**EDITORIAL COMMENT**

**Programmed Electrical Stimulation for Risk Assessment in Brugada Syndrome**

**Time to Change the Guidelines?**

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Brugada syndrome (BrS) is a rare inheritable disorder identified by characteristic abnormalities in the anterior electrocardiographic (ECG) leads (1). The main clinical problem is sudden cardiac death (SCD). The only accepted form of SCD prevention is an implantable cardioverter defibrillator (ICD). However, the patient who undergoes ICD implantation is exposed to pain, inconvenience, and a wide variety of serious mechanical and psychological complications that might have a major negative impact on quality of life, and result in considerable cost to healthcare systems.

The clinician must decide whether or not to recommend ICD insertion and must justify the decision and reassure all those concerned—not only the patient but also family, friends, and other healthcare providers—that the risk of SCD warrants the adverse effects of ICD therapy or that the risk of SCD for the patient is so low that the disadvantages of an ICD outweigh the benefit. This is often difficult, because any risk of SCD is intolerable to some and likely contributes to the observation that the majority of patients who receive ICDs for primary prevention in BrS never receive a life-saving intervention. This has driven an intense effort to identify risk factors for SCD in patients with BrS. Programmed electrical stimulation (PES)—an invasive test, which is used to determine whether sustained ventricular tachyarrhythmia (VTA) that often requires countershock can be induced—has been used to evaluate the disorder since it was described in 1992 (1). However, several investigators and laboratories have not found PES to be helpful in identifying BrS patients at risk for SCD. Acknowledging the debate and lack of definitive evidence, the committee that produced the American College of Cardiology/American Heart Association/European Society of Cardiology 2006 Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death assigned a Level IIb recommendation (i.e., that PES “may be considered for risk stratification in asymptomatic Brugada syndrome patients with spontaneous ST–segment elevation...”) (2). In 2006 and 2007, 2 meta-analyses were published that concluded that PES did not provide significant prediction of arrhythmic events in patients with BrS (3,4). Despite the lack of uniform supporting evidence and the practice guideline recommendations, PES continues to be used for risk stratification of symptomatic and asymptomatic BrS patients and those with and without spontaneous ST–segment elevation.

In this issue of the *Journal*, Priori et al. (5) report the findings of the PRELUDE (PRogrammed ELectrical stimUlation preDictive value) study. The investigators enrolled 308 patients with spontaneous or pharmacologically induced type I BrS ECG pattern who had no history of cardiac arrest or sustained VTA. A uniform stimulation protocol at least as aggressive as those previously reported was specified in advance, consisting of 2 drive cycle lengths with up to 3 ventricular extrastimuli at 2 right ventricular sites with the coupling interval of the last (S4) extrastimulus shortened to refractoriness. During a mean follow-up of 36 months, 14 of 308 patients (4.5%; 1.5% annually) experienced the primary endpoint (appropriate ICD intervention [n = 13] or resuscitated cardiac arrest [n = 1]). There were no deaths. The main finding was that arrhythmia-free survival was nearly identical between those with and without induced sustained VTA. Discrimination was not improved if only patients with VTA induced by a less aggressive stimulation program (1 or 2 extrastimuli) were considered. Programmed electrical stimulation was insensitive at predicting those with arrhythmic events (sensitivity 36%) and not specific (59%). Sensitivity declined to 25%, with a small increase in specificity (74%), when including only those with induction related to 1 or 2 extrastimuli. The event rate after approximately 4 years was slightly but not significantly worse among non-inducible patients (4.9%), compared with inducible patients (3.9%). Therefore, a negative PES response was not associated with a low risk of an arrhythmic event. When the response to PES was included in multivariate analyses with other risk factors demonstrating significant predictive value (spontaneous BrS Type I ECG pattern, syncope, ventricular refractory period [VRP] <200 ms and ≥2 spikes in the QRS complex in leads V1 to V3 [QRS fragmentation (QRS-f)]), no significant predictive value of inducibility status was identified. Moreover, the PRELUDE investigators demonstrated that the immediate reproducibility of a positive PES was only 34%.

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The PRELUDE investigators found significant independent predictive value for other covariates supported by findings of significant discrimination of the cumulative probability of arrhythmic event outcomes. Sensitivities were greater for each of the other covariates examined, compared with PES. The highest sensitivity was observed for spontaneous BrS Type I ECG pattern (92.9%), although specificity was low (47.5%). The highest specificities were observed for QRS-f (93.5%) and the combination of syncope and spontaneous Type 1 ECG pattern (90.5%), but both had relatively low sensitivity (both 42.9%). The absence of spontaneous BrS ECG pattern and VRP ≥200 ms demonstrated greater cumulative probability of arrhythmic event-free survival than a negative PES response, although statistical significance was not evaluated.

The PRELUDE investigators used a prospective registry design with pre-specified inclusion and exclusion criteria and uniform PES protocols and endpoints. These techniques reduce but might not eliminate recruitment bias, data errors, and protocol violations. In an ideal world where funding was commensurate with clinical impact, registries such as the PRELUDE registry would provide access to detailed information with regard to operations and execution, including flow of patients from screening to end of follow-up with documentation of reasons for exclusions and loss to follow-up, methods of data verification, and results of audits that allow estimation of errors in data and protocol violations. Although implied, it was not stated that this was an inception cohort. A bias favoring ICD therapy was suggested by the fact that 78% of the 126 patients who had a VTA induced with PES underwent ICD insertion compared with 21% of noninducible patients. The PRELUDE investigators used a surrogate endpoint “arrhythmic events” defined as “occurrence of ventricular fibrillation or appropriate ICD interventions based on the clinical judgment of the cardiologist in charge of the patient.” Assessment of endpoints by independent observers unaware of clinical data would be more objective. Moreover, it has been shown in large ICD trials of patients with dilated or ischemic cardiomyopathies that appropriate ICD therapy rates are 2 to 3 times higher than SCD events in control (non-ICD) subjects (6). The mechanism for this phenomenon (i.e., a proarrhythmic effect or treatment of events that would have terminated spontaneously) is not known. It is also unknown if this phenomenon occurs in BrS patients with ICDs. Either mechanism would result in an ascertainment bias favoring detection of arrhythmic events in patients with ICDs as well as those with inducible VTA, most of whom (78%) had an ICD. Therefore, it is possible that the rate of arrhythmic events was overestimated in PES-positive patients and/or underestimated in PES-negative patients (21% with ICDs) in the PRELUDE study. The PRELUDE investigators did not report the occurrence of potentially arrhythmic syncopal events during the follow-up period, which might have provided insight on the occurrence of self-terminating arrhythmias in the patients without ICDs and syncope mechanisms in those with ICDs.

In addition to the findings for PES, the investigators presented interesting findings with regard to 2 novel risk predictors. The measurement referred to as “VRP <200” (ventricular refractory period <200 ms) demonstrated a relatively high sensitivity (78.6%), modest specificity (62.9%), and high cumulative probability of arrhythmic events, judging from the Kaplan–Meier plot in Figure 5A of Priori et al. (5). This measurement was obtained with the protocol typically used in clinical laboratories for arrhythmia induction. However, VRP is sensitive to autonomic tone as well as the duration of the drive train and previous ventricular extrastimuli (7). Greater precision in the measurement might be obtained with autonomic blockade and by a continuous stable drive train with initial extrastimuli delivered within the refractory period and gradually extended with no compensatory pause to avoid perturbing the underlying cycle length. In addition, the arbitrarily selected 200-ms threshold might not be the optimal cut point, because it dichotomizes patients on the basis of a single coupling interval decrement (10 to 20 ms). Additional data analysis from the PRELUDE registry and confirmatory studies are needed before this measurement can be recommended.

QRS fragmentation was the most specific risk factor (93.5%), with a relatively high cumulative probability of arrhythmic events, and it was associated with the lowest number of patients needed to treat with an ICD to save a life (4.7, assuming an arrhythmic event is a perfect surrogate for death). High-frequency deflections (fragmentation, spikes) in extracellular potentials probably result from asynchronous electrical activation, often due to nonuniform anisotropic propagation. It has long been known that the right ventricular outflow tract is a region prone to nonuniform activation that can modulate repolarization properties and could result in re-entry in some conditions (8). Because BrS is associated with abnormalities in repolarization and propagation and it has been reported that ventricular arrhythmias might originate from the right ventricular outflow tract in this disorder, an association between QRS-f and arrhythmic events in BrS has biological plausibility (9). However, consistent recording of high-frequency deflections in ECGs requires careful attention to filter settings, amplification, sampling rate, and impedance (9).

Despite some concerns with regard to the design and execution of the PRELUDE study, there were notable strengths compared with some previous studies that used retrospectively collected baseline and follow-up data and used a variety of stimulation protocols (3–5). Despite design differences, the PRELUDE study confirmed several previous studies and the 2 meta-analyses in the main finding that PES does not provide significant SCD risk prediction or absence of SCD risk. It also confirmed greater risk in patients with a spontaneous (vs. drug-induced) BrS ECG pattern and in patients with a history of syncope (3–5).
The PRELUDE investigators have provided the most rigorous evidence to date with regard to the poor utility of PES for risk stratification of patients with BrS and have set a high standard for new studies. Nevertheless, there is no unequivocal explanation for why some investigators report that PES has predictive value, in contradiction to the PRELUDE study and previous investigations (3–5). One cannot exclude the possibility that some unidentified differences in patient characteristics, induction techniques, treatments, or follow-up protocols are responsible for the discrepant findings. Nevertheless, the weight of available evidence suggests that the use of PES in patients with BrS receive a Class III level recommendation (risk ≥ benefit), because of the potential for harm from both the invasive nature of the procedure and the potential for misleading information. Clinicians and investigators who believe in the continued use of PES should enroll patients in rigorously designed inception cohort prospective registries or trials to develop an up-to-date evidence-base to support their practice. Although the observations of the PRELUDE investigators signal the demise of PES for BrS, they have provided promising new opportunities for risk stratification in this challenging disorder.

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