Brugada syndrome in Thailand: Three decades of progress

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Our group began investigating the cause of sudden unexplained death syndrome in Thailand in 1994 and found that among sudden unexplained death syndrome patients, the Brugada phenotype was ubiquitous. Following this important observation, Brugada syndrome (BrS) became our main research focus and has galvanized our collaboration with several global prominent scientists over the past 30 years. Through this collaborative research, we made major progress toward better understanding of the syndrome and gained knowledge in genetic background, pathophysiology, and new management. Two consensus reports were published to help define diagnostic criteria, risk stratification, and management of BrS patients. In this review, we share our experiences and progress of our research and development of our program that was designed to identify the cause of sudden death, understand pathophysiology of the syndrome, and develop effective and safe management and therapy of BrS patients. Although our work in Thailand was challenging at the beginning, it later blossomed into a multicollaborative research enterprise that has produced several important findings that have shed light on the pathophysiology of BrS and development of a new effective treatment modality, catheter ablation.

KEYWORDS Ventricular fibrillation; Sudden cardiac death; Ablation; Brugada syndrome; Ion channelopathy; Sudden unexplained death syndrome

(Heart Rhythm O2 2022;3:743–751)

Three decades ago, we commenced our work to determine the cause of peculiar nocturnal deaths in young Thai men who were otherwise healthy with no apparent structural heart disease. This work led us to continue research in the Brugada syndrome (BrS). The purpose of this review is to share what we learned from these challenging but rewarding endeavors including how our work in Thailand provided opportunities for collaboration with arrhythmia scholars and researchers worldwide. This collaboration resulted in a better understanding of pathophysiologic and genetic aspects of BrS and much improvement in patient management, yielding better clinical and survival rates in BrS patients.

Identification of Brugada marker in sudden unexplained death syndrome

During the 1980s, almost a decade after the end of the Vietnam war, there was an alarming observation of unexplained nocturnal deaths in young, otherwise healthy, Southeast Asian (Laotians, Vietnamese, and Cambodians)[1,2] refugees who migrated to the United States or lived in refugee camps. At that time, the cause of death was unknown even after the postmortem examination, which prompted the Centers for Disease Control and Prevention to track these deaths and coin the term *sudden unexplained death syndrome* (SUDS).[1–4] SUDS drew great interest among epidemiologists, pathologists, and researchers who sought to determine the underlying cause of SUDS, many of whom came to carry out their studies among Southeast Asian refugees at their camps in Thailand and in turn spurred interest of Thai researchers.[5,6] While SUDS had been well known among the locals and indigenous people in the Northeastern part of the country and was known as "Lai Tai," meaning to dream or scream during sleep until death,[5–8] there had been no systematic studies in Thailand before the Centers for Disease Control and Prevention report of SUDS in the United States. In 1990, SUDS received even more public attention after a cluster of Thai workers in Singapore died.[9] Several hypotheses about the cause of death had been proposed: hypokalemia, thiamine deficiency, noxious agents, and emotional stress.[7–10] None of these hypotheses have been proven. However, ventricular fibrillation (VF) was implicated the rhythm at the terminal event or was the resuscitated rhythm in

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2666-5018/

https://doi.org/10.1016/j.hroo.2022.08.011

KEY FINDINGS

- Brugada syndrome (BrS) was the main cause of sudden unexplained death syndrome in Thailand.
- Two consensus reports on BrS diagnostic criteria were published in 2002 and 2005 and helped define diagnostic criteria, risk stratification, and management of BrS patients.
- Successful ablations of Brugada substrates at the right ventricular outflow tract epicardium were first reported in 2010 and established substrate ablations as a safe and effective treatment for symptomatic BrS patients. Subtle epicardial and subepicardial fibrosis were discovered as the underlying pathology of BrS in 2015.

survivors of SUDS.[11] The knowledge gleaned from these studies or lack thereof galvanized our group to launch a prospective study of the SUDS patient population[12]: (1) in SUDS survivors defined as patients who had been apparently healthy before developing sudden cardiac arrest due to VF but had been successfully resuscitated and 2) improbable SUDS patients defined as those who experienced symptoms that reflected the clinical presentation of SUDS (ie, agonal respiration, unresponsiveness after labored respiration during sleep), transient symptoms of distress (eg, moaning, thrashing, grimacing), and syncope or seizure-like symptoms. We excluded patients who had structural heart disease or identifiable causes of VF causing cardiac arrest, such as prolonged QT syndrome, myocardial ischemia, or drug-induced life-threatening arrhythmias.

Our study population included 27 Thai men (mean age 39.7 ± 11 years): 17 SUDS survivors and 10 probable SUDS survivors.[12] All patients underwent cardiac testing including 2-dimensional echocardiography, cardiac imaging with magnetic resonance imaging or computed tomography of the heart, cardiac catheterization, and electrophysiologic studies. Although we found no structural heart abnormalities in all 27 patients, we found that 59% (n = 16) of patients had Brugada electrocardiography (ECG) pattern and well-defined electrophysiological abnormalities: prolonged His-Purkinje conduction time (HV interval, 63 ± 11 ms vs 49 ± 6 ms; $P = .007$), a higher incidence of inducible VF (93%), and a positive signal-averaged ECG (92%) which was associated with a higher incidence of VF or death during the follow-up period when compared with the remaining 11 patients who had normal ECG. From this study, we were the first to establish that the Brugada ECG pattern is the marker for SUDS and the first to shed light on the pathophysiologic mechanisms underlying SUDS to BrS and its electrophysiological derangement leading to VF and the fatal event of SUDS.[12]

Coincidentally, we also learned early on that right precordial lead positioning (V1–V3) at higher intercostal space (ICS) could enhance the detection of Brugada ECG phenotype. As a result, we prospectively studied 16 male SUDS survivors with documented VF at the index event (mean age 42 years) in whom the Brugada ECG pattern was absent on the standard (fourth ICS) position, as shown in one example (Figure 1). By applying the high ICS lead positioning, we could further detect the Brugada ECG pattern in 7 (43.8%) of 16 cases.[13] Subsequently, after having learned the role of sodium-channel blockade for unmasking the Brugada phenotype, our group found that ajmaline could increase sensitivity in detecting BrS patients who might have been otherwise labeled as idiopathic VF survivors. Figure 2 shows an example of a patient who survived nocturnal cardiac arrests but exhibited no Brugada ECG pattern in all lead positioning, and only after ajmaline 50 mg administration did the Brugada ECG pattern appear in lead V2 at the third ICS lead positioning and in both V1 and V2 at the second ICS. We then systematically studied the role of sodium-channel blockade in conjunction with higher ICS lead positioning in SUDS patients. The study, which compared the sensitivity and specificity of ajmaline and procainamide in unmasking the Brugada ECG pattern, included 21 SUDS patients (mean age 44 years): 11 had survived VF arrests and 10 others had SUDS-like symptoms during sleep, and the control group consisted of 12 normal healthy male volunteers (mean age 36 years). Procainamide and ajmaline were given, at least 24 hours apart, by intravenous infusion over 15 minutes at a dosage of 10 mg/kg and 1 mg/kg, respectively. Figure 3 shows an example of a patient whose Brugada ECG pattern was present only with ajmaline and higher lead positioning (second and third ICS) and was absent at baseline and with procainamide administration at all ICS positionings of the right precordial leads. In the 27 patients, Brugada ECG pattern was unmasked by the regular lead position (fourth ICS) in 33% with procainamide and in 38% with ajmaline. In contrast, at the higher ICS lead positioning (third and second ICS), the detection rate increased significantly to 76% with procainamide and 95% with ajmaline ($P < .05$).[14,15] In the control group, there was no Brugada pattern detected by either regular or high ICS position. Based on these findings, we concluded that to increase the detection rate of the Brugada phenotype among SUDS survivors with a normal ECG, it is imperative to perform a 12-lead ECG with higher ICS lead positioning in combination with sodium-channel blockade, and that ajmaline is superior to procainamide for the provocative test to unmask the concealed Brugada phenotype of SUDS. Last, and importantly, these findings remove the mystery surrounding SUDS and firmly portray BrS as the main underlying disease of SUDS.

Our work on SUDS started around the same time that researchers found that the Brugada ECG pattern was associated with sudden death.[16] Both topics have fascinated scientists worldwide, and our discovery that BrS is part of SUDS led us to join forces with colleagues from the United States, Europe, and Japan to better understand and search for better risk stratification, treatment, and preventive measures. To that end, we developed 2 widely cited consensus documents that set up the ECG criteria for diagnosis of the Brugada

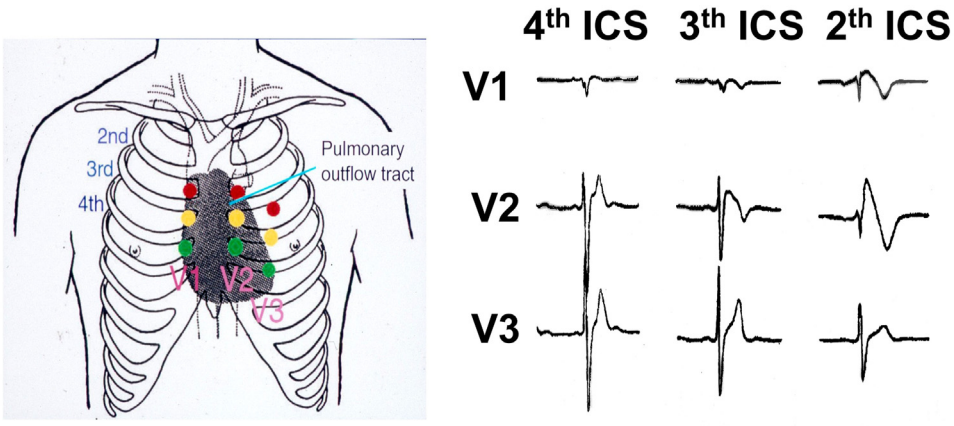

Figure 1 An example of how higher lead positioning can unmask a Brugada electrocardiography pattern. Note that the Brugada electrocardiography pattern is absent in the standard lead positioning at the fourth intercostal space (ICS) but is present in V2 at the third ICS and present in both V1 and V2 at the second ICS.

ECG phenotype, discuss the pathophysiologic mechanism of the syndrome, and detail genetic risk stratification and management of BrS.[17,18]

SUDS/BRS genetic studies in Thailand.

At the outset, we recognized that SUDS/BrS had a pattern of an inheritance syndrome via an autosomal-dominant mode of transmission with incomplete penetration. This encouraged us to join collaborative work with Professors Antzelevitch and Towbin to commence genetic studies in our patients. Following the breakthrough finding of *SCN5A* mutation underlying BrS,[19] our collaborative work also found a similar *SCN5A* mutation in 3 of 10 SUDS (Lai Tai and Pokkuri ["death during sleep" in Japanese]) families. We then concluded that SUDS and BrS are phenotypically, genetically, and functionally the same disorder.[20]

However, over 90% of our patients with SUDS/BrS do not carry pathogenic *SCN5A* variants in the BrS-associated genes. Probst et al[21] studied 13 large families with *SCN5A* mutations and found that many of the mutation carriers did not have the Brugada ECG pattern, nor it could be provoked by a sodium-channel blocker. Moreover, some of the affected individuals with the Brugada phenotype did not have the familial *SCN5A* mutations. Thus, it is clear that the monogenic contribution of *SCN5A* toward the BrS phenotype is modest and suggests that the genetic basis of BrS is more complex, in which disease susceptibility is determined by genetic variants

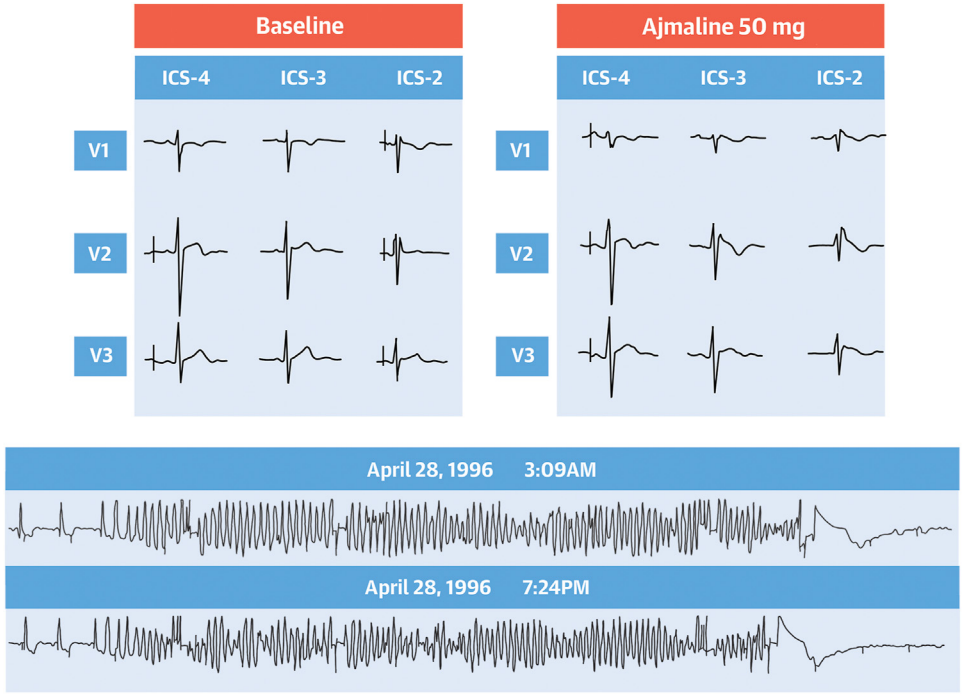

Figure 2 An example of how ajmaline, sodium-channel blocker, unmasks the Brugada electrocardiography pattern in conjunction with higher intercostal space (ICS) lead positioning (see text for details).

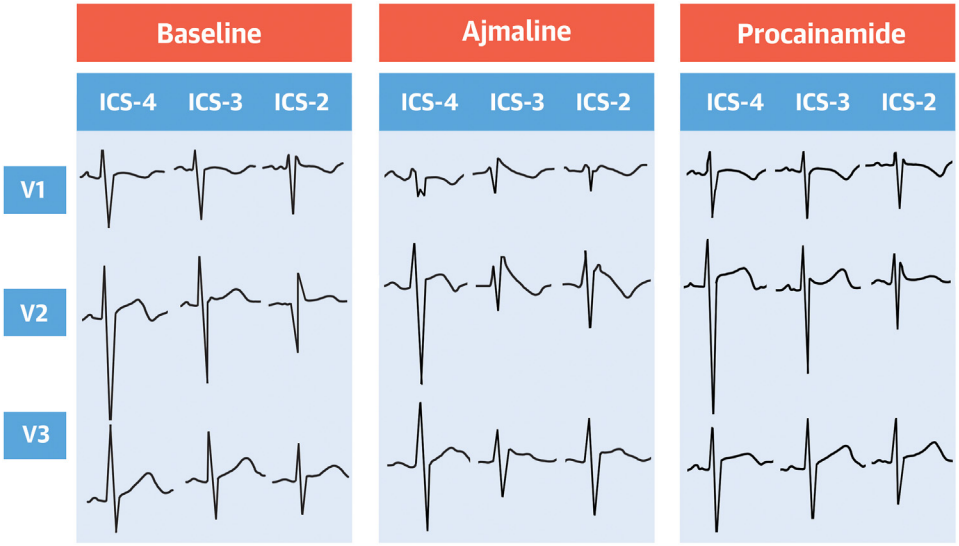

Figure 3 A comparison of the effects of ajmaline vs procainamide for unmasking Brugada intercostal space (ICS) pattern (see text for detail). ICS, intercostal space.

of diverse allele frequencies and effect sizes. This supposition was confirmed by Bezzina et al's[22] genome-wide association study that found an association between common variants at the SCN5A-SCN10A locus and a locus close to HEY2 with BrS susceptibility in individuals of European and Japanese ancestry. In alliance with the Amsterdam Medical Center (AMC) group, we conducted our own genome-wide association study to explore the association of common variants in 154 Thai BrS cases and 432 controls. We sequenced SCN5A in 131 cases and 205 controls. Our study found that common variants near SCN5A/SCN10A and HEY2 are also associated with BrS in the Thai population[23] further confirming the observation of Bezzina et al, and firmly established that BrS is a polygenic disease.

We also found that the prevalence of *SCN5A* rare variants (gnomAD exomes, filtering allele frequency <0.0001) in Thai BrS patients was lower (6.1%) than that reported in European (20%) patients and that enrichment of the intermediate-range low-frequency *SCN5A* variants (gnomAD exomes filtering allele frequency <0.001 and >0.0001) in our BrS population was higher than that in the control group (6.9% vs 0.5%; odds ratio, 15.0; $P = 1.2 \times 10^{-3}$).[23] Particularly, we also found that 4.6% of Thai BrS cases carried a variant *SCN5A* p.R965C compared with 0.5% in sex-matched controls (odds ratio, 9.8; $P = .015$). As a result, we further explored the clinical characteristics of Thai probands and family members with *SCN5A* p.R965C with or without BrS phenotype. Our study group comprised 7 hospitals in Thailand (NCT04232787), and we found that out of the 151 BrS cases and 358 controls, 12 (10 cases and 2 controls) carried the *SCN5A* p.R965C variant.[24] Of these 12 probands, we were able to contact 6 families, screening 63 family members including first-, second-, and third-degree relatives (42.9% male, 47 ± 19 years of age) and found an additional 11 *SCN5A* p.R965C carriers, 1 of whom had BrS. Thus, of 23 carriers of *SCN5A* R965C, 11 had BrS; 7 (64%) of the 11 BrS patients were symptomatic, including 5 VF and 2 unexplained syncope (n = 2), whereas all variant carriers without BrS were asymptomatic. Haplotype reconstruction was carried out in *SCN5A* p.R965C carriers and 574 Thais without this variant.[24] All *SCN5A* p.R965C carriers had the 70-kb haplotype at the genomic region up- and downstream to the location of this variant, while it was found in only 16 of 574 in the control group, suggesting that all 23 *SCN5A* p.R965C carriers have the same ancestor. Thus, we concluded that this variant is likely a result of founder mutation and may be one reason for high prevalence of BrS in Thailand.[24]

We thank Professors Bezzina and Wilde at AMC who helped to train our group and who continue to actively guide and participate in our genetic studies. Our collaborative work, as clearly evidenced previously, enabled our genetic studies in Thailand to be productive, active, and ongoing. Bezzina et al completed the European whole genome sequencing (WGS) studies in BrS[22] and has helped our group carry out and complete similar WGS studies in BrS Thai patients and control subjects.[23] We believe that the results of these studies will help us better understand the role of the genetic disorder in BrS and improve BrS diagnosis and risk stratification.

Treatment conundrum in Thailand at the early stage

The initial excitement from identification of the Brugada marker among the majority of SUDS patients was tempered by the reality that there was no effective treatment available in Thailand for symptomatic BrS patients during the 1990s. Quinidine was not accessible in Thailand. Implantable cardioverter-defibrillators (ICDs) were very expensive, not reimbursable, and not yet available in Thailand at that time. Also, ICD technology was still developing and just began

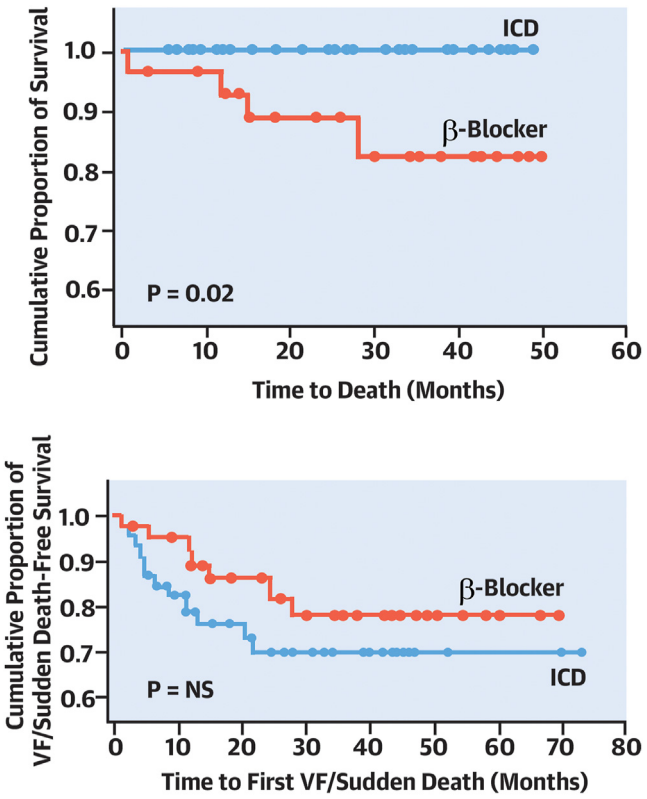

Figure 4 (Top) Kaplan-Meier survival curves for the 2 treatment arms (implantable cardioverter-defibrillator vs β-blocker (propranolol). The primary endpoint was mortality. Modified from Nademanee et al[28] with permission. (Bottom) Cumulative proportion of ventricular fibrillation/death occurrence using the composite endpoints of recurrent ventricular tachycardia/ventricular fibrillation (VF) or cardiac arrest from which the patient was resuscitated or death.

to change from open thoracotomy with epicardial defibrillation electrode patches and abdominal ICD pocket to transvenous ICD with a smaller pectoral device.[25] Furthermore, it had not yet been clearly established that ICDs were superior to antiarrhythmic drugs because several large ICD clinical trials, both primary and secondary prevention, were not completed. The MADIT (Multicenter Automatic Defibrillator Trial) and AVID (Antiarrhythmic versus Implantable Defibrillator Trial) trials were published in 1996 and 1997, respectively.[26,27] In short, the Thai health care system was not ready to approve an expensive major operation of ICD implantation for Thai BrS/SUDS patients who could not afford it and were likely to reject an open thoracotomy with the device in their abdomen. As a result, most symptomatic Brugada/SUDS patients were treated with amiodarone or beta-blockers, even though some arrhythmia scholars thought that they might be ineffective.

ICD odyssey in Thailand

Fortunately, in 1995, when the transvenous ICD became available, the late Dr Mower, a co-founder of the ICD with Dr Mirowski and at that time vice president of research at Guidant Inc (now part of Boston Scientific [Marlborough, Massachusetts]), donated a couple of transvenous Guidant ICD devices to us for 2 young BrS/SUDS patients who survived VF out-of-hospital cardiac arrests. Because the first ever ICD implanted in Southeast Asia was for our BrS patient and not an ischemic heart patient, as was commonly done in the Western world, it created an impetus for us to launch an ICD trial in SUDS/BrS patients.

Because there were no ICD trials at that time for patients with a primary electrical disease such as SUDS/BrS, we conducted a randomized trial to determine the efficacy and safety of ICD treatment for SUDS/BrS patients. We hypothesized that an ICD could prevent death in SUDS/BrS cases. With the support of Drs Mower and Guidant, in 1996, we launched a randomized clinical trial, the DEBUT (Defibrillator vs Beta-blocker for Sudden Unexplained Death in Thailand) trial,[28] after approval from the Institutional and Ministry of Public Health Review Board of Human Research Committee. The trial was conducted in 2 phases (pilot study followed by the main trial) to compare the annual all-cause mortality rates among SUDS patients treated with beta-blockers vs those treated with an ICD. A total of 86 patients, SUDS survivors and probable SUDS survivors, were randomized to an ICD (n = 47) or propranolol (n = 39). The primary endpoint was death from all causes. The secondary endpoint was recurrent ventricular tachycardia (VT)/VF or cardiac arrest. ICDs were donated by Guidant (St Paul, Minnesota). Our findings showed that ICDs are effective in preventing death (Figure 4). During 3-year follow-up, 12 (26%) ICD-treated patients had multiple VF episodes effectively terminated by the device and no deaths, compared with 7 (18%) deaths in propranolol-treated patients ($P = .02$). As shown in the bottom panel of Figure 4, a Kaplan-Meier survival curve of a composite of the primary and secondary endpoints (sudden death or VF episodes) shows relatively higher event rates (VF episodes or sudden death) in the ICD patients at an annual rate of 20% compared with only a 10% event rate in the propranolol treatment group, translating to a 50% reduction of recurrent VF episodes by propranolol; however, the drug is not totally effective in preventing deaths in the SUDS/BrS population, whereas an ICD is 100% effective. Based on the main trial results, the Data Safety Monitoring Board stopped the study on December 15, 2000, and all patients from the beta-blocker arm were offered ICD treatment free of charge.

The dilemma following the DEBUT study was how could we get ICDs for symptomatic SUDS/BrS patients who mostly were low-income blue-collar workers and main breadwinners for large families? Our group then created a nonprofit foundation that could receive donations to create funding for ICD purchases for these patients. In addition, we received donations of explanted ICDs that could be reused for our patients. These measures allowed us to treat and save many patients during the trial time in the early 2000s. Thankfully, later, the Thai government and Ministry of Health approved ICDs for SUDS/BrS in 2005.

While everyone agrees that symptomatic BrS patients should be treated with an ICD, the same cannot be stated

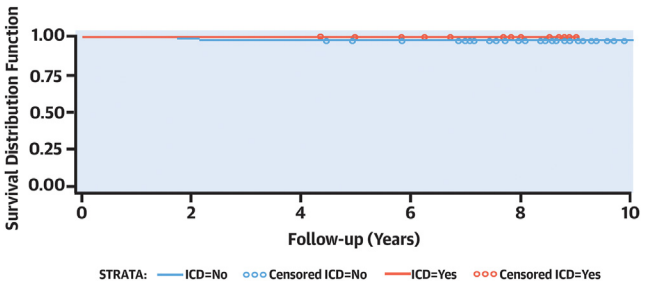

Figure 5 Kaplan-Meier survival curves for 2 treatment arms (implantable cardioverter-defibrillator [ICD] vs no ICD) in asymptomatic Brugada syndrome patients. The primary endpoint was mortality.

for asymptomatic BrS patients. ICD treatment remains controversial as to whether prophylactic implantation of ICD in asymptomatic BrS patients is truly beneficial. Our randomized, prospective, multicenter study, aiming to evaluate ICD as primary prevention of sudden cardiac death for asymptomatic BrS patients, was conducted between 1997 and 2008.[29] The study was supported by Grant-in Aid from Medtronic, including donation of ICD devices. We found that asymptomatic BrS patients had low rates of both spontaneous VF events and mortality rates. Figure 5 shows that the Kaplan-Meier 5-year and the annual mortality rate of asymptomatic BrS without ICD were only 2.3% and 0.25%, respectively, compared with 0% in the ICD group ($P = .5$). Based on these findings, we concluded that asymptomatic BrS patients have a very low mortality rate and prophylactic ICD offers no benefit, especially when balanced with unwanted effects of ICDs, which are relatively common among young BrS patients.

In our DEBUT trial and the previously mentioned primary prevention BrS study in asymptomatic BrS patients, we found that unwanted effects of ICDs occurred in 30% of ICD-treated patients.[28,29] The most common complication was inappropriate shocks caused by sinus tachycardia, which occurred during exertional activities, supraventricular tachycardia, and atrial tachyarrhythmias with rapid ventricular response. ICD and lead removals were necessary in 7% of our study patients because of either pocket infections or lead fractures causing multiple false shocks.

Therefore, even though an ICD saves lives of many Thai SUDS/BrS patients, we also have learned to judiciously utilize ICD treatment for appropriate patients, being mindful of its potential complications, including the need for multiple ICD changes in the future. Last, an ICD does not prevent VF recurrences, and its most important function is terminating the VF and restoring normal sinus rhythm. So, it is a daunting task to manage BrS patients who have frequent recurrent VF episodes with multiple ICD discharges.

Catheter ablation and Brugada arrhythmogenic substrates

Before an advent of catheter ablation of BrS substrates as discussed subsequently, there was no direct, reliable treatment to prevent VF recurrences. No antiarrhythmic agent was effective at preventing VF recurrences in BrS except quinidine, which was not available in Thailand or many other countries[30] and was often ineffective in severely symptomatic BrS patients. Thus, finding an alternative treatment modality for such BrS patients became a necessity.

The Bordeaux group pioneered ablation of VF trigger in symptomatic BrS patients. Their initial experiences demonstrated that a VF trigger, once identified and ablated, yielded good outcomes.[31] However, the occurrence of VF triggering premature ventricular contractions in BrS patients is quite inconsistent, and spontaneous VF triggering premature ventricular contractions often are not present to be mapped, making this approach impractical for treating many BrS patients.

Having to manage BrS patients with ICD storms and recurrent VF episodes forced us to find the alternative treatment approach for these patients.[32] In 2009, one such patient who suffered electrical storms (>20 VF episodes in 1 week) was our first patient in whom we found abnormal low-voltage fractionated electrograms that were present in a wide area of the anterior right ventricular outflow tract [RVOT]) epicardium and not elsewhere (Figure 6). After we ablated these areas, the Brugada ECG pattern normalized, VF became noninducible, and there were no VF recurrences in this patient. We then subsequently studied and ablated 8 more male patients, making a total of 9 patients who had multiple recurrent VF episodes necessitating multiple ICD shocks. CARTO electroanatomical mapping (Biosense Webster, Diamond Bar, California) of the right ventricle—both endocardially and epicardially—and epicardial mapping of the left ventricle were performed in all patients during sinus rhythm. All patients had abnormal electrograms characterized by low voltage (<1 mV), prolonged duration (>120 ms), fractionated late potentials (beyond QRS complex) clustering in the anterior aspect of the RVOT epicardium, and inducible VF. Ablation at these sites rendered VT/VF noninducible and normalization of the Brugada ECG pattern in the majority of the patients with no recurrent VT/VF in all patients off medication. We reported these findings in 2011 and stated that the anterior RVOT epicardium was exclusively the primary substrate site of BrS, and ablation at this substrate site normalizes the Brugada ECG and prevents recurrent VF.[32] However, as we expanded our experiences, we came to recognize that these conclusions were not entirely correct; we also found that about 30% of BrS patients also have arrhythmogenic substrates in the inferior right ventricular epicardium.[33]

Since our initial report, there have been several studies worldwide confirming our findings of the epicardial ablation of the VF substrates, and the procedure has been increasingly utilized for treatment of symptomatic BrS patients.[34–37] In Thailand alone, over the past 5 years, several tertiary centers have trained electrophysiologists and have performed mapping and ablation safely and effectively of >60 symptomatic BrS patients. And our center continues to serve as the training center not only in Thailand, but also in centers in Southeast Asia as well.

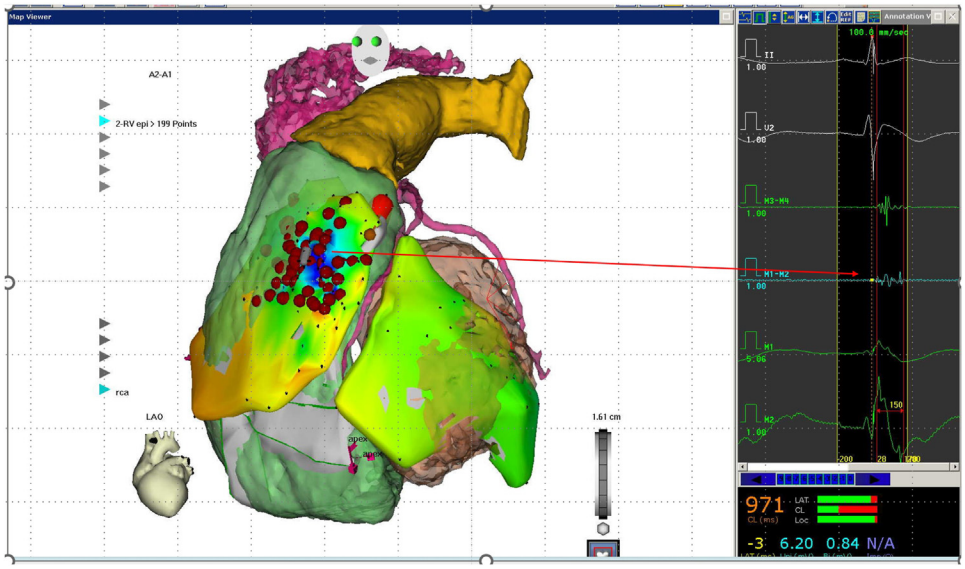

Figure 6 A composite picture of the CARTO-merge maps showing the cardiac computed tomography that is merged with the electroanatomic maps of the right ventricular outflow tract (RVOT) epicardium. The double annotation map (A2-A1), shown on the left, illustrates the scale of abnormal prolonged duration of the ventricular electrograms in the anterior RVOT as displayed in the color-coded area; the blue represents the longest duration (>160 ms) during sinus rhythm. The right inset displays the electrograms recorded from the NaviStar-ThermoCool catheter at the site of the anterior aspect of the RVOT epicardium (arrow). Red dots represent ablation points. Note that the duration of the electrograms in this area is quite prolonged (>160 ms) and low voltage (0.84 mV), is fractionated, and has prolonged duration (183 ms) and delayed depolarization beyond the end of the lead II-QRS complex (150 ms). M1 = unipolar distal; M1M2 = bipolar distal; M2 = unipolar of the second electrode; M3M4 = bipolar proximal.

We believe that the unique electrogram characteristics at the substrate sites mainly located in the RV epicardium would enable operators to identify them precisely and easily as long as they learn how to gain access to pericardial space and how to manipulate and navigate the catheter in the epicardial space. Detail of how to map and ablate the BrS substrate can be found in our online YouTube video (https://youtu.be/t5zBB1Y7oU0).

Low-voltage fractionated late-potential abnormal electrograms have been shown to be associated with fibrotic tissues or scar.[38] However, virtually all BrS patients have no evidence of structural abnormalities based on cardiac imaging. magnetic resonance imaging of the right ventricle often found no fibrosis in the RVOT.[32,39] Thus, the findings of such abnormal fractionated electrograms in the RVOT/right ventricular epicardium puzzled us initially as to what are the underlying pathological mechanisms of these abnormal electrograms?

It was just an opportune happenstance that we had to perform open thoracotomy for direct mapping and ablations in 6 symptomatic BrS patients with frequent ICD discharges (4 patients from our center in Thailand and 2 from Professor Nogami's laboratory at Tsukuba University); thoracotomy was indicated for ICD lead extraction (n = 4) or to permit epicardial access for ablation after a failed percutaneous attempt (n = 2). Ablations via thoracotomy allowed us to perform a biopsy of the substrate sites that harbored these abnormal fractionated electrograms.[40] The findings were quite remarkable: All 6 patients had thickened epicardial fibrosis and interstitial fibrosis. We then joined forces to collaborative study with Professor Behr at St George's, University of London in the United Kingdom and Professor Wilde at AMC with their necropsy study, which showed that SUDS victims with a family history of BrS had higher collagen content and lower connexin 43 expression in the RVOT and right ventricle compared with control subjects, with evidence of epicardial fibrosis and interstitial fibrosis similar to our in vivo study.[40] These pathological findings, therefore, firmly show that BrS is not truly and solely a primary electrical disease. Subsequently, we also further collaborated with Professor Haïssaguerre and Professors Hocini, Coronel, and Boukens, from Bordeaux and Amsterdam, in studying electrophysiological characteristics of these fibrotic substrates: We clearly showed that I_{Na} reduction with ajmaline and/or high rate pacing severely compromises impulse conduction in the BrS substrates and can uncover the fibrotic sites by producing fractionated electrograms, conduction block, or excitation failure that create milieu for a current-to-load mismatch phenomenon that leads to VF genesis and the signature Brugada ECG pattern.[41] Using electrocardiographic imaging and noninvasive VF mapping, we also demonstrated that during the first 5 seconds of VF, either spontaneously occurring or induced, VF drivers indeed were located at these fibrotic sites in the right ventricular epicardium.[41–43] Armed with the aforementioned findings, we have concluded that the pathophysiological mechanism underlying BrS is a complex interplay between subtle myopathic epicardial/subepicardial changes mainly in the RV and conditions that promote reduction of I_{Na}.[36–39,42,44] Last, we found that ajmaline is critically useful in guiding catheter ablations to eliminate all arrhythmogenic areas, as evidenced by a 2-fold increase in the size of the target area for the ablation.

Role of ablation for long-term treatment: Can it be a substitute for ICD?

Brugada substrate ablation now has been accepted as an important effective treatment modality and is being utilized in several centers worldwide. However, long-term outcomes are still needed. Therefore, we have created a world-wide BRAVO (Brugada Ablation of VF Substrate Ongoing Multicenter) registry study of catheter ablation (NCT04420078) for treatment of symptomatic BrS patients and presented the interim results at the 39th Annual Heart Rhythm Scientific Sessions in 2019; the full manuscript is under review. The BRAVO registry results confirm our initial observation that BrS substrate ablation is safe and very effective and provides excellent long-term outcomes. The only major complication is pericardial bleeding (1%) with no procedural death. Recently, several patients who had been free of VF for several years and did not want an ICD anymore requested that the device be taken out or did not want a replacement device at the end of the current ICD's battery life. Similarly, new symptomatic Brugada patients who sought ablation treatment did not want an ICD implanted after the ablation.

We believe that it would be premature to recommend catheter ablation alone without an ICD for symptomatic BrS patients, especially those who survived aborted sudden cardiac death. One also has to be mindful that BrS is part of J-wave syndrome that includes early repolarization syndrome, and often the 2 syndromes coexist.[40] This combined BrS and early repolarization syndrome has a higher rate of VF recurrences after ablation, and thus many of those with J-wave syndrome will continue to need ICD backup. That said, however, we hypothesize that symptomatic BrS patients who had no overlapping syndrome of BrS and early repolarization syndrome could be treated after substrate ablations without ICD if normalization of the right precordial ECG at the higher ICS lead positioning after sodium-channel blocker challenge could be achieved. To address this hypothesis, we are carrying out a randomized clinical trial, the BRAVE (Brugada Syndrome Ablation for the prevention of VF Episodes) study (NCT02704416). Once this trial is completed, it is very likely that we will have the answer as to whether we can treat symptomatic BrS patients without an ICD.

Conclusions and future direction

Three decades have passed since we started working on the enigma of SUDS that quickly changed into a rigorous effort on research and management of BrS in Thailand. Throughout this time, we have made major strides in advancing our understanding and management of the syndrome: we believe we have made seminal contributions in diagnosing and identifying high-risk BrS patients, bringing to light the pathophysiology of the syndrome and pioneering the catheter ablation approach for prevention of VF episodes. It is important to appreciate the quality of our work, despite some logistical obstacles at the beginning, which were overcome by the collaborative work and support from multidisciplinary groups including Thai and international researchers and scientists, industries, Thai Research Councils, several major Thai university hospitals and the Thai Airforce Hospital. As a result, our work has twice benefitted: (1) it benefits those BrS patients who now will receive objective quality evaluation not only for them, but for their families, and will get effective treatment that improves both their quality of life and survival; and (2) it benefits researchers who work on SUDS/inherited arrhythmic syndrome by providing insights into how subtle myopathic changes in the heart can interact with genetic or external factors that in turn create milieu for VF genesis. Our work partly contributes to several guidelines and consensus statements on BrS and sudden death investigation and provides knowledge that will shape future research as well.

Presently, we have formed a strong consortium among major arrhythmia centers in the universities of each region in Thailand: each region is fully set up to evaluate and treat BrS patients, including catheter ablation of Brugada substrates. This consortium with international collaboration also actively participates in ongoing research in the BRAVE randomized clinical trial, which is funded by National Research Council of Thailand and Biosense Webster, WGS, and artificial intelligence and machine learning for risk stratifications and genetic analysis. We also actively collaborate with industries like Biosense Webster and Medtronic to develop better tools to map and ablate epicardial substrate sites, hoping that we will be able to make the ablation procedure easier, less demanding, and more effective. Last, we believe that our experience can be share with other neighboring countries in Southeast Asia, and hopefully they too will be able to duplicate what we have done or even make it better for their countries. To this end, we are pleased to announce our team now plans to develop similar programs like ours in Hanoi, Vietnam, this year. If the program comes to fruition, many Vietnamese SUDS/BrS patients will greatly benefit from our work by not having to worry about VF or sudden death, and this makes our Brugada journey over the past 30 years so worthwhile!

Funding Sources: This work is partially supported by the National Research Council of Thailand (3/2562), a Grant in Aid from Bumrungrad Hospital, and Biosense Webster Inc.

Disclosures: The authors have no conflicts of interest to disclose.

Authorship: All authors attest they meet the current ICMJE criteria for authorship.

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