

STATE-OF-THE-ART PAPER

Brugada Syndrome: 1992–2002

A Historical Perspective

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An intriguing new clinical entity characterized by ST-segment elevation in the right precordial electrocardiographic leads and a high incidence of sudden death in individuals with structurally normal hearts was described by Pedro and Josep Brugada in 1992. The past decade has witnessed an exponential rise in the number of reported cases and a dramatic proliferation of papers serving to define the clinical, genetic, cellular, ionic, and molecular aspects of this disease. The purpose of this brief review is to chronicle the historical highlights that have brought us to our present understanding of Brugada syndrome. (J Am Coll Cardiol 2003;41:1665–71) © 2003 by the American College of Cardiology Foundation

Evolution of a new clinical entity responsible for sudden cardiac death: Brugada syndrome. The first such case brought to the attention of the Brugada brothers involved a three-year-old boy from Poland who presented in 1986 following multiple episodes of syncope. His electrocardiogram (ECG) showed ST-segment elevation limited to leads V₁ through V₃. His sister displayed a similar clinical and ECG profile and died at two years of age, despite combined treatment with a pacemaker and amiodarone. Six similar cases came to their attention in succeeding years, and in 1992, they reported these eight cases as the basis for a new and distinct clinical entity (1).

In 1996, Yan and Antzelevitch (2), in their description of the cellular basis for the J-wave of the ECG, highlighted the importance of ST-segment elevation (accentuated J-wave) and apparent right bundle branch block (RBBB) syndrome, described by Brugada and Brugada, and named it the “Brugada syndrome.” Kobayashi et al. (3) and Miyazaki et al. (4) followed suit that same year.

The ECG pattern of ST-segment elevation and inversion of the T-wave in the right precordial leads (Fig. 1), with and without RBBB, was described as early as 1953 (5). This ECG phenomenon was largely ignored until Martini et al. in 1989 (6) and Aihara et al. (7) in 1990 brought attention to a possible link between this ventricular repolarization abnormality and sudden death. It is noteworthy that the Padua group (6) described only one patient with the typical Brugada ECG (Patient no. 3). Two others displayed RBBB

without ST-segment elevation, another showed an rsR' with barely detectable ST-segment elevation, and the rest showed only inverted T waves. In this publication, as in subsequent ones, the Padua group emphasized the anatomic abnormalities, however subtle, attempting to link these and similar cases to arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C).

Whereas Martini et al. (6) maintain that structural or morphologic defects are involved, Brugada et al. exclude these from the diagnosis, stressing the functional basis for the syndrome. In 2001, Corrado et al. (8) elegantly described a subpopulation of ARVC patients displaying features of Brugada syndrome, including ST-segment elevation in leads V₁ through V₃ and polymorphic ventricular tachycardia (VT). This study clearly suggested that a subgroup of ARVC patients can display a Brugada-like phenotype during the relatively early stages of the disease.

The ARVD/C and Brugada syndromes are quite distinct genetically. Brugada syndrome has thus far been linked only to mutations in SCN5A, the gene encoding for the alpha-subunit of the sodium channel, whereas ARVD/C has been linked to seven different chromosomal sites and three putative genes (9). In a recent study of a large group of Brugada patients, Remme et al. (10) reported that the vast majority of patients showed no evidence of structural disease. Subsequent follow-up uncovered ARVC in only one patient (11).

Using electron beam computed tomography, Takagi et al. (12) recently demonstrated wall motion abnormalities in the right ventricular outflow tract (RVOT) (n = 17) and inferior wall (n = 4) in 21 of 26 Brugada patients. Although wall motion abnormalities are commonly considered indicative of structural problems, recent studies (13,14) suggest that such contractile dysfunction can result from a loss of the action potential dome in regions of right ventricular (RV) epicardium, unrelated to any type of morphologic defect.

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Abbreviations and Acronyms

- ARVD/C = arrhythmogenic right ventricular dysplasia/
cardiomyopathy
- ECG = electrocardiogram/electrocardiographic
- EPS = electrophysiologic study
- ICD = implantable cardioverter-defibrillator
- I_{Na} = sodium channel current
- I_{to} = transient outward current
- RBBB = right bundle branch block
- RV = right ventricle/ventricular
- RVOT = right ventricular outflow tract
- SAECG = signal-averaged electrocardiogram
- VF = ventricular fibrillation
- VT = ventricular tachycardia

Also pertinent to this issue is the finding that signal-averaged electrocardiogram (SAECG) recordings demonstrate late potentials in patients with Brugada syndrome, especially in the anterior wall of the RVOT (15,16). Nagase *et al.* (17) recently recorded delayed potentials from the epicardial surface of the anterior wall of the RVOT, coinciding with late potentials on the SAECG, in patients with Brugada syndrome. Although late potentials are commonly regarded as representative of delayed activation of the myocardium, often due to structural defects, recent studies suggest that in the case of Brugada syndrome, these late and delayed potentials may represent the delayed second upstroke of the epicardial action potential or local phase 2 reentry (14).

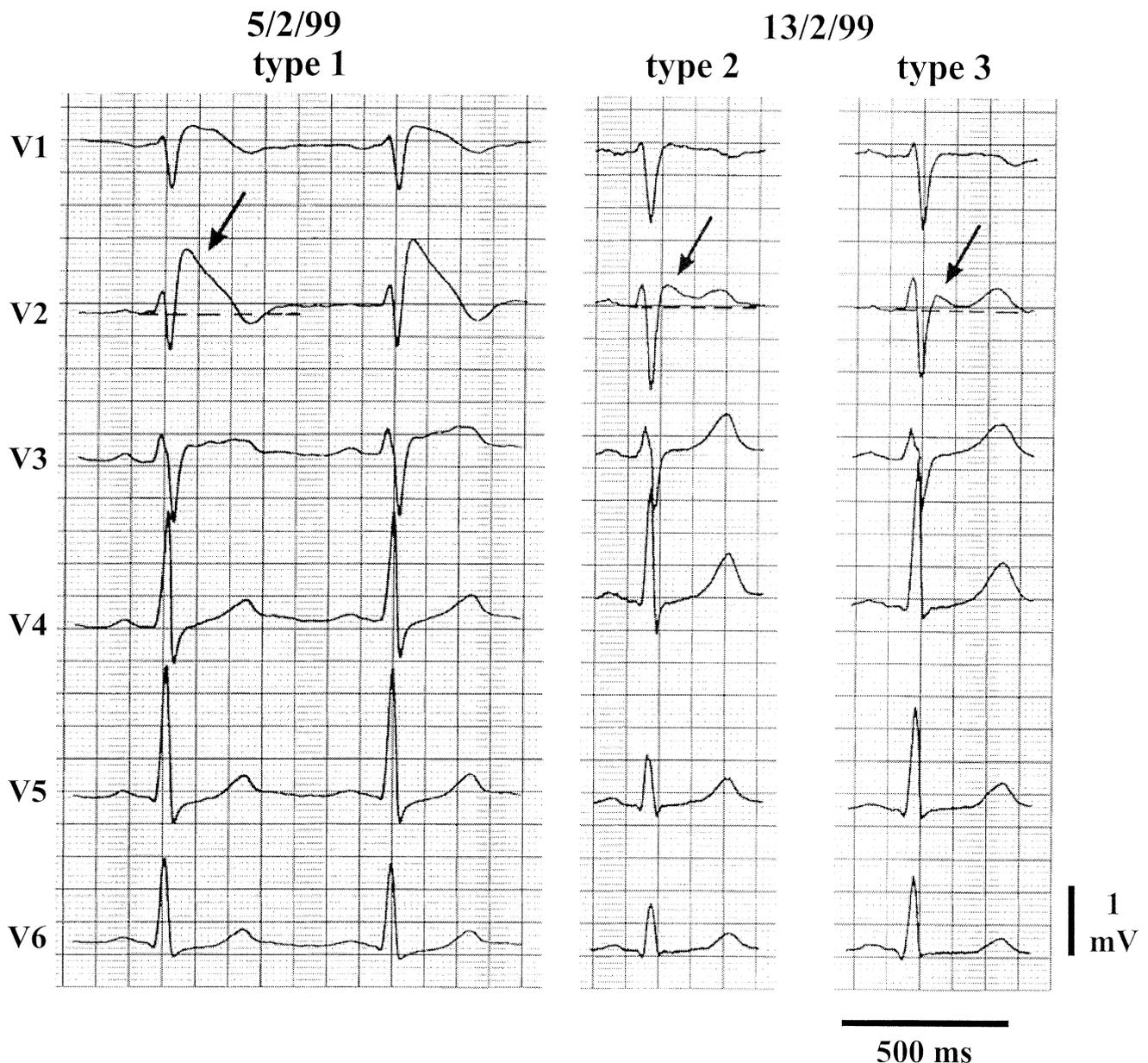


Figure 1. Precordial leads of a patient with Brugada syndrome. Note the dynamic electrocardiographic (ECG) changes in the course of a week. Three distinct patterns are apparent. **Arrows** denote the J-wave. The **left panel** shows a type 1 ECG, whereas the **middle and right panels** depict type 2 and 3 Brugada ECGs. Reproduced from reference 39, with permission.

Genetic aspects. The familial nature of the syndrome soon became evident, and an autosomal mode of transmission was demonstrated. Chen et al. (18) were the first to link the syndrome to the alpha-subunit of the cardiac sodium channel gene, SCN5A, in 1998. Nearly five dozen mutations in SCN5A have been linked to the syndrome over the past four years (19–21). Approximately two dozen of these mutations have been studied in expression systems and have been shown to result in a loss of function due to either: 1) a failure of the sodium channel current (I_{Na}) to express; 2) a shift in the voltage- and time-dependent I_{Na} activation, inactivation, or reactivation; 3) entry of I_{Na} into an intermediate state of inactivation from which it recovers more slowly; or 4) accelerated inactivation of I_{Na} . This last mechanism involving premature closure of the sodium channel was observed at physiologic temperatures, but not at room temperature (22). Because this characteristic of the mutant channel was exaggerated at temperatures above the physiologic range, we suggested that the syndrome may be unmasked, and that patients with Brugada syndrome may be at an increased risk during a febrile state (22). A number of Brugada patients displaying fever-induced polymorphic VT have been identified since the publication of this report (23). Earlier this year, another locus on chromosome 3, close to but distinct from SCN5A, was linked to the syndrome (24). Brugada syndrome in this single, large pedigree was associated with progressive conduction disease, a low sensitivity to procainamide, and a relatively good prognosis.

Cellular mechanisms. The cellular mechanisms believed to underlie Brugada syndrome evolved on a parallel but separate track from that of the clinical syndrome. The concepts of all-or-none repolarization of the ventricular epicardial action potential and of phase 2 reentry were developed in the early 1990s (25–27). It was on a bus ride to the airport following a meeting of the International Society of Computerized Electrocardiography (ISCE) in Florida that Dr. Antzelevitch, fortuitously seated next to Dr. Phillippe Coumel, expressed surprise that there was apparently no clinical counterpart to phase 2 reentry as a mechanism of arrhythmogenesis. After some discussion, Dr. Coumel suggested that Dr. Antzelevitch contact the Brugada brothers, who had recently described a syndrome with somewhat similar characteristics. The rest, as they say, is history. Drs. Antzelevitch, Pedro, Josep, and Ramon Brugada, Jeffrey Towbin, and Kolawanee Nademane have worked as a cohesive team since the mid 1990s.

Basic studies conducted over the past dozen years suggest that a rebalancing of the currents active at the end of phase 1, leading to an accentuation of the action potential notch in the RV epicardium, is responsible for the accentuated J wave or ST-segment elevation associated with Brugada syndrome (19). In larger mammals, the presence of a transient outward current (I_{to})-mediated spike and dome morphology, or notch, in the ventricular epicardium, but not in the endocardium, creates a transmural voltage gradient responsible

for the inscription of the ECG J-wave (Fig. 2A) (2,28). The ST-segment is isoelectric because of the absence of transmural voltage gradients at the level of the action potential plateau. Accentuation of the RV notch under pathophysiologic conditions leads to exaggeration of transmural voltage gradients and thus to accentuation of the J-wave or J-point elevation. This would be expected to give rise to a saddle-back configuration of the repolarization waves. The development of a prominent J-wave under these conditions is indistinguishable from ST-segment elevation. Under these conditions, the T-wave remains positive because epicardial repolarization precedes repolarization of the cells in the M and endocardial regions. Further accentuation of the notch may be accompanied by a prolongation of the epicardial action potential, such that the direction of repolarization across the RV wall and transmural voltage gradients are reversed, leading to the development of a coved-type ST-segment elevation and inversion of the T-wave, typically observed on the ECG of Brugada patients (Fig. 2B). A delay in epicardial activation may also contribute to inversion of the T-wave. The downsloping ST-segment elevation, or accentuated J-wave, observed in the experimental wedge models often appears as an R', suggesting that the appearance of RBBB morphology in Brugada patients may be at least partly due to early repolarization of the RV epicardium, rather than to impulse conduction block in the right bundle. Indeed, a rigorous application of RBBB criteria reveals that a large majority of RBBB-like morphologies encountered in cases of Brugada syndrome do not fit the criteria for RBBB (29). Moreover, attempts by Miyazaki et al. (4) to record delayed activation of the RV in Brugada patients met with failure. It is noteworthy that despite the appearance of a typical Brugada sign, the electrophysiologic changes shown in Figure 2B do not give rise to an arrhythmogenic substrate. We believe that the arrhythmogenic substrate develops with a further shift in the balance of current leading to a loss of the action potential dome at some epicardial sites but not in others (Fig. 2C). A loss of the action potential dome in the epicardium but not in the endocardium results in the development of a marked transmural dispersion of repolarization and refractoriness, responsible for the development of a vulnerable window during which a premature impulse or extrasystole can induce a reentrant arrhythmia. A loss of the action potential dome in the epicardium is usually heterogeneous, leading to the development of epicardial dispersion of repolarization. Conduction of the action potential dome from sites at which it is maintained to sites at which it is lost causes local re-excitation via a phase 2 reentry mechanism (Fig. 2D), leading to the development of a very closely coupled extrasystole, which captures the vulnerable window across the wall, thus triggering a circus movement reentry in the form of VT or ventricular fibrillation (VF) (30,31). The phase 2 reentrant beat fuses with the negative T-wave of the basic response. Because the extrasystole originates in the epicardium, the QRS complex is largely comprised of a

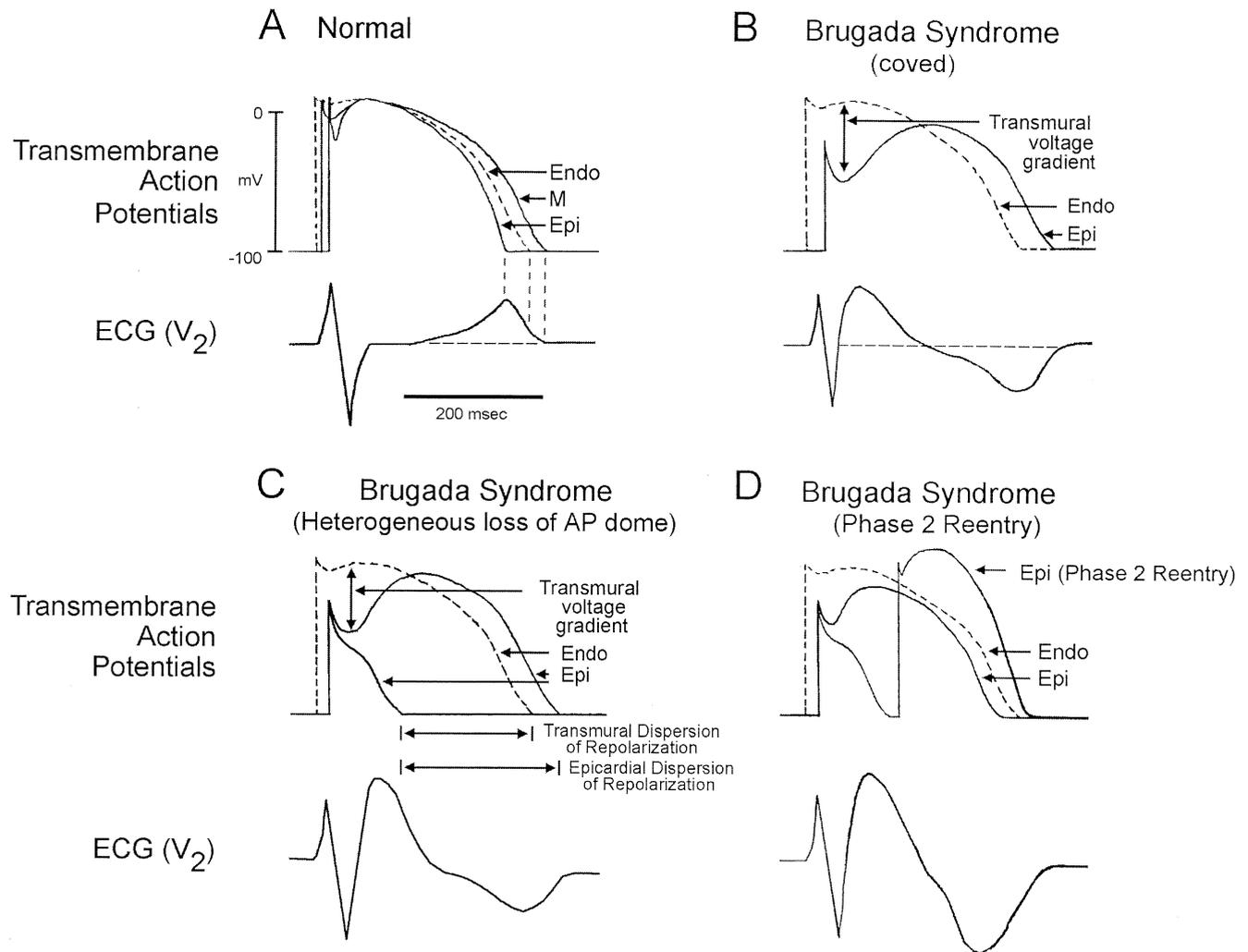


Figure 2. Schematic representation of right ventricle epicardial action potential (AP) changes thought to underlie the electrocardiographic (ECG) manifestation of Brugada syndrome. Modified from reference 28, with permission.

Q-wave, which serves to accentuate the negative deflection of the inverted T-wave, giving the ECG a more symmetrical appearance. This morphology is often observed in the clinic preceding the onset of polymorphic VT. Support for these hypotheses is derived from experiments involving the arterially perfused RV wedge preparation (31) and from recent studies in which monophasic action potential electrodes were positioned on the epicardial and endocardial surfaces of the RVOT in a patient with Brugada syndrome (32,33).

One of the intriguing aspects of Brugada syndrome is that despite equal genetic transmission of the disease, the clinical phenotype is 8 to 10 times more prevalent in males than in females. The basis for this gender-related distinction was recently shown to be due to a more prominent I_{to} -mediated action potential notch in the RV epicardium of males versus females (34). As a result, the end of phase 1 of the RV epicardial action potential was more negative in tissue and arterially perfused wedge preparations from males, facilitating a loss of the action potential dome and the development of phase 2 reentry and polymorphic VT.

Diagnostic criteria. ST-segment elevation is associated with a wide variety of benign as well as malignant pathophysiologic conditions. A differential diagnosis is difficult at times, particularly when the degree of ST-segment elevation is relatively small and the specificity of sodium channel blockers (e.g., flecainide, ajmaline, procainamide, disopyramide, propafenone, pilsicainide) (35-37) to identify patients at risk is uncertain. A consensus report recently published by the Arrhythmia Working Group of the European Society of Cardiology addresses these and other ambiguities concerning the diagnostic criteria for Brugada syndrome (38,39).

Clinical characteristics. Although long suspected, it was only recently definitively shown that sudden unexplained death syndrome, a disorder most prevalent in southeast Asia, and Brugada syndrome are phenotypically, genetically, and functionally the same disorder (40). Sudden and unexpected death of young adults during sleep, known in the Philippines as *bangungut* ("to rise and moan in sleep"), was first described in the Philippine medical literature in 1917.

In 1948, the Honolulu Medical Examiner reported a series of 81 similar deaths of Philippine men in Oahu County (41). In Japan this syndrome, known as *pokkuri* ("sudden and unexpectedly ceased phenomena"), was reported as early as 1959 (42). In 1997, Nademanee et al. (43) reported that among 27 Thai men referred for aborted cases of what was known in Thailand as *Lai Tai* ("death during sleep"), as many as 16 had the ECG pattern of Brugada syndrome. When Alings and Wilde (44) reviewed the literature in 1999, they found that of the 163 patients who met the criteria for Brugada syndrome, 58% were of Asian origin.

In the span of 10 years, the syndrome has gained wide recognition throughout the world and today is believed to be responsible for 4% to 12% of all sudden deaths and ~20% of deaths in patients with a structurally normal heart. The incidence of the disease is on the order of 5 per 10,000 inhabitants and, apart from accidents, is the leading cause of death of men under the age of 40 years in regions of the world where the syndrome is endemic.

In addition to sodium channel blockers and a febrile state, vagotonic agents, alpha-adrenergic agonists, beta-adrenergic blockers, tricyclic antidepressants, first-generation antihistamines (dimenhydrinate), and cocaine toxicity have been shown to unmask Brugada syndrome or to accentuate ST-segment elevation in patients with the syndrome (4,35,45-51). Like the long QT syndrome, Brugada syndrome has both congenital and acquired forms; the latter is just beginning to be appreciated.

Identification of patients at risk of sudden death has been a primary goal of research teams worldwide (20,52). Patients initially presenting with aborted sudden death are at the highest risk for a recurrence (69%), whereas those presenting with syncope and a spontaneously appearing Brugada ECG sign have a recurrence rate of 19%. The study by Brugada et al. (52) found an 8% occurrence of cardiac events in initially asymptomatic patients. Asymptomatic patients at highest risk were those who displayed the Brugada sign spontaneously; those in whom ST-segment elevation appeared only after provocation with sodium channel blockers appeared to be at minimal or no risk for arrhythmic events. Of the 667 patients with the Brugada phenotype seen by Pedro and Josep Brugada, those at highest risk were males with inducible VT and a spontaneously elevated ST-segment. However, controversy exists regarding the role of electrophysiologic study (EPS) in identifying high-risk patients.

The study by Brugada et al. (52) also suggested that among asymptomatic patients, inducibility of VT during EPS may be prognostic of risk. Studies by Priori et al. (20), Kanda et al. (53), and Eckardt et al. (54) failed to find an association between inducibility and recurrence of VT/VF among Brugada patients (both asymptomatic and symptomatic). These discrepancies may be a consequence of several confounding variables. For example, Kanda et al. (53) had no asymptomatic patients in their study, and the number of asymptomatic patients in Priori et al.'s study (20) was

Table 1. Device and Pharmacologic Considerations for Therapy in Brugada Syndrome

Devices
✓ ICD—only established effective therapy
? Pacemaker
Pharmacologic
X Amiodarone—does not protect (57)
X Beta-blockers—does not protect (57)
✓ Beta-adrenergic agonists— <i>isoproterenol</i> (4, 60)
✓ Phosphodiesterase inhibitors— <i>cilostazol</i> (65)
X Class IC anti-arrhythmics— <i>flecainide</i> and <i>propafenone</i> contraindicated
Class IA anti-arrhythmics
X <i>Procainamide</i> and <i>disopyramide</i> contraindicated
✓ <i>Quinidine</i> (31, 59, 63, 64)
? <i>Tedisamil</i>
✓ I_{to} blockers—cardioselective and ion channel specific

ICD = implantable cardioverter-defibrillator; I_{to} = transient outward current.

relatively small; 14 patients were not inducible (1 patient had a subsequent cardiac event [8%]) and 35 patients were inducible (3 patients had an event [8%]). Moreover, both the studies by Brugada et al. (1,35,45,52,55-57) and Priori et al. (20,37) involved multiple electrophysiology centers with nonstandardized stimulation protocols. All studies clearly showed that symptomatic patients have a much higher risk of sudden death than asymptomatic patients. However, the overall 8% event rate in young asymptomatic individuals with the Brugada ECG pattern is too high to ignore. Additional studies are needed to further define the evolving therapeutic approach for asymptomatic patients. Meanwhile, we recommend, based on the current available data, that symptomatic patients with the Brugada pattern (aborted sudden cardiac death or syncope) should have an implantable cardioverter-defibrillator (ICD), regardless of the EPS finding. Asymptomatic patients, however, should undergo EPS, and, if inducible, ICD implantation is recommended. As more data become available, the role of EPS in risk stratification of Brugada syndrome patients may have to be modified or abandoned. At the present, however, we believe that it should remain an integral part of our search for high-risk asymptomatic individuals.

Advances in therapy. Although great progress has been achieved in the identification and characterization of Brugada syndrome over the past decade, relatively little progress has been made in the approach to therapy. Table 1 lists the various device and pharmacologic therapies that have been tested clinically or suggested based on experimental evidence. Implantation of an ICD is the only established effective treatment for the disease (55,56). However, this is not the optimal solution for infants and young children or for adults residing in regions of the world where an ICD is unaffordable. The role of pacemaker therapy is largely unexplored. Arrhythmias and sudden death generally occur during sleep or at rest and are commonly associated with bradycardic states, suggesting a potential therapeutic role for pacing.

The need for cost-effective treatment or preventative

measures is evident. The pharmacologic approach to therapy has been geared to a rebalancing of currents active during the early phases of the RV epicardial action potential, so as to reduce the magnitude of the action potential notch and/or restore the action potential dome. Antiarrhythmic agents such as amiodarone and beta-blockers have been shown to be ineffective (57). Class IC antiarrhythmic drugs such as flecainide and propafenone are clearly contraindicated for reasons previously discussed. Class IA agents such as procainamide and disopyramide are contraindicated for similar reasons. Other class IA agents such as quinidine and tedisamil may exert a therapeutic action, however. Because the presence of a prominent I_{to} is at the heart of the mechanism underlying Brugada syndrome, any agent that blocks this current is likely to be protective. Regrettably, cardioselective and I_{to} -specific blockers are not currently available. The only agent on the market in the U.S. with significant I_{to} -blocking properties is quinidine. It is for this reason that we suggested several years ago that this agent may be of therapeutic value in Brugada syndrome (58). Experimental studies have since shown quinidine to be effective in restoring the epicardial action potential dome, thus normalizing the ST-segment and preventing phase 2 reentry and polymorphic VT in experimental models of Brugada syndrome (31). Agents that boost the calcium current, such as isoproterenol, may be useful as well (19,31). Both types of agents have been shown to be effective in normalizing ST-segment elevation in patients with Brugada syndrome and in controlling electrical storms, particularly in children (59-63). Other than the studies by Belhassen et al. (63,64) involving quinidine, none have yet demonstrated long-term efficacy in the prevention of sudden death. The most recent addition to the pharmacologic armamentarium is the phosphodiesterase III inhibitor cilostazol (65), which normalizes the ST-segment most likely by reducing I_{to} secondary to an increase in heart rate, as well as by augmenting the calcium current. Finally, an experimental antiarrhythmic agent, tedisamil, with potent actions to block I_{to} , among other outward currents, has been suggested as a therapeutic candidate (19). Tedisamil may be more potent than quinidine because it lacks the relatively strong inward current blocking actions of quinidine. The development of a cardioselective and I_{to} -specific blocker would be a most welcome addition to the limited therapeutic armamentarium currently available to combat this disease, and appropriate clinical trials are needed to establish the effectiveness of all of the aforementioned pharmacologic agents, as well as the possible role of pacemakers.

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