ORIGINAL ARTICLE

Diagnostic criteria for the Brugada syndrome: Can they be improved?☆

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KEYWORDS
Brugada syndrome; Diagnostic score; SCN5A gene

Abstract
Introduction: Diagnosis of Brugada syndrome (BS) currently requires documentation of a characteristic repolarization pattern (type 1 Brugada ECG). Mutations in the SCN5A gene, which codes for sodium channel NaV1.5, are found in 38% of familial cases of BS. Sodium current dysfunction negatively affects the cardiac fast response action potential, particularly in atrial and ventricular myocytes and in the fast-conducting Purkinje system.

Objectives: To detect carriers of SCN5A mutations without using the characteristic repolarization pattern (type 1 Brugada ECG).

Methods: Of a total of 141 members of three different families including 55 carriers of two nonsense SCN5A mutations causing BS, all those aged over 16 (113 individuals, 42 carriers) were studied. The PR interval (PR) and QT dispersion (QTd) between leads V1 and V3 were measured on conventional ECG. Using signal-averaged ECG the total duration of the filtered QRS complex (fQRS), the root-mean-square (RMS40) and the low-amplitude signal (LAS) were measured. The following procedures were developed to detect carriers: (1) a screening test (ScreenTest) with PS (PR + fQRS) ≥ 250 (250 ms is 80% of the theoretical maximum in healthy individuals); and (2) a diagnostic test (DiagTest) for the simultaneous fulfillment of four conditions: PS ≥ 250 and QTd ≥ 10 and LAS > 26 and RMS40 ≤ 29 (the latter two cut-offs are approximately 70% of the theoretical maximum in healthy carriers).

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Results: Significant differences in PR, QTd, fQRS, RMS40 and LAS were found between carriers and non-carriers. The SCN5A gene was associated with all these variables, the strongest association being with PR. Both tests were applied to 63 family members (38 carriers). The ScreenTest was positive in 38 of 38 carriers, with eight false positives in 27 non-carriers (sensitivity [SE] = 100% and specificity [SP] = 66.67%). From ROC curve analysis a cut-off of PS = 252.5 shows SE = 100% and SP = 76% and a cut-off of PS = 260 shows SE = 94.7% and SP = 84%. The DiagTest was positive in 36 of 38 carriers, with three false positives: SE = 94.74% and SP = 88.89%. From ROC curve analysis a multivariate logistic model identifies a cut-off with SE = 92% and SP = 92%. In the same group the SE and SP of the characteristic spontaneous repolarization pattern (type 1 Brugada ECG) to detect carriers were 52.4% and 97.2%, respectively, and the difference between the SE of the DiagTest and of the typical repolarization pattern is statistically significant.

Conclusions: The ScreenTest and DiagTest are more effective tools than the characteristic repolarization pattern to discriminate between carriers and non-carriers of these two nonsense SCN5A mutations. We suggest their use in first-degree relatives of Brugada patients when the results of genetic testing are not available, in a score of disease probability in individuals with idiopathic Brugada ECG, and in patients with arrhythmias or other Brugada-related symptoms presenting type 2 or type 3 Brugada ECG.

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Introduction

Brugada syndrome (BS) was first described as a new entity in 1992. It has a characteristic electrocardiographic pattern (right bundle branch block and ST-segment elevation in the right precordial leads) and is associated with increased risk for malignant ventricular arrhythmias and sudden death in individuals without structural heart disease. In two decades it has ceased to be a medical curiosity and has become an entity that must be diagnosed, stratified and treated, since it is estimated to be responsible for 20–50% of cases of sudden death in individuals with structurally normal hearts, and the mean age at diagnosis and/or the event that prompts it (which is often sudden death) is 40 ± 22 years. BS belongs to the group of channelopathies, diseases that are caused by primary dysfunction of the ion channels responsible for cardiac action potentials, which triggers or perpetuates arrhythmias without concomitant structural disease.

Historical perspective

BS is a congenital disease and familial transmission is frequent. The first mutation associated with BS, in the SCNS5A gene which codes for the α subunit of the cardiac sodium channel NaV
text
which was described in 1998, and since then over 100 different mutations in this gene have been reported. These mutations may be nonsense or missense, and not all have the same pathophysiological effects. The former are usually more serious, as they produce a truncated protein that is dysfunctional because it is a different length than normal. Missense mutations cause substitution of an amino acid but the protein remains complete. In this case the biological effects on protein function are unclear, and in vitro functional studies are needed to ascertain their importance.

Mutations in the SCNS5A gene can lead to a decrease in sodium current (I
which in the cardiac action potential, either through quantitative decrease (failure in expression) or through qualitative dysfunction of the channel. However, mutations are found in only 18–30% of patients and in only 38% of familial cases. This low incidence may be explained by genetic heterogeneity, i.e. mutations in other genes that are associated with BS, as well as many others presumably yet to be discovered, including: (1) GPD1-L, the gene that codes for glycerol-3-phosphate dehydrogenase 1 like peptide, which is responsible for the transport of NaV1.5 to the cell surface and, when mutated, leads to a 31% reduction in the quantity of channels available in the membrane and a 50% reduction in sodium current, resulting in BS; (2) mutations in cardiac calcium channel genes (CACNA1C and CACNB2b) associated with an overlapping entity, short QT syndrome with Brugada ECG pattern; and (3) mutations in the KCNE3 gene, which modulates the function of the KVG4.3 channel, which is responsible for the transient potassium outward current (I

From gene to electrocardiogram

There are two theories to explain the electrocardiographic manifestations of BS: (1) delayed conduction in the free wall epicardium of the right ventricular outflow tract; (2) premature repolarization of the right ventricular epicardial action potential; or a combination of the two. In the first, asynchronous activation of the epicardium in relation to the endocardium, due to dysfunction of an ion channel (NaV1.5 or another), creates a voltage gradient between the two layers of cells. In the second (Fig. 1), dysfunction of a channel (NaV1.5 or another) leads to an imbalance in phase 1 that favors repolarization due to the disproportionate I

Difficulties in the diagnosis of BS

A diagnosis of BS is simple in its most characteristic form of presentation, i.e. spontaneous type 1 repolarization pattern in the right precordial leads together with aborted cardiac arrest. Type 1 repolarization pattern with no other criteria should be described as idiopathic Brugada ECG (not Brugada syndrome), and there is considerable controversy concerning the appropriate clinical approach. A wide range of differential diagnoses that can mimic the BS ECG...
alterations should be considered (Table 1), but it should be borne in mind that the first symptom that confirms a diagnosis of BS may be catastrophic: cardiac arrest is the first manifestation in 77% of patients. There are also difficulties with diagnosis in cases of borderline or Brugada-like repolarization patterns. Besides type 1 Brugada ECG, there are two other repolarization patterns associated with BS (Fig. 3): type 2 (≥2 mm J-point elevation, downsloping ST segment but at least 1 mm above the isoelectric line, and positive or biphasic ('saddle-back') T wave; and type 3, with ≥2 mm J-point elevation and <1 mm ST-segment elevation, coved or saddle-back or both. According to the consensus conference on Brugada syndrome, types 2 and 3 are merely suggestive and not diagnostic, a recommendation that is not followed by all authors. Whether only type 1, or all three types of pattern, are taken to be diagnostic obviously affects the sensitivity and specificity of the ECG to detect BS, sensitivity being greater when all three are used and specificity being higher with only type 1. Type 3 pattern is virtually indistinguishable from the incomplete right bundle branch block found in the young; disregarding it could have catastrophic results, but an incorrect diagnosis of BS would place an enormous burden on a healthy individual and their family, with serious consequences for their personal, social, and professional life. This dilemma has aroused controversy in the literature and is presumed to have "contaminated" some databases with healthy individuals, which would explain the significant differences in reported prognosis for this entity.

When diagnosis is confirmed in any index case, all family members who might be affected should be tested with baseline ECG and/or provocation testing. Baseline ECG alone
Diagnostic criteria for the Brugada syndrome

### Table 1
Clinical situations that can mimic the Brugada repolarization pattern.

- Atypical right bundle branch block
- Right ventricular myocardial infarction
- Acute pericarditis
- Hemopericardium
- Pulmonary thromboembolism
- Aortic dissection
- Central nervous system disorders
- Duchenne muscular dystrophy
- Friedreich’s ataxia
- Left ventricular hypertrophy
- Arrhythmogenic right ventricular cardiomyopathy
- Mechanical compression of the right ventricular outflow tract (tumor/pectus excavatum)
- Following electrical cardioversion
- Early repolarization
- Hypothermia

is insufficient, since 51% of affected individuals fluctuate between diagnostic and non-diagnostic ECGs. Provocation testing with sodium channel blockers such as flecainide, ajmaline or procainamide is thus essential to detect intermittent or occult forms of the disease, although little is known of their sensitivity, specificity and reproducibility.

**Signal-averaged ECG**

Signal-averaged ECG (SAECG) is a computer-based technique that is able to detect QRS abnormalities that are too subtle for conventional ECG. This exam (Fig. 4) shows the arithmetic mean of the sum of multiple (usually 200) QRS complexes, obtained over a period of approximately five minutes with as little background noise as possible. The process increases the signal-to-noise ratio of the selected cardiac complexes so that signals of the order of one microvolt in the terminal QRS complex can be detected and measured to within a few milliseconds. These signals are commonly known as ventricular late potentials.

**Objectives**

The aims of the study were to construct a model to detect carriers of nonsense or missense SCN5A mutations with significant functional repercussions based on subclinical disturbances in intra-atrial, atrioventricular and intraventricular conduction. This is used to develop a score of disease probability which we suggest should be used in first-degree relatives of Brugada patients and in individuals with idiopathic Brugada ECG.

**Methods**

Of a total of 141 members of three different families including 55 carriers of two nonsense SCN5A mutations causing BS (43 with Arg222STOP and 12 with Thr1754ProfsX32), all those aged over 16 were studied.

The PR interval (PR) in DII and QT dispersion (QTd) between leads V1 and V3 were measured on conventional ECG, calibrated so that 20 mm=1 mV, and with a velocity of 50 mm/s. Signal-averaged ECG was performed with time-domain analysis, and the total duration of the filtered QRS complex (fQRS), the root-mean-square (RMS40) and the low-amplitude signal (LAS) were measured. Two tests were developed to detect carriers:

1. A screening test (ScreenTest) with PS (the sum of PR and fQRS $\geq$ 250 (the theoretical maximum of this interval in
Table 2  Clinical, demographic and electrical characteristics of the study population.

<table>
<thead>
<tr>
<th></th>
<th>Carriers</th>
<th>Non-carriers</th>
<th>p</th>
<th>Association with SCN5A mutation (eta coefficient)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical and demographic characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male - n (%)</td>
<td>20 (47.6)</td>
<td>34 (47.9)</td>
<td>0.567</td>
<td>-</td>
</tr>
<tr>
<td>Age (years)</td>
<td>40.31 ± 14.81</td>
<td>35.08 ± 13.05</td>
<td>0.059</td>
<td>-</td>
</tr>
<tr>
<td>Spontaneous type 1 ECG(^a) - n (%)</td>
<td>22 (52.4)</td>
<td>2 (2.8)</td>
<td>&lt;0.001</td>
<td>-</td>
</tr>
<tr>
<td>Spontaneous type 2/3 ECG(^b) - n (%)</td>
<td>5 (11.9)</td>
<td>4 (5.6)</td>
<td>0.490</td>
<td>-</td>
</tr>
<tr>
<td>Provocation test - n total/n positive</td>
<td>17/8</td>
<td>10/2</td>
<td>0.161</td>
<td>-</td>
</tr>
<tr>
<td>Symptoms - n (%)</td>
<td>6 (14.3)</td>
<td>4 (5.6)</td>
<td>0.112</td>
<td>-</td>
</tr>
<tr>
<td>EPS - n total/n positive</td>
<td>18/3</td>
<td>5/0</td>
<td>0.461</td>
<td>-</td>
</tr>
<tr>
<td>ICD - n (%)</td>
<td>8 (25.8)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>ECG and SAECG</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>190.98 ± 27.09</td>
<td>151.37 ± 22.18</td>
<td>&lt;0.001</td>
<td>0.653</td>
</tr>
<tr>
<td>QTd</td>
<td>47.14 ± 23.51</td>
<td>28.95 ± 18.04</td>
<td>&lt;0.001</td>
<td>0.472</td>
</tr>
<tr>
<td>fQRS</td>
<td>106.13 ± 9.40</td>
<td>92.41 ± 10.76</td>
<td>&lt;0.001</td>
<td>0.544</td>
</tr>
<tr>
<td>LAS</td>
<td>41.92 ± 9.75</td>
<td>31.59 ± 11.82</td>
<td>&lt;0.001</td>
<td>0.401</td>
</tr>
<tr>
<td>RMS40</td>
<td>18 ± 6.55</td>
<td>35.26 ± 21.8</td>
<td>&lt;0.001</td>
<td>0.47</td>
</tr>
</tbody>
</table>

ICD: implantable cardioverter-defibrillator; LAS: low-amplitude signal; PS: PR interval + filtered QRS complex; QTd: QT dispersion; RMS40: root-mean-square; SAECG: signal-averaged ECG.
\(^a\) Patients with at least one type 1 ECG.
\(^b\) Patients with at least one type 2/3 ECG and no type 1.

healthy individuals is 314 ms [200 + 114], 250 ms being 80% of this figure).

(2) a diagnostic test (DiagTest) for the simultaneous fulfillment of four conditions: PS ≥ 250 and QTd > 10 and LAS > 26 and RMS40 ≤ 29 (the latter two cut-offs are approximately 70% of the theoretical maximum in healthy carriers).

Results

The study population consisted of 113 individuals, 42 of them carriers. Significant differences in PR, QTd, fQRS, RMS40 and LAS were found between carriers and non-carriers. The SCN5A gene was associated with all these variables, the strongest association being with PR (Table 2). Both tests were applied to 63 family members (38 carriers). The ScreenTest was positive in 38 of 38 carriers, with eight false positives in 27 non-carriers (sensitivity = 100% and specificity = 66.67%). From ROC curve analysis (Fig. 5) a cut-off of PS = 252.5 shows sensitivity = 100% and specificity = 76% and a cut-off of PS = 260 shows sensitivity = 94.7% and specificity = 84%. The DiagTest was positive in 36 of 38 carriers, with three false positives: sensitivity = 94.74% and specificity = 88.89%. From ROC curve analysis a multivariate logistic model identifies a cut-off with sensitivity = 92% and specificity = 92%. The area under the curve was 0.927 (p < 0.001), demonstrating that this test has an excellent ability to discriminate between carriers and non-carriers.\(^21\) In the same group the sensitivity and specificity of the characteristic spontaneous repolarization pattern (type 1 Brugada ECG) to detect carriers were 52.4% and 97.2%, respectively, and the difference between the sensitivity of the DiagTest and of the typical repolarization pattern is statistically significant.

Discussion

In 2008 it was demonstrated that carriers of truncating (nonsense) SCN5A mutations have more symptomatic forms of BS, and atrioventricular conduction disturbances were also described, both through increased PR interval\(^22\),\(^23\) and increased HV interval measured invasively during electrophysiological study.\(^24\) SAECG was proposed around the same time as a possible tool for arrhythmic risk stratification in BS.\(^25\)

However, this study is the first to propose incorporating conduction parameters into the diagnostic process. As with long QT syndrome and arrhythmogenic right ventricular cardiomyopathy,\(^27\) the proposed test could be included in a score of disease probability (Table 3), which we consider would be useful given the shortcomings discussed above of using patterns of ventricular repolarization in isolation and the clinical and social burdens arising from a diagnosis of BS.

When there is clinical and/or electrocardiographic suspicion of BS, intra-atrial, atrioventricular and intraventricular conduction times should be measured, ideally with SAECG, since the fast response cardiac action potential that is dysfunctional in BS is involved in all three. Simultaneous detection of times above the normal-high limit of these three depolarization times (in this study the limit used was 70–80% of the theoretical maximum in healthy individuals) may indicate the likelihood of the individual having the disease due to nonsense or missense mutations in SCN5A with significant functional impact. We suggest their use in adult
Table 3  Diagnostic criteria of Brugada syndrome.

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ECG</strong></td>
<td></td>
</tr>
<tr>
<td>Type 1 ECG</td>
<td>5</td>
</tr>
<tr>
<td>Type 2/3 ECG</td>
<td>4</td>
</tr>
<tr>
<td>PS ≥ 250 and QTd &gt; 10 and LAS ≥ 26 and RMS40 ≤ 29</td>
<td>2</td>
</tr>
<tr>
<td>Type 1 ECG in relative(s)</td>
<td>3</td>
</tr>
<tr>
<td>Documented VF</td>
<td>3</td>
</tr>
<tr>
<td>Documented VT</td>
<td>3</td>
</tr>
<tr>
<td>VF/VT inducible by programmed electrical stimulation</td>
<td>3</td>
</tr>
<tr>
<td><strong>Clinical features</strong></td>
<td></td>
</tr>
<tr>
<td>Family history of sudden cardiac death at &lt;45 years old</td>
<td>3</td>
</tr>
<tr>
<td>Syncope</td>
<td>3</td>
</tr>
<tr>
<td>Nocturnal agonal respiration</td>
<td>3</td>
</tr>
<tr>
<td><strong>Probability of BS</strong></td>
<td></td>
</tr>
<tr>
<td>≥ 8 points: confirmed</td>
<td></td>
</tr>
<tr>
<td>7 points: highly probable</td>
<td></td>
</tr>
<tr>
<td>6 points: possible</td>
<td></td>
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<tr>
<td>≤ 5 points: unlikely</td>
<td></td>
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</tbody>
</table>


first-degree relatives of index cases when the results of genetic testing are not available. Another possible use would be to calculate the probability of disease in individuals with idiopathic Brugada ECG or with arrhythmias and type 2 or 3 Brugada repolarization pattern. In these cases, the proposed score could support the diagnosis (score 7), raise suspicion (score 6), or render it unlikely (score ≤5).

Conclusion

We have shown that the ScreenTest and DiagTest are more effective tools than the characteristic Brugada repolarization pattern to discriminate between carriers and non-carriers of nonsense SCN5A mutations. These tests may be useful in diagnosing this entity by determining the probability that a given repolarization pattern in fact corresponds to BS.

Limitations

Our study has two major limitations:

1. The number of carriers was relatively small and only two mutations were studied. In order to prove the usefulness and reproducibility of the proposed score, it will be necessary to apply it to other Brugada patients and their families.
2. The P wave and the PR interval were not measured with the precision of SAECG, since the means to do so were not available to our group. Measurement of the PS interval, or the PR + fQRS wave, entirely by SAECG (without interference from the atrioventricular node) could make the score even more effective.

We accordingly urge all clinicians working with BS patients who may be interested in collaborating with this work to contact us.

Conflicts of interest

The authors have no conflicts of interest to declare.

References


