Brugada Syndrome
– Two Decades of Progress –
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Two decades ago, a series of 8 idiopathic ventricular fibrillation patients who each had an abnormal ECG (right bundle branch block with coved-type ECG), but otherwise had normal hearts were described by Brugada and Brugada. Since then, the clinical entity has become known as Brugada syndrome (BS). Shortly thereafter, mutations of the SCN5A gene that encodes for the α-subunit of the sodium channel were found, galvanizing the field of ion channelopathies following in the footsteps of the breakthrough in long QT syndrome. Over the past 20 years, extensive research in this field has produced major progress toward better understanding of BS and the gaining of knowledge of the genetic background, pathophysiology and new management. Two consensus reports were published to help define the diagnostic criteria, risk stratification and management of BS patients. However, there are controversies. In this review, we will share our experiences of BS patients in Thailand and discuss advances in many aspects of the syndrome (ie, genetics and pathophysiology) and some of these pertinent controversies, as well as new treatment of the syndrome with catheter ablation. (Circ J 2012; 76: 2713–2722)

Key Words: Ablation; Electrophysiology; Genetics; Ion channels; Ventricular arrhythmia

It was 2 decades ago that Brugada and Brugada linked an abnormal ECG with right bundle branch block pattern and coved-type ST elevation over the right precordial leads to primary ventricular fibrillation (VF) and sudden cardiac death (SCD) in patients with structurally normal hearts.1 It instantly became known as Brugada syndrome (BS) and has drawn the worldwide attention of cardiologists, electrophysiologists and molecular biologists/geneticists. In Thailand, we discovered that most of the victims and patients with sudden unexplained death syndrome (SUDS) had the same phenotype as BS,2 and shortly thereafter we reported that both syndromes also shared the same genetic and biophysical basis.3 Over the past 20 years, we have witnessed major progress toward better understanding of the syndrome and knowledge gained in genetic aspects of the syndrome, pathophysiology and new management.4–9 Although 2 consensus reports were published to help define diagnostic criteria, risk stratification and management of BS patients,4,5 there are controversies, especially in the electrophysiologic mechanisms underlying the syndrome,6–9 risk stratification,10–13 and treatment of asymptomatic patients.11,14–20

In this review, we will share our experiences of BS patients in Thailand, and discuss these controversies, as well as new treatment of the syndrome with catheter ablation.

Clinical Characteristics and Presentation
The clinical spectrum of the BS patient ranges from asymptomatic to SCD.5 Patients may have a late onset of VF, despite having had an abnormal ECG pattern for decades.2,6 Syncope or seizures because of self-terminating VF episodes are also common, as are agonal respiration and difficulty in arousal at night, again caused by self-terminating VF episodes.2,5 The majority of BS patients are relatively young, between 20 and 40 years of age, but the youngest patient diagnosed with the syndrome was 2 days old and the oldest 84 years.4,5 Despite an autosomal dominant inheritance pattern, BS prevalence is up to 10-fold higher in males and with greater severity.2,22 In Thailand, the majority of BS patients are young men (<40 years old) and it is the leading cause of death in young Thai men after automobile accidents.2 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.4,5 There is also a difference between the incidence of the Brugada type 1 ECG pattern and the syndrome itself, as defined by the 2005 Consensus criteria. Miyasaka et al observed a type 1 Brugada ECG pattern in 12 per 10,000 inhabitants; type 2 and 3 ECGs were more prevalent, appearing in 58 per 10,000 inhabitants.23 The prevalence of a Brugada ECG is higher in Asia (0.36%) and Europe (0.25%) than in the USA (0.03%).6 However, the true prevalence of BS is unknown because the ECG pattern can be wax and wane, making it very likely that the true incidence is underestimated.

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Signature ECG and Diagnostic Criteria

The 2 Brugada consensus reports classified the Brugada ECG pattern into 3 types (Figure 1): (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; (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 saddleback type; (3) type 3 is the coved- or saddleback-type with <1 mm ST-elevation ST-segment elevation. One has to be cognizant that the Brugada ECG pattern is dynamic and can be concealed. The sodium channel blockers, ajmaline, procainamide and flecainide, can be used to unmask the ECG pattern (the details of performing a drug challenge test to unmask the Brugada ECG pattern have been nicely reviewed elsewhere, so we shall not repeat them here). 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 3rd and 2nd intercostal spaces. We and others have demonstrated that placement of right precordial lead ECG recordings over the higher intercostal spaces (3rd and 2nd intercostal spaces) significantly increases the diagnostic yield in bringing to light the Brugada ECG pattern. In our institution, we routinely record the right precordial lead ECG (V1–3) from 4th, 3rd and 2nd intercostal spaces in every patient suspected of BS. Figure 2 shows an example of the ECG tracings from a patient with BS: the Brugada ECG pattern is absent in the conventional 4th intercostal space lead placement, but becomes apparent in the higher (3rd and 2nd) intercostal spaces.

It should be emphasized, however, that to fulfill the diagnostic criteria for BS, the consensus reports recommend that the patient has the type 1 Brugada ECG pattern with or without a sodium channel blocker challenge test and the following clinical manifestations: (1) history of spontaneous VT/VF episode or aborted SCD; (2) family history of SCD or coved-type ECG; (3) agonal respiration during sleep; or (4) inducibility of VT/VF by programmed electrical stimulation (PES).

Genetics of BS

In 1998, Chen et al reported the first mutation, linked to BS, in the SCN5A gene, which encodes for the α-subunit of the sodium channel. Since then, there have been an increasing number of gene mutations identified. Functional studies demonstrate that SCN5A mutations in BS patients cause loss-of-function of the sodium channel because of decreased expression of the sodium channel protein (Na1.5), sarcolemmal expression of non-functional channels or altered gating properties (delayed activation, earlier inactivation, faster inactivation, enhanced slow inactivation and delayed recovery from inactivation). The loss of function of the sodium channel...
results in a decrease in the sodium current, which in turn impairs the fast upstroke of phase 0 of the action potential (AP), causing slow conduction in the heart.

Even though SCN5A mutations are the most common type found in 11–28% of BS probands, the genetics of BS have become heterogeneous. In addition to the SCN5A mutations, more mutations are found in the gene encoding the proteins of the potassium and calcium channels. The Table lists 12 subtypes of BS based on mutations of different genes that have been discussed recently and thus will not be discussed in depth here.

Despite a number of genes having been identified and linked to the syndrome, gene mutation alone cannot completely explain the phenotype. Kapplinger et al found nearly 300 SCN5A mutations in 211 unrelated probands.36 The SCN5A mutations were found in 21% of patients with the BS phenotype and 2–5% of healthy controls. That finding suggests an important role of SCN5A mutation causing loss-of-function of the sodium channel in the phenotype manifestation. However, 80% of these mutations were only present in 1 individual or 1 family and a causal role of these mutations in BS is far from clearly established.39

Probst et al studied 13 large families with SCN5A mutations and revealed the following intriguing finding: many of the mutation carriers did not have the Brugada signature sign on ECG nor could it be provoked by sodium channel blocker.33 Moreover, in 5 of the 13 families with more than 5 clinically affected individuals, there were 1 or 2 affected individuals with the BS phenotype who did not have the familial SCN5A mutation. Furthermore, the Brugada ECG pattern was induced in 8 mutation-negative patients.33 These findings, together with a recent report of a case of identical twins with SCN5A mutations but only 1 twin displayed the BS phenotype, suggest that SCN5A mutations may act as modifiers rather than cause.40

SCN5A mutations may cause not only BS but other diseases as well. Indeed, SCN5A mutations have also been associated with long QT syndrome,33,41 cardiac conduction disease,42 sick sinus syndrome,43 atrial fibrillation (AF),44,45 and dilated cardiomyopathy with overlap syndromes identified in specific families.46

The role of genetic testing in risk stratification remains unclear. Recently, Crotti et al reported their findings of a comprehensive mutational analysis of all 12 BS genes for a single, large cohort of BS patients. They found a putative pathogenic mutation in 21% of their BS cohort. As in other reports, 78% of the mutations were still confined to SCN5A and BS. 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 50% in male patients younger than 40 years of age. The BS patients with prolonged PR interval 2200 ms had a very high incidence of SCN5A mutations (39%) compared with those with a normal PR interval. But the yield of identifying the mutations was similar between those who had only the typical type 1 Brugada ECG pattern and those with clinically established syndrome. Based on their findings, the authors recommend genetic testing of all BS patients and patients who just have the type 1 Brugada ECG pattern. These recommendations concur with the position paper of the Canadian Cardiovascular Society, but not with consensus of the Heart Rhythm Society/European Heart Rhythm Association.48–50 Based on their finding of a low prevalence of non-SCN5A mutations, they suggest that it is reasonable to initially test most patients for SCN5A mutations alone, with further testing for the other minor BS genes only in special circumstances.

### Table. Gene Mutations in Brugada Syndrome

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Locus</th>
<th>Ion channel</th>
<th>Gene/protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>BS 1</td>
<td>3p21</td>
<td>Na↓</td>
<td>SCN5A, Na1.5</td>
</tr>
<tr>
<td>BS 2</td>
<td>3p24</td>
<td>Na↓</td>
<td>GPD1L</td>
</tr>
<tr>
<td>BS 3</td>
<td>12p13.3</td>
<td>Ica↓</td>
<td>CACNA1C, Ca1.2</td>
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<tr>
<td>BS 4</td>
<td>10p12.33</td>
<td>Ica↓</td>
<td>CACNB2b, Caβb</td>
</tr>
<tr>
<td>BS 5</td>
<td>19q13.1</td>
<td>Ica↑</td>
<td>SCN1B, Naβ1</td>
</tr>
<tr>
<td>BS 6</td>
<td>11q13-q14</td>
<td>Ica↑</td>
<td>KCNE3, MiRP2</td>
</tr>
<tr>
<td>BS 7</td>
<td>11q23.3</td>
<td>Ica↓</td>
<td>SCN3B, Naβ3</td>
</tr>
<tr>
<td>BS 8</td>
<td>12p11.23</td>
<td>Ica,ATP↑</td>
<td>KCNJ8</td>
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<tr>
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<td>7q21-q22</td>
<td>Ica↑</td>
<td>CACNA2D1, Caα2δ</td>
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<td>BS 10</td>
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<td>KCND3</td>
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<td>Ica↓</td>
<td>MOG1</td>
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<td>BS 12</td>
<td>12p12.1</td>
<td>Ica,ATP↑</td>
<td>ABC9, SURF2</td>
</tr>
</tbody>
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### Pathophysiology of BS

In recent years, there has been a well-recognized debate of the pathophysiology and electrophysiology underlying BS; that is, repolarization disorder vs. depolarization disorder.54 Antzelevitch and colleagues proposed the repolarization theory, shortly after the syndrome was introduced, as the electrophysiologic abnormality underlying BS.55–58 They proposed the repolarization hypothesis based largely on results from an arterially perfused wedge preparation of the canine right ventricle (RV). In their experimental studies, Yan and Antzelevitch observed a transmembrane voltage gradient between the RV epicardium and endocardium because of the loss of the AP dome in the epicardium but not in the endocardium.55 The RV epicardium is well known as having abundant Ica, which is effective in treating BS patients could be inferred as support for this theory.59 Thus far, the only clinical relevance to support this theory is 1 case report in which monophasic AP recordings from the epicardium of a BS patient who had an RVOT epicardium was observed.59 The transmembrane gradient of the AP between the epicardium and endocardium were performed simultaneously in a BS patient.56 The transmembrane gradient of the AP between the epicardium and endocardium was observed, but those authors did not find shortening of the epicardial AP in certain regions, leading to pronounced heterogeneity of transmembrane voltage potentials and, in turn, causing phase 2 reentry and triggered VF. Thus far, the only clinical relevance to support this theory is a case report in which monophasic AP recordings from the epicardium and endocardium were performed simultaneously in a BS patient.56 The transmembrane gradient of the AP between the epicardium and endocardium was observed, but those authors did not find shortening of the epicardial AP. Perhaps, the observational study showing that quinidine, a strong Ica blocker, is effective in treating BS patients could be inferred as weak (ie, indirect) evidence that supports the repolarization theory.54 Although the repolarization theory enjoyed its popularity early on, the lack of strong, clinically relevant findings to convincingly support the concept and then subsequent clinical evidence led to the other theory, depolarization disorder.

Using an electrical guidewire to record an epicardial electrogram from a conus branch of the right coronary artery, Nagase et al were the first to show abnormal electrograms characterized by a late potential (LP) after the QRS, which were recorded from the free wall of the RVOT epicardium in BS patients.55 Their findings suggest a conduction delay in the RVOT epicardium. A couple of years later, investigators from the Academic Medical Center of Amsterdam reported their findings from the explanted heart of a BS patient who had an SCN5A mutation with medically-treated failure of VF storms, neces-
sitting heart transplantation surgery.56 The explanted heart showed no evidence of a repolarization abnormality; instead, they found evidence of interstitial fibrosis causing conduction delay. The RVOT endocardium showed activation slowing and was the origin of VF without a transmural repolarization gradient. The RVOT endocardium showed activation slowing and was the origin of VF without a transmural repolarization gradient. The Amsterdam group then proposed the depolarization hypothesis, which contends that in BS, the RVOT is the last to depolarize.57 As a result, the delay in the AP of the RVOT causes an electrical gradient from the more positive RV to the RVOT, leading to ST-elevation in 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 towards the RV, resulting in a negative T-wave in the same right precordial leads. The experimental study from the same group in this explanted heart also showed that this site is the arrhythmogenic site during programmed stimulation-induced VF. Frustaci et al also reported their biopsy findings showing fibrosis in patients with the BS phenotype.58 There are a number of clinical studies that show that delayed activation of the RVOT in BS patients indeed occurs.59–65 Perhaps the strongest clinical evidence came from our own study describing the arrhythmogenic substrates of BS patients with frequent discharges of their implanted cardioverter defibrillators (ICD).9 Aiming to determine the arrhythmogenic substrate and underlying electrophysiological abnormalities in BS, we studied 9 symptomatic patients with BS (all males; mean age, 39 years) who had multiple recurrent VF episodes (±1.5) per month, necessitating ICD discharges. Using CARTO (Biosense Webster, Diamond Bar, CA, USA), electroanatomic mapping of the RV, both endocardial and epicardial, and epicardial mapping of the left ventricle (LV) were performed in all patients during sinus rhythm. All patients had the typical type 1 Brugada ECG pattern and inducible VT/VF. Figure 3 shows an example of a CARTO map in a BS patient with frequent ICD discharges showing abnormal ventricular electrograms recorded in the area of the anterior RVOT epicardium. The double annotation map (A2–A1) shows that patient 4 had abnormal prolonged ventricular electrograms (>200 ms; displayed in purple). Note that the sample of electrograms recorded from this area of the RVOT epicardium display markedly delayed depolarization, as shown by the LP that continued to depolarize beyond the QRS complex (261 ms), with a width of the electrogram of 251 ms. We found that all other patients in this study also had abnormal depolarization, similar to this patient, characterized by abnormal low-voltage fractionated ventricular electrograms (<1 mV) that have a markedly delayed conduction time after the QRS complex on the surface ECG (>100 ms), and a markedly prolonged duration (>130 ms). These abnormal electrograms are exclusively localized in a cluster over the epicardium of the anterior aspect of the RVOT, and are not seen anywhere else in the RV or LV (Figures 4, 5). As shown in Figure 4, the endocardial site (arrowed) displays a single potential of 4.09 mV, with a duration of 47 ms and only 8 ms beyond the QRS, compared with the epicardial counterpart that shows a low-voltage LP (0.27 mV), with a duration of 231 ms with the LP potential extending 132 ms beyond the QRS. Figure 5 shows epicardial electrograms recorded from various sites of the epicardium in both the LV and RV. Note that the abnormal fractionated electro-
grams and double potential electrograms are only localized in the anterior aspect of the RVOT epicardium. The distribution of abnormal fractionated electrograms (ie, low-voltage signals [<1 mV], LP >100 ms from the end of QRS complex, and wide duration >80 ms) is almost exclusively located at the anterior RVOT epicardium. Ablation at these sites has rendered VT/VF non-inducible in 78% and normalization of the Brugada ECG pattern in 89% of our patients. Therefore, we conclude that delayed depolarization at this site is also the most likely underlying electrophysiologic mechanism, as evidenced by the fact that catheter ablation over this site results in the disappearance of the Brugada ECG pattern and prevention of both spontaneous and induced VT/VF episodes.
Modulating and Precipitating Factors

As mentioned, 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 by alcohol or cocaine toxicity. These modulating and predisposing factors can affect the arrhythmia and the clinical outcomes by: (1) modifying the VF substrate; (2) affecting the gene expression of ion channel defects; (3) triggering premature ventricular contractions (PVCs) and the initiating process of VF; and (4) influencing the sustaining process of the VF episodes.

Autonomic Nervous System

The effect of sympathetic stimulation by isoproterenol infusion, resulting in normalization of the BS pattern, suggests that sympathetic activity could modify the VF substrate.66 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.6 This concept is strengthened by the fact that some patients with “VF storms” associated with BS can be effectively treated with isoproterenol infusion.66 On the other hand, increased vagal tone may be arrhythmogenic in BS patients. Increased vagal tone, as well as acute β-blockade, was found to promote VF induction in the electrophysiology laboratory.68 Recently, Abe et al found that fluctuations in LPs on signal-averaged ECG (SAECG) occurred predominantly at night, suggesting that conduction delay and, by inference, the arrhythmogenic substrate are autonomically modulated.69 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.66 However, Krittayaphong et al studied HRV from 24-hour Holter data of SUDS patients with the Brugada ECG marker, aiming to determine the circadian pattern of sympathetic and parasympathetic activity.70 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 sympathetic-vagal balance in the BS patients plays a significant role in the circadian variation of VF occurrence. However, further studies are needed to clearly define and understand the complex interplay between the autonomous nervous system and the arrhythmic mechanisms of BS.

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.71 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.72 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.

An interesting case report of a 60-year-old man who had asymptomatic BS, without a family history of SCD, showed how hypokalemia could provoke VF leading to syncope/cardiac arrest.73 This patient initially received steroid treatment for asthma, lowering his serum potassium from 3.8 mmol/L on admission to 3.4 and 2.9 mmol/L on the 7th day and 8th days of admission, respectively. On both occasions, this was associated with unconsciousness and spontaneously-terminated VF episodes. This case shares many similarities with BS patients in Thailand and provides a very strong argument that hypokalemia is an important precipitating factor in BS patients.

Sleep and Heavy Meals

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 BS 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. A recent 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.74 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.

Body Temperature and Febrile Illness

Dumaine et al discovered that the T162OM missense mutation causes accelerated inactivation of the sodium channel at physiologic body temperature but not at room temperature.75 Identification of this temperature-sensitive gene 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 could unmask BS and precipitate VF occurrence.76–80 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 BS pattern, but had not had a prior medical problem and had been asymptomatic. Unfortunately, we did not have an opportunity to perform a genetic study to determine whether the patient had this abnormal mutation.

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 mutational channels in other genes responsible for BS. In the meantime, physicians should factor in temperature as a cause for arrhythmogenesis in BS. They should be cognizant of the association between temperature and BS during diagnosis and treatment, advising patients to promptly treat fevers.
**Combined Syndromes**

In addition to the described precipitating factors, BS patients often have other concomitant arrhythmias or arrhythmic syndromes. AF is a common arrhythmia in BS. The incidence of combined early repolarization syndrome in BS patients was reported as 15% and in this subset the incidence of recurrent VF episodes was significantly higher than in those with BS alone. Similarly, combined syndromes of a progressive conduction defect and BS, and of long QT syndrome and BS, are not uncommon. Also, patients with BS can have other concomitant diseases that could precipitate VF occurrence. For example, vasospastic angina could cause ischemia, and in tandem with the BS substrate could clearly precipitate VF. As research into the syndrome continues apace, we will learn more about the factors that contribute to both the genesis of VF and the clinical presentations of the syndrome. Undoubtedly, this will lead to better protection and treatment of BS patients.

**Risk Stratification**

There is little to debate that a BS survivor of out-of-hospital cardiac arrest is at high risk of recurrent VF episodes and needs ICD treatment. Likewise, symptomatic patients with recurrent syncope, agonal respiration at night during sleep or unknown seizures are at risk of dying suddenly without protection and have a Class I indication for ICD treatment. The heated debate is more on how to best identify high-risk patients for sudden death and need of ICD treatment among asymptomatic BS patients. Initially, the Brugada registry reported a significantly high risk of asymptomatic patients with positive VT-inducibility by PES. However, more recent studies found a much lower incidence of sudden death or VF in this group and questioned the specificity of PES role in risk stratifying asymptomatic BS patients. Our own experience of asymptomatic patients shows that the annual cardiac event rate (VF or death) is so low at 0.25% per year that it is very unlikely that any risk stratification strategy will be able to identify high-risk patients for ICD treatment as a primary prevention. Recent studies have found that QRS fragmentation, exercise testing, and shortening of the ventricular refractory period are valuable tools for identifying high-risk patients. However, it is unclear how useful any of these parameters are for identifying asymptomatic BS patients for ICD treatment. In our own asymptomatic cohort of 115 patients, after 10 years of follow-up, we found only 2 patients with either VF or sudden death (1 was EPS positive and the other EPS negative). 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 ICD treatment in our patient population.

**Treatment**

BS patients should be informed of the various modulating and precipitating factors (as discussed earlier) that could precipitate malignant arrhythmias (ie, fever, electrolyte abnormalities and a whole host of drugs as listed in www.brugadadrugs.org). VF and sudden death in BS 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 that are likely to contribute to this circadian pattern. Bradycardia, because of altered sympathovagal balance or other factors, may also contribute to arrhythmia initiation. Isoproterenol infusion is very effective in treating VF storm and, more recently, to suppress induction of VF on programmed ventricular stimulation.

**Antiarrhythmic Drugs**

Thus far, quinidine has been the only drug that shows benefit in preventing recurrent VF episodes. Quinidine has been shown in small studies to suppress inducibility of VF on PES and reduce the number of appropriate ICD shocks. Unfortunately, there are 2 major problems with quinidine: (1) only two-thirds of patients can tolerate the drug and side-effects such as thrombocytopenia can be very serious; and (2) quinidine is not available in many countries. In Thailand, there is no supply of the drug and the only drug we can use is amiodarone, with variable success. Bepridil, which is only available in Japan, has been used in BS patients.

**ICD**

As mentioned earlier, symptomatic BS patients (past history of VT/VF or syncope) have a Class I indication for ICD treatment. In the DEBUT study (Defibrillator versus β-blocker in Unexplained Death in Thailand: a randomized clinical trial), we found that ICD treatment provided full protection from death related to primary VF in the study population, which included 59% of patients with BS. However, we also found that unwanted side-effects of the ICD were also frequent (30%). Most of the complications were minor and included defibrillation discharges caused by supraventricular tachycardia or sinus tachycardia and T-wave oversensing. All of the complications were corrected by reprogramming the devices without major intervention. However, 1 patient had a pocket erosion with infection that required removal of the ICD, and 1 patient needed to have his ICD lead replaced because of an insulation breakage. Other studies report similar results; that is, long-term follow-up of Brugada ICD patients shows a high complication rate in up to one-third of patients. The majority of the complications, similar to our study, are mostly inappropriate shocks occurring in 36% of patients at follow-up; however, 1 registry recorded an 18% rate of serious events, including pericardial effusion, lead fracture, infection and subclavian vein thrombosis. Because of the relatively high complication rate in BS patients with ICDs, one has to be extremely cautious about using ICDs in asymptomatic BS patients. The fact that event rates in the asymptomatic BS population are quite low in most series, makes ICD treatment in this subset questionable with respect to whether ICD benefit outweighs 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.

The recent approval of leadless ICDs, which have been shown to be quite effective in terminating VT/VF episodes, is a welcome addition to the therapeutic modalities for BS patients. However, further studies and clinical trials to determine efficacy and safety in the high-risk BS population are warranted.

**Catheter Ablation**

The early attempts of catheter ablation in treating BS patients were limited to a few reported cases of patients with electrical storms. The initial approach was designed to target the initiating PVCs that trigger VF, which were found to come from the RVOT. The ablation was performed on the endocardial site of the RVOT. However, this approach has not been widely successful, largely because patients with BS rarely had PVCs frequently enough to be mapped and therefore it was quite difficult to identify the precise targets for ablation and clearly...
assess the acute outcome of the ablation. We have recently reported our epicardial approach for substrate ablation that is safe and effective. We have identified and proved that the anterior RVOT epicardium is the arrhythmogenic substrate site in our BS patients. This site consistently has abnormal LPs, and low-voltage fractionated ventricular electrograms; these abnormal electrograms tended to cluster exclusively in this area and nowhere else. After ablation at the RVOT epicardial site, the Brugada ECG pattern normalizes and VT/VF episodes subside. We have now performed ablations in 14 BS patients with frequent ICD discharges. Long-term outcomes (median, 32 months) have been excellent, with no recurrent VT/VF in all patients off medication.

We believe that our study provides major findings that have therapeutic implications: we now can locate the arrhythmogenic substrate that serves very well as the target site for catheter ablation, and thus can expect a good clinical outcome. Whether ablation will substitute for an ICD in high-risk BS patients remains unknown. Further studies clearly need to be done to assess the value and limitations of catheter ablation in patients with BS.

**Conclusions and Future Perspectives**

The 2 decades since the discovery of BS have witnessed impressive progress in our understanding of several aspects of the syndrome with respect to the role of genetics, electrophysiologic mechanisms and clinical characteristics. However, many questions and controversies remain regarding the role of genetic background, including polymorphism, and other confounding factors, such as fever and the patient’s sex, in this population. It is certain that the debate will continue regarding the role of delayed repolarization in BS and whether our finding of abnormal delayed depolarization in the anterior RVOT epicardium is seen in other centers and more specifically other population besides ours. In addition, how to best treat asymptomatic BS patients or whether there will be any better risk stratification strategy to identify the high-risk group are ongoing discussion topics. Why is the anterior RVOT epicardium the arrhythmogenic site in these patients? Why is there such a male preponderance and why do most of the VF episodes usually occur at night? 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 randomized trial studies, which are being conducted currently. In the near future, more study of the subcutaneous leadless ICD will be forthcoming. An expanded role of catheter ablation of the epicardial substrate beyond the population of BS with frequent VF also needs to be evaluated by assessing the risks and benefits of the procedure, 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 BS patients.

**Disclosure**

Dr Koonlawee Nademanee has consulting agreements, grant support and shared intellectual property with Biosense Webster.

**References**


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