Brugada syndrome: clinical and pathophysiological aspects
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Citation for published version (APA):

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Brugada Syndrome
Clinical and Genetic Aspects

Paola G. Meregalli, Hanno L. Tan and Arthur A.M. Wilde

This chapter is in part published in “Electrical diseases of the heart”
Edited by Ihor Gussak, Charles Antzelevitch, Arthur Wilde, Paul Friedman,
Michael Ackerman, and Win-Kuang Shen, Springer Verlag, London 2008
Clinical Features of Brugada Syndrome

Demography and Clinical Presentation
Since its recognition as a distinct subgroup of idiopathic ventricular fibrillation (VF) in 1992, Brugada syndrome is increasingly described worldwide, although its exact prevalence remains unclear and can vary significantly between different regions of the world. It is endemic in East and Southeast Asia, where it underlies the Sudden Unexplained Nocturnal Death Syndrome (SUNDS) and is also particularly prevalent in Japan, the Philippines and Thailand, being one of the leading causes of sudden death among young men. In China and Korea, the reported incidence is lower. In Europe, Brugada syndrome is extensively described with the exception of the Scandinavian countries and its prevalence is estimated at 5-50 cases per 10,000 inhabitants. Conversely, occurrence of the Brugada-type ECG in the United States seems to be very uncommon. In Iran, the reported prevalence of the typical Brugada ECG among subjects presenting with palpitations is greater than some European Countries and lower than in Japan.

Arrhythmic events in Brugada syndrome can occur at all ages, from childhood to the elderly (range 2 days-77 years), with a peak around the fourth decade. The oldest described patient with a persistent Brugada ECG pattern is an asymptomatic man of 85 years.

It is estimated that Brugada syndrome causes 4-12% of all sudden cardiac death (SCD), and up to 20% among patients without identifiable structural abnormalities.

The clinical presentation is heterogeneous and may include palpitations, dizziness, syncope, and (aborted) sudden death, but many subjects remain asymptomatic.

Sudden death results from fast polymorphic ventricular tachycardia (VT) originating from the right ventricular outflow tract (RVOT), degenerating into VF. Ventricular arrhythmias and aborted-SCD in Brugada syndrome - distinct from arrhythmogenic right ventricular cardiomyopathy (ARVC) - typically occur...
Chapter 1

at rest when the vagal tone is augmented \(^{{30}}\), and often at night \(^{{31, 32}}\), or after large meals \(^{{33, 34}}\).

Interestingly, it has recently been reported that arrhythmias in Brugada syndrome patients occur twice as often in spring and early summer, compared to the late fall and winter seasons \(^{{35}}\). No real explanation is found for this phenomenon. This data comes from stored electrograms of internal cardioverter defibrillators (ICD) and is limited by the small number of included patients. Among all kinds of symptoms associated with Brugada syndrome, syncope is the most common by far. Episodes of syncope may be provoked by self-terminating VT and this may explain why patients experience agonal respiration at night after which they wake up \(^{{36-40}}\). An estimated 80% of patients with documented VT/VF have a history of syncope \(^{{12}}\). Clinical presentation with sustained monomorphic VT, although uncommon, has also been described \(^{{41-43}}\). Again, data obtained from ICDs have demonstrated that, although premature ventricular complexes (PVCs) in patients affected with Brugada syndrome are rare \(^{{44}}\), their prevalence increases prior to spontaneous VF \(^{{45}}\). These PVCs appear to have the same morphology as the first VT beat, and different VT episodes are initiated by similar PVCs in the same subject \(^{{45, 46}}\). They show a left bundle branch block (LBBB) morphology \(^{{47}}\) and endocardial mapping localized their origin in the RVOT \(^{{48}}\). Further confirmation of the role of these initiating PVCs and of the RVOT derives from the clinical benefit resulting from their elimination via catheter ablation \(^{{48}}\).

No significant variations in QTc intervals precede spontaneous VF episodes \(^{{1, 45}}\). Occurrence of supraventricular tachycardia is also more prevalent and episodes of atrial flutter/fibrillation are often documented \(^{{1, 49-54}}\) with an estimated prevalence of 10-30% \(^{{31, 55}}\). Given that a history of atrial arrhythmias correlates with VT/VF inducibility during EPS, and that ST segment elevation correlates with the onset of atrial fibrillation episodes \(^{{31}}\), Brugada syndrome patients with paroxysmal atrial arrhythmias may constitute a population at higher risk with a more advanced disease state \(^{{56}}\), but these data are still limited \(^{{57}}\). Importantly, atrial arrhythmias may also lead to inappropriate ICD shocks \(^{{58, 59}}\). A salient property in the clinical manifestation of Brugada syndrome is the higher disease prevalence in males (70-80% of all affected subjects), particularly in regions where this syndrome is
endemic, despite equal genetic transmission among both genders. That a role in gender disparity could be played by sex hormones, in particular by testosterone, was suggested by the demonstration that castration attenuated ST elevations in two asymptomatic male Brugada syndrome patients and by the revelation that men affected with Brugada syndrome have significantly higher levels of testosterone than age-matched control subjects. Also, a very recent report showed the male subjects with a Brugada-like ECG have a higher risk for prostate cancer, independently of their smoking habit, age or radiation exposure (the study population was constituted by atomic bomb survivors). A possible explanation for this phenomenon, derived from clinical and experimental studies, is that sex hormones may modulate potassium currents during the early repolarization phase of the cardiac action potential (AP).

Among affected patients, men and women differ in their clinical presentation. This is represented by a greater average amount of ST segment elevation in men, while women reveal more severe conduction disorders in response to sodium channel blockers. Also, men have a worse prognosis than women. Another relevant characteristic in Brugada syndrome is that hyperthermia, e.g. fever, may also induce/aggravate ECG changes or provoke arrhythmias in a subset of affected patients. This is illustrated by an increasing number of reports on fever-induced Brugada syndrome and more recently by a systematic work of our group, whose results are reported in chapter 5.3.1 of this thesis.

Finally, a large number of drugs have been reported to induce Brugada syndrome, or Brugada syndrome-like ECG characteristics, among which antiarrhythmic drugs, antianginal drugs, psychotropic drugs and also substances like cocaine and alcohol (see further in this chapter).

**Genetic Aspects**

In 1998, Brugada syndrome was linked to mutations in the \( SCN5A \) gene, encoding the pore-forming \( \alpha \)-subunit of the human cardiac sodium (Na\(^+\)) channel protein.

The \( SCN5A \) gene is situated on chromosome 3p21 and encodes a large transmembrane protein (~260 KDa), of 2016 amino acid residues. The \( \alpha \)-subunits
constitute the main component of the cardiac Na\(^+\) channel complex and are assembled with four ancillaries β-subunits (cytoskeleton proteins) to form the voltage-dependent cardiac sodium channel. Every α-subunit contains four homologous domains (DI-DIV), each composed of six segments (S1-S6) (Figure 1). The S5-S6 segments and the p-loop between them form the inner pore of the channel, which is high selective for Na\(^+\) ions. S4 segments act as the voltage sensor \(^{74}\). This channel belongs to a family with different isoforms and different biophysical properties according to its tissue distribution \(^{75}\). In the heart, it is responsible for the rapid initiating phase of the AP and thus plays a major role in impulse formation and propagation through the cardiac conduction system and muscle.

The Na\(^+\) channel is dynamic and undergoes rapid structural transformations in response to the voltage changes across the sarcolemma. This process is known as “gating”. Upon membrane depolarization the channel activates allowing the opening of the pore. This increases channel permeability for Na\(^+\) ions. The resulting inward current causes the rapid upstroke of the AP. After few milliseconds fast inactivation of the channel occurs, a state in which the pore cannot re-open. Membrane repolarization is necessary to allow the Na\(^+\) channels to recover from inactivation into the resting state (closed state), from which they can re-open during the next cardiac cycle.

In the last years, more than 100 SCN5A gene mutations (inherited Arrhythmia Database: http://www.fsm.it/cardmoc/) have been described in patients with the Brugada syndrome phenotype, alone or in combination with Long QT Syndrome type 3 (LQT3) and/or progressive cardiac conduction defects (PCCD, also called Lev-Lenègre disease), in which SCN5A mutations may also be present \(^{76-80}\).
Of interest, some SCN5A mutations may cause a combination of Brugada syndrome and LQT3 or Lev-Lenègre disease within the same family or even within the same individual\textsuperscript{81,82}. While LQT3 associated SCN5A mutations generally increase peak sodium channel current (I\textsubscript{Na}), those associated with Lev-Lenègre disease reduce it, similar to those in Brugada syndrome\textsuperscript{78}. Reduction in peak I\textsubscript{Na} during phase 0 of the AP results from failure of expression of the mutant sodium channel in the cell membrane (trafficking) or changes in its functional properties (gating), deriving from: 1) shift in the voltage and time-dependence of I\textsubscript{Na} activation and/or inactivation; 2) enhanced entry into an intermediate state of inactivation from which the channel recovers more slowly; 3) accelerated inactivation\textsuperscript{78,83-85}.

The reduction in peak I\textsubscript{Na} caused by the mutant sodium channels in Brugada syndrome is in agreement with the clinical observation that sodium channel blockers accentuate ST segment abnormalities in affected subjects\textsuperscript{86}. Moreover, this finding concurs with the demonstration that Brugada syndrome patients who carry a SCN5A mutation have significantly more conduction disorders than non-carriers\textsuperscript{87,88}.

Despite the increasing number of SCN5A mutations recognized in Brugada syndrome, the proportion of clinically diagnosed Brugada syndrome patients who
carry a SCN5A mutation is estimated around 30%, suggesting that the genetic basis of Brugada syndrome is heterogeneous. Other three genes, linked to Brugada syndrome are identified and other genes still await discovery; till now they lead to a loss-of-function in sodium and calcium channel activity. All genes that modulate INa amplitude and other ion currents active during early repolarization phases of the AP, such as the transient outward potassium current Ito, calcium current ICa-L, and potassium delayed rectifier currents IKs, IKr are possible candidates. Alternatively, genes encoding adrenergic receptors, cholinergic receptors, ion-channel interacting proteins, transcriptional factors and transporters could be the target.

Weiss et al. described a novel mutation in the glycerol-3-phosphate dehydrogenase 1-like gene (GPD1L) on chromosome 3p22-24, linked to the Brugada syndrome phenotype, in a large family. This gene encodes a protein whose function in the heart still remains unknown, but the mutant protein, when studied in cell lines, was responsible for a diminished inward sodium current, similar to the other SCN5A mutations in Brugada syndrome studied so far. The exact prevalence of GPD1L-related Brugada syndrome is unknown, but it seems to be rare.

More recently, genetic and heterologous expression studies revealed loss-of-function calcium channel (L-type) missense mutations in CACNA1c (Ca1.2) and its β-subunit CACNB2b in Brugada syndrome patients with short QT intervals. Also mutations in the SCN1B subunit were found to have an effect on the INa, leading either to Brugada syndrome or PCCD phenotype in three small families. Lately, a missense mutation in the KCNE3 gene was found to be associated with the Brugada syndrome phenotype in one family. When the mutated KCNE3 was co-transfected with KCND3 in Chinese hamster ovary cells, this resulted in a significant augmentation in the amplitude of the Ito current, compared with the wild type.

Though SCN5A mutations account, so far, for about 30% of all affected patients, genetic testing is recommended during work-up in Brugada syndrome to support the clinical diagnosis, to identify affected relatives, and to better elucidate the genotype-phenotype relationship with a potential role in risk stratification in Brugada syndrome patients. In chapter 4 of this thesis the results a genotype-
phenotype relationship among the carriers of a SCN5A mutation are reported. This study illustrates that carriers of a truncation mutation present a more severe phenotype than carriers of a missense SCN5A mutation. Interestingly, the more severe the conduction disorders are, on baseline and provocation ECG, the worse the clinical presentation and prognosis.

ECG Characteristics
Typical electrocardiographic abnormalities have represented, since its first description, the fundamental aspect in recognition of subjects affected by Brugada syndrome. Particular attention was given to the presence of a (incomplete) right bundle branch block (RBBB), accompanied by ST segment elevation in the right precordial leads, not related to ischemia, electrolyte imbalance and structural heart disease. At present, diagnosis of Brugada syndrome revolves around characteristic ST segment elevations in leads V1-V3 and in leads positioned at the superior intercostal spaces (Figure 2), whereas the presence of a RBBB is no longer required. Rarely, ST segment elevation can be found in the inferior or lateral leads.

A total of three ECG repolarization patterns were described as potential manifestations of Brugada syndrome: 1) type I ECG, referred to as coved-type, consists of > 2 mm J point elevation, followed by a down-sloping ST segment and a negative T wave; 2) type II ECG, called saddle-back type, also shows a elevated J point (> 2 mm) with a gradually descending ST segment that does not reach the baseline and gives rise to a positive or biphasic T wave; 3) type III ECG could be of any of the previously described morphologies and is characterized by a smaller magnitude of ST segment elevation (≤ 1 mm) (Figure 2).

Crucially, the presence of a type I ECG is required for the diagnosis, while types II and III are intermediate forms that require provocation testing with sodium channel blockers.
Figure 2: Four ECG traces of a resuscitated Brugada syndrome patient showing most severe ST-T abnormalities in leads positioned over the second and third intercostal space (right two panels) where a coved-type ECG is present (arrows). Intermediate ST-T abnormalities (saddleback-type) are recorded in the fourth intercostal space (leads V2-V3). Calibrations are given.

Courtesy of Dr. W. Shimizu.

Important considerations and cautions in interpretation of the ECG in diagnosing Brugada syndrome have to be taken into account. Firstly, the ST segment in Brugada syndrome is typically highly dynamic, exhibiting profound day-to-day
variation in amplitude and morphology, even within the same patient. This aspect may contribute to possible bias and underestimation of the prevalence of Brugada syndrome and it is also of crucial importance for correct risk stratification. An inter-individual variation of the ST segment can also be observed between members of the same family who carry the same SCN5A mutation. The magnitude of ST segment elevation does not differ between SCN5A mutation carriers and Brugada syndrome patients without SCN5A mutation, while it differs between men and women.

Secondly, many agents and conditions are reported to significantly influence ST segment elevation in genetically predisposed individuals (Table 1). Sodium channel blockers, α-adrenoreceptor agonists and cholinergic stimulation (increased vagal tone) provoke an augmentation of ST segment elevation, while α-adrenoreceptor blockade and β-adrenoreceptor stimulation with isoprenaline reduce the amount of ST segment abnormalities. Since accentuation of ST elevation immediately preceding episodes of VF has been extensively reported, all these drugs also modulate susceptibility to arrhythmias.

Table 1

<table>
<thead>
<tr>
<th>Medications to be avoided in Brugada syndrome patients</th>
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<tr>
<td>Sodium channel blockers</td>
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<tr>
<td>• Class I anti-arrhythmic drugs (flecainide, ajmaline, propafenone, pilsicainide, procainamide, disopyramide, cibenzoline)</td>
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<td>• Local anesthetics (lidocaine, bupivacaine)</td>
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<td>• Carbamazepine, Phenothiazine</td>
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<tr>
<td>Tricyclic and tetracyclic anti-depressants</td>
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<td>Alpha adrenergic stimulation (norepinephrine, methoxamine)</td>
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<tr>
<th>Medications to be used with caution in Brugada syndrome patients</th>
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<tr>
<td>β-adrenergic blockers</td>
</tr>
<tr>
<td>Calcium antagonists, non-dihydropyridines (verapamil, diltiazem)</td>
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<tr>
<td>Nitrates</td>
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<tr>
<td>General anesthetics/antagonism of anesthesia</td>
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<tr>
<td>• Muscarinic drugs (i.e. neostigmine)</td>
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Some clinically relevant aspects derive from these observations: 1) A variety of Na⁺ channel blockers are utilized as diagnostic tool for unmasking concealed forms of Brugada syndrome; 2) Use of any Na⁺ channel blocker and other medications capable to provoke ST elevation must be avoided in patients with Brugada syndrome; Particular attention must be also given to clinical management surrounding local or general anesthesia of patients affected with Brugada syndrome; 3) Administration of isoprenaline, a β-adrenoreceptor agonist, can be effectively used in case of repetitive VT and arrhythmic storms in Brugada syndrome patients.

As also described in the paragraph on clinical presentation, body temperature represents a very important modulating factor in ECG patterns and arrhythmogenesis. Several case reports revealed that febrile illness or prolonged contact with hot water could precipitate arrhythmic events in Brugada syndrome patients. It is also my experience that asymptomatic Brugada patients with a normal basal ECG can, during an episode of fever, display typical ECG changes with different amounts of ST segment elevations up to appearance of a type I pattern (Figure 3).

Figure 3: ECG recorded at normal temperature and during fever in a male subject affected with Brugada syndrome. Leads V₁IC₃ and V₂IC₃ are positioned above V₁ and V₂, respectively, in the third intercostal space. This patient had multiple syncopes during fever with documented VF. Screening of the SCN5A gene for known mutations was negative. During fever, we recorded ST segment elevation with appearance of type I ECG in leads V₁, V₁IC₃ and V₂IC₃ and type II ECG in lead V₂ (right panel), while ECGs of the same patient during normothermia display only minimal ST segment elevation (left panel).
General Introduction

In 1999 Dumaine et al. discovered that the changes in Na⁺ channel gating properties, induced by the SCN5A mutant T1620, were more prominent at higher temperature (32°C compared to room temperature) which supports the notion that the consequences of possessing a certain SCN5A mutation or a mutation in other genes responsible for Brugada syndrome, can be manifested only during fever. For this reason, appropriate treatment of fever illnesses is strongly recommended in all patients with Brugada syndrome, with special attention for the young patients, who suffer more often of infections and fever than adults. Also, activities and conditions that may provoke augmentation of the body temperature must be discouraged in affected individuals.

Importance of Positioning of the Precordial Leads and new ECG Parameters

The signature ST elevations in Brugada syndrome are usually observed in leads V1-V3, with rare occurrences in inferior or lateral limb leads. More strikingly, leads positioned cranially from V1 and V2 in the third (V1_{IC3} and V2_{IC3}) or second (V1_{IC2} and V2_{IC2}) intercostal spaces often produce the most severe abnormalities, both in the presence and absence of pharmacological challenge, as also demonstrated with body surface mapping. The use of 87-lead body surface maps permitted to demonstrate that in 7 out of 28 Brugada patients the typical ECG pattern was located at the level of the RVOT (second and third intercostal space), while conventional leads V1 and V2 registered only minimal ST segment elevation. Conversely, investigation of the more cranial leads in 40 control subjects did not reveal any significant ST elevation, neither at baseline, nor after disopyramide. The clinical investigation reported in chapter 2 of this thesis shows that 45% (21 out of 47) of the subjects with a positive response under flecainide, are identified after a type I ECG has exclusively occurred in leads positioned over the third intercostal space. Therefore, we believe that ECG investigation in these more cranial leads should be performed whenever a case of Brugada syndrome is suspected. Data from the literature show that, with the placement of leads in the 3rd intercostal space above V1 and V2, sensitivity increases and there do not seem to be false positive test results. Also, the prognosis of patients with a spontaneous type I morphology...
exclusively in the leads positioned in the 3rd intercostal seems to be similar to patients with a spontaneous type I morphology in V1 and V2. However, large prospective studies into the use of V1IC3 and V2IC3 are lacking. Attention has also been paid to the recognition of other ECG criteria, in addition to the amount of J point elevation that may aid in identifying subjects at risk for sudden death. Two additional ECG parameters are: 1) S wave width in leads II and III, to be considered a mirror image of the electrical activity taking place in the RVOT, a core area in the pathophysiology of Brugada syndrome; these S waves were significantly wider in the individuals with a positive response to flecainide, than in the negative responders (see also chapter 2 of this thesis), 2) S wave width in lead V1 ≥ 0.08 sec was shown to be a good predictor of arrhythmic events in Brugada syndrome patients. Recently, other ECG criteria have been proposed for risk assessment in Brugada syndrome patients. This topic is also discussed later on in this chapter (paragraph “Risk Stratification”).

**Other Electrocardiographic Features in Brugada Syndrome**

Brugada syndrome has habitually been accompanied by right bundle branch block, thought atypical because of the absence of a wide S wave in the left lateral leads. Nowadays, the presence of a RBBB is no longer considered necessary for the diagnosis, though a widening of the QRS complex is frequently observed in patients affected by Brugada syndrome. Actually, signs of conduction defects are found in any of the cardiac compartments, particularly in patients carrying a SCN5A mutation. These signs are: QRS axis deviation, P wave width enlargement and PQ prolongation, presumably reflecting prolonged His-Ventricular conduction time and, as already mentioned, QRS prolongation. Moreover, sinus node dysfunction and AV node dysfunction have been extensively reported. In contrast, QTc duration generally is within the normal range, but it may be occasionally prolonged. ECG parameters for depolarization and repolarization times have been also studied for prognostic purposes. In 200 consecutive and well characterized
Brugada syndrome patients PR, QRS, QTc and T peak-T end intervals where compared between symptomatic and asymptomatic patients. Only QRS duration in leads II and V2 (115 ± 26 vs 104 ± 19 msec) showed significant prolongation in symptomatic patients, when compared to asymptomatic patients. In a multicenter French cohort, the presence of a SCN5A mutation greatly influenced the phenotype with more exhibition of clinically relevant conduction defects (first degree AV block, complete RBBB, LBBB, hemiblocks) in SCN5A carriers versus the non carriers, independently from the amount of ST segment elevation.

Drug Tests
Due to the wide variability and spontaneous dynamic changes of ST segment morphology in Brugada syndrome patients, diagnosis revolves around provocation tests in order to unmask a type I ECG in affected patients in which it may be concealed. Provocation tools are required when ST segment elevation is not initially present or when type II or III ECG patterns are seen in individuals suspected to have Brugada syndrome. A test is defined positive when types II-III turn into a type I ECG. Subjects in whom administration of sodium channel blockers does not provoke a change in the form and amount of ST segment elevation (negative tests) have a good prognosis: no major arrhythmic events occurred in a recent study with an average follow-up of 3 years. Importantly, in the presence of a spontaneous type I ECG a provocation test is not recommended and could be even harmful.

Pharmacological challenges utilize intravenous administration of sodium channel blockers, i.e., class IA (except quinidine) and IC, but not class IB antiarrhythmic drugs. Sodium channel blockers are the drug of choice, since they have proven to provoke/exaggerate ST segment changes in affected individuals. Many sodium channel blockers have been used for this purpose: intravenous administration of propafenon (class IC), procainamide (class IC, 10 mg/Kg body weight over 10 min), pilsecinid (class IC, 1 mg/Kg over 10 min, available only in Japan), disopyramide (class IA), flecainide (2 mg/Kg; max 150 mg) and ajmaline (1 mg/Kg; 10 mg/min) can unmask ST segment elevation in affected patients within 10 minutes.
The specific diagnostic yield of such tests has not been systematically studied for all of them. Currently, these data are available for tests performed with ajmaline (class 1A) or flecainide (class 1C), in genotyped adult populations\textsuperscript{147, 199}. In a study where the two drugs were compared, ajmaline has shown to be the most powerful\textsuperscript{160}. Our group has also studied the safety issue of these tests in a large series of patients, and our conclusion is that the tests are safe\textsuperscript{147}, provided that they are conducted according to the guidelines of the European Society of Cardiology\textsuperscript{101}, under continuous ECG monitoring.

In particular, drug infusion must be given step by step and must be discontinued as soon as a type I ECG is reached or when PVCs/(non)sustained VT occur or when QRS duration increases by $\geq 130\%$ of the basal value. If not, life-threatening ventricular tachyarrhythmias may develop\textsuperscript{27, 155}.

Interestingly, the presence of a SC\textsubscript{N}5\textsubscript{A} mutation seems to increase the risk of arrhythmias during infusion with sodium channel blockers\textsuperscript{155}.
Figure 4: ECG recorded after intravenous infusion of 80 mg flecainide in a 45 year old male subject showing a saddle-back ST segment elevation in leads V1 and V2 (type II) and the appearance of premature ventricular beats, isolated and in couples, from the right ventricle. The ectopic beats show a short coupling interval. Flecainide challenge was performed to pose the diagnosis of Brugada syndrome after an aborted sudden death.

Pathophysiological Mechanism

Nowadays, the mechanistic basis for ST segment elevation in Brugada syndrome is still not completely understood. Experimental studies conducted from the mid-1990s support the theory that the ECG pattern in Brugada syndrome arises from unbalance between the inward and the outward currents during phase 1 of the AP, leading to a faster repolarization of the myocytes situated in the epicardial layers. The initiating factor is a reduced peak $I_{Na}$ which leaves the transient potassium outward current $I_{to}$ unopposed. This alteration brings to a faster repolarization of the myocytes situated in the epicardial layer with an AP duration shortening/
loss of dome, but not in the endocardium, since in endocardial cells Ito expression is very low\textsuperscript{162}. Therefore, a transmural voltage gradient between the layers is caused and that is translated into J wave exaggeration on surface ECG. According to this theory, arrhythmias in Brugada syndrome develop in the epicardium, where heterogeneity in the loss of the original AP dome occurs, and generating dispersion of repolarization within the same layer. This condition favours the development of very closely coupled extra-systole, which triggers a re-entry phenomenon\textsuperscript{163}. Another theory assumes that right precordial ST elevation in Brugada syndrome derives from a delay in activation of the RVOT. This causes asynchronous depolarization and therefore, voltage gradients between areas that are already depolarized and areas that are not. This second scenario presupposes the presence of subtle structural abnormalities in the RVOT area, which may be themselves consequential to dysfunctional sodium channels\textsuperscript{164, 165}. A recent publication demonstrated that, in a one-dimensional model of transmural RV conduction, mutant F2004L (found in a proband with Brugada syndrome), caused decremental excitation from endo-to epicardium at slow rates. This caused ST elevation in a pseudo ECG waveform\textsuperscript{166}.

A comprehensive review article on existing data on the two main theories about the aetiology of Brugada syndrome constitutes chapter 3 of this book.

**Structural Abnormalities**

One striking clinical characteristic of Brugada syndrome is the absence of clear structural abnormalities\textsuperscript{1, 29}. Nonetheless, there has been evidence that Brugada syndrome may represent a mild form of right ventricle cardiomyopathy, not apparent with routine diagnostic tools\textsuperscript{148, 167}. Similarities with arrhythmogenic right ventricular cardiomyopathy (ARVC) were pointed out especially by Italian researchers\textsuperscript{148, 168} and were strengthened by the discovery of a \textit{SCN5A} mutation in a family with ARVC\textsuperscript{169}. The sensitivity to detect slight structural abnormalities has become greater with electron beam CT scan and cardiac magnetic resonance (MRI). These imaging methods have revealed RV wall motion abnormalities and RVOT enlargement in two series of Brugada syndrome patients, compared to control subjects\textsuperscript{170-172}. More recently, 18 Brugada syndrome patients underwent
biventricular endomyocardial biopsies, which revealed changes compatible with myocarditis (n=14) or with right ventricular cardiomyopathy (n=4), although the hearts appeared normal at non-invasive evaluation. However, in this study a control group was lacking. Interestingly, the presence of a SCN5A mutation was found in all the 4 patients with cardiomyopathy-like changes on biopsy specimens. Furthermore, in eight out of these eighteen patients (45%) similar findings were also found in the left ventricle. Interestingly, both MRI and echocardiography did not show structural changes in any of the patients.

Also, right ventricular fibrosis and epicardial fatty infiltration were documented in the explanted heart of a SCN5A mutation carrying Brugada syndrome patient who experienced intolerable numbers of ICD discharges (up to 129 appropriate shocks in 5 months). Again, in this patient there were no clinically detected cardiac structural abnormalities, but it should be mentioned that MRI had not been performed due to ICD implantation, 10 years before cardiac transplantation.

These findings demonstrate a link between functional and structural abnormalities and also support the hypothesis that sodium channel mutations themselves may induce subtle structural derangements and myocardial cell death. This hypothesis has been tested in transgenic adult mice with SCN5A haploinsufficiency where a significant amount of cardiac fibrosis was found and is supported by the clinical observation that certain SCN5A defects were associated with fibrosis in the conduction system and in the ventricular myocardium.

**Differential Diagnosis in Brugada Syndrome**

A number of clinical conditions which are also accompanied by ST segment elevation should be carefully ruled out before the diagnosis of Brugada syndrome is made (Table 2). Relatively common causes of ST segment elevation include: 1) early repolarization syndrome; 2) acute anterior myocardial infarction; 3) isolated right ventricular infarction or left ventricular aneurysm; 4) Prinzmetal’s angina, which may also coexist with Brugada syndrome; 5) electrolyte disturbances, such as hyperkalemia and hypercalcaemia; 6) acute pericarditis/myocarditis; 7) RBBB or LBBB and left ventricular hypertrophy; 8) ECG recorded after electrical cardioversion.
More rarely, ST segment elevation may occur under the following conditions: 1) acute pulmonary embolism 187 2) acute aortic dissection 188; 3) ARVC 168, 189; 4) Long QT syndrome type III 190; 5) hypothermia 191; 6) Duchenne muscular dystrophy and Friedreich’s ataxia 192, 193; 7) central and autonomic nervous system abnormalities 194, 195; 8) mechanical compression of the RVOT by a mediastinal tumor 196.

Furthermore, a variety of drugs and intoxications can lead to a Brugada-like ST segment elevation (see also Table 1). This group also includes cardiac anti-ischemic medication, such as calcium channel blockers or nitrates and medications used to provoke/antagonize anesthesia 119-121.

Finally, tricyclic or tetracyclic antidepressant medications as well as selective serotonin re-uptake inhibitors and cocaine should be mentioned. All these drugs have been reported to cause a Brugada-like ST segment elevation 114, 115, 117, 118, 197 and tricyclic antidepressants have been reported to provoke VF, even when used in normal dosages 116.

Table 2: Conditions that can lead to ST elevation, mimicking Brugada syndrome

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<th>Condition</th>
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<tr>
<td>Early repolarization syndrome</td>
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<td>Cocaine intoxication</td>
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<tr>
<td>Acute myocardial infarction or isolated right ventricular infarction</td>
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<td>Prinzmetal’s angina</td>
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<td>Hyperkalemia and Hypercalcaemia</td>
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<td>Acute pericarditis/myocarditis</td>
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<td>RBBB or LBBB and left ventricular hypertrophy</td>
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<tr>
<td>Acute pulmonary embolism</td>
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<tr>
<td>Acute aortic dissection</td>
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<tr>
<td>Arrhythmogenic right ventricular cardiomyopathy</td>
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<tr>
<td>Long QT syndrome type III</td>
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<tr>
<td>Hypothermia</td>
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<tr>
<td>Duchenne muscular dystrophy</td>
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<td>Friedreich’s ataxia</td>
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<tr>
<td>Various central and autonomic nervous system abnormalities</td>
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<tr>
<td>Mechanical compression of the RVOT by a mediastinal tumor</td>
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Risk Stratification and Therapy

The most effective prevention of sudden death in patients affected by Brugada syndrome, considered at high risk for ventricular arrhythmias, is implantation of ICDs\(^1\),\(^{20}\). The role of drug therapy is currently limited and discussed further in this chapter. Recommendations for ICD implantations are largely discussed in the Second Consensus Report about Brugada syndrome\(^{154}\) and are summarized as follow: 1) symptomatic patients displaying a type I ECG should receive an ICD, without additional need of electrophysiological study (EPS); 2) asymptomatic patients displaying a type I ECG spontaneously should undergo EPS 3) asymptomatic patients displaying a type I ECG only after provocation test, but with a positive family history for SCD, should also undergo EPS. When inducible, patients in categories 2) and 3) should be implanted with an ICD\(^{154}\).

Finally, asymptomatic patients with a type I ECG only after provocation challenge and negative family history for SCD need a close follow-up\(^{154}\).

Despite the recommendations of this Consensus paper at the beginning of 2005, the results of newer studies were not able to confirm the utility of the proposed strategy. Especially, risk stratification strategy in Brugada syndrome has been strongly debated and some authors do not encourage ICD implantation in asymptomatic patients at all. Even nowadays, in 2009, the prognosis of Brugada syndrome patients is far from being resolved. While it is accepted that patients with aborted SCD or those who have had symptoms like dizziness, syncope or nocturnal agonal respiration should receive an ICD, conflicting data exist regarding risk stratification and therapeutic options in asymptomatic individuals. Brugada et al. reported a high incidence of cardiac death or documented VF (8%) in a large series of asymptomatic patients (n=190) with a Brugada syndrome ECG (mean follow up 2 years)\(^{13,201}\).

In contrast, a multicenter study conducted in North Italy by Priori et al\(^{12}\), showed that asymptomatic patients have a very good prognosis (no arrhythmic events during a mean follow up of 33 months in 30 asymptomatic patients) and similar results were found by Eckardt et al.\(^{202}\) who reported data on a large multicentre population with a type I ECG (n= 212) with the longest follow up (40 months on average) so far. They observed only one episode of VF on a total of 123 asymptomatic individuals (0.8%).
Hence, according to these two European groups, implantation of an ICD in asymptomatic subjects, highly recommended by Brugada et al., would be not justified.

Also the role of EPS in asymptomatic patients remains controversial. A large recent meta-analysis including 1217 patients (of which 1036 underwent EPS) failed to show that inducibility of VT/VF during EPS was able to predict arrhythmic events during follow-up in 14 out of the 15 studies included.

Importantly, EPS protocols often diverge between the centers and this makes it more difficult to compare the results. Another important limitation of all studies focusing on prognosis of Brugada syndrome patients is that the average follow-up is still quite short: around 3 years in the largest series. The risk for an asymptomatic patient to develop SCD in the long term is, therefore, currently, unknown. Consequently, finding new tools for risk stratification that could help in the recognition of high risk patients has become a real challenge.

A recently published meta-analysis on prognosis in Brugada syndrome, including more than 1.500 patients, identified some clinical parameters associated with an increased risk of arrhythmic events. These parameters are: 1) history of syncope or aborted-SCD, 2) male gender and 3) spontaneous appearance of a type I ECG. This confirms the notion that the presence of a spontaneous type I ECG has also prognostic implications. Patients displaying type I ECG naturally are at higher risk (2-fold greater risk of cardiac events and more appropriate ICD shocks), compared to patients with types II and III ECGs that convert to a type I ECG only after sodium channel blocker infusion.

It is also known that spontaneous ST segment fluctuations measured on separate days in Brugada syndrome patients is associated with the highest risk of arrhythmic events and can be used as non-invasive method for risk stratification. Also, prolongation of QRS duration on a standard 12-leads ECG is associated with symptoms and could serve as a simple marker of vulnerability for development of tachyarrhythmias. The cut-off value of QRS ≥ 120 ms (lead V2) yielded a specificity and sensitivity, respectively of 70% and 52% in identifying subjects with symptoms.
When looking at the morphology of the QRS interval, some authors identified the terminal part (S wave width in lead V1) as the strongest distinguishing factor between high and low risk patients. Also, the presence of late potentials (LP) on signal-averaged ECGs (SAECG) has gained attention as a useful non-invasive method able to predict arrhythmic events in Brugada syndrome. LP are especially found in the anterior wall of the RVOT in symptomatic Brugada syndrome patients and can be exaggerated by infusion with flecainide. They are generally regarded as delayed and disorganized ventricular activation (at the terminal portion of the QRS) and are related to a high risk of developing ventricular tachyarrhythmias. The value of LP as predictors of arrhythmic events has been mainly tested in patients with structurally abnormal hearts, especially in studies of patients after a myocardial infarction. In Brugada syndrome LP could represent delayed activation in the RVOT area, or, according to some other authors, they may be an extension beyond the QRS of the second epicardial upstroke generated by a phase 2 reentry mechanism.

Surely, SAECG detects a higher prevalence of LP in symptomatic patients, in comparison with asymptomatic patients. Moreover, daily fluctuations in LP are also more accentuated in symptomatic versus asymptomatic patients.

**Pharmacological Treatment**

In contrast to other primary arrhythmic syndromes, the use of common antiarrhythmic drugs in Brugada syndrome patients has not resulted in acceptable results.

In the 1990’s a small randomized trial in Thailand has shown that β-blockers are not protective against SCD in patients affected by SUDS and survivors of aborted-SCD. The study was prematurely stopped because of 7 deaths in the propranolol group. Sotalol, a class III anti-arrhythmic drug (equipped with a partial β-blockade effect) has been reported to suppress further episodes of syncope in a 53 year-old man affected by Brugada syndrome and carrier of a truncation mutation of SCN5A gene for 13 years. Yet, its efficacy in series has never been tested. Treatment with amiodarone, a potent potassium blocker (Vaughan Williams class III) has also proven not to be effective and it may even be harmful. In two cases of
female patients, administration of amiodarone provoked coved-type ST segment elevation (type I), which resolved after discontinuation of the drug \textsuperscript{221, 222}. As reported before in this chapter, treatment with sodium channel blockers should be avoided in Brugada syndrome due to their ability to aggravate ST segment changes in affected patients. Still, among all sodium channel blockers (class I) there are strong differences in the amount and specificity of sodium channel blockade. Surprisingly, quinidine, a class IA sodium channel blocker which also blocks $I_{\text{to}}$, is the only oral agent which has proven to normalize the ST segment \textsuperscript{223} and to be effective in suppressing arrhythmic events in some patients with Brugada syndrome (both spontaneous events and inducible VT/VF during EPS) \textsuperscript{224, 225}. Treatment with quinidine, despite the known side effects of this medication (diarrhea, vomiting, prolongation of QT interval, thrombocytopenia, hearing impairment), should be considered especially in the younger individuals, who are exposed to a high rate of ICD-related complications \textsuperscript{226}. Future studies dealing with the efficacy and the tolerance of quinidine in larger series of affected patients are needed.

In addition, radiofrequency catheter ablation of repetitive PVC originating in the RVOT could be considered and will certainly occupy an important role in the future treatment of symptomatic patients in which PVC’s trigger multiple episodes of VT/VF \textsuperscript{227}.

**Emergency Treatment**

When a patient suffers from hemodynamic instability due to VT/VF resuscitation manoeuvres should be started. Ventricular arrhythmias could also occur during diagnostic tests with sodium channel blockers \textsuperscript{155, 228}. For this reason, not only must these tests be stopped when PVC’s occur or when QRS duration reaches 130% of the basal value \textsuperscript{101}, but they should also be performed by expert cardiologists in hospital settings equipped with resuscitation facilities at hand. Incessant VT’s and electrical storms are also described in Brugada syndrome \textsuperscript{229}. In such cases it is important to immediately administer isoproterenol, a $\beta$-adrenergic agonist which has proven to restore normal ST segments in patients affected by Brugada syndrome \textsuperscript{100} and prevent the recurrence of VT/VF \textsuperscript{230}. Also, since an augmented
vagal tone could represent a trigger for malignant arrhythmias, i.v. atropine (parasympathetic antagonist) could be helpful 21. After have given these two drugs, oral administration of quinidine, titrated to the patient’s weight, should be started 23. All other types of anti-arrhythmic drugs should be avoided in Brugada syndrome patients in case of electrical storms: β-blockers, dobutamine, amiodarone, lidocaine and magnesium have all been tested in acute settings without success 111, 232.

If, despite the initial manoeuvres and administration of drugs, recurrence of VT/ VF persists, sedation and intubation are recommended. When episodes of VT/VF are clearly triggered by monomorphic PVC’s (usually with a LBBB configuration and an inferior axis) and do not respond to medical treatment, radiofrequency catheter ablation should be considered 227. When no other treatment is helpful, heart transplantation represents the last option 233.

It should be stressed that, as already written in this chapter, the development of severe (and often recurrent) episodes of VT/VF in Brugada syndrome are favoured by high body temperature 234. Prompt restoration of normal body temperature and continuous cardiac monitoring is indicated in affected patients and represents a cornerstone in the prevention of recurrence of potentially lethal arrhythmias, especially in children.

When a resuscitated patient undergoes a cooling protocol in order to preserve the cerebral function, the rapid cooling could let ST segment elevations disappear, making the diagnosis impossible. This is illustrated by the unique presentation of a young male who survived a nightly episode of VF and was admitted at the intensive care department at our institution. The case is described in chapter 5.3.2 of this book.
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(188) Myers GB. Other QRS-T pattern that may be mistaken for myocardial infarction. IV. Alteration in blood potassium: myocardial ischemia; subepicardial myocarditis; distortion associated with arrhythmias. *Circulation* 1950;2:75.


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