

Brugada syndrome: From diagnosis to treatment

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Abstract

Brugada syndrome is electrocardiographically characterised by ST segment elevation in right precordial leads and the occurrence of episodes of polymorphic ventricular tachycardia. It is also associated with a high risk of sudden death, which may be the first manifestation of the disease. Various mutations of SCN5A gene encoding for the cardiac sodium channel are among the proven causes of BS. ICD remains the only treatment for BS of proven efficacy. However, many questions about etiology, underlying mechanisms, safety of asymptomatic patients and treatment options for BS remain unanswered. (Cardiol J 2007; 14: 429–435)

Key words: Brugada syndrome, SCN5A mutations, implantable cardioverter-defibrillator

Introduction

The term “Brugada syndrome” (BS), as a clinical entity, was coined in 1992. It is now recognised as the most common cause of genetically determined malignant ventricular arrhythmia and sudden cardiac death in young patients with a structurally normal heart. Patients with this syndrome present with a characteristic electrocardiographic picture consisting of elevated ST segments in the right precordial leads which develop spontaneously or as a result of drugs, fever or electrolyte imbalance.

Because, in some countries, BS is the second most common cause of death in young adults, this disease entity is generating increasing interest. This article focuses on selected issues relating to the dis-

covery, pathogenesis, clinical picture, electrographic features and treatment of Brugada syndrome.

Discovery of the new disease entity

In 1953 an ECG was described which consisted of ST segment elevation and T wave reversion in the right precordial leads with or without right bundle branch block. However, for over thirty years this electrocardiographic phenomenon was not linked to any specific clinical entity. Martini et al. in 1989 and Aihara et al. [1] in 1990 started to associate abnormalities in right ventricular repolarisation with sudden cardiac death. The Italian scientists incorrectly associated them with anatomic defects (with arrhythmogenic right ventricular dysplasia).

In 1986 the Brugada brothers described the case of a 3-year-old boy, the son of Polish immigrants, who developed episodes of syncope, and whose electrocardiogram revealed ST segment elevation limited to precordial leads V1–V3. The patient’s sister, who presented with similar clinical and electrocardiographic manifestations, died at the

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age of 2 years [2]. Interestingly, the boy died suddenly at the age of 18 years at a disco, having already been implanted with an implantable cardioverter-defibrillator (ICD) (it is unknown whether the death was caused by electrical storm or by a failure of the cardioverter to fire).

By 1992, the authors had reported 8 such cases, which formed the basis for proposing a new clinical entity. The brothers maintained that the ECG picture consisted of right bundle branch block and ST segment elevation in V1–V3 even though the signs of the bundle branch block were only present in two of the eight reported electrocardiograms [2]. In 1996 Yan and Antzelevitch [3] established that this was not a “true” right bundle branch block but a “pseudo” right bundle branch block in which the high elevation of the J point mimics the secondary R wave in V1. However, the authority of the Brugada brothers was so strong that for over 6 years the presence of right bundle branch block (RBBB) continued to form the basis for ECG diagnosis. It was not until the consensus report in 2002 that it was emphasised that right bundle branch block may or may not be present in the ECGs of patients with BS [4, 5].

Of note is the fact that a variant BS has been reported in which ST segment elevation was observed in inferior wall leads. It was demonstrated to be associated with a new mutation of the SCN5A gene [6].

Incidence of Brugada syndrome

Brugada syndrome most commonly manifests in adulthood with the mean age of sudden death being 41 ± 15 years (the youngest patient was 2 days old and the oldest was 84 years old) [4].

Brugada syndrome seems to account for 4–12% of all cases of sudden death and approximately 20% of deaths of patients without structural changes in the myocardium. It is believed that in some countries, BS is the second most common cause of death in the population of young adults after road traffic accidents [4, 7].

The incidence of BS is estimated to be 5 cases per 10,000 inhabitants [4]. However, the real incidence of the disease in the general population is difficult to ascertain for the following reasons: firstly, due to the dynamic nature of the ECG picture, secondly, due to the more common occurrence of type 2 and type 3 electrocardiograms, which do not form the basis for diagnosis of BS and thirdly, and possibly most importantly, due to insufficient awareness of this electrocardiographic phenomenon among doctors.

The relationship between sudden unexpected nocturnal death syndrome and Brugada syndrome

Research studies have confirmed previous suppositions that sudden unexpected nocturnal death (SUND) syndrome and BS are phenotypically, genetically and functionally the same disease entity [7, 8]. Sudden unexpected nocturnal death syndrome has been known in Southeast Asia and the Pacific Rim for decades. It is known as “bangungut” in the Philippines, “pokkuri” in Japan and “lai tai” in Thailand [8].

One report described 25 sudden deaths in one family, 16 of which occurred during sleep. Of the 82 described cases of patients with SUND in Southeast Asia, the age of the patients ranged from 16 to 63 years (mean, 32 years) and all but one were male [8].

The three patterns of electrocardiographic abnormalities in Brugada syndrome

The common feature of all three types of electrocardiographic abnormalities seen in BS is a J point elevation of at least 2 mm in two or three right precordial leads (V1–V3) in the absence of a known cause. The three patterns of ECG abnormalities in BS differ in terms of the nature of ST segment elevation and the T wave morphology.

- type 1 is characterised by a convex (“lacunar”) ST segment elevation of at least 2 mm followed by a negative T wave (Fig. 1).
- type 2 is characterised by a concave (“sellar”) ST segment elevation of at least 1 mm followed by a positive or biphasic T wave (Fig. 1).
- type 3 is characterised by a concave ST segment elevation of less than 1 mm followed by a positive T wave (Fig. 1).

While type 1 is diagnostic of BS, the electrocardiographic diagnosis in the case of types 2 and 3 requires a positive challenge test with a sodium channel blocker (ajmaline, flecainide, procainamide). The challenge test with ajmaline (1 mg/kg IV) is considered positive if type 2 or type 3 converts into type 1 and/or there is a J point elevation of over 2 mm from baseline.

Clinical BS is diagnosed when type 1 electrocardiographic abnormalities are present in conjunction with at least one of the following criteria:

- documented ventricular fibrillation;
- documented polymorphic ventricular tachycardia;
- family history of sudden cardiac death before 45 years of age;
- recurrent syncope or nocturnal agonal respiration;

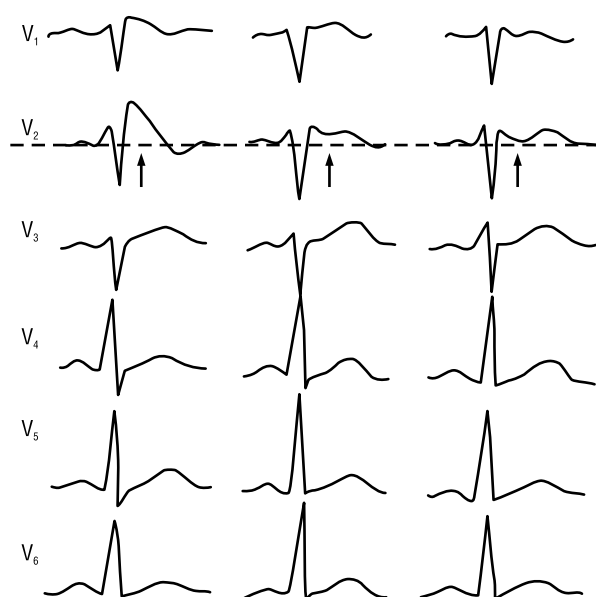


Figure 1. Electrocardiogram of a patient with Brugada syndrome. Precordial leads: the three different ECG patterns: type 1 (left), type 2 (middle) and type 3 (right). Arrows indicate ST segment elevation.

- ECG abnormalities typical of BS among the patient's relatives;
- inducibility of ventricular tachycardia using programmable electrostimulation [4].

Genetic background of Brugada syndrome

Brugada syndrome is inherited as an autosomal dominant trait of varying penetration. So far, the only gene linked to BS is *SCN5A*, a gene encoding for the alpha subunit of the cardiac sodium channel [9, 10]. Over 80 mutations of this gene have been discovered [4].

Analysis of the genetic background of BS draws attention to three aspects. Firstly, *SCN5A* mutation is also associated with type 3 congenital long QT syndrome, which results in two different phenotypes of sodium channel disease [11, 12]. Secondly, the above mutation has only been proven in 15–30% of BS cases. If so, what causes BS in the remaining patients? Thirdly, despite the even distribution of genetic transmission, the clinical phenotype is observed 8 to 10 times more frequently in men than in women. This is most probably due to the higher intensity of the transient outward current (*I_{to}*) in the right ventricular epicardium in men than in women. This may result from a more rapid inactivation of *I_{to}* channels in females or the difference

in their density between the sexes [13]. It is speculated that the relative excess of the male phenotype may be consequent to the role of testosterone [9].

Brugada syndrome has recently been linked to another locus on chromosome 3, other than the *SCN5A* locus. Brugada syndrome in this family tree is characterised by progressive conduction abnormalities, weak response to procainamide and a relatively good prognosis [14].

Brugada syndrome: An “electrical” heart disease

Brugada syndrome is an “electrical” disease caused by dysfunction of the characteristic ion channels. Studies have shown that in the overwhelming majority of patients, no structural substrate for heart disease is present. Studies are, however, ongoing to establish the potential role of structural abnormalities in the pathophysiology of this syndrome. Recently, Tagaki et al. [15] have used computed tomography to demonstrate abnormalities of myocardial contractility in the right ventricular outflow tract and in the inferior wall of the left ventricle in 21 of 26 patients with BS. The studies have shown that these abnormalities of contractility may be associated with the abnormal shape of the action potential in certain regions of the epicardium. The limitation of calcium influx into the cells is thought to be responsible for the loss of convexity in the plateau phase of the action potential in subepicardial regions of the right ventricle. Calcium content in the sarcoplasmic reticulum is lower; therefore, the contractility abnormalities are a reflection of “electrical” rather than morphological changes in the myocardium [15].

Is there any evidence to suggest a relationship between BS and structural changes in the heart? There has been a case report describing a patient after a cardiac arrest with ECG abnormalities typical of BS, in whom magnetic resonance imaging revealed signal hyperintensity in the left ventricular myocardium. Additional microscopic examination and polymerase chain reaction assay demonstrated locally limited myocarditis caused by parvovirus B19. It is believed that local myocarditis could have been the triggering factor of ventricular arrhythmia in this patient [16].

Arrhythmogenic substrate in patients with Brugada syndrome

The mechanism of ST segment elevation and ventricular arrhythmias in patients with BS has not

been fully elucidated. Sodium channel dysfunction is manifested by a lack of sodium channel expression, its underactivation or increased inactivation [17]. The decrease of the inward sodium current results in the domination of the Ito outward potassium current. The Ito current is more active in the epicardial cells than it is in the endocardium and the M cells, which is most pronounced in the right ventricle. This potential gradient at the end of phase 1 of the action potential is responsible for the high J wave in the right precordial leads of the ECG. The further course of the ECG curve depends on the order of repolarisation events: If repolarisation of the epicardium precedes repolarisation of the M cells and endocardial cells, then the T wave remains positive, but if the duration of the active potential in the epicardium is prolonged, then the direction of right ventricular wall repolarisation is reversed (which means that the endocardial repolarisation precedes epicardial repolarisation), resulting in the cup-like ST segment elevation and T wave reversal, a typical Brugada-like pattern (Fig. 2) [18].

The vast dispersion of repolarisation in the epicardium and between the epicardium and endocardium predisposes to phase 2 re-entry (through premature excitation during phase 2 of the action potential). This is the triggering factor for polymorphic tachycardia and ventricular flutter or fibrillation [10, 18–21].

Factors predisposing to ECG signs of Brugada syndrome and associated arrhythmias

Several groups of factors triggering Brugada-type ECG patterns and inducing polymorphic ventricular tachycardia have been distinguished. These include:

- **autonomic imbalance:** Bradycardia may contribute to triggering the arrhythmia. Japanese scientists searched for the SCN5A gene mutation in 38 unrelated patients with a clinical diagnosis of BS. The mutation was identified in 4 of 38 patients. All these patients had bradyarrhythmic complications: three were diagnosed with sick sinus syndrome, and one was diagnosed with third-degree atrioventricular block. It was hypothesised that patients with BS associated with the SCN5A mutation were at higher risk of an episode of bradyarrhythmia than patients with SB but without this mutation [22];
- **electrolyte imbalance:** hypokalemia, hyperkalemia, hypercalcemia [4];
- **fever:** fever may trigger Brugada-type ECG abnormalities, polymorphic tachycardia and ventricular fibrillation [23, 24];
- **myocardial ischemia:** Recent myocardial infarction or vasospastic myocardial ischemia affecting the right ventricular outflow tract mimic ST segment elevation similarly to BS. This is most likely a result of the decrease of the cal-

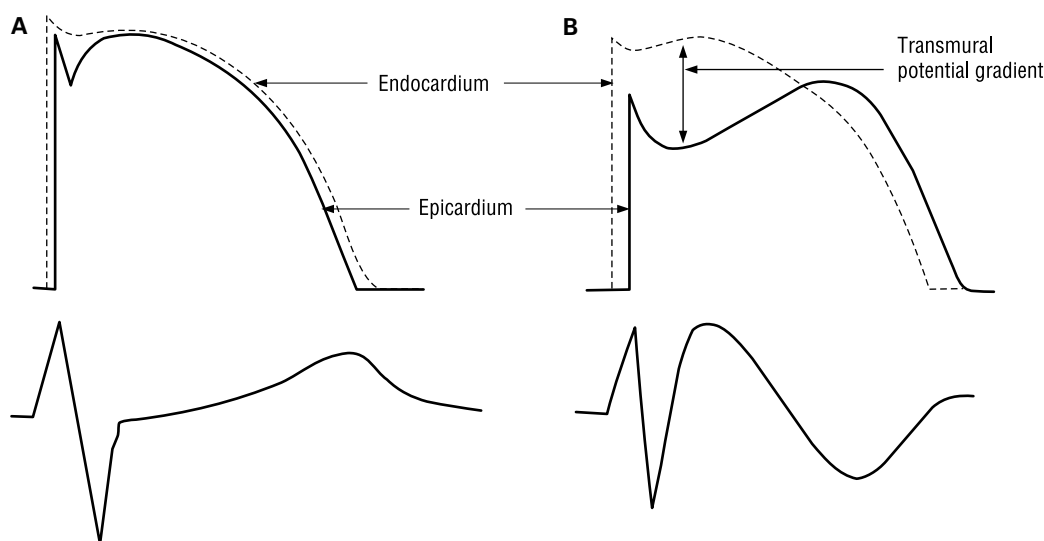


Figure 2. Diagrammatic representation of the action potential of the epicardial cells and the endocardial cells of the right ventricle. **A.** Normal pattern; **B.** Brugada-type pattern.

cium channel current and the activation of the ATP-dependent potassium channel during ischemia, which suggests that patients with BS may be more susceptible to sudden death if ischemia coexists [4];

— **drugs:**

- antiarrhythmic drugs (sodium channel blockers: class IA and IC, calcium antagonists: verapamil, beta-blockers),
- psychotropic drugs (tricyclic and tetracyclic antidepressants, selective serotonin reuptake inhibitors),
- first generation antihistamines,
- alpha adrenergic agonists,
- potassium channel opening drugs,
- miscellaneous (toxic action of cocaine and alcohol intoxication) [4, 25].

The above factors may occur in combination. A case of transient Brugada-type ECG abnormalities has been reported in a patient taking psychotropic medication (with sodium channel blocking properties) with renal failure and hyperkalemia. The ECG abnormalities resolved upon hemodialysis [26].

Identification of patients at risk of sudden death

In light of the research studies conducted so far, patients with aborted cardiac arrest have the greatest risk of recurrence (69%), while in patients with syncope and spontaneous signs of BS, the risk is 19% [27].

Priori et al. [28] analysed a group of 200 patients with BS. Based on the clinical, electrocardiographic and genetic characteristics, they distinguished three groups of patients:

- group 1: high-risk group (10% of the study population) consisting of patients with a history of syncope and ST segment abnormalities in resting ECG (cardiac arrest rate: 44%).
- group 2: intermediate-risk group (41% of the study population) consisting of patients without a history of syncope but with ST segment abnormalities in resting ECG (cardiac arrest rate: 14%).
- group 3: low-risk group (49% of the study population) consisting of patients with sodium gene mutations and ECG abnormalities induced in a drug challenge test (cardiac arrest rate: 5%).

The prognostic and therapeutic approaches in asymptomatic patients are controversial.

No prognostic markers have been identified in asymptomatic patients. In a study of 30 asymptomatic

patients, a double SCN5A gene mutation was demonstrated in most cases. It is believed that severe sodium channel dysfunction, as a result of the SCN5A gene mutation, is not the only factor causing the symptoms. Other unknown factors, which may affect the prognosis, are postulated [29].

An interesting case of a 48-year-old asymptomatic female with BS along with a retrospective 22-year analysis of ECG, Holter monitoring and electrophysiological study (EPS) was reported in “Kardiologia Polska”. The asymptomatic patient without a family history of sudden cardiac death, arrhythmic events or induced arrhythmia during EPS qualified to the close observation group (she falls within the intermediate-risk category according to the stratification proposed by Priori et al.) [30].

The importance of ECG studies in patients with electrocardiographic features of Brugada syndrome (in accordance with ESC recommendations)

There is controversy as to the importance of electrophysiological studies (EPS) in asymptomatic patients. Brugada et al. [31] demonstrated a relationship between the triggering of VT/VF and the risk of sudden death, which has not been confirmed in other studies [28, 32]. The possible causes of this discrepancy may include differences in stimulation protocols or in the duration of follow-up.

According to the current European Society of Cardiology (ESC) guidelines, EPS may be considered to estimate the risk in patients with asymptomatic BS with spontaneous ST segment elevation with or without the SCN5A gene mutation (Class IIb, Level C) [33].

Genetic analysis in Brugada syndrome

According to current opinion, genetic analysis has no role in the estimation of risk in BS. Nevertheless, it may help to identify asymptomatic carriers of the mutation, who may then be provided with clinical monitoring and genetic counselling [33].

In an article recently published in “Folia Cardiologica” reporting a 40-year-old symptomatic patient with a family history of sudden deaths, the possibility has been pointed out of performing genetic testing for BS (using the polymerase chain reaction) courtesy of Dr Ramon Brugada (New York Heart Center), thanks to which a mutation of SCN5A exon 27 has been detected, and an identical mutation has been detected in the patient’s 17-year-old son [34].

Treatment of Brugada syndrome

The only proven treatment option for BS is an ICD. According to the current ESC guidelines, implantation of an ICD is indicated for patients with BS and aborted cardiac arrest who receive optimal long-term treatment and whose life expectancy in good general condition exceeds one year (Class I, Level C). Implantation of an ICD is justified in patients with BS and:

- spontaneous ST segment elevation in V1–V3, with a history of syncope with or without the SCN5A gene mutation and whose life expectancy in good general condition exceeds one year.
- documented VT which did not lead to cardiac arrest, whose life expectancy in good general condition exceeds one year (Class IIa, Level C) [33].

Alternative treatments for Brugada syndrome

A potential role of pacemakers in the treatment of BS has been suggested because arrhythmias and sudden cardiac death occur more frequently during sleep or at rest, two states associated with bradycardia. However, the role of cardiac stimulation in the treatment of BS remains to be investigated [17].

The idea of drug treatment rests on the assumption that balancing the active currents during early phases of the action potential in the right ventricular epicardium will restore the normal doming of the action potential. Because it is believed that the considerable outward current (Ito) is an underlying cause of BS, all agents that block this type of current may have cardioprotective effects. Unfortunately, no selective blockers of the outward current Ito are available. Quinidine remains the only agent that effectively restores the normal doming of the action potential (and normalises the ST segment) and prevents polymorphic ventricular tachycardia. It inhibits the Ito current and has been shown to normalise effectively ST segment elevation in patients with BS. According to ESC guidelines, administration of quinidine may be justified in the treatment of electrical storm in patients with BS (Class IIb, Level C).

It is believed that drugs that increase the calcium current (such as isoproterenol) may also prove therapeutically effective [4]. Isoproterenol is recommended in the treatment of electrical storm (Class IIa, Level C) [33].

Cilostazol, a phosphodiesterase III inhibitor, is a new addition to the pharmacological arsenal. It normalises the ST segment by reducing the Ito current and increasing the calcium current. Tedis-

amil is an investigational antiarrhythmic agent with a potential inhibitory effect on the Ito current [4].

An ideal drug would consist of a cardioselective and Ito-selective blocker, especially for use in newborns and those adults for whom an ICD is unreachable.

Summary

Brugada syndrome is electrocardiographically characterised by ST segment elevation in right precordial leads and the occurrence of episodes of polymorphic ventricular tachycardia. It is also associated with a high risk of sudden death, which may be the first manifestation of the disease. Various mutations of SCN5A gene encoding for the cardiac sodium channel are one of the proven causes of BS. ICD remains the only treatment for BS of proven efficacy.

Many questions about BS remain unanswered, such as:

- What is the etiology of the majority of cases of BS? (Genetic defects undetected so far? Perhaps these are acquired forms?)
- Is the dispersion of repolarisation the only factor responsible for electrical instability of the ventricles in these patients?
- Can poor prognostic markers be identified in asymptomatic patients?
- Can patients with BS be effectively managed pharmacologically?

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