MINI-FOCUS ISSUE: BRUGADA SYNDROME   **Editorial Comment**

The Brugada Syndrome*

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Fifteen years ago in this *Journal,* Brugada and Brugada (1) reported a new syndrome with ST-segment elevation in ECG leads V_1 to V_3, right bundle branch appearance during sinus rhythm, and a high incidence of ventricular fibrillation (VF) and sudden cardiac death. There were 8 patients (6 males and 2 females) in that original report. Patient #7, an 8-year-old girl, was the only 1 with a history of paroxysmal atrial fibrillation (AF). The paroxysmal AF occurred soon after birth, and the first episode of syncope occurred at the age of 8 years. She was a subject in another case report 12 years later because of multiple documented episodes of VFs induced by short-coupled premature ventricular contractions (2). Programmed stimulation induced nonsustained polymorphic ventricular tachycardia in 3 patients at baseline and during isoproterenol infusion. In 4 patients, including Patient #7, the same programmed stimulation induced VF.

See pages 1154, 1162, and 1169

In this issue of the *Journal,* 3 articles (3–5) provided new insights into the characteristic T-wave changes in Brugada syndrome, the prevalence of AF, and the mechanisms that determine the inducibility of VF during electrophysiological studies. These studies have significantly advanced the understanding of Brugada syndrome.
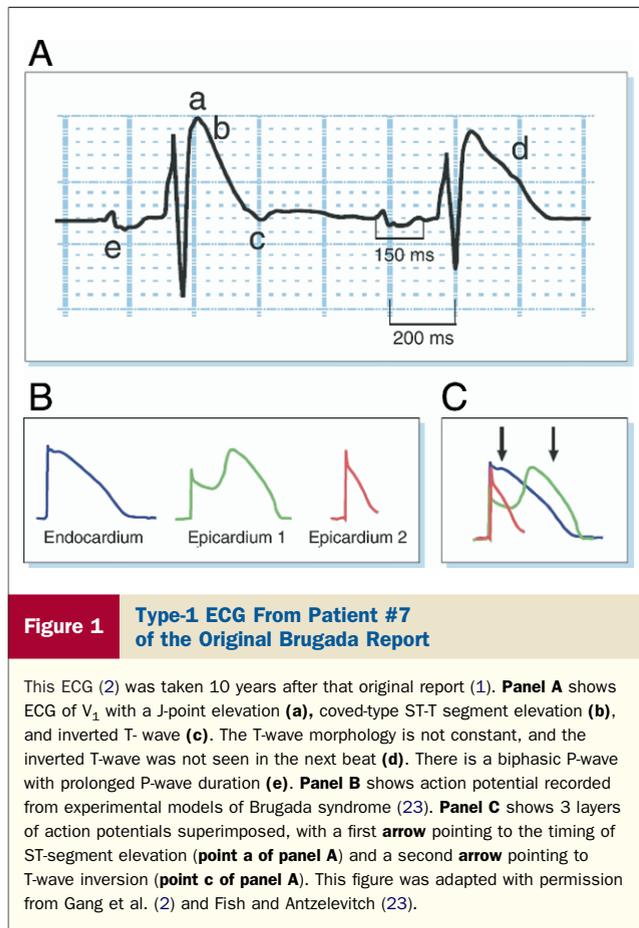
Prevalence of Brugada syndrome. Though uncommon in the rest of the world, sudden unexpected death syndrome (SUDS) in East Asia and Southeast Asia is a major cause of death in young men without known underlying cardiac diseases (6). Similar clinical manifestations were also found in the U.S. among immigrants from Southeast Asia (7), suggesting a genetic basis of this disease. Roughly 80% of the clinically affected patients are male, and the sudden death typically occurs at night. Epidemiological studies in Japan showed the prevalence of Brugada syndrome to be from 0.12% to 0.14% in the general population (8,9).

Genetic basis of Brugada syndrome. Roughly 15% to 20% of the patients with Brugada syndrome had mutations at the alpha subunit of the sodium channel gene (SCN5A) (10,11). Since the first report by Chen et al. (12), over 100 different mutations of SCN5A have been identified and more mutations are being added to the list on a regular basis (13). In addition to the mutations of the sodium channel itself, mutations of genes that modulate sodium channel function are also associated with Brugada syndrome. For example, mutation of the ankyrin-binding motif of $Na_v1.5$ results in a loss of binding of $Na_v1.5$ with its intracellular target chaperon ankyrin G, leading to Brugada syndrome (14). Mutation of glycerol-3-phosphate dehydrogenase 1-like (GPD1-L) gene may affect trafficking of the sodium channel to the cell surface, which in turn reduces sodium current and causes Brugada syndrome (15). Abnormalities of the sodium current are not the only genetic defects identified in Brugada syndrome. Antzelevitch et al. (16) screened 82 consecutive probands of Brugada syndrome patients for ion channel mutations. In 7 of the 82 (8.5%) patients, there were mutations in genes encoding the cardiac L-type calcium channel. Among them, 3 exhibited a new clinical entity of short QT interval, sudden death, and type-1 Brugada ECGs. These findings indicate that, in addition to abnormalities of sodium currents, the reduced calcium current can also contribute to the development of Brugada syndrome. However, the genetic basis of the majority of the patients remains unclear. Because different genetic defects may result in different phenotypes, large gaps of knowledge exist in the understanding of not only the genetic basis, but also the clinical manifestations of the diseases.

The Brugada ECG: abnormalities of ST-T waves. The ECG patterns associated with typical Brugada syndrome were first reported by Martini et al. (17). Subsequent studies showed 3 different types of ECG changes to be associated with Brugada syndrome based on the morphology in V_1 and V_2 (18). Type-1 ECG is characterized by a ≥2-mm J-point elevation, coved type ST-T segment elevation, and inverted T-wave in leads V_1 and V_2 (Fig. 1A). Type-2 ECG is characterized by a ≥2-mm J-point elevation, ≥1-mm ST-segment elevation, saddleback ST-T segment, and a positive or biphasic T-wave. Type-3 ECG is the same as type 2, except that the ST-segment elevation is <1 mm. Among these 3 types of ECGs, only the type 1 is diagnostic of Brugada syndrome. A simple method to document type-1 ECG is to move the V_1 lead from the third intercostal's space to the

Figure 1 **Type-1 ECG From Patient #7
of the Original Brugada Report**

This ECG (2) was taken 10 years after that original report (1). **Panel A** shows ECG of V_1 with a J-point elevation **(a)**, coved-type ST-T segment elevation **(b)**, and inverted T- wave **(c)**. The T-wave morphology is not constant, and the inverted T-wave was not seen in the next beat **(d)**. There is a biphasic P-wave with prolonged P-wave duration **(e)**. **Panel B** shows action potential recorded from experimental models of Brugada syndrome (23). **Panel C** shows 3 layers of action potentials superimposed, with a first **arrow** pointing to the timing of ST-segment elevation (**point a of panel A**) and a second **arrow** pointing to T-wave inversion (**point c of panel A**). This figure was adapted with permission from Gang et al. (2) and Fish and Antzelevitch (23).

second intercostal's space. However, the sensitivity and specificity of the diagnosis established with upward displacement of leads are unknown. Another method is to take an ECG after a large meal (19), which is positive in approximately one-half of the patients. If these simple maneuvers do not work, infusion of sodium channel blockers might prove effective (20). The commonly used drugs for this test include intravenous flecainide, ajmaline, pilsicainide, and procainamide. The latter is the favorite in the U.S., as the other 3 are not readily available. However, it is important to note that the previous, large studies of Brugada syndrome (21,22) have used either flecainide or ajmaline. The diagnostic accuracy of the procainamide test remains unknown. The ability of the sodium channel blockade to induce type-1 ECG patterns of Brugada syndrome supports a causal relationship between the reduced sodium current and the generation of the type-1 ECG. The putative mechanism (23) is that after the sodium channel blockade, the transient outward current (I_{to}) was unopposed, resulting in abbreviated action potential in some cells (epicardium 1 in Fig. 1B). Other cells have delayed onset of phase 2 due to the strong, unopposed I_{to} that prolonged phase 1 of the action potential (epicardium 2 in Fig. 1B). The weaker I_{to} in the endocardium allows its action potential to maintain the usual morphology. The vector between endocardium and epicardium during phase 1 accounts for the ST-segment elevation

(point a in Fig. 1A). The prolonged action potential of epicardium 2 accounts for the vector that created the negative terminal T-wave (point c in Fig. 1A). Because I_{to} is stronger in male patients than in female patients, and in the right ventricle than in the left ventricle, this hypothesis nicely matches the clinical manifestation of Brugada syndrome (18). To test whether or not this hypothesis applies to human patients, Nagase et al. (5) inserted a catheter in the conus branch of the right coronary artery to measure the electrograms from the right ventricular outflow tract. They also placed an endocardial catheter in the right ventricular endocardium to measure endocardial electrograms. Using the activation-recovery interval (ARI) to estimate the action potential duration (APD), the investigators were able to determine the differences of APD between the epicardium and the endocardium both at baseline and after the infusion of pilsicainide, a commonly used sodium channel blocker in Japan. The primary finding was that the ARI at the epicardium was longer than the endocardium when the type-1 ECG pattern was recorded, which is consistent with the experimental data shown in Figure 1B. In contrast, none of the normal control patients had type-1 ECGs induced by pilsicainide infusion. They propose that these findings are consistent with the hypothesis that both sodium current and I_{to} played important roles in the generation of the type-1 ECG.

The investigators ought to be congratulated for their ability to record ARI simultaneously from the epicardium and endocardium. This new approach provided important support for the Antzelevitch et al. (1) hypothesis of ST-T wave changes in Brugada syndrome. However, there are also a couple of very interesting additional findings in the study. First, if the reduced sodium current is the only mechanism for the ECG patterns of Brugada syndrome, then pilsicainide, which blocks sodium current, should induce Brugada-type ECGs in all patients. However, the investigators reported that the ARI at both epicardial and endocardial sites of normal control patients decreased after pilsicainide administration. Second, the investigators found that the SCN5A mutation was found in only 4 of the 19 patients with Brugada syndrome, but pilsicainide-induced type-1 ECGs and epicardial ARI prolongation were found in all Brugada syndrome patients. These findings suggest that the Brugada-type ECG cannot be explained solely by a reduction of sodium current. A possible additional factor is a mutation involving other ionic currents, such as the calcium current (16). Alternatively, it could also be related to structural abnormalities that can affect the activation and repolarization characteristics of the hearts. In fact, endomyocardial biopsy of patients with Brugada syndrome has a high yield for detecting hidden histological abnormalities that could contribute to the clinical phenotypes of Brugada syndrome (24).
The Brugada ECG: abnormalities of P waves. In addition to the abnormalities of the ST-T segments, the Brugada ECG is also characterized by abnormalities of the P waves. Figure 1A shows an example of abnormally prolonged and biphasic P

waves in a patient with both paroxysmal AF and VF. Yamada et al. (25) found that filtered P-wave duration was significantly increased in patients with Brugada syndrome and Brugada-type ECGs in comparison with control subjects. Electrophysiological studies showed induction of both AF and VF in these patients. Yokokawa et al. (26) found that P-wave duration in patients with the SCN5A mutation is 155 ± 19 ms, much longer than the P wave in patients without SCN5A mutation (119 ± 16 ms). These findings suggest that the reduced sodium current and the intra-atrial conduction velocity underlie the mechanisms of increased P-wave duration in patients with Brugada syndrome.

AF in Brugada syndrome. In this issue of the *Journal*, Kusano et al. (4) provided new insights into the mechanisms of AF in Brugada syndrome. The investigators studied 73 patients and found spontaneous AF in 10 of them. Among patients with documented VF, there is a higher incidence of spontaneous AF, the inducibility of AF by extrastimuli and prolonged interatrial conduction time. This study is an extension of a similar study reported in 2002, in this *Journal*, in which the same group of investigators (11) reported a high incidence of AF (7 of 18) in patients with Brugada syndrome. With the increased number of patients, the incidence of AF dropped to 10 of 73, which is similar to that originally reported by Brugada and Brugada (1). In addition, an association between AF and VF was documented in the present study. This latter finding is consistent with a report by Bigi et al. (27), who showed that the most important predictor of AF in Brugada syndrome is the occurrence of previous life-threatening cardiac events.

Kusano et al. (4) reported that just like VF, the AF in patients with Brugada syndrome occurs mostly (70%) at night. It is generally assumed that the vagal tone is higher at night than during the day. However, Ogawa et al. (28) recently reported, in this *Journal*, the results of simultaneous sympathetic and vagal nerve recordings in ambulatory dogs 24 h a day, 7 days a week. They found a clear circadian variation of sympathetic nerve activity with a higher sympathetic tone during the day than at night. However, the activity in the left thoracic vagal nerve did not show a circadian variation. The vagal tone was not increased at night in these ambulatory animals. The increased vagal dominance at night is explained by sympathetic withdrawal rather than by an increased vagal nerve activity. This finding has potential implications on the arrhythmogenesis in Brugada syndrome. The sympathetic nerve activity is the primary regulator of the L-type calcium current responsible for phase 2 of the action potential. Because the arrhythmogenic mechanism in Brugada syndrome is related in part to the heterogeneous loss of action potential dome and phase 2 re-entry (29), the sympathetic withdrawal at night could reduce the calcium entry through the L-type calcium current, leading to a loss of dome of the action potential. In contrast, the circadian increase of the sympathetic tone during the day helps maintain the dome of the action potential and prevent arrhythmia.

APD restitution and VF. Among patients with Brugada-type ECGs, not all are symptomatic or die suddenly. It is unclear why some patients seem to be prone to VF but others are not. A report by Hayashi et al. (3), in this issue of the *Journal,* provided clues to the risk of VF in patients with Brugada syndrome. The investigators performed programmed stimulation in 21 patients with type-1 ECG patterns. The investigators then plotted the ARI against the preceding diastolic interval to construct the APD restitution curve and calculated the slope of APD restitution in all patients. Their results showed that the slope of APD restitution was steeper in patients with inducible VF than in patients without inducible VF. They concluded that the repolarization restitution property is a contributing factor for the propensity of VF in patients with Brugada syndrome.

Nolasco and Dahlen (30) found that the slope of the APD restitution is an important determinant of the stability of the heart rhythm. Subsequent studies (31,32) have supported the importance of APD restitution slope in arrhythmogenesis in the animal models. Nash et al. (33) observed in humans a significant spatial heterogeneity of APD restitution slope. Their computer modeling shows that the heterogeneity of the APD restitution slope may provide a substrate for arrhythmia. The work by Hayashi et al. (3) also showed different slopes at right ventricular apical sites and outflow tracts, suggesting the existence of significant spatial heterogeneity. These findings are consistent with the studies in animal models that showed the spatiotemporal heterogeneity of cellular restitution is important in cardiac arrhythmogenesis (34).

Recent studies have suggested that intracellular calcium dynamics are important factors in determining the APD restitution (35). The work by Hayashi et al. (3) suggests the calcium dynamics might be important in determining the inducibility of VF in Brugada syndrome patients. In addition to calcium handling and APD restitution, excitability and the conduction velocity restitution are also known to be important factors in the development of VF (36). The excitability and conduction velocity are critically dependent on the availability of the sodium current. Significantly reduced excitability associated with a short-coupling interval could lead to a complete failure of conduction and the development of wave breaks in the process. The investigators (3) have observed in their data longer paced QRS duration and conduction time in patients with inducible VF than in those without inducible VF, suggesting that there are differential reduction of sodium channel activity in the 2 groups of patients.

Mechanisms of arrhythmogenesis. The mechanisms of arrhythmogenesis in Brugada syndrome can be explained by the heterogeneous shortening of the APD on the right ventricular epicardium (Fig. 2) (18,37). Insufficient sodium current and calcium current coupled with strong I_{to} can result in the loss of action potential dome and early repolarization in some of the epicardial cells (AP1) (Fig. 2A). The same reduction of sodium current, however, can also lead to a delayed onset of phase 2 and paradoxically
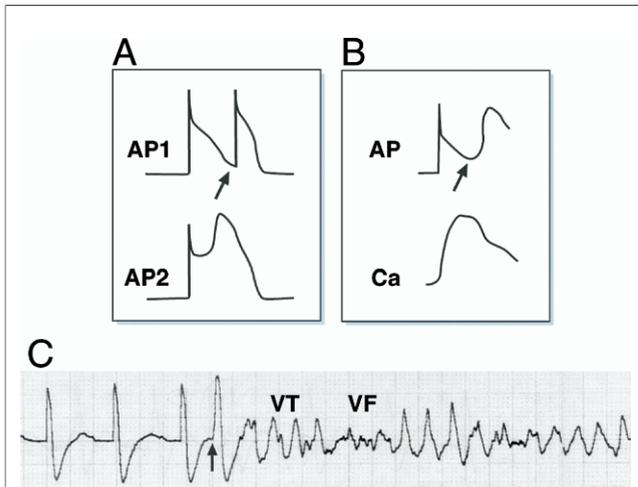
Figure 2 **Schematics of Possible Arrhythmogenic Mechanisms**

The first beat of arrhythmia (premature ventricular contraction) might happen by phase 2 re-entry **(A)** or late phase 3 early afterdepolarization **(B)**. If the first beat conducts to the rest of the ventricles, it results in a short-coupled premature ventricular contraction **(arrow, C)**. The degeneration of ventricular tachycardia to ventricular fibrillation occurs if the slope of the activation potential duration restitution curve is steep (3). AP = action potential; Ca = intracellular calcium concentration. This figure was adapted with permission from Gang et al. (2) and Fish and Antzelevitch (23).

prolongs the action potential (AP2) (Fig. 2A). The electrophysiological heterogeneity creates an electrical gradient between AP2 and AP1 (arrow, Fig. 2A), resulting in phase 2 re-entry. Mechanism 2 is phase 3 early afterdepolarization (38,39). Figure 2B shows a schematic of this mechanism. Acute shortening of the APD allows the intracellular calcium to be elevated during the late phase 3 of the action potential (Fig. 2B) and activates the Na-Ca exchange current. Because the Na-Ca exchange current exchanges 3 sodium ions (3 positive charges) with 1 calcium ion (2 positive charges), there is a net inward (depolarizing) current that promotes the afterdepolarization (arrow in Fig. 2B) and triggered activity (40). This hypothesis is best documented in the atria, where vagal activation strongly shortens the action potential. Because of an association between AF and VF in Brugada syndrome patients (4), it is possible that the same mechanism is operative in both the atria and the ventricles.

The occurrence of phase 2 re-entry or triggered activity by late phase 3 early afterdepolarizations both predict that the arrhythmia in Brugada syndrome should be initiated by short-coupled premature ventricular contractions that occur during the T wave of the preceding depolarization (Fig. 2C). However, a short-coupled premature ventricular contraction, as shown in this case (2), was an unusual occurrence in Brugada syndrome (41). Both reported cases have a history of electrical storm (2,41), which is also unusual in patients with Brugada syndrome. The coincidental occurrence of 2 rare phenomena (the short-coupled premature ventricular contractions and electrical storms) suggests a causal link between them. A possible explanation is that all arrhythmias in Brugada syndrome started with phase 2 re-entry or late phase 3 early

afterdepolarization. However, in patients with only a small amount of cells showing shortened APD, the local re-entry or triggered activity was not able to find an immediate exit from the right ventricle. The re-entrant wavefront propagates locally and finds an exit only when most of the ventricles are repolarized, resulting in a long-coupled premature ventricular contraction. However, in patients with a more severe form of the syndrome, sufficient cells had APD shortening to allow the immediate exit of the phase 2 re-entry or triggered activity to both ventricles. Therefore, only in the more severe form of the Brugada syndrome will short-coupled premature ventricular contractions occur. The beat-to-beat changes of T-wave morphology (Fig. 1A) support the idea that the relative number of AP1 and AP2 varies from time to time. The dynamic changes of AP1 and AP2 balance could also account for the wax and wane of Brugada-type ECG patterns commonly observed in many patients with Brugada syndrome (6).

Management of patients with Brugada syndrome. The current practice guidelines (42) recommend the placement of an implantable cardioverter-defibrillator (ICD) in Brugada syndrome patients with a previous history of cardiac arrest and who are receiving optimal medical therapy. This class I indication is supported by a prospective randomized trial (DEBUT [Defibrillator Versus beta-Blockers for Unexplained Death in Thailand]) that showed effective prevention of sudden death by the ICD (43). The class IIA indications for ICD implantation include patients with a history of syncope and documented ventricular tachycardia with a history of cardiac arrest.

Drugs that inhibit the I_{to} (such as quinidine) and increase the calcium current (such as isoproterenol) are recognized as effective treatments of the Brugada syndrome by the current practice guidelines (42). Belhassen et al. (44) reported that quinidine bisulfate ($1,483 \pm 240$ mg/day) effectively prevents VF induction in patients with Brugada syndrome and suppresses spontaneous arrhythmias. A more recent study showed that a much lower dosage of quinidine (300 to 600 mg a day) may be effective in preventing VF (45). In a recent report, isoproterenol infusion (0.003 ± 0.003 μg/kg/min) completely suppressed electrical storm of VF in all 5 patients treated (46).

Summary. The terminal T-wave inversion in Brugada syndrome ECG is explained by the prolongation of epicardial ARI more than by the endocardial ARI when sodium current is reduced either spontaneously or by pilsicainide infusion (5). The APD restitution characteristics are important factors in determining the inducibility of VF. Patients with spontaneous AF have higher incidence of syncope and documented VF (3). However, there are still many unanswered questions. For example, suppression of sodium current in normal individuals failed to produce Brugada-type ECGs or prolong the epicardial ARI (5). The SCN5A mutation is found only in a small percentage of the patients, and the presence of SCN5A mutation does not predict the severity of the disease (4). The mechanism that resulted in the association between AF and VF remains unclear. More work is still needed to understand the mechanisms of arrhythmia in Brugada syndrome.

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