Overlapping Risks of Early Repolarization and Brugada Syndrome*

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Over the past 2 decades, we have witnessed major progress toward a better understanding of the Brugada syndrome (BrS) and have gained knowledge of the genetic aspects, pathophysiology, and new management of the syndrome (1–3). However, controversies exist, especially concerning the role of sodium channel mutation and electrophysiological mechanisms underlying the syndrome (2,4), as well as risk stratification (5–9). The latter has drawn much attention and discussion from many arrhythmia scholars who have been searching for the best strategy to identify high-risk BrS patients.

Risk stratification is desirable in BrS patients, mainly for these 2 reasons: 1) the majority of patients with the Brugada electrocardiogram (ECG) pattern are asymptomatic and young; and 2) thus far, the only proven treatment for BrS is an implantable cardioverter-defibrillator (ICD), which is not benign and could pose significant morbidity (1,2). There is no debate that a BrS survivor who experiences out-of-hospital cardiac arrest is at high risk of recurrent ventricular fibrillation (VF) episodes and needs ICD treatment. Likewise, symptomatic patients with recurrent syncope, agonal respiration at night during sleep, or unknown seizures are at risk of dying suddenly without protection and have a class I indication for ICD treatment. The heated debate is more about how to best identify asymptomatic BrS patients who are at high risk of sudden death and need ICD treatment.

When the Brugada registry first began, it reported a significantly high number of asymptomatic patients who had positive ventricular tachycardia (VT) inducibility by programmed electrical stimulation (+PES) (6,10). However, more recent studies found a much lower incidence of sudden death or VF in this group and questioned the specificity of the role of +PES in risk-stratifying asymptomatic BrS patients (2,5). Recent studies have found that QRS fragmentation (f-QRS) (5,11), exercise testing (12), signal-averaged ECG (13), and shortening of the ventricular refractory period (<200 ms) (5) are valuable tools for identifying high-risk patients. However, it remains unclear how useful any of these parameters would be in identifying asymptomatic BrS patients who need ICD treatment.

Tokioka et al. (14), in this issue of the Journal, report on their observational retrospective study cohort of 246 BrS patients (~21% were symptomatic, 16% had syncope, and 5% survived VF episodes). They made the key observation that only 4 variables were independent risk factors for recurrent life-threatening arrhythmias: f-QRS, inferolateral early repolarization (ER) pattern, history of VF episodes, and history of syncope. In this study, +PES was associated with an increased incidence of recurrent VF episodes on univariate analysis, but by itself, it was not an independent risk factor. Tokioka et al. (14) also found that BrS patients with a combination of f-QRS and ER represented the highest risk group in their study cohort, and the opposite was also true that BrS patients without f-QRS or ER pattern had a very low risk of life-threatening arrhythmias.

Undoubtedly, these findings are of clinical significance and have major implications for risk stratification. However, one must be cautious in interpreting the results of this study because of the retrospective nature and relatively smaller sample size in certain subsets of patients. For example, only 9 of 246 patients (3.6%) have a combined f-QRS and ER pattern. Furthermore, like the Brugada ECG pattern, the ER pattern can also be “wax and wane,” which poses a challenge when using it as a risk-stratifying parameter. Nevertheless, it is impressive that the patients who have neither of the 2 patterns have an excellent prognosis and clearly warrant no further treatment or investigation.

More importantly, the current study confirms previous studies that demonstrated overlapping features of ER syndrome in BrS patients (15,16), which occurred in 10% to 15% of this subset (n = 82), and the incidence of recurrent VF episodes is significantly higher than that of the BrS alone. Similarly, the current study showed that combined syndromes of a progressive conduction defect and BrS and long QT syndrome, especially those of SCN5A mutation and BrS, are not uncommon (17,18). The Tokioka et al. study (14) also showed that a significant number of their patients had prolonged QT interval and QRS complexes in addition to the f-QRS finding, which suggests that in this population, several overlapping syndromes are present as well.

The heterogeneity and overlapping features of the syndrome and myriad precipitating factors of VF in BrS partially explain why BrS risk stratification is so problematic, because so many factors play a role in the genesis of VF that
leads to sudden death. The majority of BrS patients who are symptomatic with life-threatening ventricular arrhythmias usually have at least 1 or more of the high-risk BrS features (i.e., ER pattern, f-QRS, or wide QRS complex) to begin with. Thus, these variables do not have much more to contribute to the management plan for these symptomatic patients who clearly need no further risk-stratifying strategy; just treat these patients with an ICD or with quinidine—if available—for those who decline an ICD.

The question that needs to be answered is what should we do if an asymptomatic patient with the Brugada ECG pattern has an ER or f-QRS pattern, or both? Tokioka et al. (14) recommend +PES to determine VT inducibility. Even though the investigators have not clearly stated that they would implant an ICD if the patient has +PES, one has to assume that would be the case. More studies are definitely needed to determine that this recommendation is valid. Our contention is that the incidence of VF in asymptomatic BrS patients is so low (1) that it will be difficult to prove or disprove this notion. Perhaps a multicenter trial or large registry effort is required to settle this issue. However, we believe that the most relevant information gleaned from the findings of Tokioka et al. (14) is that asymptomatic patients who have neither ER nor f-QRS pass the risk-stratification test of being high-risk BrS subsets and need no further investigation or treatment.

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