Brugada Syndrome: Current Practices in Diagnosis, Prognosis, and Treatment

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Introduction

Brugada syndrome (BrS) is a hereditary syndrome, first reported in 1992, characterized by right bundle branch block and an uncommon form of ST-T wave elevation in the V1 and V2 leads and associated with risk of sudden cardiac death (SCD) arising from polymorphic ventricular tachyarrhythmias. BrS is an autosomal dominant inherited condition; however, more than 50% of BrS cases may be sporadic. Approximately 20% to 25% of BrS cases originate from loss of function mutations in the SCN5A cardiac sodium channel. The diagnosis of BrS is mainly based on electrocardiogram. SCD due to ventricular fibrillation can be the first clinical presentation of BrS. The insertion of an implantable cardioverter-defibrillator remains the only approved effective measure to prevent SCD in BrS patients. Risk stratification in BrS is still challenging. Because the role of electrophysiological study (EPS) for estimating prognosis in BrS patients has been controversial, but the expert consensus published in 2013 (Priori et al, 2013) considered the performance of EPS, class IIb. Future randomized studies focused on risk stratification and the value of radiofrequency ablation in BrS patients are needed.

This review provides a succinct general overview of BrS focusing on current practices in diagnosis, prognosis, and treatment.

Genetic basis of Brugada syndrome

BrS can show an autosomal dominant inheritance pattern; however, more than 50% of BrS cases may be sporadic [6]. Approximately 18% to 30% of BrS cases originate from loss of function mutations in the SCN5A cardiac sodium channel [7] (Figure 1) and are classified as BrS type 1. The mutation detection rate may be considerably higher amongst familial cases than in sporadic cases. Schulze-Bahr et al [8] identified SCN5A mutations in 38% of the familial BrS cases compared with none of the sporadic cases they tested (P = 0.001).

Additionally, common polymorphisms may influence BrS. Bezzina et al [9] reported a haplotype of six SCN5A promoter polymorphisms with a prevalence of 22% in Asians but relatively absent from white and black populations. Brugada et al [2] reported that the H558R polymorphism can modulate the BrS phenotype such that, among 75 genotyped BrS patients, the minor allele (R558) was associated with a less severe clinical process. Patients homozygous for H558 had a wider QRS complex in lead II, higher J-point altitude in lead V2, and tended to demonstrate more severe symptoms than those who were H558R heterozygous or R558 homozygous.

Diagnostic criteria and typical ECG patterns

Of the three recognized types of BrS ECG morphology [10] (Figure 2), type 1 is characterized by a coved-type ST-segment elevation ≥2 mm (0.2 mV) followed by a negative T-wave in the right precordial leads. Type 2 has saddleback-type ST-segment elevation with J-point amplitude ≥2 mm and ST-segment elevation ≥1 mm followed by a positive or biphasic T-wave in the right precordial leads. Type 3 has either coved- or saddleback-type with <1-mm ST-segment elevation in the right precordial leads.
The 2013 expert consensus recommendations on inherited primary arrhythmia syndromes [11] list the following criteria for diagnosis of BrS:

1. BrS is diagnosed if a patient has ST-segment elevation with type 1 morphology ≥ 2 mm in at least one right precordial lead (V1, V2) placed in the second, third, or fourth intercostal space, occurring either spontaneously or induced by intravenous administration of class I antiarrhythmic agents (sodium-channel blockers).

2. BrS is diagnosed if patient has type 2 or type 3 ST-segment elevation with type 1 in least one right precordial lead (V1, V2) placed in the second, third, or fourth intercostal space, occurring when a challenge test with intravenous administration of class I antiarrhythmic agents evokes a type I ECG morphology.

The differential diagnosis involves conditions and diseases with Brugada-like ECG changes (acute myocardial ischemia, pericarditis, myocarditis, pulmonary embolism, acute stroke, aortic dissection, Duchenne muscular dystrophy, hypothermia, hypercalcemia, hyperkalemia, arrhythmogenic right ventricular dysplasia, pectus excavatum, and mechanical compression of the right ventricular outflow tract) [12], which must be ruled out before the ultimate diagnosis of BrS can be made [10].

**Clinical presentation and epidemiology**

SCD due to ventricular fibrillation (VF) can be the first clinical presentation of BrS [13].

The incidence of BrS is about four times higher in men than in women [13]. Most BrS patients are asymptomatic, and more than one-third are diagnosed through familial screening [13]. Some BrS cases manifest with syncpe, which can be caused by either non-sustained VF or vaso-vagal episodes [14]. Some cases manifest with seizures and nocturnal agonal respiration. Patients’ mean age at the onset of VF episodes is 41 ± 15 years [10], but BrS is also known as cause of sudden infant death syndrome or SCD in young children [15,16]. Fever is a trigger for Brugada ECG changes [10,17].

The prevalence of BrS appears to be low in the general population. Recent studies in Europe have shown that the prevalence of SCD in the general European population (age 7–64 years) is 1.34 per 100 000 per year [18], and approximately 5% of deaths do not involve structural heart problems [19]. Familial screening of such cases may reveal hereditary cardiomyopathies or inherited cardiac arrhythmias, including BrS, in about 40% to 53% of tested families [20,21]. Brugada-type ECG findings appear to be more common in Asia than in European countries and the United States [10,22,23] (Figure 3). There are three types of BrS-ECG morphologies. The prevalence of Brugada type 1 ECG is more common in Asia (0–0.36%) [22,24] and Europe (0–0.25%) [25,26] than in the United States (0.03%) [27,28]. The prevalence of Brugada type 2 and type 3 ECG is higher in Asia (0.12–2.23%) [22,24] than in European countries (0.0–0.6%) [25,26] or the United States (0.02%) [28,29].

Yan et al. [31] described the repolarization theory based on an experimental study; the administration of a combination of sodium channel blockers and acetylcholine leads to loss of the action potential dome in the canine right ventricular epicardium, causing a transmural voltage gradient. The prominence of cardiac transient outward potassium current (I_o) in the right ventricular outflow tract (RVOT) epicardium is explained by the predisposition of this area for a pronounced action potential notch and consecutive shortening of action potentials, which causes the coved-type ST-segment elevation in the right ventricular outflow tract; phase 2 reentry, which triggers a closely coupled extrasystole (R-on-T extrasystole); and consequent polymorphic VT or VF (Figure 4) [7].

The depolarization disorder hypothesis involves a conduction delay in the RVOT due to ultrastructural changes in the right ventricle of BrS patients [10,32,33,34]. Although neither cardiac CT nor cardiac MRI could detect abnormal structural changes in the RVOT in study populations, slight electrophysiological changes in the RVOT may be detectable by more sensitive techniques such as body surface map electrocardiogram, vectocardiogram, and signal-averaged ECG [35-37].

![Figure 1](https://example.com/figure1.png)

**Figure 1.** Topology of the SCN5A with mutations locations and their associated disorders. From Antzelevitch [7] with permission.

![Figure 2](https://example.com/figure2.png)

**Figure 2.** Types of BrS-ECG morphology. From Mizusawa and Wilde [10] with permission.
Risk stratification

Patients with a history of surviving cardiac death or syncope of unknown origin and spontaneous type 1 ECG morphology are at high risk for recurrent arrhythmic events [11,13,16,38-40]. A new study, first published on August 2016 [41] evaluated the clinical presentation of BrS probands over time. The study showed that newly diagnosed probands were significantly less symptomatic than those in the latter diagnosed group, with a lower prevalence of SCD as the first clinical presentation, spontaneous type I ECG pattern, and less often inducible during electrophysiological study (EPS). Male sex has been consistently associated with an increased rate of arrhythmic episodes [21]. Spontaneous atrial fibrillation (AF) has been seen in association with an increased incidence of syncope and VF in BrS patients [42,43].

Large BrS registries could not confirm the value of right ventricular programmed electrical stimulation for estimating prognosis in BrS patients without a history of ventricular tachycardia (VT) or VF [11,39], whereas the presence of QRS fragmentation in leads V1 to V3 and a ventricular effective refractory period <200 ms have been associated with a high rate of arrhythmic events in such patients [11,39,44]. The role of EPS for estimating prognosis in BrS patients remains controversial [11].

Current management

Currently the insertion of an implantable cardioverter-defibrillator (ICD) remains the only approved measure to effectively prevent SCD in BrS patients. Considering the very low risk for VF in asymptomatic BrS patients [11,45], they may not be eligible for an ICD. An individual estimation of other associated risk factors is recommended in this group of patients.

Pharmacological treatment

The International Expert Consensus conference in May 2013 [11] recommended isoproterenol and quinidine for BrS, which inhibit the short-term outward potassium current (I_{to}) or increase the sodium and calcium current. Isoproterenol enhances the L-type calcium current and has proved useful in the treatment of BrS patients with electrical storm [46], but no controlled data are available on its therapeutic impact. Quinidine is an antiarrhythmic class Ia drug with I_{to} and IKr inhibitor effects. It prevents triggering of VF and inhibits ventricular arrhythmias. Quinidine is presently used in patients with repeated ICD shocks, a contraindication for ICD implantation, or supraventricular arrhythmias [47]. Some studies have suggested the use of quinidine treatment in children with BrS as a bridge or alternative to ICD implantation [48,49]; however, randomized studies are lacking on this issue.

Radiofrequency catheter ablation

Nademane et al [50] demonstrated that epicardial ablation of the right ventricular outflow tract (RVOT) may prevent VF inducibility in high-risk BrS patients. Although epicardial ablation is a more complicated procedure than endocardial ablation [51], in several studies of BrS patients with implanted ICD due to VF, radiofrequency ablation suppressed the short-term recurrence of VF [52-54]. A recent study published in 2015 [55], in which 14 BrS patients underwent epicardial ablation of the RVOT and anterior right free wall, and the ablation of the arrhythmogenic substrate eliminated the BrS phenotype. However, no randomized studies have reported the influence of radiofrequency ablation on spontaneous arrhythmic episodes.

Conclusion

SCD due to VF can be the first clinical presentation of BrS. Most BrS patients are asymptomatic, and about two-thirds have a negative familial screening test. Large BrS registries could not validate the role of right ventricular programmed electrical stimulation for estimating the prognosis in asymptomatic BrS patients. The role of EPS for estimating prognosis in BrS patients is controversial, and ICD implantation is the only approved procedure to effectively prevent SCD in such patients. Several studies have reported the successful prevention of VF inducibility in high-risk patients through epicardial ablation of the RVOT. Future randomized studies focused on risk stratification and the value of radiofrequency ablation in BrS patients are needed. Increased awareness of Brugada syndrome is hoped to improve patient diagnosis and management.

Declaration of interest

The author declares no conflicts of interest.
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