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THE PRESENT AND FUTURE

JACC STATE-OF-THE-ART REVIEW

Present Status of Brugada Syndrome

JACC State-of-the-Art Review

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ABSTRACT

The Brugada syndrome is an inherited disorder associated with risk of ventricular fibrillation and sudden cardiac death in a structurally normal heart. Diagnosis is based on a characteristic electrocardiographic pattern (coved type ST-segment elevation ≥2 mm followed by a negative T-wave in ≥1 of the right precordial leads V_1 to V_2), observed either spontaneously or during a sodium-channel blocker test. The prevalence varies among regions and ethnicities, affecting mostly males. The risk stratification and management of patients, principally asymptomatic, still remains challenging. The current main therapy is an implantable cardioverter-defibrillator, but radiofrequency catheter ablation has been recently reported as an effective new treatment. Since its first description in 1992, continuous achievements have expanded our understanding of the genetics basis and electrophysiological mechanisms underlying the disease. Currently, despite several genes identified, *SCN5A* has attracted most attention, and in approximately 30% of patients, a genetic variant may be implicated in causation after a comprehensive analysis. (J Am Coll Cardiol 2018;72:1046-59)

In 1992, a report was published concerning 8 individuals resuscitated from sudden cardiac death (SCD) caused by documented ventricular fibrillation (VF). These individuals had a characteristic ST-segment elevation in the right precordial leads of the electrocardiogram (ECG) in a structurally normal heart (1). This disease was known as *"right bundle branch block, persistent ST-segment elevation, and sudden death syndrome"* until 1996, when this new arrhythmogenic entity was named Brugada syndrome (BrS) for the first time (2). Several years before, the ST-segment elevation was previously reported in acute severe myocardial ischemia cases leading to SCD (3). In 1997, BrS was recognized as the same entity as sudden unexplained nocturnal death syndrome (4), first described in 1917 in the Philippines (5). *Bangungut* refers to sudden deaths in apparently healthy young males that took place at night during sleep, and autopsy revealed no pathological evidence to explain the cause of the death. The same disease is called *Lai Tai* in Thailand, *Pokkuri Death Syndrome* in Japan, *Dolyeonsa* in Korea, *Dream Disease* in Hawaii, or *Sudden manhood death syndrome* in China. Nowadays it is well-known that sudden unexplained nocturnal death syndrome is an entity highly prevalent in Southeast Asian ethnic groups. It was considered a familial disease due to the presence of syncope and/or sudden deaths in several relatives of

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a same family, but the first genetic alteration was not identified until 1998 (6). In the last 25 years, there has been progressive understanding of the genetic basis and cellular electrophysiological mechanisms of BrS, as well as the clinical diagnostic and treatment approaches. However, several areas remain to be clarified. This review will primarily focus on clinical identification, evaluation, and management of patients with BrS and the genetic basis.

DEFINITION

Current guidelines for the management of patients with ventricular arrhythmias and the prevention of SCD define this entity as a syndrome. The diagnosis of BrS is based on an ECG showing an ST-segment elevation with type 1 morphology ≥2 mm in 1 or more leads among the right precordial leads V_1 and/or V_2 positioned in the second, third, or fourth intercostal space, occurring either spontaneously or after provocative drug test with intravenous administration of sodium-channel blockers (such as ajmaline, flecainide, procainamide, or pilsicainide). The presence of all other known causes of ST-segment elevation in right precordial leads (known as phenocopies) should be excluded before making the diagnosis of BrS (7). BrS shows age- and sex-related penetrance, and incomplete penetrance and variable expressivity are hallmarks of this cardiac entity (8).

DISEASE BURDEN

Nowadays, it is difficult to discern the true burden of BrS due to the unknown real prevalence of asymptomatic patients and the dynamic variability of the ECG pattern in individuals. Nonetheless, the prevalence of BrS is believed to range from 1 in 5,000 to 1 in 2,000. The incidence of BrS pattern on ECG has ranged from 0.12% to 0.8% in several studies. It has been considered responsible for 4% to 12% of all sudden deaths and up to 20% of sudden deaths in patients with structurally normal hearts, and it is 8 to 10 times more prevalent in men than women. Despite all of these facts, the current accepted percentages of sudden death and SCD due to BrS will need to be updated as more data become available to establish the real incidence of BrS in unexpected deceases in different populations (9).

CLINICAL MANIFESTATIONS

SYMPTOMS. Patients with BrS can present with syncope, seizures, and nocturnal agonal breathing due to polymorphic ventricular tachycardia (PVT) or VF. If these arrhythmias are sustained, SCD may result. Syncope or SCD ranges from 17% to 42% (10). However, this number likely overestimates the true incidence, because most asymptomatic patients are never diagnosed. In fact, recent accounts report a significantly lower proportion of SCD as the first symptom (4.6%) and a lower incidence of recurrent arrhythmia during follow-up (5%) (11). Due to the BrS ECG pattern that is now widely recognized, the denominator of patients identified has increased to include many asymptomatic individuals, so that the percentage of SCD in the total population of BrS has decreased.

Lethal arrhythmias usually occur during resting or sleeping, suggesting an association with bradycardia or vagal events. There are no data differentiating between vagal or bradycardia-dependent 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 (12). Symptoms typically first occur during adulthood, with a mean age of SCD presentation of 41 ± 15 years, although the onset of first symptoms can also be in children and aged individuals (13). Hormonal influences may underlie these age-related differences, although the mechanism of these differences is poorly understood. Differences between sexes are thought to be secondary to differences in the transmembrane ion current expression between sexes (14). For example, after castration in men with prostate cancer, sex-related BrS ECG differences become minimized (15). In addition, a higher concentration of testosterone has been noted in men with BrS. Further, the male predominance among BrS patients does not occur in children younger than age 16 years, when testosterone levels are low and similar between boys and girls (16).

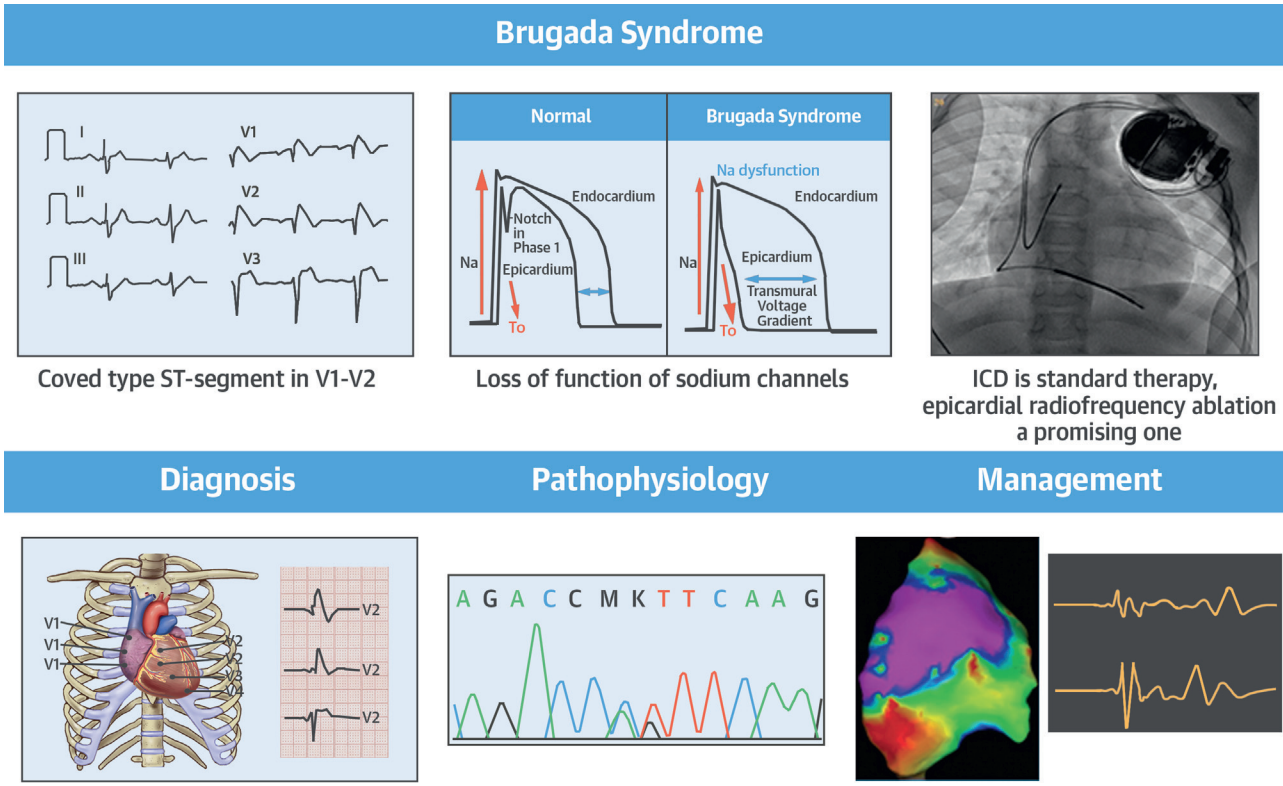
RESTING ECG. Following the original description of BrS, there was much confusion about its ECG characteristics and diagnostic criteria (**Central Illustration**). To clarify these ambiguities, an expert consensus document was published in 2012 establishing 2 descriptive ECG abnormalities for BrS (17):

- **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 (V_1 to V_3), followed by an r′-wave and a concave or straight ST segment. The descending ST segment crosses the isoelectric line and is followed by a negative and symmetric T-wave.

ABBREVIATIONS AND ACRONYMS

BrS = Brugada syndrome
ECG = electrocardiogram
ICD = implantable cardioverter-defibrillator
PVT = polymorphic ventricular tachycardia
RV = right ventricle/ventricular
SCD = sudden cardiac death
VF = ventricular fibrillation

CENTRAL ILLUSTRATION **Main Characteristics of Brugada Syndrome**



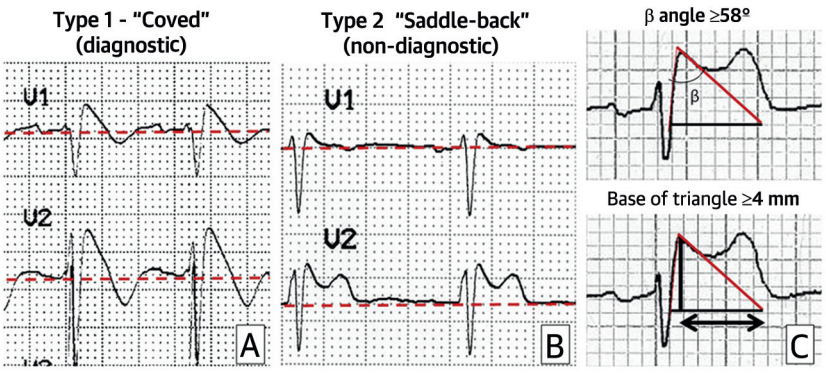
Brugada, J. et al. J Am Coll Cardiol. 2018;72(9):1046–59.

Knowledge about Brugada syndrome has grown over the last 30 years, from diagnostic criteria **(left)**, to pathophysiological mechanisms **(center)**, and finally, to management options **(right)**. ICD = implantable cardioverter-defibrillator.

- **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 (generally ≥2 mm in V_2) in ≥1 right precordial lead (V_1 to V_3), 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 V_2 and is of variable morphology in V_1. To facilitate the differentiation of type 2 ECGs highly indicative of BrS from other Brugada-like patterns (such as athletes, *pectus excavatum*, and arrhythmogenic cardiomyopathy), several additional criteria have been suggested. These criteria utilize the triangle formed by the ascending and descending branch of the r′-wave (Figure 1C):
  - *β angle*: A cut-off value ≥58° provided the best predictive values for conversion to a type 1 BrS pattern (73% positive and 87% negative values) (18).
  - *Length of the base triangle of the r′-wave 5 mm below the maximum rise point*: A cutoff value of 4 mm (≥4 mm in patients with BrS) demonstrated 96% specificity and 85% sensitivity (positive predictive value of 95% and negative predictive value 88%) for differentiating the BrS ECG pattern in BrS patients from the ECG pattern of healthy individuals (19).
  - *Other criteria:* The triangle base duration at the isoelectric line (>1.5 mm in patients with BrS) and the relationship between the triangle base at the isoelectric line and its height (>1.3 in BrS patients) may be distinguishing ECG patterns in BrS (20).

Frequent variations in the ECG patterns can occur within a single patient, including the absence of a classic ECG pattern on a given day (concealed BrS)

FIGURE 1 Electrocardiographic Patterns in Brugada Syndrome



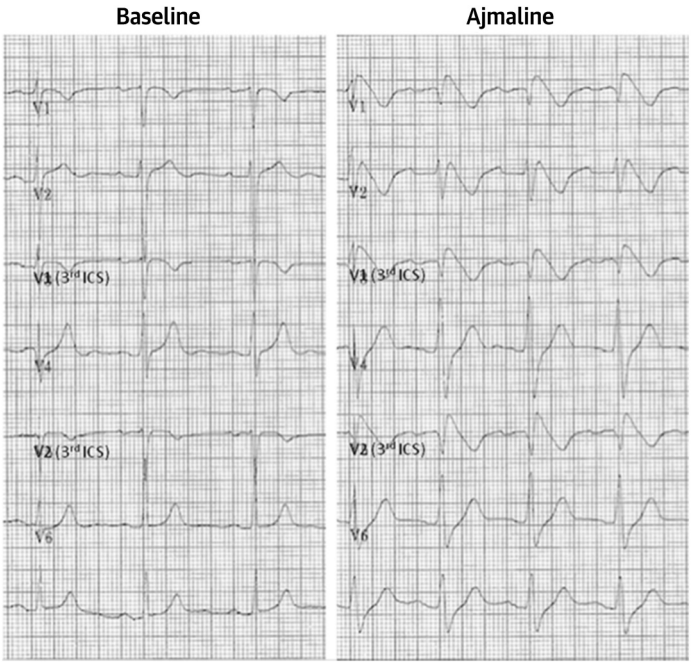
(A) Type 1 Brugada electrocardiogram pattern showing a concave ST-segment elevation ≥2 mm in ≥1 right precordial lead, followed by a negative T-wave. **(B)** Type 2 Brugada electrocardiogram pattern showing a convex ST-segment elevation ≥0.5 mm (generally ≥2 mm) in ≥1 right precordial lead followed by a positive T-wave. **(C)** Additional criteria for the diagnosis of Brugada electrocardiogram pattern type 2 (**top**: the β angle, described by Chevallier et al. (18); **bottom:** the length of the base triangle of the r′ wave 5 mm below the maximum rise point).

(21). The placement of the right precordial leads in more cranial positions (in the 3rd or 2nd intercostal spaces) increases sensitivity in some patients due to the variable anatomical correlation between the right ventricular outflow tract and V_1 to V_2 in the standard position (22) (**Figure 2**). 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 position of V_1 to V_2 (23). Additionally, prolonged ECG monitoring has uncovered spontaneous intermittent type 1 ECG patterns in 20% to 34% of patients with only drug-induced type 1 ECG (24,25).

Prolonged P-wave, PR, or QRS duration are frequently observed, particularly in patients with an *SCN5A* mutation, and sinus node dysfunction may also occur (26). PR prolongation likely represents an HV conduction delay. The QT interval is generally normal, but it can occasionally be slightly prolonged in the right precordial leads (27). Repolarization abnormalities in the inferior and lateral leads have been reported in up to 11% of patients; these abnormalities are seemingly related to a more severe phenotype. In up to 20% of cases, there may be supraventricular arrhythmias, mainly manifesting as atrial fibrillation, although AV nodal re-entry and Wolff-Parkinson-White have also been described in isolated case reports, probably as coincidental findings rather than genetic association (28,29).

PHARMACOLOGICAL TESTS AND OTHER DIAGNOSTIC TOOLS. When there is a clinical suspicion of the disease (syncope, agonal respiration, aborted sudden death, or only a family history of BrS or a suggestive but not diagnostic ECG) without a spontaneous type 1 ECG pattern, a pharmacological test with a sodium-channel blocking agent should be performed

FIGURE 2 Electrocardiographic Pattern of Brugada Syndrome Induced By a Pharmacological Drug



Ajmaline test to unmask the diagnostic Brugada syndrome pattern (type 1 pattern: coved-type).

to unmask the disease (30). The test must be performed under continuous ECG monitoring, and it is considered positive when a type 1 ECG pattern is identified during the infusion (**Figure 2**). Widening of the QRS to >130% over the baseline value or the presence of frequent ventricular premature beats or more complex ventricular arrhythmias should be a warning sign to stop administration to avoid ventricular arrhythmias. Intravenous ajmaline and flecainide are the most widely used pharmacological tests, although in some countries, procainamide is the only Class I intravenous antiarrhythmic drug available. In some countries, there are no Class I intravenous antiarrhythmic drugs available, and oral doses of flecainide or propafenone are used instead (31). Continuous monitoring should be maintained until the ECG reverts to the baseline situation (i.e., no persistent type 1 pattern or QRS widening >130% is seen). It is important to remark that nearly 25% of drug-induced tests might be false-negative (32), and this should be taken into consideration when, for instance, a patient experiencing aborted SCD has a negative flecainide test. A repeated drug test using ajmaline should be considered whenever possible.

STRUCTURAL CHANGES. The vast majority of BrS patients have a structurally normal heart, although several clinical studies have described the presence of minor structural alterations in both ventricles (33,34). Further, genetic and immunohistological analyses of 6 forensic samples from BrS family members revealed tissue- and molecular-level changes, specifically, an increase in epicardial collagen and fibrosis and a decrease in gap junction Connexin43 expression, especially in the right ventricular (RV) outflow tract area (35). Despite these reports, the role of fibrosis in BrS is uncertain, and the clinical phenotype concomitant with cardiac fibrosis remains a matter of ongoing scientific investigation, although a strong association has been shown in some genetic studies (36).

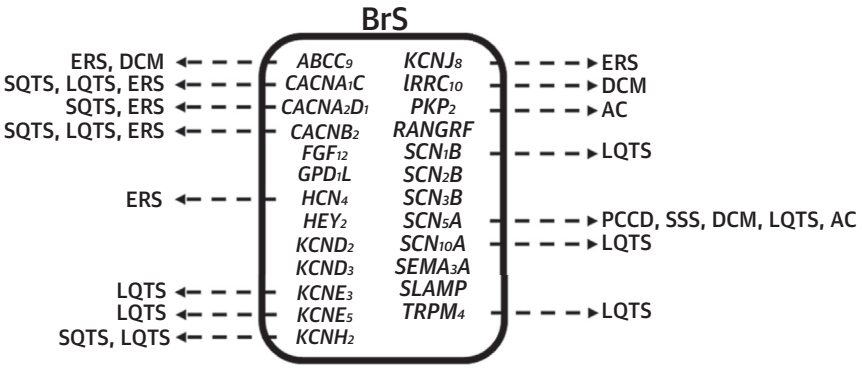
GENETIC BASIS

In 1998, our group identified the first genetic alteration in the *SCN5A* gene associated with BrS within a family (6). This gene encodes the alpha subunit of the cardiac sodium channel Nav1.5. This sodium channel subunit is responsible for phase 0 of the cardiac action potential. Currently, more than 1,000 reports have subsequently described genetic components of BrS (PubMed search for "Brugada syndrome" AND "genetics"). Indeed, more than 500 pathogenic variations have been associated with BrS so far, supporting an autosomal dominant pattern of inheritance (37). The majority of all pathogenic variants reported so far are located in *SCN5A* (Human Gene Mutation Database), and are responsible for nearly 30% of all cases in which a genes variant is implicated. However, this percentage may be an overestimate, as many variants previously classified as pathogenic may be of ambiguous significance following recent guidelines of the American College of Medical Genetics (38).

Several potentially pathogenic variants associated with BrS have been reported in other genes (*CACNA1C*, *GPD1L*, *HEY2*, *PKP2*, *RANGRF*, *SCN10A*, *SCN1B*, *SCN2B*, *SCN3*B, *SLMAP*, and *TRPM4*) and all together may be responsible for 2% to 5% of diagnosed cases. Despite this progress in genetic diagnosis, nearly 70% of families remain without an implicated genetic variant (39). In recent years, other genes have been suggested as potential causes of BrS (*ABCC9, CACNA2D1, CACNB2, FGF12, HCN4, KCND2, KCND3, KCNE3, KCNE5, KCNH2, KCNJ8, LRRC10,* and *SEMA3A*), but no comprehensive clinical and cellular studies have confirmed the association (**Figure 3**). Considering all data, current guidelines recommend a comprehensive genetic analysis of only *SCN5A*. Despite these recent advances, results of genetic screening do not currently influence prognosis or treatment, but merely document the presence of a genetic mutation with either probable or possible cause to explain symptoms in patients with a BrS ECG (8).

CURRENT CHALLENGES. One of the main challenges in modern clinical genetics is the interpretation of genetic alterations and their translation into clinical practice. The American College of Medical Genetics has recently published recommendations focused on classification of genetic variants to clarify their pathogenic roles (38,40). Yet, despite these guidelines, most of the BrS genetic variants remain of unknown or ambiguous significance, and translation into clinical practice must be done with caution (41). The proportion of pathogenic variants associated with BrS should be further analyzed to clarify the real percentage of BrS cases associated with each gene. Family segregation and a comprehensive genotype-phenotype correlation help to interpret genetic variation in BrS; however, incomplete penetrance and variable expressivity exacerbated by the unknown pathophysiological mechanism induced by each genetic variant clouds their definitive roles. Therefore, the main role of *SCN5A* as a cause of pathology has been questioned (42). To provide insight into the functional effects of the genetic variants, a novel

FIGURE 3 Genes Associated With BrS



All genes currently associated with BrS. Some of these genes are also associated with other arrhythmogenic disease. AC = arrhythmogenic cardiomyopathy; BrS = Brugada syndrome; DCM = dilated cardiomyopathy; ERS = early repolarization syndrome; LQTS = long QT syndrome; PCCD = progressive conduction cardiac disease; SQTS = short QT syndrome; SSS = sick sinus syndrome.

human cellular model using cardiomyocytes (CMs) has been developed from human induced pluripotent stem cells (hiPSCs). These patient-specific hiPSC-CMs are able to incorporate phenotype features of single cells from a patient in vitro, and allow study of the electrophysiological properties of myocytes that lead to characteristic ECG alterations in BrS (43,44). Although a recent study using hiPSC-CMs from 2 BrS patients carrying STOP-codon variants in the *SCN5A* gene did not show rescue of the electrophysiological phenotype by the tested compounds, it initiated a new pharmacological approach in BrS research (45). Despite these hopeful recent advances, further wide-ranging cellular studies using hiPSC-CM in BrS should be performed to clarify their role in potential therapeutic approaches.

DIAGNOSTIC CRITERIA

Until 2013, BrS diagnosis required demonstrating the presence of a type 1 ECG pattern and clinical manifestations such as resuscitated SCD, documented PVT, history of nonvasovagal syncope, and/or 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 (8): "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 (V_1 and V_2), placed in a standard or superior position (up to the 2nd intercostal space)," without requiring any further evidence of malignant arrhythmias.

DIFFERENTIAL DIAGNOSIS

Before establishing a diagnosis of BrS, other causes of ST-segment elevation should be excluded. Some ST-segment elevation may arise from different diseases, whereas others may be induced by an underlying genetic predisposition.

An ECG mimicking a BrS type 1 pattern that is triggered by other factors has been called *Brugada ECG phenocopy* (7). Other causes of Brugada phenocopies primarily or exclusively affect the RV and, in particular, the RV outflow tract. These medical illnesses can also result in ECG changes that mimic the BrS pattern ECG. Examples include RV ischemia, acute pulmonary embolism, or mechanical compression of the RV outflow tract. Key findings that support the suspicion of Brugada phenocopies include the presence of an identifiable underlying condition, disappearance of the pattern with resolution of the condition, absence of family history of sudden death or type 1 BrS pattern in first-degree relatives, absence of symptoms such as syncope, seizures or nocturnal agonal respiration, and a negative sodium channel-blocker challenge test (46). There are also *Brugada-like ECG patterns* with ST-segment abnormalities that could be interpreted as a type 1 or type 2 BrS ECG. They are usually associated with additional alterations in other leads that allow a differential diagnosis. Further, an ST-segment elevation in V_1 to V_2 is not identical to that of BrS. Situations that may produce a type 1 Brugada-like ECG mostly correspond to ST-segment elevation secondary to acute ischemia or occlusion of the left anterior descendent artery.

Situations that may produce a type 2 Brugada-like ECG are more common and include right bundle branch block, left ventricular hypertrophy, *pectus excavatum*, and arrhythmogenic cardiomyopathy (ACM) (47). As in the case of Brugada phenocopies, a sodium-channel blocker challenge test will usually be negative.

There are also *modulating factors* that can unmask or exacerbate a typical BrS pattern, which may be due to effects on transmembrane ionic currents (48,49). Bradycardia and vagal tone may decrease calcium currents and consequently contribute to ST-segment elevation and pro-arrhythmia (50). In the case of drugs, 1 or multiple ionic currents may be affected (decrease in sodium/calcium currents and/or increase in potassium currents). Modulating factors play a major role in the dynamic nature of an ECG and may be responsible for ST-segment elevation in genetically predisposed patients. If any of these modulating factors are present, they should be corrected. Apart from sodium-channel blockers, many other drugs have been reported to induce the type 1 BrS ECG pattern, including propofol, tricyclic antidepressants, fluoxetine, lithium, trifluoperazine, antihistamines, and cocaine (51,52). This induction is described as an "*acquired form of BrS.*" It remains unknown whether acquired BrS is due to individual susceptibility resulting from an increase in latent ion channel dysfunction (53). For this reason, management during anesthesia and surgery must provide some precautions and drug restrictions (54). However, the lack of studies focused on this point impedes establishing general rules, and the decision of using each drug must be made after careful consideration of the risks. Their use should always be in controlled conditions and avoiding other factors that are known to have the potential to induce arrhythmias (55). Premature inactivation of the sodium channel is accentuated at higher temperatures in some *SCN5A* mutations, suggesting that febrile states may unmask certain BrS patients or temporarily increase the risk of arrhythmias (12). Fever is a particularly important trigger among pediatric populations (56). Finally, ECG changes compatible with BrS can appear immediately after electrical cardioversion, although it is unknown whether they occur in BrS mutation carriers (57).

RISK STRATIFICATION

Accurate identification and treatment of individuals at high risk of sudden death are major challenges in the clinical management of BrS patients. Syncope is an indisputable risk factor and recognized by all studies, and between 17% and 62% of BrS patients will have a new arrhythmic event 48 to 84 months after diagnosis, which might lead to sudden death (10,58). Further, most studies agree that the presence of syncope in combination with a spontaneous type 1 ECG pattern is a robust marker of poor prognosis during follow-up (6% to 19% of patients will have an arrhythmic event within 24 to 39 months of follow-up) (58). Appropriate assessment to rule out purely vasovagal/neuromediated syncope is recommended, as these patients do not appear to have an increased risk of ventricular arrhythmias during follow-up (59,60).

No clear-cut recommendations have been defined for risk stratification in asymptomatic patients. Ambiguity surrounding the severity of the disease in this group and the value of PVT/VF inducibility to identify high-risk patients exacerbates the difficulty. The reported annual rate of asymptomatic BrS events has decreased over time. This change probably reflects an inherent early referral bias, when particularly severe forms of the disease were more likely to be diagnosed. Even among more recent studies, the rate of arrhythmic events in asymptomatic BrS patients is not negligible (0.5% to 1.2% annual incidence), leading to a 12% malignant ventricular arrhythmia rate at 10-year follow-up in a population with a mean age of 40 years (61–63). Nonetheless, an important stratification is a fever-induced type 1 ECG, because patients exhibiting this feature show an intermediate risk for sudden death (64).

Controversial evidence suggests that symptomatic patients have more easily induced arrhythmias during an electrophysiological study (EPS). The expert consensus document and the current guidelines for prevention of sudden death neither encourage nor discourage EPS for BrS stratification, but simply state that an implantable cardioverter-defibrillator (ICD) may be considered in cases of inducible ventricular arrhythmias (8). Our group has traditionally used EPS for risk stratification in asymptomatic patients with a spontaneous BrS type 1 ECG pattern. Using EPS for risk stratification is supported by several large prospective registries and by a recent pooled individual patient data analysis that included 8 prospective studies (65). A ventricular refractory period <200 ms has also been proposed as a predictor of adverse events in BrS. Women with BrS typically show more benign clinical features with a lower percentage of type 1 BrS ECG and a lower prevalence of symptoms (66). However, events still occur in women and no appropriate sex-specific risk predictors exist (62).

Currently, no conclusive studies published focus on prognostic value with regard to the genetic analysis. Interestingly, neither family history of sudden death nor the presence of an *SCN5A* mutation have been identified as risk factors in any of the large series reported to date (67). However, combinations of risk factors with specific genetic mutations may be predictive, such as the combination of a *SCN5A* mutation with a history of sudden death in a young first-degree relative (age <35 years) or in specific mutations such as those that result in a truncated Nav1.5 protein (68,69). Conversely, the presence of common polymorphisms located in *SCN5A* may counterbalance some deleterious consequences of pathogenic variants, resulting in a milder BrS phenotype and suggesting the possibility that polymorphism may be a useful tool in risk stratification (70,71).

Several noninvasive markers of arrhythmic risk in BrS have also been suggested; these include the presence of QRS fragmentation (72), ST-segment elevation during recovery from exercise, or the presence of late potentials (73). Atrial fibrillation, which occurs spontaneously in up to 30% of BrS patients, has also been associated with poor prognosis. Likewise, an early repolarization pattern in the inferior and/or lateral leads is associated with an increased risk of arrhythmic events and may be present in 10% to 15% of patients (74,75). A prolonged T-peak–T-end interval has also been suggested as a marker of risk in BrS (76–78). Other ECG patterns that affect risk include the presence of sinus node dysfunction, prolonged QRS in V_2 (≥120 ms), a V_6 ≥90 ms, duration of the S-wave in DI (≥0.1 mV and/or ≥40 ms), prolonged QTc in V_2 (>460 ms), the "aVR sign" (R-wave ≥0.3 mV or R/q ≥0.75 in lead aVR), presence of the type 1 ECG pattern on limb leads (79), presence of T-wave alternants (80,81), augmentation of ST-segment elevation during the recovery phase of a stress test (82), and the presence of late potentials assessed by signal-averaged ECG. However, the latter risk factors are derived from small observational studies and require validation in larger series.

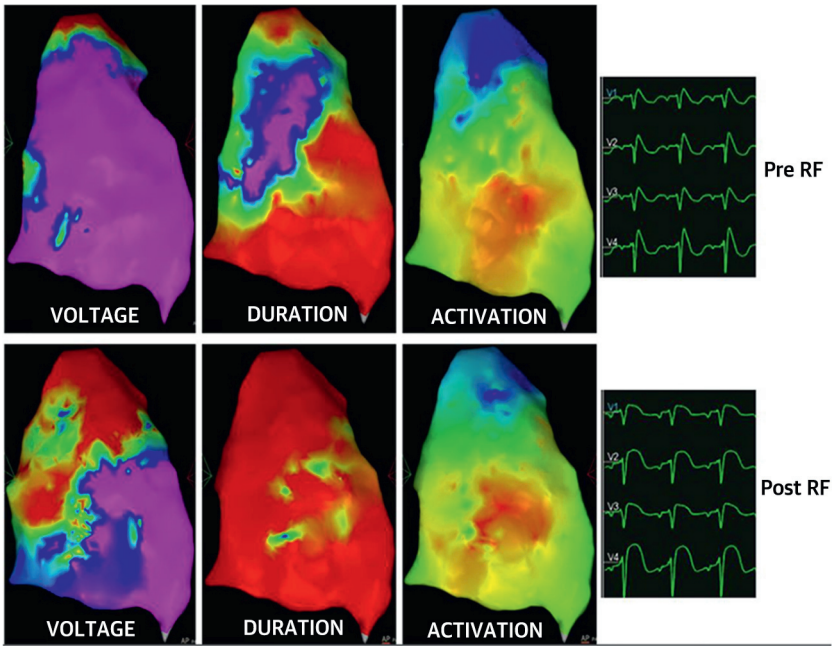
MANAGEMENT

To date, treatment options in the BrS have been limited to ICDs or drugs. However, education and lifestyle changes for the prevention of arrhythmias are critical. All BrS patients should be informed of the various modulators and precipitating factors that could induce malignant arrhythmias. Fever should be treated promptly with antipyretics and/or physical measures. In addition, any contraindicated substance should be avoided.

Following the recommendations of the international consensus and international guidelines for the prevention of ventricular arrhythmias and SCD, an ICD should always be implanted in symptomatic patients (i.e., resuscitated SCD and/or nonvagal syncope, seizures, or nocturnal agonal respiration). In asymptomatic patients with a spontaneous type 1 pattern, the EPS can be used to assess the need for an ICD (8). Quinidine, an antiarrhythmic drug with blocking activity in the Ito and IKr currents, has been shown to prevent phase II re-entry and VF in in vitro studies of BrS. Quinidine has rendered patients noninducible in 76% to 88% of patients with inducible VF at baseline EPS (83,84). It has also successfully been used in certain clinical settings such as arrhythmic storms or multiple ICD discharges, or as an alternative to an ICD in children (56). In rare occasions, quinidine has been observed in a few patients to normalize the electrocardiogram (85). Unfortunately, quinidine may have undesirable side effects (thrombocytopenia, intolerable diarrhea, esophagitis, allergic reaction, aggravation of sinus node dysfunction, and the potential for QT prolongation and torsade de pointes) and remains unavailable in regions where BrS is endemic, such as Southeast Asia (86).

Ablation has been suggested as a possible therapeutic option. Initial work in patients with electrical storm proved to be effective in controlling ventricular arrhythmias during follow-up in 8 of 9 patients (87). More recently, identification and elimination of the arrhythmic electrophysiological substrate (AES) has been performed to potentially eliminate the arrhythmias seen in BrS (88–90). Some studies have reported the AES responsible for abnormalities seen in the ECG to be located in the epicardium of the RV anterior wall and outflow tract, and in many cases, catheter ablation of this area resolves the ECG abnormalities (91). Identification, characterization, and treatment of the AES has been shown to be effective in normalizing the ECG. Furthermore, provocative drug tests have rendered patients noninducible for ventricular arrhythmias and prevented spontaneous arrhythmic events in symptomatic patients. Ajmaline administration (1 mg/kg in 5 min) has been shown useful to unmask and determine the location of the AES, and the extension and size of all abnormal areas (89) (**Figure 4**). These abnormal potentials are only observed when ST-segment elevation is present either spontaneously or after drug administration (**Figure 5**). The nature of these potentials (depolarization abnormalities or repolarization changes) is still

FIGURE 4 Voltage Mapping, Potential Duration Mapping, Activation Mapping of the RV Epicardium, and Electrocardiogram Before and After RV Epicardial Ablation



Voltage mappings show normal electrocardiogram all along the epicardium before ablation and slight decrease in the voltage of the electrocardiogram after ablation. Potential duration mappings show an area with prolonged potentials before ablation (Pre-RF) normalized after ablation (Post-RF). Activation mappings are basically normal and identical before and after ablation. Electrocardiogram shows typical type 1 before ablation, and a rounded type ST-segment elevation after ablation with no characteristics electrocardiogram for Brugada syndrome. RV = right ventricular.

a matter of debate. The ability to use ajmaline or other Class I drugs and 3-dimensional electroanatomical mapping to ablate and persistently normalize the ECG pattern and prevent VF inducibility is very promising for the long-term value of epicardial ablation. However, longer follow-up times are required before a definitive conclusion can be made as to its lasting therapeutic potential.

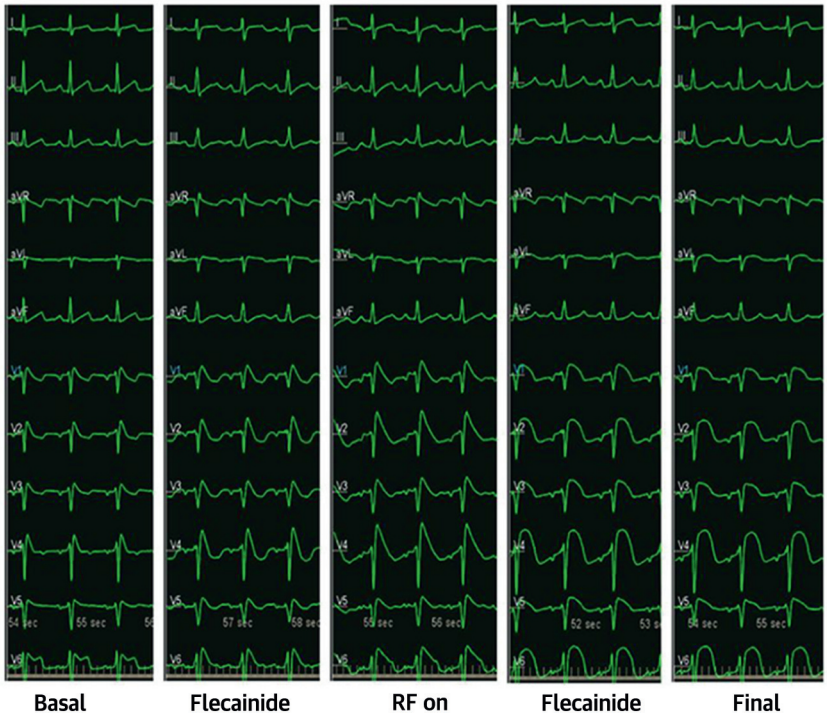
PEDIATRIC AND YOUNG POPULATIONS

Although the first description in 1992 of BrS included 3 pediatric patients, few new cases have been published. Therefore, the prevalence and clinical implications of BrS in children and young populations remain unclear. In large studies of asymptomatic children from Japan, a BrS ECG pattern was found in 0.01% to 0.02% (92,93), suggesting that BrS may exist in children, but becomes clinically unmasked with increasing age. Despite its low incidence, some recommendations for children with BrS have been published (8).

Current diagnosis in children is based on ECG patterns similar to adults. Overt disease is rarely reported in children, but malignant conditions such as SCD and syncope due to documented PVT have been reported (56,94). One of the main difficulties of the ECG recording is the optimal positioning of the right precordial leads. Positioning is especially problematic in children due to the different shape of the chest in a growing body. The use of Holter monitors can help identify overt asymptomatic arrhythmias, and the treadmill exercise test can unmask chronotropic incompetence as a sign of conduction system dysfunction. As noted earlier, the low incidence of BrS in pre-adolescents suggests the potential important role of hormones in BrS (95).

One large study of pediatric BrS patients included 30 cases from 13 European institutions. This study identified fever as the most important precipitating factor for arrhythmic events, and, like adult populations, the risk of arrhythmic events was higher in previously symptomatic patients and in those displaying a spontaneous type 1 ECG (96). The data

FIGURE 5 **Electrocardiograms in a Brugada Syndrome Patient**



Series of electrocardiograms (from **left to right**) before ablation (Basal), after flecainide test (Flecainide), during radiofrequency application (RF on), during new flecainide test (Flecainide) and final electrocardiogram (Final). Precordial leads are arranged as follows: V_1, V_2 are placed in 2nd intercostal space, V_3 and V_4 are V_1 and V_2 placed in 3rd intercostal space, and V_5 and V_6 are V_1 and V_2 placed in the 4th intercostal space.

concur with previous information showing that fever is a triggering factor for ventricular arrhythmias in BrS patients and increased temperature may unmask a BrS ECG pattern (49). Hence, it is recommended that a 12-lead ECG be performed during febrile episodes in children with a family history of BrS and in all children with febrile seizures. There are very limited data concerning pharmacological tests in BrS children. A sodium-channel blocker test (ajmaline 1 mg/kg or flecainide 2 mg/kg treatment over 10 min) should be performed after onset of puberty in patients with a family history of BrS. A drug challenge should be performed if these patients have an abnormal nondiagnostic ECG or if symptoms such as syncope, febrile seizures, or palpitations have appeared.

In children, a spontaneous type 1 ECG pattern is considered diagnostic of BrS, as also occurs in adults (97). The observation of an age-dependent response to ajmaline challenge is an intriguing recent finding that might have relevant clinical implications (98). When a patient has received a drug challenge before puberty (symptoms, abnormal ECG), some studies recommend repeating it after puberty. Regarding EPS, if used, the electrophysiology protocol is the same as in adults.

A pharmacological approach in children at risk using hydroquinidine has been suggested as an alternative to ICD implantation, but little data are available to support this approach (99). Indications for an ICD in children and adolescents remains challenging, but children presenting with syncope and with a spontaneous type 1 ECG are clearly at high risk for SCD, and an ICD should be considered irrespective of age (56,94). A recent study shows that ICD therapy is an effective strategy treating potentially lethal arrhythmias. At follow-up, 25% of patients have had appropriate shocks. The risks associated with ICDs include device-related complications and inappropriate shocks (100). Decision-making in children with BrS is challenging and should be individualized according to the specific clinical presentation, family history, and genetic data. As in adults, risk stratification remains a current challenge in the pediatric population. A recent

study suggests a model of risk prediction using 4 characteristics: SCD or syncope, spontaneous type 1 ECG, sinus node dysfunction and/or atrial tachycardia, and conduction abnormality (101). Additional studies in large populations of children are needed to validate this risk model.

AGED POPULATION

In 2005, a consensus conference reported that older BrS patients with syncope should undergo ICD implantation if life expectancy is at least 6 months (13). Currently, only a limited number of studies have focused on clinical features of BrS in aged populations. Therefore, the prevalence and long-term prognosis of individuals with the Brugada ECG pattern in the geriatric population is unknown, and the clinical course and prognosis of BrS in the elderly population remains unclear. One large series found a benign prognosis for BrS in patients older than age 70 years (102). Further, a case report identified an older man who showed a type 1 ECG pattern after a febrile episode. No previous family history of sudden death or heart disease was reported, and his basal ECG was normal before and after the febrile episode (85). In another report, 86% of the elderly patients evaluated displayed a type 1 BrS pattern in ECGs after ajmaline challenge, suggesting that older patients presented less ventricular arrhythmias and less family history of SCD. In a Taiwanese study focused on spontaneous Brugada ECG patterns in a population age 55 years and older (103), the prevalence of Brugada ECG patterns was higher than the global average, mainly due to endemic expression of BrS in Southeast Asia (104–106). However, the report also disclosed that the all-cause mortality and cardiac mortality were not significantly different between subjects with and without Brugada ECG patterns, in accordance with a previous study. Similar to clinical strategies for children with BrS, decisions in older populations regarding use of drug-induced tests and device-guided management should be analyzed on a case-by-case basis due to sparse data specific to BrS in aged individuals.

CONCLUSIONS

BrS is a rare genetic entity characterized by a typical ECG leading to VF and SCD. Despite recent advances, pathophysiological mechanisms responsible for incomplete penetrance and variable expressivity remain to be elucidated. The only gene convincingly implicated is *SCN5A*. Recent reclassification of pathogenic variants associated with BrS will change the percentage of patients identified with a clear pathological gene. The distinctive BrS or BrS-like ECG may be due to a variety of distinctly different underlying mechanisms. These variables, the asymptomatic and symptomatic presentations, the unmasking of BrS only in the setting of specific triggers all lead to the present uncertainty and difficulty in forming the correct clinical diagnosis, risk stratification, and management. Currently, the ICD is the most accepted therapy to protect patients at risk. Recently, epicardial ablation in selected patients has been used as a new therapy. Therefore, physicians with expertise regarding BrS should assess patients with definite or possible BrS to implement personalized therapies. Further studies of large cohorts including clinical assessment and genetic analysis will be essential for improving the current BrS guidelines.

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