Even a Pooled Analysis Does Not Resolve the Debate of Electrophysiology Testing in Brugada Syndrome

Emile G. Daoud, MD

Since the first description, investigatory work into the pathophysiology and clinical management of Brugada syndrome (BrS) has been active. Like other channelopathies, BrS is a cause of sudden cardiac arrest (SCA) in young, otherwise healthy, individuals. Initially attributed to the loss of sodium channel function, BrS has also been attributed to the loss of calcium channel function. Thus, the disease is not solely a sodium channelopathy, but rather related to an imbalance between inward and outward currents during phase 1 of the action potential. The hallmark ECG feature is a type 1 pattern of a coved ST-segment elevation of ≥2 mm followed by a negative T wave, present in >1 right precordial lead (V1 through V3), occurring either spontaneously or provoked with a sodium channel antagonist. However, the ECG in BrS can demonstrate type 1, 2, or 3 patterns, or be normal; and these changes can occur either spontaneously or be related to autonomic tone, physiological parameters (eg, fever), and ECG lead position. BrS, therefore, is a dynamic disease, influenced by ethnicity, sex, genotype, autonomic tone, regionally abnormal myocardium; and varied physiological and pharmacological stimuli. With this interplay of pathophysiology, risk stratification of patients with BrS ECG pattern is challenging. Programmed electric stimulation (PES) has been reported to be a useful tool for risk stratification; however, this recommendation is controversial.3–11

In this issue of Circulation, Stroube et al12 report on the relationship between inducible malignant ventricular arrhythmias with PES and future occurrence of the primary outcome, defined as SCA or appropriate implantable cardioverter-decfibrillator (ICD) shock therapy. The database consists of multicenter pooled participant-level data from prospective studies identified from a literature search. Included patients were those who underwent PES, who had a spontaneous or sodium channel blocker–induced type 1 BrS ECG pattern, and who had not experienced SCA. Of 18 identified studies, authors from 8 publications participated.

The relationship between the induction of malignant ventricular arrhythmias and the primary outcome was assessed by using multivariable proportional hazards regression. PES was analyzed by 2 methods. The first method correlated the number of extrastimuli resulting in the induction to the primary outcome. PES results were categorized as induction with single extrastimulus, with up to double extrastimuli, or with up to triple extrastimuli. This terminology denotes that, if a patient was induced with a single extrastimulus, then that individual was also considered to be induced with up to double and with up to triple extrastimuli. A similar analysis applied to patients induced with double extrastimuli. The second method of evaluating PES was to determine the incremental prognostic value of additional extrastimuli on the primary outcome by comparing outcomes of patients induced with double extrastimuli, but not single, and those induced with triple extrastimuli, but not with either single or double extrastimuli.

Of the 1312 patients, the mean age was 45, 1034 (79%) were male, 429 (33%) presented with syncope, and 696 (53%) had a spontaneous type 1 pattern. During a follow-up of 38.3 months, 65 (5%) patients experienced the primary outcome, 5 with SCA and 60 with appropriate ICD therapy. Ventricular arrhythmia induction occurred in 527 of 1247 (42%): 22 with single extrastimulus, 231 with double extrastimuli, and 274 with triple extrastimuli. Induction with up to double (hazard ratio [HR], 2.66; P = 0.002) or with up to triple (HR, 2.66; P = 0.002) extrastimuli were significantly associated with the primary outcome, but this was not true with single extrastimuli (HR, 2.39; P = 0.20). When assessing the incremental prognostic value of extrastimuli, of 1290 patients not induced with single extrastimulus, 231 of 1290 (18%) were induced with double extrastimuli and 274 of 994 (28%) were induced with triple extrastimuli. Induction with double extrastimuli was significantly associated with the primary outcome (HR, 2.55; P = 0.005), but induction with triple extrastimuli only trended to significance (HR, 2.08; 95% confidence interval, 0.98–4.39; P = 0.06). Furthermore, an induced arrhythmia (HR, 2.66; P = 0.002) remained significantly associated with future events even when considering syncope (HR, 2.51; P = 0.002) and a spontaneous type 1 ECG pattern (HR, 3.07; P = 0.002). Although the data regarding PES are compelling, the event rate was high regardless of the results of PES. The primary outcome occurred in 40 of 527 (7.59%) patients with induced malignant ventricular arrhythmias and in 25 of 720 (3.47%) patients with normal PES. The study concludes that the induction of malignant ventricular arrhythmias is associated with a 2- to 3-fold increased risk of SCA or appropriate ICD shock; however, the incremental prognostic value of abnormal PES beyond solely clinical parameters, syncope, and a spontaneous type 1 ECG pattern is small. Electrophysiology testing, therefore, may be best reserved for patients who are not clearly stratified by clinical features.
Sroubek et al.12 completed a substantial investigation of collated data from multiple studies published from 2006 to 2012. The strength of the study is that the large population and extended period of follow-up provide weighty statistical analysis. However, there are important limitations. First, this is a nonrandomized, observational study without a control group. Second, the reliability to convert multicenter data from several years ago into a different standardized form that is then updated with recent outcomes would be limited. Third, of the 18 identified studies, only 8 participated and 84% of the study population was pooled from 3 studies.9–11 Fourth, the included studies have little contribution from the high-risk Asian population, and none are authored by one of the Brugada brothers. It is well recognized that their experience strongly endorses risk stratification with PES.4 Fifth, the vast majority of the primary outcome was ICD shock therapy. Last, the protocol for PES was rather varied. Although subtle, these differences can be quite potent.13

The challenges in managing patients with BrS are common to patients with other inherited arrhythmias. The disease may not be manifested for many years, if ever; the timeline of risk is not uniform; and the first presentation could be SCA. Another consideration is that a low annual risk translates into a high lifetime risk for the young patient. Also, PES is considered of little value, because the pathology is molecular and variable. However, BrS not only has a heterogeneous molecular component, but also regional structural abnormalities associated with a substrate that favors reentry.2 This unique interaction between channelopathy and substrate may, in part, explain the inconsistent findings reported with PES. Considering conflicting literature,3–11 consensus statements suggesting a lesser role,14 and statistical analysis of the current publication, if and how PES should be incorporated into the algorithm for managing BrS remains unsettled.

Perhaps the better place to start with the management of BrS is with easier subgroups: the easily identifiable high- and low-risk groups. Patients with SCA or malignant syncope and any form of type 1 BrS ECG pattern warrant ICD therapy. The low-risk subgroup includes asymptomatic patients with drug-induced type 1 BrS. As reported in the current study, for these subgroups, PES offers little incremental prognostic value.

The remaining question is, does PES offer accurate risk assessment to guide therapy for the patients who, based on clinical features, are at intermediate risk (Figure)? When considering only clinical parameters, if malignant syncope and any type 1 BrS ECG is defined as the lowest threshold of risk indicating ICD therapy, and asymptomatic drug-induced type 1 ECG pattern is the highest threshold of risk not requiring ICD therapy, then, based on the results from the current study, the intermediate range equates to an annual incidence of 0.45% (asymptomatic drug-induced type 1 ECG) to 1.29% (malignant syncope and drug-induced type 1 ECG). The

Figure. This figure summarizes data presented in Table 2 of the article.12 The annual incidence of the primary outcome is plotted according to the subgroup of patients who: either have symptoms (Sx) or are asymptomatic (ASx); have spontaneous (Sp) or drug-induced (Dr) type 1 ECG pattern; and are inducible (I) or noninducible (NI). When considering only clinical parameters, if malignant syncope with any form of type 1 BrS ECG is defined as the lowest threshold of risk indicating ICD therapy, then this risk level is 1.29% represented by the red line, corresponding to patients with Sx+Dr+NI. In the same manner, if patients with asymptomatic drug-induced type 1 ECG pattern is the highest threshold of risk not requiring ICD therapy, then this equates to an annual incidence of 0.45%, represented by the green line associated with the subgroup ASx+Dr+I. Therefore, the intermediate-risk population, highlighted in orange, would comprise patients who are asymptomatic and have a spontaneous type 1 ECG pattern. Within this subgroup, PES may discern who require ICD therapy. If a malignant ventricular arrhythmia is induced (ASx+Dr+I), the annual incidence is 1.70% and an ICD would be recommended. If, however, the patient is noninducible (ASx+Dr+NI), then the risk would be lower, 0.78%. In this intermediate population, PES would then differentiate an absolute annual incidence of 0.92%. Br indicates Brugada; CA, cardiac arrest; ICD, implantable cardiac defibrillator; and PES, programmed electric stimulation.
intermediate-risk population would then comprise patients who are asymptomatic and have a spontaneous type 1 ECG pattern. In this subgroup, induction was associated with an annual incidence of 1.70% and noninduction was associated with a rate of 0.78%. Electrophysiology testing thus seemed to differentiate an absolute annual incidence rate of 0.92% (Figure). Does it seem feasible that PES offers this precise differentiation in the setting of a channelopathy? Furthermore, despite their compelling data, the authors then insert some doubt by adding “...in asymptomatic patients with spontaneous type-1 electrocardiographic patterns, considerable risk of arrhythmia may persist even among those in whom arrhythmias are not induced.”

Even if one accepts PES as a useful tool for stratification of the intermediate-risk patient, there are, of course, limitations. One must recognize the potential lack of reproducibility and the absence of permanency of a single PES. Should PES be repeated on a regular basis for the asymptomatic patient?

The detailed analysis provided by Sroubek et al.12 has helped focus the management of BrS on a few albeit complex variables. The decision to proceed with an ICD can first be addressed by assessing clinical parameters and categorizing the patient in either a high- or low-risk subgroup. Further differentiation of the remaining patients is likely best approached in a manner similar to other channelopathies. The clinician must consider the dynamic pathophysiology, the presenting symptoms, careful inspection, and repeated assessment of the 12-lead ECG and an open discussion of risks and benefits. As for PES, it is unlikely to provide incremental value for the intermediate-risk patient, there are, of course, limitations are not induced."

Disclosures

None.

References


Key Words: Editorials ■ Brugada syndrome ■ electrophysiology ■ prognosis ■ syncope
Even a Pooled Analysis Does Not Resolve the Debate of Electrophysiology Testing in Brugada Syndrome
Emile G. Daoud

Circulation. 2016;133:619-621; originally published online January 21, 2016;
doi: 10.1161/CIRCULATIONAHA.116.021174
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2016 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circ.ahajournals.org/content/133/7/619

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/