Exercise stress test reveals ineligibility for subcutaneous implantable cardioverter defibrillator in patients with Brugada syndrome

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Abstract
Background: The eligibility of patients with Brugada syndrome (BrS) for implantation of a subcutaneous implantable cardioverter defibrillator (S-ICD) is not well known. This study aimed to clarify the eligibility of BrS patients for S-ICD using electrocardiography (ECG) at rest and during exercise testing. We also analyzed factors associated with ineligibility for S-ICD from standard 12-lead ECG at rest.

Methods: We enrolled 110 consecutive BrS patients who visited Okayama university hospital from December 2015 to December 2016. All patients were assessed for S-ICD eligibility, which required one lead to satisfy the S-ICD screening template. We assessed standard 12-lead ECG parameters in all participants. Of those who passed S-ICD screening, 45 patients were assessed for S-ICD eligibility during treadmill stress test.

Results: Mean age of study patients was 54 ± 13 years and 108 (98%) were men. In total, 89 patients (81%) satisfied S-ICD indications at rest. Existence of complete right bundle branch block (CRBBB) on standard 12-lead ECG was a significant predictor of ineligibility for S-ICD (odds ratio, 5.00; P = 0.03; 95%CI, 1.14–21.98). Of the 45 patients who underwent treadmill stress testing, 11 patients (24%) showed ineligibility for S-ICD during the test.

Conclusion: CRBBB was a predictor of ineligibility for S-ICD in patients with BrS. Sinus tachycardia changes ECG morphology in some patients and stress testing should be considered before S-ICD implantation.

KEYWORDS
Brugada syndrome, exercise stress test, implantable cardioverter defibrillator, inappropriate shock, subcutaneous implantable cardioverter defibrillator

1 | INTRODUCTION

Brugada syndrome (BrS) is a genetic disease responsible for 4–12% of cases of sudden cardiac death (SCD). The syndrome is characterized by an electrocardiographic pattern of ST segment elevation with type 1 morphology in the right precordial leads V1 to V3. Most cardiac events occur in middle-aged men.2,3

Symptoms often arise at rest or during sleep, in a febrile state. Lethal ventricular arrhythmias tend to occur during the recovery phase after exercise, in association with significant augmentation of ST elevation.4

A subcutaneous implantable cardioverter-defibrillator (S-ICD) does not require placement of leads directly into the heart, so use of these devices could avoid the complications related to the use of transvenous ICD leads. Moreover, since the incidence of lead injury increases over time after transvenous ICD implantation, use of S-ICDs is expected to avoid troubles concerning cardiac leads,5–7 especially in younger patients without organic heart disease, such as patients...
with BrS, who do not usually need ventricular pacing. However, the eligibility of BrS patients for S-ICD use is not well known, and data from a large cohort of this specific patient population have not been reported.

The most common problem with S-ICD systems in the real world is administration of inappropriate shocks because of T-wave oversensing. To avoid this problem, the manufacturer has developed a system to identify patients who are likely to be unsuitable for S-ICD, using supine and standing surface ECG screening templates. Moreover, ST-T morphology shows fluctuations, particularly in high-risk patients with BrS. This suggests that ECG at rest should not be considered sufficient as S-ICD screening for patients with diurnal variations. Exercise is one of the most important factors for ST-T fluctuations, and exercise-induced ST-T changes thus need to be considered when making decisions regarding S-ICD implantation. In addition, because the specific ECG system templates proposed for determining S-ICD eligibility are uncommon and inconvenient for actual clinical practice, parameters derived from standard 12-lead ECG are expected to be used to eliminate clearly unsuitable patients as candidates for S-ICD implantation.

We aimed to clarify both the eligibility of patients with BrS for S-ICD implantation according to the surface ECG screening template at rest and the influence of exercise on ECG morphology in determining eligibility.

2 | METHODS

2.1 Patients

All study protocols were approved by the Ethics Committee of Okayama University Hospital. All 112 patients with BrS who visited Okayama University Hospital from December 2015 to December 2016 were recruited. BrS was diagnosed based on the existence of type 1 ECG spontaneously or during drug challenge testing. After excluding 2 patients (paced QRS complex, n = 1; inability to stand, n = 1), 110 patients were included in this study. Of these, 13 patients experienced ventricular fibrillation (VF) or aborted cardiac arrest and 39 patients experienced syncope. We assessed the clinical characteristics of participants, including age, sex, body mass index (BMI) and family history of sudden death before 45 years old. Genetic analysis for mutation of SCN5A was performed in 51 patients, and complied with the guidelines for human genome studies from the Ethics Committee of Okayama University.

2.2 Standard 12-lead ECG

Standard 12-lead ECG was recorded for all participants on the same day as S-ICD screening ECG at rest was obtained. We collected ECG parameters including QRS duration, QT interval in lead II, presence or absence of a negative T wave in leads I, II or aVF, complete right bundle branch block (CRBBB), incomplete right bundle branch block (IRBBB), S wave (≥0.1 mV and/or ≥40 milliseconds) in lead I, and QRS-T discordance in leads I, II or aVF. QRS-T discordance was defined as oppositely oriented vectors of QRS and T waves.

2.3 S-ICD screening ECG at rest

All subjects were assessed using supine and standing ECG limb lead recordings to simulate the three S-ICD sensing vectors, as reported previously. ECG lead positions are shown in Figure 1.

We aimed to clarify both the eligibility of patients with BrS for S-ICD implantation according to the surface ECG screening template at rest and the influence of exercise on ECG morphology in determining eligibility.

2.4 S-ICD screening ECG during exercise stress test

Forty-five consecutive patients who met the indication for S-ICD at rest and consented to further testing underwent a symptom-limited treadmill exercise test (TMT) using the Bruce protocol. Patients who declined to undergo the TMT or were unable to run on a treadmill machine were excluded. Limb lead recordings simulated the three S-ICD sensing vectors and the precordial lead was in the ordinary position. The symptom-limited Bruce protocol starts with a warm-up stage at low workload, followed by successive 2-minute stages with stepwise increments in workload. Tests were completed with a 5-minute recovery phase after reaching peak exercise. ECGs were acquired every 1 minute during and after exercise testing up to 5 minute into the recovery period. S-ICD eligibility was determined using the Boston Scientific screening template, at the following time points: (1) supine rest; (2) on standing; (3) at peak exercise; (4) at 1-minute recovery; (5) at 3-minute recovery; and (6) at 5-minute recovery. Peak voltages of QRS and T wave, the ratio of peak voltages of QRS to T wave, QRS duration, and corrected QT interval (QTc) were measured at each point. QTc was calculated using the Buzzet formula.
2.5 Statistical analysis

Categorical variables are presented as the number of patients (percentage), and continuous variables are expressed as mean ± standard deviation or median. For each variable, differences were evaluated using Pearson’s χ² test for categorical variables and Student’s t test or the Mann–Whitney U test for continuous variables.

Logistic regression analysis was applied for assessing the effects of standard 12-lead characteristics on S-ICD eligibility according to the surface S-ICD ECG screening template. SPSS software (IBM SPSS Statistics, Chicago, IL, USA) was used for all analyses. Values of P < 0.05 were considered statistically significant.

3 RESULTS

3.1 Baseline characteristics of patients and S-ICD eligibility at rest

Table 1 shows the baseline clinical characteristics of study participants. No significant differences in baseline clinical characteristics were seen between eligibility and ineligibility for S-ICD screening ECG.

3.2 Predictors of failure on standard 12-lead ECG

The results of uni- and multivariate analyses for comparison of factors associated with S-ICD screening ineligibility are shown in Table 2. With univariate analysis, compared to those who were eligible, patients who were ineligible (n = 21) for S-ICD showed significantly greater frequencies of CRBBB and wide QRS interval in the standard 12-lead ECG.

Multivariate regression analysis identified CRBBB as an independent predictor of ineligibility for S-ICD according to screening ECG (Table 2).

3.3 Change in eligibility for S-ICD during exercise stress test

Of the 45 patients who were eligible for S-ICD according to screening at rest and underwent exercise testing, 11 patients became ineligible from S-ICD screening template during TMT. ECGs at peak exercise and during the recovery phase excluded these patients from eligibility for S-ICD (Fig. 2). To clarify what kind of changes in morphology led to ineligibility during TMT, we assessed the point at which the 11 patients became ineligible. For this purpose, we chose the 3-minute recovery time point to assess for eligibility during TMT, because 9 of the 11 ineligible patients were found to be ineligible at this time point. Patients who became ineligible during TMT showed significantly higher voltage of T wave and lower ratio of voltages of QRS to T wave at the time of ineligibility compared to patients who remained eligible during TMT (Table 3). Figure 3 shows a representative example of a patient who became ineligible for S-ICD during exercise testing.

4 DISCUSSION

4.1 Main findings

S-ICD has been widely applied to patients, but evidence has been lacking regarding the eligibility of patients with BrS for S-ICD. The present findings represent early data from S-ICD screening in patients with BrS, and, to the best of our knowledge, the cohort of BrS patients in this investigation is the largest yet reported on. Eighty-one percent of BrS patients who were eligible according to the screening template at rest, but 24% of patients who passed the screening at rest became ineligible during exercise testing. CRBBB was the only independent predictor of ineligibility for S-ICD on standard 12-lead ECG.

4.2 Eligibility for S-ICD in BrS patients

Sinus tachycardia during exercise attenuates ST elevation, but vagal activation during the recovery phase augments ST elevation and unmasks type 1 ECG in patients with BrS. Makimoto et al. demonstrated augmentation of ST-segment elevation during the recovery phase of stress testing in 37% of BrS patients, and this change was associated with VF events. Subramanian et al. also reported that morphological changes during exercise stress testing are more often observed among high-risk BrS patients on standard 12-lead ECG. In our study, dramatic morphological changes were observed on S-ICD screening ECG in TMT, as in previous reports assessed using standard 12-lead ECG. The fact that 24% of patients who passed the criteria of the screening template at rest became ineligible during exercise testing is notable. This result suggests that stress testing should be

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### Table 1 Baseline characteristics of study participants

<table>
<thead>
<tr>
<th></th>
<th>All Patients (n = 110)</th>
<th>Eligible (n = 89)</th>
<th>Ineligible (n = 21)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>108 (98)</td>
<td>87 (98)</td>
<td>21 (100)</td>
<td>0.49</td>
</tr>
<tr>
<td>Age (years)</td>
<td>54 ± 13</td>
<td>54 ± 13</td>
<td>55 ± 12</td>
<td>0.84</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22 ± 3</td>
<td>22 ± 3</td>
<td>22 ± 2</td>
<td>0.26</td>
</tr>
<tr>
<td>Type 1 at S-ICD screening</td>
<td>50 (45)</td>
<td>40 (45)</td>
<td>10 (48)</td>
<td>0.83</td>
</tr>
<tr>
<td>Spontaneous type 1</td>
<td>91 (83)</td>
<td>71 (80)</td>
<td>20 (95)</td>
<td>0.09</td>
</tr>
<tr>
<td>CRBBB, n (%)</td>
<td>21 (19)</td>
<td>11 (12)</td>
<td>10 (48)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>QRS interval (ms)</td>
<td>100 ± 21</td>
<td>97 ± 18</td>
<td>112 ± 28</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>QT interval (ms)</td>
<td>400 ± 35</td>
<td>397 ± 30</td>
<td>418 ± 48</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>ICD implantation</td>
<td>49 (45)</td>
<td>39 (44)</td>
<td>10 (48)</td>
<td>0.75</td>
</tr>
<tr>
<td>SCN5A mutation</td>
<td>6/51 (12)</td>
<td>4/41 (10)</td>
<td>2/10 (20)</td>
<td>0.37</td>
</tr>
<tr>
<td>Episode of ventricular fibrillation</td>
<td>13 (12)</td>
<td>10 (11)</td>
<td>3 (14)</td>
<td>0.71</td>
</tr>
<tr>
<td>Episode of syncope</td>
<td>39 (35)</td>
<td>29 (33)</td>
<td>10 (48)</td>
<td>0.20</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>70 (64)</td>
<td>59 (66)</td>
<td>11 (52)</td>
<td>0.23</td>
</tr>
<tr>
<td>Family history of SCD at &lt;45 years old</td>
<td>20 (18)</td>
<td>17 (19)</td>
<td>3 (14)</td>
<td>0.61</td>
</tr>
</tbody>
</table>

Categorical variables are shown as the number of patients (percentage). Continuous variables are shown as mean ± SD. BMI = body mass index; CRBBB = complete right bundle branch block; ICD = implantable cardioverter defibrillator; SCD = sudden cardiac death; Spontaneous type 1 = history of spontaneous type 1 Brugada morphology on 12-lead ECG; Type 1 at S-ICD screening = type 1 Brugada morphology on 12-lead S-ICD screening ECG.
TABLE 2  Predictors of screening failure

<table>
<thead>
<tr>
<th></th>
<th>Univariate</th>
<th>Mutivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Age</td>
<td>1.01</td>
<td>0.97–1.05</td>
</tr>
<tr>
<td>CRBBB</td>
<td>6.45</td>
<td>2.22–18.68</td>
</tr>
<tr>
<td>S wave in lead I</td>
<td>2.24</td>
<td>0.83–6.07</td>
</tr>
<tr>
<td>QRS-T discordance</td>
<td>1.86</td>
<td>0.52–6.64</td>
</tr>
<tr>
<td>QRS interval (ms)</td>
<td>1.03</td>
<td>1.01–1.05</td>
</tr>
<tr>
<td>QT interval (ms)</td>
<td>1.02</td>
<td>1.00–1.03</td>
</tr>
</tbody>
</table>

CRBBB = complete right bundle branch block; OR = odds ratio; 95% CI = 95% confidence interval.

FIGURE 2  Change in eligibility for S-ICD during exercise stress test. Of the 45 patients who were eligible for S-ICD according to screening at rest and underwent exercise testing, 11 patients became ineligible from the S-ICD screening template during the treadmill test. These 11 patients became ineligible during peak to 3-minute recovery, and all appeared eligible again at 5-minute recovery.

TABLE 3  Patient characteristics of S-ICD screening ECG during TMT

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>Eligible</th>
<th>Ineligible</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 45)</td>
<td>(n = 34)</td>
<td>(n = 11)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Differences in S-ICD screening ECG morphology at rest (on standing)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak voltage of QRS (mV)a</td>
<td>1.2 ± 0.7</td>
<td>1.3 ± 0.5</td>
<td>1.2 ± 1</td>
<td>0.89</td>
</tr>
<tr>
<td>T-wave voltage (mV)a</td>
<td>0.23 ± 0.16</td>
<td>0.22 ± 0.12</td>
<td>0.26 ± 0.26</td>
<td>0.56</td>
</tr>
<tr>
<td>Ratio of QRS/T-wave voltage</td>
<td>6.2 ± 3.0</td>
<td>6.4 ± 3.0</td>
<td>5.3 ± 2.9</td>
<td>0.28</td>
</tr>
<tr>
<td>QRS duration (ms)</td>
<td>103 ± 23</td>
<td>101 ± 19</td>
<td>114 ± 27</td>
<td>0.87</td>
</tr>
<tr>
<td>QTc (ms)</td>
<td>407 ± 35</td>
<td>408 ± 30</td>
<td>407 ± 49</td>
<td>0.93</td>
</tr>
<tr>
<td>Differences in S-ICD screening ECG morphology at time of ineligibility</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak voltage of QRS (mV)a</td>
<td>1.2 ± 0.6</td>
<td>1.2 ± 0.5</td>
<td>1.2 ± 1.0</td>
<td>0.88</td>
</tr>
<tr>
<td>T-wave voltage (mV)a</td>
<td>0.27 ± 0.19</td>
<td>0.21 ± 0.10</td>
<td>0.46 ± 0.27</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Ratio of QRS/T-wave voltage</td>
<td>5.7 ± 2.9</td>
<td>6.7 ± 2.7</td>
<td>2.7 ± 0.9</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>QRS duration (ms)</td>
<td>108 ± 23</td>
<td>107 ± 23</td>
<td>114 ± 24</td>
<td>0.37</td>
</tr>
<tr>
<td>QTc (ms)</td>
<td>434 ± 48</td>
<td>437 ± 49</td>
<td>423 ± 49</td>
<td>0.42</td>
</tr>
</tbody>
</table>

Categorical variables are shown as number of patients. Continuous variables are shown as mean ± SD. Statistical differences were evaluated using the Mann–Whitney U test.

aAbsolute value; QTc = corrected QT interval.
performed before S-ICD implantation in BrS patients. Another stress test for BrS is the antiarrhythmic drug challenge test, which can unmask type 1 ECG in BrS.\(^9,17\) This test may provide helpful information to identify patients unsuitable for S-ICD from among those deemed suitable before the test. Whether S-ICD implantation should be avoided for patients who are eligible at rest and become ineligible during stress testing is currently unclear. In the present study, we selected an exercise stress test using the Bruce protocol instead of a drug challenge test. This was because exercise tests simulate behaviors frequently encountered in daily life, and may thus be better suited to identifying patients in whom therapy with S-ICD may be inappropriate. In addition, exercise tests are easier for outpatients to perform, because follow-up ECG for hours after the stress test is not necessary, whereas drug challenge tests may sometimes induce ventricular arrhythmia even several hours after testing, until the drug is washed out from the body.

4.3 Prediction of factors for ineligibility for S-ICD on standard 12-lead ECG

Similar to conventional transvenous ICD, efforts should be made to ensure avoidance of inappropriate cardiac shocks from an S-ICD. Olde Nordcamp et al. reported that the most common cause of inappropriate shock from an S-ICD was cardiac signal oversensing (73%), such as T-wave oversensing.\(^10\) Previous reports have shown that patients with a negative T wave,\(^18,19\) extension of the QRS duration,\(^20\) or QT interval prolongation\(^19\) on standard 12-lead ECG have tended to fail the criteria of the screening template. In our study, multivariate analysis showed that only CRBBB was a significant predictor of ineligibility for S-ICD. To avoid inappropriate cardioversion of S-ICD, morphological changes on standard 12-lead ECG can provide initial clues to physicians to reconsider whether patients will be eligible for S-ICD. In particular, intermittent CRBBB is sometimes observed in BrS, and could be associated with inappropriate therapy using S-ICD.\(^21\)

4.4 Limitations

Several limitations need to be considered for this study. First, only a single center was included, and not all patients who passed the S-ICD indication at rest could be included in exercise stress testing. Multicenter studies including larger numbers of patients thus need to be conducted. Second, we did not evaluate morphological changes in S-ICD ECG during TMT in normal controls. Concluding that only patients with BrS should undergo TMT before S-ICD implantation would thus be somewhat premature. Finally, improvements have recently been made in S-ICD technology, such as the SMARTPASS algorithm, which uses high-pass filtering to minimize T-wave oversensing. With these developments, current screening methods may overestimate actual ineligibility for S-ICD. However, to minimize inappropriate therapy with S-ICD, stricter screening methods such as inclusion of an exercise test should be considered before S-ICD implantation for patients with BrS.

5 Conclusions

In this study, 19% of BrS patients for S-ICD were considered unsuitable for S-ICD when evaluated with a surface ECG screening template at rest. In addition, almost a quarter of patients who initially appeared eligible under resting screening ECG became ineligible during TMT. Exercise stress testing should be considered for patients with BrS before S-ICD implantation. On standard 12-lead ECG, CRBBB represented an independent predictor of failure to meet the indications for S-ICD. During follow-up after S-ICD implantation, morphological changes in QRS on standard 12-lead ECG may alert physicians to patient ineligibility for implantation of this device.

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**FIGURE 3** Representative example of a patient identified as unsuitable for S-ICD during TMT. ECG recorded at: (A) supine rest; (B) stand rest; (C) peak exercise; (D) 1-minute recovery; (E) 3-minute recovery; and (F) 5-minute recovery. ✓ = passed screening template; × = failed screening template. Primary lead considered as eligible at rest became ineligible at 3-minute recovery, and eligible again at 5-minute recovery.
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