

## The Brugada Syndrome, ST-elevation on ECG

### Introduction

Brugada syndrome is characterized by abnormal electrical activity in the right ventricular epicardium due to a defect in Na channels, which results in a specific abnormal ECG pattern with ST elevation in leads V1 to V3. Clinically it is associated with life threatening ventricular arrhythmias and sudden cardiac death.<sup>1</sup> This syndrome was described by Brugada and Brugada in 1992, and since then it has attracted great interest with an exponential rise in reported cases and papers.

### Genetic Factors

In about one fourth of Brugada patients a mutation in SCN5A gene on chromosome 3, which encodes for the alpha subunit of the cardiac sodium channel gene, has been reported. The mode of transmission is autosomal dominant and the mutated gene has been seen more with familial than sporadic cases. About 60 different mutations have been reported on this gene that produce the syndrome, and a number of them may cause overlapping conditions with the long QT syndrome, as the same gene is involved in a congenital form of the long QT syndrome. The result of the mutation is failure of expression of sodium channels, or a disturbance in their function by accelerated inactivation of the channels, prolonged recovery or a shift in time and voltage dependence of  $I_{Na}$  activation or inactivation. No relation has been found between a specific mutation and risk of arrhythmic event, but genetic testing can provide more support to confirm the diagnosis and detect the relatives at risk.<sup>2-4</sup>

### Pathogenesis

The working hypothesis is unopposed outward current of potassium at the end of phase 1 of the action potential because of the Na channelopathy. This creates a gradient of voltage between epicardium and endocardium and leads to J point elevation in V1 to V3. As there is no

transmural voltage gradient in the plateau phase of the action potential, the ST segment remains isoelectric. In the next phase of action potential, if the epicardium repolarizes normally before or close to endocardium then the T wave remains positive in V2, otherwise it becomes negative. Loosing action potential dome in some parts of epicardium, but not all parts of it, leads to local re-excitation via phase 2 reentry. The local re-excitation may lead to development of closely coupled extrasystoles and triggering of VT/VF. Thus, the transient outward current causes loss of the action potential dome in some sites of epicardium and a voltage gradient between epicardium and endocardium is responsible for ST elevation, whereas the gradient between different sites of the epicardium leads to a phase 2 reentry, and then extrasystole and VT/VF.<sup>3</sup>

It has been seen that the transient outward current at the end of phase 1 is more prominent in males than females and this explains why, despite an autosomal transmission, the symptomatic phenotype is about 10 times more common in males. There are other working hypotheses to explain this gender difference in Brugada syndrome including a possible role for testosterone.<sup>2</sup>

Any condition or medication that increases outward currents or decreases inward sodium or calcium currents may precipitate or unmask the syndrome. Therefore, sodium channel blockers like procainamide will unmask the syndrome by decreasing the inward current and so do Ca channel blockers, beta-blockers, cocaine and antidepressants. On the other hand vagotonic agents,  $I_k$ -ATP activators, and hypokalemia have the same effect via enhancing the outward current.<sup>3,5</sup>

A normal sodium channel may be inactivated prematurely in physiologic or above physiologic temperatures, and this characteristic is exaggerated in the Brugada syndrome. This can explain why a number of Brugada patients have shown unmasking of the syndrome and polymorphic VT in a febrile state.<sup>3</sup>

## Clinical and Epidemiological Characteristics

As the ECG changes are dynamic and transient, it is difficult to know the true prevalence and incidence of the syndrome, but it is known to be common in south Asia and it has been reported as common as 0.16% of the population in Japan.<sup>6</sup> It is more common in males than females and more commonly presents for the first time in the fourth decade of life, although it has been reported in children as young as two days and in the elderly at 84 years-of-age.<sup>3</sup> It is the most common cause of sudden cardiac death in patients with a structurally normal heart. It is estimated to be responsible for 4 to 12% of all sudden deaths. The most common presentation of the Brugada syndrome is syncope.

It may show three types of electrocardiographic changes on 12 lead ECG. In type 1 the ECG shows greater than 2 mm J point elevation with down sloping coved ST segments and usually a negative T wave. Type 2 and 3 show the same 2 mm or greater J point elevation, but the positive T wave gives the “saddleback” appearance to the ST-T portion. In type 2 the terminal portion of ST segment is elevated greater than 1 mm and the T wave may be positive or biphasic, whereas the terminal ST elevation in type 3 is less than 1 mm and T wave is only positive. As the Brugada syndrome is dynamic, all the above ECG changes may be seen in the same patient at different times. Type 1 is diagnostic whereas type 2 and 3 need further diagnostic test to confirm the presence of the syndrome.

Placing the right precordial ECG leads in an upper position like the second intercostal space increases the sensitivity of ECG to detect all types of the syndrome; however it decreases its specificity.<sup>3</sup>

## Diagnostic Criteria

The diagnosis of the Brugada syndrome is considered definite when one of the ECG criteria and one of the clinical criteria are present. ECG criteria are presence of type 1 ECG changes, or conversion from type 2 and 3 to type 1 after administration of sodium channel blockers such as procainamide or flecainide. Type 2 and 3 changes are considered nonspecific for Brugada syndrome unless they turn to type 1 after a sodium challenge test. In addition to ECG criteria, one of the following should be present to confirm the diagnosis: syncope, history of VT or VF, family history of sudden cardiac death, or inducibility of VT at electrophysiology study (EPS). Inducibility of sustained VT during programmed ventricular stimulation is a very good predictor of outcome in Brugada syndrome and is associated with more spontaneous VT.<sup>7</sup>

## Figure 1.

**Type 1 Brugada pattern on ECG of a 75-year-old Caucasian female who presented to Carle Foundation Hospital with a transient shortness of breath. Of course this is an atypical presentation for Brugada syndrome.**

Vent. rate	115	BPM	Sinus Rhythm
PR Interval	*	mx	ST elevation consider anterior injury or acute infarct
QRS duration	90	mx	Probably Brugada Syndrome
QT/QTc	356/492	mx	Abnormal ECG has changed
P-R-T axes	76 89	74	



As ST elevation can be associated with many different underlying conditions, it is a good practice to exclude other causes of ST elevation. The most common and important etiologies of ST elevation on ECG are acute myocardial ischemia or infarction, atypical right bundle branch block, Prinzmetal's angina, hyperkalemia, hypercalcemia, early repolarization and acute pericarditis. Some more rare conditions have also been reported to mimic the Brugada ECG changes, such as hypothermia and mediastinal tumor with mechanical compression on the right ventricle.<sup>8,9</sup>

## Treatment

To date, the only approved treatment for the Brugada syndrome is implantable cardioverter defibrillator (ICD) placement, which has been shown to be 100% effective in a large multicenter trial after five years follow up of 690 Brugada patients. In this study, appropriate shocks were delivered in 51% of the patients who initially presented with syncope and in 37% of the patients who initially were asymptomatic.<sup>10</sup>

ICD implantation is recommended mainly for two groups of Brugada patients: symptomatic patients with type 1 ECG changes (with or without sodium blocker challenge), and asymptomatic patients who show inducible ventricular arrhythmia undergoing electrophysiologic studies. Regarding the first group, it is important to rule out other causes of syncope

or seizure before attributing them to the Brugada syndrome. Asymptomatic patients with type 1 ECG changes should undergo EPS if there is a family history of sudden cardiac death; then ICD placement is recommended if ventricular arrhythmia is inducible. There is controversy as to whether to do EPS in asymptomatic patients who show type 1 changes spontaneously with no family history of sudden cardiac death. The authors suggest considering age and comorbidities in this situation to make the best decision for the patient. Alternative treatments are pacemaker placement, radiofrequency ablation and some antiarrhythmic medications.

Pharmacologic therapy is based on the idea of rebalancing of the current at the end of phase 1 of the action potential. In experimental models, quinidine decreases ST elevation, and prevents phase 2 reentry and associated VT. However, there are studies that have shown augmentation of ST elevation following administration of quinidine.<sup>11</sup> Isoproterenol, which is a beta-agonist, and cilostazol, which is a phosphodiesterase inhibitor, are potentially helpful too.

As those sudden cardiac deaths that occur at sleep or rest are usually associated with a slow heart rate, a permanent pacemaker can be a potential treatment. Also there is the potential for ablation of the ventricular premature beats that trigger VT/VF to be a treatment option. Currently, there is insufficient data to support any of the above alternative treatments and ICD placement remains the only definitive therapy for treating VT/VF in Brugada syndrome.

## Summary

The Brugada syndrome was first described in 1992 by Brugada and Brugada. It is more common in young males and in south Asia. The true incidence and prevalence in the US is not known. In up to 30% of the cases a mutation in the cardiac sodium channel gene SCN5A on chromosome 3 has been found, which causes loss of the action potential dome in some parts of right ventricular epicardium. The voltage gradient between those sites of the epicardium and endocardium causes J point elevation in the right precordial leads of ECG. The gradient between those sites of epicardium and the intact sites leads to local re-excitation via phase 2 reentry and this may lead to development of closely coupled extrasystole and triggering VT/VF.

The syndrome has three main ECG types. Type 1, which is diagnostic for the syndrome, is associated with J point elevation on leads V1 to V3 with down sloping ST segment and negative T waves; there is no reciprocal ST depression and the QT interval is normal.

The most common clinical presentation is syncope and it is important to remember this syndrome as one of the potentially dangerous differential diagnoses of ST elevation on ECG. The diagnosis is confirmed with type 1 ECG pattern, or conversion of other types to type 1 after administration of sodium channel blocker agents plus one of the clinical criteria: syncope, history of VT or VF, family history of sudden cardiac death or type 1 ECG changes, or inducibility of VT on EPS. The only approved treatment is ICD placement; it is recommended for symptomatic patients and asymptomatic patients with spontaneous type 1 ECG pattern and a history of sudden death in the family, who show inducible ventricular arrhythmia on EPS. The prognostic value of different types of mutations and evaluation of other treatment options are potential areas for further research.

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### CME Questions 7a-d

Please select the best answer to each of the following questions:

- 7a. What is the most common clinical presentation of the Brugada syndrome?
- Syncope
  - Sudden Cardiac Death (SCD)
  - Chest pain
  - Seizure
  - Nausea and vomiting
- 7b. A 58-year-old male patient comes to the emergency room complaining of a syncopal episode 12 hours ago while he was driving. The episode happened abruptly and without warning and he regained his consciousness equally as suddenly. His wife, who was with him at the time, states they had just left their home when this happened and that the patient lost consciousness for about two minutes while she tried to keep the control of the car. The patient states he had a similar episode a few years ago and that his brother has also had a few episodes of syncope with unknown etiology. The patient's physical examination and past medical history is unremarkable. An ECG was taken and showed a 3 mm J point elevation with down sloping ST segment and inversion of T wave in leads V1, V2 and V3. Cardiac enzymes are within normal limits. What is the best next step in diagnosis or treatment of this patient's condition?
- Cardiac catheterization for diagnosis of STEMI
  - ICD placement for symptomatic Brugada syndrome
  - EPS to evaluate inducibility of ventricular arrhythmia
  - Discharge the patient to home with event monitor device

- 7c. Which of the following statements best describes the pathophysiology of ST elevation in the Brugada syndrome?
- There is ST elevation because of early repolarization
  - The ST elevation is because of associated ischemia
  - The ST elevation is because of voltage gradient between epicardium and endocardium at the end of phase 1 of action potential
  - The ST elevation is mainly because of associated inflammation in pericardium (pericarditis)
  - The ST elevation is part of associated right bundle branch block
- 7d. Which one is NOT a diagnostic criterion for the Brugada syndrome?
- Type 1 ECG pattern after administration of procainamide
  - Syncope
  - Family history of type 1 ECG pattern
  - Family history of sudden death
  - Spontaneous type 2 ECG pattern

## Answers to the CME Questions

1a. c  
1b. e  
1c. a

2a. c  
2b. c  
2c. a

3a. a  
3b. b  
3c. b  
3d. a  
3e. c  
3f. b

4a. b  
4b. d  
4c. b

5a. a  
5b. a  
5c. a

6a. b  
6b. a  
6c. b  
6d. a

7a. a  
7b. b  
7c. c  
7d. e