Brugada syndrome: Epidemiology and pathogenesis

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INTRODUCTION

The vast majority of cases of sudden cardiac arrest (SCA) and sudden cardiac death (SCD) are caused by ventricular tachyarrhythmias, with most of these associated with structural heart disease, particularly coronary heart disease. SCA in the apparently normal heart is an uncommon occurrence, accounting for only 5 to 10 percent of SCA cases. (See "Pathophysiology and etiology of sudden cardiac arrest".)

Some causes of SCA in patients with apparently normal hearts have been identified and include:

- Brugada syndrome
- Congenital long QT syndrome (LQTS) (see "Congenital long QT syndrome: Epidemiology and clinical manifestations")
- Acquired LQTS with polymorphic ventricular tachycardia (VT) (see "Acquired long QT syndrome: Definitions, pathophysiology, and causes")
- Catecholaminergic polymorphic VT (see "Catecholaminergic polymorphic ventricular tachycardia")
- Idiopathic VT (see "Ventricular tachycardia in the absence of apparent structural heart disease")
- Idiopathic ventricular fibrillation
- Short QT syndrome (see "Short QT syndrome")
- Commotio cordis (see "Commotio cordis")

The epidemiology and pathogenesis of the Brugada syndrome will be reviewed here. The clinical manifestations, evaluation, diagnosis, management, and prognosis of the Brugada syndrome, along with a discussion of the other causes of SCA in apparently normal hearts, are discussed elsewhere. (See "Approach to sudden cardiac arrest in the absence of apparent structural heart disease" and "Brugada syndrome: Clinical presentation, diagnosis, and evaluation" and "Brugada syndrome or pattern: Management and approach to screening of relatives".)

DEFINITION

The Brugada syndrome is an autosomal dominant genetic disorder with variable expression characterized by abnormal findings on the surface electrocardiogram (ECG) in conjunction with an increased risk of ventricular tachyarrhythmias and sudden cardiac death [1]. Typically, the ECG findings consist of a pseudo-right bundle branch block and persistent ST segment elevation in leads V1 to V2 (waveform 1), although isolated cases have described similar findings involving the inferior ECG leads [2-5].

Brugada pattern versus Brugada syndrome — Two terms, distinguished by the presence or absence of symptoms, have been used to describe patients with the typical ECG findings of a pseudo-right bundle branch block and persistent ST segment elevation in leads V1 to V2:

- Patients with typical ECG features who are asymptomatic and have no other clinical criteria are said to have the **Brugada pattern**.
- Patients with typical ECG features who have experienced sudden cardiac death or a sustained ventricular tachyarrhythmia, or who have one or more of the other associated clinical criteria, are said to have the **Brugada syndrome**. Patients with ventricular premature beats or nonsustained ventricular tachycardia, however, are generally not considered to have Brugada syndrome but only the Brugada pattern.

Persons with either the Brugada pattern or the Brugada syndrome can have identical findings on the surface ECG. (See "Brugada syndrome: Clinical presentation, diagnosis, and evaluation", section on '12-lead ECG'.)

EPIDEMIOLOGY

Prevalence — The prevalence of the asymptomatic Brugada ECG pattern has been evaluated in a number of different populations and appears to be between 0.1 and 1 percent depending

upon the population studied [5-12]. The prevalence of symptomatic Brugada syndrome is significantly lower than the prevalence of the Brugada pattern but is less well studied [13,14].

Studies in heterogeneous populations suggest that the majority of affected individuals are of Asian descent, with the highest prevalence in Southeast Asia [5].

- In two reports from Japan, the prevalence was 0.7 and 1.0 percent [6,7]; 0.12 to 0.16 percent of the Japanese population have type 1 (coved type) ST segment elevation [6,8,9].
- In a Finnish cohort, the prevalence of type 2 ST segment elevation was 0.6 percent; no type 1 patients were found in a screen of over 3000 apparently healthy individuals [10].
- In two samples of urban populations in the United States, the prevalence was 0.4 and 0.012 percent, respectively [11].

The prevalence of Brugada syndrome among patients with Brugada pattern ECGs has not been well studied, but a meta-analysis of 30 published reports of patients with Brugada pattern ECGs demonstrated a 10 percent event rate at 2.5 years [13]. The prevalence of the Brugada pattern is much greater in patients who present with apparent idiopathic ventricular fibrillation (VF; 3 to 24 percent in one series of 37 patients, depending upon the diagnostic criteria used) [14]. (See "Approach to sudden cardiac arrest in the absence of apparent structural heart disease", section on 'Idiopathic VF'.)

Male predominance — The Brugada ECG pattern is more common in men than in women, with estimates ranging from 2 to 9 times more likely in men [12,15-18].

- Among a Japanese cohort of 4788 persons without baseline ECG abnormalities who were less than 50 years of age at enrollment and were followed for up to 41 years, 32 persons developed a Brugada pattern on ECG (at an average age of 45 years), with the incidence in men being 9 times higher than the incidence in women [9].
- Among a series of 384 persons identified with Brugada pattern ECGs at one of two high volume referral centers in Belgium and Spain, men represented over 70 percent of the cases (n = 272) [15]. Among the 83 patients in this series with Brugada syndrome at the time of diagnosis, 66 (80 percent) were men.
- Among a series of 542 persons identified with Brugada pattern ECGs at a single high volume referral center in Belgium from 1992 to 2013 (which likely included some of the same patients as the study above), men represented 58 percent of the cases (n = 314) [16]. Among the 156 patients in this series who presented with syncope or sudden cardiac death, 99 (63 percent) were men.

- Females may have lower event rates than males. In a multicenter retrospective study of 770 patients with Brugada syndrome, 23 percent were female. Over a follow-up of 10 years, females presented less frequently with type 1 ECG pattern (30.5 versus 55 percent) and had lower cardiovascular event rates over mean follow-up of 10 years (2.8 versus 7.1 percent) than males [19].

Reasons for the prominent male predominance in an autosomal dominant disorder are unclear. Animal models suggest that the impact of testosterone on ion currents, particularly outward potassium currents, may contribute to the increased incidence of clinical manifestations of Brugada syndrome in males [20,21]. (See 'Genetics' below.)

Age at diagnosis — Brugada pattern ECG and Brugada syndrome are usually diagnosed in adulthood. In two of the larger series of patients, which combined those with Brugada pattern ECGs as well as those with symptomatic Brugada syndrome, the average patient age was 41 years [22,23].

However, Brugada syndrome can be diagnosed in children. A single-center case series from Italy of 43 patients younger than 12 years reported a higher incidence of malignant arrhythmia events in patients with syncope (37.5 percent) than in patients without syncope (0 percent). No significant difference in outcomes was observed in patients with drug- or fever-induced type 1 pattern versus spontaneous, or between males and females in this young population followed for a mean of four years [24].

Association with schizophrenia — Patients with schizophrenia appear significantly more likely to have Brugada pattern ECGs than the general population. Among a cohort of 275 patients with schizophrenia (with two separate cohorts of nonschizophrenic patients serving as control groups), Brugada pattern ECGs were significantly more common (11.6 percent of patients with schizophrenia versus 1.1 and 2.4 percent of the cohorts without schizophrenia, respectively), with no significant impact of antipsychotic medications with sodium channel blocking activity used to treat schizophrenia [25]. The clinical relevance of this association remains undetermined, but there may be an association between this finding and the risk of sudden death in patients with schizophrenia. (See "Schizophrenia in adults: Epidemiology and pathogenesis" and "Schizophrenia in adults: Clinical features, assessment, and diagnosis".)

PATHOGENESIS

A variety of factors may contribute to the electrocardiographic and clinical manifestations of Brugada syndrome including mutations in the cardiac sodium channel SCN genes, right

ventricular (RV) abnormalities, autonomic tone, fever, and the use of cocaine and certain psychotropic drugs.

Genetics — The Brugada syndrome demonstrates autosomal dominant inheritance with variable expression [12]. Genetic analysis has led to the identification of purportedly causative mutations in the SCN genes SCN5A and SCN10A, encoding subunits of a cardiac sodium channel. Reasons for the variable expression of Brugada syndrome are not completely understood, although compound heterozygosity (manifestation of a recessive disease due to two different mutations in the same gene) had been described in one family [26].

Sodium channel genes — The defective myocardial sodium channels reduce sodium inflow currents, thereby reducing the duration of normal action potentials. In the RV outflow tract (RVOT) epicardium, there is a prominent transient outward current, called I_{to}, which causes marked shortening of the action potential in the setting of reduced sodium inflow [27].

The relationship between sodium channel abnormalities and ST segment elevation is not fully understood. The ventricular myocardium is composed of at least three electrophysiologically distinct cell types:

- Epicardial cells
- Endocardial cells
- M cells

The ST segment elevation and T wave inversions seen in the right precordial leads in Brugada pattern ECGs are thought to be due to an alteration in the action potential in the epicardial and possibly the M cells, but not the endocardial cells [5,27-29]. The resulting dispersion of repolarization across the ventricular wall, which on noninvasive ECG mapping is isolated in the RVOT, results in a transmural voltage gradient that is manifested in the electrocardiogram as ST segment elevation [30]. In addition, noninvasive ECG mapping has also shown evidence of an arrhythmogenic substrate in the RVOT with delayed activation, slow conduction, and steep repolarization gradients between the RVOT and the rest of the RV [30]. This substrate may predispose to local reentry and ventricular arrhythmias.

SCN5A — Mutations in SCN5A, the gene that encodes the $Na_v1.5$ subunit of the cardiac sodium channel gene, have been found in 15 to 30 percent of families with Brugada syndrome [22,31-34]. The gene locus is on chromosome 3p21-24.

The SCN5A mutations seen in Brugada syndrome are "loss of function" mutations and result in a variety of abnormalities in sodium channel activity including failure of expression, alterations in the voltage and time dependence of activation, and accelerated or prolonged recovery from

inactivation [31]. In addition, mutations may explain the ability of sodium channel blockers to expose the ECG changes in some patients with this disorder [3,31,35-37]. Probands with SCN5A mutations have been reported to have higher rates of cardiac events beginning at a younger age [34]. Women with Brugada syndrome have a higher rate of SCN5A mutations than men (48 versus 28 percent) [18]. A critical appraisal of all candidate genes identified SCN5a as the only gene with definitive evidence for causation of Brugada syndrome [38].

SCN10A — Mutations in SCN10A, the gene that encodes the $Na_v1.8$ subunit of the cardiac sodium channel gene, have been reported in 17 percent of Brugada syndrome probands, which is comparable to the 20 percent of probands found to have SCN5A mutations [39]. Coexpression of the mutant SCN10A gene with wild-type SCN5A causes a major loss of function of the sodium channel, with reduced current and slower recovery from inactivation. A longer PR interval, longer QRS duration, and higher incidence of ventricular tachyarrhythmias and sudden death were noted in patients carrying mutations of SCN10A compared with gene-negative patients with Brugada syndrome.

Other sodium channel mutations — Other mutations that decrease the sodium channel current have been identified in isolated kindreds with Brugada syndrome. These include a mutation in SCN1B, an accessory subunit that interacts with the sodium channel and is also associated with conduction system disease [40], and a mutation in GPD1-L, a gene that affects trafficking of the sodium channel [41].

Related disorders with SCN mutations — Mutations in the SCN5 gene have also been associated with other electrophysiologic abnormalities:

- Isolated atrioventricular (AV) conduction defect
- Congenital long QT syndrome type 3 (LQT3) [42-44]
- Congenital sinus node dysfunction (SND)
- Familial dilated cardiomyopathy with conduction defects and susceptibility to atrial fibrillation
- Early repolarization syndrome

The differences in clinical manifestations are probably due to differences in the electrophysiologic abnormalities induced by the specific mutations [44-48]. Certain SCN5A and SCN10A mutations have been associated with an "overlap" syndrome, with affected patients exhibiting SND or complete heart block as well as Brugada syndrome [46-49]. Patients with longer PR intervals may be more likely to have a SNC10A mutation [39]. (See "Etiology of atrioventricular block", section on 'Familial disease' and "Congenital long QT syndrome: Pathophysiology and genetics", section on 'Type 3 LQTS (LQT3)' and "Genetics of dilated

cardiomyopathy" and "Sinus node dysfunction: Epidemiology, etiology, and natural history", section on 'Childhood and familial disease' and "Early repolarization".)

Non-sodium channel genes — Since only a minority of affected families have an identified abnormality of SCN, it is possible that additional genetic abnormalities may produce the phenotypic characteristics of Brugada syndrome.

- Cardiac calcium channel gene – In a series of 82 probands with a clinical diagnosis of Brugada syndrome, seven individuals (8.5 percent) were found to have mutations in the alpha1 or beta2 subunit of the cardiac L-type calcium channel [50]. Three of these patients had a unique phenotype in that in association with the typical ECG findings of Brugada syndrome, they also had shortened QT intervals (≤360 milliseconds). The relationship of this disorder to the usual form of Brugada syndrome and to short QT syndrome remains to be defined.

- A locus on chromosome 3p22-25 has been identified in a large family with an autosomal dominant syndrome similar to Brugada syndrome (RBBB and ventricular arrhythmias) [51]. The mutation is also associated with progressive conduction disease. Compared with patients with SCN5A mutations, affected members of this family had a good prognosis with a very low incidence of sudden cardiac death (SCD). A specific disease-causing gene at this locus has not yet been identified, which limits full characterization of this disorder and its relationship to the usual form of Brugada syndrome.

- Mutations in KCNE3 and KCNE2 causing gain of function in the transient outward current (I_{to}) and Brugada Syndrome have been identified in rare probands [52,53]. As discussed below, increased I_{to} current may lead to arrhythmias in Brugada.

Microscopic structural abnormalities and fibrosis — Brugada syndrome is not usually associated with structural heart disease. Standard cardiac testing, including echocardiography, stress testing, and cardiac magnetic resonance imaging often reveal no abnormalities. However, it is probably more accurate to categorize Brugada syndrome as a disorder that occurs in hearts that are apparently normal since there is some evidence that subtle structural or microscopic abnormalities occur, including dilation of the RVOT and localized inflammation and fibrosis [54-58].

Supporting a pathogenic role of fibrosis in Brugada syndrome, a mouse model of heterozygous SCN5A knockout revealed age-dependent fibrosis and marked slowing of conduction velocity in the RV [55]. Similarly, evaluation of an explanted heart from a transplant recipient with Brugada syndrome revealed microscopic fibrosis and conduction abnormalities [59].

Evidence of microscopic abnormalities in Brugada syndrome comes from a series of 18 patients who underwent endomyocardial biopsy [54]. Although noninvasive evaluation was normal in each patient, all had evidence of microscopic structural abnormalities, including signs of RV myocarditis in 14. The ECG changes resolved at follow-up in 8 of the 14 patients with signs of RV myocarditis, raising the possibility that the Brugada pattern ECG seen in these patients at presentation may have been a manifestation of RV myocarditis rather than an intrinsic cardiac ion channel abnormality.

A study of six post-mortem hearts from patients thought to have Brugada syndrome and six patients undergoing epicardial ablation via thoracotomy for Brugada syndrome demonstrated further evidence for fibrosis in the pathogenesis of Brugada syndrome. These patients showed increased collagen and fibrosis in the RVOT epicardium and reduced Connexin 43 signal in the RVOT. Fibrosis was located in areas of abnormal potentials during in vivo mapping [59].

Ventricular arrhythmias and phase 2 reentry — Ventricular arrhythmias may result from the heterogeneity of myocardial refractory periods in the RV. This heterogeneity arises from the presence of both normal and abnormal sodium channels in the same tissue, and from the differential impact of the sodium current in the three layers of the myocardium [27,28,60]. (See 'Sodium channel genes' above.)

Within the epicardium, the juxtaposition of myocytes with different refractory periods can produce the triggers that initiate sustained arrhythmias (eg, closely-coupled premature beats) via a unique type of reentry called phase two reentry. In cardiac myocytes with defective sodium channels, initial depolarization is blunted (phase zero), and the counterbalancing effect of I_{to} (phase 1) may be more significant. This phenomenon is more dramatic in the RVOT epicardium where I_{to} currents are greater. In combination, this results in less initial depolarization and reduced activation of the calcium channels that maintain the depolarized state during phase 2. Thus, phase 2 of the cardiac action potential can be dramatically shortened.

The cells with impaired sodium channel function may fail to propagate the action potential, resulting in localized conduction block. However, due to the abbreviation of phase 2, these same cells have a much shorter refractory period and recover excitability before the surrounding cells. The combination of localized conduction block and a shortened refractory period provides the substrate for localized reentry, which, in this case, is referred to as phase 2 reentry. The closely-coupled ventricular premature beats that result from phase 2 reentry may precipitate sustained ventricular arrhythmias. Noninvasive ECG mapping has also revealed delayed activation, slow conduction, and steep repolarization gradients between the RVOT and the rest of the RV, further supporting the role of the RVOT as the location of abnormal electrophysiologic substrate in Brugada syndrome [30].

Autonomic tone — An imbalance between sympathetic and parasympathetic tone may be important in the pathogenesis of Brugada ECG pattern and Brugada syndrome, as suggested by the nocturnal occurrence of the associated tachyarrhythmias and the alteration of typical ECG changes by pharmacologic modulation of autonomic tone [61-63].

Further support for the role of autonomic dysfunction comes from a study of 17 patients with Brugada syndrome who underwent scanning with iobenguane I-123 (diagnostic), a radiolabeled guanethidine analog that is actively taken up by sympathetic nerve terminals [62]. A segmental reduction in MIBG uptake was seen in 8 of the 17 patients but in none of 10 controls.

Augmentation of ST elevation ≥0.05 mV in leads V1-V2 during recovery from exercise is seen in some patients with Brugada syndrome and has been associated with worse arrhythmic outcomes. In a study of 93 patients with Brugada syndrome (57 patients) or asymptomatic Brugada pattern (36 patients), 37 percent had augmentation of ST elevation in exercise recovery, and during follow-up, 44 percent of these patients versus 17 percent of patients without ST augmentation had arrhythmic events [64]. The mechanism may be a response to parasympathetic reactivation during recovery from exercise.

Fever — Fever can be a trigger for both induction of Brugada pattern ECG abnormalities and cardiac arrest among persons known to have Brugada pattern ECG or Brugada syndrome. The clinical impact of fever in patients with Brugada pattern ECGs is discussed separately. (See "Brugada syndrome: Clinical presentation, diagnosis, and evaluation".)

Drugs — A 2020 scientific statement from the American Heart Association details drugs associated with the Brugada syndrome [65].

Cocaine abuse — The ECG findings of Brugada pattern can be transiently induced by cocaine use [66]. Cocaine acts like a class I antiarrhythmic agent, producing local anesthetic effects via sodium channel blockade in the heart; this could explain the relation to the Brugada pattern. (See "Clinical manifestations, diagnosis, and management of the cardiovascular complications of cocaine abuse".)

Psychotropic drugs — Other drugs that block cardiac sodium channels have been associated with a transient Brugada pattern ECG, including overdoses with neuroleptic drugs or cyclic antidepressants [67-70]. In one report, a Brugada pattern was seen in 15 of 98 cases (15.3 percent) of a cyclic antidepressant overdose [68]. One patient with the Brugada pattern and one without died of refractory ventricular fibrillation.

SUMMARY AND RECOMMENDATIONS

- **Definition** – The Brugada syndrome is an autosomal dominant genetic disorder with variable expression characterized by abnormal findings on the surface electrocardiogram (ECG) in conjunction with an increased risk of ventricular tachyarrhythmias and sudden cardiac death. Typically, the ECG findings consist of a pseudo-right bundle branch block and persistent ST segment elevation in leads V1 to V2 (waveform 1), although isolated cases have described similar findings involving the inferior ECG leads.

- **Brugada syndrome versus pattern** – Patients with typical ECG features who have experienced sudden cardiac death or a sustained ventricular tachyarrhythmia, or who have one or more of the other associated clinical criteria, are said to have the **Brugada syndrome**, whereas patients with typical ECG features who are asymptomatic and have no other clinical criteria are said to have the **Brugada pattern**. (See 'Definition' above.)

- **Epidemiology**

  - Prevalence of asymptomatic Brugada ECG pattern is between 0.1 and 1 percent, depending upon the population studied. (See 'Epidemiology' above.)

  - Prevalence of symptomatic Brugada syndrome is significantly lower than the prevalence of the Brugada pattern but is less well studied.

  - The Brugada ECG pattern is more common in men than in women, with estimates ranging from two to nine times more likely in men.

- **Pathogenesis** – A variety of factors may contribute to the electrocardiographic and clinical manifestations of Brugada syndrome including mutations in the cardiac sodium channel SCN genes, right ventricular abnormalities, autonomic tone, fever, and the use of cocaine and certain psychotropic drugs. (See 'Pathogenesis' above.)

- **Genetics** – The Brugada syndrome demonstrates autosomal dominant inheritance with variable expression. Genetic analysis has led to the identification of purportedly causative mutations in the SCN gene SCN5A, encoding subunits of a cardiac sodium channel. Reasons for the variable expression of Brugada syndrome are not completely understood. (See 'Genetics' above.)

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GRAPHICS

12-lead electrocardiogram (ECG) from a patient with the Brugada syndrome shows downsloping ST elevation

ST segment elevation and T wave inversion in the right precordial leads V1 and V2 (arrows); the QRS is normal. The widened S wave in the left lateral leads (V5 and V6) that is characteristic of right bundle branch block is absent.

Courtesy of Rory Childers, MD, University of Chicago.

Graphic 64510 Version 10.0