Management of Asymptomatic Patients with the Brugada Syndrome

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Patients with the Brugada syndrome are at high risk for sudden cardiac death. In this article, the determinants of occurrence of sudden cardiac death in asymptomatic individuals with an electrocardiogram diagnostic of the Brugada syndrome are reviewed.

Patients with an abnormal electrocardiographic pattern of right bundle branch block and ST segment elevation in the right precordial leads, compatible with the diagnosis of Brugada syndrome (1) have a high risk of sudden cardiac death (2-3). Patients in whom the diagnosis is made after an episode of aborted sudden death have a very high recurrence rate and at present an implantable defibrillator is mandatory in them. However, more and more patients are identified with the diagnostic electrocardiogram but have no previous history of sudden cardiac death, and their prognosis is still a matter of discussion. In this article the prognostic value of clinical and electrocardiographic variables in 547 individuals with an electrocardiogram compatible with Brugada syndrome are reviewed.

During a mean follow-up of 24±32 months, 44 individuals (8%) suffered an event (sudden cardiac death or documented ventricular fibrillation). The strongest predictor of outcome in patients with an electrocardiogram leading to a diagnosis of the Brugada syndrome and no previous cardiac arrest is inducibility during programmed ventricular stimulation. Over the course of an electrophysiological study 40% of individuals were inducible. Inducible individuals have an 8 times higher risk of suffering from sudden death or ventricular fibrillation within the subsequent 2 years as compared to non-inducible ones. A spontaneously abnormal electrocardiogram was the second best predictor of outcome with a 7 times greater risk of arrhythmic events as compared to individuals in whom the electrocardiogram was observed only after antiarrhythmic drug challenge. The male sex carries 5 times the risk of the female sex. The next best predictor was a previous history of syncope.

The lowest risk group can be defined as the one whose individuals have no syncopal episodes, and whose electrocardiogram reveals the Brugada syndrome only after an antiarrhythmic drug challenge and who display non-inducibility during programmed ventricular stimulation (0.5% incidence of events). The highest risk group presents a combination of a previous history of syncope, a spontaneously abnormal electrocardiogram and inducible sustained arrhythmias during programmed ventricular stimulation (27,2% incidence of events).

In patients with the Brugada electrocardiogram and no previous cardiac arrest, inducibility during programmed ventricular stimulation is the best technique for risk stratification. That justifies the use of this technique in all individuals with this disease.

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Molecular Biology of Sodium Channels and Their Role in Cardiac Arrhythmias

The sodium channel is an integral membrane protein that plays a central role in conduction of the cardiac impulse in working myocardial cells of the atrium and ventricle, and in cells of the His-Purkinje system.

The channel has two fundamental properties:

Conduction -- the mechanism of the selective movement of sodium ions across the pore in the cell membrane
Gating -- the mechanisms that open and close the sodium channel pore in response to a change in membrane potential

Hodgkin and Huxley described the functional properties of the neuronal channel nearly 50 years ago. (1) They established that conductance was time invariant and that the action potential was generated by the gating of the channels with fixed conductance and selective permeability to a singe ion, for example Na, K, Ca or Cl-. They proposed that gating involved transitions between three groups of states: resting, open and inactivated.

Depolarization (a reduction in the degree of electronegativity in a resting cell) initiates an inward sodium current by activating "m gates" that rapidly change the sodium-channel state from closed resting to open. The same depolarizing stimulus, however, also initiates a slower inactivation mechanism called "h gates" that closes sodium channels by favoring the closed inactivated state.

Because sodium ions can cross the membrane only when both the m and h gates are open, closure of either channel gate blocks movement of sodium ions across the cell membrane. During inactivation, the sodium channel is converted to a refractory state. The membrane must repolarize (return to resting potential) before a second conductance increase can occur. The channel then assumes its resting state with closed activation and open inactivation gates. Subsequent studies have confirmed that these essential features of sodium channel gating exist in most excitable cells, including the heart.

Over the past decade, the techniques of molecular genetics and biophysics have provided remarkable advances in our understanding of sodium channel structure and the relationship of function to structure. These new developments suggest that electrocardiographic abnormalities and arrhythmias cannot only arise from physiological and metabolic causes, but may also arise from altered gene expression. This has provided us with a fundamental understanding of the inherited cardiac arrhythmias. These new techniques also may provide clues to the basis of more common arrhythmias and apparently idiosyncratic drug reactions.

Role of the Cardiac Sodium Channel in Genesis of Inherited Cardiac Arrhythmias

The cardiac action potential is orchestrated by the sequential changes of the permeability of specific ion channels. The sodium channel makes a major contribution to two phases of the action potential:

the period of rapid depolarization (phase zero)
the plateau of the action potential (phase two)
Spontaneous secondary depolarizations during the plateau phase can trigger arrhythmia. Once triggered, arrhythmia is maintained by a regenerative circuit of electrical activity around relatively inexcitable tissue. This phenomenon is known as reentry. The development of multiple reentrant circuits within the heart can cause ventricular fibrillation, the arrhythmia of sudden death. Mutations in the sodium channel contribute to the genesis of cardiac arrhythmias by one of two mechanisms:

Loss of function mutations that result in the synthesis of nonfunctional channels or channels that inactivate rapidly. These mutations lead to a reduction in available sodium current during phase zero of the action potentials. This causes conduction abnormalities.
Gain of function mutations that result in slowing or an increase in the reversibility of inactivation and an increase in the late component of sodium current. This prolongs the action potential duration and the QT interval on the ECG.
Genetic defects in membrane ion channels can disrupt the delicate balance of dynamic interactions between the ion channels and the cellular environment, leading to altered cell function. A single mutation in the cardiac sodium channel is sufficient to cause both the Brugada and Long-QT syndrome phenotypes. The Brugada syndrome is characterized by ST segment elevation in the ECG, while LQTS is marked by a prolonged QT interval.

The defect results in a loss of Na+ channel function that is consistent with the Brugada phenotype, but contrasts with a gain of function typically associated with LQTS. No matter the mechanism, the end result in both LQTS and Brugada syndrome is the same: the creation of a voltage gradient at the ventricular level that is the substrate for malignant arrhythmias and sudden death. In patients with the Brugada syndrome, a very rapid polymorphic tachycardia develops, causing them to pass out. In some cases sudden death is the first symptom.

Loss of Function Mutations: Brugada Syndrome

In 1992, Brugada and Brugada (2) described a syndrome of recurrent episodes of aborted sudden death, right bundle branch block, persistent ST segment elevation in leads V1 to V3 and normal QT interval in 8 patients with structurally normal hearts. The index arrhythmia was polymorphic ventricular tachycardia. A similar arrhythmia was inducible at electrophysiology in four patients by programmed stimulation. The HV interval was prolonged in these patients. Follow-up of larger groups of patients identified additional features of the syndrome (3, 4) Transient normalizations of the ECG may be observed. In patients showing normalization, the characteristic ECG pattern could be unmasked by administration of the sodium channel blockers ajmaline, procainamide and flecainide (5). The case fatality rate was high.

Over a mean follow-up of 3 years, mortality was 31 percent in patients receiving no therapy, 36 percent in patients treated with amiodarone and/or b-adrenergic blockers and 0 percent in patients receiving an implantable defibrillator. In the 1980s, the Centers for Disease Control and Prevention reported a high incidence of sudden death

among young males of Southeast Asian descent. Nademanee et al (6) showed that a subgroup of those individuals had the ECG features characteristic of the Brugada syndrome.

Chen et al (7) used the candidate gene approach to examine six families with Brugada syndrome. In one family, two C to T base substitutions were identified in the sodium channel gene SCN5A. One substitution, an arginine by a trypotophan at codon 1232 (R1232W) was located in the S1-S2 extracellular loop of domain III. This is believed to be a rare polymorphism. The second substitution was of a highly conserved threonine by methionine at codon 1620 (T1620M), also located in an extracellular loop, S3-S4, of domain 4. When expressed in frog oocytes, the R1232W/ T1620M gene gave sodium currents with half-potential for inactivation shifted to more positive potential. The shift is increased when the double mutant is coexpressed with the b subunit. When expressed in mammalian cells (e.g., HEK 293) the T1620M mutation produced sodium currents with accelerated decay kinetics. Raising the temperature from 22 to 32 degrees C markedly increased the rate of inactivation (8). In another family a two-nucleotide insertion interrupted the splice donor sequence of an intron. In another family, a single nucleotide deflection produced a stop codon, resulting in the elimination of DIII/S6 and DIV S1-S6. In approximately 50 percent of patients with Brugada syndrome, no genetic defect has been identified.

Yan and Antzelevitch (9) have proposed a mechanism for the ST segment shift and the occurrence of ventricular fibrillation in Brugada syndrome. The ST segment elevation is the result of an epicardium to endocardium voltage gradient during the early repolarization phases of the action potential. The transient outward current ITO is the dominant outward current during this phase of the action potential. ITO magnitude is greater in epicardial myocytes than in endocardial myocytes, and greater in the right ventricle than in the left ventricle. A reduction in the size of the balancing inward sodium current would produce the most marked reduction in the action potential duration in the epicardium myocytes of the right ventricle, and would produce the epicardial to endocardial voltage gradient. Brugada syndrome-associated mutations reduce the number of functional sodium channels or accelerate their inactivation. The proposed mechanism is consistent with observations that the characteristic ECG pattern may be precipitated in patients with the syndrome by administration of sodium channel blocking drugs. An increase in the magnitude of the transient inward potassium ITO would have a similar effect, contributing to the dispersion of repolarization between epicardial and endocardial myocytes. However, this mechanism has not been identified in Brugada syndrome patients to date.

Loss of Function Mutations: Progressive Conduction System Disease

Lenegre (10) and Lev et al (11) described a progressive conduction system disease with right or left bundle branch block leading to complete heart block. Middle-aged or elderly patients usually present with syncope or complete heart block. Histologically, the heart demonstrates fibrosis of the conduction system. However, similar fibrosis may be observed in patients without conduction system disease. Recently Schott et al described two families with syncope and right or left bundle branch block (12). The defect mapped to the locus of the sodium channel gene SCN5A. There was a donor splicing in intron 22 that produced a sodium channel lacking DIII S4. Although no functional data were presented, one would predict that the mutant channel would be nonfunctional. The reason that this defect would present only later in life is not clear. The conduction defect may require the presence of the mutant channel and the structural changes that occur with aging for its expression. In principle, a mutation that results in the decrease of the number of functional channels also may cause Brugada syndrome. However, the ECG changes characteristic of that syndrome were not identified in either family.

Gain of Function Mutations: LQT3

The syndrome of familial QT interval prolongation, polymorphic ventricular tachycardia (VT), and sudden death (LQTS) has been linked to inherited defects of membrane ion channels or their regulatory subunits. LQT1 and LQT2 are caused by defects in potassium-channel genes (KVLQT1 and HERG) involved in the repolarization phase of the action potential. LQT3 is caused by a defective sodium-channel gene, SCN5A. A common SCN5A mutation involves the deletion of three amino acids (KPQ) in the DIII-DIV linker loop. This loop is known to regulate inactivation. The mutant sodium channel fails to become completely inactivated. This results in sustained depolarization and prolonged inward current that lengthens the cardiac action potential, and thus the QT interval. The ion channel defect maps to a gene that encodes the sodium channel SCN5A in 10 to 25 percent of patients with LQTS. The subgroup of patients with sodium channel defects (LQT3) presents later in life than those with potassium channel defects. However, the initial event is more likely to be fatal (13.) Patients with LQT3 tend to have a resting bradycardia. However, shortening of the QT interval in response to exercise is exaggerated. Attacks of ventricular tachycardia or cardiac arrest are more likely to occur at rest or during sleep in LQT3. Sodium channel blockers, for example, mexiletine and flecainide, shorten the QT interval in LQT3. (14, 15) However, they have not been shown to prevent arrhythmia recurrence in LQT3.

Expression of both the wild-type and LQT3 mutant sodium channels in the frog oocyte and mammalian cells have permitted exploration of the molecular basis of LQT3. At most membrane potentials, sodium channels open once in response to depolarization and close by inactivation. The inactivation process is usually not reversible unless

repolarization occurs. In fewer than 5 percent of depolarizations, sodium channels may re-open at a later time during depolarization only to close again by inactivation. As a rare event (approximately .1 percent of depolarizations), the inactivation process may fail altogether and the sodium channel may open repetitively for hundreds of milliseconds. Those late components of sodium current contribute inward depolarizing current during the plateau of the action potential, prolonging its function. Several sodium channel mutations in the cytoplasmic loop between domains III and IV (IDIII/IV), consisting of single base substitutions, deletions or insertions, decrease the stability of inactivation and produce an increase in the size of the late components of sodium current. (16) Other mutations slow the rate of inactivation by prolongation of the duration of the individual channel openings. (17, 18)

Marked prolongation of the action potential alters the voltage-time trajectory of the action potential such that repetitive depolarizations occur at the level of the action potential plateau. These depolarizations are termed early afterdepolarizations. When the gating defects of LQT3 are incorporated into a computer model of the cardiac action potential, prolongation and early afterdepolarizations could be reproduced (19). Early afterdepolarizations are believed to initiate polymorphic VT and ventricular fibrillation in LQTS. These arrhythmias may be sustained by reentry. The bradycardia and the frequency dependence of the QT interval in LQT3 have not been adequately explained to date.

The sodium channel blocking drugs, lidocaine, mexiletine and flecainide selectively block the late component of sodium current in wild-type and LQT3 mutant channels (20, 21) The selective blockade of the late current could account for the QT interval shortening without QRS prolongation observed with mexiletine and flecainide.

The Overlap Syndrome

As genetic studies are applied to larger groups of patients, it is becoming clear that there may be considerable overlap in syndromes associated with sodium channel mutations. Bezzina et al (22) described an eight-generation kindred with a high incidence of nocturnal sudden death, QT interval prolongation and ECG changes characteristic of Brugada syndrome. The molecular defect was the insertion of an aspartate residue in the carboxy terminal of the sodium channel resulting in maintained depolarization and an increase in inactivation (23, 24). The former effect would prolong the action potential duration and the QT interval; the latter effect would reduce the available sodium current during phase one of the action potential.

As we have discussed above, flecainide blocks the late component of sodium current and has been proposed as a treatment for LQTS. Priori et al (25) administered flecainide intravenously to 13 patients with LQT3. As expected, the QT interval was shortened. However, in six patients, concomitant ST-segment elevation in leads VI to V3 characteristic of Brugada syndrome was observed. Those observations suggest that the relationship between the underlying gene defect and the phenotype is dynamic. The phenotype will depend on the ionic current that makes contributions to the action potential under specific circumstances.

Summary

The cardiac sodium channel is a complex multimeric protein consisting of an a subunit and a regulatory b1 subunit. The basic properties of ion conduction and gating reside in the a subunit. The use of specific toxins and site-directed mutogenesis has localized the channel domains that are responsible for ion conduction and inactivation. Mutations in the sodium channel gene result in the long QT and Brugada syndromes. These syndromes are associated with a high fatality rate. The implantable defibrillator is the most effective form of treatment for either syndrome.

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Review Article

Brugada Syndrome:

The Syndrome of Right Bundle Branch Block, ST segment Elevation in V_1 to V_3 and Sudden Death

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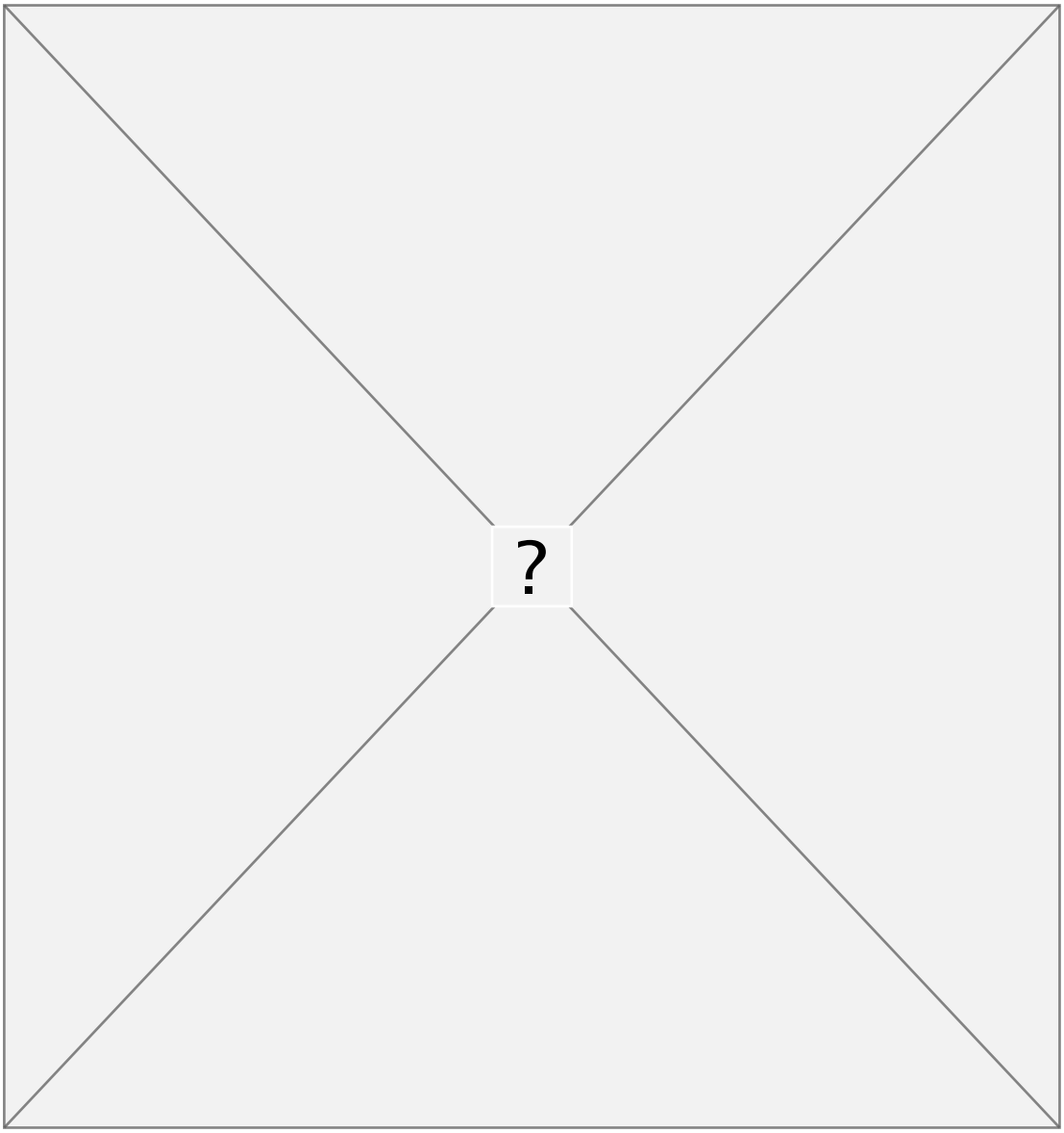
Introduction

In 1992 a new syndrome consisting of syncopal episodes and/or sudden death in patients with a structurally normal heart and a characteristic electrocardiogram (ECG) with a pattern of right bundle branch block with an ST segment elevation in leads V1 to V3 was described [1] In 1998 the poor prognosis of patients with the syndrome not receiving an implantable defibrillator was reported [2],[3] In 1998 the genetic nature of the disease and its assotiation to a mutation in the cardiac sodium channel gene was described [4] . Because the diagnosis is easily made by means of the ECG, an increasing number of patients with the ECG pattern are being identified worldwide. In this article we will review our present knowledge concerning patients with the classical ECG pattern of the disease.

In the Brugada syndrome, the diagnosis is based on the history of aborted sudden death with the typical electrocardiographic pattern of ST segment elevation in leads V1-V3, with or without right bundle branch block [1] (Fig. 1). In some cases, however, the diagnosis is different because some individuals present with an abnormal electrocardiogram but are completely asymptomatic or there is a history of sudden death in the family and the electrocardiographic criteria are observed.



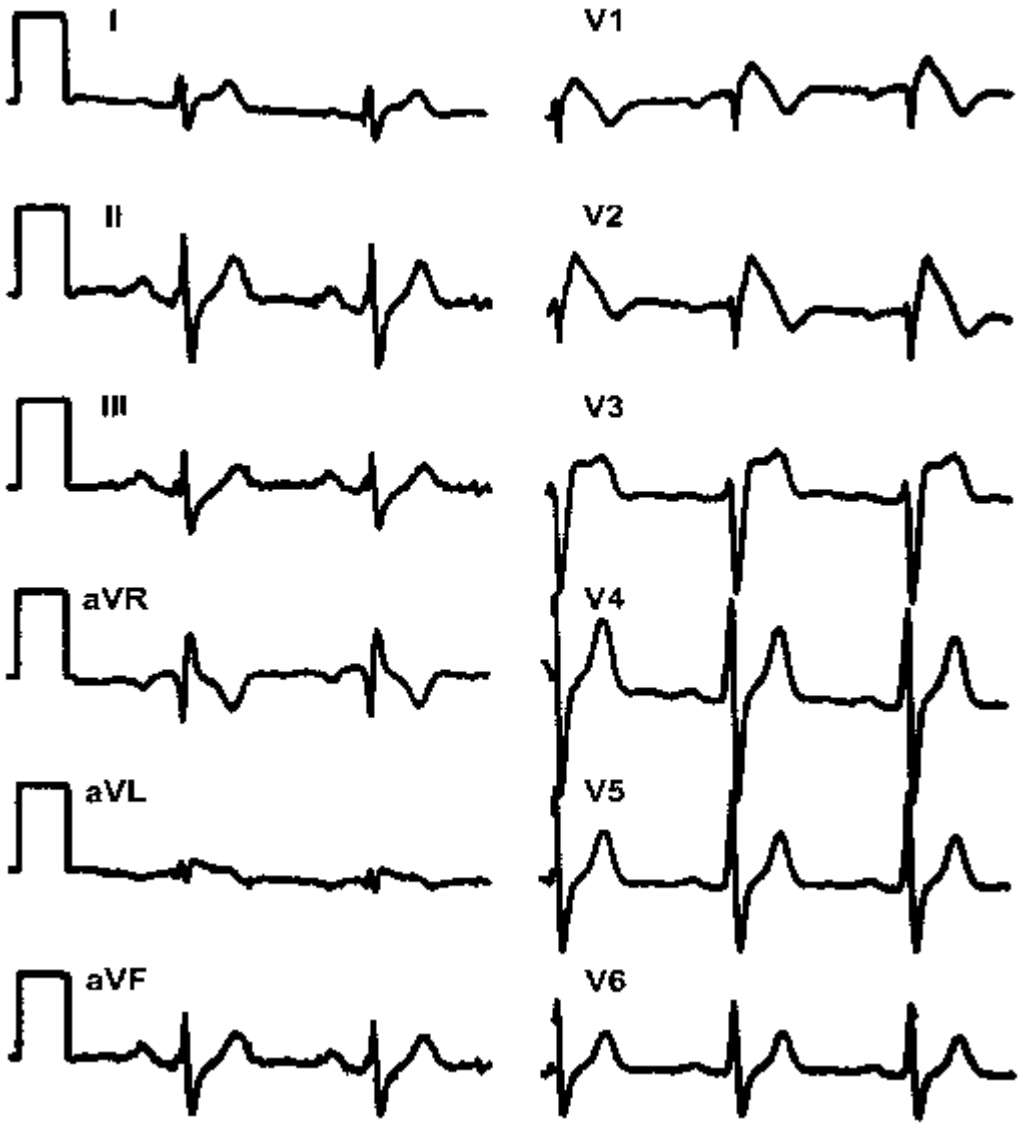


Fig. 1. Typical ECG of the syndrome. Please note the pattern resembling a right bundle branch block in lead V1 and the ST segment elevation in leads V1 to V3. Paper speed 25 mm/s.

Incidence of an abnormal ECG in the general population

A prospective study of an adult Japanese population (22,027 subjects) showed an incidence of 0.05% of ECG's compatible with the syndrome (12 subjects)[5]. A second study of adults in Awa (Japan) showed an incidence of 0.6 % (66 cases out of 10,420) [6]. However, a third study in children from Japan showed an incidence of ECG's compatible with the syndrome of only 0.0006% (1 case in 163,110)[7]. 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 presence of concealed and intermittent forms, however, makes the diagnosis difficult in some patients. The ECG can be modulated by changes in autonomic balance and the administration of antiarrhythmic drugs[8]. Beta-adrenergic stimulation normalises the ECG, while IV ajmaline, flecainide or procainamide accentuate the ST segment elevation and are capable of unmasking concealed and intermittent forms of the disease. These data are very important when we deal with family members of a patient with the syndrome. We

know that a normal ECG in the resting state is not sufficient to exclude that a family member is affected with the syndrome. Some family members only manifest the typical ECG pattern after ajmaline or flecainide administration.

Recent data suggest that loss of the action potential dome in right ventricular epicardium but not endocardium underlies the ST segment elevation seen in the Brugada syndrome [9,10]. Also, electrical heterogeneity within right ventricular epicardium leads to the development of closely coupled extrasystoles via a phase 2 reentrant mechanism, which then precipitate ventricular tachycardia-ventricular fibrillation. Right ventricular epicardium is preferentially affected because of the predominance of transient outward current in this tissue.

Clinical manifestations

The **complete syndrome** is characterised 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 manifestations of the syndrome are caused by episodes of polymorphic VT/VF. When the episodes terminate spontaneously the patient develops syncopal attacks. When the episodes are sustained, cardiac arrest and eventually sudden death occur.

There exist **asymptomatic** individuals in whom the atypical ECG is detected 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 vaso-vagal 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 typical pattern 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.

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 syncopes caused by a polymorphic VT. The ST segment elevation in V1 to V3 with the right bundle branch block pattern is characteristic. The ST changes are different from the ones observed in acute septal ischemia, pericarditis, ventricular aneurysm and in some normal variants like early repolarization. There are though, ECG's which are not as characteristic, and they are only recognised by a physician who is thinking of the syndrome. 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 flecainide.

It is possible that the electrocardiographic patterns are different depending on the genetic abnormality. This is the case in other genetic diseases like the long QT syndrome [11]. The mutations that have been discovered give proof of this fact in Brugada syndrome: their ECG's are similar, but not identical. Even though the affected gene is the same, the exact mutation is different. It will be necessary to identify more mutations and make 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 autonomous system and by antiarrhythmic drugs. The study by Myazaki et al [8] was the first one 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 the ST segment elevation while vagal stimulation worsens it. The administration of class Ia, Ic and III drugs increase the ST segment elevation. 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.

Genetic characterisation.

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 the cardiac ionic channels. In animal studies, blockade of the calcium-independent 4-aminopyridine-sensitive transient outward potassium current (I_{to}) results in surface ECG findings of elevated, downsloping ST-segments due to greater prolongation in the epicardial action potential compared to the endocardium (which lacks a plateau phase). Loss of the action potential plateau (or dome) in the epicardium but not 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 I_{to} and I_{Ca}), autonomic neurotransmitters like acetylcholine facilitate loss of the action potential dome by suppressing calcium current and augmenting potassium current. b-adrenergic agonists (i.e. isoproterenol, dobutamine) restore the dome by augmenting I_{Ca}. 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. Hence, I_{to}, I_{Ca}, and I_{Na} would be good candidate genes to study. Since I_{Na} (SCN5A) has been shown to cause VT/VF in humans (in the long QT syndrome) this gene certainly is worthy of study.

Recently, we reported the findings on six families and several sporadic cases of Brugada syndrome [4]. 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 by 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 the electrocardiographic changes after the administration of ajmaline iv. This test proved 100% sensitive and specific, as all the patients who developed the ST segment elevation had the mutation in the subsequent genetic analysis. Likewise, none of the individuals without the electrocardiographic abnormalities had the genetic abnormality.

Biophysical analysis of the mutants in *Xenopus* oocytes demonstrated a reduction in the number of functional sodium channels in both the splicing mutation and one-nucleotide deletion mutation, which should promote development of reentrant arrhythmias. In the missense mutation, sodium channels inactivated 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 depolarisation 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. 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 INa carried by SCN5A channels.

Prognosis and treatment.

Symptomatic patients: Our recent data on 334 patients with the syndrome confirm the generally accepted view that symptomatic patients with this syndrome have an unacceptably high rate of arrhythmic events. Because no effective antiarrhythmic drug or other therapies are available, implantation of a cardioverter-defibrillator is mandatory in these patients. Better understanding of the genetic basis and electrophysiologic mechanisms of the disease may make other therapies possible in the future. Recurrent arrhythmic events were more frequent in patients with aborted sudden death as the presenting symptom as compared to patients with repetitive syncopal episodes. This could suggest a more severe disease in the former group with more frequent and longer-lasting arrhythmias. However, a word of caution is in order because the mean follow-up period of patients with aborted sudden death was significantly longer than the mean follow-up of patients with syncopal episodes. For both categories of symptomatic patients, the recurrence rates approximate a mean of 11% per mean follow-up year (8.8% per year in syncope patients and 13.7% per year in patients resuscitated from sudden cardiac death) and are unacceptably high. The gravity of the problem is amplified when one considers the mean age of the patients.

Asymptomatic individuals: The major concern at present is with the group of individuals displaying an electrocardiogram compatible with the diagnosis of Brugada syndrome but who are asymptomatic. The initial diagnosis in these individuals was arrived at by different means: In some individuals a spontaneously abnormal electrocardiogram was recorded as part of a routine screening, for instance before surgery. In other individuals, the abnormal electrocardiogram was obtained because of a family history of sudden death. In some, the abnormal electrocardiogram appeared only during treatment with

antiarrhythmic drugs given for the treatment of atrial fibrillation or other arrhythmias. Finally, in still others, the abnormal electrocardiogram was obtained only after pharmacologic challenge performed because of the suspicion or documentation of Brugada syndrome in the family. The most recent data allow important conclusions in terms of the management of these asymptomatic individuals.

First, it is confirmed that a *spontaneously abnormal electrocardiogram* is a marker of possible sudden arrhythmic death: 16 of 111 (14%) asymptomatic individuals with a spontaneously abnormal electrocardiogram developed an arrhythmic event during a mean follow-up period of only 27±29 months. The arrhythmic event occurred within one year of diagnosis in 7 individuals, within 2 years in another 3 patients, but after more than 4 years in the remaining 6 individuals. The longest time interval between diagnosis and first arrhythmic event was 10 years. These data demonstrate that a mean follow-up time of slightly more than 2 years underestimates the total number of events that can occur in this population.

Second, the data allowed recognition of groups of asymptomatic individuals with a good prognosis. The group of asymptomatic individuals in whom the *abnormal electrocardiogram was recognized only after pharmacologic challenge* had no events during follow-up. This observation has important implications for the management of individuals who are members of a family with Brugada syndrome. When the individual is asymptomatic and the electrocardiogram is normal, the unmasking of the abnormal electrocardiogram with a drug identifies a carrier of the disease. However, because no events occurred in this group, it is not justified to recommend further investigations in terms of management.

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 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.

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