

Brugada Syndrome

Begoña Benito, Ramon Brugada, Josep Brugada and Pedro Brugada

Since its first description in 1992 as a new clinical entity, the Brugada syndrome has aroused great interest among physicians and basic scientists. Two consensus conferences held in 2002 and 2005 helped refine the current accepted definite diagnostic criteria for the syndrome, briefly, the characteristic ECG pattern (right bundle branch block and persistent ST segment elevation in right precordial leads) together with the susceptibility for ventricular fibrillation and sudden death. In the last years, clinical and basic research have provided very valuable knowledge on the genetic basis, the cellular mechanisms responsible for the typical ECG features and the electrical susceptibility, the clinical particularities and modulators, the diagnostic value of drug challenge, the risk stratification of sudden death (possibly the most controversial issue) and, finally, the possible therapeutic approaches for the disease. Each one of these points is discussed in this review, which intends to provide updated information supplied by recent clinical and basic studies.

© 2008 Elsevier Inc. All rights reserved.

The Brugada syndrome was described in 1992 as a new clinical entity characterized by a typical electrocardiogram pattern (right bundle branch block and persistent ST-segment elevation in right precordial leads) and sudden cardiac death.¹ The first description of 8 patients was followed by other case reports,^{2,3} and subsequently, numerous works appeared either focusing on clinical characteristics of greater populations of patients⁴⁻⁸ or defining the genetic, molecular, and cellular aspects of the disease.⁹⁻¹³ In fact, the number of scientific publications dealing with the syndrome has increased substantially in the last years, and even continues to do so (Fig 1). Major advances in clinical and mechanistic knowledge have provided very valuable information about the disease, but remaining questions still propel today a large research activity on the subject. This article reviews the current knowledge on clinical, genetic, and mole-

cular features of the Brugada syndrome, and provides updated information supplied by recent clinical and basic studies.

Diagnostic Criteria and General Characteristics

After the initial description of the syndrome, several ambiguities appeared in the first years concerning the diagnosis and the specific electrocardiographic criteria. Three repolarization patterns were soon identified (Fig 2)¹⁴: (a) type-1 electrocardiogram (ECG) pattern, the one described in the initial report in 1992, in which a coved ST-segment elevation greater than or equal to 2 mm is followed by a negative T wave, with little or no isoelectric separation, this feature being present in more than 1 right precordial lead (from V1 to V3); (b) type-2 ECG pattern, also characterized by an ST-segment elevation but followed by a positive or biphasic T wave that results in a saddle-back configuration; (c) type-3 ECG pattern, a right precordial ST-segment elevation less than or equal to 1 mm either with a coved-type or a saddle-back morphology. Although all the 3 patterns can be present in Brugada syndrome patients, only the presence of a type-1 ECG pattern defines the diagnosis of the syndrome, as it was stated in the first consensus report of the Arrhythmia Working Group of the European Society of Cardiology¹⁴ and subsequently confirmed in the second consensus conference published in 2005.¹⁵ These 2 documents helped clarify

From the Cardiovascular Genetics Center, Montreal Heart Institute, Montreal, Canada, Cardiology Department, The Thorax Institute, Hospital Clínic of Barcelona, Barcelona, Spain, and Heart Rhythm Management Centre, Cardiovascular Institute, UZ Brussel, VUB Brussels, Belgium.

Address reprint requests to Begoña Benito, Cardiovascular Genetics Center, Montreal Heart Institute, Montreal, Canada. E-mail: bbenito@clinic.ub.es

0033-0620/\$ - see front matter

© 2008 Elsevier Inc. All rights reserved.

doi:10.1016/j.pcad.2008.05.002

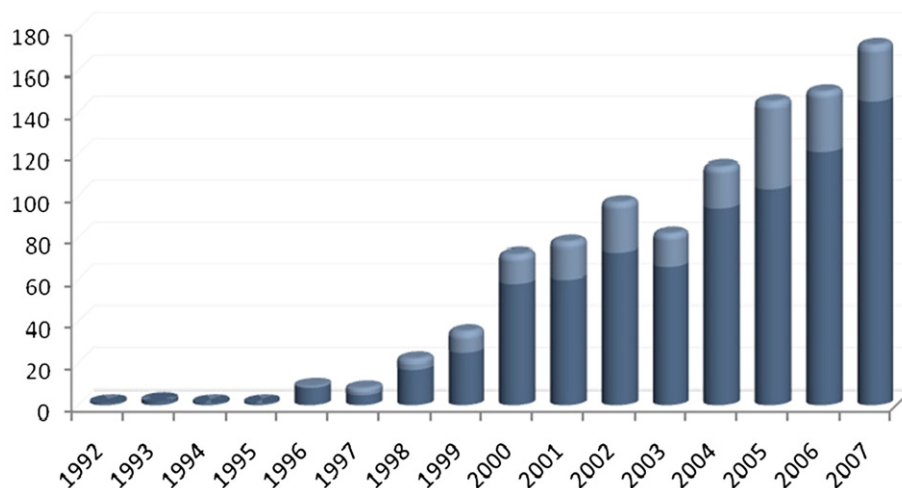


Fig 1. Scientific publications on Brugada syndrome since its first description to date. Articles searched in PubMed database using the search keywords “Right bundle branch block AND ST-segment elevation AND sudden death” OR “Brugada syndrome.” Light areas indicate review articles.

previous confusion and proposed the current accepted diagnostic criteria for the syndrome, which are depicted in Table 1. The Brugada syndrome can be definitely diagnosed when a type-1 ECG pattern is observed in more than 1 right precordial lead (V1-V3), in the presence or absence of a sodium channel blocker agent, and in conjunction with one of the following: documented ventricular fibrillation (VF), polymorphic ventricular tachycardia (VT), a family history of sudden death (SD) at an age younger than 45 years, the

presence of coved-type ECG in family members, inducibility of ventricular arrhythmias with programmed electrical stimulation, syncope, or nocturnal agonal respiration.^{14,15} Note that patients displaying the characteristic type-1 ECG without further clinical criteria should be referred to as having an idiopathic Brugada ECG pattern and not a Brugada syndrome.¹⁴

The Brugada syndrome is currently understood as a channelopathy, that is, a disorder produced by the dysfunction of a cardiac channel participating

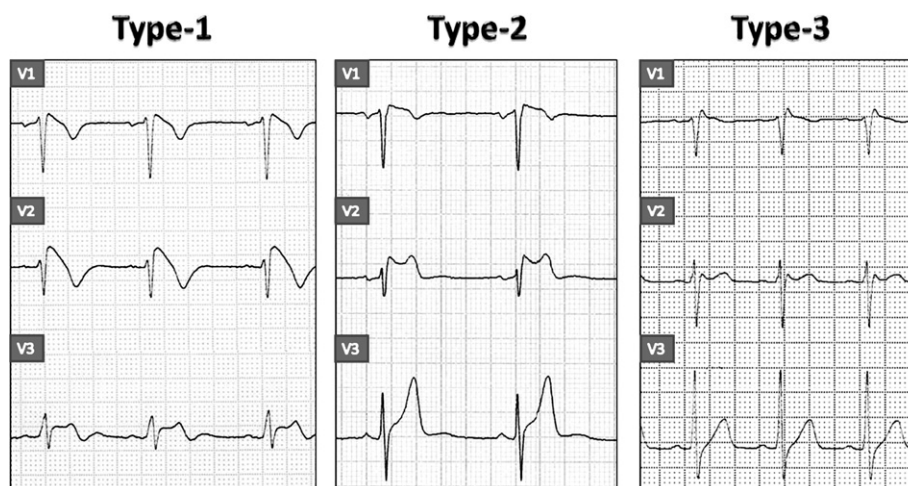


Fig 2. Three different ECG patterns in right precordial leads frequently observed in patients with Brugada syndrome. Type-1 or otherwise called coved-type ECG pattern, in which a descendant ST-segment elevation is followed by negative T waves. Type-2 or saddle-back pattern, an ST-segment elevation followed by positive or biphasic T waves. Type-3, either a coved-type or a saddle-back morphology with ST-segment elevation less than 1 mm (see text for more detailed description). A type-1 ECG pattern is required to establish the definite diagnosis of Brugada syndrome.

Table 1. Diagnostic Criteria of the Brugada Syndrome¹⁵

• Appearance of a type-1 ST-segment elevation (coved-type) ≥ 2 mm in more than 1 right precordial lead (V1-V3); either spontaneously or after sodium-blocker exposure	
AND	
• One of the following:	
Documented ventricular fibrillation,	} Documented ventricular arrhythmias
(Self-terminating) polymorphic ventricular tachycardia,	
Inducibility of ventricular arrhythmias with programmed electrical stimulation,	
Family history of sudden death before age 45 years,	} Family history
Presence of a coved-type ECG in family members,	
Syncope,	} Arrhythmia-related symptoms
Nocturnal agonal respiration	
Other factor(s) accounting for the ECG abnormality should be ruled out.	

Abbreviation: ECG, electrocardiogram.

in the action potential, the electrical change favoring the development of arrhythmias. The electrical disorder seems to be primary, that is, without concomitant underlying structural heart disease responsible for the arrhythmic complications. In fact, the Brugada syndrome is thought to be responsible for 4% to 12% of all SD and for up to 20% of SD in subjects without concomitant cardiopathy.^{15,16} Its prevalence has been estimated in 5 of 10000 inhabitants, although this rate should be understood cautiously, first, because many patients present concealed forms of the disease, thus making it likely that the real prevalence is higher, and second, because important ethnic and geographic differences have been described.¹⁵ For example, whereas in a Japanese study, a type-1 ECG pattern was observed in 12 of 10000 inhabitants,¹⁷ the few available data on North American and European populations point to a much lower prevalence.^{18,19} In fact, southeast Asian culture have long recognized the so-called sudden unexplained death syndrome (SUDS), also named *bangungot* (in the Philippines), *Pokkuri* (in Japan), or *Lai Tai* (in Thailand), today known to be phenotypically, genetically, and functionally the same disorder as the Brugada syndrome.²⁰ The SUDS is considered to be endemic in these countries and one of the leading causes of death in males younger than 50 years.¹⁶

Genetics of the Brugada Syndrome

Inheritance in the Brugada syndrome occurs via an autosomal dominant mode of transmission,¹⁵ although in some patients, the disease can be sporadic, that is, absent in parents and other relatives.²¹ The first mutation related to the

syndrome was described in 1998 by Chen and coworkers,⁹ and was identified in SCN5A, the gene encoding the α subunit of the cardiac sodium channel (locus 3p21, 28 exons). To date, more than 80 other different mutations associated to the syndrome have been found in the same gene.^{12,13,20,22-25} Functional studies performed with expression systems have demonstrated, for most of the mutations, a loss of function of the sodium channel current (INa), which is achieved through different mechanisms^{9,12,13,20,22-25} (Fig 3):

- a quantitative decrease in the sodium channels because of a failure in their expression (Fig 3A).
- a qualitative dysfunction of the sodium channels because of impaired kinetics (a shift in the voltage- and time-dependent activation, inactivation, or reactivation; an entry into an intermediate state of inactivation; or an accelerated inactivation; Fig 3B).

However, mutations in the SCN5A gene are currently found in only 18% to 30% of patients with Brugada syndrome.¹⁵ In a study by Schulze Bahr et al,²⁶ the incidence of SCN5A mutations varied widely according to whether the patients were familial or sporadic cases of Brugada syndrome. Although SCN5A mutations were present in 38% of familial forms of the disease, the authors could not identify any SCN5A mutation among the 27 sporadic cases ($P = .001$). Overall, the low incidence of SCN5A mutations identified in both familial and sporadic Brugada syndrome patients suggested a genetic heterogeneity of the disease.

According to this hypothesis, a different locus on chromosome 3 (3p22-p24), not linked to SCN5A,

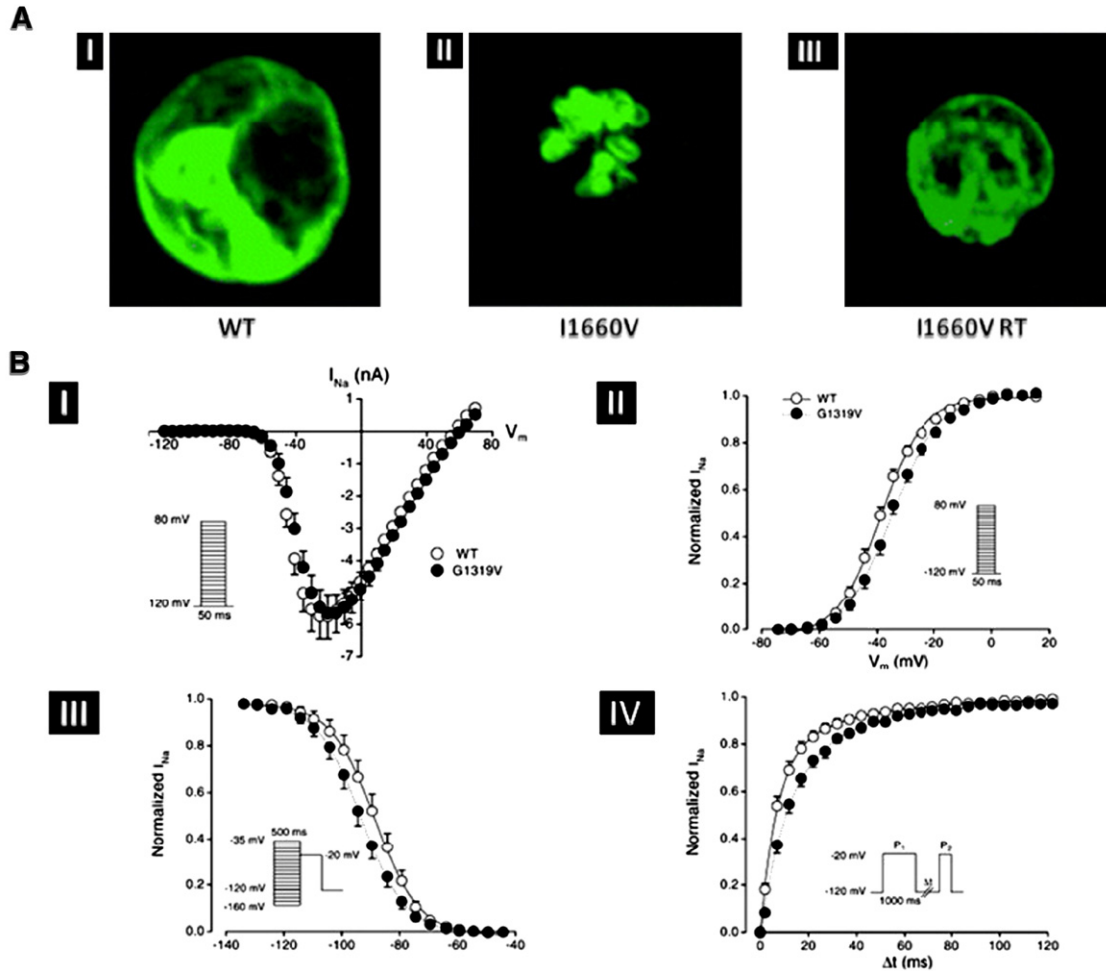


Fig 3. Examples of 2 different mutations in SCN5A leading to a loss of function of the sodium (Na) channel. A, Mutation I1660V, producing a trafficking defect of the Na channel, and thus a decrease of Na channels present in the sarcolemma. Mutant and WT Na channels have been expressed in TSA201 cells and tagged with green fluorescent protein. A-I, WT channels are present both in the center and the periphery of the cell, suggesting that WT channels are manufactured in the cell center and trafficked to the cell membrane. A-II, The fluorescence distribution of I1660V channels is essentially localized in intracellular organelles, which suggests that mutant channels are manufactured but remain trapped within the cell. A-III, Rescue of the mutant channels by incubation at RT. Modified from Cordeiro et al²⁵ with permission. B, Mutation G1319V, which modifies the kinetics of the sodium channel. Functional studies performed in HEK-293 cells. B-I, Maximal peak current amplitudes are similar in WT and mutant cells, indicating that the number of functional channels is similar for WT and mutants. B-II, Voltage-dependence of activation, showing a small depolarizing shift in mutant channels compared with WT channels, with no change in slopes. B-III, Voltage-dependence of steady-state inactivation, reflecting enhanced inactivation in mutant channels compared with WT. B-IV, Recovery from inactivation, which is markedly slowed in G1319V channels. Modified from Casini et al²⁴ with permission. *Abbreviations:* RT, room temperature; WT, wild-type.

was identified by positional cloning in a large family with Brugada syndrome in 2002.²⁷ The gene involved has been very recently described, the glycerol-3-phosphate dehydrogenase 1-like (*GPD-1L*), which seems to affect the trafficking of the cardiac sodium channel to the cell surface.²⁸ In fact, the responsible mutation (A280V) reduces inward

sodium currents by approximately 50% and SCN5A cell surface mutations by approximately 31%.²⁸

Also very interestingly, a recent report demonstrates that not only mutations leading to a loss of function in the sodium channel (either through SCN5A or *GPD-1L*) can cause the Brugada syndrome, but also loss-of-function mutations in

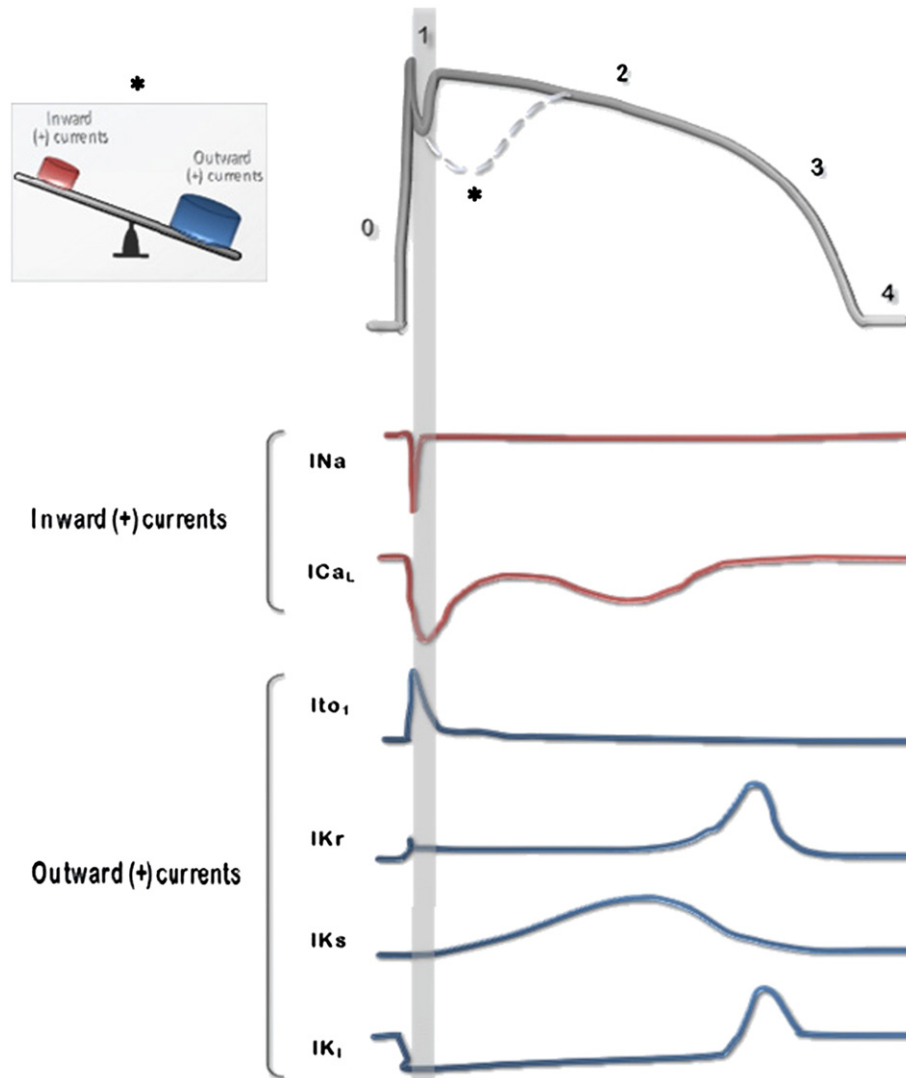


Fig 4. Ventricular myocyte action potential and main underlying ionic currents. The shaded area highlights phase 1, mostly determined by the balance between I_{Na} and I_{Ca} , and I_{to} . When positive inward currents are impaired with respect to positive outward currents (*), the cell achieves a greater degree of repolarization, and the normal dome of the action potential is lost, leading to the development of a particular notch at the end of phase 1 (dashed line). This is the basis of sodium loss-of-function channelopathies like the Brugada syndrome. *Abbreviations:* I_{Ca} , inward calcium current; I_{Na} , inward sodium current; I_{to} , transient outward potassium current.

the cardiac calcium channel $CACNA1c$ ($Ca_v1.2$) and its β subunit $CACNB2b$ can be responsible for a syndrome overlapping short QT and the Brugada ECG pattern.²⁹ These findings open up new lines of research, in which the concept of Brugada syndrome as a pure sodium channelopathy gives way to the concept of the syndrome as an ionic imbalance between the inward and outward currents during the phase 1 of the action potential (see Cellular and Ionic Mechanisms).

In the last years, polymorphisms are acquiring greater importance to explain certain phenotypes of genetic diseases. In the $SCN5A$ locus, the common H558R polymorphism has been shown to restore (at least partially) the sodium current impaired by other simultaneous mutations causing either cardiac conduction disturbances (T512I)³⁰ or Brugada syndrome (R282H).³¹ Thus, this polymorphism seems to give rise to less severe phenotypes by mitigating the effect of nearby

mutations. According to this, our clinical data on H558R polymorphism among genotyped Brugada syndrome patients demonstrate that those carrying the H558R or R558R polymorphisms present less pathological ECG features (article submitted).

Cellular and Ionic Mechanisms

Experimental studies have elucidated the cellular and molecular basis for the 2 main clinical diagnostic criteria of the Brugada syndrome: the particular ECG morphology (ST-segment elevation in right precordial leads) and the susceptibility for VF and SD.

Fig 4 represents the normal ventricular myocyte action potential and the major ionic currents involved in each one of the phases. Sodium loss-of-function conditions, the most encountered disorder in SCN5A mutations related to Brugada syndrome, create an imbalance between outward and inward positive currents during phase 1, favoring repolarization and the appearance of a particular notch in the action potential mediated by the outward transient potassium currents (I_{to}) (dashed line). Although some degree of phase-1 notch of the action potential can be present in epicardium (especially in right ventricle) under normal conditions,³² the accentuated notch present in Brugada syndrome patients gives rise to a transmural voltage gradient

between epicardium and endocardium, producing the characteristic ST-segment elevation on the ECG (Fig 5).¹⁶ This hypothesis has been confirmed in experimental studies with arterially perfused canine wedge preparations¹¹ and also in human studies with recordings of monophasic action potentials in epicardium and endocardium of right ventricular outflow tract.³³

Ventricular arrhythmias in Brugada syndrome can also be explained as a consequence of the imbalance between outward and inward positive currents during phase 1 of the action potential. The proposed mechanism would be a phase-2 reentry, which is represented in Fig 6. When the notch is such that phase 1 reaches approximately -30 mV, all-or-none repolarization leads to a complete loss of the action potential dome. The heterogeneity of the loss of the dome among different sites within the epicardium and between the epicardium and the endocardium results in epicardial and transmural dispersion of repolarization, respectively (Fig 6A). This substrate may facilitate the development of premature beats, by means of conduction of the action potential dome from the sites where it is maintained to the sites where it is lost (Fig 6B).^{11,16} Studies with high-resolution optical mapping in arterially perfused canine RV preparations confirm the presence of a gradient between dome-loss regions and dome-restoration regions in the

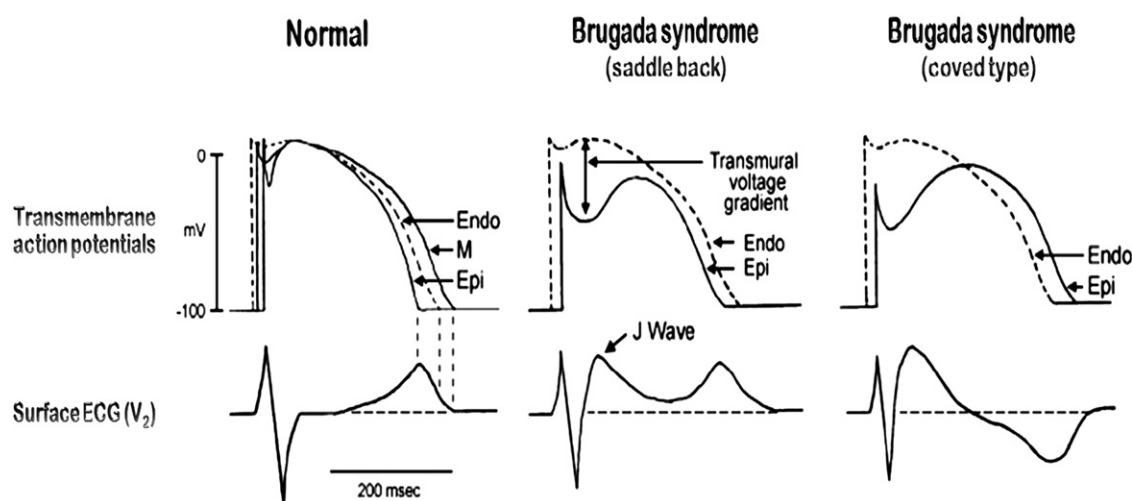


Fig 5. Proposed mechanism that underlies ST-segment elevation in Brugada syndrome. The accentuated notch present in epicardium but not in endocardium gives rise to transmural voltage gradient and J-point elevation (Brugada saddle-back). Further accentuation of the notch may be accompanied by a prolongation of the action potential in epicardium, which becomes longer than in endocardium, thus leading to the development of negative T waves in addition to the ST-segment elevation (Brugada coved-type). Modified from Antzelevitch¹⁶ with permission.

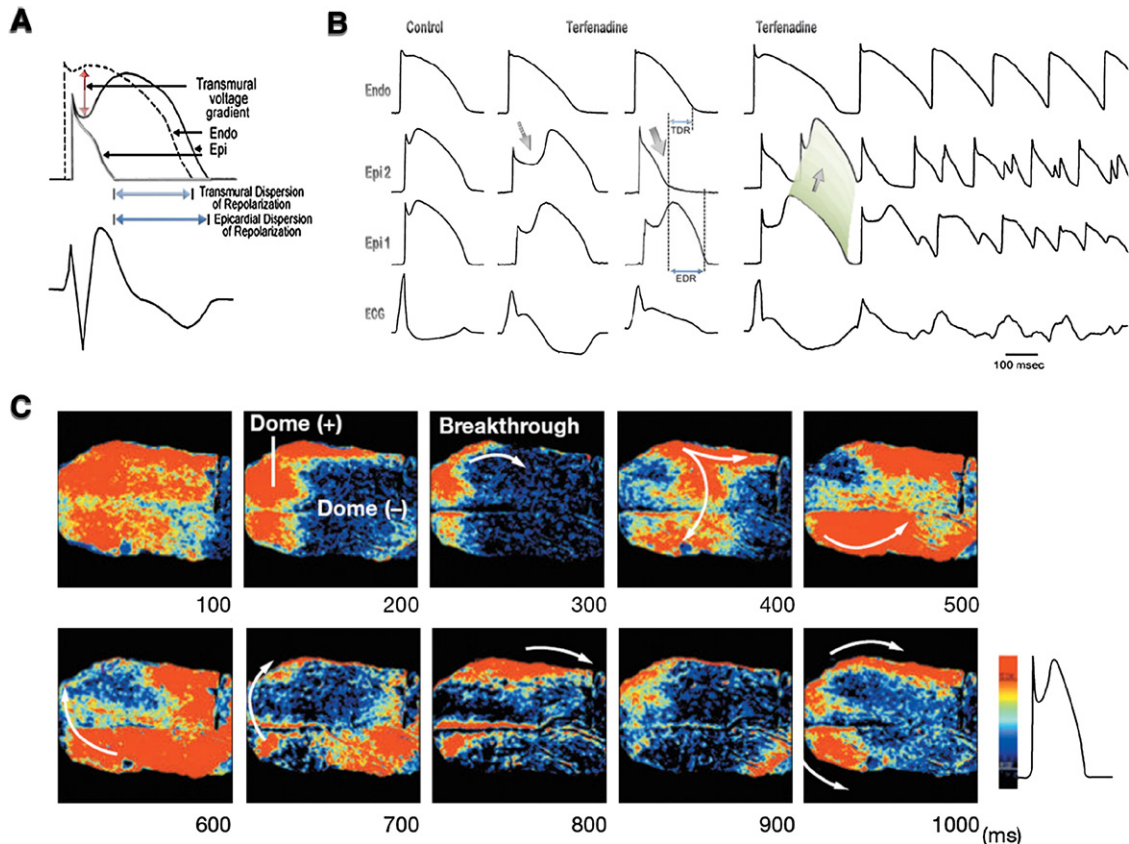


Fig 6. Proposed mechanism that underlies ventricular arrhythmias in Brugada syndrome. **A**, With a further shift in the balance of currents at the end of phase 1, all-or-none repolarization occurs and leads to a complete loss of the action potential dome (silver figure). The arrhythmogenic substrate is thought to develop when the loss of dome appears at some epicardial site but not at others, creating both transmural dispersion of repolarization and epicardial dispersion of repolarization (blue arrows). At this point, a premature impulse or extrasystole can induce a reentrant arrhythmia. **B**, Simultaneous transmembrane action potentials at 2 epicardial sites and 1 endocardial site together with a (modified from Antzelevitch et al¹⁶ with permission) transmural electrocardiogram recorded from a canine arterially perfused right ventricular wedge preparation. The administration of terfenadine ($5 \mu\text{M}$), a potent sodium and calcium channel blocker, accentuates the epicardial action potential notch (dashed arrow). When combined with continued pacing at BCL 400 milliseconds, all-or-none repolarization occurs heterogeneously at the end of phase 1, creating local epicardial transmural of repolarization (EDR) and transmural dispersion of repolarization (TDR) (solid arrow). Propagation from the site where the dome is maintained (epicardial site 1) to the site where it is lost (epicardial site 2) results in the development of a premature beat induced by phase 2 reentry, triggering spontaneous polymorphic ventricular tachycardia. Modified from Shimizu et al³⁴ with permission. **C**, High-resolution optical mapping system with transmembrane action potentials from 256 sites simultaneously (epicardial and endocardial surface) of an arterially perfused canine right ventricular wedge preparation. Recording at the beginning of a polymorphic ventricular tachycardia. Propagation by phase-2 reentry occurs from red areas (where the dome is maintained) toward blue areas (where the dome is lost). The initial reentrant pathway mainly rotates in the epicardium and gradually involves the transmural myocardium, precipitating nonsustained polymorphic ventricular tachycardia. Modified from Shimizu et al³⁴ with permission.

epicardium, and a subsequent development of a reentrant pathway that rotates in the epicardium and gradually involves the transmural myocardium (Fig 6C).³⁴

The understanding that the imbalance between inward and outward ionic currents at phase 1 defines the pathologic substrate for the Brugada

syndrome (Fig 4) has helped develop experimental models of the disease, and explains the effects of certain modulators and certain particularities of the syndrome. It also provides very valuable information for the development of possible therapeutic approaches. In this regard, experimental models of the syndrome have been developed using the intact

wall of arterially perfused canine heart preparations by adding the potassium opener pinacidil or a combination of a sodium channel blocker (flecainide) and acetylcholine.¹¹ These interventions create a relative predominance of outward positive currents at the end of phase 1, and thus accentuate the notch. Recently, the combined sodium channel and calcium channel blocker effect of terfenadine was shown to be more effective than sodium channel inhibitors alone in precipitating the Brugada syndrome in experimental models.³⁵ Even a combination of terfenadine and pilsicainide (another sodium channel blocker) has been used to create phase-2 reentry.³⁴

Modulators of autonomic tone seem to play a role in the Brugada syndrome through a direct effect on ionic currents. Acetylcholine has been shown to decrease calcium currents (ICa), whereas β -adrenergic agonists increase them.³⁶ Consequently, with these findings, patients with Brugada syndrome have been reported to increase ST-segment elevation after vagal maneuvers and to attenuate the ECG signature after exposure to β -adrenergic agents.³⁷ On the basis of this, it appears that interventions that decrease inward positive currents (as do sodium channel or calcium channel block-

ers) could increase ST-segment elevation and thus be harmful for patients with Brugada syndrome, although they could be notwithstanding useful for unmasking concealed forms of the disease.³⁸ In contrast, Ito blockers such as quinidine could be a good therapeutic option by reducing the notch at the end of phase 1 (see Treatment).³⁹

In addition, constitutional differences in density of ionic currents may provide an explanation for some of the characteristics of the syndrome. Examples supplied by experimental models are the greater density of Ito currents in right ventricle with respect to left ventricle epicardium⁴⁰ and also the greater Ito density in male RV as compared with female RV,⁴¹ these findings giving a possible explanation for why Brugada syndrome is a disease mainly of the RV and why its phenotypic manifestation is more frequent among male than female patients (see Clinical Manifestations).

Clinical Manifestations of the Brugada Syndrome

Patients with Brugada syndrome usually remain asymptomatic. However, syncope or cardiac arrest, a consequence of an arrhythmic complication such

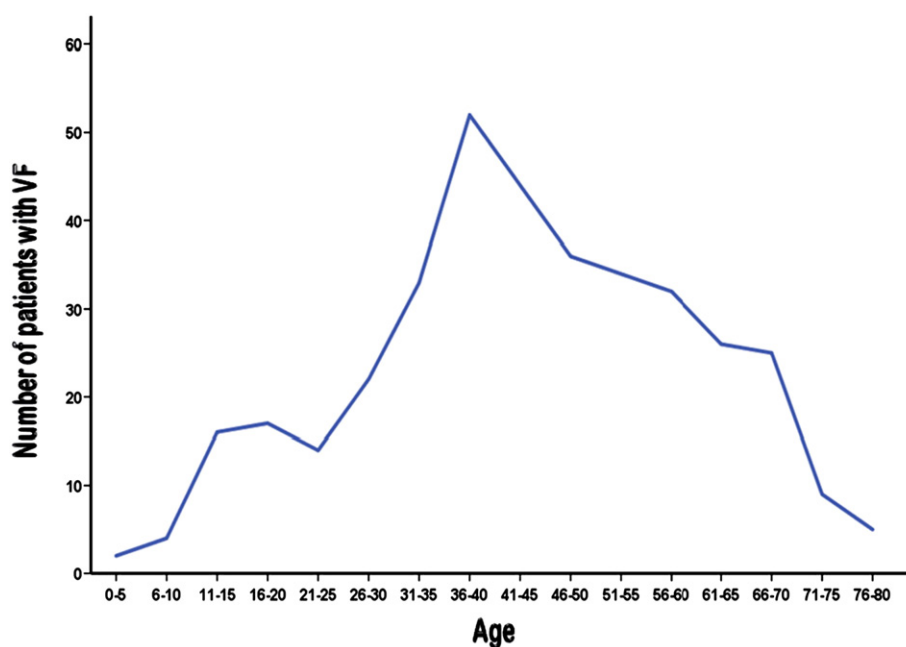


Fig 7. Incidence of spontaneous VF or SD in a lifetime among patients with Brugada syndrome. Data from 370 updated patients of the international registry. The SD or VF occurred in 120 (32.4%) patients.⁴⁶ Abbreviations: SD, sudden death; VF, ventricular fibrillation.

as polymorphic VT or VF, has been described in up to 17% to 42% of diagnosed individuals.⁴²⁻⁴⁵ This rate probably overestimates the real prevalence of symptoms among Brugada syndrome patients, given that most asymptomatic patients remain underdiagnosed. The age of symptom occurrence (especially cardiac arrest) is consistently around the fourth decade of life in all the series⁴²⁻⁴⁶ (Fig 7), with no definite explanation for this observation thus far. Previous syncope may be present in up to 23% of patients who present with cardiac arrest.⁴³

Up to 20% of patients with Brugada syndrome may present supraventricular arrhythmias⁴⁷ and thus complain of palpitations and/or dizziness. An increased atrial vulnerability to both spontaneous and induced atrial fibrillation has been reported in patients with Brugada syndrome.⁴⁸ The electrophysiologic basis could be an abnormal atrial conduction.⁴⁸ Whether atrial vulnerability is correlated to an increased susceptibility for ventricular arrhythmias is thus far unknown. Other symptoms, such as neurally mediated syncope have been also recently associated to the Brugada syndrome, but their implications for prognosis have not yet been established.^{49,50}

As in the case of other sodium channel-related disorders as type-3 long-QT syndrome, ventricular arrhythmias in the Brugada syndrome typically occur at rest, especially during nighttime or sleep. In a study by Matsuo et al,⁵¹ 26 of 30 episodes of VF documented in implantable cardioverter defibrillator (ICD) recordings of Brugada syndrome patients appeared during sleep, suggesting that vagal activity may play an important role in the arrhythmogenesis of Brugada syndrome. Indeed, recent data on cardiac autonomic nervous system assessed by positron emission tomography confirm that Brugada syndrome patients display a certain degree of sympathetic autonomic dysfunction, with increased presynaptic norepinephrine recycling and thus a decrease in the concentration of norepinephrine at the synaptic cleft, this imbalance facilitating arrhythmogenicity by decreasing intracellular levels of 3'-5'-cyclic adenosine monophosphate.^{52,53}

Sex Differences

It is currently accepted that the clinical phenotype of the Brugada syndrome is 8 to 10 times more

prevalent in male than in female patients.^{16,54} Consequently, the main clinical studies published thus far include a 71% to 77% of male population, which generally appears to be more symptomatic with regard to female population.⁴²⁻⁴⁵ In fact, the observation that SD mainly occurs in young males during sleep has long been recognized in south-east Asia for the SUDS, where males from certain small villages would dress in women's bedclothes given that the syndrome was understood as a female spirit searching for young males at night.

Because specific clinical data on the sex distinction are, however, lacking, we recently conducted a study aimed to analyze sex differences in a large population of patients with Brugada syndrome (article submitted). From our data, it can be concluded that males with Brugada syndrome display a higher risk profile than females, presenting more frequently with symptoms at the time of diagnosis, spontaneous type-1 ECG and inducibility of VF during programmed ventricular stimulation. Consequently, males in our series experience a worse prognosis during follow-up. However, some data point out that male sex per se could be related to a worse prognosis even after adjusting for variables such as symptoms or ECG parameters. In this regard, in a recent meta-analysis pooling data of 30 studies and including more than 1500 patients, male sex appeared as an independent predictor of cardiac events defined as SD, syncope, or internal defibrillator shock, with a relative risk of 3.47 (95% CI, 1.58-7.63) with regard to females.⁵⁵

Two main hypotheses have been proposed for the sex distinction, perhaps interacting with each other: the sex-related intrinsic differences in ionic currents and the hormonal influence. Di Diego and coworkers⁴¹ elegantly demonstrated that Ito density quantified by whole-cell patch-clamp techniques was significantly greater in male than female right ventricle epicardia of arterially perfused canine heart preparations, thus explaining the deeper notch in phase 1 of the action potential in males as compared with females⁴¹ (Fig 8). The administration of terfenadine (a sodium and calcium channel blocker) in this model induced ST-segment elevation and provided a basis for phase-2 reentry and VF.⁴¹ Both phenomena were mainly observed in male samples because of their deeper phase-1 magnitude at baseline.

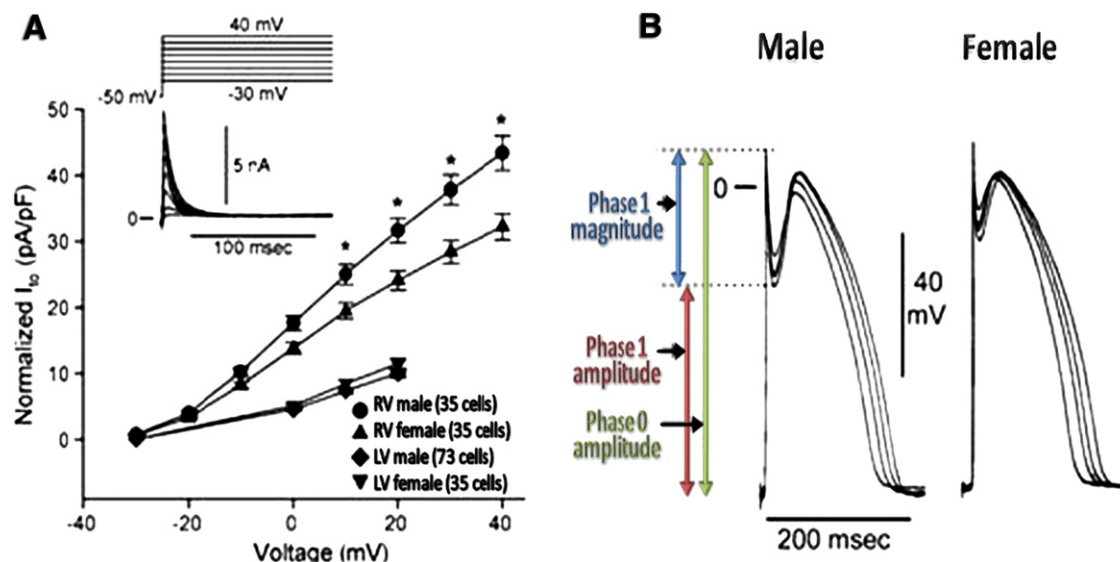


Fig 8. Sex-based differences in I_{to} currents and transmembrane action potentials in a model of arterially perfused wedge preparations. A, I_{to} density is significantly greater in male vs female RV epicardia, with no differences in LV. B, Consequently, male samples present greater phase-1 magnitude than females. Modified from Di Diego et al⁴¹ with permission. *Abbreviations:* I_{to} , transient outward potassium current; LV, left ventricle; RV, right ventricle.

The role of sex hormones is currently less established, although some data exist suggesting that they might also play a role in the phenotypic manifestations of Brugada syndrome. For example, regression of the typical ECG features has been reported in castrated men,⁵⁶ and levels of testosterone seem to be higher in Brugada male patients as compared with controls.⁵⁷ Some experimental works point out that hormones could modify the ionic membrane currents,^{58,59} but their effect among human currents is still unclear. Consequently with the hormonal hypothesis, the few available data existing thus far of Brugada syndrome in children have not shown a difference in phenotypic presentation between boys and girls.⁶⁰

Children

Although 3 of the 8 patients reported in the first description of the disease were within pediatric ages, little information has been thus far available on the behavior of the Brugada syndrome during childhood. Probst et al⁶⁰ recently provided data from a multicenter study including 30 Brugada syndrome patients aged less than 16 years (mean age, 8 ± 5 years). More than half ($n = 17$) had been diagnosed during family screening, but symptoms

were present in 11 patients (1 aborted SD and 10 syncope). Interestingly, 10 of the 11 symptomatic patients displayed spontaneous type-1 ECG, and in 5 of them, symptoms were precipitated by a febrile illness. Five patients received an ICD and 4 were treated with hydroquinidine. During a mean follow-up period of 37 ± 23 months, 3 patients (10% of the population) experienced SD ($n = 1$) or appropriate shock by ICD ($n = 2$). Importantly, all the 3 patients had presented with syncope at the time of diagnosis and displayed spontaneous type-1 ECG. The 4 patients under quinidine remained asymptomatic during 28 ± 24 months of follow-up.⁶⁰

Our results on 58 pediatric patients with Brugada syndrome⁶¹ are in line with the ones by Probst et al⁶⁰ and provide further data on prognostic markers during childhood. In our population (mean age, 11.8 ± 4 years), up to 22 patients (38%) were symptomatic (11 with previous syncope and 11 with aborted SD), whereas 36 had been diagnosed during family screening. Spontaneous type-1 ECG was present in 18 patients (31%), and the electrophysiological study (EPS), performed in 31 patients, induced VF in 7 of them. An ICD was indicated in 14 patients. Cardiac events appeared in 6 patients (2 SD and 4 appropriate ICD shocks) during a mean follow-up

of 48.8 ± 48 months, this rate of 2.5% per year being somewhat lower than the 3.2% per year reported by Probst et al⁶⁰ Cardiac events occurred more frequently among patients with spontaneous type-1 ECG and among those with inducible VF at the EPS, but in our series, symptoms at diagnosis was the strongest variable to predict events during follow-up.⁶¹

Although small, these studies suggest that:

- The Brugada syndrome can manifest during childhood.
- Symptoms may appear during febrile episodes.
- Symptomatic patients, especially if they present with a spontaneous type-1 ECG, may be at a high risk of cardiac events in a relatively short period of follow-up (48 months).
- Patients at risk can be protected with an ICD, although quinidine could be an option in certain patients, particularly the youngest.

ECG and Modulating Factors

It is important to underline that ECG typically fluctuates over time in Brugada syndrome patients and thus can change between the three patterns (Fig 2) or even be transiently normal. The prevalence of spontaneous ECG fluctuations has been recently assessed in a work by Veltmann et al,⁶² including 310 ECGs on 43 patients followed during 17.7 months. Among 15 patients with an initial diagnostic ECG, 14 revealed at least 1 nondiagnostic ECG in a median time of 12 days, whereas 8 of 28 patients with nondiagnostic ECG developed a type-1 ECG pattern in a median time of 16 days.⁶² On the basis of these results, it seems that repetitive ECG recordings may be mandatory in patients with the syndrome, and on the other hand, that the role of the basal ECG as a risk marker should be better specified (see Risk Stratification).^{62,63}

It is worth noting that some factors can account for an ECG abnormality that can closely resemble the Brugada ECG (Table 2). Importantly, some of them are conditions different from the syndrome and should be carefully excluded during the differential diagnosis, whereas others may induce

Table 2. ECG Abnormalities That Can Lead to ST-Segment Elevation in V1-V3

Differential Diagnosis	Genetic Predisposition?
Atypical right bundle branch block	Hyperkalemia
Acute myocardial infarction, especially of RV	Hypercalcemia
Acute pericarditis/myopericarditis	Cocaine intoxication/ Alcohol intoxication
Hemopericardium	Treatment with:
Pulmonary embolism	I. Antiarrhythmic drugs:
Dissecting aortic aneurysm	Na channel blockers (class IC, class IA)
	Ca channel blockers
Central and autonomic nervous system disorders	
Duchenne muscular dystrophy	β blockers
Friedreich ataxia	II. Antianginal drugs:
LV hypertrophy	Ca channel blockers
Arrhythmogenic RV cardiomyopathy	Nitrates
Mechanical compression of RV outflow tract	III. Psychotropic drugs:
Mediastinal tumor	Tricyclic antidepressants
	Tetracyclic antidepressants
Pectus excavatum	Phenothiazines
After electrical cardioversion	
Early repolarization, especially in athletes	Selective serotonin reuptake inhibitors
Hypothermia	Lithium

Abbreviations: ECG electrocardiogram; LV, left ventricular; RV, right ventricular.

ST-segment elevation probably when an underlying genetic predisposition is present.

Modulating factors play a major role in the dynamic nature of the ECG and also may be responsible for the ST-segment elevation in genetically predisposed patients (Table 2). Sympathovagal balance, hormones, metabolic factors, and pharmacologic agents, by means of specific effects on transmembrane ionic currents (Fig 4), are thought to modulate not only the ECG morphology, but also to explain the development of ventricular arrhythmias under certain conditions. Indeed, bradycardia and vagal tone may contribute to ST-segment elevation and arrhythmia initiation by decreasing calcium currents.¹¹ This explains the greater ST-segment elevation recorded in vagal settings^{37,64-66} and the notorious incidence of cardiac arrhythmias and SD at night in patients with Brugada syndrome.⁵¹ The role of hormones (especially sex hormones) as modulating factors is less established but is deeply suspected on the basis of some experimental

works and the evident male predominance on the clinical manifestations of the syndrome (see Sex Differences).^{16,56,57,67}

Temperature may be an important modulator in some patients with Brugada syndrome. Premature inactivation of the sodium channel has been shown to be accentuated at higher temperatures in some SCN5A mutations, suggesting that febrile states may unmask certain Brugada syndrome patients or temporarily increase the risk of arrhythmias.¹⁰ In fact, several case reports in which fever precipitates the syndrome or an arrhythmic complication have been published in the last years.^{68,69} It seems that fever would be a particularly important trigger factor among the pediatric population.⁶⁰

Numerous studies have analyzed the ECG of the Brugada syndrome aiming to identify new electrocardiographic hallmarks or risk markers. Pitzalis and coworkers⁷⁰ described a prolongation of the corrected QT interval (QTc) in right but not in left precordial leads after administration of flecainide to patients with Brugada syndrome and nondiagnostic basal ECG. Subsequently, other groups have correlated a QTc greater than or equal to 460 milliseconds in V2 to the occurrence of life-threatening arrhythmias.⁷¹ More recently, the aVR sign (an R wave ≥ 3 mm or an R/q ratio ≥ 0.75 in lead aVR) has also been defined as a risk marker of cardiac events in Brugada syndrome, the prominent R wave possibly reflecting some right ventricular conduction delay and subsequently more electrical heterogeneity.⁷² Studies with 12-lead ECG and signal-averaged ECG show that daily fluctuations of ST-segment elevation are more prominent in symptomatic than in asymptomatic patients, with a strong dependence on heart rate and vagal activity.^{64,65} In addition, T-wave alternans has been reported after administration of sodium channel blockers and is thought to be associated with an increased risk for development of VF in patients with Brugada syndrome because it may reflect transmural dispersion of repolarization.⁷³ Indeed, in a very recent study conducted in 77 Brugada syndrome patients undergoing a pharmacologic test, the presence of T-wave alternans after the sodium channel blocker exposure identified a subgroup of patients with a higher risk of spontaneous VF (52.9% vs 8.3%, $P < .001$).⁷⁴

Cardiac conduction disturbances may be present in patients with Brugada syndrome. Both

phenotypes (Brugada syndrome and cardiac conduction disorders) can be explained by a reduction in the sodium current and have been described within the same family carrying a mutation on the SCN5A gene.⁷⁵ Consequently, conduction parameters (specifically PQ interval, QRS duration, and HV interval) seem to be longer among those patients with Brugada syndrome who are SCN5A genetic carriers (and do have a mutation in the sodium channel) as compared with non-SCN5A genetic carriers, in which the underlying mechanism or mutation is not identified.⁷⁶ These differences have been recently shown to progressively accentuate during follow-up.⁷⁷ In addition, we recently identified that some conduction parameters such as QRS duration are more frequent among symptomatic patients. In a population of 200 Brugada syndrome patients, of whom 66 (33%) were symptomatic, QRS duration in V2 was 115 ± 26 milliseconds in symptomatic and 104 ± 19 milliseconds in asymptomatic patients, this difference being statistically significant ($P < .001$). The optimized cutoff point of V2 QRS greater than or equal to 120 milliseconds gave an odds ratio of 2.5 (95% CI, 1.4-4.6; $P = .003$) for being symptomatic.⁷⁸

Although sinus rhythm is the most common, supraventricular arrhythmias can be found in up to 20% of patients with Brugada syndrome.⁴⁷ Atrial fibrillation is the most encountered atrial arrhythmia and is thought to be a consequence of the electrical dysfunction in the sodium channels present at the atria. Other rhythm disorders, as bradycardia secondary to sick sinus syndrome or atrial standstill, have also been reported in association to Brugada syndrome.¹⁶

Diagnostic Tools: Drug Challenge

Given that the ECG is dynamic and thus the characteristic ECG hallmark may be concealed, drug challenge with sodium channel blockers, which increase the sodium channel dysfunction, has been proposed as a useful tool for the diagnosis of Brugada syndrome.³⁸ Ajmaline, flecainide, procainamide, pilsicainide, disopyramide, and propafenone have been used,¹⁵ although the specific diagnostic value for all of them has not yet been systematically studied. The recommended dose regimens for the most

Table 3. Drugs Used to Unmask Brugada Syndrome¹⁵

Drug	Dosage	Administration
Ajmaline	1 mg/kg over 5 min	IV
Flecainide	2 mg/kg over 10 min	IV
	400 mg	PO
Procainamide	10 mg/kg over 10 min	IV
Pilsicainide	1 mg/kg over 10 min	IV

Abbreviations: IV, intravenous; PO, orally.

Modified from Antzelevitch et al¹⁵ with permission.

commonly used drugs are listed in Table 3. Brugada syndrome is diagnosed if a coved-type (type-1 ECG pattern) appears after the sodium channel blocker administration. The pharmacologic test should be monitored with a continuous ECG recording and should be terminated when: (1) the diagnostic test is positive, (2) premature ventricular beats or other arrhythmias develop, and (3) QRS widens to greater than or equal to 130% of baseline.

Current data point out that ajmaline is probably the best available drug to unmask the Brugada

syndrome. In a study with 147 individuals from 4 large families with identified SCN5A mutations, ajmaline provided a sensitivity of 80%, a specificity of 94.4%, a positive predictive value of 93.3%, and a negative predictive value of 82.9% for the diagnosis of Brugada syndrome.⁷⁹ Penetrance of the disease phenotype increased from 32.7% to 78.6% with the use of the sodium channel blocker.⁷⁹ These results are considerably higher than those obtained for flecainide in another study with 110 genotyped patients, in which the sensitivity, the specificity, and the positive and the negative predictive values for the diagnosis were 77%, 80%, 96%, and 36%, respectively.⁸⁰ Of note, the low negative predictive value should be taken into account when using flecainide, especially during genetic screening. In fact, Priori and Napolitano⁸¹ have reported from their series that among 115 genetically affected individuals, a type-1 ECG (spontaneous or induced by flecainide) was lacking in 29 patients (25%).

Ajmaline and flecainide were compared in a study with 22 patients with confirmed Brugada syndrome,

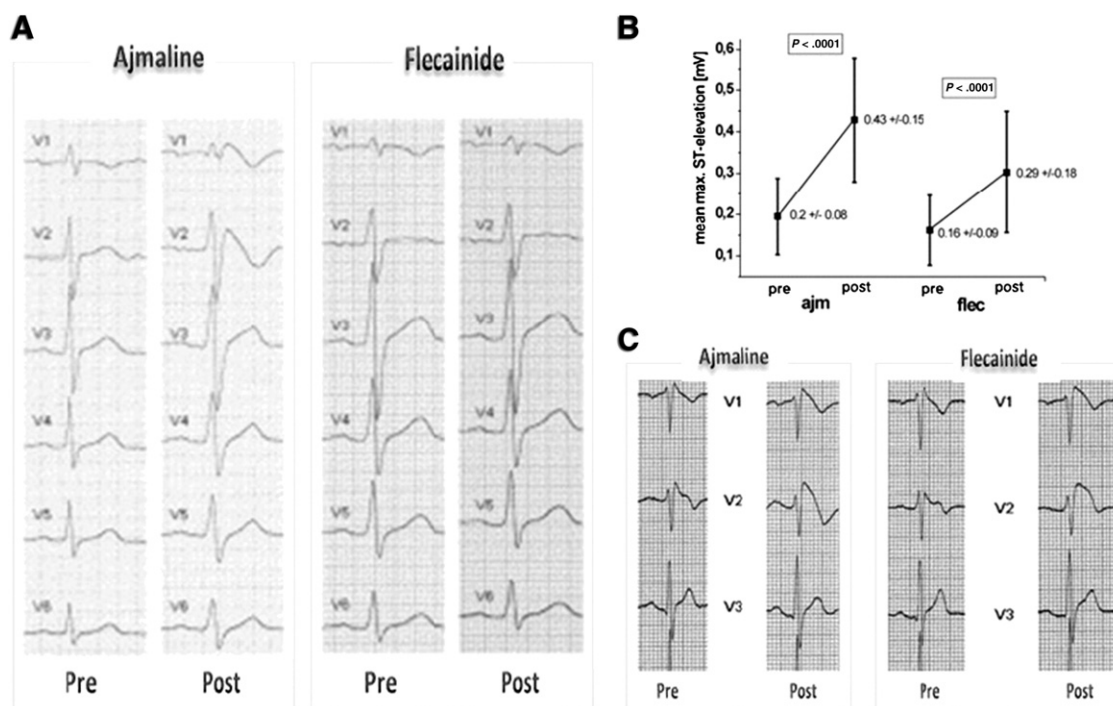


Fig 9. Ajmaline vs flecainide in the diagnosis of Brugada syndrome. A, Flecainide failed in 7 (32%) of 22 cases, which were unmasked by ajmaline. B, Change in maximal ST-segment elevation before (pre) and after (post) intravenous AJM and FLEC administration. C, Example of greater ST-segment elevation in the same patient with AJM than with FLEC. Modified from Wolpert et al⁸² with permission. Abbreviations: AJM, ajmaline; FLEC, flecainide.

who were submitted to both ajmaline and flecainide tests. Although the test was positive in 22 of 22 patients after ajmaline administration, only 15 patients showed a positive response to flecainide.⁸² In addition, the increase of the ST-segment elevation after the test was larger with ajmaline than with flecainide (Fig 9). Whole-cell patch clamp experiments revealed that, although both of them being sodium channel blockers, flecainide reduced Ito to a greater extent than ajmaline, thus explaining its lesser effectiveness.⁸²

Given the limitations of genetic analysis and drug availability, new strategies have been searched for to make the clinical diagnosis accurate. Placement of the right precordial leads in a upper position (second or third intercostal spaces) can increase the sensitivity of the ECG for detecting the Brugada phenotype, both in the presence or absence of a drug challenge,^{83,84} although whether the greater sensitivity is at the expense of a lower specificity is still uncertain. Recent data demonstrate that the presence of a type-1 ECG pattern recorded at higher intercostal spaces, even when the standard ECG is normal, can identify a subgroup of patients that behaves similarly in terms of prognosis to those

with spontaneous type-1 ECG pattern at standard leads (Fig 10).⁸⁵ Therefore, the diagnosis of Brugada syndrome seems to be improved by recording at upper intercostal spaces, this strategy allowing identification of a subset of patients at risk that would otherwise be underdiagnosed.

Prognosis and Risk Stratification

Prognosis and risk stratification are probably the most controversial issues in Brugada syndrome. The main clinical studies arising from the largest databases differ on the risk of SD or VF in the population with Brugada syndrome, and particularly on defining the specific risk markers with regard to prognosis.

In our most updated population with Brugada syndrome coming from the international registry, the percentage of patients who experienced SD or VF throughout a lifetime was 25% (178 of 724 patients). The mean age at cardiac events was 42 ± 15 years. Of course, such a high rate might have been influenced by a baseline high-risk population referred for the international registry and included

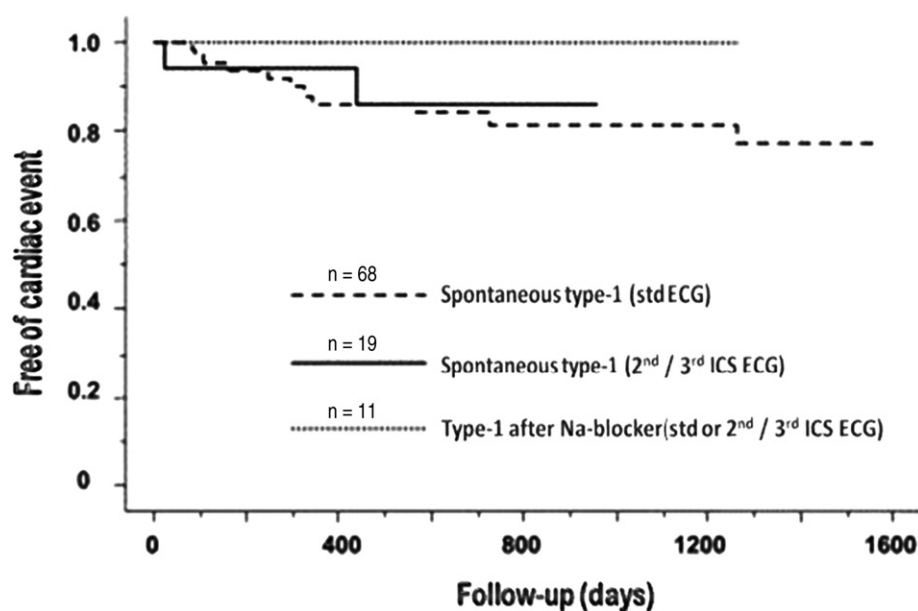


Fig 10. Kaplan-Meier analysis of cardiac events (documented VF or SD) during follow-up in patients with spontaneous type-1 ECG pattern at STD leads (dashed line), patients with spontaneous type-1 ECG recorded *only* at a higher intercostal space (solid line), and patients with type-1 ECG pattern at standard and/or higher intercostal spaces after receiving a sodium channel blocker (dotted line). No significant difference was observed in the frequency of cardiac events between the first 2 groups. Modified from Miyamoto et al⁸⁵ with permission. *Abbreviations:* ECG, electrocardiogram; SD, sudden death; STD, standard; VF, ventricular fibrillation.

in this analysis. In fact, our reported annual rate of events has decreased from the first patients included in the registry⁵ to the most recent published series,^{42,44,86} the change probably reflecting the inherent bias during the first years after the description of a novel disease, in which particularly severe forms of the disease are most likely to be diagnosed. It is important to note that in the global series, the probability of having a cardiac event during a lifetime varied widely (from 3% to 45%) depending on the baseline characteristics of the individuals. Thus, a careful risk stratification of every individual seems mandatory.

Several clinical variables have been demonstrated to predict a worse outcome in patients with Brugada syndrome. In all the analysis of our series over time, the presence of symptoms before diagnosis, a spontaneous type-1 ECG at baseline, the inducibility of ventricular arrhythmias at the EPS and male sex have consistently shown to be related to the occurrence of cardiac events in follow-up.^{5,42,44,86}

Little controversy exists on the value of a previous cardiac arrest as a risk marker for future events. Our data state that up to 62% of patients recovered from an aborted SD are at risk for a new arrhythmic event within the following 54 months.⁴² Thus, these patients should be pro-

tected with an ICD irrespective of the presence of other risk factors (indication class I).¹⁵ Because there is not such a general agreement on the best approach toward patients who have never developed ventricular fibrillation, we conducted a prospective study including 547 individuals with Brugada syndrome and no previous cardiac arrest.^{44,86} Of those (mean age, 41 ± 45 years; 408 males), 124 (22.7%) had presented with syncope, and 423 (77.3%) were asymptomatic and had been diagnosed during routine ECG or family screening. The baseline ECG showed a type-1 ECG pattern spontaneously in 391 patients (71.5%) and after a sodium channel blocker challenge in 156 (28.5%). During a mean follow-up of 24 ± 32 months, 45 individuals (8.2%) developed a first cardiac event (documented VF or SD).⁴⁴ By univariate analysis, a previous history of syncope (HR, 2.79; 95% CI, 1.5-5.1; $P = .002$), a spontaneous type-1 ECG (HR 7.69; 95% CI, 1.9-33.3; $P = .0001$), male sex (HR 5.26; 95% CI, 1.6-16.6; $P = .001$), and inducibility of ventricular arrhythmias at the EPS (HR 8.33; 95% CI, 2.8-25; $P = .0001$) were significantly related to VF or SD in follow-up. Multivariate analysis identified previous syncope and inducibility of VF as the only independent risk factors for the occurrence of events in follow-

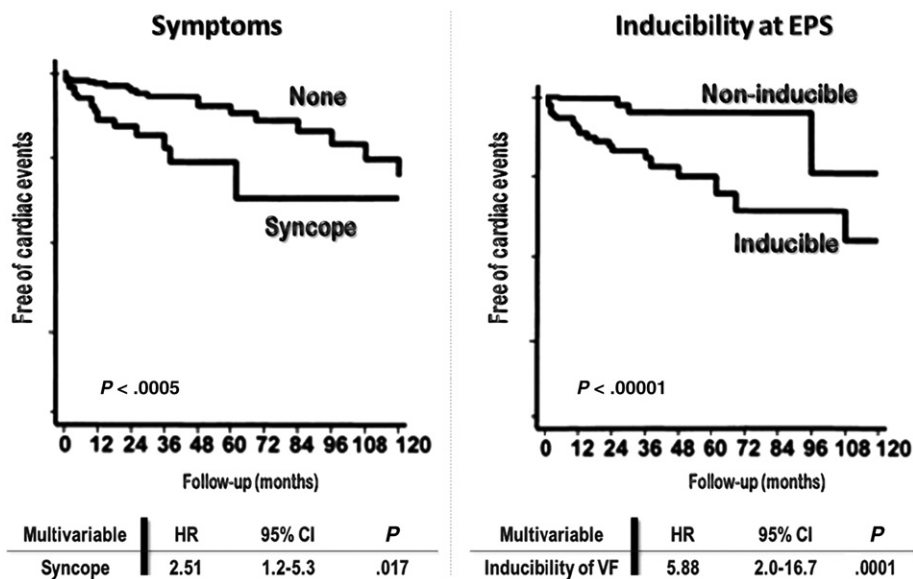


Fig 11. Kaplan-Meier of arrhythmic events (SD or documented VF) during follow-up depending on symptoms and inducibility of VF at the EPS. Modified from Brugada et al⁴⁴ with permission. *Abbreviations:* CI, confidence interval; EPS, electrophysiological study; HR, hazards ratio; SD, sudden death; VF, ventricular fibrillation.

up (Fig 11).⁴⁴ Logistic regression analysis allowed the definition of 8 categories of risk, of which asymptomatic patients with normal ECG at baseline and noninducible VF at the EPS would represent the lowest-risk population, and patients with syncope, spontaneous type-1 ECG, and inducibility at EPS would have the worst outcome (Fig 12). Further analysis indicated that EPS was particularly useful in predicting cardiac events among asymptomatic patients with no family history of SD (named fortuitous cases, $n = 167$).⁸⁶ Indeed, 11 (6%) of 167 patients presented with VF during follow-up, and the only independent predictor was inducibility at EPS, whereas the lack of an EPS was shown to be predictive of effective SD ($P = .002$).⁸⁶

Other groups agree that previous symptoms and a spontaneous type-1 ECG are risk factors, although they have found a much lower incidence of arrhythmic events for the whole population (6.5% in 34 ± 44 months of follow-up in the work of Priori et al⁴³ and 4.2% in 40 ± 50 months of follow-up in that of Eckardt et al⁴⁵). The worse outcome in our series may probably reflect a more severely ill baseline population.⁴⁵ The other large registries also agree that EPS inducibility is greatest among patients with previous SD or

syncope,^{43,45} but failed to demonstrate a value of the EPS in predicting outcome. Several reasons could explain this discrepancy⁸⁶: (1) the use of multiple testing centers with nonstandardized stimulation protocols; (2) the inclusion of patients with type-2 and type-3 ST-segment elevation (and not type-1) in some series, suggesting that they may contain individuals who do not have the syndrome; (3) the lack of events during follow-up in the other registries. The latter might change when longer follow-ups are available because events can only increase in follow-up and so does the positive predictive value.⁸⁶ Because this issue is a source of ongoing controversy, we are currently performing a prospective study to determine the role of EPS in the risk stratification of Brugada syndrome.

Male sex has consistently shown a trend to present more arrhythmic events in all the studies, and even has been defined as an independent predictor for a worse outcome in a recent meta-analysis.⁵⁵ A very recent study by our group indicates that males with Brugada syndrome display a higher risk profile than females, and thus present a worse prognosis during follow-up (see Sex Differences). Multiple ECG parameters have been assessed in the search for new risk

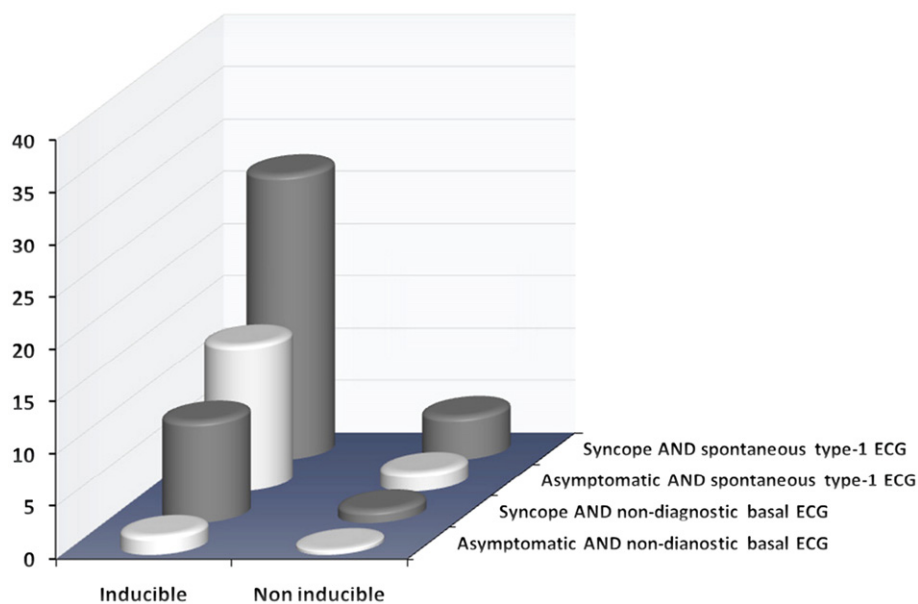


Fig 12. Probability of events in follow-up by logistic regression according to symptoms, inducibility of ventricular arrhythmias at the EPS, and baseline ECG. Data from Brugada et al⁴⁴ *Abbreviations:* ECG, electrocardiogram; EPS, electrophysiological study.

markers, of which a prolonged QTc in right precordial leads, the aVR sign, the presence of T-wave alternans, and probably a wide QRS complex seem to be the most important (see ECG and Modulating Factors). Interestingly, a positive family history of SD or the presence of an SCN5A mutation have not been proven to be risk markers in any of the large studies conducted thus far.^{42-45,55}

Treatment

Implantable Cardioverter Defibrillator

The ICD is the only proven effective treatment of the Brugada syndrome thus far. On the basis of available clinical and basic science data, a II consensus conference was held in September 2003, focused on risk stratification schemes and approaches to therapy.¹⁵ The recommendations

for ICD implantation stated by this consensus are summarized in Fig 13. Briefly, symptomatic patients should always receive an ICD. The EPS in these patients could be performed to better assess the sensitivity and specificity of the test to predict outcome, and also for the study of supraventricular arrhythmias. Asymptomatic patients may benefit from EPS for risk stratification: ICD should be implanted in those with inducible VF having a spontaneous type-1 ECG at baseline or a sodium channel blocker-induced ECG with a positive family history of SD. Finally, asymptomatic patients who have no family history of SD and who develop a type-1 ECG only after sodium channel blockade should be closely followed up, without enough evidence existing for the usefulness of EPS or a direct indication for ICD.¹⁵

From the 2 main retrospective studies conducted on patients with Brugada syndrome who

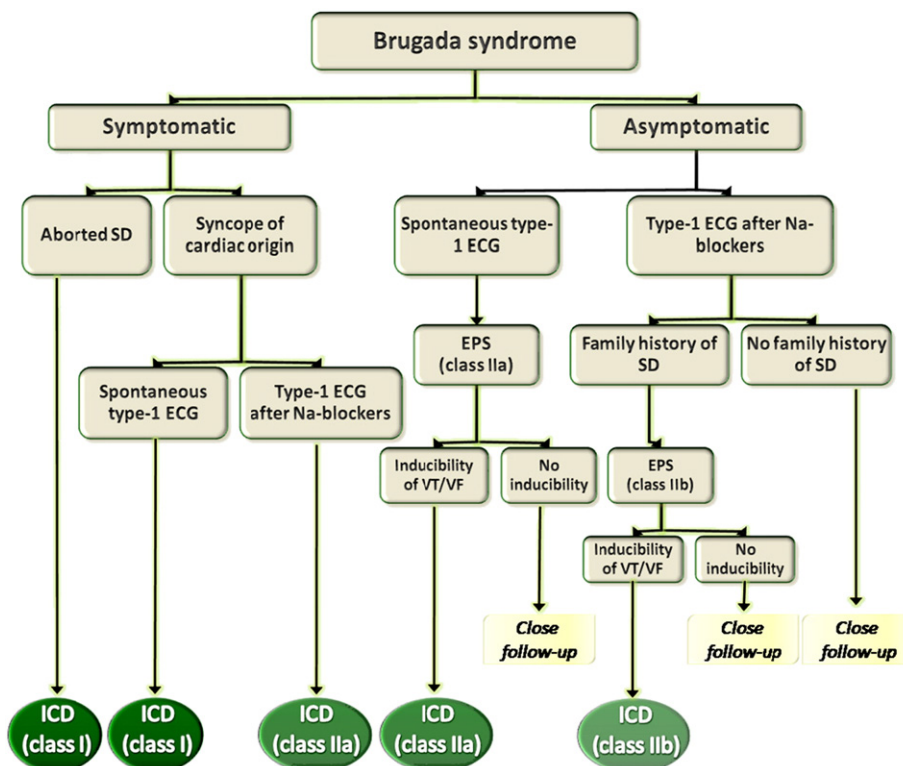


Fig 13. Indications for ICD implantation in patients with Brugada syndrome. Class I designation indicates clear evidence that the procedure or treatment is useful or effective; Class II, conflicting evidence about usefulness or efficacy; Class IIa, weight of evidence in favor of usefulness or efficacy; Class IIb, usefulness or efficacy less well established. *Abbreviations:* ECG, electrocardiogram; EPS, electrophysiological study; ICD, implantable cardioverter defibrillator; SD, sudden death; VF, ventricular fibrillation; VT, ventricular tachycardia.

have received primary prophylactic ICD, it can be concluded that ICD is an effective therapy for patients at risk,^{87,88} which can have an annual rate of appropriate shocks of up to 3.7%.⁸⁸ It is important to note that this rate is not only comparable to ICD trials^{89,90} dealing with other cardiac diseases, but also is affecting young and otherwise healthy people, whose life expectancy could be more than 30 years. Therefore, should this rate remain constant in time, it seems that most patients would be likely to experience an appropriate shock in a lifetime.

However, perhaps just because of being young, a noteworthy rate of inappropriate shocks by the device has also been reported. In the study by Sacher et al,⁸⁷ 45 (20%) out of 220 patients had inappropriate shocks in a follow-up. In our series, the rate was even higher (36%).⁸⁸ The reasons for inappropriate therapies were mainly sinus tachycardia, supraventricular arrhythmias, T-wave oversensing, and lead failure in both studies.^{87,88} On the basis of these results and because ICD is not affordable worldwide, there is growing effort to find pharmacologic approaches to help treat the disease.

Pharmacologic Options

With the aim of rebalancing the ion channel currents active during phase 1 of the action potential, so as to reduce the magnitude of the notch (Fig 4),

2 main pharmacologic approaches have been assessed (Table 4):

- drugs that decrease outward positive currents, as Ito inhibitors, and
- drugs that increase inward positive currents (ICa, INa).

Quinidine, a drug with Ito- and IKr-blocking properties, has been the most assayed drug in clinical studies. In a work by Belhassen et al,³⁹ 25 patients with inducible VF were treated with quinidine (1483 ± 240 mg orally). After treatment, 22 (88%) of 25 patients were no longer inducible at the EPS, and none of the 19 patients with ongoing medical therapy with oral quinidine developed arrhythmias during follow-up (56 ± 67 months).³⁹ However, 36% of the patients had transient side effects that led to drug discontinuation.³⁹ Preliminary data have also proven quinidine as a good adjunctive therapy in patients with ICD and multiple shocks⁹¹ and as an effective treatment of electrical storms associated to Brugada syndrome.⁹² More recently, quinidine has been proposed as a good alternative to ICD implantation in children with the syndrome and at high risk for malignant arrhythmias.⁶⁰ However, large, randomized, controlled clinical trials assessing the effectiveness of quinidine (which should be addressed in patients who have already received an ICD) are still lacking.

Table 4. Pharmacologic Approach to Therapy in the Brugada Syndrome

Action	Proved on
• Ito blockers: 4-Aminopyridine	Effective in experimental models (suppression of phase-2 reentry) ¹¹ Probable neurotoxicity in humans
Quinidine	Effective in experimental models (suppression of phase-2 reentry) ¹¹ Initial results showing effectiveness in clinical practice: ↓ inducibility of VF ³⁹ ↓ spontaneous VF in follow-up ^{39,89} Adjunctive therapy in patients with ICD and multiple shocks ⁸⁹ Effective in electrical storm ⁹⁰ A possible option in children ⁶⁰
Tedisamil AVE0118	Effective in experimental models (suppression of phase-2 reentry) ¹⁶ Effective in experimental models (suppression of phase-2 reentry) ¹⁶
• ICa activators: Isoproterenol (β-adrenergic agents)	Effective in experimental models (suppression of phase-2 reentry) ¹¹ Effective in electrical storm ⁹¹
Cilostazol (phosphodiesterase III inhibitor)	Controversial preliminary results in preventing VF ^{92,93}
• INa openers: Dimethyl lithospermate B	Effective in experimental models (suppression of phase-2 reentry) ¹⁶

Abbreviations: ICa, inward calcium current; ICD, implantable cardioverter defibrillator; VF, ventricular fibrillation.

β -Adrenergic agents, through an increase in ICa currents, decrease transmural dispersion of repolarization and epicardial dispersion of repolarization in experimental models.¹¹ Clinically, they have proven effectiveness in the treatment of electrical storms associated to Brugada syndrome.⁹³ Recently, phosphodiesterase III inhibitors have appeared as a new appealing option because they would increase ICa and decrease Ito. Indeed, cilostazol was effective in preventing ICD shocks in a patient with recurrent episodes of VF.⁹⁴ However, a recent publication reports the failure of such drug in another patient with multiple ICD discharges despite sustained therapy.⁹⁵

Dimethyl Lithospermate B, an extract of Danshen, a traditional Chinese herbal remedy that slows inactivation of INa, have recently been assayed in experimental models, demonstrating a reduction of both transmural and epicardial dispersion of repolarization, and abolishing phase 2 reentry-induced extrasystoles and VT/VF in 9 of 9 preparations. Clinical data with this agent are, however, not yet available, but the results of experimental studies suggest that this agent could be a new candidate for the pharmacologic treatment of Brugada syndrome.¹⁶

References

1. Brugada P, Brugada J: Right bundle branch block, persistent ST segment elevation and sudden cardiac death: a distinct clinical and electrocardiographic syndrome. A multicenter report. *J Am Coll Cardiol* 20:1391-1396, 1992
2. Ferracci A, Fromer M, Schlapfer J, et al: Primary ventricular fibrillation and early recurrence: apropos of a case of association of right bundle branch block and persistent ST segment elevation. *Arch Mal Coeur Vaiss* 87:1359-1362, 1994
3. Proclemer A, Facchin D, Feruglio GA, et al: Recurrent ventricular fibrillation, right bundle-branch block and persistent ST segment elevation in V1-V3: A new arrhythmia syndrome? A clinical case report. *G Ital Cardiol* 23:1211-1218, 1993
4. Brugada J, Brugada P: Further characterization of the syndrome of right bundle branch block, ST segment elevation, and sudden cardiac death. *J Cardiovasc Electrophysiol* 8:325-331, 1997
5. Brugada J, Brugada R, Brugada P: Right bundle-branch block and ST-segment elevation in leads V1 through V3: a marker for sudden death in patients without demonstrable structural heart disease. *Circulation* 97:457-460, 1998
6. Alings M, Wilde A: "Brugada" syndrome: clinical data and suggested pathophysiological mechanism. *Circulation* 99:666-673, 1999
7. Priori SG, Napolitano C, Gasparini M, et al: Clinical and genetic heterogeneity of right bundle branch block and ST-segment elevation syndrome: a prospective evaluation of 52 families. *Circulation* 102:2509-2515, 2000
8. Brugada P, Brugada R, Brugada J: Sudden death in patients and relatives with the syndrome of right bundle branch block, ST segment elevation in the precordial leads V1 to V3 and sudden death. *Eur Heart J* 21:321-326, 2000
9. Chen Q, Kirsch GE, Zhang D, et al: Genetic basis and molecular mechanism for idiopathic ventricular fibrillation. *Nature* 392:293-296, 1998
10. Dumaine R, Towbin JA, Brugada P, et al: Ionic mechanisms responsible for the electrocardiographic phenotype of the Brugada syndrome are temperature dependent. *Circ Res* 85:803-809, 1999
11. Yan GX, Antzelevitch C: Cellular basis for the Brugada syndrome and other mechanisms of arrhythmogenesis associated with ST-segment elevation. *Circulation* 100:1660-1666, 1999
12. Rook MB, Bezzina Alshinawi C, Groenewegen WA, et al: Human SCN5A gene mutations alter cardiac sodium channel kinetics and are associated with the Brugada syndrome. *Cardiovasc Res* 44:507-517, 1999
13. Deschênes I, Baroudi G, Berthet M, et al: Electrophysiological characterization of SCN5A mutations causing long QT (E1784K) and Brugada (R1512W and R1432G) syndromes. *Cardiovasc Res* 46:55-65, 2000
14. Wilde AAM, Antzelevitch C, Borggrefe M, et al: Proposed diagnostic criteria for the Brugada syndrome. *Eur Heart J* 23:1648-1654, 2002
15. Antzelevitch C, Brugada P, Borggrefe M, et al: Brugada syndrome: report of the Second Consensus Conference: endorsed by the Heart Rhythm Society and the European Heart Rhythm Association. *Circulation* 111:659-670, 2005
16. Antzelevitch C: Brugada syndrome. *Pacing Clin Electrophysiol* 29:1130-1159, 2006
17. Miyasaka Y, Tsuji H, Yamada K, et al: Prevalence and mortality of the Brugada-type electrocardiogram in one city in Japan. *J Am Coll Cardiol* 38:771-774, 2001
18. Donohue D, Tehrani F, Jamehdor R, et al: The prevalence of Brugada ECG in adult patients in a large university hospital in the western United States. *Am Heart Hosp J* 6:48-50, 2008
19. Hermida JS, Lemoine JL, Aoun FB, et al: Prevalence of the Brugada syndrome in an apparently healthy population. *Am J Cardiol* 86:91-94, 2000
20. Vatta M, Dumaine R, Varghese G, et al: Genetic and biophysical basis of sudden unexplained nocturnal death syndrome (SUNDS), a disease allelic to Brugada syndrome. *Hum Mol Genet* 11:337-345, 2002
21. Schulze-Bahr E, Eckardt L, Paul M, et al: Molecular genetics of the Brugada syndrome, in: Antzelevitch C, Brugada P (eds): *The Brugada Syndrome: from Bench to Bedside* (ed 1). Blackwell Publishing, 2005, p. 42-51
22. Vatta M, Dumaine R, Antzelevitch C, et al: Novel mutations in domain I of SCN5A cause Brugada syndrome. *Mol Genet Metab* 75:317-324, 2002

23. Pfahnl AE, Viswanathan PC, Weiss R, et al: A sodium channel pore mutation causing Brugada syndrome. *Heart Rhythm* 4:46-53, 2007
24. Casini S, Tan HL, Bhuiyan ZA, et al: Characterization of a novel SCN5A mutation associated with Brugada syndrome reveals involvement of DIIIS4-S5 linker in slow inactivation. *Cardiovasc Res* 76: 418-429, 2007
25. Cordeiro JM, Barajas-Martinez H, Hong K, et al: Compound heterozygous mutations P336L and I1660V in the human cardiac sodium channel associated with the Brugada syndrome. *Circulation* 114: 2026-2033, 2006
26. Schulze-Bahr E, Eckardt L, Breithardt G, et al: Sodium channel gene (SCN5A) mutations in 44 index patients with Brugada syndrome: different incidences in familial and sporadic disease. *Hum Mutat* 2:651-652, 2003
27. Weiss R, Barmada MM, Nguyen T, et al: Clinical and molecular heterogeneity in the Brugada syndrome: a novel gene locus on chromosome 3. *Circulation* 105:707-713, 2002
28. London B, Michalec M, Mehdi H, et al: Mutation in glycerol-3-phosphate dehydrogenase 1 like gene (GPD1-L) decreases cardiac Na⁺ current and causes inherited arrhythmias. *Circulation* 116:2260-2268, 2007
29. Antzelevitch C, Pollevick GD, Cordeiro JM, et al: Loss-of-function mutations in the cardiac calcium channel underlie a new clinical entity characterized by ST-segment elevation, short QT intervals, and sudden cardiac death. *Circulation* 115:442-449, 2007
30. Viswanathan PC, Benson DW, Balsler JR: A common SCN5A polymorphism modulates the biophysical effects of an SCN5A mutation. *J Clin Invest* 111: 341-346, 2003
31. Poelzing S, Forleo C, Samodell M, et al: SCN5A polymorphism restores trafficking of a Brugada syndrome mutation on a separate gene. *Circulation* 114:368-376, 2006
32. Litovsky SH, Antzelevitch C: Transient outward current prominent in canine ventricular epicardium but not endocardium. *Circ Res* 62:116-126, 1988
33. Kurita T, Shimizu W, Inagaki M, et al: The electrophysiologic mechanism of ST-segment elevation in Brugada syndrome. *J Am Coll Cardiol* 40:330-334, 2002
34. Shimizu W, Aiba T, Kamakura S: Mechanisms of disease: current understanding and future challenges in Brugada syndrome. *Nat Clin Pract Cardiovasc Med* 2:408-414, 2005
35. Fish J, Antzelevitch C: Role of sodium and calcium channel block in unmasking the Brugada syndrome. *Heart Rhythm* 1:210-217, 2004
36. Litovsky SH, Antzelevitch C: Differences in the electrophysiological response of canine ventricular subendocardium and subepicardium to acetylcholine and isoproterenol. A direct effect of acetylcholine in ventricular myocardium. *Circ Res* 67:615-627, 1990
37. Miyazaki T, Mitamura H, Miyoshi S, et al: Autonomic and antiarrhythmic drug modulation of ST segment elevation in patients with Brugada syndrome. *J Am Coll Cardiol* 27:1061-1070, 1996
38. Brugada R, Brugada J, Antzelevitch C, et al: Sodium channel blockers identify risk for sudden death in patients with ST-segment elevation and right bundle branch block but structurally normal hearts. *Circulation* 101:510-515, 2000
39. Belhassen B, Glick A, Viskin S: Efficacy of quinidine in high-risk patients with Brugada syndrome. *Circulation* 110:1731-1737, 2004
40. Di Diego JM, Sun ZQ, Antzelevitch C: I(to) and action potential notch are smaller in left vs. right canine ventricular epicardium. *Am J Physiol* 271:H548-H561, 1996 (2 Pt 2)
41. Di Diego JM, Cordeiro JM, Goodrow RJ, et al: Ionic and cellular basis for the predominance of the Brugada syndrome phenotype in males. *Circulation* 106: 2004-2011, 2002
42. Brugada J, Brugada R, Antzelevitch C, et al: Long-term follow-up of individuals with the electrocardiographic pattern of right bundle-branch block and ST-segment elevation in precordial leads V1 to V3. *Circulation* 105:73-78, 2002
43. Priori SG, Napolitano C, Gasparini M, et al: Natural history of Brugada syndrome: insights for risk stratification and management. *Circulation* 105:1342-1347, 2002
44. Brugada J, Brugada R, Brugada P: Determinants of sudden cardiac death in individuals with the electrocardiographic pattern of Brugada syndrome and no previous cardiac arrest. *Circulation* 108:3092-3096, 2003
45. Eckardt L, Probst V, Smits JPP, et al: Long-term prognosis of individuals with right precordial ST-segment-elevation Brugada syndrome. *Circulation* 111:257-263, 2005
46. Benito B, Arzamendi D, Porres J, et al: Seguimiento a largo plazo de los pacientes con síndrome de Brugada. Estudio multicéntrico de los factores de mal pronóstico; 2007. (Congreso de las Enfermedades Cardiovasculares de la SEC 2007 Ref Type: Abstract)
47. Eckardt L, Kirchhof P, Loh P, et al: Brugada syndrome and supraventricular tachyarrhythmias: a novel association? *J Cardiovasc Electrophysiol* 12:680-685, 2001
48. Morita H, Kusano-Fukushima K, Nagase S, et al: Atrial fibrillation and atrial vulnerability in patients with Brugada syndrome. *J Am Coll Cardiol* 40:1437-1444, 2002
49. Benito B, Brugada J: Recurrent syncope: an unusual presentation of Brugada syndrome. *Nat Clin Pract Cardiovasc Med* 3:573-577, 2006
50. Makita N, Sumitomo N, Watanabe I, et al: Novel SCN5A mutation (Q55X) associated with age-dependent expression of Brugada syndrome presenting as neurally mediated syncope. *Heart Rhythm* 4:516-519, 2007
51. Matsuo K, Kurita T, Inagaki M, et al: The circadian pattern of the development of ventricular fibrillation in patients with Brugada syndrome. *Eur Heart J* 20: 465-470, 1999

52. Wichter T, Matheja P, Eckardt L, et al: Cardiac autonomic dysfunction in Brugada syndrome. *Circulation* 105:702-706, 2002
53. Kies P, Wichter T, Schafers M, et al: Abnormal myocardial presynaptic norepinephrine recycling in patients with Brugada syndrome. *Circulation* 110:3017-3022, 2004
54. Eckardt L: Gender differences in Brugada syndrome. *J Cardiovasc Electrophysiol* 18:422-424, 2007
55. Gehi A, Duong T, Metz L, et al: Risk stratification of individuals with the Brugada electrocardiogram: a meta-analysis. *J Cardiovasc Electrophysiol* 17:577-583, 2006
56. Matsuo K, Akahoshi M, Seto S, et al: Disappearance of the Brugada-type electrocardiogram after surgical castration: a role for testosterone and an explanation for the male preponderance. *Pacing Clin Electrophysiol* 26:1551-1553, 2003
57. Shimizu W, Matsuo K, Kokubo Y, et al: Sex hormone and gender difference—role of testosterone on male predominance in Brugada syndrome. *J Cardiovasc Electrophysiol* 18:415-421, 2007
58. Bai CX, Kurokawa J, Tamagawa M, et al: Nontranscriptional regulation of cardiac repolarization currents by testosterone. *Circulation* 112:1701-1710, 2005
59. Song M, Helguera G, Eghbali M, et al: Remodeling of Kv4.3 potassium channel gene expression under the control of sex hormones. *J Biol Chem* 276:31883-31890, 2001
60. Probst V, Denjoy I, Meregalli PG, et al: Clinical aspects and prognosis of Brugada syndrome in children. *Circulation* 115:2042-2048, 2007
61. Benito B, Sarkozy A, Berne P, et al: Características clínicas y pronóstico del síndrome de Brugada en la población pediátrica; 2007. (Congreso de las Enfermedades Cardiovasculares de la SEC 2007 Ref Type: Abstract)
62. Veltmann C, Schimpf R, Echternach C, et al: A prospective study on spontaneous fluctuations between diagnostic and non-diagnostic ECGs in Brugada syndrome: implications for correct phenotyping and risk stratification. *Eur Heart J* 27:2544-2552, 2006
63. Wilde AA: Spontaneous electrocardiographic fluctuations in Brugada syndrome: does it matter? *Eur Heart J* 27:2493-2494, 2006
64. Extramiana F, Seitz J, Maison-Blanche P, et al: Quantitative assessment of ST segment elevation in Brugada patients. *Heart Rhythm* 3:1175-1181, 2006
65. Tatsumi H, Takagi M, Nakagawa E, et al: Risk stratification in patients with Brugada syndrome: analysis of daily fluctuations in 12-lead electrocardiogram (ECG) and signal-averaged electrocardiogram (SAECG). *J Cardiovasc Electrophysiol* 17:705-711, 2006
66. Mizumaki K, Fujiki A, Tsuneda T, et al: Vagal activity modulates spontaneous augmentation of ST elevation in the daily life of patients with Brugada syndrome. *J Cardiovasc Electrophysiol* 15:667-673, 2004
67. Shimizu W: Gender difference and drug challenge in Brugada syndrome. *J Cardiovasc Electrophysiol* 15:70-71, 2004
68. Gonzalez Rebollo JM, Hernandez MA, Garcia A, et al: Recurrent ventricular fibrillation during a febrile illness in a patient with the Brugada syndrome. *Rev Esp Cardiol* 53:755-757, 2000
69. Porres JM, Brugada J, Urbistondo V, et al: Fever unmasking the Brugada syndrome. *Pacing Clin Electrophysiol* 25:1646-1648, 2002
70. Pitzalis MV, Anaclerio M, Iacoviello M, et al: QT-interval prolongation in right precordial leads: an additional electrocardiographic hallmark of Brugada syndrome. *J Am Coll Cardiol* 42:1632-1637, 2003
71. Castro Hevia J, Antzelevitch C, Tornés Bázquez F, et al: Tpeak-Tend and Tpeak-Tend dispersion as risk factors for ventricular tachycardia/ventricular fibrillation in patients with the Brugada syndrome. *J Am Coll Cardiol* 47:1828-1834, 2006
72. Babai Bigi MA, Aslani A, Shahrzad S: aVR sign as a risk factor for life-threatening arrhythmic events in patients with Brugada syndrome. *Heart Rhythm* 4:1009-1012, 2007
73. Fish JM, Antzelevitch C: Cellular mechanism and arrhythmogenic potential of T-wave alternans in the Brugada syndrome. *J Cardiovasc Electrophysiol* 19:301-308, 2008
74. Tada T, Kusano KF, Nagase S, et al: The relationship between the magnitude of T wave alternans and amplitude of the corresponding T wave in patients with Brugada syndrome. *J Cardiovasc Electrophysiol*, 2008
75. Kyndt F, Probst V, Potet F, et al: Novel SCN5A mutation leading either to isolated cardiac conduction defect or Brugada syndrome in a large French family. *Circulation* 104:3081-3086, 2001
76. Smits JP, Eckardt L, Probst V, et al: Genotype-phenotype relationship in Brugada syndrome: electrocardiographic features differentiate SCN5A-related patients from non-SCN5A-related patients. *J Am Coll Cardiol* 40:350-356, 2002
77. Yokokawa M, Noda T, Okamura H, et al: Comparison of long-term follow-up of electrocardiographic features in Brugada syndrome between the SCN5A-positive probands and the SCN5A-negative probands. *Am J Cardiol* 100:649-655, 2007
78. Junttila MJ, Brugada P, Hong K, et al: Differences in 12-lead electrocardiogram between symptomatic and asymptomatic Brugada syndrome patients. *J Cardiovasc Electrophysiol*
79. Hong K, Brugada J, Oliva A, et al: Value of electrocardiographic parameters and ajmaline test in the diagnosis of Brugada syndrome caused by SCN5A mutations. *Circulation* 110:3023-3027, 2004
80. Meregalli PG, Ruijter JM, Hofman N, et al: Diagnostic value of flecainide testing in unmasking SCN5A-related Brugada syndrome. *J Cardiovasc Electrophysiol* 17:857-864, 2006
81. Priori SG, Napolitano C: Should patients with an asymptomatic Brugada electrocardiogram undergo pharmacological and electrophysiological testing? *Circulation* 112:279-292, 2005

82. Wolpert C, Echternach C, Veltmann C, et al: Intravenous drug challenge using flecainide and ajmaline in patients with Brugada syndrome. *Heart Rhythm* 2: 254-260, 2005
83. Sangwatanaroj S, Prechawat S, Sunsaneewitayakul B, et al: New electrocardiographic leads and the procainamide test for the detection of the Brugada sign in sudden unexplained death syndrome survivors and their relatives. *Eur Heart J* 22:2290-2296, 2001
84. Shimizu W, Matsuo K, Takagi M, et al: Body surface distribution and response to drugs of ST segment elevation in Brugada syndrome: clinical implication of eighty-seven-lead body surface potential mapping and its application to twelve-lead electrocardiograms. *J Cardiovasc Electrophysiol* 11:396-404, 2000
85. Miyamoto K, Yokokawa M, Tanaka K, et al: Diagnostic and prognostic value of a type 1 Brugada electrocardiogram at higher (third or second) V1 to V2 recording in men with Brugada syndrome. *Am J Cardiol* 99:53-57, 2007
86. Brugada P, Brugada R, Brugada J, et al: Should patients with an asymptomatic Brugada electrocardiogram undergo pharmacological and electrophysiological testing? *Circulation* 112:279-292, 2005
87. Sacher F, Probst V, Lesaka Y, et al: Outcome after implantation of a cardioverter-defibrillator in patients with Brugada syndrome: a multicenter study. *Circulation* 114:2317-2324, 2006
88. Sarkozy A, Boussy T, Kourgiannides G, et al: Long-term follow-up of primary prophylactic implantable cardioverter-defibrillator therapy in Brugada syndrome. *Eur Heart J* 28:334-344, 2007
89. Maron BJ, Shen WK, Link MS, et al: Efficacy of implantable cardioverter-defibrillators for the prevention of sudden death in patients with hypertrophic cardiomyopathy. *N Engl J Med* 342:365-373, 2000
90. Bardy GH, Lee KL, Mark DB, et al: Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med* 352:225-237, 2005
91. Hermida JS, Denjoy I, Clerc J, et al: Hydroquinidine therapy in Brugada syndrome. *J Am Coll Cardiol* 43: 1853-1860, 2004
92. Mok NS, Chan NY, Chiu AC: Successful use of quinidine in treatment of electrical storm in Brugada syndrome. *Pacing Clin Electrophysiol* 27:821-823, 2004 (6 Pt 1)
93. Ohgo T, Okamura H, Noda T, et al: Acute and chronic management in patients with Brugada syndrome associated with electrical storm of ventricular fibrillation. *Heart Rhythm* 4:695-700, 2007
94. Tsuchiya T, Ashikaga K, Honda T, et al: Prevention of ventricular fibrillation by cilostazol, an oral phosphodiesterase inhibitor, in a patient with Brugada syndrome. *J Cardiovasc Electrophysiol* 13:698-701, 2002
95. Abud A, Bagattin D, Goyeneche R, et al: Failure of cilostazol in the prevention of ventricular fibrillation in a patient with Brugada syndrome. *J Cardiovasc Electrophysiol* 17:210-212, 2006