EDITORIAL COMMENT

Clinical Diagnosis and Risk Stratification in Patients With Brugada Syndrome*

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In patients with Brugada syndrome (BRS), especially those who are asymptomatic, preclinical diagnosis and risk stratification are vital to the prevention of the fatal ventricular arrhythmias. The initial optimism that a diagnosis of BRS could be made simply on the basis of distinct electrocardiographic (ECG) changes (see the following text) has been tempered, both by a high incidence of false-positive and false-negative cases related to “waxing” and “waning” ECG signature (1,2) and by drug- or disease-induced ECG abnormalities resembling those in BRS (3–5). Thus, the need for additional diagnostic tools and strict clinical criteria for diagnosing of BRS has become evident.

In their well documented retrospective study published elsewhere in this issue of the Journal, Dr. Ikeda et al. (6) have presented evidence that signal-averaged electrocardiography may be useful for risk stratification of patients with ECG evidence of BRS. In a study population of BRS patients (primarily male) with structurally normal hearts, who had ECGs showing “a pattern of RBBB and ST-segment elevation in leads V1 to V3,” compared to healthy individuals with normal ECGs, they report a sensitivity of 89%, specificity of 50%, positive predictive value of 70%, and negative predictive value of 77% for late potentials (LP) for risk of life-threatening events. They found no correlation between LP and the magnitude of ST-segment elevation in leads V1 to V3 compared to healthy control subjects. The only treatment presently known to be effective against sudden cardiac death (SCD) in these patients is the implantable defibrillator (1,7).

Patients with BRS usually present themselves in one of two situations: 1) when a resting 12-lead ECG has shown changes compatible with BRS, or 2) when the clinical picture (either in terms of symptoms or family history) suggests increased risk of SCD in the setting of a structurally normal heart.

Resting ECG. The ECG marker of BRS is difficult to describe using ordinary ECG terminology (8), but typically there are three components: 1) elevated terminal portion of the QRS complex (prominent J-wave); 2) non-injury-related (“idiopathic”) elevated descending ST-segment; and 3) negative T-wave in the same right-sided precordial leads. These peculiar ECG abnormalities of ventricular repolarization are often associated with right bundle branch block (RBBB) and normal QT interval (2,7,8). The prevalence of the ECG marker for BRS in subjects with idiopathic ventricular fibrillation and in healthy control subjects is the subject of ongoing investigation (9,10).

Ikeda et al. (6) used the original description of ECG findings in BRS (“pattern” of RBBB and ST-segment elevation in leads V1 to V3) to characterize their patients, but at the same time stated that none of their patients had RBBB. Compounding the diagnostic difficulties in BRS is the clear distinction between the presence or absence of RBBB on the 12-lead ECG. The introduction of new ECG terms, such as “pseudo-RBBB,” “RBBB-like,” and “RBBB-pattern,” has been of no help. We pointed out (11,12) that in patients with BRS, early repolarization abnormalities, but not RBBB, are an integral part of its ECG signature. When published ECGs from BRS patients were further scrutinized, it became clear that the broad terminal S-wave in leads V5 and V6 (a hallmark of RBBB) was rarely seen and that the QRS duration in these leads was usually normal (7). A diagnosis of RBBB should not be made in the absence of such an S-wave and of abnormal QRS widening in all leads. Moreover, if RBBB is truly present in a patient with BRS,

BRS is a “useful noninvasive technique for identifying high-risk patients” and “may support the idea that conduction disturbance per se is arrhythmogenic.” This challenges the prevailing opinion that early repolarization abnormalities but not conduction disturbances could determine the arrhythmogenic substrate in the BRS population.

The study by Ikeda et al. (6), however, emphasizes some important and clinically relevant questions. In this review, we will seek to define the clinical utility and interpretation of noninvasive and invasive diagnostic methods in BRS.

DISCUSSION

Clinical assessment of patients with suspected or documented BRS. Patients with BRS present a great challenge, both in establishing the diagnosis and determining the prognosis. The only treatment presently known to be effective against sudden cardiac death (SCD) in these patients is the implantable defibrillator (1,7).

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it becomes difficult to interpret the signal-averaged ECG, since the usual criteria for LP cannot be applied (13) (see the following text).

When the inclusion of RBBB as part of BRS is challenged, the J-point elevation followed by downsloping ST-segment and negative T-wave must be explained. Similar findings in some patients with right ventricular (RV) dysplasia (consistent with marked difference in QRS duration in lead V₆ and V₅ in the absence of other classical ECG criteria for RBBB) have been referred to as parietal intraventricular conduction delay or block (14), suggesting that the conduction disturbance is related not specifically to the conduction system but to the myocardial tissue as a whole. In patients with BRS, this would occur without obvious pathologic findings; in patients with RV dysplasia, myocardial cells are replaced by fatty tissue.

Interlead QTD as an index of dispersion of ventricular repolarization is not an appropriate focus in this article. The problems in use of this ECG parameter have been extensively reviewed (15–17), and we believe that QTD is not meaningful for independent interpretation, in general, and is without clinical value in BRS patients, particularly.

As in the case of long-QT syndrome, a diagnosis of BRS can be established with only a degree of certainty and must rely on both clinical presentation and diagnostic findings. The ECG findings described above are the cornerstones for the diagnosis and must occur either spontaneously or following provocative testing with sodium-blocking drugs. Since there are false-positive findings, other possible causes for such ECG changes must be ruled out.

Signal-averaged ECG. Detection of LP is a noninvasive diagnostic tool that can be used to identify the presence of slow conduction and fragmentation of electrical impulse propagation within the ventricular myocardium. This method is used to identify high-risk patients predisposed to ventricular tachyarrhythmias. Its sensitivity and specificity in the prediction of arrhythmogenic events vary dependent on the clinical setting (18,19) and the arrhythmogenic mechanisms that underlie disease, and are significantly compromised in the presence of the intraventricular conduction defects (20).

Although Ikeda et al. (6) do not specifically address how slow conduction in the RV, frequently described in BRS patients, may be related to LP detected by signal-averaged ECG, this is an issue of great interest. Normal values for signal-averaged ECG in the presence of RBBB are not mentioned, but only the QRS width is removed from the definition. Their observation that the QRS width in lead V₆ was normal in all patients may justify their data interpretation without reference to presence or absence of RBBB. The statement that a normal HV interval in all their patients is evidence against the presence of RBBB is not valid. Right bundle branch block does not usually affect the HV interval, since the earliest ventricular activation is via the left bundle branch. It has been demonstrated, however, that RBBB shortens the root-mean-square voltage of the terminal 40 ms in the filtered QRS complex (RMS₄₀) and prolongs the duration of low amplitude signals <40 µV in the terminal filtered QRS complex (LAS₄₀) (20). To our knowledge, there are no data available regarding criteria for an abnormal signal-averaged ECG in the setting of RBBB and it would therefore be particularly difficult to apply signal-average electrocardiography to patients with RBBB who are considered to have BRS.

Programmed electrical stimulation and sodium channel blockade. Sodium channel blocking drugs have been used to unmask ECG changes in concealed forms of BRS (21). Antiarrhythmic drugs like ajmaline, flecainide, propafenone and procainamide have been shown to: 1) produce or augment ECG changes typical of BRS, and 2) evaluate inducibility of ventricular tachycardia/ventricular fibrillation (VT/VF) during programmed electrical stimulation (PES) in both apparent and concealed forms of BRS (21). Since ajmaline is not available in the U.S., procainamide or flecainide could be the agents of choice in this country.

In predicting patients at risk, PES has a positive predictive value of 50% and a negative predictive value of 46%, whereas the positive predictive value of pharmacologic challenge with sodium channel blockers is 35% (22). Programmed electrical stimulation, with or without drug testing, is limited by its failure to unmask most silent gene carriers that underlie the phenotypic ST-segment elevation in BRS. Nevertheless, electrophysiologic testing—including provocative tests of inducibility of VT/VF and drug effects on: 1) the magnitude of ST-segment elevation, and 2) inducibility of VT/VF—remains the tool most appropriate for confirmation of diagnosis and risk stratification in patients with BRS.

In addition, an assessment of the sensitivity or specificity of such an approach is still limited by insufficient data. In evaluating the results of a PES, the normal ventricular response of early repolarization and conduction in the RV after the administration of various sodium channels blockers must be known in order to determine the specificity and the sensitivity of those drugs in mediating the magnitude of ST-segment elevation and conduction velocity. Unfortunately, this information is also not available presently. Since sodium channels blockers do not normally provoke malignant ventricular tachyarrhythmias, electrophysiologic testing is primarily indicated for evaluating the inducibility of VT/VF before or after drug administration.

In summary, an asymptomatic individual with drug-induced ECG abnormalities consistent with BRS has a good prognosis if VT/VF is not inducible during PES; an asymptomatic individual with a spontaneously abnormal ECG will most likely develop symptoms during follow-up, if VT/VF is not inducible; and the patient with syncopal episodes and an abnormal ECG is at highest risk and requires implantable cardioverter-defibrillator (23).

Thus, as a primary electrical disease of the heart, BRS is still not well defined, and a search for better ways to establish the diagnosis continues. We propose that the
Table 1. Diagnostic Criteria for BRS

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<th>Major criteria</th>
<th>Minor criteria</th>
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<td>1. Presence of the ECG marker of Brugada syndrome in patients with structurally normal heart</td>
<td>1. Family history of sudden cardiac death</td>
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<tr>
<td>2. Appearance of the ECG marker of Brugada syndrome after administration of sodium channel blockers</td>
<td>2. Syncope of unknown origin</td>
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<td>3. Documented episodes of ventricular tachycardia/ventricular fibrillation</td>
<td>3. Documented episodes of ventricular tachycardia/ventricular fibrillation</td>
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<td>4. Positive programmed electrocardiostimulation test on ventricular tachycardia/ventricular fibrillation</td>
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<td>5. Genetic mutations of ion channels (to be defined)</td>
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presence of one major and one minor criterion from Table 1 can serve to establish a diagnosis of BRS until better and more sensitive tests become available. Because the conditions of some patients may still remain undiagnosed by such an approach, we must work to expand the diagnostic armamentarium and seek additional insight into the management of these patients.

Mechanisms of arrhythmia: delayed conduction versus early repolarization abnormalities. The finding of a variable degree of intraventricular conduction in patients with BRS delay is not a surprising finding when the well-documented genetic mutations of the sodium ion channels are considered (24–26). While no correlation between RBBB and SCD has yet been established in a population other than those with BRS, the magnitude of ST-segment elevation has been linked to the incidence of life-threatening arrhythmic events, particularly in BRS patients (7,11).

The reentry mechanism that underlies the arrhythmogenic potential in BRS has been considered based on the high inducibility and reproducibility of VT/VF during electrophysiologic testing (1,2). Whether development and maintenance of re-entry are due to a delayed conduction and/or its degree of dispersion of repolarization, however, is not known. Moreover, it must be emphasized that all mechanisms currently proposed to explain the arrhythmogenic potential of BRS are speculative and inconclusive, and neither of the noninvasive “markers” identified by Ikeda et al. (6) can be used to determine the full scope of arrhythmogenic potential in BRS or render one hypothesis more attractive and favorable than another.

RECOMMENDATION AND FUTURE DIRECTIONS

Because ST-T changes are seen in healthy individuals with a good prognosis, and no (or subtle) ST-T changes are sometimes seen in BRS patients at high risk for sudden death, it is evident that resting ECG can never serve as an independent tool to diagnose BRS. In the context of the findings of Ikeda et al. (6), signal-averaged ECG would be a reasonable next step in the diagnostic workup, and positive detection of LP could strengthen the indication for invasive electrophysiologic testing. Criteria defining LP are specific for each commercial system due to differences in filters, lead configuration and analysis algorithms (26). We favor either an abnormal RMS40 or LAS40 (27) to define the presence of LP in patients being evaluated for BRS. No single noninvasive diagnostic method can presently establish the clinical diagnosis of BRS, and only clinically validated invasive electrophysiologic testing can provide risk stratification for BRS patients. Any BRS patient with either spontaneous or inducible ventricular tachyarrhythmias should be considered to be at high risk for SCD and treated with an implantable cardioverter defibrillator. Finally, the questions generated by the study of Ikeda et al. (6) may be resolved by analysis of follow-up data.

REFERENCES