# Brugada syndrome: a review

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## Abstract

**Brugada syndrome was described 10 years ago. It is a syndrome of sudden cardiac death associated with partial right bundle branch block and ST segment elevation in the right precordial leads V1-V3 on the resting ECG. Those affected have structurally normal hearts (as demonstrated by standard techniques) but they have a mortality rate of 10% a year, whether they are symptomatic or asymptomatic.**

**It is thought to be primarily a disease of cardiac conduction and has been linked to abnormalities in the sodium channel (SCN5A). Differential diagnoses include arrhythmogenic right ventricular dysplasia, idiopathic ventricular fibrillation and polymorphic ventricular tachycardia. Brugada *et al.* suggest that the Brugada shift pattern on 12-lead ECG is a specific marker for those at risk of sudden death. They recommend that symptomatic individuals be protected with an implantable cardiac defibrillator. Asymptomatic individuals remain a diagnostic dilemma.**


**Key words:** Brugada syndrome, sudden cardiac death, ventricular tachycardia, ventricular fibrillation, genetic defect, right bundle branch block, ST segment changes.

## Introduction

In 1992 Brugada *et al.* described a syndrome of sudden cardiac death associated with partial right bundle branch block (RBBB) and ST segment elevation in the right precordial leads V1-V3 on the resting ECG.[1] Those affected have normal QT intervals, no electrolyte imbalance and structurally normal hearts. The syndrome is familial and it carries a high mortality rate of 10% a year in both symptomatic and asymptomatic individuals. The only recommended treatment is an implantable cardiac defibrillator (ICD).[2] The prevalence of the Brugada ECG pattern is 0.05–0.1% in the overall population, making recognition important.[3-5]

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## The Brugada syndrome ECG

The typical ECG findings are conduction delay and/or premature repolarisation in the right precordial leads V1-V3. The ST segment is downsloping with an inverted T wave. This is often described as 'coved' type ST shift. The widened S waves characteristic of true RBBB are absent in the lateral leads. The T wave may also be positive giving the 'saddleback' ST elevation (see figures 1 and 2). The ECG may change from 'coved' to 'saddleback' and may even normalise over time in approximately 40% of cases.[2] Sodium channel blockers such as ajmaline, procainamide, flecainide and propafenone can provoke Brugada shift patterns on ECG.[6] These drugs can unmask the changes in affected individuals with normal ECGs or accentuate changes already present and they have been used as the basis for a diagnostic test.

## Mechanism of arrhythmogenesis

Brugada syndrome is thought to be primarily a disease of cardiac conduction and it has been linked to abnormalities in the sodium channel (SCN5A).[2] The underlying electrophysiological mechanism in Brugada syndrome is thought to result from abnormal outward shifts in the ionic current during phase I of the right ventricular epicardial action potential. This is mainly due to changes in the sodium current. Under normal conditions, a prominent outward potassium current present in epicardial cells of the right ventricle leads to a prominent spike and dome morphology of the epicardial action potential. This creates a transmural voltage gradient between epicardium and endocardium, which is responsible for the inscription of the J wave[7] (normally buried in the QRS complex).

Pathological or physiological conditions that accentuate the outward shift of ionic current lead to a widening of the action potential notch and eventually to a loss of dome morphology. If epicardial precedes endocardial repolarisation then there will be 'saddleback' ST elevation, as the T wave remains positive. Further reduction in the outward current results in prolongation of the action potential in the epicardial cells, causing reversal of the transmural voltage. This leads to ST elevation with T wave inversion, that is the 'coved' Brugada shift.

These changes are insufficient to cause fatal ventricular arrhythmias: a further change which leads to the loss of the epicardial action potential dome morphology at some sites is required. This causes an increased dispersion of refractories, creating a window by which an extrasystole can lead to re-entry. The resulting tachyarrhythmia is usually a rapid polymorphic ventricular tachycardia similar to torsades de pointes and can degenerate into ventricular fibrillation.

**Figure 1.** The initial standard ECG leads $V_1$ to $V_3$ of a near sudden unexplained death syndrome showed no typical right bundle branch block or ST elevation typical of the Brugada syndrome (Brugada sign) but when the new higher intercostal space ECG leads ($-V_1$ to $-V_3$ and $-2V_1$, to $-2V_3$) were employed, the 'coved' types of the Brugada syndrome were revealed in lead $-2V_2$ and the 'saddleback' type in leads $-V_1$ and $-2V_1$.

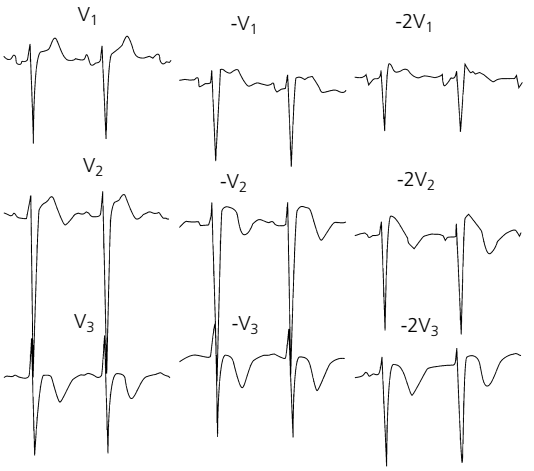


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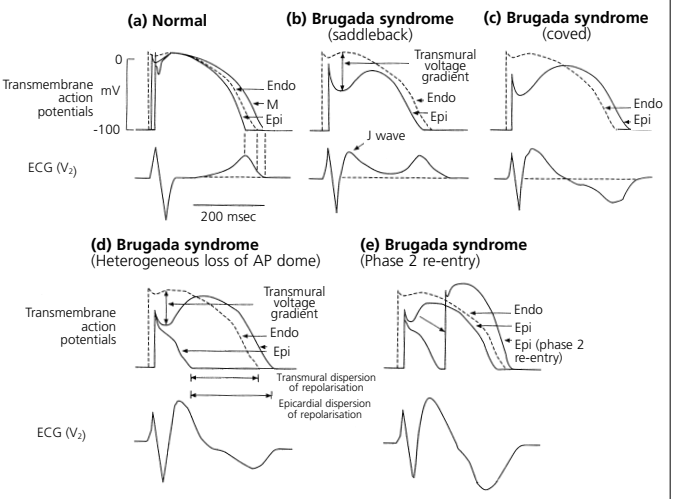
**Figure 2.** Schematic diagram showing right ventricular action potential changes thought to underlie the electrocardiographic phenotype of Brugada syndrome.

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Experiments carried out in animal models form the basis of these conclusions. Conditions such as hypothermia, ischaemia, metabolic disturbance and local pressure can also provoke Brugada shift patterns on the ECG and lead to re-entry.[2,8] There is a role for the autonomic nervous system in the ionic currents. Increased vagal tone can provoke Brugada shift patterns and lead to re-entry whereas sympathetic drive appears to be protective. This offers a potential explanation for why Brugada patients typically die in their sleep or at rest.[9]

## Inheritance and genetics

In patients with the Brugada syndrome phenotype, 50% of cases are familial. Only half show autosomal dominant inheritance, and the genetics are unclear in the remaining cases. The other 50% of cases are sporadic. Because 50% of the offspring of affected parents are themselves affected, family screening is advised.[2]

At present 15% of patients with Brugada syndrome have documented abnormalities in the $\alpha$ subunit of the SCN5A on chromosome 3.[2] This is the same gene implicated in the congenital long QT syndrome, LQT3. The different effects on sodium currents by the various mutations are thought to lead to one or other syndrome. However, this potentially neat explanation has become rather blurred by individuals with mutations that express phenotypes of both Brugada and LQT3 syndrome.[10]

## Clinical features

The patients described have been male (8:1) Caucasian or Asian. No cases have been recorded in the black Afro-Caribbean population.[2] Striking similarities between Brugada syndrome and the sudden unexpected death syndrome described in the South Asian population make it likely that they represent the same entity.[11] These patients present with sudden cardiac death at rest or in their sleep and have Brugada shift on their ECG. The rest of their history and physical examination are unremarkable. A family history of sudden death, syncope or ventricular fibrillation is present in 22%.[12]

## Diagnosis

Although there are no established diagnostic criteria for Brugada syndrome, reviews of the relevant literature suggest that the syndrome is characterised by: a family history of sudden cardiac death, polymorphic ventricular tachycardia, Brugada shift on 12-lead ECG, no evidence of structural heart disease demonstrated by standard techniques (cardiac catheterisation, echocardiography, magnetic resonance imaging and cardiac biopsy), accentuation of ECG changes with antiarrhythmic Vaughan Williams class Ia or Ic drugs and demonstration of genetic defects on SCN5A on chromosome 3 (see table 1).[2,8]

Differential diagnoses include: arrhythmogenic right ventricular dysplasia (ARVD), idiopathic ventricular fibrillation, polymorphic ventricular tachycardia (inherited or acquired prolonged QT) and asymptomatic variants (table 2). One of the asymptomatic variants is early repolarisation syndrome, which is characterised by ST elevation in leads V2–V4 with an upward concavity and positive T wave.

## Brugada versus idiopathic ventricular fibrillation

Approximately 5% of sudden cardiac death patients have no

**Table 1.** Characteristics of Brugada syndrome

- Familial history of sudden cardiac death
- Polymorphic ventricular tachycardia
- Brugada shift on 12-lead ECG
- No evidence of structural heart disease
- Accentuation of ST segment elevation by antiarrhythmic class Ia or 1c drugs
- Genetic defects in the sodium channel (SCN5A) on chromosome 3

**Table 2.** Differential diagnoses of Brugada syndrome

- Arrhythmogenic right ventricular dysplasia
- Idiopathic ventricular fibrillation
- Polymorphic ventricular tachycardia (inherited or acquired prolonged QT)

demonstrable cause of death and are classified as idiopathic ventricular fibrillation.[6] The prevalence of Brugada syndrome in patients with idiopathic ventricular fibrillation in a Japanese population was originally estimated by Chen *et al.* to be 40–60%.[13] More recent studies have suggested a lower prevalence of 3–24%.[14] This variation in figures may be attributed to different diagnostic criteria.[14] In the absence of any clear guidelines it is difficult to obtain a true figure for prevalence. In both these studies the sodium channel blocker challenge was not used in some patients and there is no widely available assay for genetic analysis. Both factors could lead to underestimation of the true prevalence.

Although Brugada *et al.* suggest a 100% sensitivity to the flecainide challenge in their genotyped population,[6] Priori *et al.* have proposed a much lower figure, about 20%.[16] In patients with LQT3 intravenous flecainide has been shown to bring out Brugada-type ECG changes in some individuals.[17] This is of particular concern as oral flecainide may be used as treatment for LQT3. Within families with the same mutation, not all members exhibit ST shift with flecainide. Priori *et al.*[17] propose that the flecainide test is therefore not only mutation-specific but may show individual variability.

## Brugada or ARVD

There is still controversy over whether Brugada syndrome is distinct from other diseases of the right ventricle, especially ARVD. Standard imaging techniques such as magnetic resonance imaging (MRI), echocardiography and angiography have failed to show any structural abnormalities in Brugada patients.[8] The genetic loci associated with ARVD are different and there are no similarities in the histopathology. Localised right ventricular morphological changes have been noted using electron beam CT[15] in Brugada syndrome patients. The sites of these lesions were also related to sites of premature ventricular contraction. Similar abnormalities were also found in a few controls. Whether these changes are normal physiological variants or even secondary to the underlying electrical disease is uncertain. Endomyocardial biopsy did not demonstrate any histopathological changes in the few subjects who were biopsied.

## Brugada or myocardial infarction

In the acute situation of an aborted sudden cardiac death, a resting ECG can be misinterpreted as a myocardial infarct and the patient may be given inappropriate thrombolysis. The Brugada shift pattern of ECG changes has been described in the context of right ventricular infarction/ischaemia.[18] The typical age group at presentation is between 30 and 40 years, so in younger patients clinicians should be aware that coronary artery disease may not be responsible (see figure 3). However, in practice it is difficult not to treat the patient as an acute myocardial infarction.

## Brugada shift ECG in asymptomatic individuals

The prevalence of Brugada type shift in asymptomatic individuals has been evaluated in populations in Japan and Europe. Tohyou *et al.* reported a 0.05% prevalence of the 'coved' pattern of ST shift in a study population of 20,027.[19] Hermida *et al.* showed a 0.1% prevalence of the 'coved' form and 6% prevalence of the 'saddleback' form.[3] More recently, Brugada shift was found in 0.14% of the general Japanese population.[5]

Brugada *et al.* reported a 27% event rate in asymptomatic individuals picked up during family screening or at random over a mean follow-up of 36 months.[20] However, some of these patients had already been identified as a high-risk group. A positive family history is a risk factor for the syndrome and this group of patients should be evaluated separately. Furuhashi *et al.* showed that there were no syncopal episodes in the individuals who had Brugada shift over a two-year follow-up period.[5] These were individuals who were asymptomatic and who had ECGs as part of a routine health screen. In a study of 11 asymptomatic individuals who did not have a positive family history of sudden death, Takenaka *et al.* showed no syncope or sudden death over a mean follow-up of 42.5 +/- 21.6 months.[21]

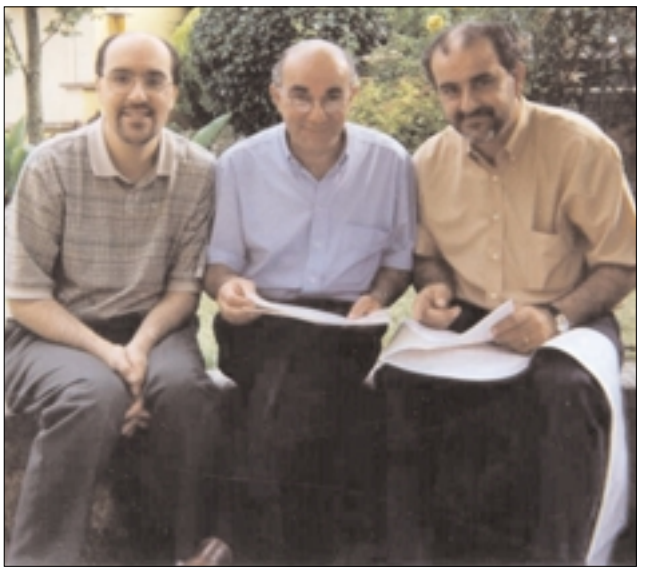
In all these studies it is important to consider the Brugada ECG used. The original cases described by Brugada *et al.* all showed 'coved' type ST changes. All the individuals in the Takenaka *et al.* study[21] had 'coved' type ST shift whereas the Furuhashi *et al.* study[5] included the 'coved' (0.05%) and 'saddleback' (0.09%) types. The high rate of 'saddleback' form in the Hermida *et al.* study[3] was attributed to overlap with the early repolarisation syndrome. Confusion still exists about the significance of the 'saddleback' form as the ECG changes over time and it can normalise or transform to the 'coved' form. The follow-up period in these studies was too short to assess the real risks in these individuals (table 3) who often remain asymptomatic between episodes (which may be separated by many years).

Brugada *et al.* argue that whether an individual is classified as asymptomatic or symptomatic is merely a matter of timing –

**Table 3.** Unanswered questions in Brugada syndrome

- The real risk for asymptomatic individuals over time
- The interplay of pathological, physiological and pharmacological factors in determining risk
- The role of electrophysiological studies in identifying those that would benefit from an ICD?

**Figure 3.** The Brugada brothers from left to right: Ramon Brugada (Houston, Texas), Pedro Brugada (Aalst, Belgium) and Josep Brugada (Barcelona, Spain).



everyone will have symptoms over time.[22] Longer-term follow-up studies are needed. Brugada *et al.* recommend intravenous flecainide challenge in order to exclude the diagnosis in patients with unexplained syncope.[22,23] In the asymptomatic individual the relevance of a positive response to antiarrhythmic class Ic agents is unclear. One of the problems is the use of different agents and oral preparations. In the Furuhashi *et al.* study,[5] only one individual had a positive response to intravenous cibenzoline, a slow kinetic sodium channel blocker. All the eleven patients in the Takenaka *et al.*[21] study showed a positive response to oral pilsicainide.

## Management

Brugada *et al.* suggest that the Brugada shift pattern on 12-lead ECG is a specific marker for those at risk from sudden death.[23] They recommend that symptomatic individuals be protected with an ICD. As yet, pharmacological treatment has not been shown to reduce mortality. Asymptomatic individuals remain a difficult diagnostic dilemma. Brugada *et al.* recommend extensive investigation of asymptomatic individuals to exclude significant cardiac disease, with implantation of an ICD in those who have inducible ventricular fibrillation/tachycardia on electrophysiological study.[23] However, there are no prospective trials to support this. Although the prevalence of the Brugada shift ECG in the normal population is concerning, there are no studies looking at the long-term follow-up of asymptomatic individuals.

### Key messages

- Brugada syndrome is characterised by a family history of sudden cardiac death, polymorphic ventricular tachycardia and Brugada shift on the 12-lead ECG
- The mortality rate is 10% per annum
- An implantable cardiac defibrillator is recommended in symptomatic patients
- Pharmacological treatment has not been shown to reduce mortality
- The risk for asymptomatic individuals over time is not known

## Conclusions

The proposed mechanisms involved in Brugada syndrome are a fascinating insight into the molecular biology of sudden cardiac death syndromes. The full role of pathophysiological mechanisms and the role of other pharmacological agents remain to be fully elucidated (table 3). The diagnosis is dependent on the correct interpretation of ECG findings, over which there is still some confusion. It is still not clear whether idiopathic ventricular fibrillation with a normal ECG and Brugada syndrome are different entities. There are no clearly identified genetic markers in the former. As the ECG changes over time, longer periods of follow-up are needed. The role of cardiac sodium channel blockers in unmasking the syndrome may also vary between individuals and over time. The prevalence of the Brugada ECG pattern in the general population makes it important to know who to investigate.

## References


1. Brugada P, Brugada J. Right bundle branch block, persisting ST elevation and sudden death: A distinct clinical and electrographic syndrome. A multi-centre report. *J Am Coll Cardiol* 1992;**20**:1391-6.
2. Naccarelli GV, Antzelevitch C. The Brugada Syndrome: clinical, genetic, cellular and molecular abnormalities. *Am J Med* 2001;**110**(7):573-81.
3. Hermida JS, Lemoine JL, Aoun FB, Jarry G, Rey JL, Quiret JC. Prevalence of Brugada syndrome in an apparently healthy population. *Am J Cardiol* 2000;**86**(1):91-4.
4. Viskin S, Fish R, Eldar M *et al*. Prevalence of Brugada sign in idiopathic ventricular fibrillation and healthy controls. *Heart* 2000;**84**(1):31-6.
5. Furuhashi M, Uno K, Tsuchihashi K *et al*. Prevalence of asymptomatic ST segment elevation in right precordial leads with right bundle branch block (Brugada-type ST shift) among the general Japanese population. *Heart* 2001;**86**:161-6.
6. Brugada R, Brugada J, Antzelevitch C *et al*. Sodium channel blockers

identify risk for sudden death in patients with ST segment elevation and right bundle branch block but structurally normal hearts. *Circulation* 2000;**101**:510-5.
7. Yan GX, Antzelevitch C. Cellular basis for electrographic J wave. *Circulation* 1996;**93**:372-9.
8. Antzelevitch C. The Brugada Syndrome; diagnostic criteria and cellular mechanisms. *Eur Heart J* 2001;**22**:356-63.
9. Kasanuki H, Ohnishi S, Ohtsuka M *et al*. Idiopathic ventricular fibrillation induced with vagal activity in patients without obvious heart disease. *Circulation* 1997;**95**:2277-85.
10. Bezzina C, Veldkemp MW, Van den Berg MP *et al*. A single Na channel mutation causing both long-QT and Brugada syndrome. *Circ Res* 1999; **85**:1206-13.
11. Nademanee K, Veerakul G, Nimmannit S *et al*. Arrhythmogenic marker for sudden unexplained death syndrome in Thai men. *Circulation* 1997; **96**:2595-600.
12. Alings M, Wilde A. "Brugada" syndrome. Clinical data and suggested pathophysiological mechanism. *Circulation* 1999;**99**:666-73.
13. Chen Q, Kirsch G, Zhang D *et al*. Genetic basis and molecular mechanisms for idiopathic ventricular fibrillation. *Nature* 1998;**392**:293-6.
14. Remmne CA, Wever EFD, Wilde AAM, Bershen R, Haver RNW. Diagnosis and long term follow-up of Brugada syndrome in patients with idiopathic ventricular fibrillation. *Eur Heart J* 2001;**22**:400-9.
15. Takagi M, Aihara N, Kuribayhashi S *et al*. Localised right ventricular morphological abnormalities detected by electron-beam computed tomography represent arrhythmogenic substrates in patients with Brugada Syndrome. *Eur Heart J* 2001:**22**:1032-41.
16. Priori SG, Napolitano C, Terrence L *et al*. Incomplete penetrance and variable response to sodium channel blockade in Brugada's syndrome. *Eur Heart J* 1999;**20**(suppl):465A (abstract).
17. Priori SG, Napolitano C, Schwartz PJ, Bloise R, Crotti L, Ronchetti E. The elusive link between LQT3 and Brugada Syndrome. The role of flecainide challenge. *Circulation* 2000;**102**:945-7.
18. Kataoka H, Kanzaki K, Mikuiya Y. Massive ST-segment elevation in precordial and inferior leads in right ventricular myocardial infarction. *Electrocardiol* 1988;**21**:115-20.
19. Tohyou K, Nahazawa K, Takenobu H, Akayi T, Miyake H, Murayama M. A survey of the incidence of right bundle branch block with ST elevation among the normal population. *Jpn J Electrophysiol* 1995:**15**:223-6.
20. Brugada J, Brugada P. Further characterisation of the syndrome of right bundle branch block, ST elevation and sudden cardiac death. *J Cardiovasc Electrophysiol* 1997;**8**:325-31.
21. Takenaka S, Kusano KF, Hisamatsu K *et al*. Relatively benign clinical course in asymptomatic patients with Brugada-type electrocardiograms without family history of sudden death. *J Cardiovasc Electrophysiol* 2001;**12**:2-6.
22. Brugada J, Brugada R, Brugada P. Asymptomatic patients with a Brugada electrocardiogram. *J Cardiovasc Electrophysiol* 2001;**12**:7-8.
23. Brugada P. Brugada Syndrome: an electrocardiographic diagnosis not to be missed. *Heart* 2000;**84**:1-2.