Brugada Syndrome: Current Clinical Aspects and Risk Stratification

Takanori Ikeda, M.D., Ph.D.

From the Third Department of Internal Medicine, Ohashi Hospital, Toho University School of Medicine, Tokyo, Japan

Brugada syndrome is a primary electrical disease of the heart that causes sudden cardiac death or life-threatening ventricular arrhythmias, especially in younger men. Genetic analysis supports that this syndrome is a cardiac ion channel disease. A typical electrocardiographic finding consists of a right bundle branch block pattern and ST-segment elevation in the right precordial leads. The higher intercostal space V₁ to V₃ lead electrocardiogram could be helpful in detecting Brugada patients. Although two types of the ST-segment elevation are present, the coved type is more relevant to the syndrome than the saddle-back type. These patterns can be present permanently or intermittently. Recent data suggest that the Brugada-type electrocardiogram is more prevalent than the manifest Brugada syndrome. Asymptomatic individuals have a much lower incidence of future cardiac events than the symptomatic patients. Although risk stratification for the Brugada syndrome is still incomplete, the inducibility of sustained ventricular arrhythmias has been proposed as a good outcome predictor in this syndrome. In noninvasive techniques, some clinical evidence supports that late potentials detected by signal-averaged electrocardiography are a useful index for identifying patients at risk. The available data recommend prophylactic implantation of an implantable cardioverter defibrillator to prevent sudden cardiac death. This review summarizes recent information of the syndrome by reviewing most of new clinical reports and speculates on its risk stratification.

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Brugada syndrome^{1,2} is an arrhythmogenic disorder associated with a high risk of sudden cardiac death in individuals with a structurally normal heart. Sudden death from the syndrome occurs particularly in younger men.³ Patients at risk often have family histories of sudden death.⁴ At present, the syndrome is considered to be a primary electrical disease of the heart caused by a defect in ion channel genes and a propensity for malignant ventricular tachyarrhythmias.⁵ Genetic bases of one variant of the Brugada syndrome have been identified as a genetic mutation in the α subunit of the cardiac sodium channel gene (*SCN5A*).⁶ Although the syndrome is characterized by a pattern of right bundle branch block (RBBB) and ST-segment

elevation in electrocardiogram (ECG) leads V₁ through V₃, some alternative ECG findings have been presented.^{7,8} In addition, a novel association of the syndrome with supraventricular tachyarrhythmias has been described.⁹ Recent studies with a large number of individuals suggest that the Brugada-type ECG is much more prevalent than the manifest Brugada syndrome.¹⁰⁻¹⁵ Although invasive electrophysiological investigations have been presented as a risk stratifier to detect high-risk patients for sudden death due to ventricular tachycardia (VT) or ventricular fibrillation (VF) and who may be candidates for an implantable cardioverter defibrillator (ICD),¹⁶ their value is still being debated.¹⁷ In identifying such patients, noninva-

Address for reprints: Takanori Ikeda, M.D., Ph.D., Director, EP & ECG Laboratories, Third Department of Internal Medicine, Ohashi Hospital, Toho University School of Medicine, 2-17-6 Ohashi, Meguro-ku, Tokyo 153-8515, Japan. Fax: +81-3-3468-1269; E-mail: iket@oha.toho-u.ac.jp

sive diagnostic techniques may be more desirable than invasive methods. Late potentials detected by a signal-averaged ECG have been proposed as a risk stratification index for Brugada patients.¹⁸

This review summarizes recent information of the syndrome and speculates on its risk stratification by reviewing mainly new clinical reports.

CLASSIC AND NEW ELECTROCARDIOGRAPHIC FINDINGS

The strict clinical criteria for Brugada syndrome remains established.¹⁹ In clinical practice, the screening for Brugada syndrome is first made by a characteristic ECG in the right precordial leads. The electrocardiographic signature of this syndrome is dynamic and often concealed.²⁰ It can be enhanced or unmasked by sodium channel blockers such as flecainide, pilsicainide, encainide, propafenone, ajmaline, procainamide, and disopyramide.²⁰⁻²⁵ Beta-adrenergic blockade (propranolol), alpha-adrenergic agonists (norepinephrine), parasympathomimetic agents (edrophonium or neostigmine), and acetylcholine can also unmask or enhance its form.^{21,22} In case reports,^{26,27} it has been reported that a patient with massive cocaine ingestion or antihistamine (dimenhydrinate) infusion had an ECG abnormality resembling the syndrome. On the contrary, it can be normalized by a beta-adrenergic agonist (isoproterenol), alpha-blockade (phenolamine or prazosin), incremental atrial pacing and exercise stress testing.^{21,22,28-31} Among the antiarrhythmic drugs, only quinidine may have a reverse effect (i.e., normalization of the ECG) because an *in vitro* experiment³² has demonstrated that drugs with a reduction effect in the magnitude of the I_{to} -mediated phase 1 normalize the ST-segment elevation linked to Brugada syndrome. In fact, Carg et al.³³ have reported a Brugada patient who had easily inducible polymorphic ventricular tachycardia suppressed by quinidine but not by procainamide or beta-blockers. Alings et al.³⁴ have also reported two Brugada patients with ECG normalization by the administration of quinidine. The QRS pattern may show true RBBB (i.e., complete RBBB) that presents a QRS duration > 0.12 seconds and a terminal widened S wave in the left lateral leads, but not mimic RBBB in leads V_1 to V_3 , as shown in some early reports of Brugada syndrome.¹ However, most patients introduced as having Brugada syndrome in recent numerous re-

Figure 1. An example of two types of ST-segment elevation from patients with Brugada-type ECG in leads V_1 to V_3 . The left panel (A) shows a coved-type ST-segment elevation. The middle panel (B) shows a saddle-back type ST-segment elevation. The right panel (C) shows a coved-type ST-segment elevation manifested by intravenous administration of Class IC antiarrhythmic drug (pilsicainide).

ports have not had complete RBBB. The pattern of the ST-segment elevation (≥ 0.1 mV in the usual value) may be convex (namely coved) or concave (namely saddle-back) (Fig. 1). The pattern and the amplitude of ST-segment elevation can vary in the same patient during the follow-up.^{14,15} In addition, some individuals may have a coved pattern in lead V_1 and a saddle-back pattern in lead V_2 or V_3 .¹³ Sangwatanaroj et al.³⁵ presented an interesting technique using the single standard 12-lead ECG, with or without the procainamide test, and suggested that the higher intercostal space V_1 to V_3 lead ECG ($-V_1$ to $-V_3$ and $-2V_1$ to $-2V_3$) is helpful in detecting the Brugada-type ECG in sudden unexplained death syndrome survivors and their relatives.

Although ECG abnormalities including the ST-segment elevation are observed in the right precordial leads (V_1 to V_3) in patients with Brugada syndrome, preliminary evidence suggested the existence of a variant of Brugada syndrome associated with ST-segment elevation in the inferior leads (II, III, aV_F). Takagi et al.⁸ have presented the

clinical characteristics of three patients with spontaneous or inducible VF without apparent heart disease who had J wave and ST-segment elevation in the inferior leads. Takagi et al.⁸ concluded that the characteristics of these patients were very similar to those of patients with Brugada syndrome. Kalla et al.⁷ have also reported a patient similar to the three patients by Takagi et al.,⁸ and addressed that prominent J waves and ST-segment elevation in the inferior leads may serve as an important diagnostic sign for detecting high-risk individuals with a history of unexplained syncope, and that ICD implantation might be the treatment of choice. It is unclear why the J wave and ST-segment elevation sites on the 12-lead ECG in these patients differed from those of patients with Brugada syndrome. Kella et al.⁷ speculated that the reduction in I_{to} density, as reflected in the reduced J waves in the inferior leads, or a change in the parasympathetic system may be contributors. Further accumulation of such patients and genetic analysis will be needed for a better understanding of the specific characteristics of these patients.

PREVALENCE OF THE SYNDROME

Regarding the prevalence of the Brugada-type ECG (i.e., only criteria with ECG morphology) in a healthy population, there are some reports from Japan, France, Israel, and the United States.¹⁰⁻¹⁵ Miyasaka et al.¹³ found the Brugada-type ECG, which was defined as the RBBB and ST-segment elevation > 0.1 mV in leads V_1 to V_2 or V_3 , in 98 of 13,929 subjects (0.7%) who had ECGs during a routine health examination; the mean age was 58 ± 10 years and 26.5% of the population were men. In this study, a coved pattern of ST-segment elevation was found in 37 subjects (0.27%) and an rsR' pattern in lead V_1 was found in 40 subjects (0.29%). Subjects with both the coved pattern and the rsR' pattern were found in 17 subjects (0.12%). Matsuo et al.¹⁴ found the Brugada-type ECG, which was defined as terminal r' wave in lead V_1 , ST-segment elevation > 0.1 mV in leads V_1 and V_2 and the coved pattern in lead V_1 , in 7 of 4788 healthy subjects (0.15%) < 50 years old in the first ECG recording that was referred to as the "prevalence" and in a total of 32 subjects (0.7%) in subsequent ECG recordings during the follow-up. Furuhashi et al.¹⁵ found the Brugada-type ECG, which was defined as the combination of RBBB and ST-segment elevation > 0.1 mV in V_1 to V_3 , in 12 of 8612

subjects (0.14%), and among them the coved pattern with an RBBB in leads V_1 found in 4 subjects (0.05%). Hermida et al.¹⁰ found one subject with the typical coved-type ST-segment elevation and rsR' pattern in V_1 of 1000 apparently healthy subjects (0.1%). Viskin et al.⁸ reported that there were no subjects with the typical Brugada-type ECG based on their definition (i.e., RsR' and ST-segment elevation in V_1 to V_3) in 592 healthy control subjects (0%), and Monroe and Littman¹² reported 52 subjects of the Brugada-type ECG including saddle-back-type ECG out of appropriately 12,000 noncardiac patients (0.43%); the coved pattern was present in only 2 subjects (0.02%). When only the coved pattern with or without RBBB in the right precordial leads was considered as the Brugada-type ECG, the prevalence was 0.27% in the study by Miyasaka et al.¹³; 0.15% in the study by Matsuo et al.¹⁴; 0.05% in the study by Furuhashi et al.¹⁵; 0.1% in the relatively small sample by Hermida et al.¹⁰; 0% in the study by Viskin et al.¹¹; 0.02% in the study by Monroe and Littman.¹² In the prevalence in the reported studies, there were differences even among reports from the same country (Japan), but the consensus is that the syndrome is not uncommon. Although the syndrome appears to be most prevalent in Japan and Southeast Asia, as stated in previous reviews,¹⁹ more carefully designed studies with a uniform population in terms of age and sex and uniform criteria defining the ECG pattern will be needed to assess the prevalence of the Brugada-type ECG throughout the world.

With respect to the prevalence of the Brugada-type ECG among patients with idiopathic VF, there are some reports.^{11,13} Viskin et al.¹¹ found the Brugada-type ECG, defined as RsR' and ST-segment elevation in the right precordial leads, in 8 of 39 consecutive patients with idiopathic VF (21%). Remme et al.³⁶ found the ECG pattern, based on the presence of (in)complete RBBB and ST-segment elevation of V_1 - V_3 of ≥ 1 mm, in 9 of 37 survivors from idiopathic VF (24%). Depending on the diagnostic criteria used, "Brugada syndrome" was attenuated to 3% of patients with idiopathic VF; the percentage (3%) was obtained when the intermittent presence of (in)complete RBBB and ST-segment elevation ≥ 2 mm and/or their (re)appearance with class I antiarrhythmic drugs were included as criteria. The variation in prevalence appears to suggest the importance of defining precise diagnostic criteria for Brugada syndrome.

Table 1. Possibilities for Risk Stratification of Arrhythmic Events or Sudden Cardiac Death in Individuals with Brugada-type ECG

Proposal Indices	Level of Risk	Positive Evidence References	Negative Evidence References
Age, 30–50 years	Suspected	[38] [46]	[37]
Gender, male	High	[38] [46]	[37]
Family history of sudden death	Presumably high		
Symptomatic episodes	Very high	[16] [38] [41] [42]	[37]
Coved-type ST-segment elevation	High	[42]	
Magnitude of ST-segment elevation	Low		[14] [18] [20]
Transient normalization of ST-segment elevation	Suspected	[20]	
Spontaneous ST-segment elevation	High	[41] [46]	
Higher intercostal space lead ECG	Suspected	[35]	
ECG manifestation by antiarrhythmic drugs	Suspected		
Increased vagal activity	High	[22] [49]	
Abnormal sympathetic nervous system	Suspected	[52]	
Late potentials by signal-averaged ECG	High	[18] [22] [28]	
T-wave alternans	Debated		[18]
QT-interval dispersion	Low		[18]
Electron-beam computed tomography	Suspected	[57]	
Inducibility by electrical stimulation	Debated	[16] [41]	[37] [38] [46]
H-V interval prolongation	Debated	[1] [28] [16?]	[16?] [18]
Sodium channel gene (SCN5A)	Suspected	[46]	

In the references to positive and negative evidence, case reports are excluded.

RISK STRATIFICATION OF THE SYNDROME

In patients with the Brugada-type ECG, particularly asymptomatic individuals, identification of high-risk patients is important for preventing fatal ventricular arrhythmias and sudden death. At present, several indices have been proposed and suspected for the risk stratification of patients with Brugada syndrome (Table 1), but most of them have not yet been fully established and some of them are still controversial.

Gender and Age

In data on 63 patients with Brugada syndrome by Brugada et al.,³⁷ there was no relationship between gender/age and recurrent arrhythmic events. In contrast, in an evaluation of 60 patients diagnosed with the syndrome from 52 families by Priori et al.,³⁸ the ECG diagnosis was predominant among males (75%), and 82% of the cardiac arrests occurred in males at a mean age of 37 years. A number of previous and subsequent reports agree with the observation by Priori et al.³⁸ Thus, being male may be a risk factor for sudden death. In addition, an age between 30 and 50 years may be also a risk factor of the syndrome because of events

that occur in that age group. As a novel observation, Priori et al.³ reported that pediatric cases of Brugada syndrome that was suspected based on a genetic analysis of five children from the same family who had died after unexplained cardiac arrest. Suzuki et al.³⁹ have also experienced an infant case with a malignant form of Brugada syndrome. Corrado et al.⁴⁰ have recently indicated that in an assessment on RBBB, right precordial ST-segment elevation and sudden death in young people (≤ 35 years), ST-segment elevation compatible with the Brugada-type ECG was found in 14% of young sudden death victims, whereas it mostly reflected underlying arrhythmogenic right ventricular cardiomyopathy. To confirm the prognostic value of gender and age, a larger population study with Brugada patients without any structural heart problems may be necessary.

Family History

Since Brugada syndrome is considered to be a genetically transmitted arrhythmogenic disease that is inherited as an autosomal dominant trait,⁶ a family history of unexpected sudden death may be a risk factor for sudden cardiac death. Numerous clinical reports have mentioned that the patients

with sudden cardiac death or life-threatening events often have a family history of this. However, the incidence of positive family history was not as high among patients with Brugada syndrome⁴ and interestingly, no study has provided any evidence that a family history of unexpected sudden death is a predictor of future arrhythmic events.

Symptomatic Episodes

Brugada et al.³⁷ initially described that asymptomatic patients with the ECG anomaly have the same risk of arrhythmic events as patients who have had an episode of aborted sudden death. Recently, two larger cohorts of individuals with a Brugada-type ECG,^{16,41} reported an alternative result regarding the incidence of arrhythmic events among symptomatic and asymptomatic patients. In the first cohort ($n = 252$) with an alternative result,¹⁶ 45 of the 116 symptomatic patients (39%) developed a recurrent or first arrhythmic event during a mean follow-up of 34 ± 40 months, and the highest incidence of arrhythmic events occurred in patients previously resuscitated from near sudden cardiac death (32 of 54 patients [59%]). In contrast, only 7 of 136 asymptomatic individuals (5%) developed a first arrhythmic event during the follow-up. In the second cohort ($n = 334$),⁴¹ 44 of the 71 patients (62%) identified after a resuscitated cardiac arrest had a new arrhythmic event during 54 ± 54 months of follow-up and 14 of the 73 patients (19%) identified after a syncopal event had a new event during 26 ± 36 months of follow-up, whereas in asymptomatic individuals, only 16 of 190 individuals (8%) had a first arrhythmic event during a mean follow-up of 27 ± 29 months. As a similar result, Atarashi et al.,⁴² reported that only one patient (1.5%) had an arrhythmic event (VF) among 67 asymptomatic individuals during a 3-year follow-up. In the study ($n = 30$) by Priori et al.³⁸ and the small sample ($n = 11$) by Takenaka et al.,⁴³ none of the asymptomatic individuals had defined arrhythmic events or sudden death during a mean follow-up of 33 ± 38 months and 43 ± 22 months, respectively. Miyasaka et al.¹³ have reported one death among 98 subjects with the Brugada-type ECG (1.0%) and 139 deaths among 13,831 subjects without the Brugada-type ECG (1.0%) during 2.6 ± 0.3 years of follow-up in a community-based population. They stated that the total mortality of subjects with the Brugada-type

ECG did not differ from the mortality of those without the Brugada-type ECG; it is unknown whether the subjects with the Brugada-type ECG had symptoms or not.

It appears that asymptomatic individuals with the Brugada-type ECG have a rare cause of sudden cardiac death and a benign clinical course that does not differ from individuals without the Brugada-type ECG. In contrast, the symptomatic patients who had a history of VF or syncope develop cardiac events more frequently, as shown in the studies by Brugada et al.¹⁶ (45/116 patients [39%] during the follow-up of an average of 34 months), Brugada et al.⁴¹ (58/144 patients [40%] during the follow-up of 26-54 months), Priori et al.³⁸ (5/30 patients [16%] during the follow-up of an average of 33 months), and Atarashi et al.⁴² (26% of the 38 patients during a 3-year follow-up). Thus, symptomatic episodes could be a useful index for identifying high-risk patients in the syndrome.

Resting Surface ECG Parameters

As shown in many clinical reports, a coved-type ST-segment elevation has been observed more frequently than the saddle-back type in patients diagnosed with Brugada syndrome, especially in patients at risk. This evidence may indicate that a coved pattern of ST-segment elevation may be one of the risk stratifiers in the syndrome. In the study by Atarashi et al.,⁴² the coved type was present in 17 of 20 patients (85%) with ventricular fibrillation and 11 of 18 patients (61%) with syncope, and the remaining lower incidence of patients had the saddle-back type. However, these types may be changed during the follow-up, as shown in the study by Matuso et al.¹⁴ This issue was not discussed in the study by Atarashi et al.⁴²

There are no reports that the magnitude of ST-segment elevation on the resting surface ECG can serve as an independent index for identifying patients at risk in the Brugada syndrome. The relationship between life-threatening events and the magnitude of J-point elevation at rest have been evaluated in patients with the syndrome.¹⁸ No relationship was found to exist among their values. Matsuo et al.¹⁴ have also compared the magnitude of ST-segment elevation in leads V_1/V_2 , QRS width, and the corrected QT interval measured during the follow-up between the unexpected death group and the other group. These ECG parameters were not associated with unexpected death. In addition,

Brugada et al.²⁰ have shown that patients with transient normalization of the ECG were at risk of ventricular arrhythmias, as well as patients in whom it was persistent. The magnitude of ST-segment elevation on the resting surface ECG would not be a risk factor. Rather the transient normalization of the ECG may represent an important diagnostic challenge.^{20,44} However, a dynamic elevation of the ST segment in lead V₁ to V₃ may be a signal for the sudden onset of ventricular arrhythmia because much clinical evidence has revealed that the ECG was dynamically enhanced before the occurrence of ventricular arrhythmias.^{29,45} In a recent study by Brugada et al.,⁴¹ it has been shown that patients with a spontaneously abnormal ECG have the poorer prognosis. As a similar result, Priori et al.⁴⁶ have reported the combined presence of a spontaneous ST-segment elevation in leads V₁-V₃ and the history of syncope identifies patients at risk in the syndrome.

Recently, Sangwatanaroj et al.³⁵ presented that the higher intercostal space V₁ to V₃ lead ECG, with or without antiarrhythmic drugs, is superior to the conventional 12-lead ECG in the detection of the Brugada-type ECG in both sudden unexplained death syndrome survivors and their relatives. This observation may suggest only that more individuals with ST-segment elevation are identified when leads are moved one intercostal space above standard positions because it remains to be proven if those patients showing the ECG abnormalities only with the leads in the modified positions are true positive or false positive individuals for the syndrome. No study on genotyped individuals has demonstrated the value of this novel position in unmasking carriers of the genetic defect that are silent with conventional position of the leads and positive when leads are moved upward. Therefore, it is unknown if this alternative technique on the resting surface ECG serve as an independent index for identifying patients at risk in the syndrome.

Pharmacological Manifestation

The ECG feature of Brugada syndrome is dynamic and sometimes concealed, but it is well known that the administration of sodium channel blockers such as flecainide, pilsicainide, ajmaline, procainamide, and disopyramide can unmask its concealed forms.^{20-25,30} Although intravenous administration of these drugs is most effective in unmasking the Brugada-type ECG,^{20-22,25,30} oral ad-

ministration of class IC antiarrhythmic drugs such as flecainide, pilsicainide, and encainide has been shown to be effective as well.^{23,24} It has also been shown that these drugs are useful in evaluating the inducibility of VT/VF during electrophysiological studies.¹⁶ Priori et al.³⁸ have shown that a pharmacological challenge with sodium channel blockers was unable to unmask most silent gene carriers of the Brugada syndrome. With respect to the prognostic significance and risk stratification of the pharmacological effect, it remains assessed fully. No study has revealed a difference in the occurrence of arrhythmic events between patients with and without the manifestation of Brugada-type ECG by antiarrhythmic drugs. Only some case reports^{47,48} that documented the spontaneous induction of ventricular tachycardia by intravenous administration of class IA antiarrhythmic drugs support this hypothesis.

Vagal Activity

First, Miyazaki et al.²¹ provided the modulator effects of the autonomic nervous system on the ST segment by intravenous administration of autonomic receptor agonists and blockades in patients with Brugada syndrome. Kasanuki et al.²² have proposed that vagal activity represented by heart rate variability patterns during 24-hour Holter monitoring influences a possible new mechanism of VF in patients associated with Brugada syndrome. Heart rate spectral analysis just before VF episodes in Holter monitoring showed a sudden rise in the HF (i.e., vagal activity) and a decrease in the LF/HF ratio (sympathetic activity) in the two patients studied. Matsuo et al.⁴⁹ also reported that increased nocturnal vagal activity and withdrawal sympathetic activity play an important role in the arrhythmogenesis of Brugada syndrome. Samniah et al.⁵⁰ demonstrated the occurrence of a vasovagal syncope during the recovery period after an exercise stress test in a patient with ECG and pharmacological findings suggestive of Brugada syndrome. Itoh et al.⁵¹ suggested that malignant ventricular arrhythmias were associated with pronounced ST-segment elevation that occurred at night or early in the morning. Although an association between vagal activity and arrhythmogenesis of the syndrome is an interesting point, no study has revealed the prognostic significance of vagal activity in the triggering of VF.

Figure 2. ECG tracings in leads V_1 to V_3 and the signal-averaged ECG for a symptomatic Brugada patient. The late potentials, represented by the shaded area, are positive, showing an $RMS_{40} < 20 \mu V$, and an $LAS_{40} > 38$ ms.

An Abnormal Sympathetic Nervous System

Recently, Wichter et al.⁵² investigated the sympathetic nervous system in 17 patients with Brugada syndrome with the use of [^{123}I]m-iodobenzylguanidine (^{123}I -MIBG), single-photon emission CT (SPECT), and quantitative 33-segment bull's-eye analysis. As a result, this study demonstrated an abnormal ^{123}I -MIBG uptake in the inferior and septal left ventricular wall in patients with Brugada syndrome, indicating presynaptic sympathetic dysfunction of the heart. These findings may have the impact on the pathophysiology in patients with Brugada syndrome. However, it remains unknown if an abnormal sympathetic nervous system is associated with arrhythmogenesis of the syndrome.

Late Potentials by Signal-Averaged ECG

Several clinical studies^{18,22,28,53} in patients with Brugada syndrome have demonstrated that late potentials by signal-averaged ECG were observed in most patients with documented VF (Fig. 2). In a small patient population compatible with this syndrome by Kananuki et al.,²² all 5 patients with a

history of VF had LP when the characteristic ECG findings were present. Kananuki et al.²² also showed a conduction delay in the area between the anterior wall and the septal region of the right ventricular outflow tract using body-surface mapping. In reports from Nademanee et al.²⁸ and Kobayashi et al.,⁵³ late potentials were shown in 11 of 13 Brugada patients and in all 4 Brugada patients studied, respectively. The value of this noninvasive marker has been assessed to identify high-risk patients in a larger population ($n = 33$).¹⁸ The results were used to test the hypothesis that arrhythmogenesis in this syndrome is associated with conduction disturbance in the right ventricle. There were a total of 33 patients (45 ± 14 years, 31 men) who had an ECG with an RBBB pattern (i.e., mimic RBBB) and ST-segment elevation ≥ 0.1 mV (either a coved or saddle-back type) in leads V_1 to V_3 , and structurally normal hearts. In this study, late potentials were defined as positive when two criteria (abnormal RMS_{40} and LAS_{40}) excluding prolonged f-QRS were met because the QRS width influences the outcome of late potentials. Late potentials were present in 24 Brugada patients (73%). The incidence of late potentials in Brugada patients was significantly higher than in the controls. Of 19 patients with life-threatening events, 17 patients (89%) documented late potentials. The presence of LP had significant correlation with the occurrence of life-threatening events (positive predictive value 71% and negative predictive value 78%). However, it is still not really known whether late potentials can serve as an independent risk stratifier for cardiac events because this study assessed the prognostic value retrospectively.⁵⁴ An analysis of the follow-up data would resolve this question.

Noninvasive Markers of Repolarization Inhomogeneity

Antzelevitch et al.^{21,32} have shown that the pathogenesis of the ECG manifestations of this syndrome are due to heterogeneous loss of the action potential dome, causing a marked epicardial and transmural dispersion of repolarization, which may result in the production of ST-segment elevation, thus giving rise to phase 2 reentry. These observations support the hypothesis that the mechanism of malignant ventricular arrhythmias in this syndrome is caused by repolarization abnormality. T-wave alternans (i.e., a temporal repolarization abnormality) and QT-interval dispersion (i.e., a

spatial repolarization abnormality) have been provided as noninvasive tools in identifying patients at risk; although there are two case reports^{55,56} showing the occurrence of visible T-wave alternans without subsequent ventricular arrhythmias after intravenous administration of class I antiarrhythmic drugs in a patient with Brugada syndrome. No study has shown the prognostic value of T-wave alternans as well as QT-interval dispersion in patients with Brugada syndrome. The prognostic value of microvolt T-wave alternans and QT-interval dispersion were assessed as noninvasive risk stratification markers in patients with Brugada syndrome.¹⁸ The incidence of microvolt T-wave alternans and QT-interval dispersion was not significantly different from that of the controls and both markers were not correlated with the occurrence of life-threatening events.

Electron-Beam Computed Tomography

Takagi et al.⁵⁷ showed that the sites of morphological abnormalities detected by electron-beam computed tomography and not detected by echocardiography and right ventriculography in patients with Brugada syndrome were related to the origins of premature ventricular contractions recorded only in the acute phase, which may trigger VF, and proposed that these morphological abnormalities may be related to arrhythmogenic substrates in the syndrome. The abnormalities were detected not only in the right ventricular outflow tract but also in the right ventricular apex in some patients. Their observations may prompt discussion regarding the relationship between these morphological abnormalities and arrhythmogenic right ventricular cardiomyopathy.⁵⁸

Electrophysiological Study

The value of programmed electrical stimulation for risk stratification is still being debated. The first experience of electrophysiological investigations in a smaller patient population ($n = 60$) by Brugada et al.³⁷ showed that the induction of ventricular arrhythmias in electrophysiological studies fails to determine its prognostic value. Priori et al.³⁸ also showed that programmed electrical stimulation is of limited value (positive predictive value 50% and negative predictive value 46% [$n = 60$]) in identifying patients at risk and as it identifies only a fraction of individuals at risk. Recently, Brugada et al.^{16, 41} presented data on the prognostic value of

electrophysiological studies in the largest cohorts ($n = 252$ and $n = 334$, respectively) of patients ever collected with Brugada syndrome. Eventually, it was shown that the inducibility of sustained ventricular arrhythmias in electrophysiological studies is a good outcome predictor in Brugada syndrome. The predictive values of electrical investigations in symptomatic patients and asymptomatic individuals were as follows: a sensitivity of 96% and 86%, a specificity of 41% and 70%, a positive predictive value of 51% and 13%, and a negative predictive value of 94% and 99%, respectively.¹⁶ However, more recently, Priori et al.⁴⁶ presented that Kaplan-Meier event-free analysis failed to demonstrate an association between the inducibility by programmed electrical stimulation and spontaneous occurrence of ventricular fibrillation in a larger cohort ($n = 200$). Overall, the sensitivity of the electrical stimulation was 66% and specificity was 34%. Although Eckardt et al.⁵⁹ have raised concerns that in patients with Brugada syndrome, the induction of ventricular arrhythmias is influenced by the protocol used and increases proportionally with the number of premature stimuli used, Priori et al.⁴⁶ have suggested the limited value of programmed electrical stimulation even though the number of premature stimuli was increased up to 3. Thus, the value of electrophysiological study for risk stratification in patients with Brugada syndrome is still unknown.

When the mechanism of arrhythmogenesis in this syndrome is considered, a high rate of electrical induction in patients who will have arrhythmic events may support the conduction abnormality hypothesis¹⁸ because inducible sustained arrhythmias, the mechanism means of which is caused by reentry, would need a conduction delay.

H-V Interval

First, Brugada et al.¹ described an association between a prolonged H-V interval during sinus rhythm and the syndrome. Nademanee et al.²⁸ also demonstrated that patients with unexpected sudden death in Thai men compatible with Brugada syndrome have an abnormally prolonged His-Purkinje conduction time. In contrast, this study,¹⁸ which includes symptomatic and asymptomatic Brugada patients, showed no relationship between the H-V interval and life-threatening events. Recently, Brugada et al.¹⁶ revealed an alternative outcome from the first experience in the largest cohort

of patients ever collected with Brugada syndrome. No significant difference was observed in the duration of the H-V interval in the symptomatic patients who remained asymptomatic during the follow-up compared with the patients who developed recurrences. However, in the asymptomatic group, individuals who developed a first arrhythmic event had a longer H-V interval compared with the individuals who remained asymptomatic ($P = 0.04$). It appears that the prognostic value of a prolonged H-V interval is still unknown.

GENETIC ANALYSIS OF THE SYNDROME

A molecular defect in the cardiac sodium channel gene, *SCN5A*,⁶⁰ which is the same gene implicated in the LQT3 form of patients with long-QT syndrome, has been reported as the genetic basis of the syndrome.⁶ Therefore, the syndrome is considered as a genetically transmitted arrhythmogenic disease that is associated with an increased risk of sudden cardiac death. Many genetic reports for Brugada syndrome have revealed the importance of mutations that enhance sodium channel inactivation.^{36,61-68} At present, the only gene linked to the syndrome is the cardiac sodium channel gene (*SCN5A*). Priori et al.³⁸ have revealed that mutations of the *SCN5A* gene were identified in 8 of 52 families (15%); 3 were symptomatic and 5 were asymptomatic. This observation may demonstrate that other genes are involved in the syndrome. Priori et al.³⁸ also reported that the administration of flecainide or ajmaline failed to unmask the disease in all carriers of the genetic defect with a normal ECG. In contrast, Brugada et al.²⁰ reported that the administration of ajmaline, procainamide, or flecainide revealed the disease in all patients with transient normalization of the ECG and *SCN5A* mutation. Thus, the pharmacological effect with sodium channel blockers in gene carriers is at variance. In addition, no study has shown the impact of genetic analysis in risk stratification of the syndrome. Assessing an *SCN5A* mutation as the index to detect patients at high risk in the syndrome will be a task of interest for electrophysiologists in this field.

NOVEL ASSOCIATION OF THE SYNDROME

Eckardt et al.⁹ have described an association of supraventricular tachyarrhythmias in Brugada syn-

drome. Among 35 Brugada patients (26 with a history of cardiac death or syncope and 9 asymptomatic) who underwent electrophysiological study, 10 patients (29%) were found to have supraventricular tachyarrhythmias; 6 had an AV nodal reentrant tachycardia with dual pathway, 2 an atrial tachycardia (1 in addition to an AV nodal reentrant tachycardia), 1 an atrial fibrillation, and 2 an AV reentrant tachycardia with an accessory pathway. Here, it was proposed that Brugada syndrome should be considered a possible additional electrophysiological abnormality and added to the list of possible causes of syncope or aborted sudden death in patients with supraventricular tachyarrhythmias. It was thought that an increased dispersion of repolarization was the mechanism for atrial fibrillation occurrence or other atrial tachyarrhythmias. Regarding AV nodal reentrant tachycardia and AV reentrant tachycardia with an accessory pathway, it is difficult to speculate on the underlying mechanism. This observation of supraventricular tachyarrhythmias has also been described by other investigators. Brugada et al.⁶⁹ reported on patients with Brugada syndrome who had atrial fibrillation. Kakishita et al.⁷⁰ reported two patients with Brugada syndrome who had supraventricular tachycardia. Ito et al.⁵¹ have also described that Brugada syndrome may be associated not only with an increased risk of ventricular tachyarrhythmias but also with an increased risk of paroxysmal fibrillation because paroxysmal atrial fibrillation occurred in 9 of 30 patients (30%) with Brugada-type ECG. Ito et al.⁵¹ speculate that it may be influenced by autonomic nervous activity. These observations prompt the question that the arrhythmogenic substrate in the syndrome may not be restricted to the ventricular level.

THERAPEUTIC MANAGEMENT

Currently available data suggest that only an ICD prevents sudden cardiac death.³⁷ No antiarrhythmic drugs, including amiodarone, have shown efficacy in the prevention of sudden cardiac death due to VF. Brugada et al.³⁷ recommended that both symptomatic patients and asymptomatic patients who are inducible by programmed electrical stimulation should be managed by ICD implantation. A definition of the criteria for the targeted use of an ICD has been provided by a task force report on sudden cardiac death by the European Society of Cardiology.⁷¹ Three indices, i.e., family

Figure 3. Proposed clinical management of individuals with Brugada-type ECG. SD indicates sudden death; SAECG, signal-averaged ECG; ICD, implantable cardioverter defibrillator.

history of sudden cardiac death, syncope and VT/VF inducibility, have been recommended as risk stratification. Belhassen et al.⁷² suggest that electrophysiologically-guided therapy with a class IA antiarrhythmic drug (quinidine) is an effective approach for the long-term management of patients with idiopathic VT with Brugada syndrome. However, the management of asymptomatic patients without a family history is still being debated. As shown in several previous studies and many case reports,^{16,18,21,24,29,38} VF or polymorphic VT can be occasionally induced by programmed ventricular stimulation in Brugada patients. In addition, non-invasive measurements are more desirable than invasive electrophysiological studies. At present, the detection of LP by signal-averaged ECG has been proposed as a useful noninvasive technique

for identifying high-risk patients with Brugada syndrome.¹⁸ The noninvasive approach of the clinical management of individuals with Brugada-type ECG is shown in diagrammatic form (Fig. 3).

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