Electrical Storm in Patients With Brugada Syndrome Is Associated With Early Repolarization

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Background—Electrical storms (ESs) in patients with Brugada syndrome (BrS) are rare though potentially lethal. Methods and Results—We studied 22 men with BrS and ES, defined as ≥3 episodes/d of ventricular fibrillation (VF) and compared their characteristics with those of 110 age-matched, control men with BrS without ES. BrS was diagnosed by a spontaneous or drug-induced type I pattern on the ECG in the absence of structural heart disease. Early repolarization (ER) was diagnosed by J waves, ie, >0.1 mV notches or slurs of the terminal portion of the QRS complex. The BrS ECG pattern was provoked with pilsicainide. A spontaneous type I ECG pattern, J waves, and horizontal/descending ST elevation were found, respectively, in 77%, 36%, and 88% of patients with ES, versus 28% (P<0.0001), 9% (P=0.003), and 60% (P=0.06) of controls. The J-wave amplitude was significantly higher in patients with than without ES (P=0.03). VF occurred during undisturbed sinus rhythm in 14 of 19 patients (74%), and ES were controlled by isoproterenol administration. All patients with ES received an implantable cardioverter defibrillator and over a 6.0±5.4 years follow-up, the prognosis of patients with ES was significantly worse than that of patients without ES. Bepridil was effective in preventing VF in 6 patients.

Conclusions—A high prevalence of ER was found in a subgroup of patients with BrS associated with ES. ES appeared to be suppressed by isoproterenol or quinidine, whereas bepridil and quinidine were effective in the long-term prevention of VF in the highest-risk patients. (Circ Arrhythm Electrophysiol. 2014;7:1122-1128.)

Key Words: bepridil◼ Brugada syndrome◼ electrocardiography◼ isoproterenol◼ ventricular fibrillation◼

B rugada syndrome (BrS), characterized by ST-segment and J-point elevation in the right precordial leads of the ECG in the absence of structural heart disease, is a cause of sudden cardiac death caused by ventricular fibrillation (VF).1 Albeit rare, a subset of patients experiencing BrS develop potentially fatal storms of VF.2-4 Their clinical characterization is important from the perspectives of risk stratification and development of new and effective therapies.

Clinical Perspective on p 1128

We recently observed a case of BrS characterized by prominent J waves in the inferolateral leads of the 12-lead ECG and electrical storms (ESs).7 Case-control studies have described a close association between J waves, a sign of early repolarization (ER), and idiopathic VF.5-10 The presence of J waves in patients presenting with BrS may also be a predictor of poor prognosis.6,11-13 The purpose of this multicenter study was to evaluate the characteristics of patients with BrS and ES, with a special attention to the presence of J waves.

Methods

Study Population

We retrospectively identified 22 men at 8 Japanese medical institutions, who presented with BrS and ES, defined as ≥3 episodes of VF/d. BrS was diagnosed according to the following currently accepted criteria2,6,11-14: (1) ≥0.2 mV elevation of the J point with type 1 ST elevation in ≥1 right precordial lead(s) at baseline or after provocation with pilsicainide; (2) normal right and left ventricular
size and function on chest radiograph and transthoracic echocardiography. Among these 22 patients, 4 had been included in previous studies. Patients who had experienced a cardiac arrest or VF underwent provocation of coronary artery spasm with acetylcysteine or ergonovine. We randomly chose 110 age-matched men presenting with BrS and no history of ES as controls and compared their clinical and ECG characteristics with those of the patients with ES.

This study complied with the guidelines of the Declaration of Helsinki and was approved by the institutional review board of Gunma University Hospital. All patients granted their written, informed consent to participate in this study.

ECG Analysis
The RR, PR, QRS, QT, and corrected QT (using Bazett formula) intervals of the ECG were measured. An ER pattern was defined as the presence of a positive J wave, defined as a notch or slur at the terminal portion of the QRS complex, >0.1 mV in amplitude above the isoelectric line in ≥2 contiguous lead(s). The J wave was classified as inferior if present in leads II, III, and aVF; left precordial if present in leads V4 to V6; and high lateral if present in leads I and aVL. Using the definitions of Tikkanen et al., the ST-segment pattern after the J-point was classified as rapidly ascending/upsloping or horizontal/descending.

Data Analysis
The clinical characteristics, ECG intervals, J-wave prevalence and amplitude, and prevalence of spontaneous type 1 ECG pattern were compared in patients with versus without ES. When available, the ECG recorded during long-term follow-up were compared with those recorded at the time of ES, with special attention to the J waves. The patients’ pharmacological and nonpharmacological therapy and long-term outcomes were recorded. The antiarrhythmic drug regimens were chosen according to each physician’s preference and, if clinically ineffective, were replaced, in a trial and error manner.

Statistical Analysis
Continuous measurements are expressed as means±SD or medians and interquartile ranges, as appropriate, and categorical variables as counts and percentages. Differences between continuous variables were examined by the Mann-Whitney test, whereas categorical variables were compared by the Fisher exact test. We performed a logistic regression analysis in search of independent electrocardiographic variables. The statistical analyses were performed with the Eksuenu-Toukei 2012 statistical software package (Social Survey Research Information Co., Ltd). A P value <0.05 was considered statistically significant.

Results
Patients With VF Storm
The characteristics of 22 men with BrS and VF storms are shown in Table 1. ES was the first episode of VF in 16 patients, while it occurred 3.2±2.4 years after implantation of cardioverter defibrillators (ICD) in the other 6 patients. A spontaneous type 1 ECG pattern was observed in 17 patients, and a pilsicainide provocation test was needed in the remaining 5 patients. Acetylcysteine or ergonovine excluded the diagnosis of vasospastic angina in 9 of 9 patients who underwent provocation tests. VF was inducible in 6 of the 11 patients who underwent programmed ventricular stimulation to confirm the presence of an arrhythmogenic substrate promoting the development of VF or ventricular tachycardia.

VF Storm Characteristics
A mean of 25.2±8.2 VF episodes occurred during the storms. VF occurred between 8:00 AM and 6:00 AM in 14 patients (64%), between 6:00 AM and 8:00 AM in 7 patients (32%), and during both time intervals in 1 patient (4%). No apparent precipitating factor was identified.

The mode of VF onset was identified in 19 patients (Figure 1) and occurred during undisturbed sinus rhythm in 14 (74%), after a short-long-short sequence in 4 (21%), and under both circumstances in 1 patient (5%). The mean coupling interval of the first VF-triggering premature ventricular complex was 329±63 ms, ranging between 280 and 420 ms. The mode of VF onset was undetermined in 3 patients.

ER was present as J waves in 8 of the 22 patients (36%). The J waves were in the inferior ECG leads in 4 (Figure 2A), inferior and left precordial leads in 2 (Figure 2B), and inferior, left precordial and high lateral leads in 2 patients. A prominent accentuation of the J wave immediately before the onset of VF (Figures 3) was observed in 2 patients. The ST-segment pattern in patients with ES and J waves was rapidly ascending/upsloping in 1 (13%) and horizontal/descending in 7 patients (87%). VF during ES developed during undisturbed sinus rhythm in 6 patients with versus 9 patients without ER, and after a short-long-short sequence in 3 patients with versus 2 patients without ER; the presence of ER did not influence the mode of VF onset during ES (P=0.40). The coupling interval of the first VF-triggering premature ventricular complex in patients with (350[94]) versus without (301[130]) J waves, was similar (P=0.54).

Short-Term Management of VF
All episodes of VF were terminated by external defibrillation or by an ICD. Overdrive pacing, left cardiac sympathetic block combined with atropine, and oral disopyramide were effective in 1 patient each. Thereafter, intravenous isoproterenol became the therapy of choice and effectively suppressed ES in the last 7 patients, combined with quinidine in 1 patient. Lidocaine, magnesium sulfate, propranolol, and mexiletine were ineffective in 4, 3, 2, and 1 patients, respectively. VF-triggering premature ventricular complexes originating from the right ventricular outflow tract were successfully eliminated by catheter ablation in 1 patient. In the other 12 patients, ES resolved spontaneously within 6 to 12 hours.

Comparisons of Patients With Versus Without ES
The characteristics of 22 men with BrS and ES versus 110 men with BrS and no ES are shown in Table 2. Among the 110 control men, 17 experienced a single VF episode, 13 experienced ≥1 syncopal episode(s), and 80 patients were asymptomatic. BrS was diagnosed by the presence of a spontaneous type 1 ECG pattern in 31 patients (28%) without ES, in contrast with 17 (77%) among the 22 patients with ES (P<0.0001). In 79 patients without ES (72%), BrS was diagnosed by a pilsicainide provocation test.

J waves >0.1 mV were observed in 10 of 110 patients without ES (9%), in contrast with 8 of 22 patients with ES (36%), a statistically significant difference (P=0.003). The J-wave amplitude was higher in patients with ES than those without ES (P=0.03). The J waves in patients without ES were

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in the inferior leads in 7, inferior and left precordial leads in 1, and high lateral in 2 patients, whereas the J waves in patients with ES were in the inferior leads in 4, inferior and left precordial leads in 2, and in the inferior, left precordial and high lateral leads in 2 patients. The distribution of leads with J waves was similar in patients with versus without ES ($P=0.08$). In 10 patients without ES and with J waves, the ST segment was horizontal/descending in 4 (40%) and rapidly ascending/upsloping in 6 (60%) patients; the ST-segment pattern in patients with versus without ES was similar ($P=0.06$). Furthermore, in patients with a history of $\geq 1$ episode of VF, the prevalence of J wave was 28% and that of spontaneous type I ST-segment elevation was 72% versus 8 ($P=0.003$) and 22% ($P<0.0001$), respectively, in patients without history of VF episodes. By multiple variable logistic regression analysis, spontaneous type I ST elevation independently predicted the development of VF (odds ratio, 4.375; 95% confidence interval, 1.6–12.0; $P=0.004$) and ES (odds ratio, 7.1; 95% confidence interval, 2.1–24.6; $P=0.002$). However, combined spontaneous type I ST elevation and (1) J waves or (2) J waves plus a horizontal or descending ST segment was not independently predictive. Among patients with any episode of VF, the prevalence of J waves and spontaneous type I ST elevation was 21% and 44%, respectively, in patients with versus 8% ($P=0.18$) and 31% ($P=0.46$) in patients without ES.

**Clinical Outcomes**

Among the 22 patients with BrS and ES, 16 underwent implantation of ICD after the ES had abated and 6 patients had already received an ICD when the ES developed. Over a follow-up (6.4±5.0 years), 12 patients experienced VF recurrences after the first ES, of whom 9 were untreated with antiarrhythmic

### Table 1. Characteristics of 22 Men With BrS and VF Storms

<table>
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<tr>
<th>Patient</th>
<th>FH of BrS/SCD</th>
<th>Age, y</th>
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<th>Mode of VF Onset</th>
<th>Suppression of VF</th>
<th>Drug Trials</th>
<th>PVS</th>
<th>LTT</th>
<th>ICD</th>
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<th>VF Recurrence (Time to Recurrence)</th>
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<td>+</td>
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Bep indicates bepridil; BrS, Brugada syndrome; DP, disopyramide; FH, family history; ICD, implantable cardioverter defibrillator; LSD, Left cardiac sympathetic denervation; LTT, long-term therapy; PVS, programmed ventricular stimulation; SCD, sudden cardiac death; SLS, short-long-short sequence; Und, Undisturbed sinus rhythm; and VF, ventricular fibrillation.

*No recurrence of VF on therapy.

drugs. However, 6 patients treated with bepridil, 100 to 200 mg daily, 2 patients treated with quinidine, 300 to 600 mg daily, and 1 patient treated with amiodarone, 100 mg daily, remained free from VF recurrences. One patient treated with disopyramide 300 mg daily experienced a single recurrence of VF. During follow-up, the J wave disappeared in 1, decreased in amplitude in 2 (Figure 3), and remained unchanged in 7 of 10 patients whose ECG were available during long-term follow-up.

ICD were implanted in 21 control patients, including 17 patients with histories of VF and 4 with histories of syncope. Quinidine was used for secondary prevention of VF in 1 patient. A single patient (5%) untreated with an antiarrhythmic drug experienced a recurrence of VF.

By Kaplan-Meier analysis of the cumulative incidence of recurrent arrhythmic events, the prognosis of patients with ES was significantly worse than that of patients without ES (Figure 4).

Discussion
The main finding of our study was a high prevalence of ER in patients presenting with BrS with versus without ES. Intravenous isoproterenol seemed effective in the short-term

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Figure 1. Onset of ventricular fibrillation (VF). A, VF developing during undisturbed sinus rhythm (patient no 3). B, VF following a short-long-short sequence with frequent premature ventricular complexes (patient no 10). C and D, J waves were absent during sinus rhythm on the 12-lead ECG of each patient.

Figure 2. Twelve-lead ECG with J waves during sinus rhythm. A, J waves followed by horizontal/descending ST elevation are present in the inferior leads (arrows; patient no 14). B, J waves followed by rapidly ascending/up sloping ST elevation are visible in the inferolateral leads (patient no 7).
suppression of ES, while oral bepridil and quinidine effectively prevented long-term recurrences of VF. Patients with BrS and ER were at higher risk of ES and VF recurrences than patients without ER.

Regarding the ECG characteristics, patients with BrS and ES in this study had a higher prevalence of type 1 ECG pattern and J waves than the controls (Table 2). The prevalence of ER was also higher than reported in general Western populations and in this country. Therefore, the prevalence of J waves in patients with BrS and ES is higher than in (1) patients with BrS without ES and (2) the general population. Several studies have suggested that the presence of inferolateral J waves in BrS is associated with a higher risk of recurrent VF. However, a relationship with ES in particular has not been described previously.

Studies in animals have suggested a common mechanism underlying (1) the ECG phenotype of BrS and (2) ER (the J wave) in idiopathic VF, both explained by a voltage gradient in the early phase of repolarization. In BrS, the presence of a J wave in V1 to V3 is explained by a notched phase 1 of the right ventricular outflow tract myocardial action potential, which, when augmented, may be followed by a secondary dome resulting in a coved ST-T segment. However, the pathophysiological mechanism(s) behind the ST-T changes observed in patients presenting with BrS remain(s) vigorously debated, and hypotheses have been formulated in favor of abnormalities of both depolarization and repolarization to explain the ECG phenotype of BrS.

In patients with idiopathic VF, J waves are more prevalent in the inferior and lateral precordial leads and may be explained by a mechanism similar to that of the J waves observed in BrS. They are augmented by an increased repolarization inhomogeneity from undetermined causes, along with the development of phase 2 reentry and subsequent VF. Although the ECG phenotype and response of VF to pharmaceuticals in BrS and J wave–associated idiopathic VF are similar, the J wave is only enhanced by class I antiarrhythmic drugs in BrS and not in J wave–associated idiopathic VF. The presence of ER in BrS increases the risk of ES and recurrent VF although the significance of the association between BrS and ER remains to be clarified.

A dissimilar mode of onset of VF has been reported in BrS–associated versus in J wave–associated idiopathic VF. In the study by Nam et al, VF was triggered by a premature ventricular complex with a short-long-short sequence in 42 of 58 patients with ER (72.4%) versus 13 of 86 patients (15.1%) with BrS (P<0.01). Furthermore, the mean coupling interval of the VF-triggering premature ventricular complexes was significantly shorter in the group of patients presenting with idiopathic VF and ER than in patients presenting with BrS (P<0.01). In the present study, the mode of VF onset was known in 19 patients and developed during regular sinus rhythm in 14 patients (74%), after a short-long-short sequence in 4 (21%),

| Table 2. Characteristics of 22 Men With BrS and ES vs 110 Men With BrS and No ES |
|---------------------------------|-----------------|-----------------|-------|
| With ES | Without ES | P |
| Age, y | 39 (23) | 44 (18) | 0.04 |
| Family history of sudden death/BrS | 3/0 | 12/3 | 0.47/0.58 |
| Electrocardiographic intervals, ms | | | |
| RR | 785 (212) | 909 (213) | 0.0005 |
| PR | 180 (26) | 162 (24) | 0.048 |
| QRS | 100 (29) | 104 (16) | 0.21 |
| QT | 340 (40) | 396 (41) | <0.0001 |
| QTc | 390 (51) | 394 (33) | 0.02 |
| Spontaneous type 1 ECG | 17 (77) | 31 (28) | <0.0001 |
| J wave >0.1 mV | 8 (36) | 10 (9) | 0.003 |
| J-wave amplitude, mV | 0.3 (0.1) | 0.2 (0.01) | 0.03 |

Values are median (interquartile range) or numbers (%) of observations. BrS indicates Brugada syndrome; and ES, electrical storm.
and in both circumstances in 1 patient (5%). Although the presence of ER did not influence the mode of onset of VF in the patients experiencing BrS complicated by ES, the role of ER in the development of VF is in need of further studies.

An association between (1) horizontal/descending ST elevation followed by ER and (2) an increased arrhythmic risk was recently observed in the general population and in patients with histories of idiopathic VF. Although we did not find a significantly higher prevalence of horizontal/descending ST elevation combined with ER in patients presenting with BrS and ES, a larger observational study is needed to clarify this point.

Intravenous isoproterenol or oral quinidine are the drugs of choice for the short-term management of ES in both BrS and ER-associated idiopathic VF. We found these drugs to be particularly effective in BrS with ER, presumably by augmenting the inward calcium currents, restoring the dome of the action potential, and mitigating the inhomogeneity of repolarization. Besides quinidine, bepridil, a class IV antiarrhythmic drug with Ito blocking properties, prevented VF in a small number of patients with BrS, although its long-term safety and efficacy was limited, especially in a severe form of BrS.

It is noteworthy that bepridil was effective in preventing VF storms on the long-term in the report of the largest observational study is needed to clarify this point.

Figure 4. Kaplan-Meier estimates of ventricular fibrillation (VF) recurrence after electrical storms.

Limitations of Our Study
The sample size of our study is small, although it is the largest collected thus far. Furthermore, a genetic screen in search of a mutation could have contributed to (1) the identification of an arrhythmogenic cause and mechanism, and (2) providing insights into the therapy of this complication of BrS, although it was not systematically performed.

Conclusions
In a subgroup of patients experiencing BrS with ER, a spontaneous type 1 ECG pattern was more prevalent than in similar patients without ER and seemed to incur a risk of ES and recurrent VF. Intravenous isoproterenol seemed effective in the short-term management of ES, while oral bepridil and quinidine prevented long-term recurrences of VF.

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Disclosures
None.

References
Electrical storms (ESs) in patients with Brugada syndrome (BrS), although rare, are potentially lethal. We compared the ECG characteristics of 22 men with BrS and ES, defined as ≥3 episodes/d of ventricular fibrillation, recruited at 8 Japanese medical centers, with those of 110 age-matched, control men with BrS without ES. We found a high prevalence of J waves in the group of patients with BrS complicated by ES. Specifically, a spontaneous type I ECG pattern and J waves and horizontal/descending ST elevation were present in 77%, 36%, and 88% of patients with ES, respectively, versus 28% (P<0.0001), 9% (P=0.003), and 60% (P=0.06) of controls, respectively. ES were suppressed by isoproterenol or quinidine. All patients with ES received an implantable cardioverter defibrillator and, over a follow-up of 6.6±5.3 years, the prognosis of patients with ES was significantly worse than that of patients without ES. Ventricular fibrillation was prevented on the long-term in 6 of 6 patients treated with bepridil. This is, to our knowledge, the largest study of patient presenting with BrS and ES. It underscores the significant association between the presence of J wave and ES in patients with BrS, and a high effectiveness of bepridil in the long-term prevention of ventricular fibrillation in the highest-risk patients with BrS.

CLINICAL PERSPECTIVE
Electrical Storm in Patients With Brugada Syndrome Is Associated With Early Repolarization

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