Arrhythmic Risk Stratification by Programmed Ventricular Stimulation in Brugada Syndrome
The End of the Debate?

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One of the most controversial issues debated by cardiac electrophysiologists during the past decade has been whether programmed ventricular stimulation (PVS) plays any role in the arrhythmic risk stratification of the Brugada syndrome (BrS). The results of the multicenter study published in 2003 by the Brugada brothers were unequivocal. In a study involving 408 BrS individuals with no previous cardiac arrest, inducibility of ventricular fibrillation (VF) was found to be a marker of poor prognosis: individuals with inducible VF had a 6 times higher risk of having sudden death because of VF during the subsequent 2 years compared with the patients with noninducible VF. Subsequent multicenter studies from Europe as well as 2 meta-analyses studies, failed to confirm these results, leading to downgrade in class indication of PVS for risk stratification from IIa in 2005 to IIb in 2013. However, in the latest reported meta-analysis of the prognostic value of PVS in BrS, Fauchier et al found that PVS actually may be useful in patients with syncope and in asymptomatic patients. The strength of that meta-analysis when compared with the first 2 reports is that it distinguished the prognostic role of PVS according to the initial clinical presentation (syncope versus asymptomatic). However, this meta-analysis did not include the results of PVS among patients with spontaneous VF during the subsequent 2 years.

About one third of these patients were already included in the initial series. All patients had a minimal follow-up of 1 year after PVS. Of the 404 patients, 17 (4.2%) presented with aborted cardiac arrest, 114 (28.6%) had at least 1 episode of syncope, and 273 (67.6%) were asymptomatic. Patients who presented with vasovagal syncope were considered as asymptomatic. There were interesting differences in the clinical profile of patients according to the year of patient enrollment (<2005 or >2005). Patients studied before 2005 (n=182) were more likely to present with a spontaneous Brugada-ECG type 1 pattern and to have a history of atrial fibrillation and sinus node dysfunction, as well a broader QRS duration; in contrast, they were less frequently probands. Sustained ventricular arrhythmias (mostly VF) were induced in 73 (18.1%) of the 404 study patients (23.5%, 32.5%, and 11.7% in the aborted cardiac arrest, syncope, and asymptomatic groups, respectively). Interestingly, the overall inducibility rate markedly dropped from 28.6% before 2005 to 9.5% from 2005. After a mean follow-up of 74.3+57.3 months, 25 arrhythmic events (mostly implantable cardioverter-defibrillator [ICD] discharges) occurred in 16 (21.9%) of 73 patients who had inducible arrhythmias and in 9 (2.7%) of 331 patients who had no inducible arrhythmias. Arrhythmia inducibility presented a hazard ratio for arrhythmic events of 8.1 (P<0.01). In addition, according to Kaplan–Meir method, event- free survival for the noninducible group was 99% at 1 year and 96.8% at 5, 10, and 15 years. Among asymptomatic patients, those with no inducible arrhythmias had an event-free survival of 100% at 1 year and 99.2% at 5, 10, and 15 years. Among asymptomatic patients, those with no inducible arrhythmias had an event-free survival of 100% at 1 year and 99.2% at 5, 10, and 15 years. Among asymptomatic patients, those with no inducible arrhythmias had an event-free survival of 100% at 1 year and 99.2% at 5, 10, and 15 years. Among asymptomatic patients, those with no inducible arrhythmias had an event-free survival of 100% at 1 year and 99.2% at 5, 10, and 15 years. Among asymptomatic patients, those with no inducible arrhythmias had an event-free survival of 100% at 1 year and 99.2% at 5, 10, and 15 years. Among asymptomatic patients, those with no inducible arrhythmias had an event-free survival of 100% at 1 year and 99.2% at 5, 10, and 15 years. Among asymptomatic patients, those with no inducible arrhythmias had an event-free survival of 100% at 1 year and 99.2% at 5, 10, and 15 years. Among asymptomatic patients, those with no inducible arrhythmias had an event-free survival of 100% at 1 year and 99.2% at 5, 10, and 15 years. Among asymptomatic patients, those with no inducible arrhythmias had an event-free survival of 100% at 1 year and 99.2% at 5, 10, and 15 years.

This study is important for several reasons: (1) it originates from the laboratory of one of the fathers of the BrS; (2) it includes the largest single-center series of patients with BrS ever published with the longest follow-up duration; (3) the results confirm and even amplify those published by the Brugada brothers 12 years ago; and (4) the article includes a fair discussion on the possible differences between their results and those obtained by others.

Goal of Electrophysiological Study in the Assessment of Patients With BrS

There are presently 2 main clinical indications for electrophysiology study in patients with BrS: (1) stratification of the arrhythmic risk in patients who have no history of cardiac arrest (such as the asymptomatic patients and those presenting with syncope): this stratification may have major therapeutic consequences, such as ICD implantation in patients...
with inducible VF or no treatment in patients without inducible arrhythmias; (2) electrophysiology testing with a class 1A antiarrhythmic drug (mainly quinidine) in those patients with inducible VF with the goal to find an alternative to ICD therapy. Another valuable indication for diagnostic electrophysiology study in patients with BrS, rightly added by Sieira et al, is the assessment of sinus node function and conduction disturbances, especially in elderly patients, as well as the induction of supraventricular tachycardia in patients with syncope.

**PVS Protocols in BrS**

Among the various factors affecting VF inducibility during PVS, the aggressiveness of the protocol used probably plays the most important role. The standard PVS protocols used by most cardiac electrophysiologists include ≤3 extrastimuli delivered from 2 right ventricular sites (apex and outflow tract) with or without limitation of the shortest coupling intervals at 200 ms. Our own PVS protocol is even more aggressive, including the repetition of the shortest coupling intervals (10 times for double and 5 times for triple extrastimulation, respectively). In contrast, the protocol used in the Pedro Brugada laboratory is the least aggressive PVS protocol ever used in the assessment of patients with BrS because it does not include pacing from the right ventricular outflow tract that has been shown to markedly increase VF inducibility rates. It is noteworthy that in the PRogrammed ELectrical stimUlation preDictive valuE registry, 46.8% of patients had their arrhythmias induced only from the right ventricular outflow tract. As a consequence, the protocol used by Sieira et al showed a low sensitivity (23.5%) in patients presenting with cardiac arrest. For comparison, using standard PVS protocols, VF inducibility rates ranged from 55% to 100% with our aggressive protocol, unpublished data. As the aggressiveness of protocol reciprocally affects its sensitivity and specificity, it is understandable that the results of this study yielded marked different results from those of previous reports using dissimilar protocols; in addition, we think it is not reasonable to gather studies that used different PVS protocols into meta-analyses.

A nonconventional stimulus current of 4 mA was used in this study. This could represent >20× the diastolic threshold in some patients. The effects of this relatively high-stimulus current on the results of the PVS protocol in this study are unknown.

**Utility of PVS in Patients With BrS According to Clinical Presentation**

**Cardiac Arrest Survivors**

The relatively small number of cardiac arrest BrS survivors collected during a 20-year period by the Pedro Brugada group (25 patients who received an ICD, 17 of whom were included in this study) attests to the rarity of the disease as a cause of aborted sudden death in the general population. In agreement with the guidelines, the authors recommended ICD implantation in this patient population and they apparently used PVS for academic purpose only. Our own approach in these patients is electrophysiology-guided class 1A antiarrhythmic therapy that privileged VF prevention rather than VF treatment with ICD discharges. Using such approach, we have found excellent results with no arrhythmic event observed to date during ≤21 years of follow-up, unpublished data.

**Syncope**

Patients with BrS presenting with syncope constitute an important diagnostic and therapeutic challenge. Although some cases of syncope may actually be related to VF that terminates spontaneously, vagal syncope is probably the most frequent cause of syncope in the BrS population. The inclusion by Sieira et al of patients with vasovagal syncope in the asymptomatic group has been adopted by many workers in the field. However, the low proportion of patients diagnosed as vasovagal syncope in the overall group of patients with syncope (17 of 131 [13%]) is surprising. More importantly, analysis of the data showed that the authors implanted ICD in all patients with syncope regardless of the electrophysiology results. A posteriori, their decision proved to be right taking in account that 4 arrhythmic events occurred during follow-up among 77 patients with syncope and negative electrophysiology study. However, such a policy may result in unjustified ICD implantation in many patients with the inherent risk of long-term complications. It is likely that a more stringent clinical distinction between syncope of unknown origin and vasovagal syncope would have resulted in inclusion of more patients with vasovagal syncope in the asymptomatic group, and thereby in a decrease of the number of ICD implants in those patients with negative electrophysiology study. In addition, it is tempting to speculate that the use of a PVS protocol more aggressive than the one used in their study would have allowed a better risk stratification in the syncope group patients.

**Asymptomatic Group**

The most important results of the study by Sieira et al concern the asymptomatic group that represents the largest BrS patient population encountered worldwide. This group of patients is considered by some specialists in the field to be at a low arrhythmic risk that does not justify any special investigation and treatment. In fact, based on a cohort of 273 asymptomatic patients followed for a mean of >6 years, Sieira et al observed arrhythmic events in 8 patients (3% of the asymptomatic patients; 0.5% mean events per year). These 8 patients comprised 6 (19%) of patients with inducible arrhythmias and 2 (0.8%) of patients without inducible arrhythmias (P<0.0001). Interestingly, the same yearly arrhythmic event rate (0.5%) was found in the FINGER (France, Italy, Netherlands, Germany) Brugada registry during a shorter period of follow-up (median, 31 months) and suggests that asymptomatic BrS patients should actually be investigated. The authors are right to point out that the high-negative predictive value of their protocol in asymptomatic patients (98.3%) may allow reassuring the immense majority of these patients. Also, it is noteworthy that their protocol achieved the highest positive predictive value (18.2%) ever reported in asymptomatic patients. However, because Brugada disease may aggravate over the time, it may be wise to recommend repeat electrophysiology testing in noninducible patients after 10 years or before if the patients’ cardiac status changes.
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Clinical Implications

In clinical practice, we do usually perform PVS using the same protocol regardless the studied population. The results of this study raise the question whether we are right to do so and if we should not use a specific protocol for the electrophysiology assessment of asymptomatic BrS patients. The high-positive and negative predictive values of the protocol used by Sieira et al suggest that it could be the protocol of choice in asymptomatic BrS patients. Its wide adoption (providing some adjustment of the stimulus current intensity to diastolic threshold and maybe addition of repetition of extra-stimulation) would be a first step for unifying PVS protocols. Hopefully, this will decrease the rate of false-positive stimulation) would be a first step for unifying PVS protocols.

Disclosures

None.

References


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