

Risk Stratification in Brugada Syndrome: Role of Programmed Electrical Stimulation

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Abstract

Brugada syndrome (BS) is an arrhythmogenic disease characterized by a typical electrocardiographic finding (type 1 Brugada electrocardiogram [ECG]) and an increased risk for sudden cardiac death (SCD) due to polymorphic ventricular tachycardia or ventricular fibrillation (VF). Risk stratification remains a challenge, especially in cases without documented cardiac arrest or VF. The role of programmed electrical stimulation (PES) for risk stratification remains controversial. Therefore, the present review describes the recent published data on the use of PES in the identification of high-risk patients and discusses the value of PES for risk assessment in BS.

Keywords: Brugada syndrome; Programmed electrical stimulation; Risk stratification

Abbreviations: BS: Brugada Syndrome; ECG: Electrocardiogram; SCD: Sudden Cardiac Death; VF: Ventricular Fibrillation; PES: Programmed Electrical Stimulation; ICD: Implantable Cardioverter Defibrillator; VT: Ventricular Tachycardia; RVA: Right Ventricular Apex; RVOT: Right Ventricular Outflow Tract

Introduction

Brugada syndrome (BS) is an arrhythmogenic disease characterized by an electrocardiogram (ECG) pattern of coved-type ST-segment elevation (type 1 Brugada ECG) in the right precordial leads. Since the first report in 1992 [1], BS has been recognized as a cause of sudden cardiac death (SCD) due to ventricular fibrillation (VF) in middle-aged individuals, especially in men [2-7]. BS is responsible for 4% of all sudden deaths and up to 20% of sudden deaths in individuals without cardiac structural disease [8]. Risk stratification in BS is still a challenge, especially in asymptomatic cases. General agreement exists that patients with BS resuscitated from documented VF should receive an implantable cardioverter defibrillator (ICD) [9]. However, in the remaining individuals with Brugada-type ECG without documented VF, the best approach to treatment is still unclear. The value of the inducibility of sustained ventricular arrhythmias at programmed electrical stimulation (PES) for risk stratification is the most controversial topic. The second consensus report on BS, published in 2005, and considered PES as the cornerstone of therapeutic strategy [8]. However, other recent studies have failed to identify the inducibility of ventricular tachycardia (VT) or VF in PES as a predictor of cardiac events (VT/VF or SCD) [2,4-7]. Therefore, the present review describes recent published data on the use of PES for the identification of high-risk patients and discusses the value of PES for risk assessment in BS.

Evidence to Support that PES Predicts Cardiac Events in BS

Brugada et al. were the first to propose that the inducibility of sustained ventricular arrhythmias at PES is useful in identifying patients at high risk of SCD [3]. Among patients with spontaneous type 1 Brugada ECG, they showed a significantly higher rate of cardiac events in patients with than in those without inducible ventricular arrhythmias during follow-up (17% vs. 2%, $p=0.007$). Another series published by Brugada et al. indicated that the number of cardiac events during follow-up was much higher in patients with than in those without inducible ventricular arrhythmias (13.0% vs. 1.1%

[10]. Subsequent data from Brugada et al. also indicated that in patients without previous cardiac arrest, the incidence of arrhythmic events was significantly higher in patients with than in those without inducible ventricular arrhythmias (13.9% vs. 1.1%, $p=0.008$) and that the inducibility of ventricular arrhythmias at PES is an independent predictor for cardiac events (hazard ratio [HR], 8.33; 95% confidence interval [CI], 2.8-25; $p=0.0001$) [11]. In 2008, Benito et al. from the Brugada group reported a prospective study including 384 patients during a mean follow-up period of 58 months [12]. In their study, the incidence of cardiac events in male patients was significantly higher in patients with than in those without inducible ventricular arrhythmias (74.1% vs. 27.6%, $p<0.001$). Multivariate analysis revealed that the inducibility of ventricular arrhythmias at PES is an independent predictor of cardiac events (HR, 2.93; 95% CI, 1.14-7.55; $p=0.02$). Recently, Delise et al. reported a very interesting combined clinical and electrophysiological approach for risk stratification in BS [13]. PES was performed in 245 patients with type 1 Brugada ECG and no previous cardiac arrest. During a median follow-up period of 40 months, major arrhythmic events (VF or SCD) occurred in 14% of patients with inducible ventricular arrhythmias, none of patients without inducible ventricular arrhythmias, and 5.3% of patients without PES ($p < 0.001$). No single clinical risk factor, including positive PES, was able to identify the patients at the highest risk. However, the patients at the highest risk were those with spontaneous type 1 Brugada ECG and at least 2 of the following risk factors: syncope, family history of sudden death, and positive PES. The best combination able to predict major arrhythmic events was that of spontaneous type 1 Brugada ECG, syncope, family history of sudden death, and positive PES (C-statistic, 0.87; 95% CI, 0.82-0.90).

All the above published studies support the prognostic value of PES alone or combined with other risk factors.

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Evidence to Deny the Predictive Value of PES for Cardiac Events

In the same year when Brugada et al. reported the prognostic value of PES as an effective predictor for cardiac events, Priori et al. could not confirm the finding and suggested that PES might lead to unnecessary overtreatment with ICD owing to the high inducible rate [2]. They performed PES in 86 patients with BS, of whom 57 (66%) had induced VF or sustained polymorphic VT. Overall, the sensitivity and specificity of the inducibility of VF or VT were 66% and 34%, respectively. A Kaplan-Meier analysis of cumulative survival from cardiac arrest failed to demonstrate an association between the inducibility of VF or VT and spontaneous occurrence of VF.

Over the years, other multicenter large studies, except those of Brugada et al., failed to confirm the capability of the inducibility of VF or VT to identify high-risk patients [4-7,14]. Eckardt et al. performed PES in 188 patients with type 1 Brugada ECG. During the mean follow-up period of 40 months, 9 patients had experienced an arrhythmic event, 5 (56%) of whom had inducible ventricular arrhythmias. Positive and negative predictive values were low (5.4% and 95.7%, and 6.6% and 96.4% up to 3 and 2 extra stimuli, respectively). The inducibility of VF or VT was not a predictor of outcome by Kaplan-Meier analysis of cumulative survival from cardiac events [4]. In the FINGER study, the largest multicenter European study that included 1029 consecutive individuals, PES was performed in 638 individuals (62%). In 262 patients (41%), the sustained ventricular tachyarrhythmias were inducible. The rate of inducible ventricular tachyarrhythmia was higher in previously symptomatic patients (125/269, 46%) than in asymptomatic individuals (137/369, 37%; $p=0.02$) but not statistically different between cardiac arrest, syncope, and asymptomatic groups (44%, 47%, and 37%, respectively; $p=0.06$). During a median follow-up period of 31.9 months, in a multivariate analysis, the inducibility of VF or VT did not show an independent predictive value for cardiac events ($p=0.48$) [7].

Recent multicenter large-scale prospective studies from Japan also indicated that the inducibility of VF or VT was not a predictor of cardiac events. In the study by Kamakura et al., which included 330 consecutive individuals, PES was performed in 232 individuals (70%). The inducible rate of VF or polymorphic VT in all the patients was significantly higher (77/109, 72%) in symptomatic than asymptomatic probands (61/123, 50%; $p < 0.005$). However, in 172 patients with type 1 Brugada ECG, the inducible rates of VF or polymorphic VT were 66% (27/41), 78% (31/40), and 57% (52/91) of the patients in the VF, syncope, and asymptomatic groups, respectively, though not statistically significant. On multivariate analysis, during a mean follow-up period of 48.6 months for patients with type 1 Brugada ECG, the inducibility of VF or VT was not an independent predictor for cardiac events ($p=0.54$) [6]. In our previous study in 2007, which included 188 patients, PES was performed in 146 patients (VF, 31; syncope, 52; and asymptomatic, 63). VF or polymorphic VT was induced in 23 (74%), 41 (79%), and 50 patients (79%) in the VF, syncope, and asymptomatic groups, respectively. No significant differences in rate of inducibility were observed between the 3 groups ($p=0.23$). The inducibility of VF or VT was not useful in predicting cardiac events during a mean follow-up period of 37 months ($p=0.63$) [5]. In our most recent study, which included 460 patients, PES was performed in 334 patients (VF, 62; syncope, 91; and asymptomatic, 181). VF or polymorphic VT was induced in 37 (60%), 66 (73%), and 121 patients (67%) in the VF, syncope, and asymptomatic groups, respectively ($p=0.25$). Similarly, the inducibility of VF or VT was not useful in predicting cardiac events

during a mean follow-up period of 50 months ($p=0.20$ in all patients and 0.66 in patients without documented VF) [14].

Some of these studies suggested that PES has some diagnostic value because of the higher inducible rate of VF or VT in symptomatic than in asymptomatic individuals. However, all of the aforementioned studies deny the prognostic value of PES for cardiac events.

Meta-Analyses of Previous Data in BS

Two meta-analyses of previous data in BS were published in 2006 and 2007 [15,16] and evaluated the role of PES as a predictor of cardiac events. Gehi et al. retrieved 30 prospective studies accumulating data on 1545 patients. They evaluated the relative risk and risk difference of an event (syncope, SCD, or ICD shock) for a variety of risk factors in BS. PES was performed in 785 patients. During a mean follow-up period of 32 months, the inducibility of VF or VT at PES was not an independent predictor of these events (HR, 1.88; 95% CI, 0.62–5.73; $p=0.27$) [15]. Paul et al. analyzed 15 studies comprising a total of 1217 patients with BS. Overall, 1036 patients (85%) underwent PES. The inducible rate of VF or VT was higher in symptomatic than in asymptomatic individuals (66%, 55%, and 25% in the VF, syncope, and asymptomatic groups, respectively). During a mean follow-up period of 34 months, the inducibility of VF or VT at PES did not show an independent predictive value for the occurrence of VF or VT (HR, 1.5; 95% CI, 0.05–4.06; $p=0.399$) [16]. With regard to the impact of the inducibility of VF or VT at PES for the occurrence of VF or VT, they analyzed only the data reported by Brugada et al. and revealed a prominent difference in the results between the reports of Brugada et al. and all other studies in the meta-analysis. Only in the studies by Brugada et al. was the hazard ratio for the occurrence of VF or VT significantly higher (HR, 10.0; 95% CI, 3.81–26.23; $p<0.0001$) than the hazard ratios in all the other studies (HR, 0.77; 95% CI, 0.42–1.41; $p=0.364$).

Based on both meta-analyses, it may be concluded that PES did not provide significant prediction of cardiac events in BS.

Possible Reasons for the Divergent Results for the Predictive Value of PES for Cardiac Events

The controversy on the predictive value of PES for risk stratification may be due to the below mentioned reasons.

First is the methodological differences in the stimulation protocols used for PES, including the number of extra stimuli, the minimum coupling interval used (up to 200 ms or refractoriness), the site of stimulation (right ventricular apex [RVA] and/or right ventricular outflow tract [RVOT]), and the amplitude of the electrical impulse during stimulation. In the studies by Brugada et al., stimulation was delivered only from the RVA, with up to 3 extra stimuli down to a minimum of 200 ms [11]. The FINGER study and 2 recent multicenter prospective studies from Japan used a PES protocol from RVA and RVOT with up to 3 extra stimuli. In the FINGER study, the minimal coupling interval was 200 ms, whereas it was up to ventricular refractoriness in the Japanese studies [6,14]. The stimulation protocol markedly influenced the extent of inducibility of VF or VT in BS [17].

To solve this methodological issue, PES using uniformed protocol was recently performed in single-center and multicenter studies. In a single-center study, Makimoto et al. performed PES using a uniform protocol in 108 consecutive patients with type 1 Brugada ECG (VF, 26; syncope, 40; and asymptomatic, 42) [18]. A maximum of 3 ventricular extra stimuli were delivered from the RVA and RVOT up to ventricular refractoriness or coupling interval of up to 180 ms. They stimulated

first the RVA up to 2 ventricular extra stimuli; second, the RVOT up to 2 ventricular extra stimuli; third, the RVA by triple extra stimuli; and finally, the RVOT by triple extra stimuli. The basic cycle length was 500 ms. VF or VT was induced by a single extrastimulus in 4 patients, double extra stimuli in 41, and triple extra stimuli in 36, and was more frequently induced from the RVOT (70%) than from the RVA (30%). During a mean follow-up period of 79 months, the overall inducibility of VF or VT was not associated with an increased risk of VF ($p=0.78$). However, the patients with inducible VF or VT by single or double extra stimuli had worse prognosis than those with inducible VF or VT by triple extra stimuli among all the patients ($p=0.004$) and those without documented VF ($p=0.001$). The positive and negative predictive values of VF and VT with up to 2 extra stimuli (36% and 87%, respectively) were better than those with up to 3 extra stimuli (23% and 81%, respectively). They concluded that single or double extra stimuli at PES were adequate for a prognostic indicator in BS and that the stimulation site and coupling interval of extra stimuli were not prognostic indicator in BS.

Priori et al. reviewed the PRELUDE prospective registry to assess the predictive accuracy of the inducibility of VF or VT by PES using a uniform protocol in 10 centers [19]. A total of 308 consecutive patients with type 1 Brugada ECG and without history of cardiac arrest were enrolled. The PES protocol consisted of 2 basic drive cycles (600 and 400 ms, S1) and up to 3 extra stimuli (S2–S4) delivered first from the RVA and then from the RVOT. The minimal coupling interval of extra stimuli was set to 200 ms for S2 and S3 and to ventricular refractoriness for S4. They also assessed the short-term reproducibility of PES. In 126 (41%) of 308 patients, VF or polymorphic VT was induced. Of the 126 patients with induced VF or polymorphic VT, 5.5% were induced by single; 44.5%, by double; and 50%, by triple extra stimuli. The inducibility site was equally distributed among the RVA (46.0%), RVOT (46.8%), and both (7.2%). The reproducible outcome of PES was only 34%. During a mean follow-up period of 36 months, the overall inducibility of VF or polymorphic VT was not associated with the occurrence of arrhythmic events (VF or appropriate ICD interventions) (individuals with vs. those without induced VF or polymorphic VT, 3.9% vs. 4.9%, $p=0.67$). Although the stimulation protocol used in this study was more aggressive than that used in the study by Delise et al. [13], the negative predictive value of PES was lower than that (100%) in the study of Delise et al. When restricted in patients with VF or polymorphic VT inducible with single or double extra stimuli, the inducibility of VF or polymorphic VT was not associated with the occurrence of arrhythmic events either ($p=0.89$). The sensitivity and specificity of VF or polymorphic VT were 25% and 74.2%, respectively, with up to 2 extra stimuli, and 35.7% and 58.8%, respectively, with up to 3 extra stimuli. They concluded that the inducibility of VF or polymorphic VT had no predictive value for the occurrence of arrhythmic events, although they performed PES with up to 2 extra stimuli. This conclusion supports the results of 2 meta-analyses, the FINGER study, and the Japanese multicenter prospective studies but is different from that in the study by Makimoto et al. One of the reasons of the discrepant results from the PRELUDE registry and the study of Makimoto et al. may be due to the different order of stimulation site (between the RVA and RVOT) in the PES protocol, as Morita et al. demonstrated that VT/VF was more easily induced at the RVOT than at the RVA [20]. It is interesting that although the inducible rate of VF or VT was identical in the PRELUDE registry and the study of Brugada et al. [11], the rate of cardiac events during follow-up was much lower in the PRELUDE registry (1.5% per year in the PRELUDE registry vs. 4.1% per year in the study by Brugada et al. [11]). Despite the similar rate of inducibility with up to 3 extra

stimuli, evaluations of the predictive value of PES were completely different. This contradiction may be due to referral bias in the studies of Brugada et al. [21,22].

Second, time of the day might have influenced the results of the PES. It is well known that the magnitude of ST-segment elevation in the right precordial leads in BS varies spontaneously over days and within the day [23,24]. Usually, the time of maximal ST-segment elevation is during nighttime. The time of PES does not generally coincide with the time of maximal ST-segment elevation. Because the degree of ST-segment elevation is associated with the arrhythmogenic substrate in BS, it is reasonable to assume that the inducible rate of VF or VT at PES will be higher if PES is performed at the time of maximal ST-segment elevation.

Third, it is still controversial whether asymptomatic individuals with Brugada ECG should undergo PES [21,22]. One potentially important reason for the divergent results in asymptomatic individuals is the relatively low rate of spontaneous cardiac events in all the series of previous studies, except in the studies of Brugada et al. Even in asymptomatic individuals with spontaneous type 1 ECG, the incidence rates of cardiac events in most published series are between 0% and 2.8% (mean follow-up period of approximately 3.5 years). The number of patients with cardiac events during follow-up among asymptomatic individuals was still too small to evaluate predictors of cardiac events, including PES. A further continuing study is needed to improve the understanding of predictors of cardiac events in asymptomatic individuals with BS.

Finally, it is possible that some unidentified differences in patient characteristics, induction techniques, or follow-up protocol were responsible for the discrepant results for the predictive value of PES for cardiac events.

In conclusion, most of the previous studies and the 2 meta-analyses have provided evidence of the poor utility of PES for risk stratification in BS. However, there is still no unequivocal explanation for the discrepant results with regard to the role of PES for risk stratification. The limitation of conventional PES should encourage investigative efforts to identify a new PES approach. We should not use the stimulation protocol used in the PRELUDE registry for risk stratification in patients without documented VF. According to recent studies, a combined clinical and electrophysiological approach or a stimulation protocol consisting of a basic drive cycle of 500 ms and up to 2 extra stimuli may be useful for risk profiling in BS. Further, large prospective studies with uniform diagnostic criteria and PES protocols are warranted to evaluate whether the new PES protocol is useful for risk stratification, especially in asymptomatic individuals with BS.

Conflict of Interest

There is a no conflict of interest and no relationships with industry.

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