THE GENETIC AND MOLECULAR BASES OF CLINICAL ARRHYTHMIC DISEASES

The syndrome of right bundle branch block ST segment elevation in V₁ to V₃ and sudden death—the Brugada syndrome

J. Brugada*, P. Brugada† and R. Brugada‡

*Arrhythmia Unit, Cardiovascular Institute, Hospital Clinic, University of Barcelona, Barcelona, Spain; †Cardiovascular Research and Teaching Institute Aalst, Cardiovascular Center, Aalst, Belgium; ‡Department of Cardiology, Baylor College of Medicine, Houston, Texas, U.S.A.

In 1992 a new syndrome was described consisting of syncopal episodes and/or sudden death in patients with a structurally normal heart and an electrocardiogram (ECG) characteristic of right bundle branch block with ST segment elevation in leads V₁ to V₃. The disease is genetically determined, with an autosomal dominant pattern of transmission. Three different mutations that affect the structure and function of the cardiac sodium channel gene SCN5A have been identified. Two mutations result in total loss of function of the sodium channel. The other mutation results in acceleration of the recovery of the sodium channel from inactivation. The incidence of the disease is difficult to estimate, but it causes 4 to 10 sudden deaths per 10 000 inhabitants per year in areas like Thailand and Laos. In these countries, the disease represents the most frequent cause of death in young adults. Up to 50% of the yearly sudden deaths in patients with a structurally normal heart are caused by this syndrome. The diagnosis is easily made by means of the ECG. The presence of concealed and intermittent forms, however, make the diagnosis difficult in some patients. The ECG can be modulated by changes in autonomic balance and the administration of antiarrhythmic drugs. Beta-adrenergic stimulation normalizes the ECG, while intravenous ajmaline, flecainide or procainamide accentuate ST segment elevation and are capable of unmasking concealed and intermittent forms of the disease. Recent data suggest that loss of the action potential dome in the right ventricular epicardium but not the endocardium underlies ST segment elevation seen in the Brugada syndrome. Also, electrical heterogeneity within the right ventricular epicardium leads to the development of closely coupled extrasystoles via a phase 2 reentrant mechanism, which then precipitates ventricular tachycardia–ventricular fibrillation. Right ventricular epicardium is preferentially affected because of the predominance of transient outward current in this tissue. Antiarrhythmic drugs like amiodarone and beta-blockers do not prevent sudden death in symptomatic or asymptomatic individuals. Gene therapy may offer a cure in future years. Implantation of an automatic cardioverter-defibrillator is the only currently proven effective therapy.

(Europace 1999; 1: 156–166)

Key Words: Sudden death, bundle branch block, Brugada syndrome, genetic diseases, cardiac arrhythmias.

Definition and history

The syndrome of right bundle branch block, ST segment elevation in V₁ to V₃ and sudden death is a clinical–electrocardiographic diagnosis based on syncopal or sudden death episodes in patients with a structurally normal heart with a characteristic electrocardiographic pattern[1]. The electrocardiogram (ECG) shows ST segment elevation in the precordial leads V₁ to V₃, with a morphology of the QRS complex resembling right bundle branch block (Fig. 1). This pattern of right bundle branch block has also been called J point elevation[2,3].

The episodes of syncope and sudden death (aborted or not) are caused by fast polymorphic ventricular...
Tachycardias (VT) or ventricular fibrillation (VF) (Fig. 2). These arrhythmias appear with no warning. There is no prolongation of the QT interval during sinus rhythm. Only in very few cases is there alternation of long–short sequences before the onset of polymorphic VT, a finding common in other arrhythmias, like torsade de pointes in the long QT syndrome[4]. There is no preceding acceleration of heart rate, as is the case of catecholamine-dependent polymorphic VT[5].

The first patient with this syndrome was seen in 1986, a 3-year-old boy. He had presented with multiple episodes of loss of consciousness and had been resuscitated numerous times by his father. The child’s sister had died suddenly at age 2 years after multiple episodes of aborted sudden death. The ECGs of the two siblings were very similar and abnormal[1]. The identification of two additional patients resulted in presentation of preliminary data at the meeting of the North American Society of Pacing and Electrophysiology (NASPE) in 1991[6]. The first paper, on eight patients, was published in 1992[1]. Since then, there has been an exponential increase in the number of patients recognised all over the world. The database of our Working Group (Working Group on Cardiac Arrhythmias of the European Society of Cardiology) contains over 400 patients at present and another 150 cases have been reported in the literature. The recent discovery of genetic abnormalities linked to this syndrome points to its being
a primary electrical disease, providing an important first step in the prevention and effective treatment of this form of sudden death in patients with a structurally normal heart.

Several authors have previously reported ECGs similar to the one presented in Fig. 1[7–12]. For the most part, these were considered variants of the normal ECG and no definitive link to sudden death was established.

It is worth noting that Asians have known about the condition for many decades. In the Philippines it was known as Bangungut (scream followed by sudden death during sleep) and in Japan as Pokkuri (unexpected sudden death at night). In Thailand, this form of death is known as Lai Tai (death during sleep). The sudden unexplained death syndrome is known as SUDS in Thailand[13]. In the Northeast of this country, the incidence of this form of sudden death has been estimated as between 26 and 38 cases per 100,000 inhabitants per year. In Laos it may cause one sudden death per 1000 inhabitants per year. It was discovered only recently that these patients suffer from the syndrome of right bundle branch block, ST segment elevation in V1 to V3 and sudden death[13]. The higher prevalence of this syndrome in some areas can be explained by its genetic transmission.

Aetiology and genetics

The Brugada syndrome is usually identified as a sporadic case. However, the majority of individuals who present with this syndrome have a family history of sudden death or malignant arrhythmia, if properly questioned. This has led to the understanding that there are strong genetic factors determining the disease. Presymptomatic identification of gene abnormalities is crucial in a disease like Brugada syndrome, in which the mortality at 2 years approaches 30%.

Phenotypic characterization

In the Brugada syndrome, the diagnosis is based on a history of aborted sudden death, with an electrocardiographic pattern typical of ST segment elevation in leads V1–V3, with or without right bundle branch block[1]. In some cases, however, the diagnosis is different for the following reasons:

(1) Some individuals present with an abnormal electrocardiogram but are completely asymptomatic. These individuals, however, are at risk of sudden death. They are considered phenotypically affected and are therefore expected to carry a gene abnormality.

(2) Many patients have a history of resuscitated sudden death, but there is a transient normalization of the ECG. This individual fits under the category of idiopathic ventricular fibrillation. Repeat ECG recording will ultimately identify the diagnostic electrocardiographic pattern and, therefore, the patient is considered as an affected individual in genetic studies. Provocative tests may be needed.

(3) There is a history of sudden death in the family (or aborted sudden death in the individual), but with no observed electrocardiographic criteria. The use of class IA antiarrhythmics, mainly ajmaline, procainamide and flecainide, has proven to be highly sensitive and specific in unmasking the ECG pattern (ST segment elevation in leads V1–V3) in these patients.

Genetic characterization

Controversy exists as to whether the Brugada syndrome is a form fruste of arrhythmogenic right ventricular dysplasia (ARVD) which may present with ventricular arrhythmias and is typically associated with fatty infiltration of the right ventricular myocardium. Although no genes have been identified for ARVD, linkage analysis has identified five genetic loci, including ARVD 1 (14q23)[14], ARVD 2 (1q42)[15], ARVD 3 (14q12)[16], ARVD 4 (2q32)[17], and Naxos disease (17q)[18]. Evaluation of families with Brugada syndrome for genetic mutations has clarified this picture somewhat.

In the Brugada syndrome, as in the long QT syndrome, the best candidate genes are those that are responsible for the formation of the cardiac action potential, namely the genes that encode for cardiac ion channels. In animal studies, blockade of the calcium-independent 4-aminopyridine-sensitive transient outward potassium current (Ito) results in surface ECG findings of elevated, downsloping ST-segments[19] due to greater prolongation of the epicardial action potential compared with the endocardium (which lacks a plateau phase). Loss of the action potential plateau (or dome) in the epicardium but not the endocardium would be expected to cause ST-segment elevation. Because loss of the dome is caused by an outward shift in the balance of currents active at the end of phase 1 of the action potential (principally INa and ICa), autonomic neurotransmitters like acetylcholine facilitate loss of the action potential dome by suppressing the calcium current and augmenting the potassium current. Beta-adrenergic agonists (i.e. isoproterenol, dobutamine) restore the dome by augmenting ICa[20–22]. Sodium channel blockers also facilitate loss of the canine right ventricular action potential dome as a result of a negative shift in the voltage at which phase 1 begins[23,24]. Hence, INa, ICa, and INa would be good candidate genes to study. Since INa (SCN5A) has been shown to cause VT/VF in humans (in the long QT syndrome)[25–27] this gene certainly is worthy of study.

Recently, we reported the findings of six families and several sporadic cases of Brugada syndrome[28]. The families were initially studied by linkage analysis using markers to the known ARVD loci and linkage was
excluded. More recently, seven other families have also excluded linkage to these loci, thus suggesting that the families recruited with the Brugada syndrome to date may indeed have an entity distinct from ARVD. Candidate gene screening using the mutation analysis approach of single strand conformation polymorphism (SSCP) analysis and DNA sequencing was performed and SCN5A was chosen for study. In three families, mutations in SCN5A were identified including: (1) a missense mutation (C-to-T base substitution) causing a substitution of a highly conserved threonine by methionine at codon 1620 (T1620M) in the extracellular loop between transmembrane segments S3 and S4 of domain IV (DIVS3 – DIVS4), an area important for coupling of channel activation to fast inactivation; (2) a two nucleotide insertion (AA) which disrupts the splice-donor sequence of intron 7 of SCN5A; and (3) a single nucleotide deletion (A) at codon 1397 which results in an in-frame stop codon that eliminates DIIIS6, DIVS1 – DIVS6, and the carboxy-terminus of SCN5A. Not all the individuals had the typical electrocardiogram at baseline. The diagnosis, for genetic purposes, was based on electrocardiographic changes after the administration of intravenous ajmaline. This test proved 100% sensitive and specific, as all the patients who developed ST segment elevation had the mutation in the subsequent genetic analysis. Likewise, none of the individuals without electrocardiographic abnormalities had the genetic abnormality (Fig. 3).

Biophysical analysis of the mutants in Xenopus oocytes demonstrated a reduction in the number of functional sodium channels in both the splicing mutation and the one-nucleotide deletion mutation, which should promote development of reentrant arrhythmias. In the missense mutation, sodium channels recover from inactivation more rapidly than normal. In this case, the presence of both normal and mutant channels in the same tissue would promote heterogeneity of the
refractory period, a well-established mechanism of arrhythmogenesis. Inhibition of the sodium channel $I_{Na}$ current causes heterogeneous loss of the action potential dome in the right ventricular epicardium, leading to a marked dispersion of depolarization and refractoriness, an ideal substrate for development of reentrant arrhythmias. Phase 2 reentry produced by the same substrate is believed to provide the premature beat necessary for initiation of the VT and VF responsible for symptoms in these patients.

Mutations in the $SCN5A$ gene were previously shown to be the cause of LQT3, a form of Romano–Ward long QT syndrome$^{[25]}$. The differences in the clinical findings between LQT3 and Brugada syndrome occur due to the different biophysical results based on the position of the mutations within the gene. Unlike the Brugada syndrome, LQT3 occurs due to an augmentation of late $I_{Na}$ carried by $SCN5A$ channels.

**Incidence and distribution**

Because the syndrome has been identified only recently, it is difficult to ascertain its incidence and distribution in the world. When we analyse the data from the different published studies, the disease is responsible for $4\%$ to $12\%$ of unexpected sudden deaths, and for up to $50\%$ of all sudden death in patients with an apparently normal heart. The incidence may even be larger in the younger population. Indeed, this syndrome is the most common cause of sudden death in individuals younger than 50 in South Africa with no underlying cardiac disease$^{[13]}$. Based on a database of 48 individuals who died suddenly without evidence of structural heart disease, $57\%$ had the right bundle branch block pattern with ST elevation in leads V$_1$ to V$_3$. It is striking that all patients who had this pattern were male. Ten of the 48 patients were female, six of whom had idiopathic VF, yet they had no evidence of an abnormal ECG pattern. Therefore, it should be emphasized that the syndrome affects male patients almost exclusively. It should also be stressed that the physician plays an important role in identifying this syndrome to estimate its real prevalence. The syndrome may possibly be more prevalent, but the magnitude of it has yet to be determined. The difficulty in estimating the incidence and prevalence of the disease becomes even more complicated as we unravel the syndrome and some of its peculiar characteristics. It is a syndrome that in some cases presents with a typical ECG, but in other cases the presentation is concealed or intermittent, meaning that the ECG is normal at certain times. Several studies have provided important clues in identifying these concealed forms; ajmaline continues to be the best medication to unmask them. Procainamide and flecainide while useful, are less sensitive. Unfortunately, these tests at present are not utilized routinely. Without a doubt this is one of the reasons why the prevalence of the disease is probably underestimated. Only prospective studies will be able to give an exact answer.

A prospective study of an adult Japanese population (22 027 subjects) showed that $0\%$ of ECGs were compatible with the syndrome (12 subjects)$^{[26]}$. A second study of adults in Awa (Japan) showed an incidence of $0\%$ (66 cases out of 10 420)$^{[30]}$. However, a third study in children from Japan showed that only $0\%$ (one case in 163 110) of ECGs were compatible with the syndrome$^{[31]}$. These results suggest that the syndrome manifests primarily during adulthood, which is in concordance with the mean age of sudden death victims (35 to 40 years). The youngest patient in our database was 2 years old at the time of sudden death, whereas the oldest was 74. The ECG is very variable over time, with periods in which it is clearly normal. This fact makes it very difficult to estimate the incidence of the disease in the general population.

**Electrophysiological substrate**

Patients with this ECG pattern clearly have a proclivity to develop rapid polymorphic VT/VF. Before the episode, the patients present with regular sinus rhythm, with no changes in the QT interval. In some rare cases it seems that the ST segment elevation increases just prior to the onset of polymorphic VT. We have observed the triggering of the arrhythmia after a short–long–short cycle in only two cases. It is evident that these patients have an electrophysiological substrate for VT/VF as shown by the fact that the majority of patients who have the syndrome have inducible polymorphic VT/VF and a positive signal-averaged ECG. This is despite their normal cardiac function and lack of gross structural cardiac abnormalities. When comparing patients with abnormal ECG patterns with those who have normal ECGs in the SUDS study$^{[13]}$, VF could be induced in 93% of patients with the Brugada pattern, but only in 11% of those with a normal ECG. Patients with the syndrome also had a prolonged His–Purkinje conduction time (H–V interval). Whether this abnormality contributed to VF occurrence is unclear.

**Triggering mechanisms**

In a recent publication from Japan, it has been suggested that in some cases the beginning of the arrhythmia is bradycardia-dependent$^{[32]}$. This fact could explain the higher incidence of sudden death at night in individuals with the syndrome. Proclemer et al. published one case of a patient in whom the episodes of ventricular arrhythmias could only be controlled during fast ventricular pacing$^{[33]}$. However, not all the patients die at night and not all the cases are controlled with fast ventricular pacing. Patients from South Asia who have the ECG pattern usually develop VT/VF during sleep at night. The episodes that were detected by the implanted cardioverter-defibrillator in these patients show no
evidence of bradycardia-dependence and in many cases the rate preceding the VF episode was relatively fast.

**Spontaneous termination of VF**

Bjerregaard et al. were the first to report a patient with the Brugada syndrome who developed a spontaneously terminating episode detected by ECG monitoring\[2\]. This patient had a typical ECG pattern with a right bundle branch block-like QRS and ST elevation from V₁ to V₃. In patients with the syndrome implanted with an automatic cardioverter–defibrillator with electrogram storage, many spontaneous episodes of VT/VF have now become available. Many of the episodes are self-terminating. This observation helps explain why many patients present with syncope or wake up at night after episodes of agonal respiration or seizure caused by the arrhythmia.

**Pathological findings**

At present we have pathological data on 22 patients with the syndrome. Seventeen cases involved endomyocardial biopsy and the other five are from autopsies. None of the patients have any structural abnormality\[34\]. Despite the suggestion of some authors\[35,36\], there is no indication that the disease is a form of arrhythmogenic right ventricular dysplasia. Other non-invasive studies, including nuclear magnetic resonance and echocardiography (available in the majority of the patients), are normal.

**Clinical manifestations**

The complete syndrome is characterized by episodes of rapid polymorphic VT in patients with an ECG pattern of right bundle branch block and ST segment elevation in leads V₁ to V₃. The syndrome is manifested by episodes of polymorphic VT/VF. When the episode terminates spontaneously the patient experiences a syncopal attack. When the episode is sustained, full blown cardiac arrest and eventually sudden death occur. Thus, these manifestations can range widely: at the one end of the spectrum we have asymptomatic individuals and at the other those who die suddenly. Other symptoms include seizures, agonal respiration, and — for those patients who suffer an episode at night during sleep — laboured respiration, agitation, loss of urinary bladder control, and not uncommonly recent memory loss (perhaps due to brain anoxia). Many patients who have the disease can appear to be otherwise very healthy and active, vigorously engaging in exertional activity or exercise. Physical examination is almost always normal. Physicians who first investigate these patients have a strong tendency to believe that the syncopal attacks are benign and of vasovagal origin. Many patients have undergone a tilt-table test which was positive, and have subsequently died suddenly. As seen in other clinical–electrocardiographic syndromes, there are different presentations of the disease.

There exist asymptomatic individuals in whom the ECG is atypical during routine examination. This ECG cannot be distinguished from that of symptomatic patients. In other patients, the characteristic ECG is recorded during screening after the sudden death of a family member with the disease. On the other hand, there is the group of symptomatic patients who have been diagnosed as suffering syncopal episodes of unknown cause, or vasovagal origin, or have a diagnosis of idiopathic ventricular fibrillation. Some of these patients are diagnosed at follow-up, when the ECG changes spontaneously from normal to the pattern typical of the syndrome. This is also the case for those individuals in whom the disease is unmasked by the administration of an antiarrhythmic drug given for other arrhythmias, for instance atrial fibrillation.

Recent studies indicate that patients displaying the ECG characteristics of the syndrome have an incidence of arrhythmia and sudden death similar to patients in whom the ECG manifestation must be unmasked with a sodium channel blocker. Up to 40% of individuals will develop a new or a first episode of polymorphic VT or sudden death during a 2–3 year follow-up.

**Diagnosis**

The diagnosis of the syndrome is easily obtained by electrocardiography as long as the patient presents the typical ECG pattern and there is a history of aborted sudden death or synapses caused by a polymorphic VT. It is difficult to forget such an ECG. The characteristic pattern is ST segment elevation in V₁ to V₃ with right bundle branch block. The ST changes are different from those observed in acute sepsal ischaemia, pericarditis, ventricular aneurysm or in some normal variants such as early repolarization. Some ECGs are not as characteristic, and are only recognised by a physician who has the syndrome in mind. There are also many patients with a normal ECG in whom the syndrome can only be recognised a posteriori, when the typical pattern appears in a follow-up ECG or after the administration of ajmaline, procainamide or flecaainide.

It is possible that the differences in the electrocardiographic patterns depend on the genetic abnormality. This is the case in other genetic diseases, such as the long QT syndrome\[3\]. The mutations that have been discovered in the two families give proof of this fact in the Brugada syndrome: their ECGs are similar, but not identical. Even though in both cases the affected gene is the same, the exact mutation is different. It will be necessary to identify more mutations and make a close genotype–phenotype correlation to establish the links. However, we cannot forget the great variability of the ECG in this syndrome, something which will certainly not facilitate analysis.
Additional diagnostic problems are caused by the changes in the ECG induced by the autonomic system and by antiarrhythmic drugs. The study by Myazaki et al. was the first to show the variability of the ECG pattern in the syndrome. Despite the fact that we described the syndrome as a persistent ECG pattern, we soon recognised that it is variable over time, depending on the autonomic interaction and the administration of antiarrhythmic drugs. Adrenergic stimulation decreases ST segment elevation (Fig. 4) while vagal stimulation worsens it. The administration of class Ia, Ic and III drugs increase ST segment elevation. Exercise decreases ST segment elevation in some patients but increases it in others. The changes in heart rate induced by atrial pacing are accompanied by changes in the degree of ST segment elevation. When the heart rate decreases, the ST segment elevation increases and when the heart rate increases the ST segment elevation decreases.

Patients with syncope of unknown cause must be challenged with antiarrhythmic drugs in order to exclude the possibility of this syndrome as a cause of ventricular arrhythmias and syncope.

**Cellular and ionic mechanisms**

**ST segment elevation**

The mechanisms responsible for ST segment elevation and the genesis of VT/VF in the Brugada syndrome are slowly coming into better focus. The available data suggest that a downsloping ST segment elevation observed in the right precordial leads of patients afflicted with the Brugada syndrome is the result of depression or loss of the action potential dome in right ventricular epicardium. It is now well established that a transient outward current (I_{to})-mediated phase 1 is much more prominent in the epicardium than in the endocardium in canine, feline, rabbit, and human ventricular cells. The spike and dome morphology of the epicardial action potential is absent in neonates and gradually appears over the first few months of life, reaching a plateau between 10 and 20 weeks of age in the dog. The progressive development of the notch parallels the appearance of I_{to}. Age-related changes in

![Figure 4](https://example.com/figure4.png)

*Figure 4* The different panels illustrate the effects of ajmaline and isoprenaline administration on ST segment elevation in lead V2 and the inducibility of arrhythmias in a patient with the syndrome. During control, ventricular stimulation using two premature extrastimuli induces a polymorphic ventricular tachycardia. After ajmaline administration, ST segment elevation increases and two premature extrastimuli induced a slower ventricular tachycardia. After isoprenaline administration, ST segment elevation decreases and no arrhythmias could be induced using up to three premature beats. Numbers indicate coupling intervals of the premature beats.
the manifestation of the spike and dome have been described in human atrial and canine Purkinje tissues and rat ventricular cells. The extent to which \( I_{\text{to}} \), a calcium-activated component of the transient outward current, differs among the three ventricular myocardial cell types is not known. \( I_{\text{to}} \), initially ascribed to a \( K^+ \) current, is believed to be largely due to a calcium-activated chloride current \( (I_{\text{Cl(Ca)}}) \). Recent studies also indicate the presence of a much larger \( I_{\text{to}} \)-mediated notch in right vs left canine ventricular epicardium.

A prominent action potential notch in the right ventricular epicardium but not endocardium gives rise to a transmural voltage gradient during ventricular activation, that is responsible for the inscription of the J wave or J point elevation in the ECG. A prominent \( I_{\text{to}} \)-mediated notch also predisposes canine right ventricular epicardium to all-or-nothing repolarization under a variety of conditions. Under normal conditions, developing inward current (principally calcium current \( (I_{\text{Ca}}) \)) overcomes the outward current (principally \( I_{\text{to}} \)) at the end of phase 1, thus producing a secondary depolarization that gives rise to the dome of the epicardial action potential. Under pathophysiological conditions, the balance of current at the end of phase 1 of the action potential can change, thus leading to important alterations in action potential morphology and the cycling of cellular calcium. The balance of current active at the end of phase 1 can easily shift outward causing a loss of the action potential dome. Much of the characterization of this phenomenon has involved studies of canine ventricular epicardium. Under ischaemic conditions and in response to a variety of drugs, including sodium and calcium channel blockers, canine ventricular epicardium exhibits an all-or-nothing repolarization as a result of the rebalancing of currents flowing at the end of phase 1 of the action potential. Failure of the dome to develop occurs when the outward currents (principally \( I_{\text{to}} \)) overwhelm the inward currents (chiefly \( I_{\text{Ca}} \), resulting in a marked (40–70%) abbreviation of the action potential. The dome can be restored by inhibition of \( I_{\text{to}} \) with 4-AP, supporting the hypothesis that a prominent \( I_{\text{to}} \) facilitates loss of the action potential dome. We with 4-AP, supporting the hypothesis that a prominent calcium-activated chloride current \( (I_{\text{Cl(Ca)}}) \). Recent studies also indicate the presence of a much larger \( I_{\text{to}} \)-mediated notch in right vs left canine ventricular epicardium.

### Relationship with other syndromes and the pseudo-syndrome

Other diseases may result in ECG manifestations similar to the Brugada syndrome. For instance, it is interesting to observe the figures published from Buenos Aires in 1982. In patients with Chagas’ disease, Chiale et al. showed that the intravenous administration of ajmaline has uncovered latent conduction disturbances, but also ‘latent disease’. In patients with positive serology, severe conduction disturbances occurred in one third after the administration of intravenous ajmaline. In 8% of patients ventricular arrhythmias were observed and in 7% elevation of the ST segment in the right precordial leads. The question arises of the relationship between Chagas’ disease and Brugada syndrome in these patients. Other conditions may result in ECGs simulating Brugada syndrome: Steinert’s disease, pectus excavatum, and mediastinal tumours. These should be excluded before diagnosing Brugada syndrome.

### Electrophysiological and haemodynamic findings

During invasive electrophysiological investigations, sinus node function has been normal in the large majority of the patients. However, isolated patients have manifest sinus node disease and are pacemaker dependent. As already discussed, about 10% of patients have paroxysmal atrial fibrillation. There are no detailed studies on the ability to induce this arrhythmia by programmed electrical stimulation.

All published studies agree on the inducibility of polymorphic VT by programmed electrical stimulation in symptomatic patients. About 80% of them are inducible by giving one or two ventricular premature beats during ventricular pacing. In some patients three premature stimuli are required. The induced arrhythmia is sustained in almost all cases, and results in

 Europace, Vol. 1, July 1999
haemodynamic collapse which has to be terminated by an external DC shock. It may be a criticism that polymorphic VT or ventricular fibrillation induced by programmed stimulation is a non-specific finding, because these arrhythmias can sometimes be induced in patients with a normal heart. There exist, however, major differences between the two situations: (1) the clinical context, with symptomatic Brugada syndrome patients who have suffered spontaneous ventricular arrhythmias; (2) patients who have inductible sustained polymorphic ventricular arrhythmia in the Brugada syndrome (80%); this is not comparable with individuals without the syndrome where a sustained polymorphic VT or ventricular fibrillation is only exceptionally induced.

The same studies coincide in the frequent finding of conduction disturbances in patients with the disease. The H-V interval is prolonged in about half of the patients. The prolongation is not marked, rarely exceeding 70 ms, but is clearly abnormal in this population with an average age of 40 years. The H-V prolongation explains the slight prolongation of the P-R interval during sinus rhythm.

Haemodynamic studies in patients who underwent right and left heart catheterization were found to be normal. In SUDS patients with or without the typical ECG also had normal findings. The coronary arteries, the right and left ventricular function and contractility are all normal.

Prognosis and treatment

This syndrome has a very poor prognosis when left untreated: one third of patients who suffer syncopal episodes, or who are resuscitated from near-sudden death develop further episodes of polymorphic VT within 2 years. Unfortunately, the prognosis of asymptomatic individuals with a typical ECG is also poor. In spite of not having any previous symptoms, one third of these individuals also present a first polymorphic VT or ventricular fibrillation within 2 years of follow-up. The observations on the prognosis of patients with the Brugada syndrome from Europe is virtually identical to that for SUDS patients in Thailand, who show an abnormal ECG pattern. The cumulative proportion of VF or cardiac arrest occurred in approximately 60% of the patients within 1 year and 40% were likely to die suddenly if untreated. Furthermore, patients, who have recurrent events but do not die face the risk of having anoxic encephalopathy, in mild to disabling forms.

These data are of extreme importance for the delineation of treatment policies of these patients. Because antiarrhythmic drugs (amiodarone or beta-blockers) do not protect against sudden cardiac death, the only available treatment is the implantable cardioverter–defibrillator. This device effectively recognises and treats the ventricular arrhythmias. When provided with the implantable defibrillator, total mortality in patients with the Brugada syndrome has been 0% with up to 10 years follow-up. These results are not surprising. These patients are young and usually devoid of other diseases. Because the heart is structurally normal, and there is no coronary artery disease, these patients do not die from heart failure or complications of ischaemic events. Thus, they are the most ideal candidates for treatment with an implantable cardioverter–defibrillator. All symptomatic patients should receive this device.

On the other hand, major concerns arise in the treatment of asymptomatic individuals. Of the six asymptomatic patients dying suddenly in our previous study, four patients were members of affected families, but two were sporadic cases. Data from electrophysiological investigations did not help us to predict prognosis, although this may be caused by a type II error (an insufficient number of patients to prove a statistically significant difference). At present, we believe four different groups of patients can be distinguished: (1) symptomatic individuals with the disease require an implantable cardioverter–defibrillator. Patients with transient normalization of the ECG during follow-up have the same prognosis as patients who have a permanently abnormal ECG (unpublished observations); (2) asymptomatic patients with a family history of sudden death, a prolonged H-V interval and inducible polymorphic VT or ventricular fibrillation who also require an implantable defibrillator; (3) asymptomatic individuals, who have no family history of sudden death but also show inducible sustained polymorphic ventricular arrhythmias, also require a defibrillator; and (4) asymptomatic individuals without a family history of sudden death and no inducible ventricular arrhythmias should not be treated but followed-up carefully for development of symptoms suggesting arrhythmias (particularly syncope). It must be appreciated, however, that these recommendations may rapidly change depending upon the availability of new data.

Conclusions

The syndrome of right bundle branch block, ST segment elevation from V₁ to V₃ and sudden death is a new entity. This disease is genetically determined and it is different from both the long QT syndrome and right ventricular dysplasia. The incidence of sudden death in this syndrome is very high and, at present, sudden death can only be prevented by implanting a cardioverter–defibrillator. The ECG is a marker of sudden death in symptomatic, but also asymptomatic individuals.

References


