Exercise-Induced ECG Changes in Brugada Syndrome

Ahmad S. Amin, MD; Elisabeth A.A. de Groot, BSc; Jan M. Ruijter, PhD; Arthur A.M. Wilde, MD, PhD; Hanno L. Tan, MD, PhD

Background—Ventricular arrhythmia occurrence during exercise is reported in Brugada syndrome (BrS). Accordingly, experimental studies suggest that BrS-linked SCN5A mutations reduce sodium current more at fast heart rates. Yet, the effects of exercise on the BrS ECG phenotype have not been studied. We aimed to assess ECG responses to exercise in BrS and determine whether these responses are affected by the presence of an SCN5A mutation.

Methods and Results—ECGs at baseline, at peak exercise, and during recovery were analyzed from 35 male control subjects, 25 BrS men without SCN5A mutation (BrS\textsubscript{SCN5A}–), and 25 BrS men with SCN5A mutation (BrS\textsubscript{SCN5A}+; 15 with missense mutation and 10 with mutation leading to premature truncation of the protein). No differences existed in clinical phenotype between BrS groups. At baseline, BrS\textsubscript{SCN5A}– and BrS\textsubscript{SCN5A}+ patients had lower heart rates, wider QRS, shorter QT\textsubscript{c}, and higher peak J-point amplitudes than control subjects; BrS\textsubscript{SCN5A}+ patients also had longer PR than BrS\textsubscript{SCN5A}– and control subjects. Exercise resulted in PR shortening in all groups, more QRS widening in BrS\textsubscript{SCN5A}+ than in BrS\textsubscript{SCN5A}– and control subjects, and less QT shortening in BrS\textsubscript{SCN5A}– and BrS\textsubscript{SCN5A}+ than in control subjects. The latter resulted in QT\textsubscript{c} shortening in control subjects but QT\textsubscript{c} prolongation in BrS\textsubscript{SCN5A}– and BrS\textsubscript{SCN5A}+. Finally, the increase in peak J-point amplitude during exercise was similar in all 3 groups but resulted in a coved-type pattern only in BrS\textsubscript{SCN5A}– and BrS\textsubscript{SCN5A}+.

Conclusions—Exercise aggravated the ECG phenotype in BrS. The presence of an SCN5A mutation was associated with further conduction slowing at fast heart rates. Possible mechanisms that may explain the observed ECG changes are discussed. (Circ Arrhythmia Electrophysiol. 2009;2:531-539.)

Key Words: Brugada syndrome ■ arrhythmia ■ exercise ■ tachycardia ■ SCN5A, mutation ■ ECG

Brugada syndrome (BrS) is a disease with increased risk for sudden death due to polymorphic ventricular tachycardia (VT) or ventricular fibrillation (VF). The disease is associated with an ECG pattern consisting of prolonged conduction intervals (eg, PR, QRS) and coved-type ST-segment elevations in the precordial leads V1–V2. Up to 30% of patients carry loss-of-function mutations in SCN5A, the gene that encodes the \(\alpha\)-subunit of the cardiac sodium (Na\(^+\)) channel.\(^1\) This channel permits an inward Na\(^+\) current (\(I_{\text{Na}}\)), which initiates the ventricular action potential, thereby controlling cardiac excitability and electric conduction velocity.\(^2\)

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The presence and type of the SCN5A mutation determines the severity of the clinical phenotype in BrS.\(^3–4\) BrS mutation carriers have prolonged conduction intervals on baseline ECG compared with noncarriers,\(^3\) and patients with SCN5A missense mutations develop a less severe phenotype than those with SCN5A truncation mutation.\(^4\) This is believed to be due to the degree of \(I_{\text{Na}}\) reduction caused by the SCN5A mutation. Missense mutations, in which a single amino acid is replaced by a different amino acid, commonly alter the gating properties of mutant channels. Because virtually all reported SCN5A mutation carriers are heterozygous, mutant channels with altered gating may cause up to 50% \(I_{\text{Na}}\) reduction. Truncation mutations, in which the mutant channel proteins are truncated due to the creation of a premature stop codon or an aberrant mRNA splicing site, commonly disrupt the trafficking of incorrectly folded mutant proteins from the endoplasmic reticulum to the sarcolemma and lead to haploinsufficiency.\(^1\) Haploinsufficiency causes 50% \(I_{\text{Na}}\) reduction.

In addition to SCN5A mutations, nongenetic factors (eg, electrolyte imbalances, fever, hypothermia, and medications) may also aggravate the clinical phenotype in BrS.\(^5–6\) Exercise is anecdotally reported to induce (further) ST-segment elevation and (monomorphic) ventricular arrhythmia in BrS, usually in patients with prolonged conduction intervals at baseline.\(^7–11\) Furthermore, occurrence of ventricular arrhythmia at peak exercise has been frequently reported in patients using therapeutic doses of flecainide (a potent Na\(^+\) channel–blocking drug).\(^12,13\) Indeed, experiments in right ventricular tissue preparations indicate that
tachycardia aggravates ST-segment elevation in BrS, and in vitro studies using heterologous expression systems suggest that BrS-linked loss-of-function mutations in SCN5A reduce Ik, more at fast heart rates. At a molecular level, further Ik reduction in BrS during tachycardia is attributed to accumulation of mutant Na+ channels in the slow inactivated state. Na+ channels activate on depolarization and inactivate within milliseconds thereafter. Before reopening, channels must recover from inactivation during diastole. At fast heart rates, the diastolic interval becomes too short for mutant channels to completely recover from the slow inactivated state, resulting in decreased availability of open channels.

Despite these clinical and experimental indications that exercise may play an arrhythmogenic role in BrS, the effects of exercise on the ECG phenotype in BrS patients have not been systematically studied yet. We aimed to assess the ECG responses to exercise in BrS and to determine whether these responses are affected by the presence of an SCN5A mutation.

Methods

Patient Selection

In this retrospective single-center study, 25 BrS patients without SCN5A mutation (BrS\textsubscript{SCN5A-}) and 25 BrS patients with SCN5A mutation (BrS\textsubscript{SCN5A+}), who had undergone an exercise test, were randomly sampled from the BrS cohort of our institution. Inclusion criteria were (1) male sex, (2) age between 20 and 65 years, and (3) no drug use at the time of the exercise test. Diagnosis of BrS was made by baseline ECG analysis and/or pharmacological challenge with I\textsubscript{Na}-blocking drugs (ajmaline or flecainide). SCN5A mutation analysis was performed in all patients. The following clinical parameters were obtained: (1) age at which exercise test was performed, (2) family history of sudden cardiac death at age <45 years, (3) results of pharmacological challenge with I\textsubscript{Na}-blocking drugs (if performed), (4) incidence of VT and/or VF, syncope, and other BrS-related symptoms (eg, palpitation, dizziness), (5) results of electrophysiological study (EPS) (if performed), and (6) whether an implantable cardioverter-defibrillator was implanted. No patient had structural heart disease (chest roentgenogram, echocardiogram, and/or cardiac MRI), ischemic heart disease (coronary angiogram), or electrolyte disturbances (laboratory tests). ECG data were compared with those from 35 age- and sex-matched control subjects, who had undergone an exercise test. Control subjects were healthy volunteers who had no history of heart disease and used no drugs with known effects on the cardiovascular system.

Mutation Analysis

Informed consent was obtained, and genomic DNA was extracted from peripheral blood lymphocytes using standard protocols. SCN5A protein-encoding exons and exon-intron boundaries were amplified using polymerase chain reaction. Mutation detection in vitro studies using heterologous expression systems suggest that BrS-linked loss-of-function mutations in SCN5A reduce Ik, more at fast heart rates. At a molecular level, further Ik reduction in BrS during tachycardia is attributed to accumulation of mutant Na+ channels in the slow inactivated state. Na+ channels activate on depolarization and inactivate within milliseconds thereafter. Before reopening, channels must recover from inactivation during diastole. At fast heart rates, the diastolic interval becomes too short for mutant channels to completely recover from the slow inactivated state, resulting in decreased availability of open channels.

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Table 1. Clinical Characteristics of Patients With BrS

<table>
<thead>
<tr>
<th></th>
<th>BrS\textsubscript{SCN5A-} (n=25)</th>
<th>BrS\textsubscript{SCN5A+} (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>42±2</td>
<td>43±3</td>
</tr>
<tr>
<td>Family history</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Type 1 ECG at baseline</td>
<td>4/25 (16)</td>
<td>5/25 (20)</td>
</tr>
<tr>
<td>Drug challenge test +</td>
<td>21/21 (100)</td>
<td>16/16 (100)</td>
</tr>
<tr>
<td>VT/VF</td>
<td>1/25 (4)</td>
<td>1/25 (4)</td>
</tr>
<tr>
<td>Syncope (nonexercise)</td>
<td>6/25 (24)</td>
<td>6/25 (24)</td>
</tr>
<tr>
<td>Palpitations/dizziness</td>
<td>4/25 (16)</td>
<td>2/25 (8)</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>15/25 (60)</td>
<td>17/25 (68)</td>
</tr>
<tr>
<td>EPS +</td>
<td>4/5 (80)</td>
<td>3/5 (60)</td>
</tr>
<tr>
<td>ICD implanted</td>
<td>8/25 (32)</td>
<td>5/25 (20)</td>
</tr>
</tbody>
</table>

Table data are expressed as mean±SEM or n/N (%). ECG variables of BrS patients were compared with those obtained from healthy male control subjects (mean age, 42±1 years). BrS\textsubscript{SCN5A-} indicates BrS patients without SCN5A mutation; BrS\textsubscript{SCN5A+}, BrS patients with SCN5A mutation; family history +, sudden cardiac death in a relative at an age of <45 years; drug challenge test +, type 1 BrS ECG after intravenous administration of ajmaline or flecainide; VT/VF, documented ventricular tachycardia and/or ventricular fibrillation; EPS +, occurrence of ventricular arrhythmia with EPS; ICD, implantable cardioverter-defibrillator.

Statistical Analysis

Fisher exact test (for 2×2 tables) and χ² test (for 2× tables) were used to compare the occurrence of different clinical characteristics in control, BrS\textsubscript{SCN5A-}, and BrS\textsubscript{SCN5A+} groups (Table 1). ECG parameters are expressed and graphed as mean (with standard error of the mean [SEM]). For each individual, the exercise and recovery effects on the ECG parameters were calculated as exercise minus baseline value and recovery minus exercise value, respectively. Differences for the ECG parameters in baseline values as well as in the exercise and recovery effects were tested among 3 groups with 1-way ANOVA (Table 2) or between 2 groups with the Student t test (Table 3). Homogeneous subsets of groups were determined with the Student-Newman-Keuls post hoc multiple comparison of groups. Because 8 tests (heart rate, PR, QRS, QT, QTc, J-point amplitude in V<sub>1</sub> and V<sub>2</sub>, and peak J-point amplitude in V<sub>1</sub>-V<sub>2</sub>) were performed for each of the 3 experimental conditions (baseline, exercise effect, and recovery effect), the significance level of the Student-Newman-Keuls test was set at 0.005. In the description of subsets (Table 2), homogeneous subsets are indicated by an equals (=) sign. Statistical analysis was carried out with SPSS version 15.0.1 (SPSS Inc).

Results

Clinical Characteristics

Control subjects were all men and ages 42±1 years. The BrS\textsubscript{SCN5A+} group comprised 15 patients with missense
mutations and 10 patients with truncation mutations. We have previously included 8 BrS 
SCN5A+ patients in a genotype-phenotype association study. 4 Missense mutations 
were NI09K, E161K, V240M, L618F, G1319V, V1405L, L1582P, R1629G, V1667I, and G1743E. Mutations leading 
to truncation of the channel protein were frameshift 
insertions (c.3142 to 3143insTG), nonsense mutations 
(L1393X and R1638X), frameshift mutations leading to premature stop codon (W774fsX28 and F861fsX90), and 
mutations leading to altered mRNA splicing (c.934+1G>A, 
c.3840+1G>A, and c. 4719C>T). There were no significant 
differences in the clinical variables between BrS 
SCN5A− and BrS 
SCN5A+ (Table 1). No patient had VT or VF during 
the exercise test.

ECG Data
Figure 1 shows a typical example of ECG changes during 
exercise in control subjects, BrS 
SCN5A−, and BrS 
SCN5A+. Values of ECG variables at baseline and their changes 
during exercise and recovery are summarized in Table 2 
and illustrated in Figures 2 to 6.

Table 2. ECG Variables at Baseline and Their Changes at Peak Exercise and During Recovery 
From Exercise

<table>
<thead>
<tr>
<th>Group</th>
<th>Control Subjects</th>
<th>BrS SCN5A−</th>
<th>BrS SCN5A+</th>
<th>P Value</th>
<th>Student-Newman-Keuls</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Heart rate, bpm</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>80±2</td>
<td>69±2</td>
<td>63±2</td>
<td>&lt;0.001</td>
<td>1&gt;2=3</td>
</tr>
<tr>
<td>∆ exercise, baseline</td>
<td>98±3</td>
<td>100±4</td>
<td>103±5</td>
<td>0.623</td>
<td></td>
</tr>
<tr>
<td>∆ recovery, exercise</td>
<td>−52±2</td>
<td>−43±4</td>
<td>−48±4</td>
<td>0.106</td>
<td></td>
</tr>
<tr>
<td><strong>PR, ms</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>158±3</td>
<td>163±5</td>
<td>195±5</td>
<td>&lt;0.001</td>
<td>1&gt;2=3</td>
</tr>
<tr>
<td>∆ exercise, baseline</td>
<td>−47±6</td>
<td>−48±6</td>
<td>−56±7</td>
<td>0.548</td>
<td></td>
</tr>
<tr>
<td>∆ recovery, exercise</td>
<td>40±4</td>
<td>34±5</td>
<td>37±6</td>
<td>0.684</td>
<td></td>
</tr>
<tr>
<td><strong>QRS, ms</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>84±1</td>
<td>103±2</td>
<td>110±3</td>
<td>&lt;0.001</td>
<td>1&gt;2=3</td>
</tr>
<tr>
<td>∆ exercise, baseline</td>
<td>0.3±1</td>
<td>4±2</td>
<td>12±2</td>
<td>&lt;0.001</td>
<td>1&gt;2=3</td>
</tr>
<tr>
<td>∆ recovery, exercise</td>
<td>3±1</td>
<td>−4±2</td>
<td>−6±1</td>
<td>&lt;0.001</td>
<td>1&gt;2=3</td>
</tr>
<tr>
<td><strong>QT, ms</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>358±4</td>
<td>361±4</td>
<td>364±7</td>
<td>0.760</td>
<td></td>
</tr>
<tr>
<td>∆ exercise, baseline</td>
<td>−157±8</td>
<td>−99±6</td>
<td>−110±7</td>
<td>&lt;0.001</td>
<td>1&gt;3=2</td>
</tr>
<tr>
<td>∆ recovery, exercise</td>
<td>75±6</td>
<td>34±5</td>
<td>40±9</td>
<td>&lt;0.001</td>
<td>1&gt;2=3</td>
</tr>
<tr>
<td><strong>QTc, ms</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>411±5</td>
<td>385±5</td>
<td>376±5</td>
<td>&lt;0.001</td>
<td>1&gt;2=3</td>
</tr>
<tr>
<td>∆ exercise, baseline</td>
<td>−66±12</td>
<td>53±8</td>
<td>44±10</td>
<td>&lt;0.001</td>
<td>1&lt;3=2</td>
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<tr>
<td>∆ recovery, exercise</td>
<td>53±11</td>
<td>−15±7</td>
<td>−5±9</td>
<td>&lt;0.001</td>
<td>1&gt;3=2</td>
</tr>
<tr>
<td><strong>J-point V1, or Vp, mV</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Baseline</td>
<td>0.6±0</td>
<td>1.5±0.1</td>
<td>1.6±0.2</td>
<td>&lt;0.001</td>
<td>1&gt;2=3</td>
</tr>
<tr>
<td>∆ exercise, baseline</td>
<td>0.3±0.1</td>
<td>0.8±0.2</td>
<td>1.0±0.3</td>
<td>0.036</td>
<td></td>
</tr>
<tr>
<td>∆ recovery, exercise</td>
<td>−0.2±0.1</td>
<td>0.5±0.3</td>
<td>0.2±0.3</td>
<td>0.093</td>
<td></td>
</tr>
</tbody>
</table>

Data are expressed as mean±SEM. Differences for the ECG parameters in baseline values as well as in the exercise and recovery 
effects were tested with 1-way ANOVA. Homogeneous subsets of groups were determined with the Student-Newman-Keuls post hoc 
multiple comparison of groups. The significance level of the Student-Newman-Keuls test was set at 0.005. Homogeneous subsets are 
indicated by an equals (=) sign.

Heart Rate
At baseline, heart rate did not differ significantly between 
BrS SCN5A− and BrS SCN5A+ but was lower in both groups 
than in control subjects (Figure 2). Baseline heart rate <60 
bpms was found in 2 control subjects (6%), 3 BrS SCN5A− 
(12%), and 13 BrS SCN5A+. (52%; P=0.002). Heart rate 
increase during exercise and its decrease during recovery 
were similar among groups.

PR Interval
At baseline, PR interval did not differ between BrS SCN5A− 
and control subjects but was longer in BrS SCN5A+ (Figure 3). 
In the 3 groups, PR interval shortened similarly during 
exercise and returned to near baseline level during recovery.

QRS Interval
At baseline, QRS interval did not differ between BrS SCN5A− 
and BrS SCN5A+ but was longer in both groups 
than in control subjects (Figure 4). During exercise, QRS 
interval widening was larger in BrS SCN5A+ compared with 
BrS SCN5A−. In BrS SCN5A−, the effect of exercise on QRS 
interval did not differ from control subjects. During
QT interval and QTc duration

(25 mm/s and 10 mm/mV). BrS during recovery from exercise. Standard calibration was used

V2) performed within 1 individual from each group (control, 

Figure 1. ECG examples during exercise. Typical ECGs (lead 

recovery, QRS interval normalized completely or partially in BrS SCN5A− and BrS SCN5A++ respectively.

**QT Interval and QTc Duration**

At baseline, QT interval did not differ among the 3 groups, but QTc duration was shorter in BrS SCN5A− and BrS SCN5A+++ than in control subjects (Figure 5). During exercise, QT interval decreased in all groups, but this decrease was less in control subjects (Figure 5). During exercise, QT interval normalized completely or partially 

result, QTc duration shortened during exercise in control subjects but increased in BrS SCN5A− and BrS SCN5A++. During recovery, QT interval increased in all groups, but this increase was again less in BrS SCN5A− and BrS SCN5A+++ than in control subjects. Consequently, QTc duration returned to near baseline levels in control subjects but only slightly shortened with respect to peak exercise level in BrS SCN5A− and BrS SCN5A+++.

**Peak J-Point Amplitude**

At baseline, the peak J-point amplitude in V1-V2 did not differ between BrS SCN5A− and BrS SCN5A+++ but was higher in both groups than in control subjects (Figure 6). The peak J-point amplitude increase during exercise was similar in all 3 groups but resulted in a coved-type pattern only in BrS SCN5A− and BrS SCN5A+++ (Figure 1). During recovery, the peak J-point amplitude in V1-V2 increased further in the BrS groups but returned to baseline levels in control subjects. However, because of large variability, the changes in peak J-point amplitude during recovery did not reach statistical significance among the groups.

**Exercise Test and Clinical Phenotype**

Because exercise aggravated the ECG abnormalities that are associated with increased risk for cardiac events in BrS, we analyzed whether ECG variables and their changes during exercise were different between BrS patients who had previously experienced syncope (n=10, including 2 patients with documented VT/VF) and those who had not (n=38), and between BrS patients with a

represent as mean±SEM. P value indicates statistical significance between 2 groups. Differences for the ECG parameters in baseline values as well as in the exercise effects were tested between the groups with Student t test.

<table>
<thead>
<tr>
<th>ECG Variable</th>
<th>Yes (n=12)</th>
<th>No (n=38)</th>
<th>P Value</th>
<th>Positive (n=8)</th>
<th>Negative (n=3)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>43±3</td>
<td>43±2</td>
<td>0.986</td>
<td>45±3</td>
<td>42±4</td>
<td>0.516</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>64±3</td>
<td>67±2</td>
<td>0.498</td>
<td>65±4</td>
<td>56±6</td>
<td>0.247</td>
</tr>
<tr>
<td>Δ exercise, baseline</td>
<td>95±7</td>
<td>104±3</td>
<td>0.231</td>
<td>88±11</td>
<td>109±8</td>
<td>0.327</td>
</tr>
<tr>
<td>PR, ms</td>
<td>184±7</td>
<td>177±5</td>
<td>0.485</td>
<td>177±15</td>
<td>199±8</td>
<td>0.382</td>
</tr>
<tr>
<td>Δ exercise, baseline</td>
<td>−54±6</td>
<td>−52±6</td>
<td>0.813</td>
<td>−36±14</td>
<td>−65±17</td>
<td>0.299</td>
</tr>
<tr>
<td>QRS, ms</td>
<td>109±4</td>
<td>106±2</td>
<td>0.511</td>
<td>112±5</td>
<td>98±5</td>
<td>0.153</td>
</tr>
<tr>
<td>Δ exercise, baseline</td>
<td>12±3</td>
<td>7±2</td>
<td>0.186</td>
<td>6±5</td>
<td>12±1</td>
<td>0.490</td>
</tr>
<tr>
<td>QT, ms</td>
<td>366±7</td>
<td>361±5</td>
<td>0.645</td>
<td>367±4</td>
<td>360±27</td>
<td>0.678</td>
</tr>
<tr>
<td>Δ exercise, baseline</td>
<td>−101±11</td>
<td>−106±6</td>
<td>0.703</td>
<td>−91±10</td>
<td>−138±31</td>
<td>0.088</td>
</tr>
<tr>
<td>QTc, ms</td>
<td>378±8</td>
<td>381±4</td>
<td>0.715</td>
<td>379±9</td>
<td>360±7</td>
<td>0.241</td>
</tr>
<tr>
<td>Δ exercise, baseline</td>
<td>50±18</td>
<td>48±7</td>
<td>0.863</td>
<td>58±21</td>
<td>9±43</td>
<td>0.272</td>
</tr>
<tr>
<td>J-point V1, or V2, mV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>1.8±0.2</td>
<td>1.5±0.2</td>
<td>0.365</td>
<td>2.2±0.4</td>
<td>1.8±0.7</td>
<td>0.702</td>
</tr>
<tr>
<td>Δ exercise, baseline</td>
<td>0.6±0.4</td>
<td>0.9±0.2</td>
<td>0.383</td>
<td>0.7±0.4</td>
<td>0.4±0.7</td>
<td>0.747</td>
</tr>
</tbody>
</table>
positive EPS outcome and those with a negative EPS outcome. No significant differences were observed in the ECG variables and their changes during exercise between these groups (Table 3).

Discussion
In this study, we aimed to assess ECG responses to exercise in BrS and to determine whether these responses are affected by the presence of an SCN5A mutation. To do this, we analyzed ECGs in control subjects, BrS SCN5A/H11002, and BrS SCN5A/H11001. Because of the male predominance in BrS and to exclude sex-related differences in ECG responses, we only analyzed male individuals. We compared ECG variables at baseline and their changes at peak exercise and during recovery from exercise. ECG analysis at peak exercise was based on experimental and clinical evidence that tachycardia aggravates ST-segment elevation in BrS7,14 and that BrS-linked loss-of-function mutations in SCN5A reduce INa more at fast heart rates.7,15 The fact that we did not find differences in the clinical variables between BrS SCN5A− and BrS SCN5A+ groups shows that these variables most probably have not confounded the interpretation of ECG differences between groups.

Heart Rate
Ventricular arrhythmia in BrS commonly occurs at rest, usually at night and during sleep. Autonomic imbalance, consisting of increased parasympathetic (vagal) activity and/or decreased sympathetic (adrenergic) activity, is believed to play a pathophysiologic role. For example, increased parasympathetic activity is suggested by a 24-hour Holter monitoring study, which showed that symptomatic BrS patients have lower mean heart rate than asymptomatic patients.17 Moreover, right precordial ST-segment elevation in BrS patients increases after intracoronary injection of the parasympathetic neurotransmitter acetylcholine.18 Decreased sympathetic activity is suggested by clinical studies, which investigated the myocardial presynaptic and postsynaptic sympathetic function in BrS patients. These studies indicated increased presynaptic reuptake and recycling of the sympathetic neurotransmitter norepinephrine from the synaptic cleft; this reduces...
postsynaptic sympathetic effects. In our study, baseline heart rates were lower in BrS patients than in control subjects, supporting these previous data. However, heart rate increase in BrS patients during exercise was similar to that in control subjects, suggesting that sympathetic response during exercise was adequate.

Lower baseline heart rates in BrS may also be due to sinus node dysfunction. Indeed, SCN5A loss-of-function mutations (including several BrS-linked mutations) are linked to sinus bradycardia, atrial standstill, and sick sinus syndrome. Moreover, recent reports suggest that INa is functionally present in the human sinoatrial node. Accordingly, a mouse model with a null mutation in SCN5A exhibited bradycardia and other signs of sinus node dysfunction. Although the mean heart rate at baseline did not differ between BrS SCN5A− and BrS SCN5A−, more BrS SCN5A− patients had baseline heart rates <60 bpm. Together, these findings support the role of SCN5A mutation in the pathophysiology of sinus node dysfunction.

**PR Interval**

The PR interval represents conduction of electric impulses from the atria to the ventricles through the atrioventricular (AV) node and the Purkinje fibers. Previous reports indicate that PR interval is prolonged in BrS patients with SCN5A mutation. Indeed, PR interval was prolonged in BrS SCN5A+ at baseline. Consistent with our data, PR interval shortening during exercise was not different in patients with paroxysmal supraventricular tachyarrhythmia (but without BrS) who used flecainide compared with patients without flecainide use. One possible mechanism may be disparate contributions of INa to action potential initiation in AV nodal cells and Purkinje fibers. INa plays a major role in the initial upstroke of the Purkinje action potential. This may explain the prolonged baseline PR intervals in BrS SCN5A+. In contrast, the role of INa in the AV node is controversial. First, AV nodal cells have a resting membrane potential of approximately −50 mV; at this potential, Na+ channels are almost fully inactivated. Second, action potentials measured from AV nodal cells display a slow upstroke, which is generated by the L-type calcium current (ICa,L), as experimental studies have indicated. Accordingly, AV nodal conduction is suppressed by calcium channel--blocking drugs. Conversely, ICa,L amplitude is markedly increased during β-adrenergic stimulation; this phenomenon may be responsible for the adequate PR interval shortening in BrS patients during exercise. Based on these data, one may conclude that PR interval response to exercise depends more on AV nodal conduction, whereas PR interval prolongation at baseline may be attributed to conduction slowing in the Purkinje fibers.

**QRS Interval**

INa is responsible for the initial upstroke of the ventricular action potential, which determines electric conduction velocity through the ventricles and thereby QRS interval duration. Accordingly, INa reduction results in lower maximum upstroke velocity, slower ventricular conduction, and QRS widening. In our study, baseline QRS intervals...
in BrS_{SCN5A−} and BrS_{SCN5A+} were not different but were both longer than in control subjects. Although this supports the role of I_{Na} in determining conduction velocity, it also indicates that other mechanisms may underlie I_{Na} reduction in BrS_{SCN5A−}, for example, mutations in genes encoding cardiac Na⁺ channel accessory subunits or regulatory proteins.²⁹–³¹ QRS widening at peak exercise in BrS_{SCN5A+} patients. This confirms reports of QRS widening during exercise in patients using therapeutic doses of flecainide²²,²³ and in BrS patients at fast pacing rates during EPS.³² These data suggest further I_{Na} reduction in BrS patients during exercise. In BrS_{SCN5A+} further I_{Na} reduction may be attributed to accumulation of mutant Na⁺ channels in the slow inactivated state during tachycardia.⁷,¹⁵ This mechanism is supported by the observation that QRS duration returned to baseline levels during recovery, when the heart rate decreased.

**QT Interval and QTc Duration**

In a previous study, 24-hour Holter ECGs of men with idiopathic VF (67% had BrS ECG at baseline) were analyzed and compared with healthy control subjects.³³ At slow heart rates (R-R intervals ≥1 second), QT intervals were significantly shorter in BrS patients. At higher rates (R-R intervals 0.6 second), QT intervals did not differ between BrS patients and control subjects. Consistent with these data, we found that BrS_{SCN5A−} and BrS_{SCN5A−} had shorter QTc than did control subjects at baseline. In contrast, at peak exercise, QTc durations in BrS patients were longer than in control subjects, due to inadequate shortening of the QT interval. That further I_{Na} reduction during exercise may mediate such repolarization changes is suggested by reports of QTc lengthening after flecainide²²,²³ and in BrS patients at fast pacing rates during EPS.³² Moreover, in experimental settings, I_{Na} inhibition by flecainide is associated with rate-dependent action potential prolongation, with more prolongation at faster stimulation rates.³⁵ I_{Na} reduction is believed to accentuate phase 1 notch of the ventricular action potential, due to an increased contribution of the transient outward potassium current (I_{TO}). This will reduce the availability of L-type calcium channels and delay phase 2 and, consequently, phase 3 of the action potential, resulting in prolonged action potential duration.³⁵ However, because repolarization abnormalities were found in both BrS_{SCN5A−} and BrS_{SCN5A+}, they cannot only be attributed to I_{Na} reduction due to SCN5A mutations.

**Peak J-Point Amplitude**

Previously, ST-segment depression during exercise has been reported in both healthy control subjects and BrS patients.⁸,⁹,³⁶ These studies have measured the ST-segment amplitude at 40 ms after the end of QRS interval (J-point). However, according to the first BrS consensus report in which the diagnostic criteria for BrS were outlined,³⁷ we selected the peak J-point amplitude in the precordial leads to measure the extent of ST-segment elevation. We observed that the peak J-point amplitude increased similarly in all 3 groups during exercise. In control subjects, the ST segment did not show a typical coved-type pattern (at baseline nor during exercise), and the increase in J-point amplitude during exercise may be attributed to tachycardia-induced incomplete right bundle-branch block. In both BrS_{SCN5A−} and BrS_{SCN5A+}, the peak J-point amplitude reached its maximum amplitude during the early recovery phase. ST-segment augmentation during the recovery phase has been described in some BrS patients and may be due to diminishing sympathetic and/or increased parasympathetic activity.⁸–¹⁰ In contrast, peak J- point amplitude augmentation at peak exercise is not fully recognized. In this study, its occurrence in conjunction with QTc lengthening during exercise is consistent with previous observations of ST-segment elevation and QT lengthening after flecainide administration in BrS patients.³⁴ Probably, the peak J-point amplitude, which we measured in this study, represents a depolarization parameter, similar to QRS duration, or, at least, a combined parameter of both depolarization and repolarization. Therefore, the peak J-point amplitude increased at peak exercise as the QRS duration did in BrS patients.

**Exercise Test and Clinical Phenotype**

This study was designed to assess ECG responses to exercise in BrS patients and to determine whether these responses are affected by the presence of an SCN5A mutation. We found that exercise aggravated ECG abnormalities that are associated with an increased risk for cardiac events in BrS. Therefore, we additionally analyzed whether ECG variables and their changes during exercise were different between symptomatic (prior syncope) and asymptomatic (no prior syncope) BrS patients and between BrS patients with a positive EPS outcome and those with a negative EPS outcome. We found no significant differences in the ECG variables and their changes during exercise between the groups. However, interpretation of these findings requires caution because of the small number of patients who had syncope or undergone EPS in our study population.

**Conclusions and Study Limitations**

In BrS, baseline ECGs are characterized by lower heart rates, prolonged QRS intervals, decreased QTc durations, and precordial peak J-point elevation. Additionally, BrS_{SCN5A+} display PR prolongation. In BrS, exercise induces (1) PR shortening to the same extent as in healthy control subjects, (2) QRS widening in BrS_{SCN5A+}, (3) QT shortening, but to a lesser extent than in control subjects, leading to QTc lengthening at peak exercise, and (4) augmentation of precordial peak J-point elevation, which reaches its maximum amplitude during the early phase of recovery from exercise. In healthy control subjects, precordial peak J-point amplitude also increased in control subjects but did not adopt the typical coved-type pattern as seen in BrS.

Mechanisms that underlie ECG responses in BrS to exercise are complex, and their identification requires further studies. Only QRS interval widening during exercise had an association with I_{Na} reduction, as determined by the presence
of an SCN5A mutation. However, it must be noted that BrS<sub>SCN5A</sub> patients were not screened for mutations in other genes that have recently been linked to BrS and that were experimentally shown to reduce INa, for example, SCN1B and SCN3B genes, which encode 2 β-subunits of the cardiac Na<sup>+</sup> channel,<sup>29</sup>–<sup>30</sup> and the glycerol-3-phosphate dehydrogenase 1-like (GPD1-L) gene, which encodes a protein involved in the intracellular Na<sup>+</sup> channel trafficking.<sup>31</sup> The presence of such mutations may have negatively biased the role of INa reduction in the ECG responses of BrS<sub>SCN5A</sub> to exercise. Furthermore, although common clinical variables were not different between BrS<sub>SCN5A</sub> and BrS<sub>SCN5A</sub>+, other yet unrecognized molecular or clinical factors may have contributed to the observed ECG differences between the study groups.

In conclusion, exercise did not induce ventricular arrhythmia in our BrS patients, but it did induce ECG changes that are known to increase the risk of cardiac arrest. Therefore, an exercise test may be an alternative safe tool for diagnosis in subjects suspected of having BrS. However, because our study was not designed to study the immediate clinical usefulness of an exercise test, future studies are required to assess the possible diagnostic and/or prognostic values of an exercise test in the clinical management of BrS patients.

**Sources of Funding**

Dr Tan was supported by the Royal Netherlands Academy of Arts and Sciences (KNAW) and the Netherlands Organisation for Scientific Research (NWO ZonMW-VICI 918.86.616). Dr Wilde was supported by the Foundation Leducq (CVD5 grant, Alliance for Sudden Cardiac Death). The funding sources had no role in the study.

**Disclosures**

None.

**References**


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**CLINICAL PERSPECTIVE**

Brugada syndrome is characterized by a typical ECG pattern (coved-type ST-segment elevations in the right precordial leads) and increased risk for fatal ventricular arrhythmia (ventricular tachycardia and/or ventricular fibrillation). In some patients, Brugada syndrome involves loss-of-function mutations in SCN5A, the gene that encodes the cardiac sodium channel. The typical ECG pattern is dynamic and often concealed but can be evoked for diagnostic purposes with drugs that possess the ability to block the cardiac sodium channel. Exercise is anecdotally reported to induce ventricular arrhythmia in patients with Brugada syndrome. In this study, we assessed the effects of exercise on ECGs of patients with Brugada syndrome. We found that exercise aggravated the ECG abnormalities in Brugada syndrome, including widening of the QRS intervals, prolongation of the QTc durations, and further elevation of the right precordial ST segments. Importantly, the latter is associated with increased risk for sudden death. These data suggest that an exercise test may be an alternative safe tool for diagnosis in subjects suspected of having Brugada syndrome. However, further research is required to test this suggestion and to investigate whether an exercise test may be used as a tool for risk stratification in patients with Brugada syndrome.
Exercise-Induced ECG Changes in Brugada Syndrome
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Circ Arrhythm Electrophysiol. 2009;2:531-539; originally published online August 24, 2009;
doi: 10.1161/CIRCEP.109.862441

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