline (Figure 4C) in both patients. This procedure revealed that, after the deflection that exposes the QRS difference, a pulse-shaped deflection arises with a width of 220 to 310 ms. This indicates that the effect of ajmaline on the ST-segment operates over this time interval. The pulse-shaped pattern mimics the configuration of an action potential as expected for an electrotonic component. The arrow in the signal marks the time of the latest epicardial late potential.

### Table 2. Electrophysiological Parameters

<table>
<thead>
<tr>
<th>Rhythm and CL, ms</th>
<th>AT, ms</th>
<th>No. of Deflections</th>
<th>Fractionation Duration, ms</th>
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<tr>
<td>1. BrS</td>
<td>SR, 660</td>
<td>27</td>
<td>5</td>
</tr>
<tr>
<td>2. BrS</td>
<td>AF, 560</td>
<td>15</td>
<td>4</td>
</tr>
<tr>
<td>3. Control</td>
<td>SR, 850</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>4. Control</td>
<td>AF, 600</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>5. Control</td>
<td>AF, 600</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>6. Control</td>
<td>AF, 900</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>7. Control</td>
<td>SR, 1200</td>
<td>9</td>
<td>2</td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation; AT, activation time; BrS, Brugada syndrome; CL, average cycle length; ms, milliseconds; and SR, sinus rhythm.

### Study 2: CARTO Mapping of Endocardial and Epicardial Right Ventricle for Epicardial Ablation

In 2 patients (no. 3 and 4, Table 1), endocardial and epicardial RV mapping was performed (Figure 2A, epicardial activation, and Figure 2B, fractionation map, at baseline and during ajmaline administration) before the mapping and ablation procedures. Patient 3 was diagnosed with BrS after an in-hospital cardiac arrest based on VF and a type I BrS-ECG. In this patient, a mutation in the SCN5A gene was found. A type 1 BrS-ECG was present at the beginning of the procedure. This patient had experienced several VT/VF episodes with multiple ICD shocks per year. Body surface voltage map showed the tallest ST-segment elevation at electrode E3, which was located immediately over the RVOT (Figure 3C, circled electrogram). The electrophysiology study was performed under general anesthesia with rocuronium, propofol, and sufentanil. Figure 4B (left) shows the patients’ ECGs with type 1 BrS-ECG during baseline, at maximal ajmaline level, and after epicardial ablation. Ajmaline increased ST-segment elevation markedly. After epicardial ablation of the area with fractionated electrograms, typical ST-segment elevation almost disappeared as compared with the ST-segment elevation before ajmaline administration. One month after epicardial ablation, ST-segment elevation was still absent. During CARTO mapping, the RV endocardial unipolar voltage map showed no abnormalities (data not shown), and endocardial RV electrograms showed only a small area of fractionated signals. Endocardial activation recovery intervals were 395±13 ms on average at the RV free wall and 370±6 ms at the RVOT. In contrast, epicardial RV mapping showed an area of low voltage and fractionated signals extending from the subpulmonary area to mid-wall RV (Figure 2B, left panel). Epicardial activation recovery intervals were 360±12 ms at the RV free wall and 310±11 ms at the RVOT. Administration of ajmaline increased the area with fractionated electrograms (Figure 2B, right panel). After epicardial ablation, ventricular arrhythmias occurred less frequently, although the patient experienced appropriate ICD shocks 6 weeks after ablation, after which quinidine therapy was reinstated.

Patient 4 had 1 mV ST-segment elevation in the right precordial leads at baseline, and BrS was diagnosed after episodes of polymorphic VT and a type 1 BrS-ECG after ajmaline administration (he had type 2 BrS-ECG at baseline). The patient also had coronary artery disease. The electrophysiology study was performed under general anesthesia with sufentanil and thiopental. The effects of ajmaline administration and epicardial ablation on ST-segment elevation were less prominent than those in patient 3. There was a moderate increase in ST-segment elevation with ajmaline, and ST-elevation was slightly lower after ablation. The endocardial unipolar electrograms of the RVOT showed no fractionated signals (data not shown). Epicardial mapping showed fractionated electrograms at the superior, mid, and posterior site of the RVOT. Activation recovery intervals were 310±18 ms on average at the epicardial RVOT and 405±9 ms at the epicardial RV free wall. After ajmaline administration, the area with abnormal electrograms expanded toward the anterior and inferior RVOT. This area was additionally marked and successfully ablated. After epicardial ablation of the fractionated signals, late potentials and fractionation diminished (Figure 4A). After the procedure, the patient remained free of ventricular arrhythmias during 12 months of follow-up. Ultimate fractionated electrograms were 270 and 220 ms (patient 3 and 4, respectively) after onset QRS, and occurred far before ST-segment elevation ended.

To reveal changes in V1 caused by ajmaline, we subtracted the ECG during baseline from the ECG during peak ajmaline (Figure 4C) in both patients. This procedure revealed that, after the deflection that exposes the QRS difference, a pulse-shaped deflection arises with a width of 220 to 310 ms. This indicates that the effect of ajmaline on the ST-segment operates over this time interval. The pulse-shaped pattern mimics the configuration of an action potential as expected for an electrotonic component. The arrow in the signal marks the time of the latest epicardial late potential.

### Study 3: Preexcitation of the RVOT

In 2 BrS patients (no. 5 and 6), preexcitation of the RVOT was performed during a diagnostic electrophysiological study. Figure 5A shows leads V1 during SR alone and during SR and RVOT prestimulation at different delays after onset QRS (numbers indicate the delay in milliseconds). Note that there is ST-segment elevation and a negative T-wave in both the basic and premature activations. Sharp deflections in the signals are the stimulus artifacts (indicated by numbers of measured coupling intervals). Figure 5B shows the subtraction of the electrograms in V1 during SR with stimulation and the SR electrogram in V1 alone (matched at onset QRS). Striking in all these differential signals is the pattern wave that follows directly after the stimulus artifact. The width of the
wave (arrows) becomes wider with increasing prematurity of the stimulus after onset QRS. By premature stimulation of the RVOT, ST-segment elevation (irrespective of its mechanism) occurs earlier in time and partly within the QRS complex, but is not removed as is evident from Figure 5. Premature stimulation of the RVOT region, therefore, only slightly altered the QRS configuration. As a result, the difference of a stimulated and a SR complex is mainly the difference of the ST-segment elevated signal during SR and virtually the same signal during stimulation but now shifted in time. The resulting pulse-shaped signal increases in width with prematurity of stimulation and

is compatible with our hypothesis that ST-segment elevation is caused by an electrotonic signal because of current-to-load mismatch (further explanation in Data Supplement; Figure 1). In both patients, the ST-segment morphology of the RVOT preexcited complex changed in a similar fashion.

**Discussion**

This study shows that ST-segment elevation and fractionated electrograms/activation delay in BrS patients arise both from the same (structurally abnormal) subepicardium of the RV/RVOT region (Figure 6). Study 1 shows that local electrograms

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**Figure 1.** Activation maps with corresponding electrograms obtained by the 8×6 grid during Video Assisted Thoracoscopic Surgical Pulmonary Vein Isolation (VATS-PVI). Two examples of activation maps (control and Brugada syndrome [BrS] patient). Colors correspond with activation time in milliseconds with regard to earliest activation within the grid. Red is earliest and blue latest activation. Asterisks are locations of the 8×6 electrode grid where unipolar electrograms at the left were recorded before PVI. A, Activation map of a control patient (middle). Purple dots in tracings correspond with the steepest negative dV/dt. Deflections prior and post the initial activation are remote as shown by the second activation map where no propagation is seen (and therefore representing remote activity). B, Color map of the propagation of the main activation (middle) and of the late potentials (right) seen in a BrS patient. Purple dots in tracings correspond with the steepest negative dV/dt, whereas red dots are the late potentials after initial activation. The secondary deflections propagate and therefore represent local activity. mV indicates millivolts.
in the RVOT are more fractionated in BrS patients than in controls. However, they may also be present in control patients, but are not related to ST-segment elevation (neither in control, nor in BrS patients). Study 2 demonstrates that ST-elevation in 1 patient disappeared when areas with fractionated local electrograms were ablated. The area of fractionation increased after sodium channel blockade. In the other patient, the typical BrS-ECG was absent despite extensive fractionation. Study 3 shows that the difference of a prestimulated and an SR complex is mainly the difference of the ST-segment elevated signal during SR and virtually the same signal during stimulation, but now shifted in time. The resulting difference wave (Figure 5B) increases in width with prematurity of stimulation. This is consistent with our hypothesis that ST-segment elevation is caused by an electrotonic signal because of current-to-load mismatch. This study with various mapping and stimulation protocols shows that BrS patients have longer activation delay, more and longer fractionated epicardial electrograms, and late potentials in the RV/RVOT compared with controls and that local fractionation is not solely responsible for the ST-elevation in the BrS-ECG. We additionally show that the area with ST-segment elevation on the body surface mapping -ECG corresponds with the area of fractionated epicardial electrograms in the RV/RVOT.

The mechanism causing the typical ST-segment elevation in the right precordial leads in BrS patients has still not completely been elucidated. Three hypotheses have been proposed. The repolarization disorder hypothesis is based on transmural voltage gradients caused by heterogeneity in action potential duration between the RV epicardium and endocardium, resulting in dispersion of repolarization measured in canine wedge preparations. According to the depolarization disorder hypothesis, late activation of the RVOT is the underlying mechanism. The electrotonic current hypothesis explains ST elevation by electrotonic currents caused by current-to-load mismatch in a structurally abnormal subepicardium of the RV/RVOT area. There is growing evidence that mild structural abnormalities in BrS patients, that are not detectable on conventional imaging modalities, result in discontinuous impulse conduction that occurs if patchy fibrosis is present in the myocardium.

Figure 2. Epicardial right ventricular (RV) CARTO map of patient no. 3 displaying activation (top) and fractionation duration (bottom) before (left) and after ajmaline (right) administration. Color bars show activation and fractionation duration (ms). Red areas indicate short activation time or electrograms of short duration, and blue areas indicate longer activation time or fractionation duration. Note that during administration of ajmaline, the area of longer fractionation duration is expanding and becomes more heterogeneous.
component for ST-segment elevation. The upper left panel shows an endocardial action potential only. Activation toward the epicardium is blocked because of current-to-load mismatch in the structurally abnormal subepicardium (electrotonic current hypothesis). The left middle and lower panels show a gradient in action potential duration from endocardium to epicardium and a strong spike and dome configuration for the epicardial action potential, respectively (repolarization disorder hypothesis). The middle column displays the configuration of the electrotonic signals that are generated because of the difference in epi- and endocardial action potentials as illustrated at the left. The signals are low pass--filtered (3 dB at 60 Hz) to cope with their electrotonic feature. The third column shows the difference between the electrotonic component and its time shifted equivalent for the 3 electrotonic components. The electrotonic components are shifted over 15, 30, and 45 U (ms), simulating premature stimulation at different coupling intervals. The pulse-shaped signals in the upper right panel best correspond with the recorded signals from Figure 5. Signals in the middle right panel start later and are more sinusoidal, whereas signals in the lower right panel have a biphasic pulse-shaped form. The figure illustrates that results obtained during premature stimulation at different coupling intervals (Figure 5; top row of Figure I in the Data Supplement) fit best with the electrotonic current hypothesis.

Figure 4 shows that if the ajmaline level increases, the ST-segment elevation increases. We expect that this occurs because ajmaline increases the number of sites with conduction block. Subtracting electrograms recorded during different ajmaline levels gives the change in the signal caused by the increase in the ajmaline concentration. Figure 4C shows that subtraction reveals a wide signal compatible with an electrotonic component generated by the duration of the action potential in the activated area. If the electrotonic current was based on a shorter action potential duration at the epicardium compared with the endocardium, electrotonic current would only flow during the time the difference in action potential duration is present and, thus, during a shorter period. In addition, this would occur later after depolarization. A role for activation delay as a single mechanism for ST segment...
Figure 4. A, Epicardial right ventricular (RV) CARTO map of patient no. 4 displaying activation at baseline (left), during ajmaline (middle) administration, and after epicardial ablation of the fractionated signals (right). Left to the CARTO images are the corresponding electrograms. Blue dots are recording points, and red points indicate ablation sites. Please note that color bars have different ranges. B, Twelve lead ECG of one of the Brugada syndrome (BrS) patients who underwent epicardial ablation. The ECG shows a type 1 Brugada syndrome during baseline, maximal ajmaline level, and after epicardial ablation of areas with outspoken fractionated electrograms. Note that ST-segment elevation increases with ajmaline and virtually disappears after ablation. C, Tracings are the difference between V1 during baseline and V1 at maximal ajmaline level of 2 Brugada syndrome patients (no. 3 and 4). Patient 3 has a type 1 and patient 4 a type 2 Brugada syndrome. In both signals, the deflection marking the difference in QRS (v) is followed by a pulse-shaped deflection with a duration of ≈220 and 300 ms, respectively. Arrows mark the time of latest epicardial late potentials in the patients. P indicates atrial complex; and Stim., stimulation artifact.
elevation is also unlikely because late potentials are not present at the end of the pulse signal as Figure 4C illustrates. In addition, late potentials with a delay >160 ms were present in only 0.04% of the electrograms with fractionation. When the substrate was modulated by catheter ablation, the ST-segment elevation diminished corroborating the study performed by Nademanee et al.12 Nademanee et al previously identified low voltage areas with fractionated electrograms and severe activation delay at the anterior epicardial aspect of the RVOT and diminishing of preexistent ST-segment elevation after ablation of this area. Recently, Szél et al34 also observed fractionated electrograms in the RV epicardium, but they suggested that this is because of a heterogeneous epicardial loss of dome and local reexcitation via a concealed phase 2 reentry, challenging abnormal depolarization or structural abnormalities as a mechanism. However, the data in our

**Figure 5.** A, Tracings are V1 of a type 1 Brugada syndrome patient during sinus rhythm (SR) and during SR with RV outflow tract (RVOT) stimulation at different times after onset of the QRS complex (S1–S4). Delay between onset QRS and the stimulus is indicated by a number left from the dashed line. Sharp deflections right from the dashed lines are the stimulus artifacts. B, Tracings are the difference between the stimulated complexes in S1 till S4 in A and the SR complex. Sharp deflections are stimulus artifacts, which are followed by a pulse-shaped signal. The width of the pulses is indicated by an arrow and increases with prematurity of the stimulus. See text for discussion.

**Figure 6.** Schematic drawing of intra and extracellular signals recorded near an isthmus site where activation in myocardial tissue proximal from the isthmus is blocked toward myocardium distal from the isthmus. Activation in the proximal area generates an action potential (intracellular) at the recording site. Because of activation block, the distal area is not activated, and the intracellular signal is a flat line (intracellular). The upper tracing shows the extracellular signal, which consists of a stimulus artifact, a remote deflection of the activation front in the proximal area, and an action potential–shaped deflection caused by electrotonic current flowing through the isthmus. At the right site, schematics of myocardial tissue subdivided in multiple myocardial bundles by electrically inexcitable barriers. Bundles are interconnected at different sites by an isthmus. Activation has to follow a tortuous route between the barriers, which results in activation delay because of the increased path length. Fractionated electrograms occur because of the asynchronous activation between the barriers. Black dots are recording sites.
patients suggest differently. Fractionated signals were clearly associated with diastolic potentials in the BrS patients undergoing VATS-PVI (see Figure 1), whereas diastolic potentials were not observed in control patients except 1 (control 3). This is not surprising because structural subepicardial abnormalities have been observed in the RVOT of healthy pig hearts. To lead to ST-elevation, however, additional electrophysiological changes, for example, reduced sodium current, are necessary.

Normally, the RV/RVOT area is activated relatively late during SR. The effect of alteration of activation of the endocardial RVOT on ST-segment elevation was investigated by premature RVOT stimulation in 2 BrS patients. Preexcitation of the right ventricular apex was described earlier by Chiale et al. Their study describes a maneuver to unmask the BrS-ECG by preexcitation of the RV apex when a right bundle branch block pattern is present on the surface ECG. Our study followed a different line of reasoning: instead of unmasking ST-segment elevation, we sought to study whether ST-segment elevation in patients without intraventricular conduction block could be caused by current-to-load mismatch of the RVOT. To test this, we advanced activation of the RVOT by pacing the RVOT instead of the RV apex. An electrotonic component that would cause ST-segment elevation must also start late after onset QRS. If, however, the RV/RVOT area during SR is activated prematurely by stimulation, the electrotonic current will start earlier as well. Indeed, the electrotonic current (elevation of the signal) started directly after the stimulus at every coupling interval (Figure 5). To reveal the electrotonic component (and discard the activation component), the electrogram during SR was subtracted from the stimulated one. By doing so, mainly the difference between the electrotonic components during SR alone and of SR with stimulation remains (small additional changes may be present because of altered activation in RV). The earlier the RV/RVOT is stimulated after onset of QRS of the sinus beat, the earlier the electrotonic component arises and the wider the component will be (Figure 5). Although subtle structural abnormalities have been described in hearts of BrS patients, during postmortem analyses or in explanted hearts, we could not document these in our patients. The standard imaging techniques may not have been sensitive enough to detect these subtle changes in RVOT architecture. However, based on the available data, the presence of subclinical structural changes in these patients is likely. In addition, ablation aimed at anatomically abnormal tissue was effective as a therapy.

Methodological Considerations and Limitations

The number of patients is small. However, we used 3 different types of experiments in 2 of which the patients served as their own control (study 2 and 3), and these studies point to a same mechanism for the electrophysiological characteristics of BrS. Analysis of the electrograms of the epicardial grid was performed during spontaneous SR, or conducted AF and heart rate may have influenced the TAD. However, we did not observe differences in activation time between patient with AF or SR and with different cycle lengths.

Conclusions

ST-segment elevation and fractionated electrograms/activation delay in BrS patients are most likely related to the (structurally abnormal) subepicardium of the RV/RVOT region. Such abnormalities may cause conduction block because of current-to-load mismatch at tissue discontinuities, resulting in ST-segment elevation. Our currently presented data support this hypothesis. The same structural abnormalities may cause fractionated electrograms and conduction delay if excitability is appropriate. These electrophysiological parameters can be modulated by sodium channel blockers like ajmaline.

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ST-Segment Elevation and Fractionated Electrograms in Brugada Syndrome Patients Arise From the Same Structurally Abnormal Subepicardial RVOT Area but Have a Different Mechanism


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SUPPLEMENTAL MATERIAL
Suppl. fig 1

Action potentials

Electrotonic component
AP endo – epi, low pass filtered

Electrotonic component
Electrotonic component shifted

AP endo
AP epi

Endo-Epi
Supplemental Figure 1. Simulation of epicardial and endocardial action potentials to differentiate between the repolarization and current to load mismatch hypothesis for ST-segment elevation on the base of the signals obtained by premature stimulation of the RVOT. Signals in the upper right panel correspond best with the recorded signals in figure 6B as for morphology and timing. Stimulus artefacts are not indicated in the simulated signals.