Brugada Syndrome: Clinical Features, Risk Stratification, and Management

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ABSTRACT

In 1992, the Brugada brothers published a patient series of aborted sudden death, who were successfully resuscitated from ventricular fibrillation (VF). These patients had a characteristic coved ST-segment elevation in the right precordial leads on their 12-lead electrocardiogram (ECG) with no apparent structural heart abnormality. This disease was referred to as “right bundle branch block, persistent ST-segment elevation, and sudden death syndrome.” The term Brugada syndrome (BrS) was first coined for this new arrhythmogenic entity in 1996. BrS is more prevalent in Southeast Asian ethnic groups and was considered a familial disease due to the presence of syncope and/or sudden deaths in several members of the same family, however, the genetic alteration was only noted in 1998. The genetic characterization of BrS has proven to be challenging. The most common and well-established BrS genotype involves loss-of-function mutations in the SCN5A gene, but only represents between 15% and 30% of the diagnosed patients. Patients with BrS can present with a range of symptoms which can include syncope, seizures, and nocturnal agonal breathing due to polymorphic ventricular tachycardia or VF. If these arrhythmias are sustained, sudden cardiac death may result. Despite the significant progress on the understanding of BrS over the last two decades, there remain a number of uncertainties and challenges; we present an update review on the subject.

Key words: Brugada syndrome, electrical storm, epicardial ablation, polymorphic ventricular tachycardia, right ventricular outflow tract ablation, sudden cardiac death, ventricular fibrillation

HISTORICAL PERSPECTIVE

In 1917, Guazon et al.[1] described a sudden nocturnal death syndrome among apparently Philippine young healthy adults, and autopsy revealed no pathological evidence to explain the cause of the death. The condition had become known locally as “Bangungut,” the meaning of which is to “rise and moan in sleep” – representing the most common preterminal clinical feature. In 1992, the Brugada brothers published a series of eight patients of aborted sudden death, who were successfully resuscitated from ventricular fibrillation (VF).[2] These patients had a characteristic coved ST-segment elevation in the right precordial leads on their 12-lead electrocardiogram (ECG) with no apparent structural heart abnormality. This disease was referred to as “right bundle branch block, persistent ST-segment elevation, and sudden death syndrome.” The term Brugada syndrome (BrS) was first coined for this new arrhythmogenic entity in 1996[3] and in 1997,[4] it was considered a familial disease due to the presence of syncope and/or sudden deaths in several members of the same family.

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was recognized as the same entity of sudden nocturnal death syndrome described by Guazon et al. in 1917.

Sudden unexplained nocturnal death syndrome is an entity more prevalent in Southeast Asian ethnic groups and was considered a familial disease due to the presence of syncope and/or sudden deaths in several members of the same family, however, the genetic alteration was first noted in 1998 by Chen et al. Despite the significant progress in the understanding of BrS over the last two decades, there remain a number of uncertainties and challenges. This review will focus primarily on the clinical manifestation, risk stratification, and management of patients with BrS.

PREVALENCE

The prevalence of BrS is believed to range from 1 in 5000 to 1 in 2000. However, the incidence of BrS pattern on ECG is higher, ranging from 0.12% to 0.8% in several studies. It is considered to be responsible for up to 20% of sudden deaths in patients with structurally normal hearts and has an 8–10 times male preponderance. The highest prevalence appears to be in South-East Asia.

CLINICAL FEATURES

Patients with BrS can present with a range of symptoms which can include syncope, seizures, and nocturnal agonal breathing due to polymorphic ventricular tachycardia (PMVT) or VF. If these arrhythmias are sustained, sudden cardiac death (SCD) may result. Syncope or SCD is reported to range from 17% to 42%, but this likely overestimates the true incidence, as most asymptomatic patients are never diagnosed. Recent data suggest a substantially lower rate of SCD as the first symptom, approximately 4.5%, and also a lower incidence of recurrent arrhythmia during follow-up, 5%.

Life-threatening arrhythmias usually occur during resting or sleeping, suggesting a possible association with bradycardia or vagal events. However, there is no data discrimination between bradycardia-dependent or vagal events, but the majority of events occur during vagal predominance, which implies bradycardia at the same time. Febrile episodes have also been frequently associated with symptoms. Symptoms typically first occur during adulthood, with a mean age of SCD presentation of 41 ± 15 years. There is an 8–10-fold male predominance and thus may be linked to hormonal influences, particularly as this gender difference is not seen in children under the age of 16 years.

DIAGNOSTIC CRITERIA

Until 2013, BrS diagnosis required demonstration of the presence of a Type 1 ECG pattern and clinical manifestations such as resuscitated SCD, documented PMVT, a history of nonvasovagal syncope, and/or a family history of noncoronary SCD age <45 years. However, because many patients with a Type 1 ECG are asymptomatic, the 2013 expert consensus statement proposed the following definition: “BrS is diagnosed when a type 1 ST elevation is observed either spontaneously or after intravenous administration of a sodium channel blocker in at least one right precordial lead (V1 and V2), placed in a standard or superior position (up to the 2nd intercostal space),” without the need for evidence of malignant arrhythmias.

ELECTROCARDIOGRAPHIC FEATURES

Following the original description of BrS, there was much uncertainty about its precise ECG features. To clarify these ambiguities, an expert consensus document was published in 2012 establishing two descriptive ECG abnormalities for BrS, when previously there had been three:

Type 1 (coved type) [Figure 1a]: This alteration is the only diagnostic pattern for BrS. It is characterized by an ST-segment elevation ≥2 mm in ≥1 right precordial lead (V1 to V3), followed by an r’-wave and a concave or straight ST segment, but not convex. The descending ST-segment crosses the isoelectric line and is accompanied by a negative and symmetric T-wave. These changes should be observed either spontaneously or following a provocative drug challenge following intravenous administration of a sodium-channel blocker, such as ajmaline, flecainide, or procainamide. All other known causes of ST-segment elevation in right precordial leads (known as phenocopies or mimics) should be excluded before making the diagnosis of BrS.

Type 2 (saddle-back type) [Figure 1b]: This ECG anomaly is only suggestive of BrS. It is characterized by an ST-segment elevation ≥0.5 mm (often ≥2 mm in V2) in ≥1 right precordial lead (V1 to V3), followed by a convex ST. The r’-wave may or may not overlap the J point, but it has a slow downward slope. The ST segment is followed by a positive T-wave in V2 and is of variable morphology in V1.

The placement of the right precordial leads in more cranial positions (in the 2nd or 3rd intercostal spaces) increases sensitivity in some patients due to the variable anatomical correlation between the right ventricular outflow tract (RVOT) and V1 to V2 in the standard positions. The identification of a spontaneous Type 1 pattern in the higher intercostal spaces conferred a similar prognosis to individuals with a Type 1 pattern in the standard positions of V1 to V2.
GENETICS OF BRUGADA SYNDROME

The genetic characterization of BrS has proven to be challenging. The most common and well-established BrS genotype involves loss-of-function mutations in the SCN5A gene, representing between 15% and 30% of the diagnosed patients. The SCN5A gene encodes for the cardiac voltage-gated sodium channel that is activated during the initial rapid depolarization of the cardiac action potential cycle. More than 250 mutations in the SCN5A gene have already been described, yet the role for genetic testing in the diagnosis of BrS is limited due to the presence of “benign” SCN5A variants in the general population. It is clear that the genetic basis for BrS is heterogeneous and no clear pathogenic genotype can be currently identified in the majority of patients. Furthermore, several large registry studies have failed to establish an independent association between genotype status and prognosis in BrS. However, recent data suggest that mutations specifically involving the pore region of the SCN5A gene may carry a more severe phenotype and were found to be independently associated with the risk of adverse cardiac events in both asymptomatic and symptomatic BrS patients.

Despite the ongoing progress in understanding the genetic causes of BrS, only 30%–35% of clinically diagnosed cases are genetically diagnosed, and most of these (25%–30%) result from pathogenic alterations in SCN5A.

PATHOPHYSIOLOGY – CHANNELOPATHY OR CARDIOMYOPATHY?

Two main pathophysiological mechanisms have been described for ventricular tachyarrhythmias (VTs) leading to SCD in BrS. Conventionally, BrS was thought to be a repolarization disorder, caused by the disparate expression of transient outward potassium current, mediated by a reduction in early sodium inflow, between the epicardium and inner myocardial layers. This results in curtailment of the epicardial action potential and a susceptibility to re-entry PMVT triggered by premature ventricular complexes, due to the epicardial-to-endocardial transmembrane ionic imbalance.

The depolarization theory is modeled around action potential conduction delay in the RVOT relative to the surrounding myocardium. In such conditions, VT can be triggered by the unequal membrane potential around the RVOT border, similar to the formation of VT seen in the circumstances of regional myocardial ischemia. This theory is supported by a number of clinical studies demonstrating relative RVOT conduction delay.

BrS was originally described as a disease of cardiac ion channel dysfunction without the presence of associated structural heart disease, leading to sudden death in otherwise healthy people. However, evidence demonstrating normalization of the pathognomonic ECG pattern and apparent significant reduction of the tendency to arrhythmia in most patients following radiofrequency ablation (RFA) of the RVOT epicardium strengthens the theory that structural abnormalities have a critical role in arrhythmogenesis in BrS.

Microanatomical changes such as increased collagen, fibrosis, and reduced gap junction expression, which may be mediated by the underlying myocardial inflammation, could be responsible for the characteristic ECG pattern and susceptibility to arrhythmia. Based on these findings, it has been suggested that BrS and arrhythmogenic cardiomyopathy represent different parts of the same disease spectrum. Although these two conditions have distinct macropathological appearances, there are many overlapping clinical features and genetic predispositions. The BrS ECG pattern has been noted in patients with arrhythmogenic cardiomyopathy, and SCD may occur in the early phase of the arrhythmogenic cardiomyopathy, in the absence of the associated characteristic structural changes.

There are a complex mix of underlying pathophysiological features which are variably expressed in individuals, which contribute toward BrS and risk of arrhythmia; these are summarized in Figure 2.

RISK STRATIFICATION

Mode of presentation – Cardiac arrest
Symptomatic presentation with aborted cardiac arrest or sustained VT confers the highest risk of future arrhythmic event in the form of PMVT/VF, with reported annual rates of approximately 8%, and secondary prevention with
implantable cardioverter-defibrillator (ICD) implantation is recommended.\textsuperscript{11,28}

**Mode of presentation – Syncope**

Syncpe is a common presentation, occurring in about 30\% of patients, and arrhythmia-related syncpe is also a well-established risk factor, with an annual event rate of about 2\%.\textsuperscript{28,29} Therefore, it is recommended that a vasovagal cause of syncpe is ruled out as these do not seem to clearly carry any additional risk.\textsuperscript{30,31} However, there is evidence that vagal tone may play an important role in precipitating spontaneous VT/VF in some BrS patients.\textsuperscript{32,33} Another challenge is that clinical symptoms suggestive of vagal syncpe may be observed in syncpe of cardiac origin.\textsuperscript{34} Nevertheless, there are some pointers to help guide clinicians identified by Nordkamp et al.\textsuperscript{35} in a study of 141 BrS patients, who, at the time of their diagnosis, had either experienced aborted sudden cardiac arrest (ACA) or syncpe. Compared to suspected nonarrhythmic syncpe patients, ACA patients tended to be older at the first event (45 vs. 20 years), were more likely to be male (relative risk 2.1) and to have urinary incontinence (relative risk 4.6), and were less likely to report prodromes. ACA was never triggered by hot/crowded surroundings, pain or other emotional stress, seeing blood, or prolonged standing.

Although there is consensus that ICD therapy is indicated for patients with clear arrhythmic syncpe and is not indicated for patients with neurocardiogenic syncpe, management of patients whose cause of syncpe is unclear remains challenging. Although not presently reflected in guidelines, there has been demonstration of the usefulness of implantable loop recorders for the evaluation of doubtful causes of syncpe, which should be considered as an important diagnostic tool in select patients.\textsuperscript{36-38} Most patients diagnosed with BrS are asymptomatic and present a greater challenge for risk stratification and management decisions.\textsuperscript{31,39} While the established risk of arrhythmic events is much lower for asymptomatic patients, about 1\% annually overall, many cases of SCD still occur in this population.\textsuperscript{28,31,40} Yet, regardless of several investigations into the predictors of arrhythmic
events in asymptomatic patients, no consensus is available for a risk stratification strategy in this population.\[^{31}\]  

**ELECTROCARDIOGRAM**

A spontaneous Type 1 Brugada ECG pattern is an important and established risk factor for cardiac events, which has been reported to confer a three-to-fourfold higher risk in asymptomatic patients.\[^{41,42}\] Despite this, only conservative surveillance and risk modification of lifestyle is universally recommended in asymptomatic patients.\[^{43}\] In contrast, a family history of SCD at any age is not an independent prognostic marker for cardiac events in either symptomatic or asymptomatic patients.\[^{39,44}\]  

While a multitude of ECG parameters have been associated with increased risk of cardiac arrhythmias, two that have been consistently reported as independent risk factors are abnormal QRS fragmentation in leads V1, V2, and V3 and early repolarization pattern in inferior and/or lateral leads.\[^{46-47}\] In addition, AF is more commonly seen in BrS than in the general population and has been reported as a risk factor for ventricular arrhythmias in several studies.\[^{48}\]  

A more recently reported\[^{49}\] ECG finding which seems to confer greater risk for VT and VF was a significant S-wave (≥0.1 mV and/or ≥40 ms) in lead I, which showed a sensitivity of 90.6% and 96.9%, a specificity of 62.2% and 61.1%, a negative predictive value of 98.5% and 99.5%, and a positive predictive value of 19.6% and 20.5%, respectively. The usefulness of this simple ECG marker is in its high negative predictive value; however, it needs further corroboration in larger studies. Figure 3 summarizes the most commonly described high-risk features.

**RISK STRATIFICATION WITH ELECTROPHYSIOLOGICAL STUDY**

There is ongoing controversy regarding the prognostic value of electrophysiological study (EPS) with programmed electrical stimulation for risk stratification in patients without a history of cardiac arrest. Several studies have demonstrated a positive association between induced PMVT/VF during EPS and the future risk of ventricular arrhythmias, while many have not.\[^{39,42,50,51}\]  

An important limitation and bias of studies in this area is that patients with a positive EPS are more likely to proceed to ICD implantation. Therefore, this population is likely to have a higher frequency of recorded ventricular arrhythmias that may not result in cardiac arrest than in patients with negative EPS and no ICD.\[^{28,30}\] Another limitation is the heterogeneity between different EPS protocols in the literature.\[^{52}\] While aggressive stimulation protocols with ≥3 extrastimuli are more sensitive, they were found to be less specific than moderate protocols with up to two extrastimuli.\[^{30,53}\]  

In spite of previous reports indicating a strong negative predictive value of EPS in patients without cardiac arrest, a recent systematic review concluded that a negative EPS does not reliably indicate low risk in asymptomatic patients in the presence of other high-risk features, such as spontaneous Type 1 ECG.\[^{30,52,54}\]  

**MANAGEMENT AND RISK MODIFICATION**

The mainstay of treatment in high-risk patients remains ICD implantation.\[^{51}\] Important risk-reducing strategies for all patients include avoidance of potentially exacerbating medications (a comprehensive list is available at http://www.brugadadrugs.org/), immediate treatment of fever with antipyretics as well as keeping away from excessive alcohol intake, and avoiding large meals.\[^{55}\]  

**QUINIDINE THERAPY**

Treatment with quinidine should be considered as an adjunct to ICD in patients experiencing electrical storms.
or frequent appropriate shocks, or as an alternative to ICD implantation where this is not possible. Quinidine seems to reduce the $I_0$ current during epicardial repolarization and normalizes the action potential and prevent re-entry and PMVT.

The efficacy of quinidine monotherapy for long-term prevention of malignant ventricular arrhythmias following implantation of ICD, has been demonstrated in a number of studies.\[56-59\] A retrospective study showed total elimination of appropriate ICD shocks in 66% (19 of 29) of patients with previous arrhythmic storm or frequent shocks over a mean period of 60 ± 41 months, as well as a significant and clinically important reduction in the number of shocks experienced for the remaining patients.

The empirical use of high-dose quinidine (600–900 mg daily) for the prevention of arrhythmic events has so far been mainly evaluated by a randomized trial of quinidine versus placebo of fifty patients with previously implanted ICD.\[56\] While treatment appeared to be effective with no associated arrhythmic events observed, a significant result could not be obtained due to low event rate in the placebo group as well as high rates of treatment discontinuation. One substantial problem with quinidine therapy used as an alternative to ICD implantation is the issue of poor compliance and treatment discontinuation due to associated adverse effects.\[60\] While treatment with low-dose quinidine (<600 mg daily) is associated with greater tolerability, it has only been investigated in a small number of patients.\[61\] Another important practical limitation is the poor availability of quinidine in most geographic regions.\[62\]

**ROLE OF RADIOFREQUENCY CATHETER ABLATION**

RFA of arrhythmogenic zones in the RV epicardium has emerged over the past decade as a possible future curative treatment option for BrS. However, only a small number of studies with limited follow-up periods have reported successful results with RFA in symptomatic Brugada patients.

The first to describe a successful RFA procedure in BrS patients were Nademanee *et al.* using a selected cohort of nine high-risk patients with frequent ICD shocks for ventricular arrhythmias.\[4\] All patients were found to have a unique arrhythmogenic focus at the anterior RVOT on epicardial mapping as well as typical Type 1 ECG and inducible VT/VF at baseline. Following ablation, the ECG had normalized in 89% and VT/VF was no longer inducible in 78% of the cohort. Only one of the nine patients had a single subsequent arrhythmic event during the follow-up period (20 ± 6 months). More recently, Brugada *et al.*\[63\] and Pappone *et al.*\[64\] described an improved technique for successful elimination of the BrS phenotype with epicardial RFA. The mapping was performed before and after the administration of flecainide/ajmaline, which resulted in the identification of more extensive arrhythmogenic segments in the RV epicardium beyond the RVOT. In the larger and more recent study, the described RFA procedure showed normalization of ECG and nondeducibility of VT/VF in all the 135 patients with symptomatic BrS and previous ICD.\[65\] In addition, a Type 1 ECG could not be provoked with ajmaline following RFA in the vast majority. During a median follow-up period of 10 months, only two patients required a repeat procedure due to recurrent VF.

The only adverse effect reported for all the above studies was mild uncomplicated pericarditis after ablation. RFA treatment is, therefore, recommended for symptomatic patients with recurrent ICD shocks or as an alternative to ICD implantation when contraindicated.\[43,55\] Whether this is a suitable alternative to ICD for people with high risk, or even an option for low-risk people as a potential “cure,” remains to be determined.

Figure 4 summarizes the proposed management strategy for BrS patients.

**CONCLUSIONS**

BrS is a rare genetic entity characterized by a typical ECG with an associated risk of VF and SCD. Despite recent advances, pathophysiological mechanisms responsible for incomplete penetrance and variable expressivity remain incompletely understood. Almost two-thirds of patients with clinically diagnosed BrS patients have no clear associated genetic basis. The only gene convincingly implicated is SCN5A. The recent reclassification of pathogenic variants associated with BrS is likely to change the percentage of patients identified with a pathological gene.

The pathophysiology of disease generation and progression is more complex than initially described with some overlap with arrhythmogenic cardiomyopathy; a greater understanding of the underlying processes will hopefully lead to further improvements in the diagnosis and management of BrS.

Currently, the ICD is the most accepted therapy to protect patients at risk, but there remain significant shortcomings in the accurate risk assessment in BrS, particularly asymptomatic patients.

Epicardial ablation in selected patients has been used as a new therapy with promise, and our personal experience, albeit limited, mirrors the literature, but as of yet is largely indicated for the treatment of BrS patients with a high burden of ICD therapy despite optimization of other risk modifiers.

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There are no conflicts of interest.

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