Clinical and Electrocardiographic Differences in Brugada Syndrome With Spontaneous or Drug-Induced Type 1 Electrocardiogram

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Background: Spontaneous type 1 electrocardiogram (ECG) in the right precordial lead is a dominant predictor of ventricular fibrillation (VF) in Brugada syndrome (BrS). In some BrS patients with VF, however, spontaneous type 1 ECG is undetectable, even in repeated ECG and immediately after VF. This study investigated differences between BrS patients with spontaneous or drug-induced type 1 ECG.

Methods and Results: We evaluated 15 BrS patients with drug-induced (D-BrS) and 29 with spontaneous type 1 ECG (SP-BrS). All patients had had a previous VF episode. In each D-BrS patient, ECG was recorded more than 15 times (mean, 46±34) during 7.2±5.1 years of follow-up. Age and family history were comparable between groups. Inferolateral early repolarization (ER) was observed in 13 D-BrS (87%) at least once but in only 3 SP-BrS (10%, P<0.01). Immediately after VF, inferolateral ER was accentuated in 9 of 10 D-BrS, while type 1 ECG was accentuated in 12 of 16 SP-BrS. Fragmented QRS in the right precordial lead and aVR sign were absent in D-BrS but present in 20 (69%, P<0.01) and 11 (38%, P<0.01) SP-BrS, respectively. There was no prognostic difference between groups.

Conclusions: Although having similar clinical profiles, there are obvious ECG differences between VF-positive BrS patients with spontaneous or drug-induced type 1 ECG. The inferolateral lead rather than the right precordial lead on ECG may be particularly crucial in some BrS patients.

Key Words: Brugada syndrome; Type 1 electrocardiogram; Ventricular fibrillation
through sodium channel-blocker administration. These patients' clinical characteristics and the differences between them and VF-positive BrS patients with spontaneous type 1 ECG have not been examined.

Recently, several reports have suggested the therapeutic effectiveness of catheter ablation on the RVOT epicardium in patients with BrS.9,10 Yet the area of abnormal low-voltage and/or fractionated electrogram recording was observed beyond the RVOT in some cases,10 and recurrence of VF has been reported in a few cases after ablation on the RVOT epicardium, despite normalization of spontaneous type 1 ECG.11 Accordingly, there is a possibility that the critical arrhythmogenic substrate extends beyond the RVOT in some BrS patients with VF episodes.

An inferolateral early repolarization (ER) pattern has also been reported to be associated with fatal arrhythmic events in BrS.12-14 Because the inferior and lateral ECG leads may represent electrophysiologic manifestation in the inferior right/left ventricle and the lateral left ventricle, respectively, the arrhythmogenic substrate could also be present beyond the RVOT in some BrS patients.

Accordingly, the aim of this study was to evaluate the clinical, electrocardiographic and electrophysiological differences between VF-positive BrS patients with spontaneous or drug-induced type 1 ECG.

Methods

Study Population

We retrospectively identified BrS patients who had experienced ≥1 episode of VF. We assessed 29 consecutive patients with spontaneous type 1 Brugada ECG (SP-BrS group) and 15 patients with drug-induced type 1 Brugada ECG (D-BrS group) between 1993 and 2018. BrS was defined as the manifestation of type 1 ECG, which is characterized by a coved-type ST-segment elevation ≥0.2 mV followed by a negative T-wave in lead V1 or V2 at the 2nd, 3rd or 4th intercostal space in the presence or absence of a Class IC antiarrhythmic drug (pilsicainide).14 Type 1 ECG was recorded after administration of pilsicainide at a dose of 1 mg/kg over a 10-min period in all D-BrS patients. Patients with complete right bundle branch block were also included in this study. All patients underwent echocardiography to exclude structural cardiac abnormalities. Patients with coronary artery disease, long QT syndrome, short QT syndrome, or catecholaminergic polymorphic ventricular tachycardia were excluded from both groups. This study was approved by the Institutional Research Board of the National Cerebral and Cardiovascular Center.

ECG Analysis

ECG characteristics were evaluated by baseline 12-lead ECGs (25 mm/s and 10 mm/mV). ECG was recorded with a 0.05-150 Hz bandwidth and no less than 15 times during a follow-up period of 12.7±8.3 years in the SP-BrS group and 7.2±5.1 years in the D-BrS group. In each D-BrS patient, ECG was recorded 46±34 times on average. In 16 of 29 SP-BrS and 10 of 15 D-BrS patients, ECG was documented immediately after VF episode and admission to an emergency room. Others lacked an ECG immediately following the recovery from VF because of transfer to our hospital. We considered the ECG recorded 24 h after a VF episode to be the chronic phase. Accentuated type 1 ECG was defined as either type 1 ECG appearing in more leads (≥1 lead) than in the chronic phase or showing exaggerated ST-segment elevation (≥0.1 mV) than in the chronic phase. The ER pattern is characterized by elevation of the J-point (≥0.1 mV), with slurring or notching of the terminal portion of the QRS complex in at least 2 consecutive inferior (II, III, aVF) or lateral (I, aVL, and V4–6) leads.17 Accentuated ER was defined as prominent ER (≥0.2 mV) recorded or, additionally, ≥1 lead showing ER was observed compared with baseline. Fragmented QRS (f-QRS) was defined as ≥4 spikes within the QRS complex in 1 lead or ≥8 spikes in all of the leads V1–3.18 Heart rate and QRS duration were measured in lead II. The QT interval was measured in leads II, V2 and V5. The corrected QT (QTc) interval in leads II, V2 and V5 was defined as the interval from the peak of a positive T-wave or the nadir of a negative T-wave to the end of the T-wave.19 Significant S-wave was defined as S-wave amplitude ≥0.1 mV and/or duration ≥40 ms in lead I as previously reported.20 As described in detail previously, we selected leads II or V5 for the analysis of ER amplitude before and after pilsicainide administration.21 All ECGs were reviewed blindly by 2 authors (T. Nagayama, S.N.).

Clinical Testing

Clinical profiles including age at the first episode of VF, sex, family history of SCD, conditions of VF occurrence, and prognosis were collected for all patients. Signal-averaged ECG (SAECG) (Spiderview, Ela Medical Inc., Arvada, CO, USA) was performed for 13 of 15 D-BrS patients and 25 of 29 SP-BrS patients. The filtered QRS duration (QRSd), the root-mean square voltage of the terminal 40 ms in the filtered QRS complex (RMS40) and the duration of low-amplitude signals <40 µV in the terminal filtered QRS complex (LAS40) were measured with SAECG. A late potential (LP) was considered to be positive when more than two-thirds of the criteria (fQRSd >114 µs, RMS40 <20 µV and LAS40 >38 ms) were met. Electrophysiological study (EPS) was conducted for 19 SP-BrS and 5 D-BrS patients to evaluate the inducibility of VF as previously described.16

aVR Sign

Previous reports have suggested that the aVR sign, which may reflect conduction delay in the anterior right ventricle, especially in the RVOT, is associated with fatal arrhythmic events in BrS patients.22 The aVR sign was defined as R wave ≥0.3 mV or R/q ≥0.75 in lead aVR as previously reported.

Gene Mutation Analysis of SCN5A

Genetic testing for mutations in the SCN5A gene was performed for 15 SP-BrS and 5 D-BrS patients as previously described.23,24

Statistical Analysis

Statistical analysis was performed using JMP version 12.0.1 statistics (SAS Institute Inc., Cary, NY, USA). All values are expressed as the mean±SEM. The chi-square test was used for categorical variables. Means were compared between 2 groups using Student’s t-test or Mann-Whitney U-test. Arrhythmic events during the follow-up period were evaluated using the log-rank test and were described using a Kaplan-Meier curve. Differences were considered statistically significant when the P-value was <0.05.
ECG Features in Brugada Syndrome

Table 1. BrS Patients’ Characteristics

<table>
<thead>
<tr>
<th></th>
<th>SP-BrS (n=29)</th>
<th>D-BrS (n=15)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>42.3±10.9</td>
<td>39.2±13.3</td>
<td>0.43</td>
</tr>
<tr>
<td>Sex: male</td>
<td>29 (100%)</td>
<td>13 (87%)</td>
<td>0.04</td>
</tr>
<tr>
<td>Family history of SCD</td>
<td>5 (17%)</td>
<td>2 (13%)</td>
<td>0.74</td>
</tr>
<tr>
<td>Prior syncope</td>
<td>11 (38%)</td>
<td>1 (7%)</td>
<td>0.03</td>
</tr>
<tr>
<td>VF occurrence during rest or sleep</td>
<td>15 (52%)</td>
<td>7 (47%)</td>
<td>0.75</td>
</tr>
<tr>
<td>Inducible VF on EPS</td>
<td>16/19 (84%)</td>
<td>3/5 (60%)</td>
<td>0.24</td>
</tr>
<tr>
<td>Late potential on SAECG</td>
<td>20/25 (80%)</td>
<td>7/13 (54%)</td>
<td>0.09</td>
</tr>
<tr>
<td>SCN5A gene mutation</td>
<td>3/15 (20%)</td>
<td>1/5 (20%)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

SP-BrS, Brugada syndrome (BrS) with spontaneous type 1 electrocardiogram (ECG); D-BrS, Brugada syndrome with drug-induced type 1 ECG; EPS, electrophysiological study; SAECG, signal-averaged electrocardiography; SCD, sudden cardiac death; VF, ventricular fibrillation.

Table 2. ECG Characteristics of BrS Patients

<table>
<thead>
<tr>
<th></th>
<th>SP-BrS (n=29)</th>
<th>D-BrS (n=15)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>64.9±9.4</td>
<td>65.2±8.4</td>
<td>0.92</td>
</tr>
<tr>
<td>QRS duration (ms)</td>
<td>112±19</td>
<td>99±12</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>QT in lead II (ms)</td>
<td>390±27</td>
<td>377±40</td>
<td>0.21</td>
</tr>
<tr>
<td>QT in lead V2 (ms)</td>
<td>410±51</td>
<td>379±44</td>
<td>0.05</td>
</tr>
<tr>
<td>QT in lead V5 (ms)</td>
<td>390±30</td>
<td>379±45</td>
<td>0.34</td>
</tr>
<tr>
<td>QTc in lead II (ms)</td>
<td>404±25</td>
<td>391±30</td>
<td>0.14</td>
</tr>
<tr>
<td>QTc in lead V2 (ms)</td>
<td>426±59</td>
<td>394±37</td>
<td>0.07</td>
</tr>
<tr>
<td>QTc in lead V5 (ms)</td>
<td>404±30</td>
<td>393±36</td>
<td>0.31</td>
</tr>
<tr>
<td>Tpeak–Tend in lead II (ms)</td>
<td>90±17</td>
<td>78±16</td>
<td>0.03</td>
</tr>
<tr>
<td>Tpeak–Tend in lead V2 (ms)</td>
<td>108±38</td>
<td>85±17</td>
<td>0.01</td>
</tr>
<tr>
<td>Tpeak–Tend in lead V5 (ms)</td>
<td>88±18</td>
<td>82±16</td>
<td>0.26</td>
</tr>
<tr>
<td>Significant S-wave (≥0.1 mV and/or ≥40 ms) in lead I</td>
<td>24 (83%)</td>
<td>8 (53%)</td>
<td>0.04</td>
</tr>
<tr>
<td>Fragmented QRS (right precordial lead)</td>
<td>20 (69%)</td>
<td>0 (0%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>ER (inferior and/or lateral lead)</td>
<td>3 (10%)</td>
<td>13 (87%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Accented ER immediately after VF</td>
<td>–</td>
<td>9/10 (90%)</td>
<td>–</td>
</tr>
<tr>
<td>Accented type 1 ECG immediately after VF</td>
<td>12/16 (75%)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>aVR sign</td>
<td>11 (38%)</td>
<td>0 (0%)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

ER, early repolarization; QTc, corrected QT. Other abbreviations as in Table 1.

Results

Clinical characteristics of the patients in each group are shown in Table 1. Mean age at diagnosis, family history of SCD, occurrence of VF during rest or sleep, inducibility of VF on EPS, and the presence of LP on SAECG were not different between the SP-BrS and D-BrS groups. Both groups were male dominant. Although all SP-BrS patients were male, the D-BrS group contained 2 female patients. Prior syncope attack before VF episode was more common in the SP-BrS group (P=0.03). Mutations in SCN5A were identified in 3 of 15 (20%) SP-BrS patients and in 1 of 5 (20%) D-BrS patients (P=1.0).

Table 2 shows the ECG characteristics. Heart rate, QT and QTc interval in leads II, V2, V5, and Tpeak–Tend in lead V5 were not different between the 2 groups. Tpeak–Tend in leads II and V2 were significantly longer in SP-BrS patients (P=0.03 and P=0.01, respectively). In the SP-BrS group (Figures 1,2), f-QRS was observed in 20 of 29 patients (69%), but none of the patients in the D-BrS group (Figures 3,4) had f-QRS in any of multiple ECG recordings (P<0.01). On the other hand, ER pattern in the inferior and/or lateral lead was observed in 13 of 15 patients (87%) in the D-BrS group at least once (Figures 3,4), but in only 3 of 29 patients (10%) in the SP-BrS group (P<0.01). Among 13 D-BrS patients with inferolateral ER, the ER was recorded continuously in 11 patients and intermittently in 2 patients. After administration of pilsicainide, the ER amplitude was attenuated in all 11 patients with continuous ER manifestation (pre: 0.20±0.09 mV, post: 0.07±0.05 mV, P<0.001). Interestingly, 12 of 16 SP-BrS patients showed an accentuation of type 1 ECG immediately after the VF episode (Figure 2). In contrast, an accentuated ER without type 1 ECG was observed in 9 of 10 D-BrS patients immediately after the VF episode (Figures 3,4). The presence of the aVR sign was significantly more common in the SP-BrS group than in the D-BrS group (11/29; 38% vs. 0/15; 0%, P=0.01). Moreover, significant S-wave in lead I was present in 24 (83%) SP-BrS patients, but in 5 (53%) D-BrS patients (P=0.04). At the initial episode, a VF storm, defined as ≥3 separate episodes of polymorphic ventricular tachycardia or VF within 24 h, occurred in 1 SP-BrS patient and 2
D-BrS patients.

The mean follow-up period in the SP-BrS and D-BrS groups was 12.8±8.3 and 7.2±5.1 years, respectively; 1 SP-BrS patient and 1 D-BrS patient were followed without ICD implantation. During the follow-up, 15 patients (52%) in the SP-BrS group and 3 patients (20%) in the D-BrS group developed VF recurrence or SCD (1 D-BrS patient). Of these, 3 patients in the SP-BrS group developed VF storm, but none in the D-BrS group (log-rank test, P=0.40). One patient in the SP-BrS group committed suicide related to depression during the follow-up period. Kaplan-Meier analysis of VF recurrence or SCD comparing the SP-BrS and D-BrS groups revealed no prognostic difference (event rate: 7.4%/year in SP-BrS, 3.4%/year in D-BrS, log-rank test; P=0.13, Figure 5).

Discussion

The major finding of our study was the impressive difference in the ECG characteristics between BrS patients with previous VF episodes who exhibited spontaneous type 1 ECG and those who exhibited drug-induced type 1 ECG. SP-BrS patients displayed spontaneous type 1 ECG in the right precordial lead and accentuation of type 1 ECG immediately after a VF episode. D-BrS patients, in contrast, displayed an ER pattern in the inferior and/or lateral leads without spontaneous type 1 ECG and accentuation of the ER pattern immediately after a VF episode. In addition, both f-QRS in the right precordial lead and the aVR sign were absent in D-BrS patients but frequently observed in SP-BrS patients.

In contrast to the ECG manifestations, clinical characteristics are quite similar between BrS patients with spontaneous or drug-induced type 1 ECG. In the present SP-BrS and D-BrS groups, VF developed under similar conditions; occurrence of VF during rest or sleep was common in both groups. Furthermore, Kaplan-Meier analysis revealed no significant difference in the recurrence
of VF or SCD between the SP-BrS and D-BrS groups. SCN5A, the most common gene associated with BrS, has been identified in approximately 20–25% of BrS patients. In the present study, the mutation rate of SCN5A was 20% in both groups. Accordingly, BrS with spontaneous type 1 ECG and that with drug-induced type 1 ECG could be considered to constitute a single entity in terms of arrhythmia mechanism.

Several studies have shown that the RVOT is crucial in the arrhythmogenesis of BrS. The RVOT correlates with the right precordial leads placed in the standard and upper intercostal spaces in the parasternal position. The locations of the ECG leads showing a type 1 pattern correlate strongly with the anatomic location of the RVOT. The presence of f-QRS in the right precordial lead correlates with increased risk for VF in BrS. In the present study, SP-BrS patients showed spontaneous type 1 ECG and f-QRS in the right precordial lead, and accentuation of type 1 ECG immediately after a VF event. We also found that the incidence of positive aVR sign was higher in SP-BrS patients than in D-BrS patients. In BrS patients, the aVR sign has been suggested to reflect right ventricular conduction delay, which is associated with arrhythmic events. The aVR lead enables us to view the heart from the right upper side and therefore primarily observe the RVOT. In addition, the presence of a deep and/or large S-wave in lead I, which represents a conduction delay in the RVOT, has been also demonstrated to be a powerful predictor of VF in patients with BrS. In the present study, the presence of a significant S-wave in lead I was higher in the SP-BrS group than in the D-BrS group. Thus, our results could indicate that the predominant arrhythmogenic substrate of SP-BrS patients may be related to the RVOT represented by the right precordial leads.

In the majority of the D-BrS patients, however, accentuation of the ER pattern was observed during VF storm or immediately after a VF episode, although type 1 ECG in the right precordial leads was undetectable in multiple ECG recordings even immediately after VF. Because type 1 ECG appeared after administration of a sodium-channel blocker. Specific features in Brugada syndrome (BrS) are shown in Figure 3. Representative typical ECG manifestation in the D-BrS group. (A) ECG immediately after VF episode. (B) ECG after pilsicainide administration. (C–G) ECG in the chronic phase. ECG shows accentuation of the ER pattern (arrows) with larger amplitude in global leads immediately after the VF episode. ECG always displayed the ER pattern in the inferolateral leads, no fragmented QRS in the right precordial leads and no aVR sign. Type 1 ECG was provoked by pilsicainide administration (*). Although ECG was recorded repeatedly, spontaneous type 1 ECG was not observed even immediately after VF. The numbers listed below each ECG indicate the period after the VF episode. D-BrS, Brugada syndrome with drug-induced type 1 ECG. Other abbreviations as in Figures 1, 2.
blocker, these patients were diagnosed with BrS based on current diagnostic criteria. Yet the occurrence ofVF may actually be associated with the ER pattern in the inferior and/or lateral leads. In other words, the arrhythmogenic substrate in D-BrS patients may be located not only in the RVOT but also in the inferior right/left ventricle and lateral left ventricle as indicated by the inferior and/or lateral leads. We also speculate that the location of the ER pattern may be associated with the morphology and origin of premature ventricular contractions (PVC), which trigger VF. As shown in Figure 4, VF was triggered by PVC with right bundle-branch block type/superior axis in 1 D-BrS case with an inferior and lateral ER pattern. Accordingly, triggering PVC might originate from the left ventricle but not from the RVOT. However, recording of triggering PVC on 12-lead ECG is quite difficult and only a small number of records could be obtained. In the future, further studies will be necessary to prove this hypothesis.

Recent studies have provided evidence for repolarization and/or depolarization abnormality within the RVOT causing ventricular arrhythmias in patients with BrS. In epicardial mapping studies of BrS patients, Nademanee et al reported low-voltage areas with fragmented and delayed potentials in the epicardial region of the RVOT. In some cases,
ECG Features in Brugada Syndrome

however, this abnormal area extends beyond the RVOT, and recurrence of VF has been reported after ablation of the RVOT epidermid despite normalization of spontaneous type 1 ECG. On another front, the arrhythmogenic substrate for ER syndrome (ERS), a form of idiopathic VF characterized by ER pattern in the inferior and/or lateral leads, is suspected to be located in the region of the left ventricle. In the present study, the ECG manifestations of D-BrS patients were similar to those of ERS patients, suggesting that the arrhythmogenic substrate may likewise be located beyond the RVOT in D-BrS patients.

Clinical Implications
In general, BrS patients without spontaneous type 1 ECG are considered to be low risk for future arrhythmic events. However, once spontaneous VF occurs, careful follow-up is necessary in D-BrS patients. In the majority of the present D-BrS patients, type 1 ECG did not appear but the inferolateral ER pattern was exaggerated immediately after a VF episode, so the appearance of inferolateral ER may be crucial for the development of VF in D-BrS patients. Because the inferolateral lead may reflect the inferior ventricle or the lateral left ventricle, the arrhythmogenic substrate in D-BrS patients can be located beyond the RVOT. We speculate that epicardial ablation other than the RVOT should be considered in these patients if ablation only in the RVOT is insufficient. This issue should be confirmed in future study.

Study Limitations
First, this study was conducted at a single center using retrospective analysis. The number of BrS patients, and especially that of D-BrS patients, was small. We will need to evaluate a larger number of BrS patients with VF episodes or perform a multicenter investigation to confirm the results of this study. Second, we cannot rule out the possibility that some instances of type 1 ECG in D-BrS patients took on rare forms, which could have caused us to overlook those instances of type 1 ECG. A previous study reported that Holter ECG recording in the upper intercostal space was more useful for detecting type 1 ECG and that type 1 ECG was most frequently observed between 6 pm and 12 pm. Because it is well known that the ST-segment morphology in BrS patients exhibits both daily and circadian fluctuation, we may be underestimating the detection rate of type 1 ECG. However, because type 1 ECG was not only apparent but accentuated immediately after VF episodes in the majority of SP-BrS patients, the absence of a type 1 ECG recorded immediately after a VF episode may suggest D-BrS. Third, direct epicardial mapping was not evaluated in this study. Accordingly, the precise location of the arrhythmogenic substrate in each group was undetermined, and the differences in the ECG characteristics between SP-BrS and D-BrS were unexplained. In the future, further studies will be necessary to prove our hypotheses. In the present study, we evaluated the differences between BrS patients with spontaneous or drug-induced type 1 ECG, whereas a previous study has mainly evaluated the differences between idiopathic VF and BrS, and reported the significance of ER pattern in idiopathic VF. Accordingly, the goal of research is different between these 2 studies.

Conclusions
In BrS patients with previous VF episodes, the ECG patterns are different between patients with spontaneous type 1 ECG and those with drug-induced type 1 ECG, although the clinical characteristics of these groups are quite similar. SP-BrS patients displayed spontaneous type 1 ECG and f-QRS in the right precordial leads, and positive aVR sign. D-BrS patients, in contrast, displayed an ER pattern in the inferior and/or lateral leads, no f-QRS, and no aVR sign. Our results suggested that the inferolateral ECG lead may be particularly crucial in some BrS patients who have had episodes of VF and aborted SCD.

Conflicts of Interest / Relationships With Industry
None.

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