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Review

Treatment of electrical storms in Brugada syndrome

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ABSTRACT

Patients with Brugada syndrome (BrS) not uncommonly suffer from recurrent and recalcitrant ventricular fibrillation episodes, the so-called "electrical storm" which is malignant and potentially lethal event. While electrical storm in BrS is a therapeutic challenge, fortunately there are effective therapeutic solutions which must be compulsory applied: Elimination of precipitating factors, isoproterenol and oral quinidine are the first 2 therapeutic steps that one must urgently commenced. And if this measure should fail, ablation of the triggering ventricular premature beats and/or substrate ablation at the anterior aspect of the right ventricular outflow tract should be performed.

Contents

1. Introduction

Two decades ago, Pedro and Joseph Brugada described a group of 8 patients with a normal heart who suffered ventricular fibrillation (VF) or sudden cardiac death and had an abnormal electrocardiogram (ECG) of coved type ST elevation over the right precordial leads [1]. It was acknowledged instantly as the Brugada syndrome (BrS), which has also been linked with sudden unexpected death syndrome (SUDS) that usually occurs at night in young Southeast Asian men with a normal heart [2,3]. BrS now is well recognized as a common autosomal dominant inherited arrhythmia disorder with gene mutations that are predominantly confined to the SCN5A gene, which encodes for α-subunit of sodium channel, causing loss of I_{Na} [3–6].

Treatment of BrS patients is a significant challenge because there are limited treatment options, and an implantable cardioverter–defibrillator (ICD) is the only choice for high-risk BrS patients (i.e., those who had aborted sudden cardiac death or had previous VF episodes) [7–10]. Unfortunately, even though ICDs are effective at

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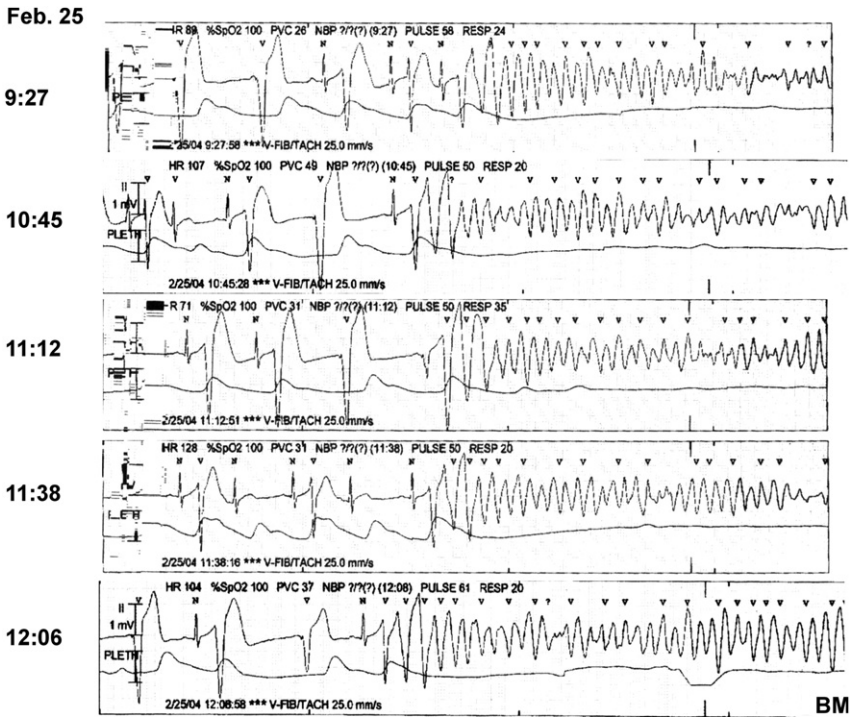

Fig. 1. An example of recurrent VF episodes in a patient with type 1 Brugada ECG pattern who presented with cardiac arrest associated with high temperature and hypokalemia. The patient had frequent PVCs triggering VF episodes 5 times over the span of 3 h on February 25, 2004. Note the identical pattern of VF episodes that were triggered by short-coupling PVCs.

reverting VF episodes to sinus rhythm, they do not prevent VF occurrence. Thus, when some BrS patients experience frequent recurrences of VF episodes necessitating frequent ICD discharges, the so-called "electrical storm" (ES), physicians face the daunting task of suppressing such VF episodes. Fortunately, in recent years, we have learned a great deal more about the syndrome and have therapeutic advances that enable us to treat BrS patients with ES much more effectively than a decade ago. Our review herewith will discuss these advances and how to treat ES in BrS patients most effectively.

2. Definition and incidence of electrical storm

ES is defined as three or more episodes of VF per day recorded by the ICD interrogation or documented in the recording in the intensive care unit (ICU) (Fig. 1). The true incidence of ES in the BrS is difficult to ascertain. Thus far, most of the reports of ES have been case reports or studies with a very small number of patients. The incidence of ES in our BrS population in Thailand is 5–7% in symptomatic patients, but none in our asymptomatic BrS population.

3. Mechanisms of ventricular fibrillation/electrical storm in the Brugada syndrome patients

One of the most consistent features of BrS is that premature ventricular contraction (PVC), which triggers VF, is almost always short-coupling [3,4]. An interesting phenomenon is that many of the VF episodes in BrS patients are self-terminating, contradicting the conventional wisdom that VF episodes are equivalent to death. Indeed, after experiencing the growing numbers of patients with this syndrome, we have learned that VF in patients with a structurally normal heart, unlike those with ischemic heart disease, often spontaneously reverts back to sinus rhythm [3,4].

Two questions arise: (1) Why are some VF episodes sustained and frequently recurrent, causing ES and leading to sudden death or cardiac arrests? (2) What are the underlying electrophysiologic mechanisms and predisposing and precipitating factors that modulate the substrate, resulting in perpetuation of the VF? While answers to these questions remain elusive, some new information in recent years has emerged, which may partially help to explain the pathogenesis of VF occurrences.

In recent years, there has been a well-recognized debate of the pathophysiologic and electrophysiologic mechanisms underlying BrS: repolarization vs. depolarization [11]. Shortly after the syndrome was introduced, Antzelevitch and colleagues proposed the repolarization theory as the electrophysiologic abnormalities of the BrS that were largely based on their arterially perfused wedge preparation of the canine right ventricle (RV) [12]. They found that a combination of sodium channel blockers and acetylcholine caused a loss of the action potential (AP) dome in RV epicardium, but not in RV endocardium, and created a transmural voltage gradient. And when the wedge preparation was exposed to these 2 drugs, this area then developed a notch and dome appearance of the epicardium AP, leading to a coved type ST-segment elevation in the right precordial leads. The RV epicardium is well known to have abundant I_{to}, which in turn makes this area more conducive to the accentuation of the AP dome and shortening of AP. If the loss of the AP dome is further accentuated, then it causes the marked shortening of the epicardial AP in certain regions, causing pronounced heterogeneity of transmembrane voltage potentials and, in turn, causing phase 2 reentry and triggered VF.

The clinical relevance to support this theory is the findings that there is a good correlation between a long RR interval and the magnitude of ST-elevation over the right precordial leads. Matsuo et al. presented a case report of a patient with BrS in whom 12-lead ECGs were recorded just before and after an episode of VF [13]. They demonstrated a progressive elevation of both the RS–T segment and *J* waves just preceding and following the VF, and a

close relationship between the amplitude of the RS–T segment and the preceding R–R intervals during atrial fibrillation. Similarly, Mizumaki et al. showed that ST elevation over the right precordial leads was augmented during bradycardia to a similar extent in both symptomatic and asymptomatic patients [14]. These findings along with the evidence that isoproterenol attenuates ST-elevation in BrS suggest that the mechanism underlying a pause dependent augmentation of the ST elevation in BrS may be due to an increase in Ito after prolonged RR interval—in turn supporting repolarization disorder.

Kurita et al. presented a case report in which monophasic AP recordings from epicardium and endocardium were performed simultaneously in the BrS patient [15]. The transmembrane gradient of AP between the epicardium and endocardium were observed; however, the authors did not find the shortening of the epicardial AP. Perhaps this observational study shows that quinidine, a strong Ito blocker, is effective in treating BrS patients also indirect evidence that supports the repolarization theory [16]. While the repolarization theory enjoyed its popularity early on, the lack of more strong clinically relevant findings to convincingly support the concept led to the other theory, depolarization disorder.

The depolarization disorder hypothesis considers that conduction delay, particularly in the RV outflow tract (RVOT), plays a role in the pathogenesis of BrS. Using an electrical guidewire to record an epicardial electrogram from a conus branch of the right coronary artery, Negase et al. were the first to show abnormal electrograms characterized by late potential after QRS, which were recorded from the free wall of the RVOT epicardium in the BrS patients [17]. Their findings suggest conduction delay in the RVOT epicardium. Coronel et al. reported their findings from the explanted heart of a BrS patient who had SCN5A mutation with medically-treated failure VF storms, necessitating heart transplantation surgery [18]. The explanted heart showed no evidence of 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 investigators then proposed the depolarization hypothesis, which contends that in BrS, the RVOT depolarizes last after the rest of the ventricular myocardium has completely depolarized [19]. As a result, the delay in the AP of the RVOT causes the electrical gradient from the more positive RV to RVOT, leading to the ST-elevation of the right precordial leads similar to the situation of a myocardial injury at the RVOT and as the RVOT depolarizes later (during repolarization of the RV), this gradient is reversed and the net current flows toward the RV, resulting in a negative *T* wave in the same right precordial leads. The experiment from the same group in this explanted heart also showed that this site is the arrhythmogenic site during programmed stimulation-induced VF. Frustaci et al. also reported the biopsy findings showing fibrosis in patients with the Brugada phenotype [20]. And there are a number of clinical studies showing that the delayed activation of the RVOT in BrS patients indeed occurred [21–27]. Regardless of which theory is correct, it becomes quite clear from the preceding studies as well as from the study by Moriata et al. [28], that the RVOT is the likely arrhythmogenic substrate site of the BrS.

Our group then carried out a study to determine the substrate sites and arrhythmogenic mechanisms of the BrS [29]. We found that all our BrS patients had abnormal low voltage, fractionated late potentials exclusively clustering in the anterior aspect of the RVOT epicardium and not seen anywhere else, and RVOT endocardium or left ventricular (LV) epicardium. Fig. 2 shows an example of low-voltage fractionated electrograms recorded from the anterior RVOT epicardium of a patient who presented with ES. Ablation at this area normalized the Brugada ECG pattern and prevented recurrent VF episodes. Similar observations were found in all our study patients, and these findings clearly provide the strongest clinical evidence that the delayed depolarization at the anterior aspect of the RVOT is the most likely underlying electrophysiologic mechanism underlying BrS (see more discussion below). Although it is quite apparent that depolarization disorder is likely to be the main mechanism underlying the BrS, one has to be mindful that repolarization abnormality could contribute to the arrhythmogenesis of the BrS patients, along with genetic mutations of ionic channel and other precipitating factors.

Genetic mutation in BrS was first described by Chen et al., who reported the first mutation linked to BrS in the SCN5A gene, which encodes for the α-subunit of the sodium channel [30]. Since then, >100 SCN5A mutations have been discovered in BrS patients, and they are the most common type found in 11–28% of BrS probands; however, the genetics of BrS have become heterogeneous. In addition to the SCN5A mutations, more mutations are found in gene encoding protein of potassium and calcium channels. These genetic findings in and the pharmacological features of BrS are generally 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 evidenced by the late fractionated potential in the anterior RVOT epicardium and by the ionic 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}. A decrease in I_{Na} (commonly seen in SCN5A

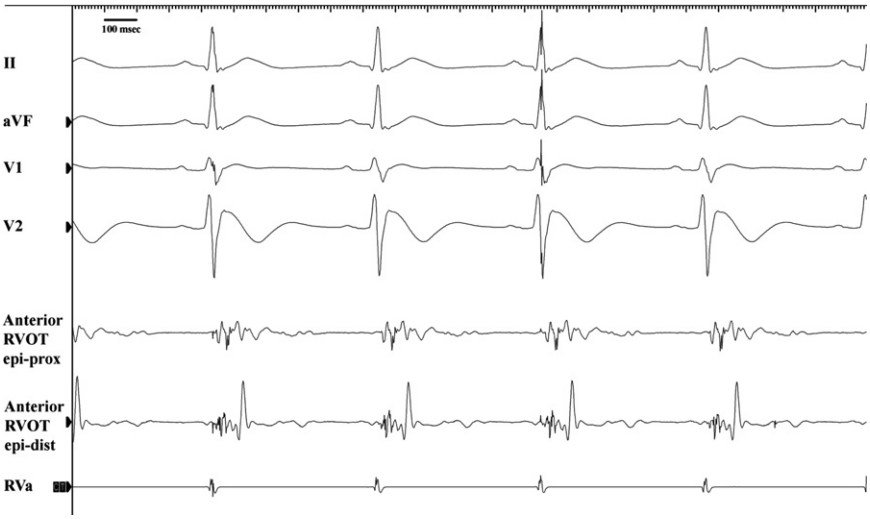

Fig. 2. A typical low-voltage fractionated late potential recorded at the anterior aspect of the RVOT in a patient with the typical type 1 Brugada ECG pattern in V_2.

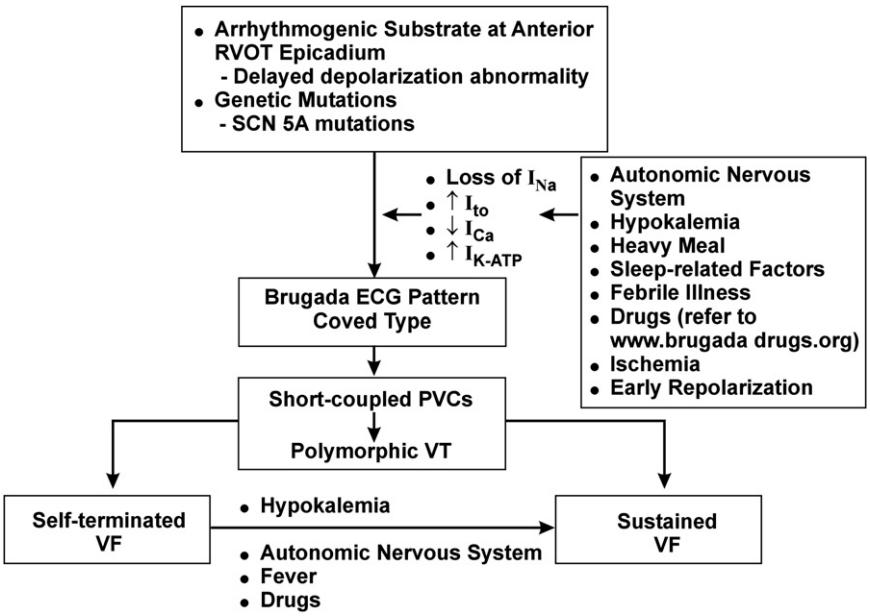

Fig. 3. Proposed pathophysiologic mechanisms of BrS with respect to predisposing factors.

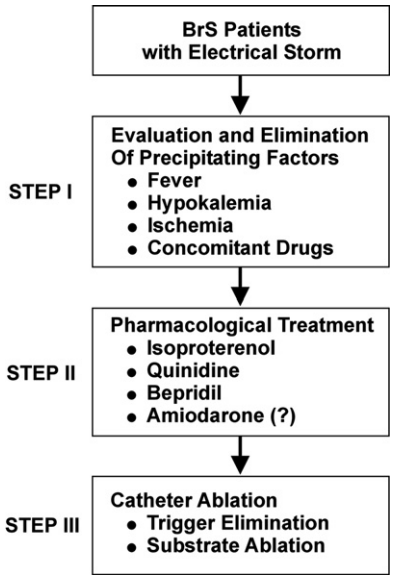

Fig. 4. Algorithm of a management approach for electrical storm associated with the Brugada syndrome.

mutations in BrS patients), a decrease in I_{Ca-L}, and an increase in I_{to} or IK_{ATP}, modify the action morphology in such a way that safety of conduction is decreased (i.e., potentially leading to conduction slowing or conduction block in structural discontinuous myocardium or at Purkinje-ventricular muscle boundaries). All of these possibilities are linked to genetic variants associated with BrS, and some of them, in particular the amplitude of I_{Ca-L}, are sensitive to changes in autonomic tone. Similarly, pharmacologic interventions that block I_{to} or increase I_{Ca-L}, respectively, quinidine and isoproterenol, 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.

Fig. 3 shows the possible pathophysiologic mechanisms underlying BrS and their modulating and precipitating factors. BrS patients had arrhythmogenic substrates displaying as late fractionated low-voltage potential in the anterior RVOT epicardium, which causes type I Brugada ECG pattern or could be accentuated or unmasked by sodium channel blocker (i.e., ajmaline, procainamide, flecainide, etc.), febrile illness, vagotonic agents, α-adrenergic agonists, β-adrenergic blockers, tricyclic or tetracyclic antidepressants, or first generation antihistaminies (dimenhydrinate).

In the presence of SCN5A mutation that results in loss of I_{Na}, BrS patients not only could have more prominent ECG abnormality, but also develop short-coupling PVCs that could trigger VT/VF. In the presence of predisposing factors such as an altered autonomic nervous system, fever, or hypokalemia, VF could become sustained and occur frequently.

4. Algorithm of treatment approach in Brugada syndrome patients with electrical storm

Fig. 4 shows the flow diagram of how we treat BrS patients with ES. Patients are admitted to the ICU and should be well sedated, and some may require general anesthesia with endotracheal intubation. The patients are evaluated to determine if there are precipitating factors to be eliminated or treated. In the acute phase of ES when patients continue to have recurrent VF episodes, Steps 1 and 2, as described below, should be carrried out simultaneously.

4.1. Step 1: elimination of precipitating factors

Precipitating factors for VF in the BrS, as shown in Fig. 2, often are present during ES, and if they were eliminated, ES often subsided. Fig. 4 shows an example of successful ES treatment of the same patient as in Fig. 1, by treating fever and replacing potassium. However, if one encounters BrS patients who continue to have recurrent VF despite having no obvious precipitating factors or have been well treated, then one has to go to the next step using pharmacological treatment.

4.2. Step 2: pharmacological treatment

Only a few drugs that been found to be effective in treating ES in BrS patients, and most published data came from case reports and studies with a small number of patients [31–35]. Nevertheless, the following drugs are found by most investigators to be useful in treating ES.

4.2.1. Isoproterenol infusion and other β-adrenergic agonists

Isoproterenol, well known to normalize the Brugada ECG pattern by increasing I_{Ca-L}, is found to be effective in acute treatment of ES. Ohgo et al. found that isoproterenol (0.003 ± 0.003 μg/kg/min), by raising heart rate by 20%, completely suppressed ES in all 5 BrS patients [31]. After this acute treatment, the investigators prescribed denopamine (an $\alpha+\beta$ adrenergic agonist) at a dose of 30 mg/day, which was found to be effective in 3 of the 5 patients at long-term follow-up; however, 2 of the remaining patients required a concomitant treatment of quinidine (see discussion below) during chronic treatment. These findings and reports by others indicate that isoproterenol is the drug of choice during the acute phase of ES in BrS patients.

Cilostazol, an oral phosphodiesterase inhibitor, has also been shown to be efficient in preventing recurrent VF in BrS patients [31,36]. Drugs that decreased the vagal tone (by decreasing IK_{Ach} and increasing I_{Ca-L}), such as atropine, may be beneficial by increasing the heart rate and in turn decreasing I_{to}. However, atropine infusion alone is not quite as effective as isoproterenol infusion. Clearly, in the presence of acute ES, isoproterenol infusion, along with the Step 1 recommendation to eliminate or correct the precipitating factors, should be commenced simultaneously.

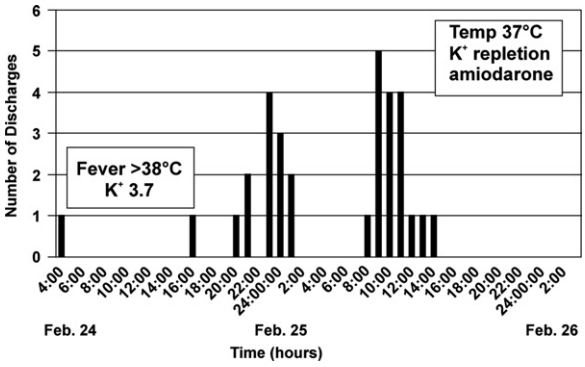

Fig. 5. Successful treatment of electrical storm by treating fever, potassium repletion, and amiodarone for the same Brugada syndrome patient as in Fig. 1.

4.2.2. Quinidine and other antiarrhythmic drugs

Bellhassen et al. demonstrated that quinidine is an effective drug for treatment of ventricular arrhythmias associated with BrS. Although the drug is a class IA antiarrhythmic agent, it is also a potent I_{to} blocker [16]. Bellhassen and colleagues found that quinidine bisulfate at a mean dose of 1.5 g daily prevented VF inducibility in 88% of patients and was associated with no recurrence of arrhythmia with a mean follow-up of 56 months. Others also have found that the drug is quite useful in BrS patients with ES. However, quinidine at the high dose is associated with a high incidence of side effects (approximately 36%): gastrointestinal symptoms, liver dysfunction, thrombocytopenia, allergic reaction, and QT prolongation are not uncommon. Marquez et al., reported a retrospective study of an efficacy of low-dose quinidine ($\leq$600 mg daily) in 6 BrS patients with VF episodes necessitating ICD discharges (including 4 patients with ES). They found that low-dose quinidine prevented VF recurrence in all 6 patients in their series [37]. The investigators also combined their patients to those reported in the literature, from which they found 14 additional BrS patients treated with the low-dose quinidine. After combing both the literature review and their cases, they found that low-dose quinidine is effective in preventing VF recurrences up to 85%, and is well tolerated. However, in many parts of the world, unfortunately, quinidine is not available, as the pharmaceutical companies have ceased its production due to low profit [38].

Bepridil, a class III drug with I_{to} blocking properties, is reported to be effective in treating BrS patients with frequent VF recurrences, but the drug is only available in Japan [31,39]. Amiodarone has not been found to be reliably effective. However, it is the only drug that could be used in Thailand with variable success, as shown in the patient in Fig. 5.

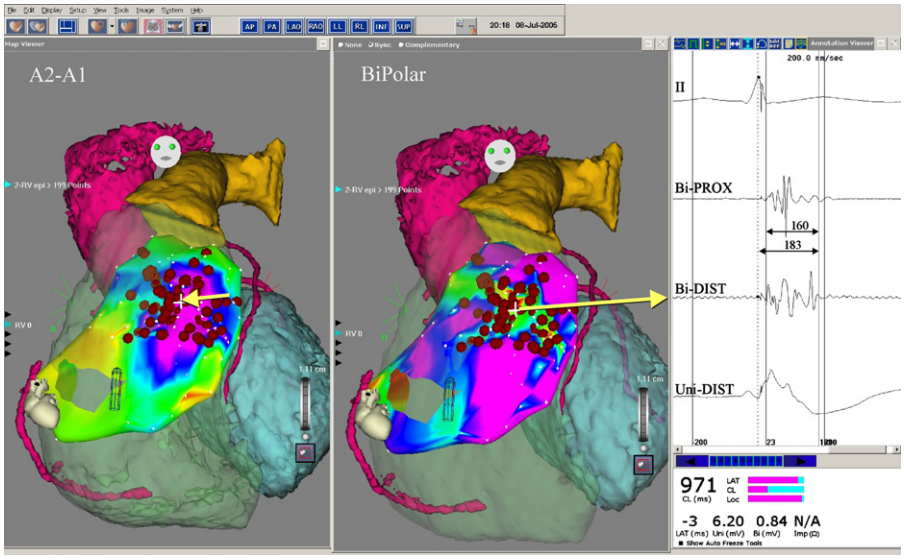

Fig. 6. A composite picture of the CARTO-merge maps of a Brugada syndrome patient with electrical storm shows the cardiac computed tomography that is merged with the electroanatomic maps of the right ventricular outflow tract (RVOT) epicardium. The double annotation map (A2–A1), shown on the left, illustrates the scale of abnormal prolonged duration of the ventricular electrograms in the anterior RVOT as displayed in the color-coded area; the purple represents the longest duration ($>$160 ms) during sinus rhythm. The voltage map, shown in the middle, is the same as the A2–A1 map, but is displayed differently, with the color-coded area of low voltage in red and high voltage in purple. The right inset displays the electrograms recorded from the NaviStar-ThermoCool catheter at the site of the anterior aspect of the RVOT epicardium (arrow); (refer to the text for details). Red dots represent ablation points. The voltage map and the representative tracing of the bipolar and unipolar electrograms are recorded from the anterior aspect of the RVOT epicardium. Note that the duration of the electrograms in this area is quite prolonged ($>$150 ms) and low voltage ($<$1 mV). The bipolar electrogram recorded from this site shows the electrogram is low voltage (0.84 mV), fractionated, and has prolonged duration (183 ms) and delayed depolarization beyond the end of the lead II-QRS complex (160 ms). Bi-DIST=bipolar distal; Bi-PROX=bipolar proximal; Uni-DIST=unipolar distal. Reproduced with permission from .
Nademanee et al. [29]

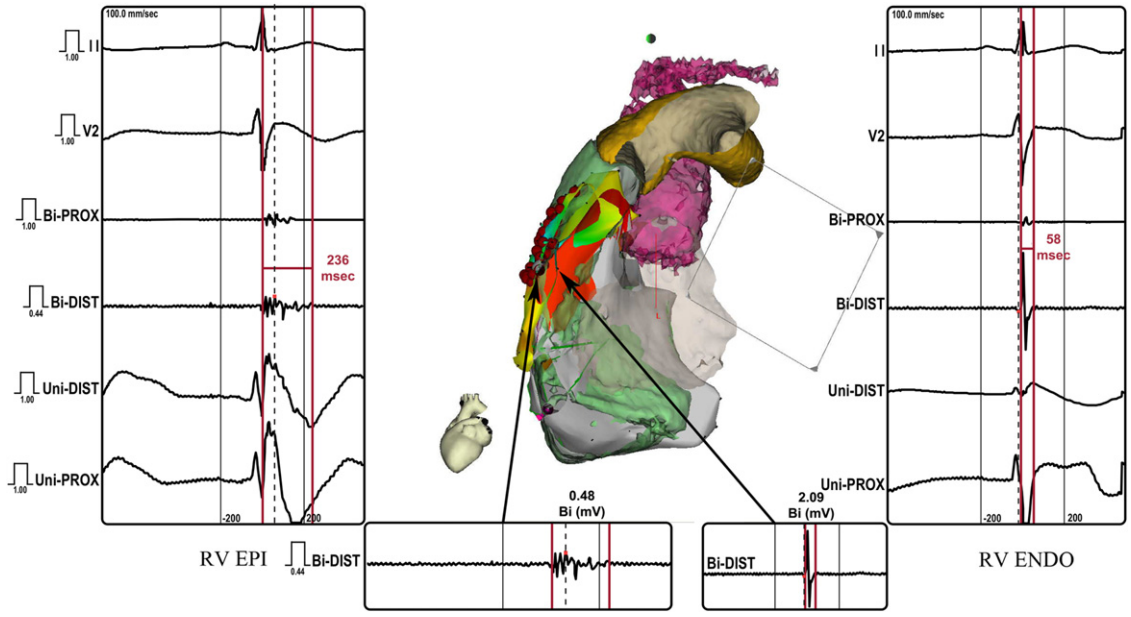

Fig. 7. A left lateral view of the right ventricular outflow tract (RVOT) displays the difference in ventricular electrograms between the endocardial and epicardial site of the anterior RVOT of the same patient as in Fig. 6. The left and right insets display bipolar and unipolar electrograms recorded from the epicardium and endocardium from the same site of the RVOT, respectively. Bi-DIST=bipolar distal; Bi-PROX=bipolar proximal; Uni-DIST=unipolar distal; Uni-PROX=unipolar proximal. Reproduced with permission from .
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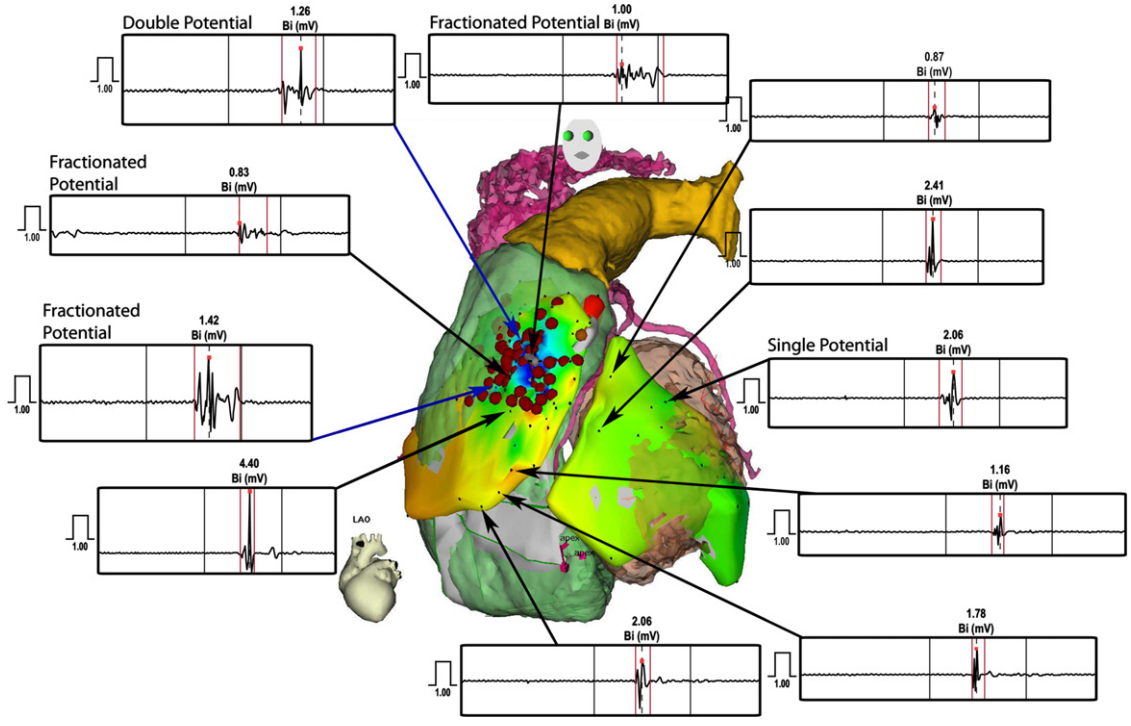

Fig. 8. Comparison of ventricular electrograms recorded from different sites in both the left ventricle (LV) and right ventricle (RV) of the same patient as in Figs. 6 and 7. Reproduced with permission from .
Nademanee et al. [29]

4.3. Step 3: catheter ablation

4.3.1. Ablation of the VF triggers

Haïssaguerre et al. was the first to report the non-pharmacologic approach using mapping and ablating PVCs that triggered VF. They found PVCs that triggered VF emanating from the RVOT in 2 patients, and from the anterior RV Purkinje network in 1 patient [40]. After ablations of these triggering PVCs, all 3 patients had no VF recurrences over a 1.5-year follow-up period. Since then, there have been a few more case reports with similar approaches and results [41,42]. Unfortunately, most of the BrS patients rarely have PVCs frequent enough to be mapped, even during the ES period. The

occurrence of triggering PVCs in BrS patients is quite capricious in nature and poses a problem for anyone attempting to map these triggers, and in turn, limited this approach from being practical in treating many BrS patients with ES, leading to the search of BrS substrates as target sites for catheter ablation.

4.3.2. Substrate ablation

As described earlier, we recently studied 9 symptomatic patients with BrS (all male; mean age 39 years) who had multiple recurrent VF episodes (4 ± 1.5) per month, necessitating multiple ICD shocks. Using CARTO Electroanatomical mapping (Biosense Webster, Diamond Bar, CA USA) of the RV both endocardially and epicardially and epicardial mapping of the LV were performed in all patients during sinus rhythm [29]. All patients had typical type 1 Brugada ECG pattern and inducible VT/VF.

Fig. 6 shows an example of our CARTO map in a BrS patient with ES showing abnormal ventricular electrograms recorded in the area of the anterior RVOT epicardium, as evidenced by abnormal prolonged ventricular electrograms (>150 ms), markedly delayed depolarization, as shown by the late potential that continued to depolarize beyond the QRS complex (>160 ms), and very low-voltage fractionated electrograms. These abnormal electrograms are exclusively localized in a cluster over the anterior RVOT epicardium and are not seen anywhere else in the right or left ventricle (Figs. 7 and 8). As shown in Fig. 7, the endocardial site (arrow) displays a single potential of 2.09 mV, with a duration of 58 ms, and did not extend beyond the QRS compared to the epicardial counterpart that showed low-voltage late potential (0.48 mV), with a duration of 236 ms with late potential extended beyond QRS.

Fig. 8 shows epicardial electrograms recorded from various sites of the epicardium in both the LV and RV epicardium. Note that abnormal fractionated electrograms and double potential electrograms are only localized in the anterior aspect of the RVOT epicardium.

We found that all other patients in this study also had identical substrates at the same area of the anterior RVOT epicardium, which is characterized by abnormal low-voltage fractionated ventricular electrograms (<1 mV) that have a markedly delayed conduction time after QRS complex on the surface ECG (>100 ms), and a markedly prolonged duration (>130 ms). Ablation at these sites rendered VT/VF non-inducible in 78% of our patients, and normalization of the Brugada ECG pattern in 89% of our patients. Thus, we have identified and shown that anterior RVOT epicardium is the arrhythmogenic substrate site for our BrS patients. We have now performed ablations in 20 BrS patients with frequent ICD discharges; 3 patients required a second ablation, but there were no complications. Long-term outcomes (median 32 months) were excellent, with no recurrent VT/VF in all patients off medication. Long-term outcomes (median 32 months) were excellent, with no recurrent VT/VF in all patients off medication. Based on these findings, our study provides major clinical implication that has therapeutic value for BrS patients with ES: We now can find the arrhythmogenic substrate that serves very well as target sites for catheter ablation, and thus can expect a good clinical outcome. Further studies clearly need to be done to assess values and limitations of catheter ablation in patients with BrS with frequent ICS shocks.

5. Conclusions

The past two decades since BrS was first reported has witnessed major progress toward understanding pathophysiology of the syndrome. We now have more therapeutic advances to deal with recurrent VF storms necessitating multiple successive ICD shocks, the electrical storm. Elimination of precipitating factors, quinidine and catheter ablation of epicardial substrate in ES cases are our best choice of treatment that is likely to be effective and not only ameliorate patient symptoms but prevent untimely death as well. In other words, we are now well equipped with both knowledge and tools to help our BrS patients ride out the electrical storm safely.

Conflict of interest

Dr. Koonlawee Nademanee has Consulting Agreements, Research Grants and Royalties from Biosense Webster.

Dr. Veerakul has no conflict of interest to declare.

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