Brugada Syndrome 2012
Paola Berne, MD; Josep Brugada, MD, PhD

Brugada syndrome (BS) is a genetically determined disease, characterized by typical electrocardiographic signs, and it predisposes to sudden cardiac death (SCD), affecting young subjects with structurally normal hearts. The prevalence of this disorder is still uncertain, presenting marked geographical differences. The syndrome has a genetic basis, and several mutations have been identified in genes encoding subunits of cardiac sodium, potassium, and calcium channels, as well as in genes involved in the trafficking or regulation of these channels. Most BS patients are asymptomatic, but those who develop symptoms present with syncope and/or SCD secondary to polymorphic ventricular tachycardia and/or ventricular fibrillation. Risk stratification is still challenging, especially in cases of asymptomatic BS patients. This is a brief review of recent advances in our understanding of the genetic and molecular bases of BS, arrhythmogenic mechanisms and clinical course, as well as an update of the tools for risk stratification and treatment of the condition. (Circ J 2012; 76: 1563–1571)

Key Words: Brugada syndrome; Channelopathies; Implantable cardioverter-defibrillator; Sudden death; Ventricular fibrillation

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Genetic Basis of BS

BS is an inherited condition transmitted in an autosomal-dominant way. The syndrome has a heterogeneous genetic basis: mutations in 10 genes have been linked to BS (Table 1), and it is very likely that the number of genetic defects responsible for it will continue increasing. Mutations in SCN5A leading to a loss of function of the cardiac sodium (Na+) channel by different mechanisms is the most common genotype found among these patients (ie, 20% of BS cases; range 11–28%). To date, almost 300 mutations in SCN5A have been described in association with BS.17 Mutations in the glycerol-3-phosphate dehydrogenase 1-like gene (GPD1L) cause abnormal trafficking of the cardiac Na+ channel to the cell surface and a reduction of approximately 50% of the inward Na+ current.18 Mutations in genes encoding the a1 (CACNA1c) and β2b (CACNB2b) subunits of the L-type cardiac calcium (Ca2+) channel leading to a decrease of the Ica current, result in a combined BS/short QT syndrome.19 Other genes recently reported to be linked to the syndrome are: SCN1B (encoding for β1- and β1b-subunits, auxiliary function-modifying subunits of the cardiac Na+ channel, resulting in a decrease of the Is current by affecting the Na+ channel trafficking);20 KCNE3 (encoding MiRP2, a protein that decreases the potassium (K+) transient outward current (Ito) current by interacting with channel Kv4.3, resulting in an increase of Ito magnitude and density);21 SCN3B (which encodes for the β3-subunit of the Na+ cardiac channel, and leading to a loss of function of the Na+ cardiac channel also cause

Table 1

<table>
<thead>
<tr>
<th>Gene</th>
<th>Mutation Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCN5A</td>
<td>Loss of function</td>
<td>Na+ channel</td>
</tr>
</tbody>
</table>
BERNE P et al.

Table 1. Identified Genes Linked to BS

<table>
<thead>
<tr>
<th>Variant</th>
<th>Gene</th>
<th>Ionic current</th>
<th>Functional effect</th>
<th>Inheritance</th>
<th>% of carriers among BS patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>BS1</td>
<td>SCN5A</td>
<td>I$_{Na}$</td>
<td>Loss of function</td>
<td>Autosomal dominant</td>
<td>11–18%</td>
</tr>
<tr>
<td>BS2</td>
<td>GPD1-L</td>
<td>I$_{Na}$</td>
<td>Loss of function</td>
<td>Autosomal dominant</td>
<td>&lt;1%</td>
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<tr>
<td>BS3</td>
<td>CACNA1c</td>
<td>I$_{Ca}$</td>
<td>Loss of function</td>
<td>Autosomal dominant</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>BS4</td>
<td>CACNB2</td>
<td>I$_{Ca}$</td>
<td>Loss of function</td>
<td>Autosomal dominant</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>BS5</td>
<td>SCN1B</td>
<td>I$_{Na}$</td>
<td>Loss of function</td>
<td>Autosomal dominant</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>BS6</td>
<td>KCNE3</td>
<td>I$_{K}$</td>
<td>Gain of function</td>
<td>Autosomal dominant</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>BS7</td>
<td>SCN3B</td>
<td>I$_{Na}$</td>
<td>Loss of function</td>
<td>Autosomal dominant</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>BS8</td>
<td>MOG1</td>
<td>I$_{Na}$</td>
<td>Loss of function</td>
<td>Autosomal dominant</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>BS9</td>
<td>KCNE5</td>
<td>I$_{K}$</td>
<td>Gain of function</td>
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</tr>
<tr>
<td>BS10</td>
<td>KCND3</td>
<td>I$_{K}$</td>
<td>Gain of function</td>
<td>Autosomal dominant</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

BS, Brugada syndrome.

**ECC Patterns in BS**

The diagnosis of BS requires the presence of a type 1 BS pattern in the right precordial leads (ie, V1–3), either spontaneous or unveiled by Class I antiarrhythmic drugs (AAD), characterized by a prominent coved ST-segment elevation displaying J-point amplitude or ST-segment elevation ≥2 mm, followed by a negative T wave. Right bundle branch block may be associated with BS, but its presence is not required for the diagnosis.26,27 The type 2 BS pattern (≥2 mm J-point elevation, ≥1 mm ST-segment elevation and a saddleback appearance, followed by a positive or biphasic T wave) and type 3 BS pattern (either a saddleback or coved appearance, but with an ST-segment elevation <1 mm) are considered to be suggestive but not confirmatory of the disease (Figure 1).

According to the consensus on BS,1,28 the ECG diagnosis is reached when a type 1 pattern is found in at least 2 right precordial leads (V1–3); however, a study on 186 BS patients established that V3 did not yield diagnostic information in that group, and that patients showing a type 1 ECG in only 1 right precordial lead (V1 or V2) presented a similar clinical profile and arrhythmic risk as BS patients with the same ECG pattern in more than 1 precordial lead.29

**Pharmacological Tests for the Diagnosis of BS**

The ECG is dynamic in BS patients,30,31 the 3 aforementioned patterns may coexist in the same patient at different moments, and patients may show normal ECGs and the diagnostic pattern is unmasked only under certain circumstances (eg, fever, vagotonic agents or Class I AAD32). This finding led to the use of Class I AAD as a diagnostic test in cases of suspected BS (Figure 2). Flecainide, ajmaline, procainamide, disopyramide, propafenone and pilsicainide have been used to unmask BS. The current recommendations on drugs, doses, route and time of administration are outlined in Table 2, with ajmaline being the drug of choice.33,34 Drug challenge is only considered positive when a type 1 BS pattern is revealed by the test.

During the basal ECG and at the beginning and end of the drug challenge test with the Class I AAD, it is recommended to place the right precordial leads at the 3rd and 2nd intercostal...
spaces, because it increases the sensitivity of the ECG for de-
tecting the diagnostic BS pattern 35–37 (Figure 3)

**ECG Modulating Factors and Differential Diagnosis**

Exposure to some drugs and ionic imbalance may produce a
Brugada-like ST-segment elevation, which may represent a ge-
netic predisposition to BS 38 (Figure 4). Fever also modulates
the phenotype and risk of arrhythmias in BS patients by caus-
ings accentuation of the inactivation of the Na⁺ channel, elic-
iting a type 1 ECG pattern and triggering ventricular arrhyth-
mas 39–43.

Many conditions may cause development of ST-segment
elevation in the right precordial leads, mimicking the BS ECG
pattern. This group of diseases and ECG abnormalities are not
related to BS, and they should be carefully ruled out (Figure 4).

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**Table 2. Drugs Used to Unmask Brugada Syndrome**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Route of administration</th>
<th>Duration of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ajmaline</td>
<td>1 mg/kg</td>
<td>Intravenous</td>
<td>10 min</td>
</tr>
<tr>
<td>Flecainide</td>
<td>2 mg/kg</td>
<td>Intravenous</td>
<td>10 min</td>
</tr>
<tr>
<td></td>
<td>400 mg</td>
<td>Oral</td>
<td>Single dose</td>
</tr>
<tr>
<td>Procainamide</td>
<td>10 mg/kg</td>
<td>Intravenous</td>
<td>10 min</td>
</tr>
<tr>
<td>Pilisicaine</td>
<td>1 mg/kg</td>
<td>Intravenous</td>
<td>10 min</td>
</tr>
</tbody>
</table>

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**Figure 2.** Flecainide test during screening for Brugada syndrome in a individual with a type 3 ECG (right precordial leads). (A) Basal ECG. (B) After infusion of 2 mg/kg of flecainide, a type 1 ECG is observed in leads V₁-2.

**Figure 3.** (Left) Basal ECG shows a suggestive but not diagnostic ECG pattern. When V₁ and V₂ are placed in the 3rd intercostal space (ICE; Right), a type 1 BS pattern (diagnostic) is observed.

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**Figure 4.**
Figure 4. Diagnostic algorithm for Brugada syndrome. BS, Brugada syndrome; ECG, electrocardiogram; RBBB, right ventricular bundle branch block; MI, myocardial infarction; RVMI, right ventricular myocardial infarction; CNS, central nervous system; ANS, autonomic nervous system; LVH, left ventricular hypertrophy; ARVC/M, arrhythmogenic right ventricular cardiomyopathy/dysplasia; RVOT, right ventricular outflow tract; SCD, sudden cardiac death; PVT, polymorphic ventricular tachycardia; VF, ventricular fibrillation; AAD, antiarrhythmic drugs.
Diagnosis of BS

Once a type 1 ECG in the right precordial leads is observed, and other conditions that may account for it are excluded, BS is definitely diagnosed when the patients also present at least 1 of the following clinical criteria:

1. Family history:
   • SCD in a family member younger than 45 years
   • ECG type 1 in family members

2. Arrhythmia-related symptoms:
   • Syncope
   • Seizures
   • Nocturnal agonal respiration

3. Documented ventricular arrhythmias:
   • PVT
   • VF.

Figure 4 is a proposed diagnostic algorithm.

Pathophysiologic Mechanism Underlying BS Phenotype

There are 2 main theories to explain the pathophysiologic mechanisms responsible for BS: repolarization and depolarization theories. Repolarization theory has been supported by animal models, as well as in humans.9,44–47 Those supporting this theory claim that the ECG manifestations of BS and the increased risk for ventricular arrhythmias are a direct consequence of a shift in balance of the ionic currents active during the end phase 1 of the action potential (AP): decrease of inward positive currents and/or increase of outward positive currents, resulting in an accentuation of the AP notch, leading to an elevation of the ST-segment with saddleback appearance, whereas repolarization of the epicardial cells precedes that of M and endocardial cells, and is followed by a positive T wave, and eventually to a loss-of-dome of the AP, mainly in the RV epicardium, where Ina is prominent. At this point, the ST-segment elevation will be higher and the morphology will adopt a coved appearance, followed by a negative T wave, secondary to a reversal of the direction of repolarization (from endocardium to epicardium, as the AP in the epicardium is prolonged). All this generates a remarkable dispersion of repolarization within the epicardium and transmurally. Propagation of the AP dome from sites where the dome is maintained to sites in which it is abolished cause local re-excitation (referred to as “phase 2 reentry”), resulting in ventricular extrasystoles originating in the epicardium. These extrasystoles may trigger episodes of PVT/VF in a patient with BS.

Those supporting the depolarization theory claim that conduction delay is the main pathophysiologic event in BS, which is evident in some basal ECGs (long PR interval, complete bundle branch block, etc) and also in different clinical studies, such as electrophysiological studies (EPS), in which some BS patients show prolonged H-V intervals; body surface, endocardial and epicardial mapping; and late potentials.1,35,48 They also sustain that mild structural abnormalities are a part of the syndrome, which would explain the late potentials and also may account for the conduction abnormalities. An ECG pattern secondary to conduction slowing in the RV, resulting in very late activation of the right ventricular outflow tract (RVOT), and an intercellular current from the RV to RVOT (responsible for the ST-segment elevation in the right precordial leads) and a subsequent current from the RVOT to RV (responsible for the negative T waves in the same leads).

Even if this theory has not been demonstrated in animal models, there is growing evidence from clinical studies supporting its role in BS.49 A recent study by Nademanee et al showed that in a small group of symptomatic BS patients with an implantable cardioverter-defibrillator (ICD) and multiple shocks, persistent spontaneous type 1 pattern and inducible VT/VF in the EPS, electroanatomical mapping (endo/epi) found abnormally low voltage, prolonged duration and fractionated late potentials in the anterior aspect of the RVOT (epicardium), and radiofrequency catheter ablation (RFCA) of these sites rendered the VT/VF not inducible (78% of patients) and normalizing the ECG pattern in 89%, with no recurrence of sustained arrhythmic events during follow-up (20±6 months).50

The controversy remains, as there is evidence supporting both theories, which might not be mutually exclusive, and further studies are needed to clarify this issue.

The different effect of estrogens (which inhibit Ina expression and trafficking) and testosterone (which increases slow potassium currents),51–54 and the differences in expression and density of the Ina current between both sexes (density of the Ina current is lower in females55,56) are the 2 main hypotheses for the predominance of BS phenotype among males.

Prognosis and Risk Stratification

All groups have identified and use some markers of high risk in BS patients, but there is still controversy on how to stratify arrhythmic risk in asymptomatic BS patients.

A previous episode of SCD and syncope are markers of high risk of presenting ventricular arrhythmias (rate of recurrence of ventricular arrhythmias in patients with aborted SCD and BS: 17–62% at 48–84 months follow-up according to different series; rate of recurrence of ventricular arrhythmias in patients with syncope and BS: 6–19% at 24–39 months follow-up in different series), and therefore the patient should receive an ICD for secondary and primary prevention of SCD (Class I indication).6–10,12,37

It is reasonable to implant an ICD in a BS patients with documented ventricular tachycardia not resulting in aborted SCD, irrespective of the symptomatic status (Class IIa indication).57

Serial monitoring of the ECG with the object of detecting the spontaneous type 1 ECG pattern in BS patients with or without previous symptoms is a Class IIa recommendation, as this pattern has been identified as an independent predictor of ventricular arrhythmias in the multivariate analysis of the largest cohort of BS patients published to date10 (hazard ratio [HR] 1.8; 95% confidence interval [CI] 1.03–3.33; P=0.04) and in other series.

The risk of lethal or near-lethal arrhythmic episodes among previously asymptomatic patients with BS varies according to the series: Brugada et al. reported an 8% recurrence rate at 33±39 months of follow-up (HR 2.5; 95% CI 1.2–5.3; P=0.017);12 Priori et al reported a 6% recurrence rate at 34±44 months of follow-up;6 Eckardt et al and Giustetto et al reported a 1% recurrence rate (after 40±50 months and 30±21 months of follow-up, respectively); Probst et al reported a 1.5% recurrence rate at 31 months of follow-up.10

The value of inducibility of sustained ventricular arrhythmias during an EPS as a tool to evaluate arrhythmic risk in BS is still the most controversial topic. The results published by Brugada et al indicate that inducibility during an EPS is an independent predictor for cardiac events (HR 8.33, 95% CI 2.8–25; P=0.0001),12 but other registries have failed to demonstrate this.6,8,10,58

There are a number of possible reasons for the differences among the cited studies: different inclusion criteria, different stimulation protocols, different statistical analysis methods, etc.
So far, some groups still use an EPS for the negative predictive value in case patients are non-inducible, whereas others simply do not perform an EPS test in asymptomatic patients with a spontaneous type 1 ECG in which case no other stratifiers can be used and the decision whether to implant an ICD or not is left to the discussion between physician and patient.

Current guidelines consider an EPS for risk stratification in asymptomatic BS patients with spontaneous type 1 ECG as a Class IIb indication.

Family history of SCD has not been identified as a reliable marker of high risk in patients affected by BS.

In all of the published series there was no difference in arrhythmic events when dividing patients according to the presence or absence of SCN5A mutations, but some studies have identified a significantly higher rate of syncope among patients carrying SCN5A truncation mutations and missense mutations resulting in non-functional Na+ channels, compared to patients with SCN5A missense mutations that produce a lesser decrease in the Na+ current. The finding that common polymorphisms located in the same gene may modulate the effect of the mutations causing BS, counterbalancing its deleterious effects and improving the BS phenotype, suggests that polymorphisms may be possible targets for therapeutic interventions.

**Figure 5** shows our proposed risk stratification scheme and recommendations for ICD in BS patients.

**Treatment and Recommendations for BS Patients**

**ICD**

The implantation of an ICD is the only proven effective strategy for the prevention of SCD in this group of patients, even if they may present several disadvantages: low rates of appropriate shocks (8–15%, median follow-up 45 months; annual appropriate discharge rate=2.6%) and high rate of inappropriate shocks (20–36% at 21–47 months follow-up). In many series the inappropriate shocks greatly exceeded (2–2.5-fold) the rate of appropriate shocks. Programming only 1 therapy zone (for VF), at a high rate cut-off (250 beats/min – patient age in years; or >210–220 beats/min) and increasing the detection window, ie, programming long detection intervals by increasing the number of intervals to detect (NID) to 18 of 24
in the VF zone helps avoid shocking a non-sustained tachycardia. Other measures to avoid ICD complications are absolute contraindication of competitive sports, and limited recreational sports, especially those with an implied higher risk of lead damage; favoring the use of 1 lead devices and treatment of supraventricular arrhythmias, including RFCA.

Pharmacological Treatment
Isoproterenol (which increases the I Ia current), has proved to be useful for treating electrical storm in BS (Class IIa indication).

Quinidine, a Class Ia AAD with Ia and IKr blocker effects has also proved to be useful for treating electrical storm in BS patients, and its use in this context is a Class IIb indication. It prevents induction of VF and suppresses spontaneous ventricular arrhythmias, being used in patients with BS and multiple ICD discharges. It has been suggested that it also could be useful as a bridge to ICD, as an alternative to it and in children; however, it has a high rate of secondary effects.

Dysopiramide and orciprenaline have also demonstrated their usefulness for treating electrical storm. Other drugs being evaluated for BS are tedisamile (a pure Ia blocker), phosphodiesterase III inhibitors (eg, cilostazol) and dimethyl lithospermate B.

Additional Management Recommendations
BS patients should be advised to avoid all drugs that may induce a type 1 ECG and/or trigger ventricular arrhythmias, and avoid unnecessary use of drugs (as the fact that a drug is not yet identified as potentially dangerous for these patients does not make it use safe). For up-to-date information on this matter, the following website has been developed: www.brugadadrugs.org.

Fever may induce the appearance of a type 1 BS ECG pattern and may trigger episodes of PVT/VF in BS patients. In the case of fever, close ECG monitoring is appropriate in combination with lowering of the body temperature.

The appearance of syncope, seizures or nocturnal agonal respiration must lead to prompt medical evaluation.

Family screening of BS in first-degree relatives is strongly recommended.

All patients must be followed-up on a regular basis, in order to identify the development of symptoms.

Genetic testing, when available, is recommended (to support clinical diagnosis, early detection of other affected family members and for research purposes).

Conclusions
Brugada syndrome is a rather recently known disease with limited information concerning long-term follow-up and risk stratification.

Patients should only be diagnosed if a type 1 ECG is present. Symptomatic patients are at risk of sudden death. Asymptomatic patients have a low risk of ventricular arrhythmias, but identification of those at risk should be the primary objective of upcoming studies.

Disclosure
The authors have nothing to disclose.

References


28. Mok NS, Priori SG, Napolitano C, Chan NY, Chahine M, Baroudi G. A newly characterized SCN5A mutation underlying Brugada syn-


