Worrisome Thoughts About the Diagnosis and Treatment of Patients With Brugada Waves and the Brugada Syndrome

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Abstract—The Brugadas have made a significant contribution to medicine. Their discovery of a new clinical syndrome and ECG abnormalities has created a great deal of interest and has opened Pandora’s box. Here, we discuss some worrisome thoughts about the condition. We stress the need for improved diagnostic criteria and treatment because it is not always possible to perform coronary arteriography, electrophysiological studies, right ventricular myocardial biopsy, and MRI in all patients in whom ST-segment abnormalities are seen in the ECG, especially in patients who are asymptomatic. Accordingly, further research is needed to guide the clinician in the diagnostic and therapeutic problems of patients who have unusual ST segments in leads V1 and V3. We present a patient who illustrates the problem. (Circulation. 2004;109:1463-1467.)

Key Words: Brugada syndrome ■ diagnosis ■ electrocardiography ■ death, sudden ■ arrhythmia

A lert practicing physicians are always searching for ECG evidence of myocardial ischemia, myocardial injury, and myocardial infarction. Accordingly, they can identify ST-segment abnormalities in leads V1 through V3, along with T-wave inversion and right ventricular conduction system block, in the ECGs of (1) patients who are asymptomatic but have abnormalities discovered in a routinely recorded tracing, (2) patients who are symptomatic because of myocardial ischemia, and (3) patients who are symptomatic because of syncope or cardiac arrest caused by ventricular fibrillation.

The following case report illustrates some of the problems associated with the diagnosis and treatment of this condition.

Patient Presentation

History
S.K., a 55-year-old man from Thailand, complained of malaise and epigastric discomfort of acute onset. He presented to a hospital on January 29, 2002, where he was diagnosed as having an acute myocardial infarction because of abnormalities in the ECG. He received thrombolytic therapy but experienced no change in symptoms or ECG. He was transferred to Emory Crawford Long Hospital (Atlanta, Ga) on January 30, 2002, for cardiac catheterization.

Essential hypertension had been controlled with triamterene/hydrochlorothiazide 37.5 mg/25 mg every day. He worked as a Buddhist monk and had not married. His mother died in her 70s and his father died in his 60s of unknown causes, and he had no siblings.

Physical Examination
The patient was an Asian man in no acute distress. His systolic and diastolic blood pressures were 149 and 90 mm Hg, respectively. His heart rate was 62 bpm and regular. His respiratory rate was 15 per minute, and he was afebrile. The physical examination was normal except for a faint systolic murmur at the base and a left atrial gallop sound at the cardiac apex.

Pertinent Laboratory Findings
The initial ECG made before admission to Emory Crawford Long Hospital showed right ventricular conduction delay and “saddleback” ST segments in leads V1 and V2 (see Figure 1). Cardiac enzymes were normal.

Hospital Course
Because of the patient’s epigastric discomfort and the referring doctors’ concern that the patient could have an acute coronary syndrome with normal cardiac enzymes, a cardiac catheterization was performed. The coronary arteriogram was normal, as was the ejection fraction. An echocardiogram revealed normal right and left ventricular size and function with mild left ventricular hypertrophy, mild aortic insufficiency, and tricuspid regurgitation considered to be unimportant echo findings. His cardiac enzymes remained normal, and telemetry revealed no arrhythmias. The saddleback abnormalities in leads V1 through V3 were replaced by slightly elevated ST segments in leads V1 through V3 (see Figure 2). A procainamide infusion of 50 mg/min for a total of 1 g was administered. This precipitated a significant, “coved”—appearing increase in ST-segment elevation in leads V2 and V3 (see Figure 3). The abnormal ST segments also revealed minute wiggles.
The symptoms of epigastric discomfort resolved and were attributed to gastrointestinal reflux disease. The patient did not have a right ventricular biopsy or an electrophysiology study to determine whether ventricular tachycardia could be induced. An internal cardiac defibrillator was not implanted, and no antiarrhythmic drugs were prescribed. He was instructed to report immediately to his doctors if he had palpitations or a fainting episode.

**Discussion**

Four articles stand out as extremely important to clinicians who might encounter such patients. They are the Brugada brothers’ original description of the condition that was published in 1992, the publication of Gussak et al in 1999 pointing out that there are numerous causes of a persistent “ST” segment elevation in leads V₁ through V₃, the summary by Surawicz of the knowledge that accumulated about the condition in 2001, and the superb recent report by Antzelevitch et al, in which they summarize the information that has been accumulated during the past 10 years.

**Criteria for Diagnosis**

There are 3 types of Brugada waves. Type I was described in 1991 by the Brugadas. The ST-segment elevation in leads V₁ through V₃ is triangular; there may or may not be right ventricular conduction system block or delay; and the T waves may be inverted in leads V₁ through V₃. There are 2 types of saddleback ST-segment abnormalities. In type 2, the downward displacement of the ST segment lies between 2 elevations of the segment in leads V₁ through V₃, and the T waves in types 2 and 3 may not be inverted, and there may or may not be right ventricular conduction system block or delay.

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**Figure 1.** This tracing was recorded on January 30, 2002. It shows type 2 Brugada waves. Note the saddleback ST segments in leads V₁ and V₂. The terminal 0.04-second vector of the QRS complex is directed to the right and anteriorly, indicating the presence of right ventricular conduction delay.

**Figure 2.** This tracing was recorded on January 31, 2002. The saddleback abnormality has been replaced by simple elevation of the ST segments in leads V₁ through V₃.
Although the unusual waves in the ECG must be present to
diagnose Brugada waves, certain other clinical features must
be present to make a definite diagnosis.

When the abnormality is due to an unprovoked mutation,
the patient is commonly quite young. Because ECGs are not
routinely recorded in young people, these patients are usually
studied because they have syncope or palpitations or have
survived cardiac resuscitation performed for sudden death.
Such waves are referred to as primary Brugada waves.

When the ECG abnormalities are precipitated by or un-
masked by drugs such as flecainide, procainamide, ajmaline,
disopyramide, propafenone, or pilsicainide, elevated body
temperature, vagotonia, β-adrenergic blockers, α-adrenergic
agonists, dimenhydrinate, cocaine, and tricyclic antidepres-
sants (see Figure 4), the ST-segment abnormalities are
referred to as secondary Brugada waves. Such patients are
commonly middle-aged or elderly adults.

When the episodes of ventricular tachycardia or fibrillation
are identified in patients with Brugada waves in the ECG, the
condition is referred to as the Brugada syndrome.

From the beginning, the Brugadas have insisted that the
heart is structurally normal. Accordingly, the coronary arte-
riogram, echocardiogram, MRI, and right ventricular endo-
myocardial biopsy must be normal.

The condition is apparently common in southeast Asia, the
Philippines, and Japan. The primary and secondary types are
seen occasionally in the United States. Obviously, more
patients will be identified in the United States as the condition
becomes more widely known.

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Treatment of a Patient With Brugada Waves or
Brugada Syndrome

As Gussak et al pointed out, there are at least 17 causes for
an alteration of the ST segments in leads V₁ through V₃. Thus,

Figure 3. This tracing was recorded on January 31, 2002, after procainamide infusion. The ST segments approach the shape com-
monly seen in patients with myocardial infarction. Note that the wiggles on the ST segments are seen easily in leads V₂ through V₄ but
are also seen in other leads. Could they possibly be Fontain (epsilon) waves?

Figure 4. This tracing, recorded on another patient, shows classic secondary
type I Brugada waves. Note that the tall-
est part of the ST segments in leads V₁ through V₃ is at its onset. This high point
is followed by rapid collapse of the ST segments. Note also that there is right
ventricular conduction delay. These dis-
tinctive Brugada waves were precipitated
by appropriate doses of the antidepressant
drug desipramine. Reprinted from Refer-
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even seasoned electrocardiographers may have difficulty identifying the Brugada waves in some patients.

When adult patients seek medical care because of syncope resulting from ventricular tachycardia or transient ventricular fibrillation, they should be evaluated with coronary arteriography and electrophysiological studies and treated with appropriate drugs and an interval cardiac defibrillator. There are obstacles to this approach, however. It is not always possible, especially in young children. In addition, such procedures are not always available. Other procedures, such as MRI, may not be available, and right ventricular biopsy may not be justified in every patient. Studies to identify the genetic abnormality are rarely available. Finally, the procedures may be available, but patients may not have the financial resources for such treatment.

There are even more worrisome thoughts when primary Brugada waves are found in routinely recorded ECGs in asymptomatic patients. It may be difficult to exclude the presence of heart disease in such patients, and what is the likelihood that they will have a lethal arrhythmia? We need additional information to answer the question more precisely.

Arrhythmogenic right ventricular dysplasia cardiomyopathy (ARVD/C) should be considered a possible cause of Brugada waves in some patients. It is now known that Brugada waves are linked to mutations in the SCN5A gene and that ARVD/C is linked to several chromosomes and 3 putative genes. The ECG abnormalities that suggest the diagnosis of ARVD/C are epsilon waves (or Fontain waves) in leads V1 through V3. Corrado et al described a subset of patients with ARVD/C who had the Brugada syndrome. Therefore, it is necessary to consider the possibility of ARVD/C in patients with the Brugada syndrome or Brugada waves. Knowing this, can a clinician state with certainty that there is no structural heart disease in every patient with Brugada waves?

The ST-segment abnormalities shown in Figure 3 also bring up 2 other questions. Are epsilon waves present? Will procainamide infusion precipitate epsilon waves? The foregoing discussion suggests that the workup of patients with Brugada waves should include an MRI in search of right ventricular wall abnormalities. If such an abnormality is found, can we conclude that it always implies that ARVD/C is the cause, because it is possible for an electrical abnormality in the myocytes to produce such an abnormality?

The interesting report by Bjerregaard and Molgaard shows epsilon waves and Brugada waves in the same tracing of a patient with biventricular dysplasia. This report illustrates how complex the problem is.

The clinician may correctly ask why we need to know if ARVD/C is present because there is no specific treatment for the condition and ventricular arrhythmias are treated with an internal cardiac defibrillator. Therefore, physicians may not obtain an MRI or right ventricular endomyocardial biopsy. These studies are used by physicians engaged in an intense study of the problem, such as the Brugadas, who use such techniques to define the clinical features of the condition.

Cardiac electrophysiological studies in patients with the Brugada syndrome may or may not be needed, depending on how they entered the healthcare system. When the patient has classic Brugada waves in the ECG after ventricular tachycardia has reverted to normal, an electrophysiological study may not be needed, but an internal cardiac defibrillator is clearly indicated.

Should electrophysiological studies be performed in asymptomatic patients in whom Brugada waves are seen in a routinely recorded ECG? Some clinicians believe that such patients should have an electrophysiological study and, if ventricular tachycardia is inducible, an internal cardiac defibrillator should be implanted. Others do not hold to such a view. The Brugadas reported that 8% of asymptomatic patients with Brugada waves had subsequent cardiac events. This figure may need to be altered as more cases are observed. Assuming that 8% is correct, does the information justify the use of an internal cardiac defibrillator? The answer to this question would vary from physician to physician. Accordingly, a definite answer to this question must be found.

Patients with secondary Brugada waves resulting from various drugs should discontinue the drugs. The question is, do the drugs cause the Brugada waves or unmask them? The use of procainamide to provoke the development of an abnormal ST-segment displacement, as occurred in the patient reported here, is not a reliable indicator of hidden Brugada waves. Therefore, should we ignore it in the patient reported here (see Figure 3)? Also, are subsequent arrhythmias as likely to occur in patients with secondary Brugada waves as they are in patients with primary Brugada waves?

Conclusions

The Brugadas are to be congratulated for observing and describing the cardiac abnormalities now known as Brugada waves and the Brugada syndrome. The brilliant work of Antzelevitch has clarified the cellular basis for the condition, and many geneticists have described abnormalities in the genes responsible for the condition.

It is clear, however, that a great deal of additional research is needed before all cases are recognized and additional treatment modalities are discovered. For example, it is not possible to justify the study of a patient’s genes, perform an endomyocardial biopsy, perform an MRI, perform an electrophysiological study, and perform a coronary arteriography in every patient in whom the condition is suspected. This problem occurs because not all of these tests are available or because the financial resources to perform them are not available. Although the value of new drugs is being investigated, it is unlikely that they will be as reliable as the internal cardiac defibrillator.

As research progresses, the investigators, in addition to further clarifying the clinical features of the condition, will undoubtedly address the problem of availability and affordability of the methods used to identify and treat this serious condition. Otherwise, without such information, we will end
up knowing a lot but may be unable to deliver what we know to patients.

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References
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