Brugada Syndrome Phenotype Elimination by Epicardial Substrate Ablation

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Background—Whether Brugada syndrome (BrS) depends on functional epicardial substrates, which may be definitively eliminated by radiofrequency ablation, remains unknown.

Methods and Results—Patients with BrS underwent epicardial mapping to identify areas of abnormal electrograms as target for radiofrequency ablation. Substrate identification consisted in mapping right ventricle epicardial surface before and after flecainide (2 mg/kg per 10 minutes). After radiofrequency ablation, flecainide and remap confirmed elimination of abnormal substrate, BrS ECG pattern, and ventricular tachycardia/ventricular fibrillation inducibility. Flecainide testing was performed at each follow-up visits ≤6 months. Fourteen patients with BrS, median age years (30.3–42.3) with implantable cardioverter–defibrillator were enrolled. Low-voltage areas (<1.5 mV) were commonly identified on the anterior right free wall and right ventricular outflow tract, which increased after flecainide from 17.6 cm² (12.1–24.2) to 28.5 cm² (21.6–30.2; P=0.001). Similarly, areas with abnormal electrograms increased after flecainide from 19.0 (17.5–23.6) to 27.3 cm² (24.0–31.2; P=0.001). After 23.8 minutes (18.1–28.5) of radiofrequency ablation, abnormal electrograms disappeared, whereas low-voltage areas were replaced by scar areas (<0.5 mV) of 25.9 cm² (19.6–31.0). Substrate elimination resulted in BrS ECG pattern disappearance and no ventricular tachycardia/ventricular fibrillation inducibility without complications. After a median follow-up of 5 months (3.8–5.3), ECG remained normal despite flecainide.

Conclusions—In patients with BrS, there is a relationship between abnormal ECG pattern, the extent of abnormal epicardial substrate, and ventricular tachycardia/ventricular fibrillation inducibility. Ablation of the substrate identified in the presence of flecainide can eliminate the BrS phenotype and warrants further study. (Circ Arrhythm Electrophysiol. 2015;8:1373-1381. DOI: 10.1161/CIRCEP.115.003220.)

Key Words: Brugada syndrome | flecainide | heart | phenotype | sudden cardiac death

B rugada syndrome (BrS) is a genetic arrhythmia syndrome, which confers an increased risk of sudden cardiac death. The phenotypic manifestation of the disease (ECG characteristic pattern, inducibility of arrhythmias, syncope, and sudden death) depends on the presence of different factors, such as sex, age, body temperature, vagal tone, and certain drugs. This phenotypic expression variability explains why BrS is diagnosed in patients with type I ST-segment–elevation morphology either spontaneously or after provocative drug test with intravenous administration of class I antiarrhythmic drugs.¹

Editorial see p 1306

Mutations in >15 genes related to different channels have been described as responsible for BrS, the majority of them affecting the early phase of repolarization, which is mediated by the balance between the sodium inward current and the transient potassium outward current (I_K). Genetic anomalies result in an increased heterogeneity of repolarization (because of the variability in the distribution of the I_K current) and create the substrate for myocardial reentry because of a stronger I_K current expression in the right ventricle (RV) epicardium.²,³

For many years, BrS has been considered a purely electric disease even if, more recently, some authors have suggested the presence of morphological and functional abnormalities, predominantly located in the RV and specifically in the outflow tract (RVOT).⁴,⁵ Endocardial radiofrequency ablation (RFA) has been proposed in 2003 by Haissaguerre et al⁶ as an investigational procedure, which was limited to the first 3 BrS patients with recurrent ventricular fibrillation (VF) and premature ventricular complexes triggering ventricular tachycardia (VT)/VF to avoid frequent implantable cardioverter–defibrillator (ICD) shocks.⁷ However, recent...
WHAT IS KNOWN
• The arrhythmogenic substrate in Brugada syndrome is located in the right ventricular outflow tract epicardium.
• Epicardial ablation of this arrhythmogenic substrate can control frequent episodes of ventricular tachycardia/ventricular fibrillation.

WHAT THE STUDY ADDS
• Epicardial mapping shows a variable extent of arrhythmogenic substrate in Brugada syndrome extending beyond the right ventricular outflow tract.
• Flecainide facilitates identification of the extension and distribution of arrhythmia substrate during epicardial mapping.
• Elimination of this arrhythmogenic substrate by ablation is associated with the absence of ventricular tachycardia/ventricular fibrillation inducibility and the absence of Brugada ECG pattern during follow-up, as confirmed by flecainide testing.

Experimental observations suggested that RFA applied to the epicardium may be more effective than applied to the endocardium in eliminating VT in patients with BrS. A more recent report from 9 symptomatic BrS patients with repetitive ICD shocks indicates that the electrophysiological substrate for the BrS is delayed depolarization exclusively over the anterior aspect of the RVOT epicardium and that catheter ablation of this abnormal area may prevent VT/VF. These observations open the possibility that eliminating localized epicardial substrates responsible for the disease phenotype may cure patients with BrS. However, it is not known if there is a relationship between the presence, location and extent of the epicardial substrate abnormalities, and typical BrS ECG pattern. In addition, many other issues such as methodology for substrate identification and elimination and testing of acute and midterm results remain to be clarified. The purpose of this study was to systematically report the methodology, results, and complications of epicardial RFA of consecutive selected patients with BrS. Particular attention was focused on endocardial/epicardial mapping and flecainide testing to characterize and establish the most appropriate target sites for successful RFA and elimination of both ECG BrS pattern and inducibility of VT/VF.

Methods

Patient Characteristics
Patients referred to the Arrhythmology Departments of Maria Cecilia Hospital, Cotignola and Policlinico San Donato, University of Milan, Italy, for management of BrS were included according to the following criteria: (1) a documented spontaneous or flecainide-induced type 1 BrS ECG pattern and symptoms attributable to ventricular arrhythmias, (2) a high vulnerability for ventricular arrhythmia induction at electrophysiology study, (3) an ICD already implanted, and (4) informed consent signed by the patient. The study was approved by the Local Ethics Committee.

Mapping and Ablation Procedure
Mapping and RFA procedures were performed under general anesthesia. An invasive arterial pressure line was obtained through radial artery access. ECG was continuously recorded during the procedure. After femoral venous access, a multipolar diagnostic catheter was positioned at the RV apex. High-density detailed endocardial and epicardial electroanatomical maps and ablation were performed using 3-dimensional (3D) mapping system (CARTO 3, Biosense Webster, Diamond Bar, CA), with incorporated area calculation software to accurately define areas of low voltage and delayed fragmented electrograms during stable sinus rhythm. Data were recorded and analyzed simultaneously with regard to amplitude, duration, relation to surface QRS, and the presence of multiple components.

BrS Functional Substrate Identification
Epicardial access was gained as previously described by Sosa et al. Epicardial contact mapping and ablation were always performed after endocardial mapping to have a good delimitation of the RV boundaries when mapping the epicardium. Epicardial RV mapping and ablation catheter manipulation were assisted by a steerable sheath (Agius St Jude Medical, St. Paul, MN). Substrate epicardial mapping was performed during sinus rhythm and areas of low voltage were identified using standard voltage cut-off values for dense scar (≤0.5 mV) and border zone (<1.5 mV), and ventricular abnormal electrograms were tagged. Abnormal electrograms were defined as those with amplitude <1.5 mV (tagged as light blue dots) or associated wide duration (>80 ms), multiple (>3), or delayed components extending beyond the end of the QRS complex (tagged as black dots). Bipolar electrograms were filtered from 10 to 400 Hz and displayed at 100 to 200 mm/s speeds. Bipolar signals were recorded between the distal electrode pair. In the presence of a low-voltage area, >3 additional points were acquired in the same area to confirm the reproducibility of the voltage measurements. Red color indicated dense scar that arbitrarily was defined as bipolar signal amplitude ≤0.5 mV, whereas green color indicated low-voltage areas (≤1.5 mV). Complete endocardial and epicardial maps were obtained to ensure reconstruction of a 3D geometry of the cardiac chambers and to identify areas of abnormal ventricular electrograms. Areas showing low-amplitude signals were mapped with greater point density to delineate the extent and borders of epicardium electroanatomical scar areas. The extent of low-voltage areas was expressed as total or percentage of RV epicardial area.

BrS functional epicardial substrate identification consisted in mapping the entire RV epicardial surface under baseline conditions and after flecainide infusion (2 mg/kg in 10 minutes).

Figures 1–3 show examples of color-coded endocardial and epicardial electroanatomical bipolar maps showing epicardial BrS functional substrate identification at baseline and after flecainide testing.

BrS Functional Substrate Ablation
Once epicardial low-voltage areas were identified and quantified after flecainide, all abnormal electrograms inside these areas were tagged to be targeted for RF delivery (Figures 2 and 3; Figure I in the Data Supplement). Radiofrequency was delivered for these areas using an externally irrigated 3.5-mm tip mapping/ablation catheter (Thermocool, Navistar, Biosense Webster) with 45°C temperature control, 40 W power limit, and 17 mL/min irrigation rate. Each RF application lasted 30 to 60 s, depending on complete elimination of the targeted electrograms. Abolition or persistence of abnormal electrograms was checked with the ablation catheter after each one of the applications. Immediate procedural end point was the elimination of all the abnormal electrograms identified inside the low-voltage areas during sinus rhythm as replaced by low-voltage (<0.5 mV) dense scar (Figure II in the Data Supplement).

BrS Functional Substrate Remapping
A remap focusing on the low-voltage area was obtained after ablation to confirm the complete elimination of abnormal electrograms. Residual abnormal electrograms identified by remapping...
were targeted with the same approach used during initial mapping and ablation. Flecainide test was repeated at the end of the RFA procedure (Figure III in the Data Supplement). The ECG was continuously recorded during the infusion and ST-segment–elevation and slope measurements were done before and after isoproterenol (Figure III in the Data Supplement). Finally, programed RV stimulation (baseline and during flecainide infusion) from the RV apex, with 3 basal cycle lengths (600–500–400 ms), and ≤3 ventricular extrastimuli until refractoriness or to 200 ms, was used for VT/VF induction.

Follow-Up
Patients were monitored for at least 3 days after the procedure. Before hospital discharge, echocardiography and 12-lead ECG were performed and each patient was followed monthly after the procedure.

Figure 1. A. Although the coved type ECG Brugada pattern is present spontaneously, during the procedure (B) Brugada pattern disappears, and mapping shows no abnormalities in the endocardium (left side) with minor low-voltage (<1.5 mV) areas (11.6 cm²) in the epicardium (right side).

Figure 2. Same patient as in Figure 1. After administration of flecainide, 12-lead ECG shows a typical coved pattern in V1–V2 (A), and the epicardial map (B) shows an increased area (from 11.6 cm² to 28.9 cm²) of high frequency low-voltage potentials characteristically located on the right ventricular outflow tract (C and D). In this area, there are also low-frequency low voltage potentials (E and F, arrows). Endocardial map remained unaltered after flecainide infusion (not shown).
After discharge, 12-lead ECG before and after flecainide testing and 24-hour ambulatory ECG monitoring were scheduled at each follow-up visit.

**Statistical Analysis**

Data are reported as medians with 25th to 75th percentiles or frequencies and percentage as necessary. The paired comparison in our sample was performed with Wilcoxon signed-rank test. Epicardial low-voltage (<1.5 mV) and epicardial black dot areas at baseline and under provocative test were analyzed with the Friedman test. A probability of <0.05 was considered significant. IBM SPSS Statistics for Windows, version 22.0 (Armonk, NY, IBM Corp) was used for the statistical analysis.

**Results**

**Study Population**

Fourteen male patients with typical BrS ECG pattern were enrolled and completed the study protocol. Table 1 shows the clinical characteristics of the study patients. Median age of the patients was 39 years (25th–75th percentiles 30.3–42.3). Most patients (79%) had a family history of sudden death, 10 patients (71%) experienced previous syncopal episodes, and 4 patients (29%) had dizziness. In 1 patient, syncope occurred during physical activity. Three patients also experienced episodes of symptomatic atrial fibrillation, whereas 1 patient had episodes of symptomatic ventricular tachycardia.

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<th>Genetic Testing</th>
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<td>VF</td>
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<td>−</td>
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**Table 1. Clinical Characteristics of the Study Patients**

**Table Notes:**

AF indicates atrial fibrillation; AVNRT, atrioventricular nodal reentrant tachycardia; BrS, Brugada syndrome; EPT, electrophysiological testing; ICD, implantable cardioverter–defibrillator; M, male; RFA, radiofrequency ablation; SVT, supraventricular tachyarrhythmias; VF, ventricular fibrillation; and VT, ventricular tachycardia.
of symptomatic supraventricular tachyarrhythmias because of atrioventricular node-reentrant tachycardia occurring during the preceding year. No patient had evidence of structural heart disease according to physical examination and echocardiography. In 2 of 8 patients magnetic resonance imaging showed minimal contractile abnormalities in the RVOT. Exercise testing in all patients excluded myocardial ischemia. No patient had evidence of structural heart disease according to physical examination and echocardiography. In 2 of 8 patients magnetic resonance imaging showed minimal contractile abnormalities in the RVOT. Exercise testing in all patients excluded myocardial ischemia. No patient had evidence of structural heart disease according to physical examination and echocardiography. In 2 of 8 patients magnetic resonance imaging showed minimal contractile abnormalities in the RVOT. Exercise testing in all patients excluded myocardial ischemia. No patient had evidence of structural heart disease according to physical examination and echocardiography. In 2 of 8 patients magnetic resonance imaging showed minimal contractile abnormalities in the RVOT. Exercise testing in all patients excluded myocardial ischemia. No patient had evidence of structural heart disease according to physical examination and echocardiography. In 2 of 8 patients magnetic resonance imaging showed minimal contractile abnormalities in the RVOT. Exercise testing in all patients excluded myocardial ischemia.

Patients with a positive type 1 BrS ECG pattern, spontaneously occurring in 12 patients or after flecainide infusion in the remaining 2 patients (Figure IV in the Data Supplement). Before enrollment, programmed electric ventricular stimulation induced VF or polymorphic rapid VT in all patients who subsequently underwent ICD implantation. Genetic testing for SCN5A was performed in all patients but it was positive only in 4 patients (28.6%). Additional genetic variants were not performed. The median procedure, fluoroscopy, and cumulative RF application times were 156 (114–172), 18.4 (15.8–25.3), and 23.8 (18.1–28.5) minutes, respectively (Table 2).

Identification of Functional BrS Substrate by Provocative Testing

Baseline epicardial voltage mapping was successfully acquired during sinus rhythm and after flecainide-induced type 1 BrS ECG pattern in all patients (Table 2; Figures 1–3). Abnormal epicardial electroanatomic voltage maps, characterized by low-voltage (<1.5 mV) areas, variable for extension and distribution before and after flecainide, were recorded in all patients (Table 3), and the involved region commonly was the right anterior free wall and RVOT (Figures 2 and 3; Figure I in the Data Supplement). Overall, the median baseline low-voltage (<1.5 mV) area was 17.6 cm² (12.1–24.2), increasing to 28.5 cm² (21.6–30.2) after flecainide (P=0.001; Table 3). Similarly, the median abnormal epicardial electrogram area increased from 19.0 cm² (17.5–23.6) to 27.3 cm² (24.0–31.2) after flecainide infusion (Table I in the Data Supplement). Delay and duration of local abnormal ventricular electrograms also increased after flecainide infusion in all patients (Table II in the Data Supplement). Of note, patient 8 showed the largest low-voltage (<1.5 mV) area (56.6 cm²; 34.9% of the total area), which after flecainide infusion increased to 64.2 cm² (41.7% of total area; Table 3).

Figure 1 shows that at baseline, in the absence of a clear type I ECG BrS pattern, electroanatomical maps demonstrated no abnormalities on endocardium, whereas minimal areas of low voltage (<1.5 mV) and abnormal electrograms were found in epicardial maps exclusively on the anterior aspect of the RV free wall or RVOT. During provocative tests and coincident with the appearance of a type 1 BrS ECG pattern, multiple additional areas variable in extension and distribution of low voltage and abnormal fragmented and delayed potentials were recorded on the RV free wall and RVOT epicardium, which became larger after flecainide. Interestingly, there was a relationship between ECG pattern changes and low-voltage area. The wider the low-voltage area (<1.5mV), the higher the ST-segment–elevation and coved type appearance.

Elimination of Functional BrS Substrate

Once the epicardial arrhythmogenic substrate was accurately identified/quantified under provocative test and tagged on the electroanatomic voltage maps, epicardial RF applications were delivered. After RFA, flecainide infusion was repeated to ensure complete elimination of the functional Br substrate with all abnormal epicardial potentials. Table 3 and Table I in the Data Supplement show low voltage and abnormal electrograms areas for each patient after epicardial RFA. In all patients, local abnormal ventricular electrograms completely disappeared in low-voltage areas (<1.5 mV) after a median RF application duration of 23.8 minutes (18.1–28.5) and were eliminated.

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Table 2. Procedural and Mapping Data of the Study Population

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RFA indicates radiofrequency ablation.
replaced by residual dense scar (<0.5 mV) areas of 25.9 cm² (19.6–31.0; Table 3; Figure II in the Data Supplement). After RFA, all patients became noninducible during programed electric stimulation using ≤3 extrastimuli. ECG did not show any change suggesting Br ECG pattern after flecainide.

Remapping
Epicardial electroanatomic voltage remap was systematically performed in all patients after substrate elimination, which confirmed complete elimination of abnormal electrograms in low-voltage areas. This substrate elimination was associated to the absence of a BrS ECG pattern.

Effect of Provocative Tests/RF Applications on the ECG BrS Pattern
Provocative testing and epicardial RF applications commonly resulted in characteristic transient changes of the BrS ECG pattern. During flecainide infusion, type I ECG BrS pattern maximized beginning more evident (Figures 2 and 4). Figure V in the Data Supplement shows that immediately after starting the first RF applications on the epicardium, varying degree of ST-segment changes developed. Although next applications were administered, the ECG pattern progressively changed to a typical ischemic-like flat ST-segment elevation in V1 and V2 (from 10 to 30 mm) with inversion in the slope from descendent to ascendant, which was not further modified after flecainide or isoproterenol infusion persisting without clinical, laboratory, or echocardiographic abnormalities ≤3 days after RFA.

Complications
There were no complications during the procedure.

Follow-Up
Postprocedure, predischarge, and follow-up 12-lead ECG confirmed the absence of BrS ECG pattern before and after flecainide test in all patients, and after a median follow-up of 5 months (3.8–5.3) ECG remained normal despite flecainide testing (Figure 4), and ICD did not show arrhythmic events.

One patient had a postablation pericarditis characterized by transient chest pain associated with diffuse ST-segment elevation (not modified by flecainide or isoproterenol infusion; Figure VI in the Data Supplement), normal serial cardiac enzymes, and higher inflammatory markers, which spontaneously normalized 2 days later. Echocardiography showed no evidence of pericardial effusion.

Discussion
Main Findings
This study while confirming the data from Nademanee et al. and Haïssaguerre et al. on epicardial ablation of BrS, for the first time systematically evaluated before and after flecainide testing the role of arrhythmogenic epicardial substrate as mechanism of type I ECG BrS pattern and VF in a series of selected consecutive patients with BrS. The results indicate that abnormal substrate, which is variable in extension and distribution, is characteristically located in the RV epicardium, usually but not exclusively in the RVOT. Its complete elimination by RFA, as confirmed by postablation remapping and flecainide testing, results in simultaneous disappearance of typical BrS ECG pattern and no inducibility of VT/VF in all patients. The proposed mapping and ablation strategy may be safely and effectively applied to a larger patient population with BrS at potential risk to prevent VF and sudden cardiac death.

### Table 3. Characteristics of Electroanatomic Voltage Areas Under Before and After Flecainide and After Radiofrequency Ablation

<table>
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<tr>
<th>Patient</th>
<th>Total Epicardial Area, cm²</th>
<th>Epicardial Low-Voltage Mapping</th>
</tr>
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<td></td>
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<td>Area ≤1.5 mV/cm²</td>
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<tr>
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<td>Baseline (%)</td>
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<tr>
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<td>18.2 (8.2)</td>
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<td>227</td>
<td>12.3 (5.4)</td>
</tr>
<tr>
<td>3</td>
<td>246</td>
<td>24.7 (10.1)</td>
</tr>
<tr>
<td>4</td>
<td>183</td>
<td>13.0 (7.1)</td>
</tr>
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<td>5</td>
<td>185</td>
<td>15.2 (8.2)</td>
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<td>6</td>
<td>400</td>
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<td>7</td>
<td>198</td>
<td>11.6 (5.8)</td>
</tr>
<tr>
<td>8</td>
<td>162</td>
<td>56.6 (34.9)</td>
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<td>9</td>
<td>201</td>
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<td>10</td>
<td>235</td>
<td>21.4 (9.1)</td>
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<tr>
<td>11</td>
<td>196</td>
<td>11.2 (5.7)</td>
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<td>12</td>
<td>198</td>
<td>24.0 (12.1)</td>
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<tr>
<td>14</td>
<td>201</td>
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<tr>
<td>Median</td>
<td>(25th–75th percentiles)</td>
<td>17.6 (12.1–24.2)</td>
</tr>
</tbody>
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RFA indicates radiofrequency ablation.
Electrophysiological and Electroanatomic Substrate in BrS

At present, ICDs represent the only treatment modality for the secondary prevention of sudden cardiac death in patients with BrS. Guidelines limit this therapy to patients with a history of cardiogenic syncope, VF, and aborted sudden cardiac death. On the basis of recent clinical observations, endocardial or epicardial RFA have been proposed as a new promising strategy just to prevent frequent ICD shocks in BrS with ICD.6,8,9 Initially, Haïssaguerre et al6 suggested focal endocardial ablation with elimination of triggers from RVOT as a promising strategy to prevent VF in patients with BrS. More recently, Nademanee et al8 have reported that epicardial RFA of abnormal electrograms, exclusively localized in the anterior aspect of the RVOT, was able to prevent VT/VF inducibility in 7 of 9 patients (78%), resulting in normalization of the Br ECG pattern in 5 of the 9 patients (55%). This study confirms and extends these preliminary observations,6,8 providing new insights on mapping/ablation strategy to more accurately identify and quantify the extent and distribution of arrhythmogenic epicardial substrates, as underlying mechanism of both BrS ECG pattern and VT/VF in patients with BrS. The results, although supporting that abnormal arrhythmogenic substrate is commonly located in the RVOT epicardium,7,9 clearly indicate...
that its extension and distribution can be variable in the single patient potentially extending beyond the RVOT. Indeed, complete elimination of abnormal functional epicardial substrate guided by flecainide testing before and after RFA resulted in disappearance of the BrS ECG pattern in all patients, remaining stable after the procedure as well as during the follow-up, as confirmed by flecainide testing. It is likely that the lower success rates and delayed effects of epicardial ablation on the Br ECG pattern, as reported by Nademanee et al., were because of incomplete or limited epicardial substrate identification and elimination in the absence of provocative tests during the procedure. We systematically performed before and after flecainide infusion and remap that allowed a more accurate identification and elimination of any arrhythmogenic substrate with regard to its extension and distribution. Of note, after flecainide the low-voltage epicardial areas expanded >2× (from 17.6 to 28.5 cm²) and the duration of abnormal electrograms increased >2× in almost all patients facilitating identification and subsequent elimination of arrhythmogenic substrates, which in many patients extended beyond the anterior aspect of the RVOT. Most importantly, epicardial substrate elimination was associated with normalization of BrS ECG pattern and the absence of VT/VF inducibility in all patients without complications with a total procedure time similar to or even shorter than that reported by Nademanee et al. Only 1 patient had a transient diffuse ST-segment elevation in the absence of pericardial effusion, which spontaneously normalized 2 days later. These findings taken together emphasize the need of an accurate identification of potentially abnormal substrates unmasked by provocative tests to acutely achieve and stably maintain definitive elimination of the ECG BrS pattern while avoiding complications.

Mechanisms of Type I BrS ECG Pattern and VF

Currently, the underlying pathophysiological mechanisms surrounding the abnormal BrS ECG pattern and VT/VF in patients with BrS is a matter of controversy. Two confronted theories suggest that either a repolarization or a depolarization defect is responsible for the characteristic phenotype. The results of this study support the role of an epicardial depolarization disorder, rather than of repolarization abnormalities as mechanisms of both ECG pattern and VF. Indeed, worsening of Br ECG pattern after flecainide was always associated with increasing areas of low voltage and abnormal depolarizations. Also, and interestingly, immediately after the first few RF applications, type I ECG BrS pattern apparently worsened in V1 and V2. Characteristically, with new applications, in the absence of symptoms there was a localized transient immediate inversion in the slope from descendent to ascend in leads V1–V2 without T-wave abnormality, as a consequence of epicardial RF application, which did not change after both flecainide and isoproterenol infusion, thus excluding a BrS-like ECG pattern or transient myocardial ischemia. Normalization of Br ECG pattern was associated with elimination of such substrate after RFA. The effect of epicardial RFA in eliminating both BrS ECG pattern and inducibility of VT/VF after flecainide is clinically important and convincingly supports the depolarization theory rather than the repolarization theory.

Clinical Implications

This study has pathophysiologic and therapeutic implications. Substrate epicardial mapping and ablation guided by provocative testing could be considered a reproducible, safe, and effective strategy to definitively treat patients with type I BrS ECG pattern and risk of sudden death. This systematic preventive strategy can result in the elimination of the BrS phenotype characteristics that are traditionally used to decide whether an ICD should be implanted.

Limitations

This study includes 14 patients and despite uniform, unequivocal, and consistent results, a larger study with longer follow-up is mandatory to confirm them. Although the persistent normalized ECG BrS pattern after epicardial RFA and during follow-up would have been because of the spontaneous disappearance of the ECG pattern, negative flecainide tests immediately after RFA, before and after discharge as well as during the follow-up strongly confirm the complete and stable elimination of the ECG BrS pattern in all patients.

Conclusions

This study provides new insights into the mechanism, prevention, and treatment of patients with BrS, who are at risk of sudden death. Epicardial areas variable in extension and distribution mainly located in the RV free wall and RVOT unmasked by flecainide testing are responsible for both BS ECG pattern and VT/VF development. Elimination of such abnormal arrhythmogenic areas by epicardial RFA is able to eliminate both BrS ECG pattern and VF inducibility without complications. Although larger studies with longer follow-up are required, our results have major physiopathological and clinical implications because they provide new important information leading to a potential definitive treatment of the phenotypic manifestations of BrS, in which current indication to ICD is recommended only for patients with previous symptoms.

Acknowledgments

We thank Dr Crisà and the staff of the Electrophysiology laboratory for their technical assistance.

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Disclosures

None.

References


Brugada Syndrome Phenotype Elimination by Epicardial Substrate Ablation
Josep Brugada, Carlo Pappone, Antonio Berruezo, Gabriele Vicedomini, Francesco Manguso, 
Giuseppe Ciconte, Luigi Giannelli and Vincenzo Santinelli

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Table S1. Characteristics of epicardial abnormal electrograms area before and after flecainide.

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<th>Flecainide, cm²</th>
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</tr>
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<td>30.2</td>
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<tr>
<td>7</td>
<td>17.3</td>
<td>31.6</td>
</tr>
<tr>
<td>8</td>
<td>59.0</td>
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<td>Median (25-th to 75-th percentiles)</td>
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<td>27.3 (24.0 to 31.2)</td>
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Table S2. Characteristics of abnormal epicardial electrograms before and after flecainide.

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<th>Duration, ms (mean; min, max)</th>
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<td>33.4 (21.8, 36.5)</td>
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<td>21.0 (13.9, 25.2)</td>
<td>48.6 (24.4, 54.9)</td>
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<td>16.0 (11.0, 18.9)</td>
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<td>22.6 (16.1, 28.0)</td>
<td>35.6 (24.8, 41.3)</td>
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<td>32.4 (23.7, 39.9)</td>
<td>48.1 (29.2, 51.7)</td>
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<td>35.1 (27.1, 41.3)</td>
<td>52.5 (34.6, 56.9)</td>
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<td>26.4 (19.3, 31.2)</td>
<td>42.7 (27.4, 49.1)</td>
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<td>18.0 (13.0, 24.3)</td>
<td>41.2 (28.0, 69.0)</td>
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<td>21.6 (11.0, 41.4)</td>
<td>36.2 (21.0, 52.4)</td>
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<td>26.4 (10.2, 45.0)</td>
<td>47.8 (19.0, 59.2)</td>
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<td>31.2 (25.8, 39.7)</td>
<td>50.9 (33.4, 55.2)</td>
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<td></td>
<td>20.2 (14.3, 26.2)</td>
<td>33.9 (22.7, 39.5)</td>
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<tr>
<td>Median</td>
<td>23.4 (20.6 to 30.5)</td>
<td>42.0 (34.9 to 48.2)</td>
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</table>

(25-th to 75-th percentiles)
Figure S1. The epicardial bipolar low-voltage ventricular potentials before (A) and after flecainide (B) are shown. Note that flecainide induces fragmentation of potentials with double potentials (B).
Figure S2. Mapping after RFA shows a dense low voltage area (< 0.5 mV) depicted in red (A). Inside this area there are low voltage ventricular potentials from 0.28 mV to 0.44 mV (B, C and D).
Figure S3

Figure S3. Twelve-lead ECG after RFA (Left panel) shows ST segment elevation, which remained unchanged after both flecainide (Middle panel) and isoproterenol (Right panel).
Figure S4. The ECG at baseline (A) and after flecainide infusion (B). Note that flecainide infusion results in type I Br ECG pattern.
Figure S5. Immediately after RFA application, there is an increase of type I BrS ECG pattern (A, arrows), which after further applications is progressively replaced by an ascendant ST segment elevation (B and C, arrows).
Figure S6. After RFA, the 12-lead ECG shows a diffuse ST segment elevation (A), which disappears one month later (B).