Epicardial Substrate Ablation in Brugada Syndrome
Time for a Randomized Trial!

Arthur A.M. Wilde, MD, PhD; Koonlawee Nademanee, MD

Brugada syndrome (BrS) is a cardiac rhythm disorder characterized by a typical ECG and a high incidence of ventricular fibrillation (VF)-related sudden cardiac death in the absence of overt structural heart disease.1,2 The disease is surrounded with controversies, including important issues, such as the genetic basis, risk stratification, and the pathophysiological substrate for the signature ECG sign.2,3 There is, however, universal agreement that the diagnosis requires a type 1 Brugada pattern ECG in at least 1 lead4 and that the most appropriate therapy is an implantable cardioverter-defibrillator (ICD) for the high-risk patient. The latter group includes patients who have been resuscitated or who have suspicious symptoms.4 ICD therapy is highly effective, but the downside is well recognized nowadays and consists of a relatively high burden of ICD trouble (ie, inappropriate shocks, lead fractures, infection, etc).5,6 In addition, in some patients, frequent recurrent arrhythmia storms necessitate the need for additional therapy. Pharmacological therapy with quinidine is an option; however, protection might not be completely sufficient and side effects potentially preclude long-term therapy. More than 10 years ago, experience with endocardial ablation was limited, but attempts to target the initiating extrasystoles appeared to be a successful alternative, invasive therapy.7 More recently, however, epicardial ablation in the right ventricular outflow tract (RVOT)/right ventricle anterior wall region, directly targeting the potential substrate, was successfully performed.8 Indeed, now there is little doubt that the arrhythmic substrate is found in the RVOT. The ST-elevation is most prominent in the leads overlying this area and closely follows its anatomic position.9 In addition, in the vast majority of patients with spontaneous ectopy, the extrasystoles originate from the RVOT area,10,11 with electrocardiographic characteristics of an epicardial origin.11 Also, induction of arrhythmias is most readily performed from the RVOT area.10 And finally, a recent multicenter study provides sound evidence that the RVOT area has profound abnormal histology, including significant fibrosis and reduced connexin 43 protein levels.12 Because of its targeted approach and its potential significance for the understanding of the pathophysiological substrate, the epicardial ablation technique gained a lot of interest.

Yet worldwide, it seems that clinical experience with this technique is still limited. Until today, the only series (n=9) published was the initial one,8 and thereafter, some individual cases were published.13,14 A welcome addition to this published experience is the series by Brugada et al (n=14), published in this issue of the journal.15 Their series included more patients, but the population seemed less symptomatic, and the follow-up time was shorter (maximum 6 months compared with 20±6 months in the initial series).8

In this study, 14 symptomatic BrS patients were enrolled, all with an ICD and inducible VF during programmed electric stimulation. Before the ablation procedure, 12 of 14 patients had documented episodes of ventricular arrhythmias with their ICD, but none of them had arrhythmic storms, unlike the Thai patients described in the initial study. Before ICD implant, 10 were syncopal and 4 complained of dizziness. Twelve had a spontaneous type 1 ECG and 2 had a drug-induced type 1 ECG.15

The strength of the current study is the systematic analysis of the effect of flecainide in determining the arrhythmic substrate. Before ablation, the area to target was delineated by a flecainide infusion. The epicardial area with low-voltage (<1.5 mV) and fractionated signals, commonly in the anterior right ventricular free wall and the RVOT area, increased significantly in size, and the delay and duration of local abnormal ventricular electrograms also increased after flecainide infusion in all patients. Notably, a relationship between ECG pattern changes and extent of the low-voltage area was noted: the wider the low-voltage area, the higher the ST-segment elevation and coved-type appearance.15 However, no quantitative objective data were presented; thus, it is unclear whether the investigators made this observation subjectively or whether they correlated the objective measurement of the degree of ST-elevation changes in the precordial leads before and after flecainide to the magnitude of the increase in low-voltage areas after flecainide.

Moreover, low-voltage area assessment is subject to several potential confounding variables: tissue contact, pericardial fat, and amount of fluid in the pericardium. Because the investigators used an irrigated 3.5-mm tip mapping catheter with continuous flushing, albeit a small amount per minute and despite partial removal during the procedure, one would...
expect the amount of pericardial fluid during the second mapping after flecainide to be larger than that at baseline mapping; the longer the operator spent time mapping at baseline, the more fluid would have accumulated. Thus, one must be cautious in using low-voltage area signals solely as a surrogate for the substrate sites.

At any rate, the area with abnormal signals, after flecainide between 10% and 20% of the total epicardial area, was targeted with radiofrequency applications, and flecainide was reinfused to ensure complete absence of fractionated activity. Also, programmed electric stimulation was performed and noninducibility was assured. No significant complications occurred. During follow-up, a flecainide challenge was performed and was negative in all patients. No arrhythmic events were recorded.

We are pleased with the results of this study. However, there are some issues to be raised. First, one has to be cautious in drawing any firm conclusions about the outcomes because of the short-term follow-up period (median 5 months). However, based on our initial study, which has now expanded to >50 patients (with a median follow-up of 3 years), patients whose BrS ECG pattern was/is completely eliminated and who did not have an overlapping syndrome with combined BrS and early repolarization syndrome, indeed, do well and have no ventricular tachycardia (VT)/VF recurrences.

Second, although the use of flecainide during the mapping procedure seems powerful in identifying substrate areas, we would like to express some caution as to the use of flecainide in this situation. Considering the relatively long half-life of intravenous flecainide (7–19 hours), one has to be concerned that any VT/VF associated with drug infusion might be recalcitrant. The use of the class lc drugs flecainide and pilsicainide in BrS patients has been reported to elicit major ventricular arrhythmias in 15% to 20% of the patients. The occurrence of major ventricular arrhythmias was found to be significantly higher in symptomatic patients and in patients with documented SCN5A mutations. As stated earlier, the patients in this study by Brugada et al were not an overtly high-risk subset; it is logical to speculate that the incidence could be much lower. Any study of this kind would probably first requires a trial in a high-risk subgroup of BrS patients so that a potentially favorable effect can be judged within a reasonable time frame. Any study of this kind would likely need a worldwide surveillance because of the limited number of patients. Yet, it needs to be confined to highly experienced centers because epicardial ablation is not without complications.

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References


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