The Brugada Syndrome: Can We Predict the Risk?

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Editorial Comment

The Brugada syndrome (BS) is now recognized as an important condition predisposing individuals with a seemingly normal heart to sudden death due to ventricular fibrillation (VF).1 Mutations in the gene encoding the cardiac sodium channel (SCN5A) have been found in 18–30% of patients with BS.2 It is believed that abnormalities in regional repolarization and/or depolarization provide the electrophysiological milieu for VF.3,4

In a recent consensus statement,5 the electrocardiographic features have been categorized as follows: type 1 (diagnostic for BS): coved ST segment elevation of ≥2 mm followed by a negative T wave in more than one of leads V1–3; type 2 (not diagnostic for BS) saddleback shaped ST segment elevation with ST elevation of ≥2 mm and a trough ≥1 mm ST elevation; or type 3 (not diagnostic for BS) coved or Saddleback ST segment elevation of <1 mm. However, type 2 and 3 pattern are considered diagnostic, if the ST segment elevation converts to a type 1 pattern after administration of a cardiac sodium channel blocking drug.

Data from the largest patient series6 have shown that the highest risk for clinical events (sudden death, syncope) occurs in those patients who have a prior aborted sudden death (62% at 54 ± 54 months follow-up), followed by those with syncope and spontaneously abnormal, type 1 pattern ECG (19% at 26 ± 36 months follow-up). However, the event rate among asymptomatic patients was still 8% (27 ± 29 months follow-up). Data from this series suggest that among these asymptomatic patients, the risk is highest in those with spontaneously diagnostic type I ECG pattern and lower if they develop this ECG pattern only after administration of a sodium channel blocking drug. The risk was also high in those with inducible VT/VF at electrophysiologic study. Other studies, however, report a much lower event risk in asymptomatic patients and found that VT/VF inducibility was not predictive of future events.7 This difference may in part relate to patient selection including only patients with type I pattern ECG versus including also those with type 2 and 3 ECG pattern as well as the electrophysiologic stimulation protocol used.8 Thus, risk stratification in asymptomatic individuals with the Brugada ECG is still a challenge. The diagnostic classification as well as risk stratification based on the three ECG patterns may be questionable since the ECG may spontaneously change from one pattern to another in the same individual.9

In 1990, the Thai Ministry of Public Health Report found an association between a large meal of glutinous rice (“sticky rice”) or carbohydrate ingested on the night of death in sudden unexpected death syndrome (SUNDS).10 In this Journal,11 Ikeda et al. report the effect of a large meal on the ECG in 35 Japanese patients with proven or suspected BS. Patients enrolled had persistent or transient coved ST segment elevation of ≥2 mm in leads V1-V3. Patients treated with cardiac sodium channel blocking drugs at the time of diagnosis were included. Patients with only saddle back ST elevation were excluded. Seventeen patients were defined as “high risk” based on either a history of clinical events (syncope in 8, aborted sudden death in 5) or a family history of sudden death in 15. Eighteen patients had neither a history of clinical events nor a family history of sudden death and were defined as “indeterminate risk.” After a large meal test, ingested over 20 minutes, this test was defined as positive if it elicited (a) an increase in the baseline ST segment elevation by >1 mm in leads V1-V3; (b) a change from saddle back to coved ST segment elevation; or (c) visible T wave amplitude alternants. This test was positive in 14 of 17 (82%) of the “high-risk” patients and only 3 of 18 (17%) of the “indeterminate patients.” The authors conclude that ECG changes characteristic for the BS are augmented after a large meal, and this effect is seen primarily in patients with clinical markers for “high risk.”

The data by Ikeda et al.11 appear to be consistent with the proposed mechanism—that gastric distension following a large meal has the effect of enhancing vagal tone with resultant ST elevation in patients with the BS. Metabolic effects such as a shift in insulin/glucose levels or electrolyte shifts seem less probable mechanisms since the ECG changes were observed very soon after a meal at a time when significant metabolic changes would not be expected.

In BS, clinical events often occur at rest or during sleep, suggesting a possible role of the autonomic nervous system. The role of enhanced vagal tone in BS is suggested by the following: muscarinic stimulation augments ST elevation typical of BS12; and increased vagal activity, assessed by heart rate variability analysis, can be seen prior to spontaneous ST segment elevation13 and prior to episodes of VF.14

The high incidence of a positive large meal test in patients with prior clinical events (“high risk”) and low incidence of a positive large meal test in patients without prior clinical events (“indeterminate risk”) raises the possibility that this test could be used for risk stratification. Does the large meal test uncover a heightened vagal tone, common to “high-risk” patients, that differentiates them from “indeterminate-risk” patients? Or, if one assumes a similar increase in vagal tone between “high-risk” and “indeterminate-risk” patients, does the large meal test expose differences in trigger (enhanced vagal tone) substrate (repolarization/depolarization abnormalities) interaction?
In a prospective study of 124 patients with coved or saddle back ST segment elevation of ≥1 mm in leads V1-V3 (24 with a history of syncope, 11 with a family history of sudden death), the same investigator identified a spontaneous change in ST segment elevation on multiple ECG recordings as the most significant factor in predicting sudden death of VT/VF during a mean follow-up of 40 ± 19 months (hazard ratio: 9). Of interest, in this study the spontaneous ST segment change was seen most often after meals, and the predictive value increased when a spontaneous ST segment change was combined with a family history of sudden death or a history of syncope.

Thus, it appears that in addition to the spontaneous coved ST segment elevation (type 1 ECG pattern) a spontaneously changing ST segment pattern (i.e., after large meal) predicts an increased event rate during follow-up. This would be in contrast to the benign prognosis of coved ST segment elevation if seen only after administration of class I antiarrhythmic drug use.

Given the uncertainty in risk stratification in asymptomatic individuals with the BS ECG pattern, a prospective evaluation of the diagnostic and prognostic clinical utility of the large meal test or other measures enhancing vagal tone, alone or in combination with other clinical parameters, may be a productive avenue of investigation.

References