Prevalence of the Brugada-Type Electrocardiogram and Incidence of Brugada Syndrome in Patients With Sick Sinus Syndrome

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Background: In the present study, clarification of the prevalence of the Brugada-type electrocardiogram (ECG) and the incidence of spontaneous ventricular fibrillation (VF) that occurred with the Brugada-type ECG in patients with sick sinus syndrome (SSS) was determined.

Methods and Results: A total of 487 consecutive patients (men 45%, mean age 69.9±12.3 years), who were defined as having an indication for cardiac pacemaker (PM) for SSS, were investigated. The ECG before an initial PM implantation and occurrence of VF or sudden cardiac death (SCD) was examined retrospectively. Brugada-type ECG was found in 14 patients (2.87%) including 4 (0.82%) with type 1 and 10 (2.05%) with type 2. During the follow-up period of 7.2±5.4 years, 2 out of the 4 patients with type 1 ECG had experienced a VF episode after the device implantation. In 10 patients with type 2 ECG, none had VF or SCD. The incidence of spontaneous VF (Brugada syndrome) in SSS patients was calculated as 14.1 per 100 person-years with type 1 ECG.

Conclusions: The prevalence of typical Brugada-type (type 1) ECG in SSS patients seems to be higher compared with the general population. In addition, SSS patients with the typical Brugada-type ECG might be a high risk for spontaneous VF. (Circ J 2010; 74: 271–277)

Key Words: Brugada syndrome; Sick sinus syndrome; Ventricular fibrillation

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sified as either coved type (type 1) or saddleback type (type 2) according to the “Proposed Diagnostic Criteria: Consensus Report in 2002”.12

Coved type (type 1) was characterized as a prominent coved ST segment elevation displaying J wave amplitude or ST segment elevation ≥2 mm or 0.2 mV at its peak followed by a negative T wave with little or no isoelectric separation.

Saddleback type (type 2) had a high take-off ST segment elevation and J wave amplitude (≥2 mm) gave rise to a gradually descending ST segment elevation (remaining ≥1 mm above the baseline) with a positive or biphasic T wave. The secondary causes that could lead to ST segment elevation in the right precordial leads were excluded according to medical records. Three cardiologists (H.H., M.S., and M.Y.) reviewed

<table>
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<tr>
<th>Case no.</th>
<th>ECG type</th>
<th>Age, years</th>
<th>Gender</th>
<th>FH of SCD</th>
<th>Atrial arrhythmias</th>
<th>SNRT, ms</th>
<th>AH interval, ms</th>
<th>HV interval, ms</th>
<th>VF episode</th>
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<td>58</td>
<td>M</td>
<td>–</td>
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<td>105</td>
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<td>2</td>
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<td>F</td>
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<td>–</td>
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<td>F</td>
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<td>M</td>
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<td>AF, AFL</td>
<td>X</td>
<td>X</td>
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</tr>
</tbody>
</table>

Table 1. Clinical Features and EPS Findings in SSS Patients With Brugada-Type ECG

EPS, electrophysiologic study; SSS, sick sinus syndrome; ECG, electrocardiogram; FH of SCD, family history of sudden cardiac death; SNRT, sinus node recovery time; AH, atrio-His; HV, his-ventricular; VF, ventricular fibrillation; AF, atrial fibrillation; AFL, atrial flutter; X, not available.

Figure 1. Twelve-lead electrocardiograms before pacemaker implantation in Case 1 (Left) and Case 2 (Right).
Statistical Analysis
Continuous variables are expressed as the mean±standard deviation.

Results
All patients had an initial PM implantation except for 1 patient. The remaining patient had an implantable cardioverter-defibrillator (ICD) implantation because he had typical type 1 Brugada ECG findings with recurrent syncope. However, he did not have documented spontaneous episodes of VF and no induction of ventricular tachyarrhythmias in the electrophysiologic study (EPS) before the device implantation.

Prevalence of the Brugada-Type ECG in SSS
The Brugada-type ECG was found in 14 patients (2.87%) including 4 (0.82%) with type 1 and 10 (2.05%) with type 2. Clinical characteristics of the patients with the Brugada-type ECG are shown in Table 1 including the patients with type 1 ECG (Cases 1–4) and type 2 ECG (Cases 5–14). Figures 1–3 show 12-lead ECG before the initial device implantation in 4 patients with type 1 ECG.

Incidence of Spontaneous VF (BS) in SSS Patients With the Brugada Type ECG
During the follow-up period of 7.2±5.4 years, 2 (50%) out of the 4 patients with type 1 ECG had experienced a spontaneous episode of VF 3 and 12 months after the device implantation, respectively. They are Case 3 (Figure 2) and Case 4 (Figure 3). In the 10 patients with type 2 ECG, none had VF or SCD during the follow-up period of 9.0±6.3 years. There was no recurrent syncope except for a VF episode in Case 3. The incidence of spontaneous VF, which means the incidence of BS, was calculated as 14.1 per 100 person-years in SSS patients with type 1 ECG, but none with type 2 ECG. During the follow-up period, we observed the day-to-day variation of ST segment elevation, which sometimes seemed normal, in all 4 patients with type 1 ECG. Remarkably, J wave amplitude and coved type ST elevation became prominent just before an episode of VF in Case 3 (Figure 4). We could not find a change to type 1 ECG in 10 patients with type 2 ECG during the follow-up period.

Clinical Features of SSS Patients With the Coved Type Brugada ECG
Case 1 A 58-year-old man was referred to us for PM implantation for SSS in 1977 (Figure 1 Left). Twelve-lead ECG showed coved-type ST segment elevation in lead V1 with frequent S-A block. PQ interval and QRS duration were 0.18 and 0.12 s, respectively. He had been asymptomatic for...
Figure 3. Twelve-lead electrocardiogram on admission for recurrent syncope (A), asymptomatic sinus pause at midnight (B), and intracardiac electrograms recorded by an implantable cardioverter-defibrillator during an episode of ventricular fibrillation that occurred 3 months later (C) in Case 4.

Figure 4. Note the prominent ST segment elevation in V2 and V3 just before an episode of spontaneous ventricular fibrillation (VF) in case 3.
14 years after cardiac PM implantation and died of colon cancer.

Case 2  A 51-year-old woman suffered from SSS and she had a PM implantation in 1985 (Figure 1 Right). Twelve-lead ECG showed coved-type ST segment elevation in leads V1 and V2 with frequent S-A block. PQ interval and QRS duration were 0.20 and 0.10 s, respectively. She has been asymptomatic without any VT or VF episodes and syncope during the follow-up period of 26 years so far. She has not agreed to the EPS including VT/VF induction or exchanging to an ICD.

Case 3  A 41-year-old man who had experienced several syncopal episodes was referred to us in 1988. Twelve-lead ECG showed typical Brugada-type ECG (Figure 2A) and Holter ECG monitoring revealed a sinus pause of 3.6 s in the evening (Figure 2B). PQ interval and QRS duration were 0.20 and 0.12 s, respectively. EPS showed a prolonged sinus node recovery time (SNRT) of 2,550 ms, then he was implanted with a VVI PM. He had a re-admission for recurrent syncope 12 months later, he developed VF (Figure 2C), which was successfully defibrillated by an external DC shock. He was awake just before the VF event, and spontaneous sinus rate was about 100 beats/min at that time. After several years, he agreed to exchange his PM to an ICD.

Case 4  A 62-year-old man was referred because of several syncopal episodes and typical Brugada-type ECG pattern in 2003 (Figure 3A). The ECG showed normal PQ interval (0.20 s) and prolonged QRS duration (0.14 s). After admission, asymptomatic sinus pause was documented at midnight (Figure 3B). EPS did not induce prolonged SNRT or ventricular tachyarrhythmias. He was implanted with an ICD, which successfully converted a spontaneous episode of VF 3 months later (Figure 3C). Spontaneous sinus rate just before the VF event was about 75 beats/min on the electrogram strip in an ICD. Genetic analysis for SCN5A mutation was negative in this patient. Cases 3 and 4 were reported as case reports elsewhere previously.13,14

Discussion

We demonstrated that the prevalence of typical Brugada-type ECG (type 1) in SSS patients was 0.82%, which might be higher compared with the general population. In addition, the incidence of spontaneous VF in SSS patients with the typical Brugada-type ECG seems to be high: 14.1 per 100 person-years.

Prevalence of Brugada-Type ECG in General Population

The prevalence of Brugada-type ECG findings (type 1 and 2) in the general population has been reported between 0.01 and 6.1%, including 0.005–0.28% for type 1 (coved type).15-23 However, this prevalence is different depending on the age of the population. The typical Brugada-type (type 1) ECG is reported to be more prevalent in adults (0.05–0.28%)15,20 than in adolescents (0.005–0.06%).12,13,21-23 Our results in SSS patients, which included only adult patients, showed more prevalence (0.82%) than in the general population of adults (Table 2). Genetic factors might influence the expression of both phenotypes; BS and SSS.

Incidence of Spontaneous VF (BS) in SSS Patients With the Brugada-Type ECG and Dynamic Change in ST Segment Elevation

Out of 4 patients with type 1 ECG, a spontaneous episode of VF occurred in 2 patients. In other words, the incidence of “BS” was 50% in SSS patients with type 1 ECG. We observed a dynamic change in ST segment elevation in all 4 patients with coved-type ECG; sometimes it showed type 2 or non-Brugada type ECG. In particular, in Case 3, who suffered from a spontaneous VF episode, J wave amplitude and ST segment elevation became prominent just before (within 30 min) the episode of VF (Figure 4). Depression or loss of the action potential dome in right ventricular epicardium is reported to be responsible for the Brugada-type ST segment elevation.24 Although dynamic change in the ST segment elevation is well known in BS,13,25-26 augmentation of J wave and ST segment elevation might be a marker for electrical instability and predictor for VF events.13,25,27

Genetic Correlation Between BS and SSS

We have recently reported 3 patients of BS concomitant with sinus node dysfunction.14 Although 2 of these 3 patients were included in this study population, we identified another 12 patients with SSS who had a Brugada-type ECG before PM implantation including 2 with type 1 (coved type) and 10 with type 2 (saddleback type). Genetic aberrations in the cardiac Na+ channel (SCN5A) have been observed to cause a variety of phenotypes including LQT3, BS, and conduction

Table 2. Prevalence of Brugada-Type ECG in General Population and SSS Patients

<table>
<thead>
<tr>
<th>Study author, year, reference number</th>
<th>Population</th>
<th>Total participants</th>
<th>Age, years</th>
<th>Male, %</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tohyou et al, 199515</td>
<td>Adults</td>
<td>4,092</td>
<td>46</td>
<td>78</td>
<td>0.07</td>
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<tr>
<td>Herman et al, 200016</td>
<td>Adults</td>
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<td>39±10</td>
<td>63</td>
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<tr>
<td>Matsuo et al, 200117</td>
<td>Adults</td>
<td>4,788</td>
<td>&lt;50</td>
<td>41</td>
<td>0.15</td>
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<tr>
<td>Miyasaka et al, 200118</td>
<td>Adults</td>
<td>13,929</td>
<td>58±10</td>
<td>27</td>
<td>0.12</td>
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<tr>
<td>Furushashi et al, 200119</td>
<td>Adults</td>
<td>8,612</td>
<td>49</td>
<td>70</td>
<td>0.05</td>
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<tr>
<td>Sakabe et al, 200320</td>
<td>Adults</td>
<td>3,339</td>
<td>&gt;18</td>
<td>79</td>
<td>0.28</td>
</tr>
<tr>
<td>Tohyou et al, 199515</td>
<td>Children</td>
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<td>9</td>
<td>54</td>
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<tr>
<td>Yamakawa et al, 200421</td>
<td>Children</td>
<td>20,387</td>
<td>9.7±3</td>
<td>51</td>
<td>0.005</td>
</tr>
<tr>
<td>Yoshinaga et al, 200422</td>
<td>Children</td>
<td>7,022</td>
<td>12</td>
<td>100</td>
<td>0.01</td>
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<tr>
<td>Yoshinaga et al, 200422</td>
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<td>15</td>
<td>100</td>
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<tr>
<td>Oe et al, 200523</td>
<td>Children</td>
<td>21,944</td>
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<td>51</td>
<td>0.005</td>
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<td>Present study</td>
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<td>487</td>
<td>70±12</td>
<td>45</td>
<td>0.82</td>
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Plus-minus values are mean±SD. Abbreviations see in Table 1.
disease at various levels within the heart including sinus node dysfunction. Clinical examples of such an “overlap syndrome” have been reported among LQT3, BS, and cardiac conduction defect or SSS. Recent reports have indicated that the loss of function of single SCN5A mutations can be responsible for both BS and SSS. A functional defect of the sodium current could account for BS and a conduction disturbance in sinoatrial region. Genetic analysis could be examined in only 1 of the 4 patients with SSS and Brugada-type ECG, which was negative in our study population.

**Study Limitations**

First, dynamic change in Brugada-type ECG is well known and sometimes it seems normal. We have identified a daily variation of ST segment elevation in 4 patients with type 1 ECG. However, we did not examine the variation of ST segment elevation after PM implantation in all study participants, because ST-T changes could be evaluated only in patients with sinus rhythm or atrial pacing, not in patients with ventricular pacing. Therefore, we might have underestimated the prevalence of the Brugada-type ECG because we only evaluated several ECGs just before an initial PM implantation. In fact, reported as a case report, we have experienced another SSS patient who suffered from VF with saddleback type ECG just after VF episode. However, she did not show the Brugada-type ECG before PM implantation. We should be careful of ECG change even after PM implantation. Second, we did not perform genetic analysis in patients with SSS and the Brugada-type ECG except for 1 patient (Case 4): he had a negative study for SCN5A mutation. Higher prevalence of genetic abnormalities has been reported in a few patients with overlap syndrome; BS and SSS or atrioventricular block. However, it is unknown whether genetic analysis can give us more information about a risk of future arrhythmic events or not. Third, although we found a high incidence of spontaneous VF in SSS patients with coved type ECG, we could evaluate only 4 patients concomitant with SSS and typical Brugada-type ECG. Fourth, we did not directly compare the prevalence of Brugada-type ECG between SSS patients and general population in this study. In addition, our data were collected from only 2 hospitals retrospectively. Therefore, we could not conclude the high prevalence of Brugada-type ECG in SSS patients in this study design. However, this is the first study to examine the prevalence of Brugada-type ECG and incidence of BS in clinically documented SSS patients who required PM therapy. Further studies including multi-centers are mandatory to clarify the risk of future cardiac events in SSS patients with the Brugada-type ECG.

**Conclusions**

Prevalence of the Brugada-type ECG and incidence of spontaneous VF with the typical Brugada-type ECG (incidence of BS) in SSS patients seem to be high. We should be careful of recurrent syncope even after PM implantation and recommend upgrading to an ICD in SSS patients with typical Brugada-type ECG.

**Acknowledgements**

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**Disclosure**

The authors have neither a conflict of interest nor financial disclosure.

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