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Editorial

Rare Disease and Low Event Rates: Challenges for Refining Risk Stratification in Brugada Syndrome

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See article by Rivard et al., pages 1355.e1–1355.e7 of this issue.

Brugada syndrome (BrS) is an inherited arrhythmia syndrome associated with an increased risk of sudden cardiac death (SCD) secondary to malignant ventricular arrhythmias.[1] Originally described approximately 25 years ago, the hallmark type 1 electrocardiographic (ECG) pattern characterizing the condition features a pseudo right bundle branch block morphology in association with coved ST-segment elevation in the right precordial leads.[2,3] The worldwide prevalence of the type 1 Brugada ECG pattern has been estimated to approximate 0.05%, although there is considerable geographic variability.[4] Since its initial description, major strides have been made toward unraveling its underlying genetic and pathophysiological mechanisms, although many questions remain.[5] To date, a total of 20 genes have been implicated in BrS; however, a genetic culprit remains elusive in approximately 60%-70% of cases.[6-9] Its culprit pathophysiologic has been localized to the right ventricular outflow tract, although experts continue to debate whether the condition is a disorder of depolarization or repolarization, or both.[10-12]

Clinical management of individuals with a type 1 Brugada ECG pattern also remains controversial. The primary treatment modality for BrS is an implantable cardioverter defibrillator (ICD), whereas quinidine is frequently reserved for suppression of recurrent malignant arrhythmias after ICD insertion.[13] Although treatment with an ICD effectively prevents SCD, it also carries the potential for significant morbidity, particularly among young individuals who may be committed to a device for the majority of their lifetimes.[14] As a result, careful evaluation of the benefit-risk balance is critical before ICD insertion, a particularly challenging task in a condition like BrS, which is characterized by low rates of catastrophic events, namely, SCD in young otherwise healthy individuals.[15]

Given the low event rate among asymptomatic individuals with type 1 Brugada ECG patterns, the recommended strategy is to limit ICD insertion to individuals who have experienced an episode of unexplained syncope (presumed to be secondary to a malignant ventricular arrhythmia) or have experienced an aborted cardiac arrest.[13,16,17] Although reasonable from epidemiologic and statistical perspectives, a major flaw associated with this approach is that asymptomatic individuals are restricted from definitive therapy until their first event, which may be fatal. Restricting therapy when the sentinel event may be death is problematic, particularly in the context of young otherwise healthy individuals, when such a catastrophic outcome is appropriately deemed unacceptable.

Given this reality, it is clear that development of more effective risk stratification of asymptomatic individuals with type 1 Brugada ECG patterns is critical, and significant efforts have been made to identify additional risk factors for SCD among this cohort of individuals.[16,17] The most intensely studied modality for risk stratification in BrS has been inducibility of ventricular fibrillation with programmed ventricular stimulation (PVS) during an invasive electrophysiologic study. Although significant controversy remains, the predominant consensus has been that inducibility of ventricular fibrillation with PVS does not accurately predict subsequent risk of SCD and should not be used routinely to risk stratify patients for primary prevention ICD insertion.[13,18,19] Beyond PVS, multiple additional clinical factors have also been evaluated for their predictive ability of arrhythmic events in BrS; however, to date, none has shown sufficiently robust associations to merit incorporation into clinical practice.[13,16,17]

In this issue of the *Canadian Journal of Cardiology*, Rivard et al.[20] sought to evaluate predictors of malignant arrhythmic events among a cohort of 105 individuals with type 1 Brugada ECG patterns from 3 separate health care centres in Quebec, Canada. The investigators screened 19 different clinical, ECG, and electrophysiological features. The primary outcome of the study was a composite of malignant ventricular arrhythmias and sudden death. At baseline, 47 of the 105 study participants had a previous history of aborted cardiac arrest or syncope, whereas the remainder were asymptomatic.

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During a mean follow-up period of 60 months, 7 study participants experienced 20 arrhythmic events that were treated with appropriate ICD therapy: antitachycardia pacing in 7 and shocks in 13. There were no aborted arrests or SCDs, and none of the asymptomatic study participants had events during the follow-up period. Because of the low number of events, the investigators elected to include events documented at baseline in their survival analyses. Among the 19 predictors evaluated, 3 exhibited statistically significant associations with the primary outcome on multivariate analysis (spontaneous type 1 Brugada ECG pattern; hazard ratio [HR], 0.80; $P = 0.0476$; QRS duration in $V_6 > 110$ ms, HR, 15.27; $P = 0.0443$; and maximal T peak-end duration ≥ 100 ms, HR, 29.73; $P = 0.0325$).

The findings from the study are interesting, and the authors should be congratulated on their work. Given the low prevalence of the type 1 Brugada ECG pattern, it is a considerable task to identify 105 study participants who have rigorous phenotype and follow-up details available. Their results suggest that the 3 ECG features identified could potentially be used to risk stratify patients with type 1 Brugada ECG patterns and subsequently help guide management. Notably, the magnitude of their point estimates for association, with HRs ranging from 10.8-29.7, suggests that each of these ECG features may be powerful predictors of adverse events and correspondingly carry significant clinical utility.

Although establishing a cohort of 105 study participants with a type 1 Brugada ECG pattern is an impressive feat in a single Canadian province, the major weaknesses of the study largely stem from its limited sample size and the low event rates observed during follow-up. The major utility of risk stratification in BrS is to guide ICD use in asymptomatic individuals. On this basis, the ideal cohort to use in this context would be asymptomatic individuals. Given that no events were observed during follow-up among the 58 asymptomatic study participants, this approach was not feasible.

Along the same lines, only 7 of the 105 study participants had arrhythmia events during follow-up, resulting in limited statistical power. In an effort to compensate for the low event rate, the investigators elected to include arrhythmia events documented at baseline in the composite primary outcome. This is not traditionally done in the context of survival analyses given that a major strength of prospective cohort studies is documentation of the predictor before development of the outcome, which helps provide support for causality. The investigators do not specify the timing of when electrocardiography was performed in relation to the arrhythmia event. Ideally, electrocardiograms used for the analysis would have been performed before the arrhythmia event to mirror the anticipated clinical context for using this information given that ECG features may evolve over time.

Another limitation that arises from the limited sample size is the precision of the point estimates identified for the predictors. This concept is highlighted by the wide 95% confidence intervals (CIs) identified for the HRs of each positive predictor (type 1 Brugada ECG pattern, 95% CI, 1.03-113.87; QRS duration in $V_6 > 110$ ms, 95% CI, 1.07-217.42; and maximal T peak-end duration ≥ 100 ms, 95% CI, 1.33-666.37). The extremely wide range of the 95% CIs limits our ability to infer the true clinical utility of each predictor, which is particularly problematic, because in each case the lower boundary approximates the null value. The wide 95% CIs of each variable analyzed also highlight the limited power of the study and emphasize that conclusions derived from negative findings (such as lack of a statistically significant association with syncope; $P = 0.053$) are limited.

In addition to the other issues related to the modest sample size and event rate, the investigators also evaluated 19 different predictors and did not adjust for multiple hypothesis testing. The probability of a false-positive result with a P value of 0.05 is 1 in 20, suggesting that it is highly probable that a spurious association may have been identified. Adjusting for multiple hypothesis testing using the traditional Bonferroni correction method would necessitate using a P value of 0.003 for statistical significance, which would render all analyses negative. The Bonferroni method is considered excessively stringent in many cases and in the current study is likely not necessary because the investigators appeared to have an a priori rationale for their hypotheses. Although a Bayesian approach is reasonable in this setting, the strong possibility of chance associations emphasizes the importance of subsequent replication of positive findings.

The ability to identify the subgroup of asymptomatic patients with a type 1 Brugada ECG pattern who will ultimately experience fatal arrhythmic events will be a crucial step forward in the management of these individuals. Although it is unlikely that a single feature will be sufficient, it is conceivable that a composite score derived from clinical, ECG, and electrophysiological factors may provide a markedly improved discriminatory capacity. In this regard, the current study has identified 3 potential ECG predictors that merit further evaluation. More definitive clarification of their clinical utility will likely require the use of meta-analyses and large multicentre registries, although it should be noted that despite these larger-scale efforts, the very low event rate in this group will continue to provide a formidable challenge, in which false-positive results may overwhelm the very few true-positive results. It is possible that additional novel insights into the condition will be necessary to achieve an acceptable discriminatory capacity that is sufficient to guide a primary prevention ICD strategy in this population.

Disclosures

The authors have no conflicts of interest to disclose.

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