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Brugada Syndrome

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Brugada syndrome (BrS) has originally been described as an autosomal-dominant inherited arrhythmic disorder characterized by ST elevation with successive negative T wave in the right precordial leads without structural cardiac abnormalities.[1,2] Patients are at risk for sudden cardiac death (SCD) due to ventricular fibrillation (VF). Since 1953, the ECG pattern similar to coved-type ST-segment elevation was reported as a normal variant in the healthy population or related to VF with structural abnormality,[3–5] but as a distinct disease entity, Brugada and Brugada[1] were the first to report 8 patients with VF, right bundle branch block, and ST-segment elevation on 12-lead ECG. Later, structural changes were reported in an explanted heart and by biopsy specimens in a small number of cases,[6,7] potentially opening up the discussion of who actually described this disease entity first.[8]

Besides this dispute,[8] BrS has been the subject of a number of controversies with regard to its pathophysiology[9]; the prognosis of asymptomatic individuals and the best way to establish their risk[10,11]; and the causal role of genetic variants, including the role of sodium channel mutations.[12] On the basis of the current knowledge acquired in the past 2 decades, these topics and others related to exciting new treatment options[13] are addressed in this review.

Genetic Background

The first putative causal mutations were found in *SCN5A* in 1998, which encodes for the α-subunit of the sodium channel.[14] Since then, >100 *SCN5A* mutations have been reported in BrS and currently represent the most common genotype, which is inherited as an autosomal-dominant trait with incomplete penetrance.[15] The reported mutations include missense mutation, nonsense mutation, nucleotide insertion/deletion (which may alter mRNA splicing or create a stop codon by shifting the open reading frame), and splice site mutation.

Functional studies of an *SCN5A* mutation in BrS using heterologous expression systems revealed loss of function of the sodium channel, which impairs the fast upstroke in phase 0 of the action potential (AP) and leads to conduction slowing in the heart. Loss of function occurs because of decreased expression of $Na_v1.5$ proteins in sarcolemma,[16] expression of nonfunctional channels,[17] or altered gating properties (delayed activation, earlier inactivation, faster inactivation, enhanced slow inactivation, and delayed recovery from inactivation).[18–22]

The type of *SCN5A* mutation may affect the phenotype. We reported in 147 patients with BrS and progressive cardiac conduction disease that *SCN5A* mutations leading to premature truncation of the $Na_v1.5$ protein or missense mutation with >90% peak sodium current (I_{Na}) reduction developed a more severe phenotype (syncope, longer PR interval at baseline, longer PR and QRS interval after a drug challenge test) than the missense mutation with ≤90% peak I_{Na} reduction.[23] Noticeably, not all *SCN5A* mutations in BrS have undergone functional analysis, and besides, a 2% to 5% background rate of rare variants was reported in healthy subjects.[24] *SCN5A* mutations in BrS are also known with incomplete penetrance and variable expressivity. Thus, the presence of an *SCN5A* mutation for the consequence of phenotype needs careful interpretation.

On the basis of this wealth of data, all obtained from single patients and small families, there is little doubt that loss-of-function sodium channel mutations play an important role in BrS. Yet, sound (classical) genetic linkage to establish a causal role for *SCN5A* beyond any doubt is lacking. The only exception is strong linkage in a large family with an overlap syndrome (discussed later in this article) in whom more abnormalities than just the Brugada signature sign were present.[18] The intriguing question of whether *SCN5A* loss-of-function variants are causal or act as a strong modifier, both meeting each other somewhere, however, has recently been addressed in a study on large *SCN5A*-related BrS families.[12] In 5 of 13 families with >5 clinically affected individuals, there appeared to be 1 or 2 clinically affected individuals without the familial *SCN5A* mutation.[12] Accordingly, a role of the involved *SCN5A* mutations, all of which were definitely linked to conduction abnormalities, as the sole factor in determining the Brugada phenotype should be questioned[12] and ought to be reconsidered.

SCN5A mutations not only may cause BrS, but also may lead to other diseases. Indeed, *SCN5A* mutations are implied in long-QT-syndrome type 3, progressive cardiac conduction disease, sick sinus syndrome, or combinations of these[25–27]; congenital atrial standstill; or dilated cardiomyopathy.[28–31]

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A single mutation of *SCN5A* can lead to several phenotypes in the same family or in a single patient, such as BrS, long-QT-syndrome type 3, sick sinus syndrome, and a variable degree of conduction disturbance (first degree to complete AV block) known as overlap syndrome. The first report was in 1999 on a single mutation leading to BrS, generalized conduction disease, and long-QT-syndrome type 3, a manifestation of both loss and gain of function of sodium channel.[18] There have been more reports thereafter on overlap syndromes.[32–34]

The genotype-phenotype relationship of an *SCN5A* mutation can be modified by the genetic background of an individual. H558R, an *SCN5A* polymorphism, was shown to modify the electrophysiological property of a BrS/related mutant sodium channel.[35] In patients of Asian origin, *SCN5A* promoter polymorphisms in a haplotype variant with a relatively high prevalence were reported to lead to a variable phenotype of cardiac conduction.[36] A study using transgenic mice with different strains (129P2 and FVB/N carrying *SCN5A*$^{1798insD/+}$) showed that low to undetectable sodium channel auxiliary subunit β4 expression levels in the ventricles of 129P2 mice led to more slow conduction in the right ventricle compared with that seen in FVB/N mice.[37]

Putative causal mutations were also found in calcium channel genes (*CACNA1C*, *CACNB2b*, *CACNA2D1*); sodium channel β-subunit genes (*SCN1B*, *SCN3B*); glycereol-3 phosphate dehydrogenase 1-like enzyme (*GPD1L*) and *MOG1*, which affects trafficking of sodium channels; and in genes that affect transient outward current (I_{to}) (*KCNE3*, *KCND3*, *KCNE5*) in single patients and families with BrS.[38–46] In basic electrophysiological studies, mutations in *CACNA1C* and *CACNB2b* showed loss of function of basal *L*-type calcium *current* ($I_{Ca,L}$); a mutation in *SCN1B*, *SCN3B*, *GPD1L*, or *MOG1* led to loss of function of I_{Na}; and a mutation in *KCNE3*, *KCND3*, or *KCNE5* to gain of function of I_{to}. Mutations in *CACNA1C* and *CACNB2b* are reported to contribute to 11.5% of BrS, where patients generally present with shorter-than-normal QT intervals. The other genes are rarely found.[24] Until now, *GPD1L* is the only gene with sound genetic linkage, and all others have been identified in only single patients or in small families through candidate gene analysis. This is an important limitation and deserves further study before genes are inferred in the pathogenesis of BrS or any other disease entity.[47]

There seems to be no role as of yet for genetic (or other molecular) markers in risk stratification.[48] Carriers of a BrS-related sodium channel variant have longer conduction intervals than patients with BrS without a sodium channel variant, and within the sodium channel cohort, some variants associate with more-significant conduction disease than others.[23]

Clinical Presentation

Demographic Data

The most severe clinical symptom in BrS is SCD due to VF, which can be the first manifestation. Some patients present with syncope or can be asymptomatic for life. The mean age of patients with VF episodes is 41±15 years. VF episodes occur predominantly in men, who carry a 5.5-fold risk of SCD compared with women, but arrhythmic events may occur from age 2 days to 84 years.[49] BrS is also known as one of the causes for sudden infant death syndrome or SCD in young children.[15,50]

The prevalence of BrS appears to be low in the general population. According to recent studies in Europe, the incidence of sudden death in the general population (age 7–64 years) is 1.34 per 100 000 per year,[51] and ≈5% show no structural heart abnormality.[52] Extensive familial examination of such cases may unmask inherited cardiomyopathies or inherited arrhythmia syndromes, including BrS, in 40% to 53% of tested families.[53,54] The prevalence of Brugada ECG is higher in Asia than in the United States and Europe (Figure 1).[55–80] Type 1 ECG appears more frequently in Asia (0%–0.36%)[55–66] and Europe (0%–0.25%)[67–74] than in the United States (0.03%).[75–79] Type 2 and type 3 ECG is more prevalent in Asia (0.12%–2.23%)[56–66] than in Europe (0.0%–0.6%)[67–74] or the United States (0.02%).[76–79] The low prevalence of Brugada-type ECG in the United States may be explained by different ethnic backgrounds among the studies. For example, the study by Patel et al[79] included subjects with Hispanic (45%) and African (35%) origin, whereas most other studies were performed in white or Asian populations. Of note, there are scarcely any data in subjects of African origin. The prevalence of type 1 ECG in children is reported to be 0.005%, which is much lower than in the adult population.[81]

Arrhythmic events are observed at rest or while asleep, most frequently from 12 AM to 6 AM, less frequently in the evening, and the least during the daytime.[82] Vagal tone might play a role in arrhythmic events.[83–86] Fever is a very important factor for ECG changes and successive VF (Figure 2).[49,87] Children were reported to manifest coved-type ST elevation during fever quite frequently.[50]

Atrial fibrillation is prevalent and observed in 11% to 14% of patients with BrS.[88,89] Supraventricular tachycardia may be observed and, rarely, monomorphic ventricular tachycardia (VT).[2,90] Because tachyarrhythmia can trigger inappropriate implantable cardioverter-defibrillator (ICD) shocks, careful ICD programming is necessary. In the case of bradycardia, sick sinus syndrome, or AV block has been reported as an overlap syndrome in BrS with *SCN5A* mutations.[27,91]

Typical ECG and Diagnosis

The diagnostic criteria of BrS consist of 2 parts: (1) detection of the typical ECG abnormality and (2) clinical characteristics.[49] Coved-type ST-segment elevation and negative T wave in the right precordial leads (Figure 3) with or without a drug challenge test in the 12-lead ECG is the hallmark of diagnosis. In conjunction with the ECG abnormality, 1 of the following criteria is necessary: (1) a history of VT/VF, (2) a family history of SCD, (3) a family history of coved-type ECG, (4) agonal respiration during sleep, or (5) inducibility of VT/VF during electrophysiological study. Importantly, the aforementioned criteria have not been proven to be good risk factors, except for a history of VT/VF. These details are discussed in the Risk Stratification section of this article.

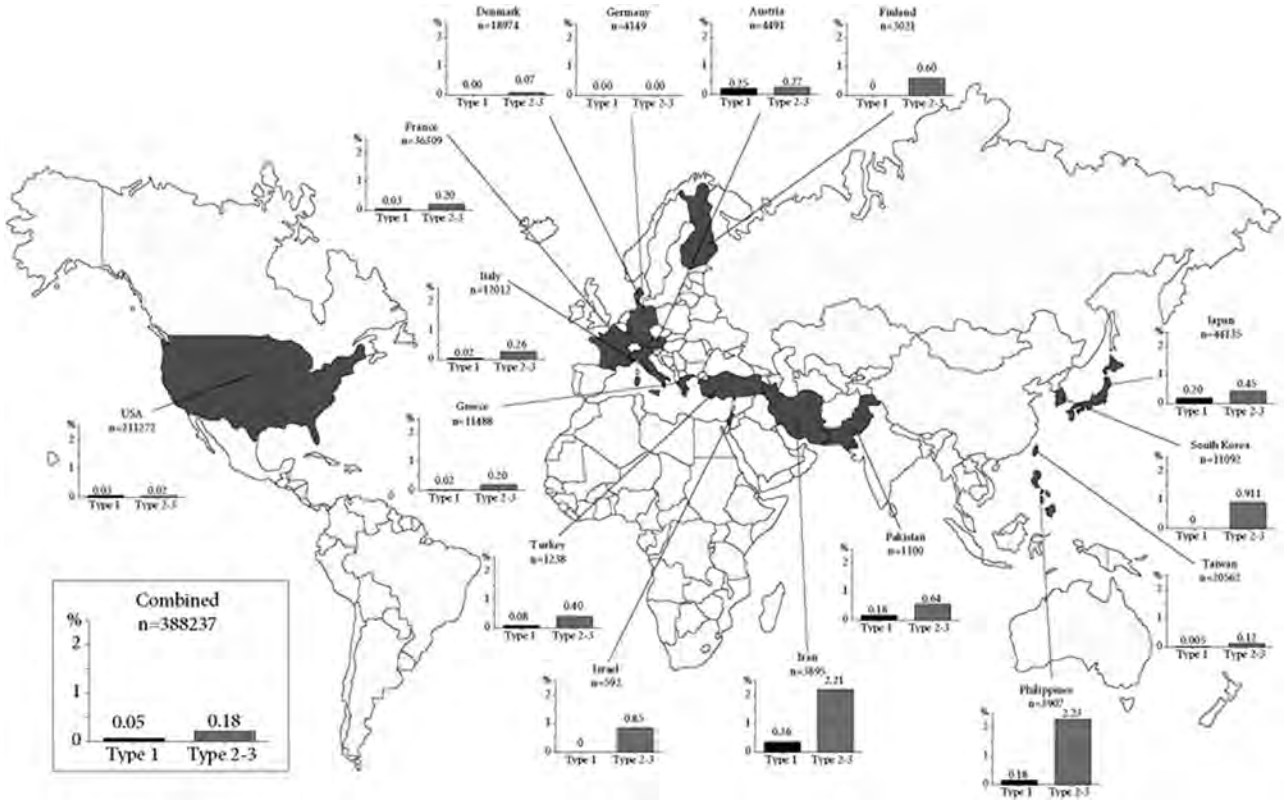

Figure 1. Prevalence of Brugada syndrome ECG is shown on the world map. Overall, type 1 and 2 Brugada ECG is more frequently observed in Asia than in Europe or the United States.

More-recent studies have shown the diagnostic value of the ECG recordings in the upper precordial leads[92] or the manifestation of coved-type ST-segment elevation in inferolateral leads in BrS.[93] These manifestations have not been addressed in the consensus reports,[2,49] which probably need to be updated.

As the magnitude of ST-segment elevation fluctuates,[94] in cases with suspicion of BrS without a diagnostic ECG, a drug challenge test is performed. Sodium channel blockers shown in the Table are used to unmask type 1 ECG. These drugs create additional conduction delay between the other part of the ventricles and the right ventricular outflow tract (RVOT) (the depolarization theory) or induce the transmural gradient of AP by shortening AP more in the RVOT epicardium than endocardium (the repolarization theory), which, theoretically, both lead to the manifestation of coved-type ECG.[95] Procainamide or flecainide may lead to false-negative results, as procainamide creates less conduction delay because it blocks less I_{Na} compared to other sodium channel blockers[96] and flecainide induces less ST-segment elevation presumably because of its stronger I_{to} blocking effect (less shortening of AP in the RVOT epicardium) (see the Mechanism of Ventricular Arrhythmia section of this article).[97] Close monitoring with continuous ECG recording and full equipment for resuscitation is necessary in every test. The infusion of a sodium channel blocker has to be terminated when a prolongation of QRS width of ≥130% of the baseline or premature ventricular stimulation is observed. Electrodes attached to the upper-right precordial leads are useful for diagnosis.[49,98] A full stomach test can unmask type 1 ECG.[99]

Spontaneous type 1 ECG may be exclusively observed preceding or soon after the cardiac events.[83,100,101] In male patients, testosterone appears to affect the level of ST-segment elevation.[102,103] Confounding factors (ischemic heart disease, myocarditis, hyperkalemia, hypercalcemia, arrhythmogenic right ventricular dysplasia, pulmonary embolism, or mechanical compression of the RVOT) need to be excluded before the definite diagnosis of BrS can be made.[49]

Risk Stratification

Patients with symptoms (a history of VT/VF or syncope of unknown origin) and spontaneous coved-type ST-segment elevation are at risk for future arrhythmic events.[48,50,104–111] However, risk stratification in asymptomatic cases is still ill defined. Although familial history of BrS was initially considered to play an important role in the diagnostic process, a family history of SCD or coved-type ST-segment elevation have not consistently been proven to be significant risk factors possibly because of the different ethnic groups or population selection in each study, the inclusion criteria of ECG with different intercostal spaces, and the number and timing of the ECG recordings.[48,106,111] Male sex is not consistently shown to be a risk factor in prognostic studies.[48,111]

Repeated ECG recordings or signal-averaged ECG may be useful in the risk stratification. A recent study showed that alteration of the ST-segment elevation in the right precordial leads between the diagnostic and nondiagnostic ECG may help to screen patients at risk.[112] A study in 74 patients with BrS reported that changes of ≥0.2 mm in the ST level of the right precordial leads were more frequently observed

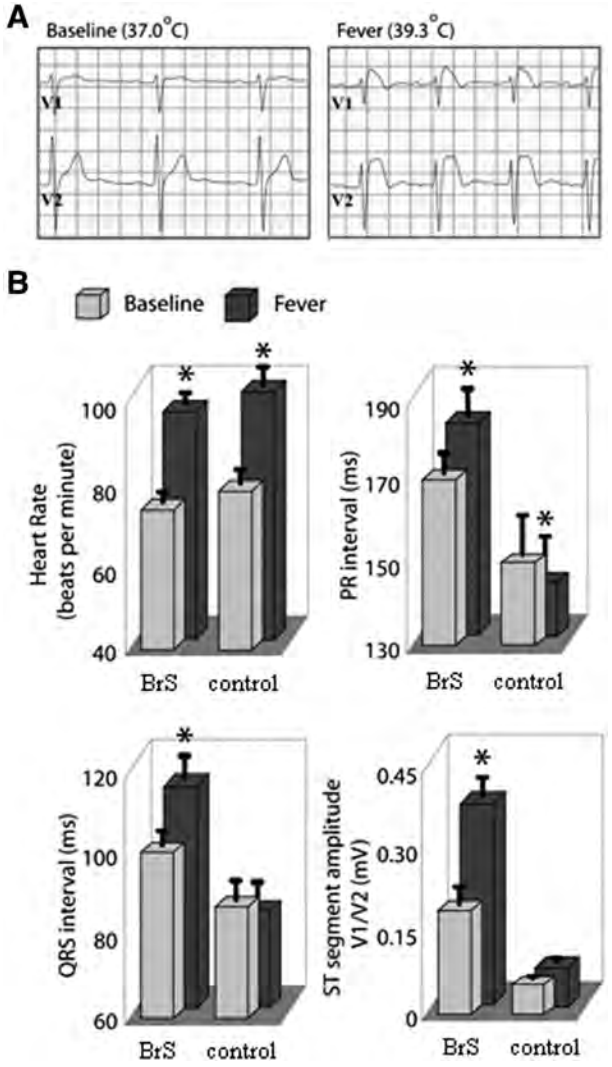

Figure 2. A, Fever-induced ST-segment elevation in a patient with BrS. **B**, ECG parameters at baseline and during fever were compared in 24 patients with BrS and 10 controls. Fever-elevated ST segment prolonged PR and QRS intervals in patients with BrS, whereas the PR interval shortened and the QRS interval or ST-segment amplitude did not change in the controls. *$P<0.05$ versus baseline. BrS indicates Brugada syndrome.

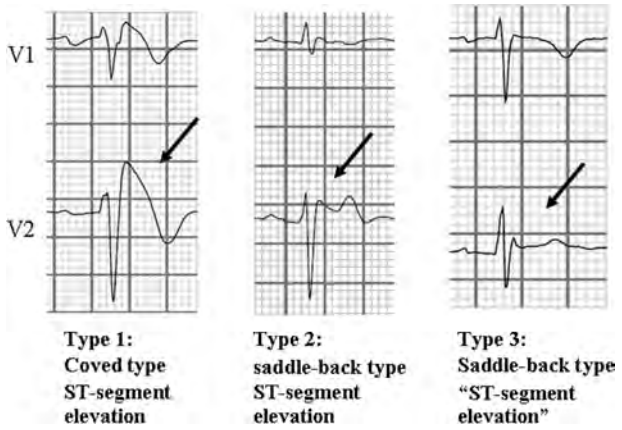

Figure 3. ECG abnormality diagnostic or suspected of Brugada syndrome. Type 1 ECG (coved-type ST-segment elevation) is the only diagnostic ECG in Brugada syndrome and is defined as a J-wave amplitude or an ST-segment elevation of ≥2 mm or 0.2 mV at its peak (followed by a negative T wave with little or no isoelectric separation). Type 2 ECG (saddle-back-type ST-segment elevation), defined as a J-wave amplitude of ≥2 mm, gives rise to a gradually descending ST-segment elevation (remaining ≥1 mm above the baseline) followed by a positive or biphasic T wave that results in a saddle-back configuration. Type 3 ECG is a right precordial ST-segment elevation (saddle-back type, coved type, or both) without meeting the aforementioned criteria.

in the VF group than in the non-VF group.[113] A prospective study using signal-averaged ECG suggested that positive late potential may have predictive value of malignant arrhythmic events in BrS.[107] Of note, these studies were performed in a small number of patients and deserved further evaluation with a larger cohort.

Regarding the inducibility of VT/VF, negative predictive value is 98% to 99% in asymptomatic patients with and without type 1 ECG, respectively,[114] but its positive predictive value (ie, in case of inducibility) is heavily discussed.[10,11] With regard to this point, it seems that the initial series published by Brugada et al were biased by inclusion of more-severe cases.[10,115] However, also in later years, inducibility of VF is a powerful predictor in the hands of some, whereas it is not in the hands of others.

Figure 4 shows the outcome data in the various studies in which the predictive value of electrophysiological study was tested in asymptomatic patients with a spontaneous type 1 ECG or a drug-induced ECG.[105,106,110,111,116–123] Indeed, the initial drop in follow-up events in the studies published by Brugada et al[110,116] can only be explained by the inclusion of patients with a more-severe condition. In the more-recent studies, the event rate during a follow-up period of 3 to 4 years is between 0% and 5%, the latter still including the patients already included in the first series published by Brugada et al.[123] It is not clear why the results diverge, but the differences in electrophysiology study protocol may be critical. However, a recent prospective study was not able to demonstrate this.[122] In asymptomatic patients with a drug-induced Brugada pattern, the follow-up event rate in almost all studies is 0% (Figure 4B). Hence, electrophysiology study cannot be predictive in this setting and should not be performed.

All together, risk stratification, particularly in asymptomatic patients with BrS is ill defined. Future studies with uniform design and long-term follow-up are needed.

Mechanism of Ventricular Arrhythmia

It is a common observation that the RVOT harbors the arrhythmogenic substrate in BrS. To explain its pathophysiology,

Table. Sodium Channel Blockers Used for the Drug Challenge Test in Brugada Syndrome

Drug	Dose and Administration
Ajmaline	1 mg/kg IV over 5 min
Flecainide	2 mg/kg IV over 10 min
Pilsicainide	1 mg/kg IV over 10 min
Procainamide	10 mg/kg IV over 10 min

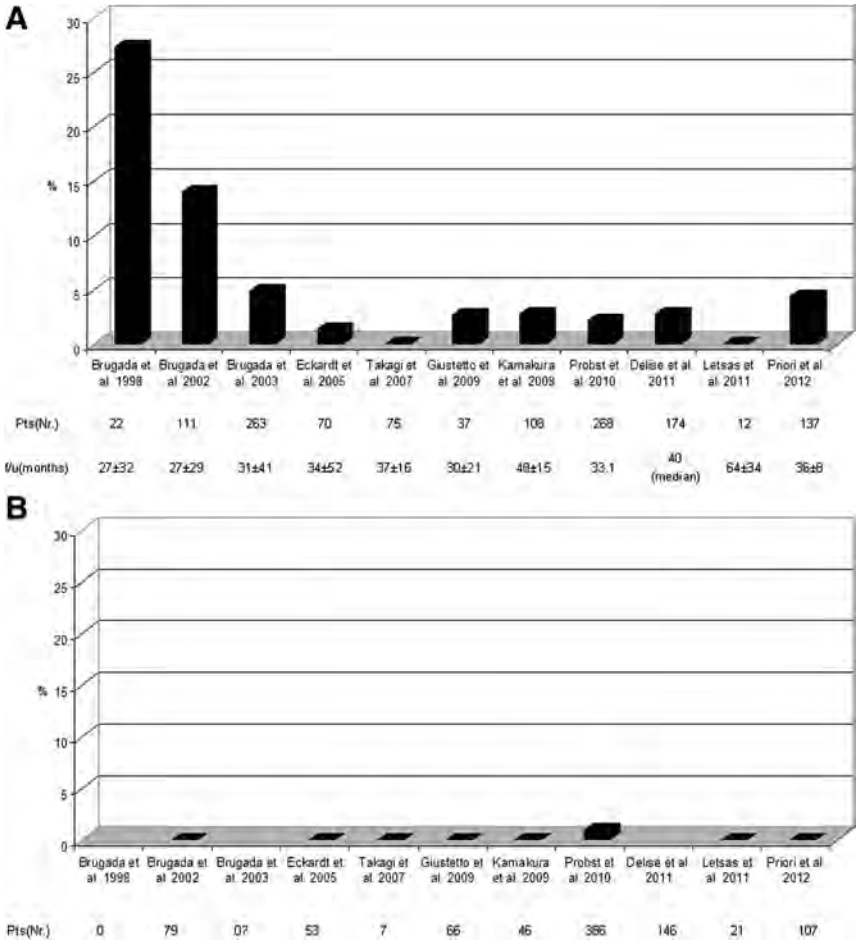

Figure 4. A and **B**, Percentage of event rates (ventricular fibrillation or an appropriate implantable cardioverter-defibrillator discharge) in asymptomatic patients with spontaneous and drug-induced, respectively, type 1 BrS ECG during follow-up. The number of patients and follow-up periods are presented. Some of the follow-up periods are of the whole study population (including symptomatic cases). Event rates of the studies by Brugada et al (1998),[90] Brugada et al (2003),[96] and Delise et al (2011)[94] include all asymptomatic patients (both spontaneous and drug-induced type 1 ECG) because the data were not available separately.

there are currently 2 hypotheses proposed: depolarization disorder and repolarization disorder.[9]

The repolarization disorder hypothesis is predominantly derived from experimental studies. Yan et al[124] recorded transmembrane APs as well as ECGs using arterially perfused wedges of canine right ventricle. After exposure to sodium channel blockers in combination with acetylcholine, loss of the AP dome in right ventricular epicardium but not in endocardium created a transmural voltage gradient. Because the RVOT epicardium has a prominent I_{to}, this region is susceptible for the accentuation of the AP notch and successive shortening of AP, which lead to coved-type ST-segment elevation in the right precordial leads, phase 2 reentry, and triggered VF.[124] This theory has been applied for decreased I_{Na} or I_{Ca} and increased I_{to}. The hypothesis needs the clinical relevance, but so far, there is only one report in which epicardial and endocardial monophasic AP recordings were taken simultaneously in 1 patient with BrS.[125] Transmural gradient of AP between epicardium and endocardium was observed, but shortening of AP was not reported.

The depolarization disorder hypothesis considers that conduction delay, particularly in the RVOT, plays a role in the pathogenesis of BrS. It has been shown in an explanted heart or through biopsy specimens that (ultra)structural changes were present in the right ventricle of patients with BrS.[6,7] Recently, Nademanee et al[13] showed in 9 patients with BrS with recurrent VF that fractionated electrograms were recorded at the epicardial side of RVOT but not in the left ventricular epicardium or RVOT endocardium (Figure 5). Catheter ablation of these signals eliminated VF and type 1 ECG in 8 of the 9 patients. Considering that CT or MRI did not detect structural abnormalities in the study population, these subtle electrophysiological (as well as structural) changes in the RVOT are probably best confirmed by signal-averaged ECG, vectocardiograms, and body surface mapping,[107,126,127] and the degree of conduction delay and structural changes may differ from one individual to another. In fact, the cardiac myocytes of the RVOT in a normal heart can be arrhythmogenic.[128] The embryonic outflow tract consists of slowly conducting tissue. While a heart develops, the outflow tract is incorporated into the ventricles and develops rapidly conducting properties. Remnants of slowly conducting tissues in the RVOT, if any, may determine the vulnerability for arrhythmias, and additional factors (fever, vagal tone, *SCN5A* mutation, or drugs to precipitate conduction slowing) could trigger ventricular arrhythmia.[95,128]

The genetic findings in and the pharmacological features of BrS generally are considered favorable evidence for the repolarization theory. However, in structural discontinuous myocardium, AP propagation is determined by the tissue architecture itself (which is abnormal in BrS as discussed previously) and by the current available for propagation. The latter is more or less determined by the AP morphology, which, in turn, is modulated by I_{Na}, $I_{Ca,L}$, and I_{to}.[129]

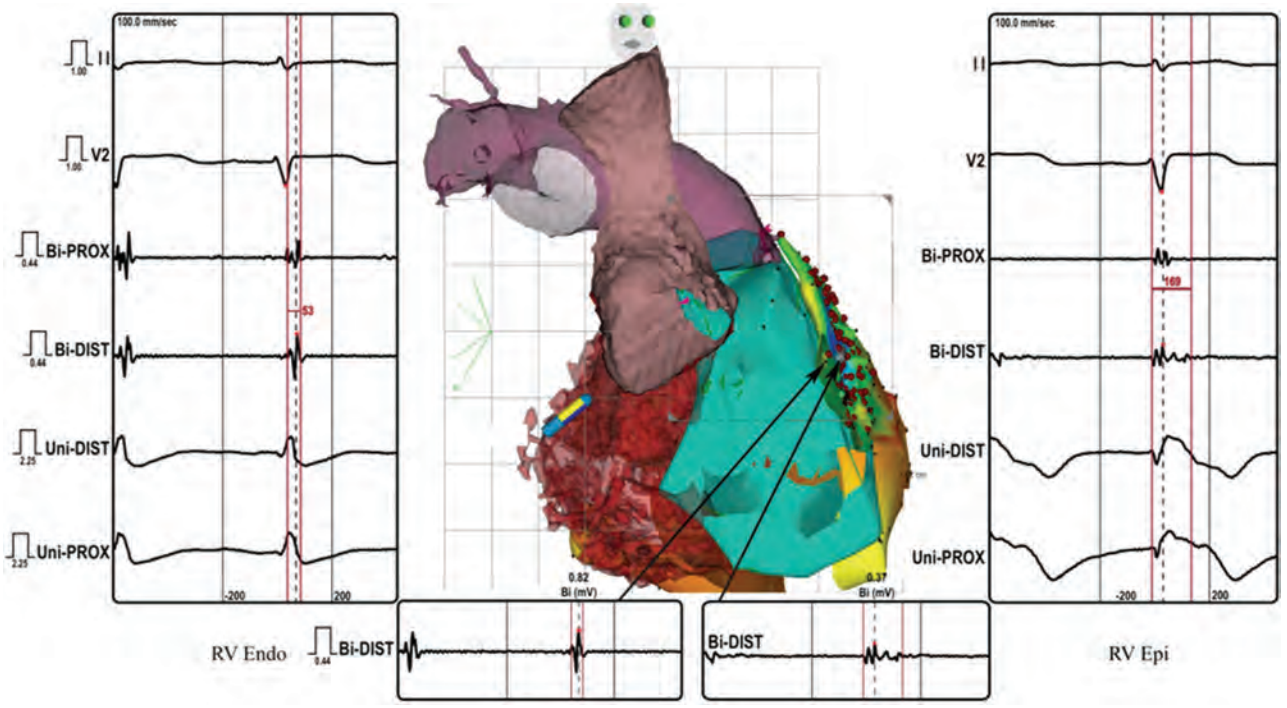

Figure 5. Right anterior oblique view of RV CARTO mapping. RV endocardial and epicardial signals recorded during electrophysiological study are shown. Electrograms shown are lead II and V2 of 12-lead ECG and bipolar (proximal, distal) and unipolar (proximal, distal) electrograms of the mapping catheter. Note that the fractionated electrogram is observed in the RV epicardium but not in the RV endocardium. RV indicates right ventricle. The figure is provided courtesy of Koonlawee Nademanee, MD.

A decrease in I_{Na} and $I_{Ca,L}$ and an increase in I_{to} or ATP-sensitive K+ current modify the AP morphology in such a way that the safety of conduction is decreased (ie, potentially leading to conduction slowing or conduction block in structural discontinuous myocardium or at Purkinje-ventricular muscle boundaries). All these possibilities are linked to genetic variants associated with BrS, and some of them, in particular the amplitude of $I_{Ca,L}$, is sensitive to changes in autonomic tone. Similarly, pharmacological interventions that block I_{to} or increase $I_{Ca,L}$ (quinidine and isoproterenol, respectively) are expected to exert the opposite effect and improve safety of conduction. Indeed, both drugs are known to attenuate the Brugada ECG pattern and suppress the associated arrhythmias.

Whereas the depolarization hypothesis as a pathogenesis of BrS has been studied extensively clinically and experimentally, including a convincing study by Nademanee et al,[13] the repolarization hypothesis lacks clinical data to support the hypothesis. The epicardial RVOT is not easily studied, and the opportunities to study it are limited to surgical or invasive electrophysiological studies in cases refractory to any treatment currently available. As yet, the study of Nademanee et al comes closest and strongly supports the existence of marked conduction delay in the RVOT as the arrhythmogenic substrate and the mechanism of right precordial ST elevation. Notably, the experimental data studied in a wedge preparation are not a whole-heart study, may not be physiological, and need careful interpretation when applied to clinical practice.

Current Management

For patients with BrS with a history of VT/VF or syncope suggestive of malignant arrhythmia origin, ICD is the first-line therapy. Importantly, ICD has a high complication rate (8.9%/year).[130] Considering the low annual rate of arrhythmic events in asymptomatic patients (0.5% versus 7.7%–10.2% in patients with VF and 0.6%–1.9% in patients with syncope)[106,111] and the negative physical and social effects,[131] ICD indication in asymptomatic patients needs careful judgment. As an alternative treatment, there is an ongoing prognostic survey in which patients with BrS receive empirical quinidine therapy.[132]

Caution should be exercised when specific drugs are used in BrS or suspected cases. Not only antiarrhythmic drugs, but also psychotropic drugs, anesthetics, antihistamine, and cocaine could manifest type 1 ECG and VF. Drugs to be avoided in BrS are listed on the Web site www.brugadadrugs.org.[133] Fever may provoke type 1 ECG and VF. If syncopal episodes in a febrile state suggests malignant arrhythmia, an ECG and a prescription of antipyretics are needed.

For patients with recurrent VF and ICD shocks, an adjunctive therapy is pertinent. In the acute phase, isoproterenol is effective to suppress VF by increasing the $I_{Ca,L}$.[134] Long-term oral medication use of quinidine, denopamine, cilostazol, or bepridil (available only in Japan) are effective in VF suppression.[135–138] Quinidine is also effective in children aged <16 years.[50] Quinidine is known for its side effects, such as gastrointestinal symptoms, liver dysfunction, thrombocytopenia, allergic reaction, sick sinus syndrome, and QT prolongation.[135–137] If a patient taking quinidine shows diarrhea alone as a side effect, cholestyramine is effective to control diarrhea with continuation of quinidine.[135,137] If a patient treated with denopamine or cilostazol experiences unbearable palpitations, oral treatment needs to be changed to another

drug. Unfortunately, quinidine is not available worldwide because the pharmaceutical companies have ceased its production because of low profit.[139]

Ablation of a fractionated electrogram in the epicardial RVOT is a promising option, at least for severely affected patients with recurrent VF. Epicardial ablation of the RVOT was shown to be effective for VF suppression and the disappearance of type 1 ECG in 8 of 9 patients with BrS at 2 years follow-up.[13] Importantly, epicardial ablation is a more-difficult procedure compared with the endocardial approach. A multicenter study on the safety of epicardial VT ablation showed that the risk of acute and delayed complications were 5% and 2%, respectively.[140] However, this study was performed in highly experienced centers with surgical backup for selected patients, and in 86% of patients, endocardial ablation had failed previously. Death may occur as a complication, and repeated epicardial mapping is sometimes not feasible.[141] Currently, the selection of patients for epicardial ablation in BrS needs to be established.

A case report of BrS and VF showed that substrate ablation from the endocardium using the pace mapping of the triggered ventricular ectopic beats suppressed VF for 6.5 years, and type 1 ECG disappeared.[142] In this case, fractionated electrograms were not reported. This maneuver is not always applicable because triggered beats of VF may scarcely appear during an electrophysiology study, which makes it difficult to target the radiofrequency energy.

Future Perspectives

Two decades of extensive research on BrS has revealed parts of its genetic background and electrophysiological and clinical characteristics. Questions remain regarding the mechanism that plays the central role of the disease; the role of its genetic background, including polymorphisms; and other confounding factors, such as fever and sex, in VF. Further research will continue to answer these questions. Meanwhile, refinement of the treatment is needed. Catheter ablation of epicardial substrate in patients with frequent VF may be a choice of treatment and will help to analyze the pathophysiology of BrS.

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Disclosures

None.

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KEY WORDS: Brugada syndrome ■ genetics ■ disease management ■ risk factors ■ death sudden

SUPPLEMENTAL MATERIAL

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