Brugada Syndrome: Current Perspectives

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Apichai Khongphatthanayothin and Koonlawee Nademanee

Abstract

Brugada syndrome was first reported as a distinct entity in 1992. It is diagnosed by signature EKG changes including at least 2-mm J-point elevation with coved-type ST elevation and T-wave inversion in at least one right precordial leads (type I Brugada marker). Initially thought of as a rare entity, Brugada syndrome is now widely recognized as a common cause of natural death among young men as a result of ventricular arrhythmia occurring at rest, particularly during sleep. The etiology of this disease is likely multifactorial, with genetic predisposition playing an important role in the pathogenesis. Mutation in the sodium channel gene *SCN5A* is seen in up to 20–25% of patients with at least 17 additional genes were reported to be associated with the disease. However, mutation in a single gene could be implicated in less than 30% of patients with Brugada syndrome, and a recent study showing association of this disease with common single nucleotide polymorphism of *SCN5A*, *SCN10A*, and *HEY2* pointed toward polygenic or oligogenic pattern of inheritance rather than a single gene defect. Despite initial reports of normal structural heart in majority of patients, recent reports showed frequent minor structural abnormalities, especially in the right ventricular outflow tract (RVOT) in these patients. Brugada syndrome is now viewed as a spectrum of cardiomyopathy as well as channelopathy. The pathophysiologic underlying cardiac arrhythmia in Brugada syndrome is still unresolved with continued debate on depolarization versus repolarization defect. Treatment is largely dependent on the symptom with implantable cardioverter-defibrillator

A. Khongphatthanayothin
Chulalongkorn University, Bangkok, Thailand

K. Nademanee (✉)
Chulalongkorn University, Bangkok, Thailand

Pacific Rim Electrophysiology Research Institute, Los Angeles, CA, USA
e-mail: wee@pacificrimep.com

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(ICD) implantation indicated in patients with severe symptoms. Avoiding medications and/or conditions that predispose the patient to ventricular arrhythmia is advised in all patients. Quinidine, by blocking transient outward current, has been used with some success. RF ablation of the epicardial substrate in the RVOT has been shown to prevent recurrence of ventricular arrhythmia in severe cases.

8.1 Introduction

In 1992, Brugada and Brugada described eight patients who had the following distinct clinical characteristics: (1) the presence of coved ST-segment elevation followed by a negative T wave in the right precordial leads and (2) life-threatening ventricular arrhythmias that could lead to sudden cardiac death, cardiac arrest, or symptoms caused by spontaneous self-terminating ventricular tachycardia (VT) or ventricular fibrillation (VF) episodes, i.e., syncope, agonal respiration, and seizure (Brugada and Brugada 1992). The entity is later widely recognized as "Brugada syndrome."

The Brugada syndrome (BrS) has also been linked with sudden unexpected death syndrome (SUDS) that usually occurs at night in young Southeast Asian men with a structurally normal heart (Nademanee et al. 1997; Vatta et al. 2002). BrS patients often have a history of unexplained sudden cardiac death in the family, and the syndrome is a well-known autosomal dominant inherited arrhythmia disorder and associated with gene mutations that are predominantly confined to the *SCN5A* gene, which encodes for the α-subunit of the cardiac sodium channel, causing loss of sodium current (INa) (Vatta et al. 2002; Wilde et al. 2002; Antzelevitch et al. 2005, 2016; Priori et al. 2013). However, the causal role of these genetic variants remains controversial.

SUDS has the same phenotype as BrS (Nademanee et al. 1997), and shortly thereafter we reported that both syndromes also shared the same genetic and biophysical basis (Vatta et al. 2002). In the past two and a half decades, we have witnessed major progress toward better understanding of the syndrome and gained knowledge in epidemiology, genetic aspects of the syndrome, pathophysiology, and patient management (Wilde et al. 2002, 2010; Antzelevitch et al. 2005, 2016; Priori et al. 2013; Probst et al. 2009; Nademanee et al. 2011; Veerakul and Nademanee 2012). Four consensus reports were published to help in defining diagnostic criteria, risk stratification, and management of BrS patients (Wilde et al. 2002; Antzelevitch et al. 2005, 2016; Priori et al. 2013). However, there are controversies, especially on the role of sodium channel mutations and electrophysiologic mechanisms underlying the syndrome(Wilde et al. 2010), risk stratification (Veerakul and Nademanee 2012; Wilde et al. 2010; Priori et al. 2012; Brugada et al. 2002; Probst et al. 2010; Kamakura et al. 2009; Paul et al. 2007; Eckardt et al. 2005; Takagi et al. 2007; Giustetto et al. 2009), and treatment of asymptomatic patients (Priori et al. 2012; Takagi et al. 2007; Giustetto et al. 2009; Viskin and Rogowski 2007; Veerakul et al. 2008).

8.2 Clinical Presentation and Diagnostic Criteria

The clinical spectrum of BrS patients ranges from asymptomatic to sudden cardiac death (Antzelevitch et al. 2005; Priori et al. 2013; Veerakul and Nademanee 2012). Patients may have a late onset of VT/VF despite having had an abnormal ECG pattern for decades (Nademanee et al. 1997; Antzelevitch et al. 2005). Syncope or seizures due to self-terminating VT/VF episodes are also common as well as agonal respiration and difficulty to arouse at night time again due to self-terminating VF episodes (Nademanee et al. 1997; Antzelevitch et al. 2005).

Life-threatening ventricular tachyarrhythmias in patients with BrS usually consist of VF or a rapid polymorphic VT although rare cases of monomorphic VT have been reported (Boersma et al. 2001; Shimada et al. 1996; Rodríguez-Mañero et al. 2016). In a study looking at the stored electrogram of the implantable cardioverter-defibrillator (ICD), polymorphic VT was often preceded by ventricular premature beats (VPB) with the same morphology as the one that initiated the VT (Kakishita et al. 2000). The VPB typically occurred at the end of the T wave and only rarely followed a long-short sequence. Site of earliest ventricular activation in patients with VT induced in the electrophysiologic lab almost always involves the right ventricular outflow tract (RVOT), at least for the initial beats. VF and sudden cardiac death mostly occur at rest or during sleep or at night in the early morning hours (Nademanee et al. 1997; Matsuo et al. 1999; Aizawa et al. 2016).

Supraventricular tachycardia, including AV nodal reentry tachycardia, atrial flutter, and atrial fibrillation, is common (Eckardt et al. 2001; Morita et al. 2002a; Rodríguez-Mañero et al. 2013). Depolarization abnormalities including prolonged P wave, PR interval, and QRS duration are also frequently observed (Antzelevitch et al. 2005; Takagi et al. 2007; Maury et al. 2013).

Diagnosis of BrS relies on the signature marker (type I Brugada pattern) on the ECG. The two original Brugada consensus (Wilde et al. 2002; Antzelevitch et al. 2005) reports classified the Brugada ECG pattern into three types (Fig. 8.1):

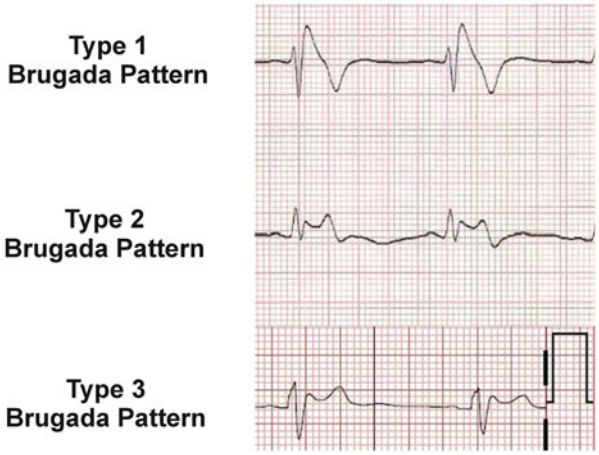

Fig. 8.1 Three types of Brugada ECG pattern. Type 1 is a coved-type pattern and type 2 is a "saddle-back" type which has the ST elevation >2 mm without T-wave inversion. Type 3 pattern is a J-point elevation without ST elevation >1 mm

1. Type 1 pattern has ST elevation >2 mm giving rise to a coved-type ST segment, in electrical continuity with a negative T wave and without a separating isoelectric line.
2. Type 2 has a high take-off ST-segment elevation. In this variant, the J-point elevation (>2 mm) gives rise to a gradually descending elevated ST segment (remaining >1 mm above the baseline) and a positive or biphasic T wave. This ST-T segment morphology is referred to as the saddle-back type.
3. Type 3 is the coved or saddle-back type with <1 mm ST-segment elevation.

One has to be cognizant that the Brugada ECG pattern often is wax and wane. Sodium channel blockers, ajmaline, procainamide, and flecainide, could be used to unmask the ECG pattern—since the details of how to perform a drug challenge test to unmask the Brugada ECG pattern have been nicely reviewed elsewhere, we shall not repeat here(Wilde et al. 2002; Antzelevitch et al. 2005, 2016). In recent years, it has become clear that the right ventricular outflow tract (RVOT) is the likely arrhythmogenic substrate site. And the RVOT is the only cardiac structure lying just beneath the third and second intercostal space. We and others have demonstrated that placement of right precordial lead ECG recordings over the higher intercostal spaces (third and second intercostal space) significantly increases diagnostic yield in bringing the Brugada ECG pattern (Veerakul et al. 2000; Shimizu et al. 2000). In our institution, we always routinely record right precordial lead ECG (V1–V3) from fourth, third, and second intercostal space in every patient suspected of BrS. Figure 8.2 shows an example of the ECG tracings from a patient with BrS: the Brugada ECG pattern is absent in the conventional fourth intercostal space lead placement but become apparent in the higher intercostal spaces (third and second).

The original criteria for the diagnosis of BrS mandate that the patient must have type 1 Brugada ECG pattern in at least two leads with or without a sodium channel blocker challenge test and one of the following clinical manifestations: (1) a history of spontaneous VT/VF episodes or aborted sudden cardiac death, (2) a family history of sudden cardiac death or coved-type ECG, (3) agonal respiration during sleep, or (4) inducibility of VT/VF by programmed electrical stimulation. However, since

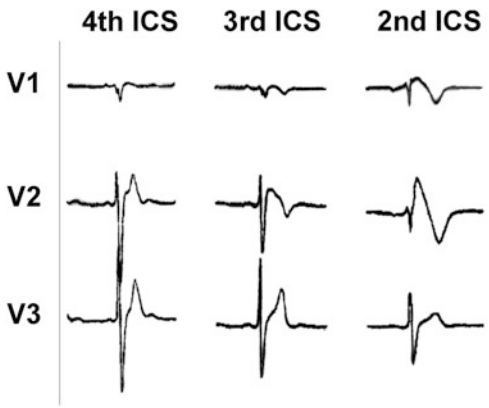

Fig. 8.2 An example of how placement of right precordial leads in higher intercostal spaces unmasks the Brugada ECG pattern in a BrS patient. The higher intercostal spaces (ICS), third and second ICS of V2 in this patients showed distinct coved-type Brugada ECG pattern (type 1)

Table 8.1 Conditions which can mimic Brugada ECG pattern (Brugada phenocopy) (Antzelevitch et al. 2016)

Atypical right bundle branch block (RBBB)
Left ventricular hypertrophy
Early depolarization Acute pericarditis
Acute myocardial ischemia or infarction
Acute stroke
Pulmonary embolism Prinzmetal angina
Dissecting aortic aneurysm
Various central and autonomic nervous system abnormalities
Duchenne muscular dystrophy
Friedreich ataxia
Spinobulbar muscular dystrophy Myoclonic dystrophy
Arrhythmogenic right ventricular cardiomyopathy (ARVC) Hypothermia
Mechanical compression of the right ventricular outflow tract (RVOT) as occurs in pectus excavatum, mediastinal tumor, or hemopericardium

several potential flaws exist in these criteria, they have since then been refined. While the clinical manifestations mentioned above remain important in recommending treatment and risk stratification, they are no longer listed among the diagnostic criteria, and type I Brugada ECG pattern in at least one lead (recorded from either the second, third, or fourth intercostal space) is now required for the diagnosis (Priori et al. 2013). Recently, another guideline was proposed utilizing a scoring system for the diagnosis of Brugada syndrome in the same fashion as the system for long QT syndrome, the so-called Shanghai score (Antzelevitch et al. 2016). Unfortunately, the benefit and the accuracy of the Shanghai score remain unclear, and one may use the old criteria and merely categorize the patients into two groups: symptomatic or asymptomatic BrS.

A Brugada ECG pattern can also be seen in several other conditions. Thus, the diagnosis can be made in a patient showing the Brugada ECG pattern with demonstration of a grossly normal heart by cardiological tests and in the absence of other conditions that can mimic the Brugada ECG pattern (Table 8.1).

8.3 Epidemiology

The prevalence of type I Brugada ECG pattern was estimated to be 1:2000 based on combined studies encompassing >400,000 patients from North America, Europe, and Asia (Postema 2012). The prevalence, however, varies widely among countries with low prevalence in North America (0.005–0.1%) and Western countries including Europe (0–0.017%) compared to Asia (0.15–0.27% in Japan, 0.18% in the Philippines) (Probst et al. 2007). Interestingly, several epidemiologic studies in Thailand have demonstrated that the prevalence of type I Brugada electrocardiogram (ECG) pattern is higher in Thailand than in other Asian countries and even much

higher than that in the European countries and the USA. The incidence is ranging from 0.8% to 1.8% in nonfebrile patients to 4% in febrile patients [fever is a well-known precipitating factor for BrS (Rattanawong et al. 2016)] compared to a much lower incidence in Europe and in the USA.

The majority of BrS patients are relatively young between 20 and 40 years (Antzelevitch et al. 2005; Probst et al. 2007) although cases have been reported in children as young as 2 days old and in elderly up until the age of 84 years (Antzelevitch et al. 2005; Probst et al. 2007). Despite what appears to be an autosomal dominant inheritance pattern, BrS has up to tenfold higher prevalence in males with greater severity (Nademanee et al. 1997; Benito et al. 2008). Worldwide, the syndrome is probably responsible for 4–12% of all sudden deaths and at least 20% of sudden deaths in patients with structurally normal hearts (Wilde et al. 2002; Antzelevitch et al. 2005).

8.4 Genetics of BrS

Because of occurrence in siblings and family history of sudden death in affected individuals, genetics was thought to play an important part of BrS since the first description in 1992 (Brugada and Brugada 1992). Transmission in familial cases is consistent with autosomal dominant with incomplete penetrance, especially in females whose incidence is up to 10 times lower than in male. In 1998, Chen et al. reported the first mutation, linked to BrS, in the *SCN5A* gene which encodes for the α-subunit of the sodium channel (Chen et al. 1998). Since then, more than 300 *SCN5A* mutations have been reported in BrS and represent currently the most common genotype. Functional studies demonstrate that *SCN5A* mutations in BrS cause loss of function of the sodium channel due to decreased expression of the sodium channel protein (Nav1.5) on the sarcolemma (Valdivia et al. 2004), expression of nonfunctional channels (Kyndt et al. 2001), or altered gating properties (delayed activation, earlier inactivation, faster inactivation, enhanced slow inactivation, and delayed recovery from inactivation) (Bezzina et al. 1999; Dumaine et al. 1999; Akai et al. 2000; Amin et al. 2005; Nakajima et al. 2015; Kinoshita et al. 2016). The loss of function of the sodium channel results in a decrease in sodium current and in turn impairs the fast upstroke of phase 0 of the action potential causing a slow conduction in the heart.

Even though *SCN5A* mutations are the most common defect found in 11–28% of BrS probands, the genetics of BrS have become heterogeneous. In addition to *SCN5A* mutations, more mutations are found in gene encoding protein of potassium and calcium channels. There have been now mutations of at least 18 genes that have been associated with BrS phenotype (Table 8.2). The contribution of the other 17 genes (except *SCN5A*) as the etiology of BrS, however, is small, and the presence of rare variants in these genes as the sole cause of BrS has been called into question due to similar percentage of normal individual carrying rare variants in these genes compared to BrS patients (Le Scouarnec et al. 2015).

Table 8.2 Gene mutations associated with Brugada syndrome (Antzelevitch et al. 2016)

Subtype	Locus	Gene/protein	Ion channel	Percent of probands
BrS1	3p21	*SCN5A*, Nav1.5	↓Ina	11–28%
BrS2	3p24	*GPD1L*	↓Ina	Rare
BrS3	12p13.3	*CACNA1C*, Cav1.2	↓Ica	6.6%
BrS4	10p12.33	*CACNB2b*, Cavβ2b	↓Ica	4.8%
BrS5	19q13.1	*SCN1B*, Navβ1	↓Ina	1.1%
BrS6	11q13-14	*KCNE3*, MiRP2	↑Ito	Rare
BrS7	11q23.3	*SCN3B*, Navβ3	↓Ina	Rare
BrS8	12p11.23	*KCNJ8*, Kir6.1	↑IK-ATP	2%
BrS9	7q21.11	*CACNA2D1*, Cav a2δ1	↓Ica	1.8%
BrS10	1p13.2	*KCND3*, Kv4.3	↑Ito	Rare
BrS11	17p13.1	*RANGRF*, MOG1	↓INa	Rare
BrS12	3p21.2-p14.3	*SLMAP*	↓Ina	Rare
BrS13	12p12.1	*ABCC9*, SUR2A	↑IK-ATP	Rare
BrS14	11q23	*SCN2B*, Navβ2	↓INa	Rare
BrS15	12p11	*PKP2*, Plakophillin-2	↓INa	Rare
BrS16	3q28	*FGF12*, FHAF1	↓INa	Rare
BrS17	3p22.2	*SCN10A*, Nav1.8	↓INa	5–16.7%
BrS18	6q	*HEY2* (Transcriptional factor)	↑Ina	Rare

Note: Upward and downward arrows show increase and decrease

Despite the fact that many genes have been identified and linked to the syndrome, gene mutation alone cannot explain the phenotype in full. Kapplinger et al. found nearly 300 *SCN5A* mutations in 211 unrelated probands (Kapplinger et al. 2010). The *SCN5A* mutations were found in 21% of patients with the Brugada phenotype and 2–5% of healthy controls, respectively. These findings suggest an important role of *SCN5A* mutations causing loss-of-function sodium channel in the phenotype manifestation. However, 80% of these mutations were only present in a single individual or one family, and a causal role of these mutations in the Brugada syndrome is far from clearly established.

Probst et al. studied 13 large families with *SCN5A* mutations and revealed the following intriguing findings: Many of the mutation carriers did not have the Brugada signature sign on ECG nor could it be provoked by sodium channel blockers (Probst et al. 2009). Moreover, in 5 of the 13 families with more than five clinically affected individuals, there were one or two affected individuals with the Brugada phenotype who did not have the familial *SCN5A* mutations. Furthermore, the Brugada ECG pattern was induced in eight mutation-negative patients (Probst et al. 2009). These findings along with a report of a case of identical twins carrying a *SCN5A* mutation of which only one displayed the phenotype suggest that *SCN5A* mutations may act as modifiers rather than causative mutations (Sakabe et al. 2002a).

SCN5A mutations may cause not only BrS but other diseases as well. Indeed, *SCN5A* mutations have also been associated with long QT syndrome (Bezzina et al.

1999; Wang et al. 1995), cardiac conduction disease (Tan et al. 2001), sick sinus syndrome (Benson et al. 2003), atrial fibrillation (Darbar et al. 2008; Olson et al. 2005), and dilated cardiomyopathy with overlap syndromes identified in specific families (Meregalli et al. 2009).

Because of the seemingly complex inheritance pattern in BrS, a genome-wide association (GWAS) study was done to explore the contribution of common single nucleotide polymorphisms (SNP) in this disease. In this study, the investigators could demonstrate association of three common SNP in *SCN5A*, *SCN10A*, and *HEY2* with BrS. Each "risk allele" was associated with an odd ratio of 1.6–2.8 for having Brugada syndrome (Bezzina et al. 2013). Risk was progressively higher with presence of more risk alleles and was as high as 21.5 if 5 or 6 risk alleles were present in a single individual. This study suggests that the genetic basis of BrS and susceptibility to VF therein in the individual patient is not caused by a single major genetic mutation (classical Mendelian view) but rather by inheritance of multiple susceptibility genetic variants (oligogenic) acting in concert through one or more mechanistic pathways. This finding partially explains why simple genetic testing may have easily missed these rare genetic variants in many of the BrS patients.

Because of the complexity of genetic mechanism in this disease, genetic testing for the diagnosis of BrS is not as helpful as some other monogenic diseases associated with sudden cardiac death like the long QT syndrome or catecholaminergic polymorphic VT (CPVT). Given the background rate of rare variants of unknown significance (VUS) in *SCN5A* of approximately 2% in normal population and 20% yield in patients with BrS (signal-to-noise ratio of 10:1), the HRS/EHRS Expert Consensus Guidelines written in 2011 listed genetic testing for the diagnosis of Brugada syndrome as "can be useful" (Class IIa) in a proband with clinical diagnosis of BrS (Ackerman et al. 2011). The test is probabilistic rather than deterministic, and interpretation of an abnormal test must consider all the clinical and molecular genetic findings. Due to presence of rare genetic variants in the normal population, a false-positive result is possible. For example, a recent study of 870 whole exome sequencing data and 6161 genotype array data in general population found that of 28 variants associated with BrS, none of whom had Brugada marker on the ECG. Syncope, ventricular arrhythmia, and mortality were also not significantly different between those who had the variants and those who did not (control group) (Ghouse et al. 2017).

The role of genetic testing in risk stratification remains unclear. Crotti et al. reported their findings of a comprehensive mutational analysis of all 12 BrS genes for a single large cohort of BrS patients (Crotti et al. 2012). They found putative pathogenic mutations in 21% of their BrS cohort. Similar to other reports, 78% of the mutations in BrS were still confined to *SCN5A*. Interestingly, in male patients, the yield of positive testing varied from 11% in those older than 40 years of age to 21% in male patients 20–40 years of age and to 83% in male patients younger than 20 years of age. The BrS patients with prolonged PR interval $>$200 ms had very high incidence of *SCN5A* mutations (39%) compared to those with normal PR interval. The yield of identifying the mutations is similar between those who have only the typical type 1 Brugada ECG pattern (asymptomatic cases) and those with symptoms

and/or family history of sudden cardiac death, so presence of identifiable mutation did not appear to correlate with the symptoms or prognosis. Based on their findings, the authors recommended genetic testing for all patients who just have the type 1 Brugada ECG pattern (asymptomatic cases) as well as symptomatic cases. Due to their findings of a low prevalence of non-*SCN5A* mutations, they suggested that it was reasonable to test most patients for *SCN5A* mutations alone first, with further testing for the other minor BrS genes only in special circumstances. This recommendation concurs with the position paper of the Canadian Cardiovascular Society but not with consensus of the Heart Rhythm Society/European Heart Rhythm Association which states that either comprehensive genetic testing or target testing for *SCN5A* can be used (Ackerman et al. 2011; Gollob et al. 2011; Kaufman 2012).

8.5 Pathophysiology

Using arterially perfused wedge preparation of canine right ventricle (RV), Antzelevitch and his colleagues proposed the repolarization theory as the electrophysiologic abnormality underlying BrS (Yan and Antzelevitch 1999). In their experimental studies, they observed the transmembrane voltage gradient between the RV epicardium and endocardium due to the loss of the action potential (AP) dome only in the epicardium but not in the endocardium; RV epicardium is well known to have abundant Ito. Upon exposure to sodium channel blockers in combination with acetylcholine, this area then developed a notch and dome appearance of the epicardium AP leading to a coved-type ST-segment elevation in the right precordial leads. When the loss of the AP dome was further accentuated, it caused marked shortening of the epicardial AP in certain regions causing pronounced heterogeneity of transmembrane voltage potentials and, in turn, causing phase 2 reentry and triggered VF (Yan and Antzelevitch 1999). However, thus far, there have not been clear clinical relevant data in humans to support this theory. Perhaps, the observational study showing that quinidine, a strong Ito blocker, is effective in treating BrS patients could be inferred as weak-indirect evidence that supports the repolarization theory (Belhassen et al. 2004). While the repolarization theory enjoyed its popularity early on, the lack of strong clinical relevant findings to convincingly support the concept and subsequent clinical evidence led to the other theory, that of depolarization disorder.

Using an electrical guidewire to record an epicardial electrogram from a conus branch of the right coronary artery, Negase et al. were the first to show abnormal electrograms characterized by late potentials following the QRS which were recorded from the free wall of RVOT epicardium in BrS patients (Nagase et al. 2002). Their findings suggest conduction delay in the RVOT epicardium. Two studies conducted in an explanted heart in addition to biopsies showing (ultra-) structural changes in the right ventricular outflow tract of BrS patients demonstrated conduction disorder in these patients. The explanted hearts showed no evidence of repolarization abnormality; instead they found evidence of interstitial fibrosis causing conduction delay in one heart (Coronel et al. 2005) and right ventricular

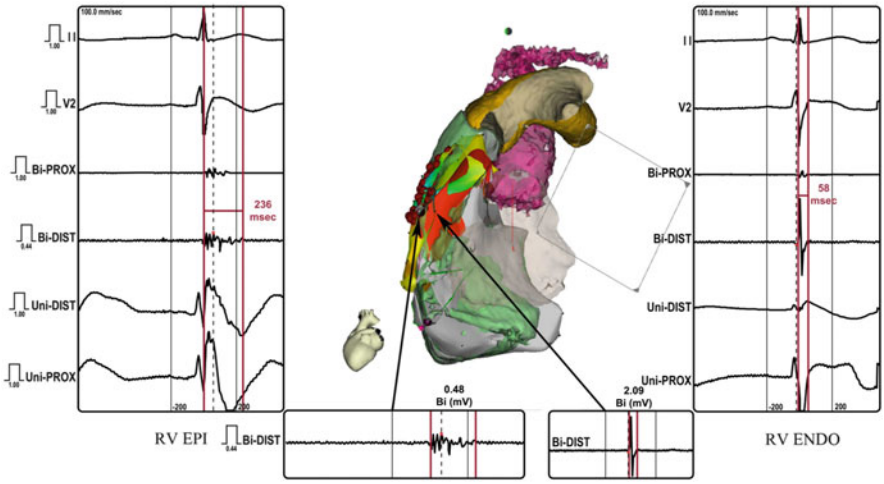

Fig. 8.3 A left lateral view of the right ventricular outflow tract (RVOT) displays the difference in ventricular electrograms between the endocardial and epicardial site of the anterior RVOT of a BrS patient with electrical storm. The left and right insets display bipolar and unipolar electrograms recorded from the epicardium and endocardium from the same site of the RVOT, respectively. *Bi-DIST* bipolar distal, *Bi-PROX* bipolar proximal, *Uni-DIST* unipolar distal, *Uni-PROX* unipolar proximal. Reproduced with permission from Nademanee K, Veerakul G, Chandanamattha P, et al. Prevention of ventricular fibrillation episodes in Brugada syndrome by catheter ablation over the anterior right ventricular outflow tract epicardium. Circulation. 2011;123:1270–9

excitation failure and activation delay by current-to-load mismatch in the sub-epicardium in the other heart (Hoogendijk et al. 2010). As a result, the delay in the AP of the RVOT causes the electrical gradient from the more positive RV to RVOT, leading to the ST elevation of the right precordial leads—similar to the situation of a myocardial injury at the RVOT—and as the RVOT depolarizes later (during repolarization of the RV), this gradient is reversed, and the net current flows toward the RV, resulting in a negative T wave in the same right precordial leads. The experiment from the same group in this explanted heart also showed that this site is the arrhythmogenic site during programmed stimulation-induced VF.

Perhaps, the most compelling findings to support depolarization disorder came from our study (Nademanee et al. 2011). Our group carried out a study to determine the substrate sites and arrhythmogenic mechanisms in this disease. We found that all our BrS patients had abnormal low-voltage, fractionated late potentials exclusively clustering in the anterior aspect of the RVOT epicardium and not seen anywhere else. Figures 8.3 and 8.4 show an example of low-voltage fractionated electrograms recorded from the anterior RVOT epicardium of a patient who presented with electrical storm. Ablation at this area normalized the Brugada ECG pattern and prevented recurrent VF episodes. As shown in Fig. 8.3, the endocardial site (arrow) displays a single potential of 2.09 mV, with a duration of 58 ms, and did not extend beyond the QRS compared to the epicardial counterpart that showed low-voltage late potential (0.48 mV), with a duration of 236 ms with late potential extended beyond

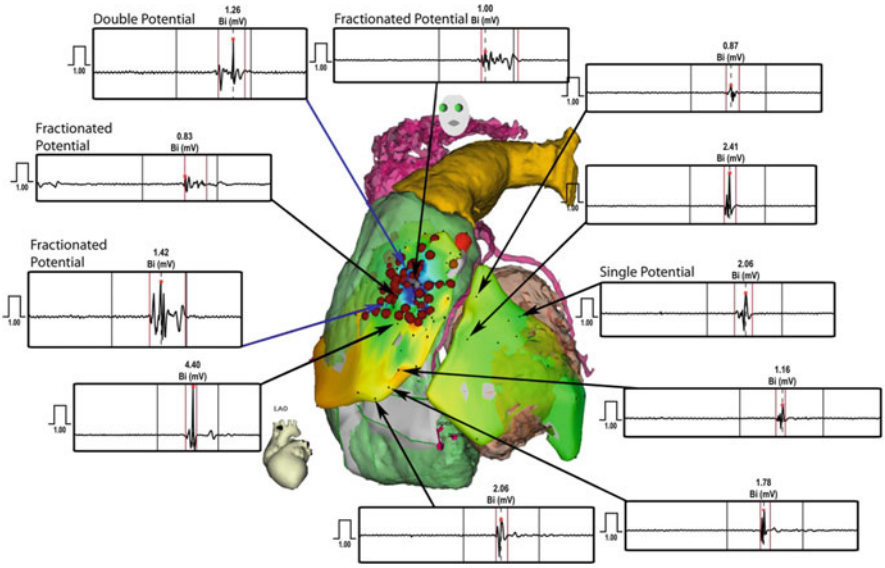

Fig. 8.4 Comparison of ventricular electrograms recorded from different sites in both the left ventricle (LV) and right ventricle (RV) of the same patient as in Fig. 8.3. Reproduced with permission from Nademanee K, Veerakul G, Chandanamattha P, et al. Prevention of ventricular fibrillation episodes in Brugada syndrome by catheter ablation over the anterior right ventricular outflow tract epicardium. Circulation. 2011;123:1270–9

the QRS. Figure 8.4 shows epicardial electrograms recorded from various sites of the epicardium in both the LV and RV epicardium. Note that abnormal fractionated electrograms and double potential electrograms are only localized in the anterior aspect of the RVOT epicardium. Similar observations were found in all our study patients, and these findings clearly provide the strongest clinical evidence that the delayed depolarization at the anterior aspect of the RVOT is the most likely underlying electrophysiologic mechanism underlying BrS.

Recently, Szél and Antzelevitch also observed fractionated electrograms in the RV epicardium, but they suggested that this is due to a heterogeneous epicardial loss of dome and local re-excitation via a concealed phase 2 reentry, rejecting the possibility of abnormal depolarization or structural abnormalities (Szél and Antzelevitch 2014). However, in our patients another mechanism seems in operation. Fractionated signals were clearly associated with diastolic potentials in the BrS patients; we observed that the fractionation was present immediately after activation, arguing against reactivation of calcium channels (which would require a minimum time delay). Fractionated activity and diastolic potentials have been shown to be associated with reentrant arrhythmias and are observed in BrS patients. Nevertheless, while it is quite apparent that depolarization disorder is likely to be the main mechanism underlying the BrS, one must be mindful that repolarization abnormality could contribute to the arrhythmogenesis of BrS patients, along with genetic mutations of ionic channel and other precipitating factors.

Brugada syndrome was classically thought of as primary electrical disease with no structural defect of the heart (Antzelevitch et al. 2005). Despite no structural abnormality detected by the usual cardiologic studies such as echocardiography, angiography, or cardiac MRI, we recently demonstrated minor yet similar pathological findings in six autopsy hearts of SADS victims who had a family history of BrS and six biopsy specimens in patients with BrS (Nademanee et al. 2015). Increased collagen in the RVOT with epicardial and interstitial fibrosis was found with corresponding area of low-amplitude, fractionated electrogram in biopsy cases. Connexin-43 signals were diminished in the RVOT of these patients which raises the possibility of cardiomyocyte electrical uncoupling as one of the pathophysiology in this disease. These findings point to the likelihood of combined structural abnormalities and ion channel defects as the basis of ventricular arrhythmia and sudden death in patients with BrS. A recent MRI study of cases with BrS compared to age- and sex-matched control demonstrated a slight but statistically significant larger RV end-systolic volume (31 vs. 28 mL/m^2, $p = 0.038$) and lower ejection fraction (61% vs. 64%, $p = 0.004$); these findings attest to these minor structural abnormalities which likely make BrS a cardiomyopathic entity as well as channelopathy (Bastiaenen et al. 2017).

8.6 Modulating and Precipitating Factors

As mentioned above, the Brugada ECG pattern is often concealed but can be unmasked or modulated by sodium channel blockers, a febrile state, vagotonic agents, autonomic nervous system changes, tricyclic or tetracyclic antidepressants, first-generation antihistamines (dimenhydrinate), a combination of glucose and insulin, hyperkalemia, hypokalemia, hypercalcemia, and alcohol and cocaine toxicity.

8.6.1 Autonomic Nervous System

The effect of sympathetic stimulation by isoproterenol infusion, resulting in normalization of the BrS pattern, suggests that sympathetic activity could modify the VF substrate (Miyazaki et al. 1996). The presence of the Brugada ECG pattern is probably a prerequisite for the increased risk of SCD, and normalization of the ECG pattern is associated with a decreased risk (Antzelevitch et al. 2005). This concept is strengthened by the fact that some patients with "VF storms" associated with BrS can be effectively treated with isoproterenol infusion (Tanaka et al. 2001). On the other hand, increased vagal tone could be arrhythmogenic in BrS patients. Increased vagal tone, as well as acute β-blockade, was found to promote VF induction in the electrophysiology laboratory (Kasanuki et al. 1997). Abe et al. found that fluctuations in late potentials on signal-averaged ECG (SAECG) occurred predominantly at night, suggesting that conduction delay and, by inference, the arrhythmogenic substrate are autonomically modulated (Abe et al. 2012). Therefore,

it is plausible that at night during sleep, when vagal tone is usually increased and associated with the withdrawal of sympathetic activity, the VF substrate is modulated and more susceptible to arrhythmogenesis. Kasanuki et al. also showed a sudden increase in vagal activity, as measured by heart rate variability (HRV), just before episodes of VF in a patient with BS (Kasanuki et al. 1997). However, Krittayaphong et al. studied HRV from 24-h Holter data of SUDS patients with the Brugada ECG marker, aiming to determine the circadian pattern of sympathetic and parasympathetic activity (Krittayaphong et al. 2003). Surprisingly, they found decreased HRV at night in SUDS patients when compared with the control group and suggested that these patients had an abnormal increase in sympathetic activity or decrease in the vagal tone at night. Although the explanation for the different findings of Kasanuki et al. and that of Krittayaphong et al. is unknown, it is clear that the sympathovagal balance in the BrS patients plays a significant role in the circadian variation of VF occurrence. However, further studies are needed to clearly define the complex interplay between the autonomic nervous system and the arrhythmic mechanisms of BrS.

8.6.2 Hypokalemia

Hypokalemia has been implicated as a contributing cause for the prevalence of SUDS in the northeastern region of Thailand where potassium deficiency is endemic (Nimmannit et al. 1991). Serum potassium levels in the northeastern population are significantly lower than those of the population in Bangkok, which lies in the central part of Thailand where potassium is abundant in food.

Hypokalemia is a well-known predisposing factor to ventricular arrhythmias. Furthermore, it has been shown that there is commonly a shift of serum potassium into the muscular compartment between midnight and 7 am, decreasing the amount of serum potassium (Andres et al. 1957). If this phenomenon indeed occurs in BS/SUDS patients in Thailand, then it is likely that low serum potassium is a key factor that precipitates VF at night in these patients.

8.6.3 Sleep, Heavy Meals, and Alcohol

Because the majority of VF episodes occur at night, the question is whether a sleep disorder is a trigger of VF. Thus far, none of our sleep studies in BrS patients has found any evidence of a sleep disorder, including sleep apnea. One theory that many SUDS researchers have informally discussed as a possible precipitating factor is eating a heavy meal at dinnertime before retiring to bed. A Thai Ministry of Public Health Report (1990) suggested that a large meal of glutinous rice ("sticky rice") or carbohydrates ingested on the night of death precipitated SUDS attacks. Both carbohydrates and glutinous rice have been shown to shift potassium into cells and thus lower the serum potassium level. Postprandial increased ST segment elevation in lead V2 has been seen in patients with symptomatic BrS on a Holter study

(Mizumaki et al. 2007). A study by Nogami et al. showed that glucose and insulin could unmask the Brugada ECG marker or accentuate the J-junction elevation of the ST segment (Nogami et al. 2003). They observed a slight decrease in the serum potassium levels of their study patients, but it did not reach statistical significance. Nevertheless, these findings bode well for a heavy carbohydrate meal being a precipitating factor for sudden death in SUDS patients. Alcohol has also been implicated in triggering recurrent VF in a patient with Brugada syndrome (Ohkubo et al. 2013).

8.6.4 Body Temperature and Febrile Illness

Dumaine et al. discovered that the *T1620M* missense mutation causes accelerated inactivation of the sodium channel at physiologic body temperature but not at room temperature (Dumaine et al. 1999). Identification of this temperature-sensitive mutation that precipitates the net loss of sodium current prompted investigators to recognize that a hot climate and body temperature may be important modulating factors. Indeed, several case reports have emerged recently, demonstrating that febrile illness or external heat could unmask BrS and/or precipitate VF occurrence (Antzelevitch and Brugada 2002; Morita et al. 2002b; Saura et al. 2002; Porres et al. 2002; Kum et al. 2002; Canpolat et al. 2017; Chung et al. 2017; De Marco et al. 2012; Skinner et al. 2007). In children, ventricular arrhythmia triggered by fever can be mistaken for episodes of febrile seizure (Skinner et al. 2007). We have encountered a case of a young male patient who died suddenly after a spiking fever of 40 °C after abdominal surgery. Upon review of the ECG, the patient had the typical BrS pattern, but had not had a prior medical problem and had been asymptomatic. The northeastern part of Thailand where SUDS is prevalent is well known for its hot climate, with temperatures reaching as high as 41 °C. It is again unclear how much climate influences the occurrence of SUDS in Thailand, but a study is underway. It is entirely possible that high climatic temperatures or a febrile state could modulate the functional expression of mutant channels in other genes responsible for BrS. In the meantime, physicians should factor in temperature as a cause for arrhythmogenesis in BrS. They should be cognizant of the association between temperature and BrS during diagnosis and treatment, advising patients to promptly treat fevers.

Figure 8.5 proposes pathophysiology of BrS and demonstrates how these modulating and predisposing factors can affect the arrhythmia and the clinical outcomes in many ways: (1) modifying the VF substrates, (2) affecting the gene expression of the ion channel defects, (3) affecting the triggering PVCs and the initiating process of VF, and (4) influencing the sustaining process of the VF episodes.

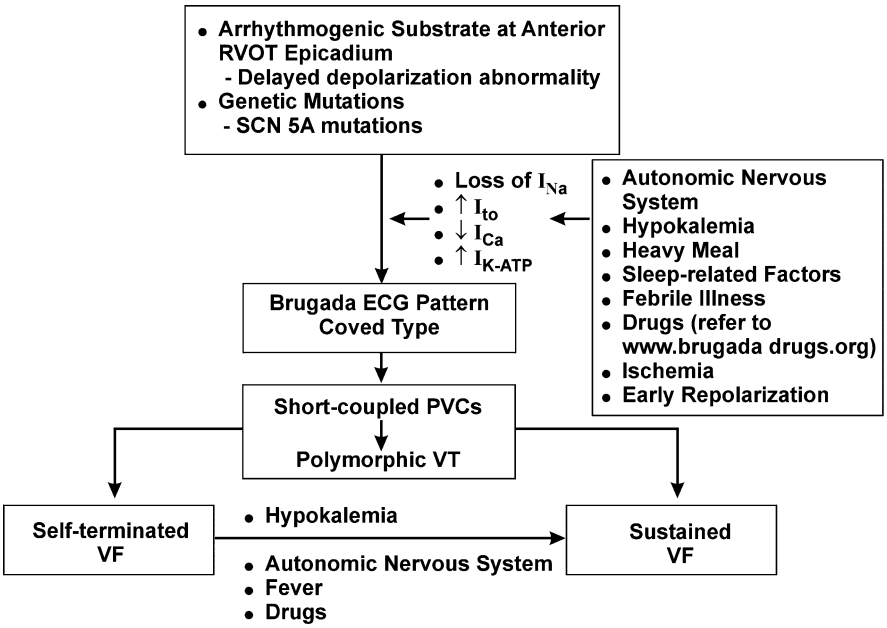

Fig. 8.5 Proposed pathophysiologic mechanisms of BrS with respect to predisposing factors

8.7 Combined Syndromes

In addition to the above precipitating factors, BrS patients often have other concomitant arrhythmias or arrhythmic syndromes. Atrial fibrillation is one of the common arrhythmias in BrS. Incidence of combined early repolarization syndrome in the BrS patients occurred in 15%, and in this subset (Letsas et al. 2008), the incidence of recurrent VF episodes is significantly higher than that of the BrS alone. Similarly, combined syndromes of a progressive conduction defect and BrS and long QT syndrome and BrS are occasionally observed (Bezzina et al. 1999; Shirai et al. 2002).

8.8 Risk Stratification

There is little to debate that BrS patients who survived an out-of-hospital cardiac arrest are at high risk of recurrent VF episodes and need ICD treatment. Likewise, symptomatic patients with recurrent syncope, agonal respiration at night during sleep, or unknown seizure are at risk of dying suddenly without protection and

have Class I indication for ICD treatment. One large study involving 1029 BrS patients in 11 European centers found annual cardiac events rate of 7.7% in patients who presented with sudden cardiac arrest, 1.9% in patients with syncope, and 0.5% in asymptomatic patients (Probst et al. 2010). The heated debate is more on how one best identifies high-risk patients for sudden death and the need of ICD treatment in asymptomatic BrS patients. At the beginning, the Brugada registry reported a significantly high risk of asymptomatic patients with positive VT inducibility by programmed electrical stimulation (Antzelevitch et al. 2005; Brugada et al. 2011). However, more recent studies found a much lower incidence of sudden death or VF in this group and questioned the specificity of programmed electrical stimulation (PES) in risk stratifying asymptomatic BrS patients (Veerakul and Nademanee 2012; Priori et al. 2012). Our own experience of asymptomatic patients shows that the annual cardiac event rate (VF or death) is so low (0.25% per year) that it will be very unlikely for any risk stratification strategy to be able to identify high-risk patients for ICD treatment as a primary prevention (Veerakul et al. 2008).

Electrocardiographic risk factors include presence of spontaneous type I Brugada pattern which carries a higher risk of arrhythmic events compared to drug-induced Brugada pattern (Adler 2016). QRS fragmentation (Priori et al. 2012; Morita et al. 2008; Tokioka et al. 2014), early repolarization pattern (Tokioka et al. 2014; Kawata et al. 2013; Kaneko et al. 2014), a significant S wave in lead I ($\geq$0.1 mV and/or $\geq$40 ms) (Calò et al. 2016), and prolonged Tpeak-Tend or Tpeak-Tend/QTc (Zumhagen et al. 2016; Maury et al. 2015) were reported to be associated with high risk for ventricular arrhythmia. Other studies found exercise testing (Makimoto et al. 2010; Amin et al. 2009), signal-averaged ECG (Huang et al. 2009), and shortening of the ventricular refractory period ($<$200 ms) (Priori et al. 2012) to be valuable tools for identifying high-risk patients. However, it is unclear how useful any of these parameters would be in identifying asymptomatic BrS for ICD treatment. In our own asymptomatic cohorts of 115 patients, we found that only two patients after 10 years of follow-up had either VF or sudden death (one EPS positive and the other EPS negative) (Veerakul et al. 2008). With this low event rate and after a decade of follow-up, it is very clear to us that any risk stratification strategy would be very unlikely to be of any value in selecting patients for an ICD treatment in our population.

8.9 Treatment

BrS patients should be informed of various modulating and precipitating factors—as discussed above—that could bring about malignant arrhythmias: fever, electrolyte abnormalities, alcohol consumption, and a whole host of drugs as listed in www.brugadadrugs.org (Postema et al. 2009). VF and sudden death in BrS usually occur at rest and at night. Therefore, one has to be cognizant of the circadian variation of sympathovagal balance, hormones, and other metabolic factors which are likely to contribute to this circadian pattern (Wilde et al. 2002; Antzelevitch et al. 2005).

8.9.1 Anti-arrhythmic Drugs

Quinidine has been the only drug that consistently shows benefits in preventing recurrent VF episodes. The drug has been shown to suppress inducibility of VF on PES and reduce the number of appropriate ICD shocks (Belhassen et al. 2004, 2015; Hermida et al. 2004; Mizusawa et al. 2006). Blockade of Ito is thought to be the mechanism by which quinidine is effective. Unfortunately, there are two major problems with quinidine: (1) Only two-third of patients could tolerate the drug, and serious side effects such as thrombocytopenia could be very serious. (2) Quinidine is not available in many countries (Viskin et al. 2007). In Thailand, there is no supply of the drug, and the only drug we could use is amiodarone with variable success. Bepridil—another Ito blocker—which is only available in Japan has been used in BrS patients to suppress VF (Kaneko et al. 2014; Ohgo et al. 2007; Murakami et al. 2010). Cilostazol—an oral phosphodiesterase inhibitor—has also been shown to be of benefit in preventing recurrent VF in Brugada syndrome (Ohgo et al. 2007; Tsuchiya et al. 2002).

However, there is very little data to objectively assess the safety and efficacy of both Bepridil and Cilostazol in BrS patients at this time.

8.9.2 Implantable Cardioverter-Defibrillator

Symptomatic BrS patients (with a past history of VT/VF or syncope) have a Class I indication for ICD treatment (Wilde et al. 2002; Antzelevitch et al. 2005, 2016; Priori et al. 2013). In our DEBUT study (Tsuchiya et al. 2002)—Defibrillator versus β-blocker in Unexplained Death in Thailand: A Randomized Clinical Trial—we found that ICDs provided full protection from death related to primary VF in the study population which included 59% of patients with BrS. However, we also found that unwanted effects of the ICD were also frequent (30%). Most of the complications were minor; they included defibrillation discharges caused by supraventricular tachycardia or sinus tachycardia and T-wave over-sensing. All of the complications were corrected by reprogramming the devices without major intervention. However, one patient had pocket erosion with infection that required removal of the ICD, and one patient needed to have his ICD lead replaced because of an insulation break. Other studies also show similar results that long-term follow-up of Brugada ICD patients has a high complication rate up to a third of patients (Nademanee et al. 2003; Sacher et al. 2006; Sarkozy et al. 2007; Steven et al. 2011). The majority of the complications, similar to our study, were mostly inappropriate shocks occurring in 36% of patients at follow-up; however, one registry recorded an 18% rate of serious vents including pericardial effusion, lead fracture, infection, and subclavian vein thrombosis (Steven et al. 2011).

With the above relatively high complication rate of ICD in BrS patients, one has to be extremely cautious to use ICD in asymptomatic BrS patients. The fact that the event rates in the asymptomatic BrS population are quite low in most series makes ICD treatment in this subset questionable with respect to whether ICD benefits

Table 8.3 Indication for ICD implantation in patients with Brugada syndrome (Priori et al. 2013)

Class I indication (ICD is recommended):
Symptomatic patients displaying the type 1 Brugada ECG (either spontaneously or after sodium channel blockade) who present with aborted sudden death should receive an ICD
Similar patients presenting with related symptoms such as syncope, seizure, or nocturnal agonal respiration and having documented ventricular fibrillation or tachycardia should also undergo ICD implantation. Electrophysiologic study (EPS) is recommended in symptomatic patients only for the assessment of supraventricular arrhythmia.
Class IIa (ICD could be useful):
In symptomatic patients with type 1 pattern, in whom syncope was likely caused by VT/VF
Class IIb (ICD may be considered):
In asymptomatic patients inducible by programmed electrical stimulation (PES)
Class III indication:
ICDs are not indicated in asymptomatic patients with drug-induced type I ECG and on the basis of a family history of SCD alone

would outweigh the risk. As mentioned in the risk stratification section, thus far there have not been any convincing methods of risk stratification to identify high-risk asymptomatic patients for ICD therapy. One could follow the guideline established by the HRS/EHRA/APHRS expert consensus statement (Priori et al. 2013) recommendations for ICD implantation, as summarized in Table 8.3.

The recent approval of leadless ICD, which has been shown to be quite effective in terminating VT/VF episode, is a welcome addition to therapeutic modalities for BrS patients 116. Early users reported issues with sensing and higher sensing screening failure rate compared to other inherited arrhythmia syndrome due to the dynamic nature of QRS and T-wave morphologies in patients with BrS (Kamakura et al. 2017; Conte et al. 2017; Olde Nordkamp et al. 2016). Further studies and clinical trials to determine efficacy and safety are warranted in the high-risk BrS population.

8.9.3 Catheter Ablation

The early attempt of catheter ablation in treating BrS syndrome patients was limited to a few report cases of patients with electrical storms. The initial approach was designed to target initiating PVCs that trigger VF, which were found to come from the RVOT (Haïssaguerre et al. 2003; Nakagawa et al. 2008; Darmon et al. 2004). The ablation was performed on the endocardial site of the RVOT. However, this approach has not been widely successful largely because patients with BrS rarely had frequent PVCs to be mapped, and therefore it was quite difficult to identify precise targets for ablation and clearly assess the acute outcomes of the ablation. We have reported our epicardial approach for substrate ablations that was indeed safe and effective (Nademanee et al. 2011). We identified and proved that anterior RVOT epicardium is the most common arrhythmogenic substrate sites for our BrS patients. However, subsequently, in a significant number of patients, the RV body and the

inferolateral aspect and the area near the tricuspid valve are also infrequently involved. These sites consistently have abnormal late potentials and low-voltage fractionate ventricular electrograms; these abnormal electrograms tended to cluster exclusively in this area but not anywhere else. After ablations at this RVOT epicardial site, the Brugada ECG pattern normalizes, and VT/VF episode subsides. We have now performed 54 BrS patients with frequent ICD discharges. Long-term outcomes (median 30 months) have been excellent with no recurrent VT/VF in all patients off medication. More recent studies ranging from individual case reports as well as collective collaborative studies have confirmed our findings that BrS arrhythmogenic substrates are ubiquitous in the RVOT epicardium and catheter ablations are beneficial in treating symptomatic BrS (Brugada et al. 2015; Zhang et al. 2016). Whether ablation would substitute for an ICD in high-risk BrS patients remains unknown. Further studies clearly need to be done to assess values and limitations of catheter ablation in patients with BrS.

8.10 Conclusions and Future Perspective

The two decades of BrS research have witnessed an impressive progress of our understanding of several aspects of the syndrome with respect to role of genetics, electrophysiological mechanisms, and clinical characteristics. However, many questions and controversies remain regarding the role of genetic background including polymorphisms as well as rare variants and gene-gene or gene-environmental interaction and other confounding factors such as fever and gender in this population. The cause and the role of fibrosis and anatomical abnormality in the RVOT in arrhythmogenesis will likely be the subject of intense investigation in the coming years. It's certain that the debate will continue regarding the role of repolarization in BrS and whether our findings of abnormal delayed depolarization in the anterior RVOT epicardium is seen in other centers and more specifically other population besides ours. How does one best treat asymptomatic BrS patients? Will there be any better risk stratification strategy to identify high-risk groups? Why is the anterior RVOT epicardium the arrhythmogenic sites for these patients? Why is there such a male preponderance and why do most of the VF episodes usually occur at night time? Whole genome sequencing may identify rare and common variants in genes modulating ion channels that may combine as multiple hits to cause abnormal conduction in the RVOT areas and in turn increase susceptibility to VF. Further research will continue to answer these questions. Meanwhile, refinement of treatment is needed. We will need to know the efficacy and safety of quinidine in the randomized trial studies which currently are being conducted. In the near future, more study of the subcutaneous leadless ICD will be forthcoming. The expanding role of catheter ablation of the epicardial substrate beyond the population of BrS with frequent VF needs to be also evaluated by assessing the risks and benefits of the procedures, especially with respect to complications related to the epicardial ablation approach. We indeed anticipate with excitement that the next decades will have these answers and in turn advance our ability to care for our BrS patients.

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Compliance with Ethical Standards

Conflict of Interest Author Apichai Khongphatthanayothin declares that he has no conflict of interest. Author Koonlawee Nademanee declares that the following conflict of interests: Research grants from Medtronic Inc & Royalty from Biosense Cordis Webster Inc.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Inform consent was obtained from all individual participants included in the study.

References

Abe A, Kobayashi K, Yuzawa H, Sato H, Fukunaga S, Fujino T, Okano Y, Yamazaki J, Miwa Y, Yoshino H, Ikeda T. Comparison of late potentials for 24 hours between Brugada syndrome and arrhythmogenic right ventricular cardiomyopathy using a novel signal-averaging system based on Holter ECG. Circ Arrhythm Electrophysiol. 2012;5:789–95.

Ackerman MJ, Priori SG, Willems S, Berul C, Brugada R, Calkins H, Camm AJ, Ellinor PT, Gollob M, Hamilton R, Hershberger RE, Judge DP, Le Marec H, McKenna WJ, Schulze-Bahr E, Semsarian C, Towbin JA, Watkins H, Wilde A, Wolpert C, Zipes DP, HRS, EHRA. HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies: this document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA). Europace. 2011;13:1077–109.

Adler A. Brugada syndrome: diagnosis, risk stratification, and management. Curr Opin Cardiol. 2016;31:37–45.

Aizawa Y, Takatsuki S, Kaneko Y, Noda T, Katsumata Y, Nishiyama T, Kimura T, Nishiyama N, Fukumoto K, Niwano S, Kurita T, Mitsuhashi T, Kamakura S, Shimizu A, Horie M, Fukuda K. Comparison of circadian, weekly, and seasonal variations of electrical storms and single events of ventricular fibrillation in patients with Brugada syndrome. Int J Cardiol Heart Vasc. 2016;11:104–10.

Akai J, Makita N, Sakurada H, Shirai N, Ueda K, Kitabatake A, Nakazawa K, Kimura A, Hiraoka M. A novel SCN5A mutation associated with idiopathic ventricular fibrillation without typical ECG findings of Brugada syndrome. FEBS Lett. 2000;479:29–34.

Amin AS, Verkerk AO, Bhuiyan ZA, Wilde AA, Tan HL. Novel Brugada syndrome-causing mutation in ion-conducting pore of cardiac Na+ channel does not affect ion selectivity properties. Acta Physiol Scand. 2005;185:291–301.

Amin AS, de Groot EA, Ruijter JM, Wilde AA, Tan HL. Exercise-induced ECG changes in Brugada syndrome. Circ Arrhythm Electrophysiol. 2009;2:531–9.

Andres R, Cader G, Goldman P, Zierler KL. Net potassium movement between resting muscle and plasma in man in the basal state and during the night. J Clin Invest. 1957;36:723–9.

Antzelevitch C, Brugada R. Fever and Brugada syndrome. Pacing Clin Electrophysiol. 2002;25:1537–9.

Antzelevitch C, Brugada P, Borggrefe M, Brugada J, Brugada R, Corrado D, Gussak I, LeMarec H, Nademanee K, Perez Riera AR, Shimizu W, Schulze-Bahr E, Tan H, Wilde A. Brugada syndrome: report of the second consensus conference: endorsed by the Heart Rhythm Society and the European Heart Rhythm Association. Circulation. 2005;111:659–70.

Antzelevitch C, Yan GX, Ackerman MJ, Borggrefe M, Corrado D, Guo J, Gussak I, Hasdemir C, Horie M, Huikuri H, Ma C, Morita H, Nam GB, Sacher F, Shimizu W, Viskin S, Wilde AA. J-Wave syndromes expert consensus conference report: emerging concepts and gaps in knowledge. Heart Rhythm. 2016;13:e295–324.

Bastiaenen R, Cox AT, Castelletti S, Wijeyeratne YD, Colbeck N, Pakroo N, Ahmed H, Bunce N, Anderson L, Moon JC, Prasad S, Sharma S, Behr ER. Late gadolinium enhancement in Brugada syndrome: a marker for subtle underlying cardiomyopathy? Heart Rhythm. 2017;14:583–9.

Belhassen B, Glick A, Viskin S. Efficacy of quinidine in high-risk patients with Brugada syndrome. Circulation. 2004;110:1731–7.

Belhassen B, Rahkovich M, Michowitz Y, Glick A, Viskin S. Management of Brugada syndrome: thirty-three-year experience using electrophysiologically guided therapy with class 1A antiarrhythmic drugs. Circ Arrhythm Electrophysiol. 2015;8:1393–402.

Benito B, Sarkozy A, Mont L, Henkens S, Berruezo A, Tamborero D, Arzamendi D, Berne P, Brugada R, Brugada P, Brugada J. Gender differences in clinical manifestations of Brugada syndrome. J Am Coll Cardiol. 2008;52:1567–73.

Benson DW, Wang DW, Dyment M, Knilans TK, Fish FA, Strieper MJ, Rhodes TH, George AL. Congenital sick sinus syndrome caused by recessive mutations in the cardiac sodium channel gene (SCN5A). J Clin Invest. 2003;112:1019–28.

Bezzina C, Veldkamp MW, van Den Berg MP, Postma AV, Rook MB, Viersma JW, van Langen IM, Tan-Sindhunata G, Bink-Boelkens MT, van Der Hout AH, Mannens MM, Wilde AA. A single Na(+) channel mutation causing both long-QT and Brugada syndromes. Circ Res. 1999;85:1206–13.

Bezzina CR, Barc J, Mizusawa Y, Remme CA, Gourraud JB, Simonet F, Verkerk AO, Schwartz PJ, Crotti L, Dagradi F, Guicheney P, Fressart V, Leenhardt A, Antzelevitch C, Bartkowiak S, Borggrefe M, Schimpf R, Schulze-Bahr E, Zumhagen S, Behr ER, Bastiaenen R, Tfelt-Hansen J, Olesen MS, Kääb S, Beckmann BM, Weeke P, Watanabe H, Endo N, Minamino T, Horie M, Ohno S, Hasegawa K, Makita N, Nogami A, Shimizu W, Aiba T, Froguel P, Balkau B, Lantieri O, Torchio M, Wiese C, Weber D, Wolswinkel R, Coronel R, Boukens BJ, Bézieau S, Charpentier E, Chatel S, Despres A, Gros F, Kyndt F, Lecointe S, Lindenbaum P, Portero V, Violleau J, Gessler M, Tan HL, Roden DM, Christoffels VM, Le Marec H, Wilde AA, Probst V, Schott JJ, Dina C, Redon R. Common variants at SCN5A-SCN10A and HEY2 are associated with Brugada syndrome, a rare disease with high risk of sudden cardiac death. Nat Genet. 2013;45:1044–9.

Boersma LV, Jaarsma W, Jessurun ER, Van Hemel NH, Wever EF. Brugada syndrome: a case report of monomorphic ventricular tachycardia. Pacing Clin Electrophysiol. 2001;24:112–5.

Brugada P, Brugada J. Right bundle branch block, persistent ST segment elevation and sudden cardiac death: a distinct clinical and electrocardiographic syndrome. A multicenter report. J Am Coll Cardiol. 1992;20:1391–6.

Brugada J, Brugada R, Antzelevitch C, Towbin J, Nademanee K, Brugada P. Long-term follow-up of individuals with the electrocardiographic pattern of right bundle-branch block and ST-segment elevation in precordial leads V1 to V3. Circulation. 2002;105:73–8.

Brugada J, Brugada R, Brugada P. Electrophysiologic testing predicts events in Brugada syndrome patients. Heart Rhythm. 2011;8:1595–7.

Brugada J, Pappone C, Berruezo A, et al. Brugada syndrome phenotype elimination by epicardial substrate ablation. Circ Arrhythm Electrophysiol. 2015;8:1373–81.

Calò L, Giustetto C, Martino A, Sciarra L, Cerrato N, Marziali M, Rauzino J, Carlino G, de Ruvo E, Guerra F, Rebecchi M, Lanzillo C, Anselmino M, Castro A, Turreni F, Penco M, Volpe M, Capucci A, Gaita F. A new electrocardiographic marker of sudden death in Brugada syndrome: the S-wave in lead I. J Am Coll Cardiol. 2016;67:1427–40.

Canpolat U, Bayazit Y, Aytemir K. Brugada syndrome unmasked by heat exhaustion. Ann Noninvasive Electrocardiol. 2017;22. https://doi.org/10.1111/anec.12356.

Chen Q, Kirsch GE, Zhang D, Brugada R, Brugada J, Brugada P, Potenza D, Moya A, Borggrefe M, Breithardt G, Ortiz-Lopez R, Wang Z, Antzelevitch C, O'Brien RE, Schulze-

Bahr E, Keating MT, Towbin JA, Wang Q. Genetic basis and molecular mechanism for idiopathic ventricular fibrillation. Nature. 1998;392:293–6.

Chung FP, Raharjo SB, Lin YJ, Chang SL, Lo LW, Hu YF, Tuan TC, Chao TF, Liao JN, Lin CY, Chang YT, Hung Y, Te A, Yamada S, Tasaka H, Wang CT, Chen SA. A novel method to enhance phenotype, epicardial functional substrates, and ventricular tachyarrhythmias in Brugada syndrome. Heart Rhythm. 2017;14:508–17.

Conte G, Kawabata M, de Asmundis C, Taravelli E, Petracca F, Ruggiero D, Caputo ML, Regoli F, Chierchia GB, Chiodini A, Del Bufalo A, Moccetti T, Goya M, Hirao K, Vicentini A, De Ferrari GM, Brugada P, Auricchio A. High rate of subcutaneous implantable cardioverter-defibrillator sensing screening failure in patients with Brugada syndrome: a comparison with other inherited primary arrhythmia syndromes. Europace. 2017. https://doi.org/10.1093/europace/eux009.

Coronel R, Casini S, Koopmann TT, Wilms-Schopman FJ, Verkerk AO, de Groot JR, Bhuiyan Z, Bezzina CR, Veldkamp MW, Linnenbank AC, van der Wal AC, Tan HL, Brugada P, Wilde AA, de Bakker JM. Right ventricular fibrosis and conduction delay in a patient with clinical signs of Brugada syndrome: a combined electrophysiological, genetic, histopathologic, and computational study. Circulation. 2005;112:2769–77.

Crotti L, Marcou CA, Tester DJ, Castelletti S, Giudicessi JR, Torchio M, Medeiros-Domingo A, Simone S, Will ML, Dagradi F, Schwartz PJ, Ackerman MJ. Spectrum and prevalence of mutations involving BrS1- through BrS12-susceptibility genes in a cohort of unrelated patients referred for Brugada syndrome genetic testing: implications for genetic testing. J Am Coll Cardiol. 2012;60:1410–8.

Darbar D, Kannankeril PJ, Donahue BS, Kucera G, Stubblefield T, Haines JL, George AL, Roden DM. Cardiac sodium channel (SCN5A) variants associated with atrial fibrillation. Circulation. 2008;117:1927–35.

Darmon JP, Bettouche S, Deswardt P, Tiger F, Ricard P, Bernasconi F, Saoudi N. Radiofrequency ablation of ventricular fibrillation and multiple right and left atrial tachycardia in a patient with Brugada syndrome. J Interv Card Electrophysiol. 2004;11:205–9.

De Marco S, Giannini C, Chiavaroli V, De Leonibus C, Chiarelli F, Mohn A. Brugada syndrome unmasked by febrile illness in an asymptomatic child. J Pediatr. 2012;161:769–769.e761.

Dumaine R, Towbin JA, Brugada P, Vatta M, Nesterenko DV, Nesterenko VV, Brugada J, Brugada R, Antzelevitch C. Ionic mechanisms responsible for the electrocardiographic phenotype of the Brugada syndrome are temperature dependent. Circ Res. 1999;85:803–9.

Eckardt L, Kirchhof P, Loh P, Schulze-Bahr E, Johna R, Wichter T, Breithardt G, Haverkamp W, Borggrefe M. Brugada syndrome and supraventricular tachyarrhythmias: a novel association? J Cardiovasc Electrophysiol. 2001;12:680–5.

Eckardt L, Probst V, Smits JP, Bahr ES, Wolpert C, Schimpf R, Wichter T, Boisseau P, Heinecke A, Breithardt G, Borggrefe M, LeMarec H, Böcker D, Wilde AA. Long-term prognosis of individuals with right precordial ST-segment-elevation Brugada syndrome. Circulation. 2005;111:257–63.

Ghouse J, Have CT, Skov MW, Andreasen L, Ahlberg G, Nielsen JB, Skaaby T, Olesen SP, Grarup N, Linneberg A, Pedersen O, Vestergaard H, Haunsø S, Svendsen JH, Hansen T, Kanters JK, Olesen MS. Numerous Brugada syndrome-associated genetic variants have no effect on J-point elevation, syncope susceptibility, malignant cardiac arrhythmia, and all-cause mortality. Genet Med. 2017;19:521–8.

Giustetto C, Drago S, Demarchi PG, Dalmasso P, Bianchi F, Masi AS, Carvalho P, Occhetta E, Rossetti G, Riccardi R, Bertona R, Gaita F, Section IAoAaCA-P. Risk stratification of the patients with Brugada type electrocardiogram: a community-based prospective study. Europace. 2009;11:507–13.

Gollob MH, Blier L, Brugada R, Champagne J, Chauhan V, Connors S, Gardner M, Green MS, Gow R, Hamilton R, Harris L, Healey JS, Hodgkinson K, Honeywell C, Kantoch M, Kirsh J, Krahn A, Mullen M, Parkash R, Redfearn D, Rutberg J, Sanatani S, Woo A. Recommendations for the use of genetic testing in the clinical evaluation of inherited cardiac arrhythmias

associated with sudden cardiac death: Canadian Cardiovascular Society/Canadian Heart Rhythm Society joint position paper. Can J Cardiol. 2011;27:232–45.

Haïssaguerre M, Extramiana F, Hocini M, Cauchemez B, Jaïs P, Cabrera JA, Farré J, Farre G, Leenhardt A, Sanders P, Scavée C, Hsu LF, Weerasooriya R, Shah DC, Frank R, Maury P, Delay M, Garrigue S, Clémenty J. Mapping and ablation of ventricular fibrillation associated with long-QT and Brugada syndromes. Circulation. 2003;108:925–8.

Hermida JS, Denjoy I, Clerc J, Extramiana F, Jarry G, Milliez P, Guicheney P, Di Fusco S, Rey JL, Cauchemez B, Leenhardt A. Hydroquinidine therapy in Brugada syndrome. J Am Coll Cardiol. 2004;43:1853–60.

Hoogendijk MG, Potse M, Linnenbank AC, Verkerk AO, den Ruijter HM, van Amersfoorth SC, Klaver EC, Beekman L, Bezzina CR, Postema PG, Tan HL, Reimer AG, van der Wal AC, Ten Harkel AD, Dalinghaus M, Vinet A, Wilde AA, de Bakker JM, Coronel R. Mechanism of right precordial ST-segment elevation in structural heart disease: excitation failure by current-to-load mismatch. Heart Rhythm. 2010;7:238–48.

Huang Z, Patel C, Li W, Xie Q, Wu R, Zhang L, Tang R, Wan X, Ma Y, Zhen W, Gao L, Yan GX. Role of signal-averaged electrocardiograms in arrhythmic risk stratification of patients with Brugada syndrome: a prospective study. Heart Rhythm. 2009;6:1156–62.

Kakishita M, Kurita T, Matsuo K, Taguchi A, Suyama K, Shimizu W, Aihara N, Kamakura S, Yamamoto F, Kobayashi J, Kosakai Y, Ohe T. Mode of onset of ventricular fibrillation in patients with Brugada syndrome detected by implantable cardioverter defibrillator therapy. J Am Coll Cardiol. 2000;36:1646–53.

Kamakura S, Ohe T, Nakazawa K, Aizawa Y, Shimizu A, Horie M, Ogawa S, Okumura K, Tsuchihashi K, Sugi K, Makita N, Hagiwara N, Inoue H, Atarashi H, Aihara N, Shimizu W, Kurita T, Suyama K, Noda T, Satomi K, Okamura H, Tomoike H, Japan BSIi. Long-term prognosis of probands with Brugada-pattern ST-elevation in leads V1-V3. Circ Arrhythm Electrophysiol. 2009;2:495–503.

Kamakura T, Wada M, Ishibashi K, Inoue YY, Miyamoto K, Okamura H, Nagase S, Noda T, Aiba T, Yasuda S, Kusano K. Impact of electrocardiogram screening during drug challenge test for the prediction of T-wave oversensing by a subcutaneous implantable cardioverter defibrillator in patients with Brugada syndrome. Heart Vessels. 2017;32:1277–83.

Kaneko Y, Horie M, Niwano S, Kusano KF, Takatsuki S, Kurita T, Mitsuhashi T, Nakajima T, Irie T, Hasegawa K, Noda T, Kamakura S, Aizawa Y, Yasuoka R, Torigoe K, Suzuki H, Ohe T, Shimizu A, Fukuda K, Kurabayashi M. Electrical storm in patients with Brugada syndrome is associated with early repolarization. Circ Arrhythm Electrophysiol. 2014;7:1122–8.

Kapplinger JD, Tester DJ, Alders M, Benito B, Berthet M, Brugada J, Brugada P, Fressart V, Guerchicoff A, Harris-Kerr C, Kamakura S, Kyndt F, Koopmann TT, Miyamoto Y, Pfeiffer R, Pollevick GD, Probst V, Zumhagen S, Vatta M, Towbin JA, Shimizu W, Schulze-Bahr E, Antzelevitch C, Salisbury BA, Guicheney P, Wilde AA, Brugada R, Schott JJ, Ackerman MJ. An international compendium of mutations in the SCN5A-encoded cardiac sodium channel in patients referred for Brugada syndrome genetic testing. Heart Rhythm. 2010;7:33–46.

Kasanuki H, Ohnishi S, Ohtuka M, Matsuda N, Nirei T, Isogai R, Shoda M, Toyoshima Y, Hosoda S. Idiopathic ventricular fibrillation induced with vagal activity in patients without obvious heart disease. Circulation. 1997;95:2277–85.

Kaufman ES. Genetic testing in Brugada syndrome. J Am Coll Cardiol. 2012;60:1419–20.

Kawata H, Morita H, Yamada Y, Noda T, Satomi K, Aiba T, Isobe M, Nagase S, Nakamura K, Fukushima Kusano K, Ito H, Kamakura S, Shimizu W. Prognostic significance of early repolarization in inferolateral leads in Brugada patients with documented ventricular fibrillation: a novel risk factor for Brugada syndrome with ventricular fibrillation. Heart Rhythm. 2013;10:1161–8.

Kinoshita K, Takahashi H, Hata Y, Nishide K, Kato M, Fujita H, Yoshida S, Murai K, Mizumaki K, Nishida K, Yamaguchi Y, Kano M, Tabata T, Nishida N. SCN5A(K817E), a novel Brugada syndrome-associated mutation that alters the activation gating of NaV1.5 channel. Heart Rhythm. 2016;13:1113–20.

Krittayaphong R, Veerakul G, Nademanee K, Kangkagate C. Heart rate variability in patients with Brugada syndrome in Thailand. Eur Heart J. 2003;24:1771–8.

Kum LC, Fung JW, Sanderson JE. Brugada syndrome unmasked by febrile illness. Pacing Clin Electrophysiol. 2002;25:1660–1.

Kyndt F, Probst V, Potet F, Demolombe S, Chevallier JC, Baro I, Moisan JP, Boisseau P, Schott JJ, Escande D, Le Marec H. Novel SCN5A mutation leading either to isolated cardiac conduction defect or Brugada syndrome in a large French family. Circulation. 2001;104:3081–6.

Le Scouarnec S, Karakachoff M, Gourraud JB, Lindenbaum P, Bonnaud S, Portero V, Duboscq-Bidot L, Daumy X, Simonet F, Teusan R, Baron E, Violleau J, Persyn E, Bellanger L, Barc J, Chatel S, Martins R, Mabo P, Sacher F, Haïssaguerre M, Kyndt F, Schmitt S, Bézieau S, Le Marec H, Dina C, Schott JJ, Probst V, Redon R. Testing the burden of rare variation in arrhythmia-susceptibility genes provides new insights into molecular diagnosis for Brugada syndrome. Hum Mol Genet. 2015;24:2757–63.

Letsas KP, Sacher F, Probst V, Weber R, Knecht S, Kalusche D, Haïssaguerre M, Arentz T. Prevalence of early repolarization pattern in inferolateral leads in patients with Brugada syndrome. Heart Rhythm. 2008;5:1685–9.

Makimoto H, Nakagawa E, Takaki H, Yamada Y, Okamura H, Noda T, Satomi K, Suyama K, Aihara N, Kurita T, Kamakura S, Shimizu W. Augmented ST-segment elevation during recovery from exercise predicts cardiac events in patients with Brugada syndrome. J Am Coll Cardiol. 2010;56:1576–84.

Matsuo K, Kurita T, Inagaki M, Kakishita M, Aihara N, Shimizu W, Taguchi A, Suyama K, Kamakura S, Shimomura K. The circadian pattern of the development of ventricular fibrillation in patients with Brugada syndrome. Eur Heart J. 1999;20:465–70.

Maury P, Rollin A, Sacher F, Gourraud JB, Raczka F, Pasquié JL, Duparc A, Mondoly P, Cardin C, Delay M, Derval N, Chatel S, Bongard V, Sadron M, Denis A, Davy JM, Hocini M, Jaïs P, Jesel L, Haïssaguerre M, Probst V. Prevalence and prognostic role of various conduction disturbances in patients with the Brugada syndrome. Am J Cardiol. 2013;112:1384–9.

Maury P, Sacher F, Gourraud JB, Pasquié JL, Raczka F, Bongard V, Duparc A, Mondoly P, Sadron M, Chatel S, Derval N, Denis A, Cardin C, Davy JM, Hocini M, Jaïs P, Jesel L, Carrié D, Galinier M, Haïssaguerre M, Probst V, Rollin A. Increased Tpeak-Tend interval is highly and independently related to arrhythmic events in Brugada syndrome. Heart Rhythm. 2015;12:2469–76.

Meregalli PG, Tan HL, Probst V, Koopmann TT, Tanck MW, Bhuiyan ZA, Sacher F, Kyndt F, Schott JJ, Albuisson J, Mabo P, Bezzina CR, Le Marec H, Wilde AA. Type of SCN5A mutation determines clinical severity and degree of conduction slowing in loss-of-function sodium channelopathies. Heart Rhythm. 2009;6:341–8.

Miyazaki T, Mitamura H, Miyoshi S, Soejima K, Aizawa Y, Ogawa S. Autonomic and antiarrhythmic drug modulation of ST segment elevation in patients with Brugada syndrome. J Am Coll Cardiol. 1996;27:1061–70.

Mizumaki K, Fujiki A, Nishida K, Iwamoto J, Sakamoto T, Sakabe M, Tsuneda T, Sugao M, Inoue H. Postprandial augmentation of bradycardia-dependent ST elevation in patients with Brugada syndrome. J Cardiovasc Electrophysiol. 2007;18:839–44.

Mizusawa Y, Sakurada H, Nishizaki M, Hiraoka M. Effects of low-dose quinidine on ventricular tachyarrhythmias in patients with Brugada syndrome: low-dose quinidine therapy as an adjunctive treatment. J Cardiovasc Pharmacol. 2006;47:359–64.

Morita H, Kusano-Fukushima K, Nagase S, Fujimoto Y, Hisamatsu K, Fujio H, Haraoka K, Kobayashi M, Morita ST, Nakamura K, Emori T, Matsubara H, Hina K, Kita T, Fukatani M, Ohe T. Atrial fibrillation and atrial vulnerability in patients with Brugada syndrome. J Am Coll Cardiol. 2002a;40:1437–44.

Morita H, Nagase S, Kusano K, Ohe T. Spontaneous T wave alternans and premature ventricular contractions during febrile illness in a patient with Brugada syndrome. J Cardiovasc Electrophysiol. 2002b;13:816–8.

Morita H, Kusano KF, Miura D, Nagase S, Nakamura K, Morita ST, Ohe T, Zipes DP, Wu J. Fragmented QRS as a marker of conduction abnormality and a predictor of prognosis of Brugada syndrome. Circulation. 2008;118:1697–704.

Murakami M, Nakamura K, Kusano KF, Morita H, Nakagawa K, Tanaka M, Tada T, Toh N, Nishii N, Nagase S, Hata Y, Kohno K, Miura D, Ohe T, Ito H. Efficacy of low-dose bepridil for prevention of ventricular fibrillation in patients with Brugada syndrome with and without SCN5A mutation. J Cardiovasc Pharmacol. 2010;56:389–95.

Nademanee K, Veerakul G, Nimmannit S, Chaowakul V, Bhuripanyo K, Likittanasombat K, Tunsanga K, Kuasirikul S, Malasit P, Tansupasawadikul S, Tatsanavivat P. Arrhythmogenic marker for the sudden unexplained death syndrome in Thai men. Circulation. 1997;96:2595–600.

Nademanee K, Veerakul G, Mower M, Likittanasombat K, Krittayapong R, Bhuripanyo K, Sitthisook S, Chaothawee L, Lai MY, Azen SP. Defibrillator versus beta-blockers for unexplained death in Thailand (DEBUT): a randomized clinical trial. Circulation. 2003;107:2221–6.

Nademanee K, Veerakul G, Chandanamattha P, Chaothawee L, Ariyachaipanich A, Jirasirirojanakorn K, Likittanasombat K, Bhuripanyo K, Ngarmukos T. Prevention of ventricular fibrillation episodes in Brugada syndrome by catheter ablation over the anterior right ventricular outflow tract epicardium. Circulation. 2011;123:1270–9.

Nademanee K, Raju H, de Noronha SV, Papadakis M, Robinson L, Rothery S, Makita N, Kowase S, Boonmee N, Vitayakritsirikul V, Ratanarapee S, Sharma S, van der Wal AC, Christiansen M, Tan HL, Wilde AA, Nogami A, Sheppard MN, Veerakul G, Behr ER. Fibrosis, Connexin-43, and conduction abnormalities in the Brugada syndrome. J Am Coll Cardiol. 2015;66:1976–86.

Nagase S, Kusano KF, Morita H, Fujimoto Y, Kakishita M, Nakamura K, Emori T, Matsubara H, Ohe T. Epicardial electrogram of the right ventricular outflow tract in patients with the Brugada syndrome: using the epicardial lead. J Am Coll Cardiol. 2002;39:1992–5.

Nakagawa E, Takagi M, Tatsumi H, Yoshiyama M. Successful radiofrequency catheter ablation for electrical storm of ventricular fibrillation in a patient with Brugada syndrome. Circ J. 2008;72:1025–9.

Nakajima T, Kaneko Y, Saito A, Ota M, Iijima T, Kurabayashi M. Enhanced fast-inactivated state stability of cardiac sodium channels by a novel voltage sensor SCN5A mutation, R1632C, as a cause of atypical Brugada syndrome. Heart Rhythm. 2015;12:2296–304.

Nimmannit S, Malasit P, Chaovakul V, Susaengrat W, Vasuvattakul S, Nilwarangkur S. Pathogenesis of sudden unexplained nocturnal death (lai tai) and endemic distal renal tubular acidosis. Lancet. 1991;338:930–2.

Nogami A, Nakao M, Kubota S, Sugiyasu A, Doi H, Yokoyama K, Yumoto K, Tamaki T, Kato K, Hosokawa N, Sagai H, Nakamura H, Nitta J, Yamauchi Y, Aonuma K. Enhancement of J-ST-segment elevation by the glucose and insulin test in Brugada syndrome. Pacing Clin Electrophysiol. 2003;26:332–7.

Ohgo T, Okamura H, Noda T, Satomi K, Suyama K, Kurita T, Aihara N, Kamakura S, Ohe T, Shimizu W. Acute and chronic management in patients with Brugada syndrome associated with electrical storm of ventricular fibrillation. Heart Rhythm. 2007;4:695–700.

Ohkubo K, Nakai T, Watanabe I. Alcohol-induced ventricular fibrillation in a case of Brugada syndrome. Europace. 2013;15:1058.

Olde Nordkamp LR, Conte G, Rosenmöller BR, Warnaars JL, Tan HL, Caputo ML, Regoli F, Moccetti T, Auricchio A, Knops RE, Wilde AA. Brugada syndrome and the subcutaneous implantable cardioverter-defibrillator. J Am Coll Cardiol. 2016;68:665–6.

Olson TM, Michels VV, Ballew JD, Reyna SP, Karst ML, Herron KJ, Horton SC, Rodeheffer RJ, Anderson JL. Sodium channel mutations and susceptibility to heart failure and atrial fibrillation. JAMA. 2005;293:447–54.

Paul M, Gerss J, Schulze-Bahr E, Wichter T, Vahlhaus C, Wilde AA, Breithardt G, Eckardt L. Role of programmed ventricular stimulation in patients with Brugada syndrome: a meta-analysis of worldwide published data. Eur Heart J. 2007;28:2126–33.

Porres JM, Brugada J, Urbistondo V, García F, Reviejo K, Marco P. Fever unmasking the Brugada syndrome. Pacing Clin Electrophysiol. 2002;25:1646–8.

Postema PG. About Brugada syndrome and its prevalence. Europace. 2012;14:925–8.

Postema PG, Wolpert C, Amin AS, Probst V, Borggrefe M, Roden DM, Priori SG, Tan HL, Hiraoka M, Brugada J, Wilde AA. Drugs and Brugada syndrome patients: review of the literature, recommendations, and an up-to-date website (www.brugadadrugs.org). Heart Rhythm. 2009;6:1335–41.

Priori SG, Gasparini M, Napolitano C, Della Bella P, Ottonelli AG, Sassone B, Giordano U, Pappone C, Mascioli G, Rossetti G, De Nardis R, Colombo M. Risk stratification in Brugada syndrome: results of the PRELUDE (PRogrammed ELectrical stimUlation preDictive valuE) registry. J Am Coll Cardiol. 2012;59:37–45.

Priori SG, Wilde AA, Horie M, Cho Y, Behr ER, Berul C, Blom N, Brugada J, Chiang CE, Huikuri H, Kannankeril P, Krahn A, Leenhardt A, Moss A, Schwartz PJ, Shimizu W, Tomaselli G, Tracy C. HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes: document endorsed by HRS, EHRA, and APHRS in May 2013 and by ACCF, AHA, PACES, and AEPC in June 2013. Heart Rhythm. 2013;10:1932–63.

Probst V, Denjoy I, Meregalli PG, Amirault JC, Sacher F, Mansourati J, Babuty D, Villain E, Victor J, Schott JJ, Lupoglazoff JM, Mabo P, Veltmann C, Jesel L, Chevalier P, Clur SA, Haissaguerre M, Wolpert C, Le Marec H, Wilde AA. Clinical aspects and prognosis of Brugada syndrome in children. Circulation. 2007;115:2042–8.

Probst V, Wilde AA, Barc J, Sacher F, Babuty D, Mabo P, Mansourati J, Le Scouarnec S, Kyndt F, Le Caignec C, Guicheney P, Gouas L, Albuisson J, Meregalli PG, Le Marec H, Tan HL, Schott JJ. SCN5A mutations and the role of genetic background in the pathophysiology of Brugada syndrome. Circ Cardiovasc Genet. 2009;2:552–7.

Probst V, Veltmann C, Eckardt L, Meregalli PG, Gaita F, Tan HL, Babuty D, Sacher F, Giustetto C, Schulze-Bahr E, Borggrefe M, Haissaguerre M, Mabo P, Le Marec H, Wolpert C, Wilde AA. Long-term prognosis of patients diagnosed with Brugada syndrome: results from the FINGER Brugada Syndrome Registry. Circulation. 2010;121:635–43.

Rattanawong P, Vutthikraivit W, Charoensri A, Jongraksak T, Prombandankul A, Kanjanahattakij N, et al. Fever-induced Brugada syndrome is more common than previously suspected: a cross-sectional study from an endemic area. Ann Noninvasive Electrocardiol. 2016;21(2):136–41.

Rodríguez-Mañero M, Namdar M, Sarkozy A, Casado-Arroyo R, Ricciardi D, de Asmundis C, Chierchia GB, Wauters K, Rao JY, Bayrak F, Van Malderen S, Brugada P. Prevalence, clinical characteristics and management of atrial fibrillation in patients with Brugada syndrome. Am J Cardiol. 2013;111:362–7.

Rodríguez-Mañero M, Sacher F, de Asmundis C, Maury P, Lambiase PD, Sarkozy A, Probst V, Gandjbakhch E, Castro-Hevia J, Saenen J, Fukushima Kusano K, Rollin A, Arbelo E, Valderrábano M, Arias MA, Mosquera-Pérez I, Schilling R, Chierchia GB, García-Bolao I, García-Seara J, Hernandez-Ojeda J, Kamakura T, Martínez-Sande L, González-Juanatey JR, Haïssaguerre M, Brugada J, Brugada P. Monomorphic ventricular tachycardia in patients with Brugada syndrome: a multicenter retrospective study. Heart Rhythm. 2016;13:669–82.

Sacher F, Probst V, Iesaka Y, Jacon P, Laborderie J, Mizon-Gérard F, Mabo P, Reuter S, Lamaison D, Takahashi Y, O'Neill MD, Garrigue S, Pierre B, Jaïs P, Pasquié JL, Hocini M, Salvador-Mazenq M, Nogami A, Amiel A, Defaye P, Bordachar P, Boveda S, Maury P, Klug D, Babuty D, Haïssaguerre M, Mansourati J, Clémenty J, Le Marec H. Outcome after implantation of a cardioverter-defibrillator in patients with Brugada syndrome: a multicenter study. Circulation. 2006;114:2317–24.

Sakabe M, Fujiki A, Tsuneda T, Nishida K, Sugao M, Mizumaki K, Inoue H. Brugada syndrome occurring in an identical twin: a case report. J Cardiol. 2002a;40:111–5.

Sakabe M, Fujiki A, Tsuneda T, Nishida K, Sugao M, Mizumaki K, Inoue H. Brugada syndrome occurring in an identical twin: a case report. J Cardiol. 2002b;40:111–5.

Sarkozy A, Boussy T, Kourgiannides G, Chierchia GB, Richter S, De Potter T, Geelen P, Wellens F, Spreeuwenberg MD, Brugada P. Long-term follow-up of primary prophylactic implantable cardioverter-defibrillator therapy in Brugada syndrome. Eur Heart J. 2007;28:334–44.

Saura D, García-Alberola A, Carrillo P, Pascual D, Martínez-Sánchez J, Valdés M. Brugada-like electrocardiographic pattern induced by fever. Pacing Clin Electrophysiol. 2002;25:856–9.

Shimada M, Miyazaki T, Miyoshi S, Soejima K, Hori S, Mitamura H, Ogawa S. Sustained monomorphic ventricular tachycardia in a patient with Brugada syndrome. Jpn Circ J. 1996;60:364–70.

Shimizu W, Matsuo K, Takagi M, Tanabe Y, Aiba T, Taguchi A, Suyama K, Kurita T, Aihara N, Kamakura S. Body surface distribution and response to drugs of ST segment elevation in Brugada syndrome: clinical implication of eighty-seven-lead body surface potential mapping and its application to twelve-lead electrocardiograms. J Cardiovasc Electrophysiol. 2000;11:396–404.

Shirai N, Makita N, Sasaki K, Yokoi H, Sakuma I, Sakurada H, Akai J, Kimura A, Hiraoka M, Kitabatake A. A mutant cardiac sodium channel with multiple biophysical defects associated with overlapping clinical features of Brugada syndrome and cardiac conduction disease. Cardiovasc Res. 2002;53:348–54.

Skinner JR, Chung SK, Nel CA, Shelling AN, Crawford JR, McKenzie N, Pinnock R, French JK, Rees MI. Brugada syndrome masquerading as febrile seizures. Pediatrics. 2007;119:e1206–11.

Steven D, Roberts-Thomson KC, Inada K, Seiler J, Koplan BA, Tedrow UB, Sweeney MO, Epstein LE, Stevenson WG. Long-term follow-up in patients with presumptive Brugada syndrome treated with implanted defibrillators. J Cardiovasc Electrophysiol. 2011;22:1115–9.

Szél T, Antzelevitch C. Abnormal repolarization as the basis for late potentials and fractionated electrograms recorded from epicardium in experimental models of Brugada syndrome. J Am Coll Cardiol. 2014;63:2037–45.

Takagi M, Yokoyama Y, Aonuma K, Aihara N, Hiraoka M, Investigators JIVFSJ-I. Clinical characteristics and risk stratification in symptomatic and asymptomatic patients with Brugada syndrome: multicenter study in Japan. J Cardiovasc Electrophysiol. 2007;18:1244–51.

Tan HL, Bink-Boelkens MT, Bezzina CR, Viswanathan PC, Beaufort-Krol GC, van Tintelen PJ, van den Berg MP, Wilde AA, Balser JR. A sodium-channel mutation causes isolated cardiac conduction disease. Nature. 2001;409:1043–7.

Tanaka H, Kinoshita O, Uchikawa S, Kasai H, Nakamura M, Izawa A, Yokoseki O, Kitabayashi H, Takahashi W, Yazaki Y, Watanabe N, Imamura H, Kubo K. Successful prevention of recurrent ventricular fibrillation by intravenous isoproterenol in a patient with Brugada syndrome. Pacing Clin Electrophysiol. 2001;24:1293–4.

Tokioka K, Kusano KF, Morita H, Miura D, Nishii N, Nagase S, Nakamura K, Kohno K, Ito H, Ohe T. Electrocardiographic parameters and fatal arrhythmic events in patients with Brugada syndrome: combination of depolarization and repolarization abnormalities. J Am Coll Cardiol. 2014;63:2131–8.

Tsuchiya T, Ashikaga K, Honda T, Arita M. Prevention of ventricular fibrillation by cilostazol, an oral phosphodiesterase inhibitor, in a patient with Brugada syndrome. J Cardiovasc Electrophysiol. 2002;13:698–701.

Valdivia CR, Tester DJ, Rok BA, Porter CB, Munger TM, Jahangir A, Makielski JC, Ackerman MJ. A trafficking defective, Brugada syndrome-causing SCN5A mutation rescued by drugs. Cardiovasc Res. 2004;62:53–62.

Vatta M, Dumaine R, Varghese G, Richard TA, Shimizu W, Aihara N, Nademanee K, Brugada R, Brugada J, Veerakul G, Li H, Bowles NE, Brugada P, Antzelevitch C, Towbin JA. Genetic and biophysical basis of sudden unexplained nocturnal death syndrome (SUNDS), a disease allelic to Brugada syndrome. Hum Mol Genet. 2002;11:337–45.

Veerakul G, Nademanee K. Brugada syndrome: two decades of progress. Circ J. 2012;76:2713–22.

Veerakul G, Chaothawee L, Nademanee K. Usefulness of positioning ECG leads at V1-3 at higher intercostal spaces to detect Brugada syndrome. Circulation. 2000;102(Suppl):18.

Veerakul G, Camblock J, Schwab M, Nademanee K. Low mortality rate among asymptomatic Brugada syndrome patients: a multi-center control-randomized study comparing ICD versus no-ICD treatment. Circulation. 2008;118:S982.

Viskin S, Rogowski O. Asymptomatic Brugada syndrome: a cardiac ticking time-bomb? Europace. 2007;9:707–10.

Viskin S, Antzelevitch C, Márquez MF, Belhassen B. Quinidine: a valuable medication joins the list of 'endangered species'. Europace. 2007;9:1105–6.

Wang Q, Shen J, Splawski I, Atkinson D, Li Z, Robinson JL, Moss AJ, Towbin JA, Keating MT. SCN5A mutations associated with an inherited cardiac arrhythmia, long QT syndrome. Cell. 1995;80:805–11.

Wilde AA, Antzelevitch C, Borggrefe M, Brugada J, Brugada R, Brugada P, Corrado D, Hauer RN, Kass RS, Nademanee K, Priori SG, Towbin JA, Cardiology SGotMBoAotESo. Proposed diagnostic criteria for the Brugada syndrome: consensus report. Circulation. 2002;106:2514–9.

Wilde AA, Postema PG, Di Diego JM, Viskin S, Morita H, Fish JM, Antzelevitch C. The pathophysiological mechanism underlying Brugada syndrome: depolarization versus repolarization. J Mol Cell Cardiol. 2010;49:543–53.

Yan GX, Antzelevitch C. Cellular basis for the Brugada syndrome and other mechanisms of arrhythmogenesis associated with ST-segment elevation. Circulation. 1999;100:1660–6.

Zhang P, Tung R, Zhang Z, et al. Characterization of the epicardial substrate for catheter ablation of Brugada syndrome. Heart Rhythm. 2016;11:2151–8.

Zumhagen S, Zeidler EM, Stallmeyer B, Ernsting M, Eckardt L, Schulze-Bahr E. Tpeak-Tend interval and Tpeak-Tend/QT ratio in patients with Brugada syndrome. Europace. 2016;18:1866–72.