Inducible Ventricular Fibrillation in the Brugada Syndrome: Diagnostic and Prognostic Implications

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Editorial Comment

Two leading groups of investigators are reporting differing conclusions regarding the value of electrophysiologic studies (EPS) in the Brugada syndrome. First, Brugada et al. reported that EPS has excellent accuracy for predicting outcome in the Brugada syndrome. Soon thereafter, however, Priori et al. concluded quite the opposite. Based on a study of 86 patients with Brugada syndrome who underwent EPS, Priori et al. found that the test was not useful in identifying patients at risk for arrhythmic events. Finally, in this issue of JACC, Brugada et al. reinforce their previous findings by reporting on more patients and a longer follow-up period, thus reaffirming that EPS effectively predicts outcome. When authorities of this scale reach opposing conclusions, statements such as “the discrepancies observed are due to differences in patient selection and EPS protocols” usually apply. Nevertheless, the clinician is left with so much uncertainty that a critical look at the evidence is warranted.

Is Inducible Ventricular Fibrillation of Diagnostic Value in the Brugada Syndrome?

The first question is whether the induction of ventricular fibrillation (VF) increases the odds that the disease “Brugada syndrome” is present in, for example, a patient with syncope, or a patient without symptoms, who has a Brugada-type ECG.

As opposed to the induction of sustained monomorphic ventricular tachycardia (VT), which is always viewed as a true-positive result of EPS, the induction of polymorphic VT and VF has generally been viewed with reservation. This reservation originates from animal studies showing that VF can be provoked with appropriately timed electrical stimuli in the normal heart. Furthermore, studies performed in the 1980s showed that VF could be induced (by double or triple ventricular extrastimulation) in 6% to 9% of patients who did not have either heart disease or ventricular arrhythmias. It should be noted that induction of nonsustained polymorphic VT, which occurred in 40% of 46% of patients, led to premature discontinuation of EPS in two of these studies. In addition, in these studies only the right ventricular apex was stimulated. One must conclude, therefore, that the false-positive rate of VF induction at EPS is likely to be higher than 9% if a complete pacing protocol, including pacing at two ventricular sites, three ventricular extrastimuli, and short coupling intervals, is used. On the other hand, it should be noted that these studies included only 16 to 32 patients. Despite this small number of patients, these studies led to the designation of VF as “a nonspecific response to aggressive extrastimulation that has no diagnostic value in patients with no heart disease and no documented arrhythmias”, a designation that is still in vogue 2 decades later. Furthermore, because the induction of these nonspecific polymorphic arrhythmias occurred mainly with short-coupled extrastimuli, physicians performing EPS with the aim of inducing monomorphic VT (the only arrhythmia perceived as “clinical arrhythmia”) avoid using extrastimuli with coupling intervals shorter than 200 msec. In fact, VF is the clinical arrhythmia in the Brugada syndrome, and spontaneous initiations of arrhythmias in idiopathic VF and Brugada syndrome invariably follow extrastoles with very short coupling intervals. Consequently, to learn about the sensitivity of EPS in the Brugada syndrome, one must focus on studies using “aggressive extrastimulation” limited by the ventricular refractory period rather than the “nominal” 200-msec interval.

The present study by Brugada et al. includes data on 80 patients with definite Brugada syndrome (cardiac arrest survivors with Brugada-type ECG); 81% of these patients had inducible VF. Smaller series reporting EPS with aggressive stimulation also report VF inducibility in 61%, 85%, and 93% of patients with “definite Brugada syndrome.” This high inducibility rate and the reproducibility of EPS results suggest that electric vulnerability of the myocardium is a distinctive feature of the Brugada syndrome. Finally, the observed “dose-response curve” (the fact that VF is induced in 81% of Brugada patients with cardiac arrest and in 61% of those with syncope but in only 35% of patients with Brugada-type ECG but no symptoms) suggests that inducible VF is a marker of this electric instability. Even the lower inducibility rate reported by Priori et al. (67% for patients with definite Brugada syndrome) using nonuniform EPS protocols is higher than the false-positive rate of “nonspecific” VF induction that one would expect based on the limited data mentioned earlier. One must conclude that inducible VF is of diagnostic value in the Brugada syndrome. Nevertheless, for the individual patient, one must remember that there is at least a 10% chance of “accidentally” inducing VF as a nonspecific response to aggressive extrastimulation. Therefore, one should recommend EPS only to those patients in whom the clinical history or the ECG changes are serious enough to accept VF induction as “positive response” if this occurs.

Is Inducible Ventricular Fibrillation of Prognostic Value in the Brugada Syndrome?

The second question is whether the induction of VF in a patient with Brugada syndrome increases the odds that VF eventually will occur spontaneously. Because the risk for future arrhythmias is so high (≥45% in patients who already experienced cardiac arrest (or syncope of arrhythmic origin), the consensus is that all such patients should undergo
placement of an implantable cardioverter defibrillator (ICD). Thus, there is no reason to perform EPS in asymptomatic patients with Brugada syndrome unless one is willing to try EPS-guided quinidine therapy.

The remaining and most controversial question is related to the value of EPS in predicting outcome in asymptomatic patients. This is not a trivial question. Increased awareness of the ECG of this disorder is leading to more frequent referral of asymptomatic patients: 59% of the asymptomatic patients in the latest series had no previous symptoms.

Positive predictive value

Brugada et al. report the outcome of 263 asymptomatic patients who underwent EPS because they had a Brugada-type ECG: 91 (35%) of the asymptomatic patients had inducible VF and 11 (12%) of them eventually had spontaneous VF. On the other hand, a very large number of patients (172 asymptomatic patients) had negative EPS and only 2 (1%) subsequently developed arrhythmias. The relatively low 12% positive predictive value is not surprising given that the patients are otherwise healthy. Although most physicians and patients probably would be willing to intervene with ICD placement to prevent a 12% risk of cardiac arrest in a young patient, one should attempt to identify those patients at higher risk to reduce the number of unnecessary ICD implantations. One would assume that the asymptomatic patients who also have a history of familial sudden death are at greater risk. Priori et al. reported a 33% incidence of spontaneous VF among asymptomatic patients with a positive family history and inducible VF. Whether the presence of “high-risk” ECG criteria will increase the predictive value of EPS remains to be established. Other authors have reported lower positive predictive values (range 0% to 8%) for EPS in asymptomatic patients. It should be noted that the number of patients included in all of those studies combined is considerably smaller than the number of patients reported by Brugada et al.

Negative predictive value

Priori et al. reported that 7% of asymptomatic patients with a negative family history and negative EPS eventually had a cardiac arrest, but this figure was derived from a single calamity out of 14 cases. The fact that only 2 (1%) of the 172 asymptomatic patients with negative EPS in the report by Brugada et al. developed VF represents the “best news.” The follow-up period of noninducible patients was shorter than that of inducible patients (29 vs 36 months), and it is possible that the negative predictive value of EPS will diminish (as more patients develop VF) with longer follow-up periods. In fact, a close look at the survival curve provided by Brugada et al. (their Fig. 1) suggests that this might be the case. Although the survival curves of inducible versus noninducible patients continued to diverge after 10 years (meaning that the excellent prognostic value of EPS persisted), the negative predictive value of EPS became unacceptable in the long term as almost 30% of asymptomatic patients with negative EPS still followed by 100 months developed cardiac arrest. These survival curves should be viewed with caution because the number of patients followed for >70 months was small. Nevertheless, we are reminded that the Brugada syndrome is a newly described entity and, therefore, follow-up periods are still short. Although the Brugada syndrome is a genetic disorder (present since birth), the majority of patients who actually develop symptoms do so only in adulthood. Therefore, one should be careful about concluding anything about the value of EPS for predicting a first event in asymptomatic patients when the mean follow-up is less than 3 years (34 ± 44 months and 31 ± 41 months), especially when the asymptomatic patients included are younger than those with symptoms. In a recent series reporting a low predictive value for EPS, the age of the asymptomatic patients—even at the end of the follow-up period—was still younger than the age recorded for symptomatic patients at the onset of the study. Time will tell the real prognostic role of EPS in the Brugada syndrome, but in view of the lethality of this disorder, patients (and physicians) should be willing to intervene based on a certain degree of uncertainty.

References


