



EDITORIAL COMMENT

Insights into the challenging risk stratification of Brugada syndrome: A complex puzzle to solve



Visão sobre o desafio da estratificação de risco na síndrome de Brugada: um puzzle de resolução complexa

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Available online 4 May 2020

Brugada syndrome (BrS) is one of the most common inherited arrhythmogenic disorders, with a worldwide prevalence of approximately 0.05%. It is characterized by a typical electrocardiographic pattern (ST-segment elevation with coved morphology in the right precordial leads and right bundle branch block) combined with malignant ventricular arrhythmias (MVA), that can lead to syncope or sudden cardiac death (SCD).^{1,2} This electrocardiographic pattern is intermittent and may be unmasked by fever or pharmacological challenge with intravenous sodium channel blockers, of which flecainide or ajmaline are most often used.

It is accepted that an implantable cardioverter-defibrillator (ICD) should be used in patients with aborted SCD, arrhythmia-related syncope or MVA.³ However, there is still a lack of consensus on the management of asymptomatic patients with BrS. Accurate identification of subjects at high risk of SCD is a major challenge in the clinical management of BrS.

A spontaneous type 1 Brugada electrocardiogram (ECG), inducible ventricular arrhythmias on electrophysiological study, syncope and family history of SCD have been reported as independent predictors of significant ventricular arrhythmias that may lead to SCD, particularly in males.^{2,4,5} The

SCN5A gene, which encodes the cardiac sodium channel, is linked to BrS, with mutations identified in around one out of four patients.² *SCN5A* mutations appear to contribute to the occurrence of events, but most genetic findings in BrS are variants of unknown significance, and caution should be exercised when translating them into clinical risk stratification.⁶

In 2006, Castro et al., in a small study with BrS patients, showed that a long corrected QT (QTc) interval in lead V2 (>460 ms) and a long interval from the peak to the end of the T wave (Tpeak-Tend) were associated with the occurrence of MVA in long-term follow-up.⁷ It is well known that long QT interval is associated with increased vulnerability to ventricular tachyarrhythmias, and spatial transmural dispersion of repolarization may be an underlying mechanism contributing to the occurrence of MVA in BrS. In recent years, Tpeak-Tend interval, Tpeak-Tend/QT ratio and Tpeak-Tend dispersion have been suggested as electrocardiographic variables that can quantify transmural dispersion of repolarization.⁸

The retrospective study by Bravo et al. published in this issue of the *Journal*, assessed the role of QTc >460 ms in multiple ECGs as a marker of MVA recurrence during a very long follow-up after ICD implantation in BrS patients.⁹ Their results showed that the group with prolonged QT on at least two ECGs (group 3) had more ventricular tachycardia or ventricular fibrillation events detected by the ICD than patients

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<https://doi.org/10.1016/j.repc.2020.04.003>

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with no long QT (group 1) or with only one ECG with QTc >460 ms (group 2), with differences in Kaplan-Meier survival curves observed immediately following ICD placement.

The data presented reveal that group 1 patients were also those with the highest rate of spontaneous type 1 ECG, family history of SCD, previous cardiac arrest, syncope and previous documented MVA. Thus, according to the state of the art, they were already considered to be at high risk based on available clinical variables. It should also be borne in mind that groups 2 and 3 included only seven and nine patients, respectively.

Another issue concerns the wide variability of QT intervals. Even in patients with at least one ECG showing QTc >460 ms during follow-up, prolonged QT was present in only 49% of the ECGs performed. Of course, significant intra- and interobserver variability of manual QT measurements would be expected, but it is accepted that cardiac autonomic tone, circadian dynamics, respiration, age, gender, certain drugs,¹⁰ and possibly the intermittent presence or absence of the typical ST elevation or abnormal QRS fragmentation and early repolarization pattern, may influence QT interval duration. Some of these variables could help explain the wide variations obtained in QT interval measurements.

The inclusion of other electrocardiographic markers of transmural dispersion of repolarization, such as Tpeak-Tend interval, Tpeak-Tend/QT ratio and Tpeak-Tend dispersion, could potentially contribute to understanding the observed variability in repolarization phenomena.

Interestingly, programmed electrical stimulation, performed in 80% of the population, did not predict the recurrence of MVA events, which is in agreement with previous studies on BrS, showing that the use of this technique is still a controversial issue in risk stratification.^{11,12}

Finally, in this study most patients (>80%) were symptomatic. It would be of interest to include asymptomatic BrS patients, a large group for whom risk stratification decisions pose great challenges, when assessing the reproducibility of these results. The indication to implant an ICD remains a source of debate in asymptomatic subjects with an ECG pattern compatible with BrS. Further investigation is therefore required to acquire a comprehensive physiological understanding of the dynamic mechanisms underlying the occurrence of spontaneous MVA in BrS, in order to obtain clinical benefits in the management of this population, who are frequently young and without symptoms.

Conflicts of interest

The author has no conflicts of interest to declare.

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