**GLOSSARY**

$I_{TO}$
A transient outward potassium current that activates rapidly and underlies the early (phase 1) action-potential repolarization

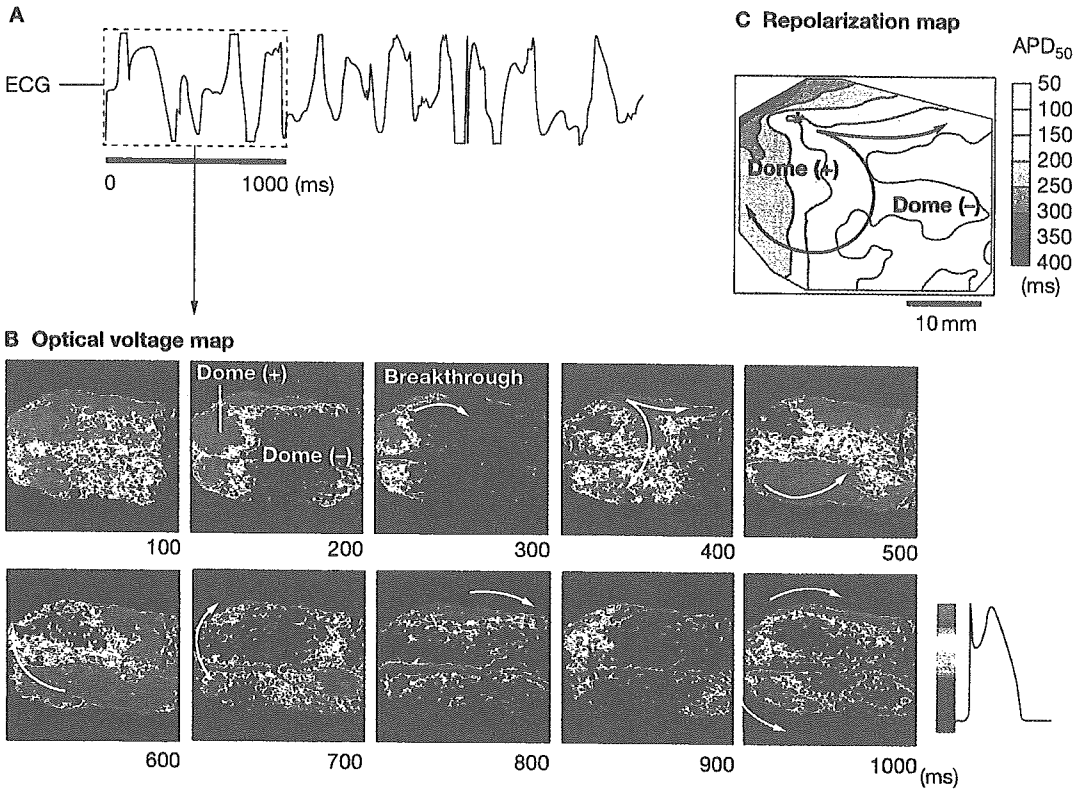


**Figure 2** Snapshots of a color isopotential optical movie of the epicardial surface at the beginning of polymorphic ventricular tachycardia, and a repolarization map of the epicardial surface just before ventricular fibrillation. (**A**) Electrocardiogram recording of polymorphic ventricular tachycardia. (**B**) At the timing of phase 2 (200–300 ms), the epicardial surface is divided into two areas: restored dome (orange–red) and loss of dome (black–blue). A significant electrotonic difference between restored dome and loss of dome within a small area creates a marked epicardial dispersion of repolarization, which develops a local re-excitation called phase 2 re-entry. The initial re-entrant pathway mainly rotates in the epicardium (300–800 ms) and gradually involves the transmural myocardium (900–1000 ms), precipitating nonsustained polymorphic ventricular tachycardia. (**C**) A steep repolarization gradient (asterisk) produces local re-excitation, which propagates on the epicardial surface (arrows). $APD_{50}$, action-potential duration (time to 50% repolarization); dome (+), restored dome; dome (–), loss of dome; ECG, electrocardiogram.

Moreover, single *SCN5A* mutations can lead to a multiple cardiac phenotype, which is a combination of the Brugada syndrome, type 3 long-QT syndrome and a cardiac conduction defect.[26,27] In patients with type 3 long-QT syndrome alone, under baseline conditions, the sodium-channel blocker flecainide has an increased propensity to elicit a Brugada phenotype,[33] and it is reported that the proarrhythmic sensitivity to flecainide is based on inactivation gating defects caused by certain *SCN5A* mutations.[28] Some common *SCN5A* polymorphisms have been reported to modulate the functional consequences of primary *SCN5A* mutations.[29–31] The genetic and functional characteristics of *SCN5A* mutations and polymorphisms discussed above underline the complexity of sodium channelopathies.

## CELLULAR MECHANISMS FOR THE BRUGADA PHENOTYPE

All functional studies of *SCN5A* mutations that are responsible for the Brugada phenotype cause a net reduction of $I_{Na}$, even though several distinct functional effects have been demonstrated. Experimental studies employing arterially perfused canine right-ventricular wedge preparations, in which transmembrane action potentials and pseudoelectrocardiograms are simultaneously recorded, have elucidated the cellular and molecular basis for typical ST-segment elevation and subsequent VF.[34,35] A phase 1 notch of the action potential, mediated by the transient outward current ($I_{TO}$), is greater in the epicardium than in the endocardium in many species, including humans.[36,37] The accentuated

$I_{to}$-mediated action-potential notch, and subsequent loss of the action-potential dome in epicardial cells (but not in endocardial cells) of the right ventricle—due to a net reduction of outward currents—gives rise to a transmural voltage gradient, producing coved-type ST-segment elevation in the electrocardiograms (Figure 1A). In coved-type ST-segment elevation, heterogeneous loss of the action-potential dome (coexistence of dome-loss regions and dome-restoration regions) in the epicardium creates a marked epicardial dispersion of repolarization (Figure 1A). This mechanism gives rise to premature beats caused by phase 2 re-entry,[38] which can precipitate nonsustained PVT or VF (Figure 1B). Although these data strongly suggest that episodes of VF in Brugada syndrome are triggered by premature beats between adjacent epicardial cells, triggered by phase 2 re-entry, the mechanism of initiation of VF remains unclear because of the small number of action-potential recording sites in wedge preparations. We have developed a high-resolution optical mapping system that allows us to record transmembrane action potentials from 256 sites simultaneously, from the epicardial or endocardial surface of an arterially perfused canine right-ventricular wedge preparation (Figure 2).[39] The optical mapping data indicate that a steep repolarization gradient between a dome-loss region and a dome-restoration region in the epicardium is essential to produce the premature beats (Figure 2C). Premature beats induced by phase 2 re-entry activate a re-entrant pathway, which initially rotates in the epicardium and gradually involves the transmural myocardium, precipitating nonsustained PVT or VF (Figure 2A and 2B).

**Box 1** Optimum pharmacologic therapy based on cellular mechanisms.

**Adjunctive oral therapy under backup with ICD**

$I_{to}$ blockade (quinidine)

$I_{Ca}$ augmentation (denopamine, atropine, cilostazol)

**Acute intravenous therapy (electrical storm of ventricular fibrillation)**

$I_{Ca}$ augmentation (isoproterenol, atropine)

ICD, implantable cardioverter-defibrillator; $I_{Ca}$, L-type calcium current; $I_{to}$, transient outward current.

## OPTIMUM MANAGEMENT STRATEGIES BASED ON CELLULAR MECHANISMS

The advances in understanding of the cellular mechanism of the ST-segment elevation and phase 2 re-entry ventricular arrhythmias derived from experimental studies suggest possibilities for development of strategies for managing and treating patients with Brugada syndrome. Any therapeutic agents or interventions that decrease outward currents (e.g. $I_{to}$, ATP-sensitive potassium-current channels [$I_{K\text{-}ATP}$], slow-activating and fast-activating components of delayed rectifier potassium current [$I_{Ks}$ and $I_{Kr}$]) or increase inward currents (e.g. L-type calcium-channel current [$I_{Ca}$] or FAST $I_{NA}$) at the end of phase 1 might normalize the Brugada phenotype. Such therapies are, therefore, candidates in patients with Brugada syndrome (Box 1). Clinical data have shown that implantable cardioverter-defibrillators have a protective effect, preventing sudden cardiac death in symptomatic Brugada patients with a history of cardiac arrest, aborted sudden cardiac death or syncope.[1,7,9,10,20,21] Several agents can be used as adjunctive pharmacologic treatments to reduce the incidence of VF episodes in all patients with symptomatic Brugada syndrome (Box 1). Oral quinidine can improve ST-segment elevation because of its strong $I_{to}$-blocking effect.[40–42] Denopamine, an oral adrenergic stimulant, or oral atropine, an anticholinergic agent that increases L-TYPE $I_{CA}$, might be alternative therapeutic choices.[43] Cilostazol, a phosphodiesterase 3 inhibitor, reduces ST-segment elevation, probably by increasing L-type $I_{Ca}$ and heart rate.[44] These adjunctive pharmacologic treatments must, however, be considered only in conjunction with an implantable cardioverter-defibrillator, because recurrence of VF is always fatal. During recurrent episodes of VF, continuous infusion of isoproterenol, a β-adrenergic agonist, at a dose of 0.005–0.02 $\mu g\,kg^{-1}\,min^{-1}$ or until a 20% increase of heart rate occurs, attenuates ST-segment elevation and prevents VF by augmenting L-type $I_{Ca}$ and heart rate.[45] Intravenous atropine is another option, although its effect is short-lived.

## ACQUIRED FORM OF BRUGADA SYNDROME

In addition to sodium-channel blockers,[17–19,46] many agents and conditions that cause an outward shift in current activity at the end of a phase 1 action potential can unmask ST-segment elevation, as found in the Brugada syndrome, leading to the acquired form of this disorder (Box 2).[11,47] Calcium-channel blockers, such as verapamil, nifedipine and diltiazem, β-receptor blockers and

**GLOSSARY**

**$I_K$**
An outward potassium current that determines the late phase (phase 3) of action-potential repolarization

**FAST $I_{NA}$**
An inward sodium current that mainly contributes to the upstroke of action-potential depolarization (phase 0)

**L-TYPE $I_{CA}$**
An inward calcium current that is activated by membrane depolarization and contributes to the plateau phase of action potential

**Box 2** Acquired Brugada syndrome.

**Drug-induced**

Fast $I_{Na}$ blockade
- Class IC sodium blockers (flecainide, pilsicainide, propafenone)
- Class IA sodium blockers (ajmaline, procainamide, disopyramide, cibenzoline)
- Tricyclic antidepressants (amitriptyline, nortriptyline, desipramine, clomipramine)
- Tetracyclic antidepressants (maprotiline)
- Phenothiazines (perphenazine, cyamemazine)
- Selective serotonin-reuptake inhibitors (fluoxetine)
- Other drugs (dimenhydrinate, cocaine intoxication, alcohol intoxication)

L-type $I_{Ca}$ blockade
- Calcium-channel blockers (verapamil, nifedipine, diltiazem)
- β-blockers (propranolol, etc.)
- Nitrates (isosorbide dinitrate, nitroglycerine)

$I_{K\text{-}ATP}$ open
- Nicorandil

**Electrolyte abnormalities**

Hyperkalemia
Hypercalcemia

**Acute ischemia**

Right-ventricular infarction, ischemia or both
Vasospastic angina

**Other causes**

Increased insulin level
Hyperthermia (febrile state)
Hypothermia

L-type $I_{Ca}$, L-type calcium current; $I_{K\text{-}ATP}$, adenosine-triphosphate-sensitive potassium current; $I_{Na}$, sodium current

**GLOSSARY**

**AUTOSOMAL DOMINANT**
A pattern of Mendelian inheritance whereby an affected individual possesses one copy of a mutant allele and one normal allele

nitrate decrease L-type $I_{Ca}$, and might, therefore, induce Brugada-like ST-segment elevation. $I_{K\text{-}ATP}$ openers, such as nicorandil, also have the potential to induce an acquired form of Brugada syndrome, as do many psychotropic agents,[48] including tricyclic and tetracyclic antidepressants, phenothiazine and selective serotonin-reuptake inhibitors. These agents are commonly used in clinical practice, and the potential risk of producing the Brugada phenotype should be taken into account. Electrolyte abnormalities, such as hyperkalemia and hypercalcemia, are reported to amplify ST-segment elevation as seen in Brugada syndrome.[49] Acute myocardial ischemia involving the right-ventricular outflow tract occasionally mimics Brugada-like ST-segment elevation due to the depression of L-type $I_{Ca}$ and the activation of $I_{K\text{-}ATP}$.[50] The increased insulin level that occurs after meals sometimes unmasks or augments ST-segment elevation in Brugada patients, mainly due to an increase in an outward current caused by activation of the sodium–potassium pump.[51] Hyperthermia (febrile state) is reported to unmask Brugada-like ST-segment elevation and provoke VF secondary to the reduced $I_{Na}$ that occurs at high temperatures.[52] Alternatively, hypothermic states sometimes induce a prominent J wave, mimicking Brugada-like ST-segment elevation, probably due to augmented $I_{to}$.[53]

## FUTURE CHALLENGES

### Risk stratification

Risk stratification for the identification of patients at raised risk of sudden death is one of the most important challenges. A previous history of aborted cardiac arrest or syncope, and the presence of a spontaneous type 1 ST-segment elevation are predictors of further arrhythmic events.[7,9,10,21] On the other hand, a positive sodium-channel challenge test and the identification of *SCN5A* mutations are not particularly helpful for risk stratification.[7,21] Whether the inducibility of VF, PVT or both with programmed electrical stimulation is a strong predictor of arrhythmic events is still controversial.[7,9,10,20,21] Further studies with higher numbers of patients, uniform stimulation protocols, and longer follow-up periods are needed before a definitive conclusion can be reached.

### Genetic heterogeneity of *SCN5A* mutations

*SCN5A* mutations are currently identified in fewer than one-third of clinically affected Brugada patients, and more than two-thirds of patients cannot be genotyped. In such patients, however, the possibility of causative *SCN5A* mutations is not ruled out, because general screening does not include investigation of the promoter region of *SCN5A*, or allow for detection of cryptic splicing mutations or gross rearrangements. Genes that code for a variety of ion channels and other proteins have been proposed as candidate genes for the Brugada phenotype, including the genes encoding $I_{to}$, $I_K$, and L-type $I_{Ca}$. Other genes that code for adrenergic receptors, cholinergic receptors, ion-channel-interacting protein, promoters, transcriptional factors, neurotransmitters, or transporters might also be candidates. In addition, environmental factors can affect the clinical manifestation of the Brugada phenotype and might influence its genetic heterogeneity.

### Differences between the sexes

Since all mutations so far identified in patients with Brugada syndrome display an AUTOSOMAL DOMINANT mode of transmission, male and

female inheritance of the defective gene would be expected to be approximately equal; however, more than 80% of Brugada probands in Western countries, and more than 90% in Asian countries, are men.[54] The difference between the sexes in the Brugada phenotype is reported to be due at least partly to intrinsic differences in ventricular action potential between males and females. Di Diego *et al.*[55] demonstrated more-prominent $I_{to}$ expression in male than in female dogs, seen in right-ventricular epicardial cells. Clinical studies suggest that testosterone might also contribute to male predominance. Matsuo *et al.*[56] reported two cases of asymptomatic Brugada syndrome in whom typical ST-segment elevation disappeared following orchiectomy as therapy for prostate cancer. We reported that men with Brugada syndrome have significantly higher testosterone levels and associated lower BMI than age-matched controls, which suggests a significant role for testosterone in male predominance.[57] This hypothesis is also supported by experimental data showing that testosterone increases $I_{Kr}$ and inward rectifier potassium currents ($I_{K1}$).

### Ethnic differences

The incidence of Brugada syndrome differs according to ethnic origin. Frequency is higher in Asian countries than in the US and Europe. Reports indicate that common polymorphisms might modulate the activity of the primary disease-causing mutation, or influence susceptibility to arrhythmia, even in the general population.[58] Some common polymorphisms are ethnically dependent and might relate to ethnic differences in the clinical phenotype in Brugada syndrome. Pfeufer and co-workers[59] reported that polymorphisms in the *SCN5A* gene promoter were associated with an increased QRS interval in a Central European general population. Further systematic investigations of ethnically dependent common polymorphisms in patients with Brugada syndrome are required to clarify their effect on the incidence of this disease.

## CONCLUSIONS

Although the sodium-channel gene *SCN5A* is so far the only gene linked to the Brugada syndrome, genetic, functional and *in vivo* experimental studies have greatly advanced our knowledge of the molecular, cellular and ionic mechanisms for the Brugada phenotype, and have enabled us to select suitable strategies for treating patients with this syndrome. Further studies of genotype–phenotype relationships, as well as research into their genetic basis, will further advance our management of Brugada syndrome.

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**Competing interests**
The authors declared that they have no competing interests.

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# Acquired forms of the Brugada syndrome

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**Abstract** The Brugada syndrome is characterized by ST-segment elevation in the right precordial leads ($V_1$ through $V_3$) and an episode of ventricular fibrillation in the absence of structural heart disease. *SCN5A*, the gene encoding the α subunit of the sodium channel, is the only gene thus far linked to the Brugada syndrome but is identified in only 18% to 30% of patients with clinically diagnosed Brugada syndrome. On the other hand, experimental studies have suggested that an intrinsically prominent transient outward current–mediated action potential (AP) notch and a subsequent loss of the AP dome in the epicardium but not in the endocardium of the right ventricular outflow tract give rise to a transmural voltage gradient, resulting in ST-segment elevation and phase 2 reentry–induced ventricular fibrillation. Therefore, any intervention that increases outward currents (eg, transient outward current, adenosine triphosphate–sensitive potassium current, delayed modifier potassium current) or decreases inward currents (eg, L-type calcium current, fast sodium current) at the end of phase 1 of the AP can accentuate or unmask ST-segment elevation, similar to that found in the Brugada syndrome, thus producing acquired forms of the Brugada syndrome. In this review, several drugs in addition to sodium-channel blockers and conditions that induce transient ST-segment elevation such as that in the Brugada syndrome, developing acquired forms of the Brugada syndrome, are discussed.



*Keywords:* Brugada syndrome; ST segment; Ventricular fibrillation; Heterogeneity; Epicardium; Drugs; Ischemia

## 1. Introduction

In 1992, Brugada and Brugada [1] first described 8 patients with a history of aborted sudden cardiac death caused by ventricular fibrillation (VF) as a distinct clinical entity associated with a high risk of sudden cardiac death. The Brugada syndrome is characterized by ST-segment elevation in the right precordial leads ($V_1$ through $V_3$) and an episode of VF in the absence of structural heart disease [2].

## 2. Genetic backgrounds

In 1998, Chen et al [3] identified the first mutation linked to the Brugada syndrome in *SCN5A*, the gene encoding the α subunit of the sodium channel. In 2002, Weiss et al [4] reported a large pedigree with the Brugada syndrome linked to the second locus on chromosome 3, which is close to but distinct from the *SCN5A* locus; however, the specific gene has not yet been identified. In contrast with congenital forms of long QT syndrome, in which 8 genotypes have been so far reported, the *SCN5A* is the only gene thus far linked to the Brugada syndrome. Moreover, *SCN5A* mutations can be detected in only 18% to 30% of patients with clinically diagnosed Brugada syndrome, indicating genetic heterogeneity in the background of Brugada syndrome. More than 80 mutations have been reported in patients with the Brugada syndrome, and functional studies have been conducted in approximately 20 mutations. Interestingly, all functional studies of the mutated channels responsible for the Brugada syndrome have shown loss of function of sodium current ($I_{Na}$) [5]. Several mechanisms have been reported to be attributable to loss of function of the $I_{Na}$ [6]; these include (1) failure of the sodium channel to express; (2) a shift in the voltage and time dependence of $I_{Na}$ activation, inactivation, or reactivation; (3) entry of the channel into an intermediate inactivation state from which it recovers more slowly; (4)

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acceleration of the inactivation of the $I_{Na}$ channel; and/or (5) trafficking deficiency.

## 3. Cellular and molecular mechanism

Experimental studies by Yan and Antzelevitch [7] using arterially perfused canine right ventricular wedge preparations have suggested the cellular and molecular mechanism of the Brugada phenotype, the typical coved-type ST-segment elevation, and the subsequent episodes of VF. An intrinsically prominent transient outward current ($I_{to}$)–mediated action potential (AP) notch and a subsequent loss of the AP dome in the epicardium but not in the endocardium of the right ventricular outflow tract (RVOT) give rise to a transmural voltage gradient, resulting in the ST-segment elevation in leads $V_1$ through $V_3$ and the initiating premature beats caused by the mechanism of phase 2 reentry. More recently, Aiba et al [8] combined high-resolution optical mapping system in the arterially perfused wedges and demonstrated that VF was triggered by the initiating phase 2 reentry–induced premature beats.

## 4. Acquired forms of the Brugada syndrome

Because the maintenance of the AP dome is determined by the balance of currents active at the end of phase 1 of the AP (principally $I_{to}$ and the L-type calcium current [$I_{Ca\text{-}L}$]), any intervention that increases outward currents (eg, $I_{to}$, adenosine triphosphate–sensitive potassium current [$I_{K\text{-}ATP}$], slow- and fast-activating components of delayed rectifier potassium current [$I_{Ks}$, $I_{Kr}$]) or decreases inward currents (eg, $I_{Ca\text{-}L}$, fast $I_{Na}$) at the end of phase 1 of the AP can accentuate ST-segment elevation, thus producing the Brugada phenotype. Among these interventions, class IC sodium-channel blockers most effectively amplify or unmask ST-segment elevation secondary to their strong effect to block fast $I_{Na}$ and are used as a diagnostic tool in latent Brugada syndrome with transient or no spontaneous ST-segment elevation [9,10]. Several drugs other than sodium-channel blockers and conditions that cause an outward shift in current active at the end of phase 1 are reported to induce transient ST-segment elevation such as that in the Brugada syndrome, developing acquired forms of the Brugada syndrome [2,11].

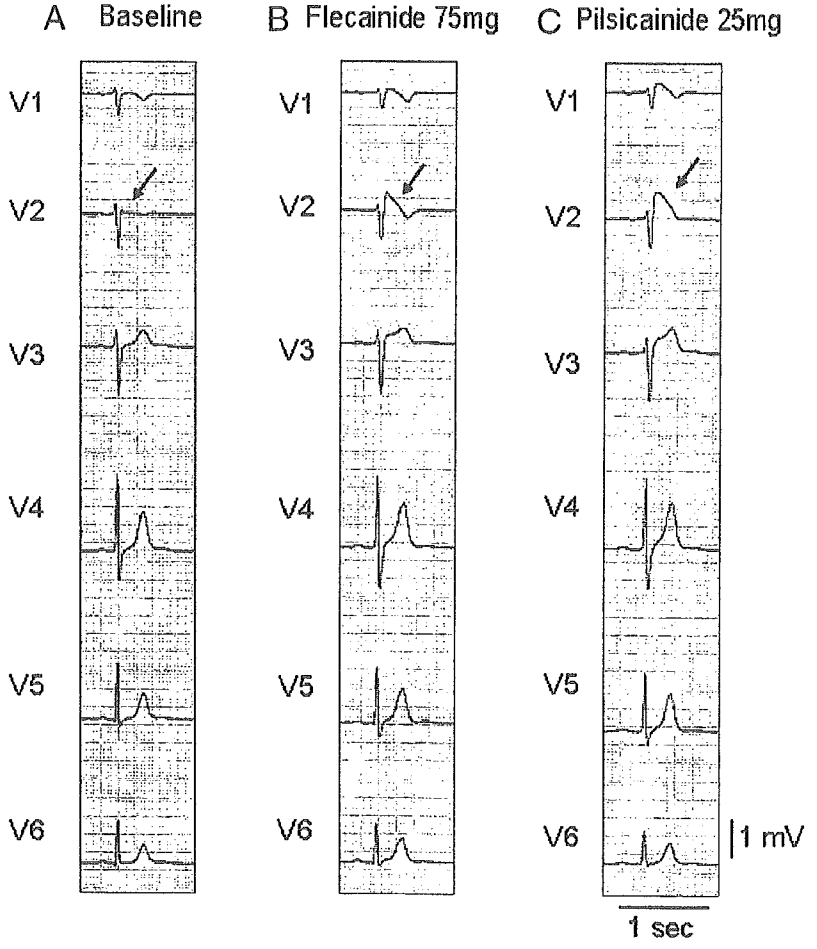


Fig. 1. Six precordial ECG leads before and after injection of class IC sodium-channel blockers flecainide and pilsicainide in a patient with the Brugada syndrome. Under baseline condition, no significant ST-segment elevation was seen in leads $V_1$ through $V_3$ (A, arrow). Flecainide injection (75 mg) unmasked coved-type ST-segment elevation in lead $V_2$ (B, arrow). A smaller dose of pilsicainide injection (25 mg) produced more pronounced ST-segment elevation in lead $V_2$ (C, arrow).

### 4.1. Antiarrhythmic drugs

Class IC sodium-channel blockers (flecainide, pilsicainide, propafenone) produce the most pronounced ST-segment elevation owing to their strongest effect to block fast $I_{Na}$ (Fig. 1); therefore, the diagnostic criteria recommended by Wilde et al [12] include type 1 coved-type ST-segment elevation induced by sodium-channel blockers for the definite diagnosis of Brugada syndrome. In other words, class IC sodium-channel blockers are the most frequent cause of the acquired forms of the Brugada syndrome. Class IA sodium-channel blockers (procainamide, disopyramide, cibenzoline, etc) show less ST-segment elevation as compared with class IC drugs [9].

Verapamil, an $I_{Ca\text{-}L}$ blocker, is reported to unmask Brugada-like ST-segment elevation after intravenous administration for terminating paroxysmal supraventricular tachycardia [11].

$\beta$-Blockers are expected to induce the acquired forms of the Brugada syndrome as a result of their effect to inhibit $I_{Ca\text{-}L}$.

### 4.2. Other drugs

Antianginal drugs for ischemic heart diseases may be another cause of acquired forms of the Brugada syndrome. Calcium-channel blockers (nifedipine, diltiazem, etc) or nitrates block $I_{Ca\text{-}L}$ and thus are expected to induce Brugada-like ST-segment elevation. Nicorandil, an $I_{K\text{-}ATP}$ opener, can produce the Brugada phenotype by increasing outward currents.

Many psychotropic agents have been reported to cause Brugada-like ST-segment elevation in patients with acquired forms of the Brugada syndrome [13]; these include tricyclic antidepressants (amitriptyline, nortriptyline, desipramine, clomipramine, etc), tetracyclic antidepressants (maprotiline, etc), and phenothiazine (perphenazine, cyamemazine, etc). Selective serotonin reuptake inhibitors such as fluoxetine are reported to induce the Brugada phenotype. The actions of psychotropic agents to induce acquired forms of the Brugada syndrome are generally a result of their effect to decrease fast $I_{Na}$ and/or $I_{Ca\text{-}L}$.

Brugada-like ST-segment elevation is also reported after use of dimenhydrinate, a sedating, first-generation histaminic H1 receptor antagonist, or cocaine intoxication.

### 4.3. Acute ischemia in the RVOT

Acute myocardial infarction or ischemia in the RVOT produces ST-segment elevation mimicking the Brugada syndrome [14] probably due to the depression of $I_{Ca\text{-}L}$ and the activation of $I_{K\text{-}ATP}$ during ischemia. Similarly, vasospasm of the coronary artery supplying the RVOT is expected to mimic Brugada-like ST-segment elevation (Fig. 2) [15]. Therefore, mild ischemia and increased vagal tone act in an additive fashion or synergistically with the substrate responsible for the Brugada syndrome to aggravate the ST-segment elevation and to precipitate VF.

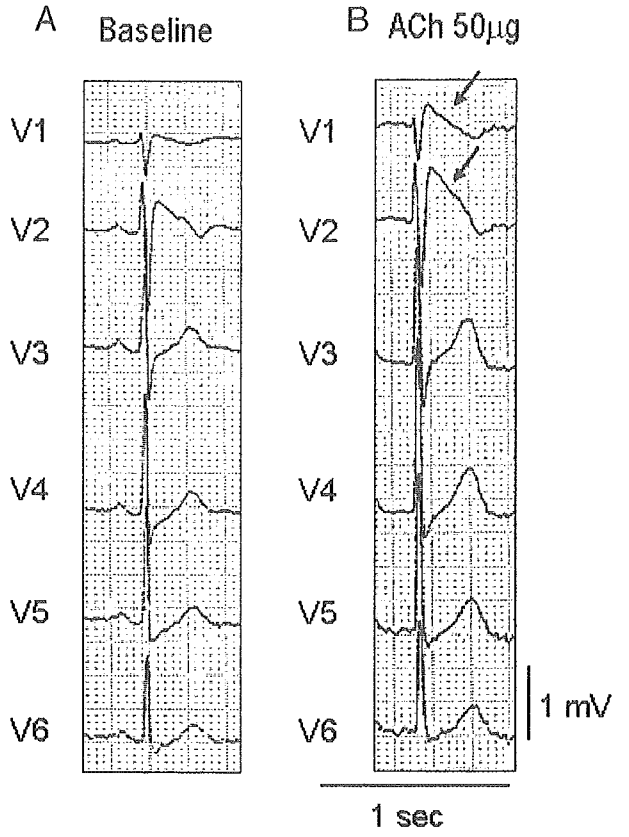


Fig. 2. Six precordial ECG leads before (A) and after (B) injection of acetylcholine (ACh) into the right coronary artery. Injection of 50 $\mu$g of ACh augmented the ST-segment elevation in leads $V_1$ and $V_2$.

### 4.4. Electrolyte abnormalities

Electrolyte abnormalities such as hyperkalemia and hypercalcemia are reported to amplify ST-segment elevation such as that in the Brugada syndrome [16,17].

### 4.5. Hyperthermia (febrile state) and hypothermia

Hyperthermia (febrile state) is reported to unmask Brugada-like ST-segment elevation and provoke VF secondary to reduced $I_{Na}$ at high temperature [18] whereas hypothermia sometimes induces a prominent J wave mimicking Brugada-like ST-segment elevation probably caused by augmented $I_{to}$ [19].

### 4.6. Elevated insulin level

The elevated insulin level after meals sometimes unmasks or augments ST-segment elevation in patients with the Brugada syndrome mainly because of an increase in an outward current by activating the $Na^+/K^+$ pump [20]. This action of elevated insulin level may contribute to circadian or day-to-day variation in the degree of ST-segment elevation in this syndrome.

### 4.7. Mechanical compression of the RVOT

Mechanical compression of the RVOT by a mediastinal tumor or hemopericardium was reported to produce Brugada-

like ST-segment elevation [21]. This effect is most likely a result of an effect of the impact on multiple ion channel currents leading to an outward shift of net current active during the early phases of the epicardial AP in the RVOT.

## Acknowledgments

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□ REVIEW ARTICLE □

# The Brugada Syndrome —An Update—

Wataru SHIMIZU

## Abstract

**Brugada syndrome is characterized by ST-segment elevation in the right precordial leads ($V_1$–$V_3$) and an episode of ventricular fibrillation (VF) in the absence of structural heart disease. A number of reports from the world have unveiled the clinical, electrocardiographic, electrophysiologic and prognostic features of Brugada syndrome, and two recent consensus reports have suggested the diagnostic criteria of Brugada syndrome and the risk stratification for the identification of high risk Brugada patients for sudden cardiac death. *SCN5A*, the gene encoding the α subunit of the sodium channel, is the only gene thus far linked to Brugada syndrome; its prognostic value remains unclear. On the other hand, advances in the understanding of the cellular mechanism for Brugada phenotype derived from experimental studies have suggested possibilities for the development of strategies for managing and treating patients with Brugada syndrome. In this review, the recent understanding and knowledge of Brugada syndrome will be updated.**
**(Internal Medicine 44: 1224–1231, 2005)**

*Key words:* Brugada syndrome, ST-segment, ventricular fibrillation, diagnosis, prognosis, risk stratification, therapy

## Introduction

In 1992, Brugada and Brugada first described 8 patients with a history of aborted sudden cardiac death due to ventricular fibrillation (VF) and a characteristic electrocardiographic (ECG) pattern, consisting of right bundle branch block (RBBB) and ST-segment elevation in the right precordial leads ($V_1$–$V_3$) as a distinct clinical entity (1–8). This syndrome is not related to acute ischemia, electrolyte abnormalities or structural heart diseases (6). Thereafter, the presence of RBBB was revealed to be not necessary for the diagnosis of Brugada syndrome, although mild to moderate widening of the QRS duration is often observed (6). Two specific types of ST segment elevation, coved and saddleback, are observed in this syndrome, the former of which is reported to relate to a higher incidence of VF and sudden cardiac death (9). However, the ST segment elevation is often accentuated and the coved type ST segment elevation is more frequently recognized just before and after episodes of VF (10, 11).

## Epidemiology

The incidence of Brugada syndrome is higher in Asian countries, including Thailand and Japan than in Western countries (12–14). Brugada syndrome usually manifests during adulthood, with a mean age of sudden death of 41±15 years, and child cases are rare (8). A family history of unexplained sudden death is present in approximately 20–40% in Western countries, and less (15–20%) in Japan (5, 8, 15, 16).

Interestingly, more than 80% of patients in Western countries and more than 90% of patients in Asian countries affected with Brugada syndrome are men (17). All of the mutations identified to date in patients with Brugada syndrome display an autosomal dominant mode of transmission. Thus, males and females are expected to inherit the defective gene equally. The male predominance in the Brugada syndrome is at least in part due to intrinsic differences in the ventricular action potential (AP) between males and females (18). Recent clinical studies suggest that the male hormone, testosterone, may be attributable to gender difference of prevalence in this syndrome. Two cases of asymptomatic Brugada syndrome in whom coved type ST segment elevation disappeared following orchiectomy as therapy for prostate cancer have been reported (19), indicating that testosterone may contribute to the Brugada phenotype in these 2 cases. Our recent data that men with Brugada syndrome have significantly higher testosterone levels and are associated

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with a lower body-mass index than age-matched controls also suggests a critical role of testosterone in the male predominance in the Brugada syndrome (20).

Cardiac events due to VF often occur at night or during sleep (8 PM–8 AM) as a form of sudden unexplained nocturnal death, syncope or agonal respiration in approximately 70–80% of patients with Brugada syndrome (8, 21), and this is probably related to increased vagal tone (22). Recent data detected by implantable cardioverter defibrillator (ICD) have demonstrated that about half of VF episodes are preceded by ventricular premature complexes with a similar morphology of initiating PVC of VF (21). Atrial fibrillation is associated in 10–20% of Brugada patients in Western countries, and in 20–30% of Brugada patients in Japan (23). The association of atrioventricular nodal reentrant tachycardia or WPW syndrome has also been reported (24).

## Clinical Characteristics

### ECG characteristics

The Brugada Consensus Report in 2002 suggested three patterns of ST-segment elevation in the right precordial leads (6). Type 1 is characterized by a coved type ST segment elevation displaying J wave amplitude or ST segment elevation of ≥0.2 mV followed by a negative T wave. Type 2 has a saddleback configuration, which has a high take-off ST segment elevation (≥0.2 mV) followed by a gradually descending ST segment elevation (remaining ≥0.1 mV above the baseline) and a positive or biphasic T wave. Type 3 has an ST segment elevation of <0.1 mV of saddleback, coved type, or both. The second Consensus Report published in 2005, however, emphasized that Type 1 ST segment elevation, which is defined as a coved ST segment elevation of ≥0.2 mV at J point with or without a terminal negative T wave, is required to diagnose Brugada syndrome (8). Type 2 and Type 3 ST segment elevation are not diagnostic for the Brugada syndrome.

ECG recordings of $V_1$ and $V_2$ leads at higher (3rd and 2nd) intercostal spaces increase the sensitivity and the specificity of the ECG diagnosis for detecting the Brugada phenotype (Fig. 1A) (8, 25), although their diagnostic and prognostic values need to be prospectively evaluated.

Widening of P wave and QRS duration, and prolongation of the PQ interval, all of which represent conduction abnormalities, are often observed in patients with Brugada syndrome. Smits and co-workers reported more prominent prolongation of PQ interval in Brugada patients with *SCN5A* mutations than in those without *SCN5A* mutations (26). A coved type ST segment elevation with terminal negative T wave is frequently associated with borderline or mildly prolonged QT interval in the right precordial leads presumably due to a preferential prolongation of action potential duration (APD) in the right ventricular (RV) epicardium secondary to accentuation of the AP notch (27).

Approximately 60–70% of patients with Brugada syndrome show late potentials (LPs) detected by signal-averaged electrocardiogram (8, 28). During treadmill exercise testing, augmentation of ST-segment elevation in the right precordial leads compared with that at baseline is observed at early recovery phase after exercise (1 or 2 minutes) in half of the patients with Brugada syndrome. However, the prognostic value of the presence of LPs or the specific ECG response by exercise remains unclear.

### Drug challenge

Sodium channel blockers amplify or unmask ST-segment elevation, and are used as a diagnostic tool in latent Brugada syndrome with transient or no spontaneous ST-segment elevation (29, 30). Class IC sodium channel blockers (flecainide, pilsicainide, etc) and ajmaline, though classified as a class IA drug, produce the most pronounced ST segment elevation secondary to strong use-dependent blocking of fast sodium current ($I_{Na}$) due to their slow dissociation from the sodium channels (30–32). Other class IA sodium channel blockers (procainamide, disopyramide, cibenzoline, etc.), which exhibit less use-dependent block of fast $I_{Na}$ due to faster dissociation of the drug for the sodium channels, show a weaker ST segment elevation than class IC drugs (30). Ajmaline has recently been reported to produce typical Brugada ECG more frequently than flecainide (33). Pilsicainide, a pure class IC drug developed in Japan, also more strongly induce ST segment elevation than flecainide (Fig. 1B) (34). Since Class IB sodium channel blockers (mexiletine, lidocaine, etc.) have little or no effect on fast $I_{Na}$ at moderate and slow heart rates, they have very little effect to cause ST segment elevation (30, 34).

### Unmasking of Brugada phenotype by other agents and conditions

In addition to sodium channel blockers, many agents and conditions are reported or expected to unmask Brugada phenotype, a coved type ST-segment elevation (8, 34). Many psychotropic agents (35), including tricyclic and tetracyclic antidepressants, phenothiazine and selective serotonin reuptake inhibitors, are reported to unmask Brugada phenotype mainly as a result of their sodium channel blocking effects. Calcium channel blockers (verapamil etc.), β-receptor blockers and nitrate decrease L-type calcium current ($I_{Ca}$), and are expected to induce Brugada-like ST segment elevation (34). Potassium channel openers, such as nicorandil, also have the potential to unmask the Brugada phenotype (34). Several reports suggested that Brugada-like ST segment elevation was unmasked during the febrile state (hyperthermia) secondary to the reduced $I_{Na}$ at high temperature (36). Electrolyte abnormalities, such as hyperkalemia and hypercalcemia, are reported to amplify ST-segment elevation like that in Brugada syndrome (37). Acute myocardial ischemia or vasospastic angina involving the RV outflow tract occasionally mimics Brugada-like ST segment elevation due to the depression of L-type $I_{Ca}$ and the activation of ATP-sensitive potassium current ($I_{K\text{-}ATP}$) (38, 39).

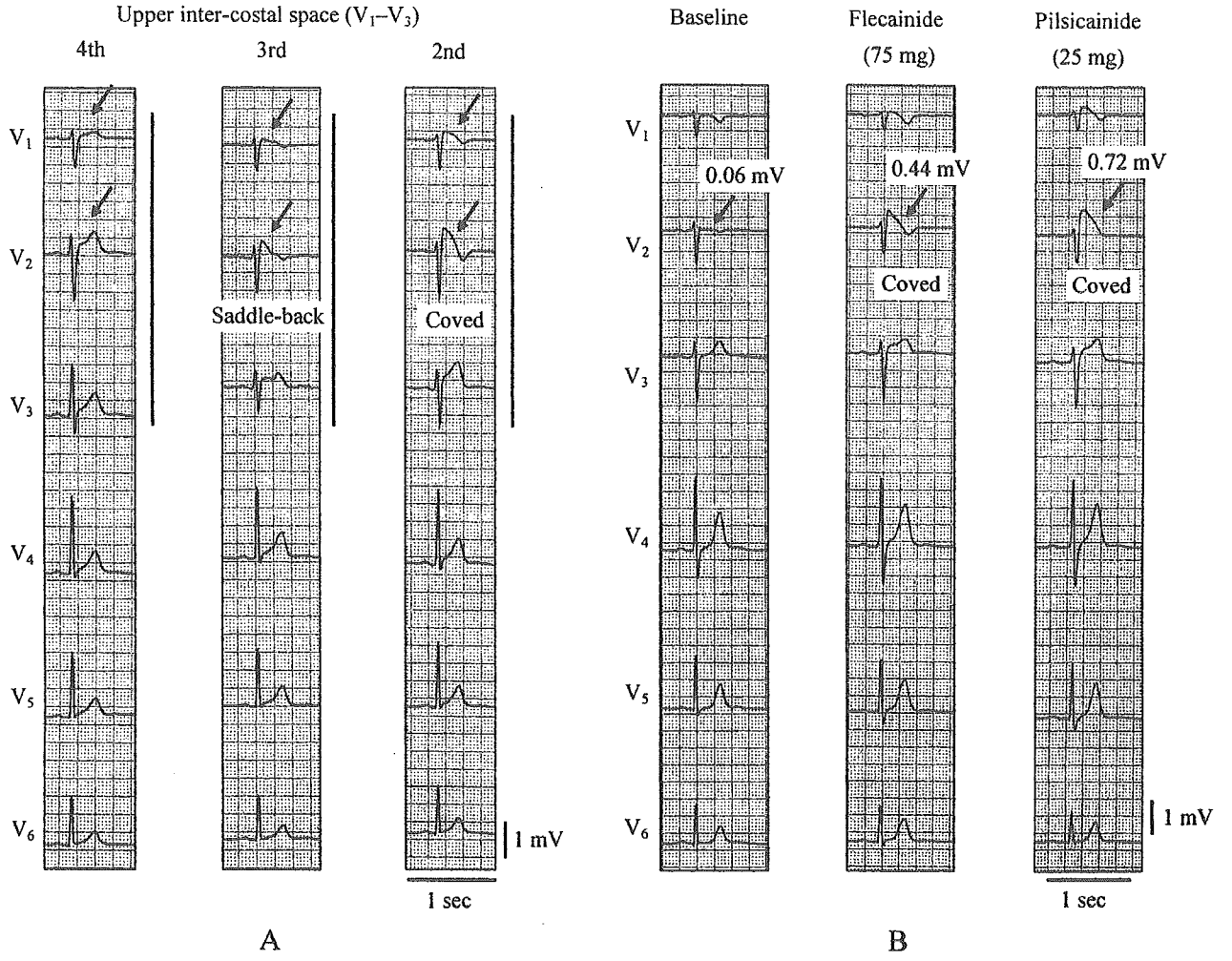


**Figure 1. A) Unmasking of a Brugada electrocardiogram (ECG) by recordings of right precordial ($V_1$–$V_2$) leads at 3rd and 2nd intercostal space in a patient with latent Brugada syndrome. No significant ST segment elevation was observed in leads $V_1$ and $V_2$ of the standard 12-lead ECG (4th intercostal space) (left, arrow), while saddleback type (middle, arrow) and typical Type 1 coved type (right, arrow) ST segment elevation were unmasked in leads $V_1$ and $V_2$ recorded from the 3rd and 2nd intercostal space, respectively. B: Unmasking of ST segment elevation by class IC sodium channel blockers in a patient with latent Brugada syndrome. No ST segment elevation was recorded in leads $V_1$ and $V_2$ under baseline conditions (left, arrow). Flecainide injection (75 mg) unmasked coved type ST segment elevation (0.44 mV) followed by a negative T wave in lead $V_2$ (middle, arrow). A smaller dose of pilsicainide injection (25 mg) produced more prominent ST segment elevation (0.72 mV) in lead $V_2$ (right, arrow).**

### *Electrophysiological characteristics*

VF or sustained polymorphic ventricular tachycardia (VT) is induced in approximately 50–70% of patients with Brugada patients during electrophysiological study (5, 7, 15, 16). Inducibility of VF is somewhat higher in symptomatic patients than in asymptomatic patients, and is reported to correlate with the degree of conduction abnormalities represented by QRS duration, the presence of RBBB or LPs etc (15). VF is more easily induced by the programmed electrical stimulation from the RV outflow tract than that from the RV apex. Prolonged sinus node recovery time and sino-atrial conduction time as well as slowed atrial conduction and atrial standstill have been reported in association with the syndrome (40).

## Diagnostic Criteria

Brugada syndrome is definitively diagnosed when a Type 1 ST segment elevation is observed in more than one right precordial lead ($V_1$–$V_3$), in the presence or absence of sodium channel blockers, and in conjunction with one of the following: documented VF, polymorphic VT, a family history of sudden cardiac death (<45 years old) or coved type Brugada ECG in family members, inducibility of VF with

programmed electrical stimulation, syncope or nocturnal agonal respiration (6).

## Clinical Outcome and Risk Stratification

Elucidation of clinical outcome and risk stratification aimed at the identification of high risk patients with Brugada syndrome for sudden cardiac death is an important goal (5, 7, 15, 16). Brugada et al (7) reported that patients with Type 1 Brugada ECG initially presenting with aborted sudden cardiac death are at the highest risk for a recurrence (69% at 54±54 months of follow-up). They reported that patients presenting with syncope and a Type 1 ECG also have a high recurrence rate of 19% at 26±36 months of follow-up. Even in asymptomatic Brugada patients, a relatively high recurrence rate (8%) was reported in their registry. Kaplan-Meier curve of arrhythmic events (sudden cardiac death or documented VF) depending on clinical presentation from the latest data of the Brugada registry (690 patients) is shown in Fig. 2A. In contrast to the Brugada registry, two registries by Priori et al (5) and Eckardt et al (16) found a lower incidence of subsequent arrhythmic events. Eckardt et al recently reported that subsequent or new arrhythmic events in patients with prior aborted sudden cardiac death and prior syncope, and asymptomatic patients are 17%, 6%, and 1%, respectively (Fig. 2B) (16). Preliminary data by an ongoing registry in Japan, conducted by Kamakura and endorsed by the Japanese Ministry of Health, Labour and Welfare, also show a lower rate of arrhythmic events than those of the Brugada registry (27%, 3%, and 1%, respectively at 24 months of follow-up) (41). The discrepancy of clinical outcome of patients between Brugada registry and other registries is most likely due to inclusion of particular families with a very severe form of the disease in the Brugada registry. In fact, our Japanese registry demonstrates that the new arrhythmic event rate in asymptomatic patients with a Type 1 ECG and a family history of sudden cardiac death is increased to 10% (41). However, a larger patient population with similar patient characteristics and a longer follow-up period are clearly needed to make a definitive conclusion about the clinical outcome of Brugada patients, particularly about asymptomatic patients.

It is agreed that a previous history of aborted cardiac arrest or syncope and the presence of a spontaneous Type 1 ST-segment elevation are strong predictors of further arrhythmic events (5, 7, 16). The only method, either non-invasively or invasively, shown to be useful to stratify risk of subsequent arrhythmic events, is the programmed electrical stimulation (7). Brugada et al suggested that an inducibility of VT/VF during electrophysiologic study (EPS) is a strong indicator of subsequent arrhythmic events in both symptomatic and asymptomatic patients (7). However, studies by Priori et al (5), Kanda et al (15) and Eckardt et al (16) failed to find an association between inducibility and recurrence of VT/VF. Non-uniform stimulation protocol during EPS and different patient characteristics may influence the discordance of the result of risk stratification by programmed electrical stimulation between studies by Brugada et al (7) and others.

## Molecular Diagnosis

In 1998, Chen and co-workers identified the first mutation linked to Brugada syndrome in *SCN5A*, the gene encoding the subunit of the sodium channel (42). Thereafter, a large family of Brugada syndrome has been reported to link to a second locus on chromosome 3, which is close to but different from the *SCN5A* locus (43), however the specific gene or genes affected have not yet been identified. Although *SCN5A* is the only gene thus far linked to the Brugada syndrome, *SCN5A* mutations account for only 18–30% of clinically diagnosed Brugada patients at present, and more than two-thirds of Brugada patients cannot be genotyped, suggesting the existence of genetic heterogeneity (44). Other candidate genes for the Brugada phenotype include the genes encoding transient outward current ($I_{to}$), delayed rectifier potassium current ($I_K$), and L-type $I_{Ca}$, or genes which code for adrenergic receptors, cholinergic receptors, ion-channel-interacting protein, promoters, transcriptional factors, neurotransmitters, or transporters. Since general screening of *SCN5A* does not include examination of the promoter region, or allow for detection of cryptic splicing mutations or gross rearrangements, the possibility of causative *SCN5A* mutations can not be completely ruled out.

Functional analysis employing expression systems was reported in approximately two dozen of the mutations in *SCN5A*, and demonstrated that all of the mutations resulted in "loss of function" of $I_{Na}$ by several mechanisms (14, 42, 45–48). These functional effects include: 1) failure of the sodium channel to express; 2) a shift in the voltage- and time-dependence of $I_{Na}$ activation, inactivation or reactivation; 3) entry of the sodium channel into an intermediate state of inactivation from which it recovers more slowly; 4) accelerated inactivation of the sodium channel; or 5) trafficking defect. Interestingly, some of the *SCN5A* mutations also combine other phenotypes, such as the LQT3 form of congenital long QT syndrome (45), cardiac conduction defect (Lenegre syndrome) (46), thus creating a category of overlapping phenotype. Some common *SCN5A* polymorphisms are reported to modulate the functional consequences of primary *SCN5A* mutations (48).

## Cellular Basis for Brugada Phenotype

Previous experimental studies between the late 1980s and early 1990s have suggested that an $I_{to}$-mediated phase 1 notch of the AP was greater in the epicardium than in the endocardium in many species, including humans (49). Because the maintenance of the AP dome is determined by the fine balance of currents active at the end of phase 1 of the AP (principally $I_{to}$ and L-type $I_{Ca\text{-}L}$), any agents that cause a net outward shift in the current active at the end of phase

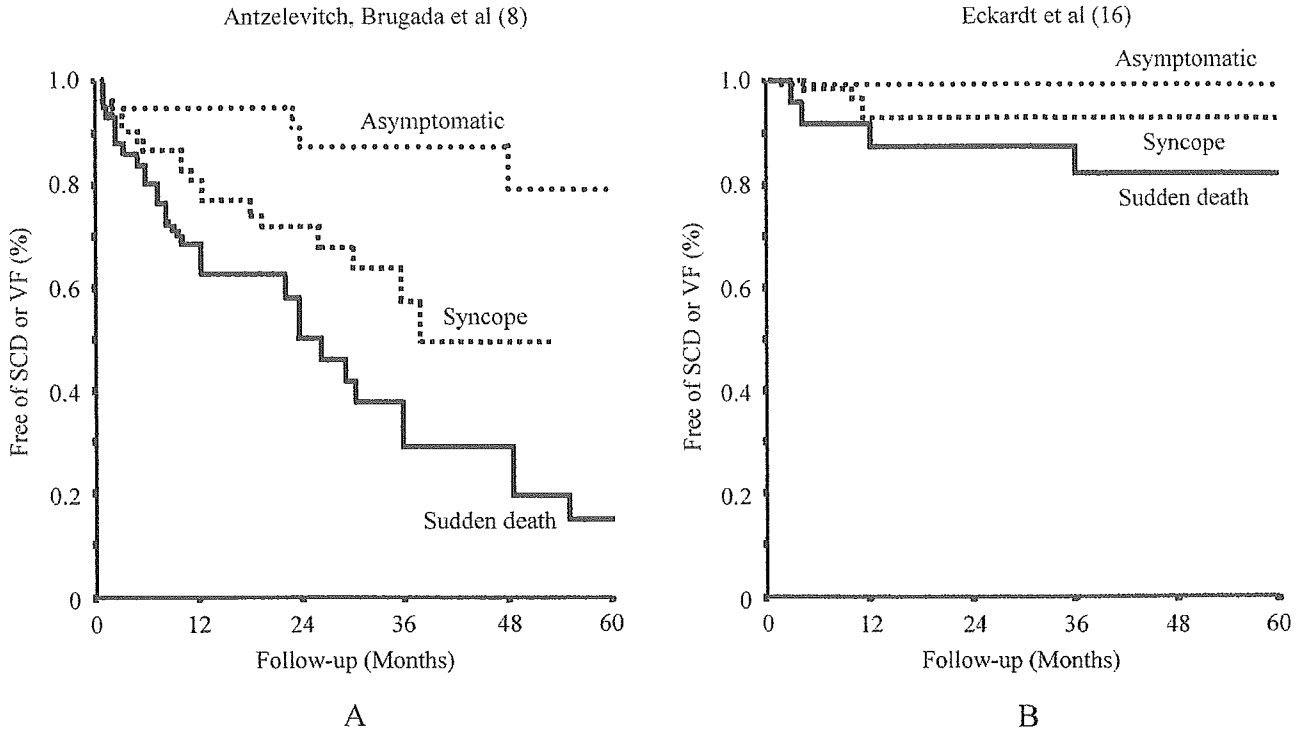


**Figure 2. Kaplan-Meier analysis of arrhythmic events [sudden cardiac death (SCD) or documented ventricular fibrillation (VF)] during follow-up depending on clinical presentation in patients with a history of aborted SCD or syncope, or asymptomatic patients from tow large cohorts by Antzelevitch, Brugada et al (8) (690 patients) and Eckardt et al (16) (212 patients). Modified from (8, 16) with permission.**

1 can increase the magnitude of the AP notch, leading to loss of the AP dome (all-or-none repolarization) in the epicardium, but not in the endocardium, contributing to a significant voltage gradient across the ventricular wall during ventricular activation (49). The heterogeneous loss of the AP dome in the epicardium was shown to produce premature beats via a mechanism of phase 2 reentry in experimental studies using isolated sheets of canine right ventricle (50). The Brugada syndrome seems to be a clinical counterpart of the mechanism of all-or-none repolarization in the epicardial cells and phase 2 reentry-induced premature beat between the adjacent epicardial cells (1).

### *Cellular basis for ST-segment elevation*

An experimental model of the Brugada syndrome employing arterially perfused canine RV wedge preparations provided direct experimental evidence for the cellular mechanism of ST-segment elevation (51, 52). The $I_{to}$-mediated AP notch and the loss of the AP dome in the epicardial cells, but not in the endocardial cells, of the right ventricle gives rise to a transmural voltage gradient, producing ST-segment elevation in the ECG in the wedge preparations. Figure 3 illustrate superimposed transmembrane APs simultaneously recorded from epicardial and endocardial sites, together with a transmural ECG in a Brugada model employing a RV wedge preparation. Under control conditions, a small J wave coincides with the small notch observed in epicardial cells, but not in endocardial cells (Fig. 3A). J-point elevation or saddleback type ST-segment elevation is created by $I_{Ca\text{-}L}$ block with terfenadine, which amplifies the transmural voltage gradient due to its accentuation of the phase 1 notch in epicardial cells, but not in endocardial cells (Fig. 3B). The typical coved type ST-segment elevation associated with a terminal negative T wave is secondary to a further accentuated phase 1 notch, greater prolongation of epicardial APD, and a resultant reversed transmural voltage gradient, which are all induced by a simulation of the *SCN5A* (sodium channel) defect with additional pilsicainide (Fig. 3C).

### *Cellular basis for premature beats and VF*

In the setting of coved type ST-segment elevation, heterogeneous loss of the AP dome (coexistence of loss of dome regions and restored dome regions) in the epicardium creates a marked epicardial dispersion of repolarization, giving rise to premature beats due to phase 2 reentry, which sometimes precipitates non-sustained polymorphic VT or VF. Our recently developed high-resolution optical mapping system allows us to record transmembrane APs from 256 sites simultaneously from the epicardial or endocardial surface of an arterially perfused canine RV wedge preparation, and further advanced our understanding of the cellular basis for

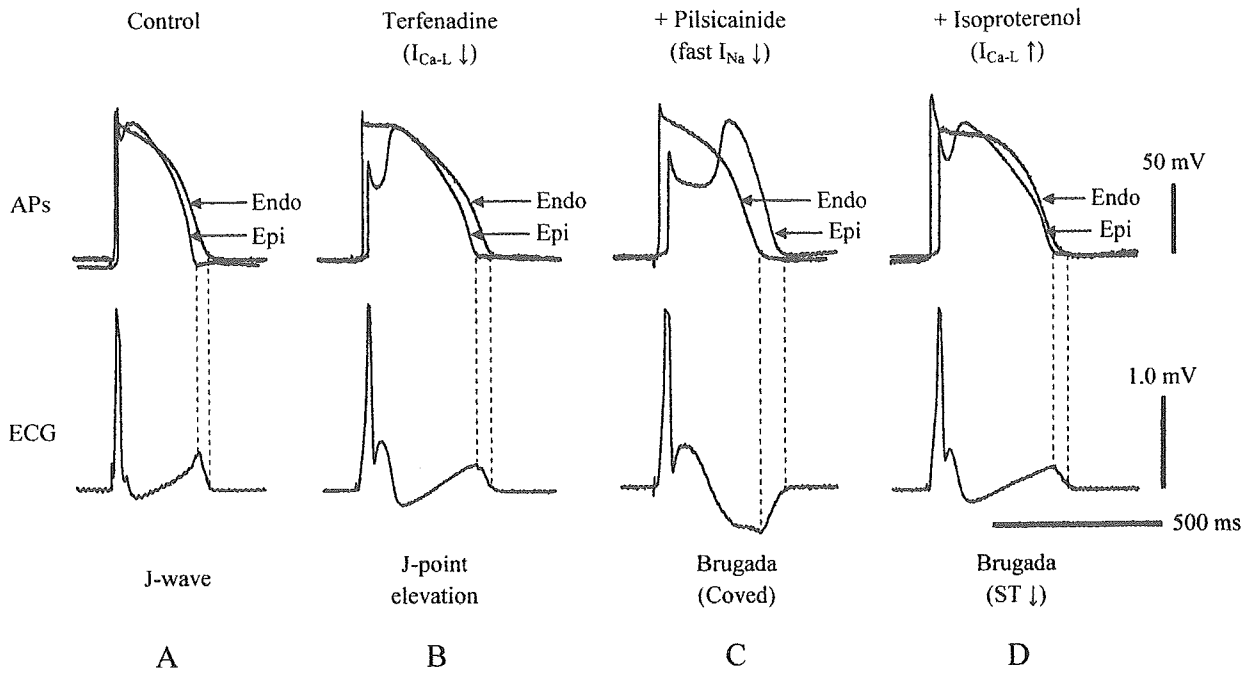


**Figure 3. The cellular basis for ST segment elevation and the effect of isoproterenol in a Brugada model employing an arterially perfused canine right ventricular wedge preparation. Shown are superimposed transmembrane action potentials (APs) simultaneously recorded from epicardial (Epi) and endocardial (Endo) sites together with a transmural ECG (BCL = 2,000 ms). A) Control. B) $I_{Ca-L}$ block with terfenadine (5 μmol/*l*) accentuates the phase 1 notch in Epi but not in Endo, and causes J-point elevation. C) Additional pilsicainide (5 μmol/*l*), mimicking *SCN5A* (sodium channel) defect, produces further accentuation of the phase 1 notch, a greater prolongation of Epi AP, and a reversed transmural voltage gradient, giving rise to coved type ST segment elevation with a terminal negative T wave. D) Isoproterenol (0.02 μg/min), a β-adrenergic agonist, restores the AP dome in Epi and attenuates the ST segment elevation.**

subsequent polymorphic VT or VF (44, 53). The optical mapping data suggest that a steep repolarization gradient between a loss of dome region and a restored dome region in the epicardium is essential to produce phase 2 reentry-induced premature beats. Phase 2 reentry-induced premature beats have been shown to induce a reentrant pathway rotated in the epicardium and finally involving the transmural myocardium, precipitating non-sustained polymorphic VT or VF.

## Current Management and Therapy

An ICD has been proven to have a protective effect, preventing sudden cardiac death in symptomatic Brugada patients with a history of cardiac arrest, aborted sudden cardiac death or syncope (5, 7, 15, 16). The recently published second Consensus Report suggested recommendations for ICD implantation in patients with symptomatic and asymptomatic Brugada syndrome (8). Symptomatic patients with a Type 1 Brugada ECG in the absence or presence of sodium channel blockers who present with aborted sudden cardiac death or symptoms such as syncope, seizure or nocturnal agonal respiration should receive an ICD without the additional need for EPS. Asymptomatic patients with a Type 1 ECG (spontaneously or after sodium channel block) should undergo EPS if there is a family history of sudden cardiac death suspected to be due to Brugada syndrome. EPS is justified when the family history is negative for sudden cardiac death if the Type 1 ECG occurs spontaneously. If VF is induced, the patient should be recommended to receive an ICD. Asymptomatic patients who have no family history and who develop a Type 1 ECG only after sodium channel blockade should be closely followed up. However, as the role of VF induction during EPS for predicting subsequent arrhythmic events is still controversial, further studies including a larger number of patients and uniform stimulation protocol are necessary to make a final conclusion about the role of EPS.

Quinidine is an oral agent which is only proven to be effective to suppress a spontaneous episode of VF in patients with Brugada syndrome (54, 55). This effectiveness is mainly due to the strong $I_{to}$ blocking effect of quinidine. The cellular basis for the Brugada phenotype discovered by experimental studies suggested possibilities for the development of strategies for managing and treating patients with Brugada syndrome (44, 52). Any therapeutic agents or interventions that decrease outward currents (e.g. $I_{to}$, $I_{K\text{-}ATP}$, slow and fast activating components of $I_K$ [$I_{Ks}$ and $I_{Kr}$]) or increase inward currents (e.g. L-type $I_{Ca}$ or $I_{Na}$) at the end of phase 1 might normalize the Brugada phenotype. In addition to

quinidine, several agents can be candidates as adjunctive pharmacologic treatments to reduce the incidence of VF episodes only in conjunction with ICD implantation. Denopamine, an oral adrenergic stimulant, oral atropine, an anticholinergic agent, and cilostazol, a phosphodiesterase III inhibitor, increase L-type $I_{Ca}$, therefore, might be alternative therapeutic choices (56, 57). For an electrical storm of VF (recurrent episodes of VF), continuous infusion of isoproterenol, a β-adrenergic agonist (0.005–0.02 μg $kg^{-1}$ $min^{-1}$, or until a 20% increase of heart rate is achieved), attenuates ST-segment elevation and prevents VF by augmenting L-type $I_{Ca}$ and heart rate (Fig. 3D) (56, 58).

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□ ORIGINAL ARTICLE □

# Metabolic Syndrome Amplifies the LDL-Cholesterol Associated Increases in Carotid Atherosclerosis

Ryuichi KAWAMOTO, Hitomi TOMITA, Yuichiro OKA, Akihiro KODAMA and Atsushi KAMITANI*

## Abstract

*Objective* **Carotid intima-media thickness (IMT) is a useful surrogate marker of cardiovascular disease. In addition to low-density lipoprotein cholesterol (LDL-C), metabolic syndrome has been linked to the pathogenesis of atherosclerosis. The present study investigated whether the clustering of multiple components of metabolic syndrome has a greater impact on vascular parameters than individual components of metabolic syndrome, and assessed the association between carotid IMT and LDL-C and metabolic syndrome.**

*Methods* **Carotid IMT was evaluated on B-mode ultrasonography in 760 patients (340 men aged 64±16 years and 420 women aged 69±13 years) in the Medical Department of Seiyo Municipal Nomura Hospital. The subjects did not demonstrate any clinical signs of cardiovascular disease. We investigated the association between carotid IMT and confounding risk factors including LDL-C and metabolic syndrome using the 2005 Japanese criteria.**

*Results* **Carotid IMT increased with increasing numbers of metabolic syndrome components (p for trend <0.001). Multiple regression models, including age, sex, body mass index, smoking status, LDL-C, diabetes mellitus as well as each individual component of metabolic syndrome as continuous variables, showed that both metabolic syndrome (β=0.100; p=0.029) and LDL-C (β=0.210, p<0.001) were independent determinants of carotid IMT. Metabolic syndrome amplified the LDL-C associated increases in carotid atherosclerosis.**

*Conclusions* **Even after taking into account each individual component of MS, the clustering of visceral obesity with at least 2 of the 3 components, and LDL-C are independently associated with increased carotid IMT. This suggests that the components of metabolic syndrome interact to synergistically impact vascular thickness.**
**(Internal Medicine 44: 1232–1238, 2005)**

***Key words:*** risk factor, atherosclerosis, lipid metabolism, LDL-cholesterol

## Introduction

The metabolic syndrome is defined as the clustering of several cardiovascular risk factors in an individual including visceral obesity, hypertension (HT), hypertriglyceridemia, low high-density lipoprotein cholesterolemia, and impaired glucose tolerance (1, 2). Epidemiologic studies have shown that metabolic syndrome is quite common, affecting 13.3～24.4% of Japanese men ≧30 years of age (3, 4), and that it is a predictor of adverse cardiovascular events (5–8). Several other metabolic disorders have also been associated with this syndrome, including microalbuminuria, and abnormalities in fibrinolysis and coagulation (9, 10).

Carotid intima-media thickness (IMT) is a useful surrogate marker of cardiovascular disease and can now be measured noninvasively by B-mode ultrasonography. Several studies have shown close associations between this parameter and conventional cardiovascular risk factors, including age, obesity, smoking, HT, dyslipidemia including low-density lipoprotein cholesterol (LDL-C), and diabetes mellitus (DM) (11, 12). However, the association between carotid IMT and LDL-C and metabolic syndrome have not been well studied.

In the present study, we examined whether the clustering of multiple components of metabolic syndrome has a greater impact on vascular parameters than individual components of metabolic syndrome, and investigated the association between carotid IMT and LDL-C and metabolic syndrome currently defined as visceral obesity and at least 2 of the 3 following conditions: HT, dyslipidemia and impaired fasting glucose.

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Special Report

# Brugada Syndrome

## Report of the Second Consensus Conference

*Endorsed by the Heart Rhythm Society and the European Heart Rhythm Association*

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***Abstract***—Since its introduction as a clinical entity in 1992, the Brugada syndrome has progressed from being a rare disease to one that is second only to automobile accidents as a cause of death among young adults in some countries. Electrocardiographically characterized by a distinct ST-segment elevation in the right precordial leads, the syndrome is associated with a high risk for sudden cardiac death in young and otherwise healthy adults, and less frequently in infants and children. Patients with a spontaneously appearing Brugada ECG have a high risk for sudden arrhythmic death secondary to ventricular tachycardia/fibrillation. The ECG manifestations of Brugada syndrome are often dynamic or concealed and may be unmasked or modulated by sodium channel blockers, a febrile state, vagotonic agents, $\alpha$-adrenergic agonists, $\beta$-adrenergic blockers, tricyclic or tetracyclic antidepressants, a combination of glucose and insulin, hypo- and hyperkalemia, hypercalcemia, and alcohol and cocaine toxicity. In recent years, an exponential rise in the number of reported cases and a striking proliferation of articles defining the clinical, genetic, cellular, ionic, and molecular aspects of the disease have occurred. The report of the first consensus conference, published in 2002, focused on diagnostic criteria. The present report, which emanated from the second consensus conference held in September 2003, elaborates further on the diagnostic criteria and examines risk stratification schemes and device and pharmacological approaches to therapy on the basis of the available clinical and basic science data. **(*Circulation*. 2005; 111:659-670.)**

**Key Words:** arrhythmia ■ death, sudden ■ electrocardiography ■ diagnosis

Since its introduction as a clinical entity in 1992,[1] the Brugada syndrome has attracted great interest because of its high incidence in many parts of the world and its association with high risk for sudden death in young and otherwise healthy adults and, less frequently, in infants and children. In recent years, an exponential rise in the number of reported cases and a striking proliferation of articles defining the clinical, genetic, cellular, ionic, and molecular aspects of the disease have occurred.[2] A consensus report published in 2002 focused on diagnostic criteria for the syndrome.[3,4] The present report, emanating from the second consensus conference held in September 2003, elaborates further on the diagnostic criteria and examines risk stratification schemes and device and pharmacological approaches to therapy. The recommendations herein are based on available clinical and basic science data and should be considered a work in progress that will require modification as additional data from molecular and clinical studies and prospective trials become available.

## Clinical Characteristics and Epidemiology

The Brugada syndrome is characterized by an ST-segment elevation in the right precordial ECG leads (so-called type 1 ECG; Figures 1 to 3) and a high incidence of sudden death in patients with structurally normal hearts. The syndrome typically manifests during adulthood, with a mean age of sudden

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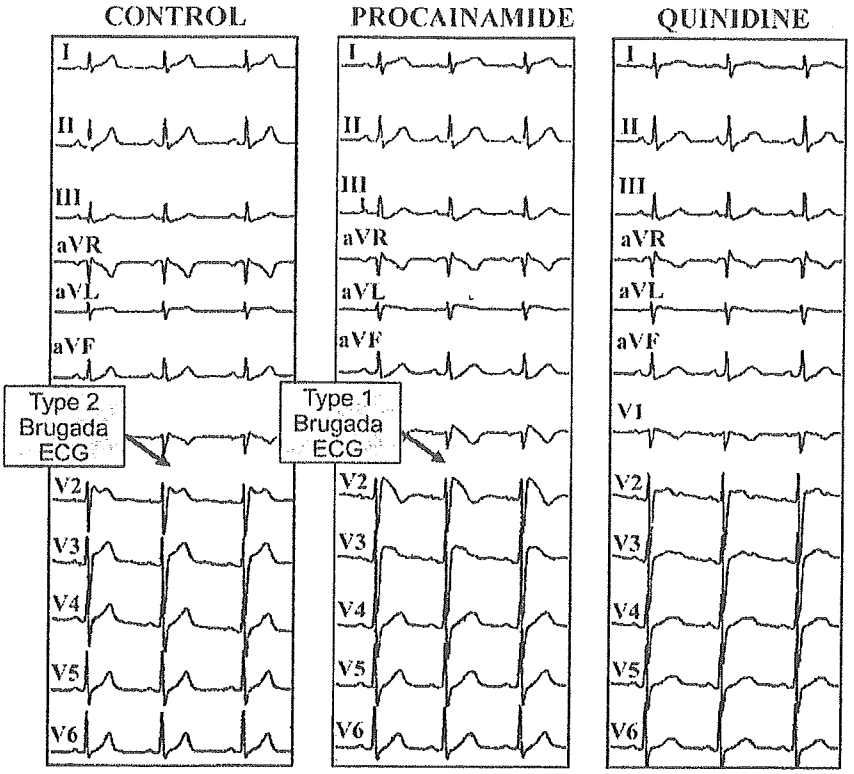


**Figure 1.** Twelve-lead ECG tracings in an asymptomatic 26-year-old man with Brugada syndrome. Left, Baseline: type 2 ECG (not diagnostic) displaying a saddleback-type ST-segment elevation is observed in $V_2$. Center, After intravenous administration of 750 mg procainamide, the type 2 ECG is converted to the diagnostic type 1 ECG, which consists of a coved-type ST-segment elevation. Right, A few days after oral administration of quinidine bisulfate (1500 mg/d, serum quinidine level 2.6 mg/L), ST-segment elevation is attenuated displaying a nonspecific abnormal pattern in the right precordial leads. VF could be induced during control and procainamide infusion but not after quinidine. Reprinted with permission from Belhassen et al.[110] Copyright 2002, Blackwell Publishing.

death of 41±15 years. The youngest patient clinically diagnosed with the syndrome is 2 days old and the oldest is 84 years old. The syndrome is estimated to be responsible for at least 4% of all sudden deaths and at least 20% of sudden deaths in patients with structurally normal hearts. The prevalence of the disease is estimated to be 5/10 000 inhabitants and, apart from accidents, is the leading cause of death in men <40 years old, particularly in countries in which the syndrome is endemic.[5] Because the ECG pattern can be dynamic and is often concealed, it is difficult to estimate the true prevalence of the disease in the general population.[6] In a recent Japanese study, a Brugada syndrome ECG (type 1) was observed in 12/10 000 inhabitants; type 2 and 3 ECGs, which are not diagnostic of Brugada syndrome, were much more prevalent, appearing in 58/10 000 inhabitants.[7] The prevalence of the Brugada syndrome among the general population in Europe and the United States is thought to be much lower,[8,9] although among Southeast Asian immigrants it may be as high as it is in Southeast Asia itself.[10]

Sudden unexplained nocturnal death syndrome (SUNDS; also known as SUDS) and Brugada syndrome have recently been shown to be phenotypically, genetically, and functionally the same disorder.[11]

Approximately 20% of patients with Brugada syndrome develop supraventricular arrhythmias.[12] Atrial fibrillation is associated in 10% to 20% of cases. Atrioventricular (AV) nodal reentrant tachycardia and Wolff-Parkinson-White syndrome also have been described.[13] Prolonged sinus node recovery time and sinoatrial conduction time,[14] as well as slowed atrial conduction and atrial standstill, have been reported in association with the syndrome.[15] A recent study reported that ventricular inducibility is positively correlated with a history of atrial arrhythmias.[16] In patients with an indication for an implantable cardioverter defibrillator (ICD), the incidence of atrial arrhythmias was 27% versus 13% in patients without an indication for an ICD ($P<0.05$), which suggests a more advanced disease process in patients with Brugada syndrome and spontaneous atrial arrhythmias. Inappropriate shocks from atrial arrhythmia episodes were observed in 14% of cases, highlighting the need for careful programming of the ICD.[15]

## Diagnostic Criteria and Recommendations

Three ECG repolarization patterns in the right precordial leads are recognized.[3,4] Type 1 is diagnostic of Brugada syndrome and is characterized by a coved ST-segment elevation ≥2 mm (0.2 mV) followed by a negative T wave (Figure 1). Brugada syndrome is definitively diagnosed when a type 1 ST-segment elevation is observed in >1 right precordial lead ($V_1$ to $V_3$) in the presence or absence of a sodium channel–blocking agent, and in conjunction with one of the following: documented ventricular fibrillation (VF), polymorphic ventricular tachycardia (VT), a family history of sudden cardiac death at <45 years old, coved-type ECGs in family members, inducibility of VT with programmed electrical stimulation, syncope, or nocturnal agonal respiration. The ECG manifestations of the Brugada syndrome, when concealed, can be unmasked primarily by sodium channel blockers but also during a febrile state or with vagotonic agents.[17–20] Drug challenge generally is not performed in asymptomatic patients displaying the type 1 ECG under baseline conditions because the additional diagnostic value is considered to be limited, the added prognostic value is not