EDITORIAL COMMENT

Brugada Syndrome: Manifest, Concealed, “Asymptomatic,” Suspected and Simulated*

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In the 2001 edition of the textbook Heart Disease (1) Brugada syndrome is defined as a “distinct form of idiopathic ventricular fibrillation (VF) in which patients have right bundle branch block (RBBB) and ST elevation in the anterior precordial leads without evidence of structural heart disease.” Although patients with such characteristics were described before the Brugada brothers reported their findings (2), the eponym “Brugada syndrome” is a deserved tribute to these investigators, who were the first to define this syndrome as a distinct functional cardiac disorder (3).

The three components of the syndrome are: 1) syncope and sudden cardiac death (SCD); 2) absence of structural heart disease, QT prolongation, and metabolic or pharmacologic factors for triggering cardiac arrest; and 3) complete or incomplete RBBB with elevation of the ST segment or of the J point in the leads V1 to V2 and V3, which will be referred to as Brugada electrocardiogram (ECG) pattern.

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Additional findings that support the diagnosis but are not universally present include 1) prevalence in men; 2) familial incidence; 3) molecular defect in the structure of the cardiac sarcolemmal sodium channel gene, SCN5A, resulting in the malfunction of this channel (channelopathy); 4) characteristic response to pharmacologic challenge with class IA or IC sodium channel-blocking drugs, which exaggerate the existing ST-segment elevation in the right precordial leads and unmask the ST-segment elevation when it ceases to be present; and 5) induction of VF, or sustained ventricular tachycardia during programmed electrical stimulation (PES). The criteria for diagnosing Brugada syndrome can be applied to some victims of the unexplained “death syndrome” in young male Southeast Asians (4) and to some patients with idiopathic VF (5). Brugada syndrome, however, should not be confused with arrhythmogenic right ventricular cardiomyopathy (ARVC), although the two conditions share the characteristic ECG pattern, and the propensity for SCD.

OTHER CAUSES OF BRUGADA ECG PATTERN

The Brugada ECG pattern resembles RBBB with ST-segment elevation caused by anteroseptal ischemia or myocardial infarction (MI), right ventricular ischemia or MI, pulmonary embolism, hyperkalemia, and by cardiac transplantation. In patients with RBBB, ST-segment elevation can be simulated by a retrograde P-wave during atrioventricular junctional rhythm, or by a Ta-wave in the presence of a deeply negative P-wave with a short PR interval.

Gussak et al. (6) listed 18 conditions that can be associated with ST-segment elevation in the right precordial leads. None of these conditions, with the possible exception of the overdose with sodium channel-blocking heterocyclic antidepressant drugs, are likely to be suspected of being related to Brugada syndrome. In some cases, however, the ST-segment elevation in the presence of RBBB remains unexplained. In my collection of 41 ECGs with the Brugada ECG pattern in patients without history of aborted SCD, 12 subjects had unexplained coved ST-segment elevation in the right precordial leads.

PROBLEMS WITH DOCUMENTING THE DIAGNOSIS OF BRUGADA SYNDROME

The problems that may complicate proper recognition of the Brugada syndrome fall into the following three categories: 1) ruling out structural heart disease that may cause SCD in subjects with Brugada ECG pattern; 2) definition of Brugada ECG pattern; and 3) clinical significance of unexplained asymptomatic Brugada ECG pattern.

Ruling out structural heart disease. Diagnosis of Brugada syndrome requires ruling out conditions known to cause SCD unless such conditions are acquired after the establishment of the Brugada syndrome.

A complete workup of a symptomatic patient with Brugada ECG pattern may require, in addition to the routine history, physical examination and ECG, a transthoracic or transesophageal echocardiogram, coronary angiogram, stress test, magnetic resonance imaging and, in some cases, myocardial biopsy. Facilities to perform such studies are not universally available. Even if the facilities are available such extensive workup cannot be justified in asymptomatic patients. Other tests are not necessarily helpful. Studies by Priori et al. (7) in 30 symptomatic and 30 asymptomatic patients with the Brugada ECG pattern showed that PES identified only a fraction of individuals at risk, and that sodium channel blockade failed to unmask most silent gene carriers. In the Priori et al. (7) study, prevalence of mutations of the cardiac sodium channel was 15%, demonstrating genetic heterogeneity of the syndrome.

Definition of Brugada ECG pattern. The QRS pattern of patients with Brugada syndrome may show complete RBBB, incomplete RBBB, or “focal” RBBB in which the QRS complex with the terminal R’ deflection in the right
The ST segment can be concave (saddle-back), convex (coved), or straight (i.e., of triangular shape) (6). These patterns can be present permanently or intermittently. The saddle-back pattern is more often encountered as a normal variant of early repolarization and in other conditions unrelated to Brugada syndrome, but it cannot be dismissed as harmless, because in the study by Atarashi et al. (8) the pattern of RBBB with saddle-back ST-segment elevation was present in 1 of 17 patients with VF and in 3 of 12 patients with syncope. These investigators have shown that both the contour and the amplitude of ST-segment elevation can vary in the same patient during the follow-up. It is also known that some subjects may have a saddle-back pattern in one of the right precordial leads and a coved pattern in the neighboring precordial lead. Gussak et al. (6) concluded that the diagnosis of Brugada syndrome cannot be made on the basis of the ECG alone. The importance of this statement should not be underestimated.

**Clinical significance of unexplained asymptomatic Brugada ECG pattern.** Prevalence of the syndrome in the surveys of Brugadas. In 1992, Brugada and Brugada described the syndrome in six men and two women (3). In 1998, Brugada et al. (9) presented data on 63 patients recruited in 33 centers around the world. In a report published in 2001 (10) these investigators described 239 patients with a “Brugada ECG.” This cohort included an unspecified number of asymptomatic patients. The growing numbers reflect the increasing recognition of the syndrome, which might have been aided by the introduction of a World Wide Web home page of the Brugada syndrome on the internet in 1997 (6).

**Prevalence of Brugada syndrome and Brugada ECG pattern in other studies.** Atarashi et al. (8) found 63 patients with RBBB and ST-segment elevation during a seven-month period of registration from 34 institutions in Japan, but the number of screened ECGs was not specified. In two other studies from Japan, the prevalence of Brugada ECG (only the coved type with rSR’ pattern) was 0.07% among 4,092 healthy adult patients (ref. 6 in ref. 11) and 0.21% among 3,300 patients undergoing routine checkup (12).

In other studies, Hermida et al. (13) found 1 case among 1,000 apparently healthy subjects (0.1%), and Monroe and Littman (14) found 52 cases of Brugada ECG pattern among approximately 12,000 unselected noncardiac patients. In their study, saddle-back pattern was present in 50 cases and coved pattern was present in 2 cases.

An important addition to the above scanty data is the study by Miyasaka et al. (11) published in this issue of the *Journal*. The investigators examined prevalence of the Brugada ECG pattern in 13,929 patients in whom ECG was recorded during routine health examination in a middle-sized Japanese city, Moriguchi, Osaka, in the year 1997. In this city the health examination was offered to patients who were older than 40 years or to younger patients suspected to have a cardiac anomaly. A Brugada-type ECG was defined as RBBB and ST-segment elevation >0.1 mV in the leads $V_1$ to $V_2$ and $V_3$. Of the two interpreters, one diagnosed the pattern in 104 subjects and the other in 133 subjects. A 99.7% agreement between these two observers was reached on 98 ECGs. As expected, the pattern was more prevalent in men. The saddle-back type of ST-segment elevation was present in 81 and the coved pattern in 37 patients. In those with coved type, 17 patients had rsR’ pattern (considered by the investigators as “typical”) and 20 had Rs’ pattern. The prevalence of all types was 0.7%; of the coved type was 0.26%, and of the coved rsR’ pattern was 0.12%. Among male patients, the prevalence of all types was 2.14%, and of the coved rsR’ pattern it was 0.38%.

The large differences in the prevalence in the reported studies are not surprising considering the lack of uniform methodology to define the population in terms of gender, age and presence or absence of heart disease, as well as the absence of uniform criteria defining the Brugada ECG pattern.

Of the three studies in which only the coved type was considered, the prevalence of this pattern was 0.016% in the study by Monroe and Littman (14); 0.1% in the small sample of Hermida et al. (13); and 0.26% in the cases studied by Miyasaka et al. (11). The latter study (11) provides the most useful assessment of the prevalence of the Brugada ECG pattern because the investigators examined the largest population group, and they reported their findings separately for men and women as well as for the three different types of Brugada ECG pattern.

It is not known, however, whether the screened cohort was representative of the population in the city of Moriguchi, Osaka, because it included only volunteers who might have been more concerned about their health status and an unspecified number of subjects suspected to have cardiac abnormalities. More carefully designed studies are needed to assess the prevalence of Brugada-type ECG throughout the world.
Follow-up of patients with Brugada-type ECG. Brugada et al. (10) reported an 8% incidence of arrhythmic events among asymptomatic patients with a Brugada-type ECG during a three-year follow-up. In contrast, no cardiac events occurred in asymptomatic patients followed for an average of about one to three years by Atarashi et al. (8) (34 patients), Takenaka et al. (12) (11 patients) and Priori et al. (7) (30 patients). In the Moriguchi, Osaka, population (11), which was followed for an average of 2.6 years, one SCD occurred among 98 subjects with the Brugada-type ECG in a 56-year-old man with a saddle-back ST-segment elevation. Among 13,831 patients without the Brugada-type ECG, 139 died during the same period. The difference in mortality between the two groups was not significant. According to Brugada et al. (10), the periods of observation in the available studies are too short to draw meaningful conclusions about the risk of serious arrhythmic events in asymptomatic subjects with Brugada-type ECG.

It appears that Brugada syndrome represents a rare cause of SCD in patients without structural heart disease. Chugh et al. (15) identified 14 structurally normal hearts among 270 hearts of SCD victims. Brugada syndrome was suspected in one patient of Southeast Asian origin who had no ECG. Corrado et al. (16) reported that of nine young victims of SCD with ST-segment elevation in the right precordial leads, eight had ARVC, and one had no structural heart disease (i.e., the Brugada syndrome).

CONCLUSIONS

Although the Brugada-type ECG cannot be defined accurately, most symptomatic patients with the manifest Brugada syndrome appear to have RBBB with a coved type ST-segment elevation. The syndrome may be concealed when the typical ECG pattern transiently disappears in subjects with the manifest Brugada syndrome. The term “asymptomatic Brugada syndrome” is an oxymoron, and it should not be used in reference to asymptomatic subjects with the Brugada-type ECG. These individuals may be diagnosed as either carriers of the pattern or as having suspected Brugada syndrome. At this time there are no guidelines to gauge the level of suspicion as strong, intermediate or weak, with the possible exception of young men of Southeast Asian origin and patients who have a family history of the syndrome. Further studies may disclose which ECG patterns should be suspected of Brugada syndrome, and which patterns can be safely dismissed as merely simulating the Brugada syndrome. The unresolved problems related to the pathogenesis (17), the ECG characteristics, the epidemiology, and the genetic features all require further studies.

The available data suggest that the Brugada-type ECG is much more prevalent than the manifest Brugada syndrome. Of the several studies in which the patients with asymptomatic Brugada-type ECG were followed prospectively, only one (10) reported occurrence of symptomatic arrhythmias. There are no established guidelines on how to handle the asymptomatic patients with an unexplained Brugada-type ECG. A concerned physician faces the dilemma of whether to conceal the ECG findings from the patient or to inform the asymptomatic patient about the presence of an “atypical” ECG, which may or may not be of consequence. There is not enough information compelling the physician to reveal the increased risk of SCD to every patient with the Brugada ECG pattern.

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REFERENCES