Epicardial substrate ablation for Brugada syndrome

Koonlawee Nademanee, MD, FHRS, Meleze Hocini, MD, Michel Haïssaguerre, MD

From the "Pacific Rim Electrophysiology Research Institute, Bangkok, Thailand, "Pacific Rim Electrophysiology Research Institute, Los Angeles, California, and Hospital Cardiologique du Haut-Leveque, CHU Bordeaux, IHU LIRYC, Bordeaux, France.

Introduction

Brugada syndrome (BrS), characterized by the presence of coved-type ST-segment elevation followed by T-wave inversion in the right precordial electrocardiogram (ECG) leads in patients who have no structural heart disease but have a high risk of sudden cardiac death from ventricular fibrillation (VF), has captivated arrhythmia scholars and electrophysiologists for more than 2 decades. As a result, major progresses have been made toward a better understanding of the syndrome with respect to its genetic basis, underlying pathophysiology, and risk stratification.¹ We have witnessed an increase in BrS cases being diagnosed as well as an exponential increase in research articles, contributing to our knowledge of the syndrome. Although a little more than 20 years have passed since BrS has been introduced, clinicians still have found few therapeutic options where an abundance of research advances lie. Implantable cardioverter-defibrillator (ICD) and quinidine are currently the only 2 mainstay therapies for patients with BrS.²

Unfortunately, the use of quinidine is limited by its unavailability in many parts of the world and its relatively high incidence of side effects. ICDs have been effective in preventing sudden cardiac deaths in symptomatic BrS. The HRS/EHRA/APHRS expert consensus statement² recommends ICD implantation as a class I indication for symptomatic patients with type 1 Brugada ECG pattern who present with aborted sudden death and VF-related symptoms such as syncope, seizure, or nocturnal agonal respiration.

However, ICD treatment is not ideal, because ICDs in patients with BrS who are young and otherwise healthy are associated with unwanted side effects such as inappropriate shocks, lead fractures/failure, and device infections. Furthermore, it is not uncommon for some patients with BrS to have recurrent VF episodes causing frequent ICD discharges or storms. In the past, physicians faced the daunting task of finding effective therapeutic modalities to control such frequent VF episodes; often they resorted to using isoproterenol infusion, quinidine, or both, with variable success. In rare instance, a heart transplant was performed to control electrical storm.³

Haïssaguerre et al⁴ were the first to attempt catheter ablation to treat patients with BrS with recurrent VF. Their ablation approach was to identify the site that initiated VF-triggering premature ventricular contractions (PVCs), which they found were located at the right ventricular (RV) outflow tract (RVOT). Ablation procedures of these triggering PVCs from the endocardial site of the RVOT prevented VF recurrences. Patients with BrS rarely have PVCs, however, hindering attempts to identify VF-triggering PVCs in BrS and making this approach impractical.

Almost a decade later, the discovery of the arrhythmogenic site at the anterior RVOT epicardium led to successful radiofrequency ablation (RFA) of these substrates, resulting in normalization of the Brugada ECG pattern and prevention of VF recurrence. Thus, this substrate ablation approach is now readily available for the vast majority of symptomatic patients with BrS. The purpose of this article was to describe how to successfully identify and ablate these substrates in patients with BrS.

BrS substrates

Despite ongoing debate about the underlying pathophysiology of BrS, repolarization abnormality vs depolarization abnormality, there is a consensus that the RVOT is the arrhythmogenic site for BrS because of the following observations: (1) Placing the electrodes of right precordial leads at the second and third intercostal spaces (ICSs)—the location where there are no other cardiac structures except the RVOT—augments the likelihood of producing a BrS ECG pattern rather than placing the electrodes only on the standard fourth ICS. (2) Haïssaguerre et al also observed that VF-triggering PVCs emanated from the RVOT in patients with VF storm. Ablation procedures of these triggering PVCs from the endocardial site of the RVOT abated VF storms as well. (3) Morita et al⁵ demonstrated in their animal model of BrS that RVOT was the main substrate site, especially at the epicardial site. (4) Lastly, the strongest
clinical evidence came from our study describing the arrhythmogenic substrates of 9 patients with BrS with frequent ICD discharges.\(^6\) We found in all 9 patients abnormal electrograms characterized by low voltage (<1 mV), prolonged duration (>120 ms), and fractionated late potentials (beyond the QRS complex) clustering in the anterior aspect of the RVOT epicardium. The arrow shows abnormal prolonged low-voltage fractionated electrograms recorded from that site of the right ventricular outflow tract epicardium. Abl-d = bipolar ablation distal; Abl-p = bipolar ablation proximal; Abl-d-Uni = unipolar ablation distal.

The answer to this question came from our recent multicenter study, which demonstrated epicardial and interstitial fibrosis and reduced gap junction expression in the RVOT of patients who died suddenly and had BrS family history with negative routine autopsy.\(^8\) In addition, there was a significant increase in collagen content in all ventricular walls in the victim diagnosed with BrS over and above the normal collagen content seen in age- and sex-matched controls. In the same study, biopsies taken from 6 patients with BrS during open heart ablation from RVOT epicardial sites, which harbored abnormal fragmented and delayed conduction, confirmed similar findings of fibrosis. After open heart RFA at these fibrosis sites, ECG patterns normalized and patients no longer had recurrent VF. Interestingly, the in vivo cases all had normal results on cardiac imaging including computed tomography/magnetic resonance imaging as well as a normal appearing heart on direct visualization during thoracotomy. The investigators from the Academic Medical Center of Amsterdam also previously reported similar findings from the explanted heart of a patient with BrS who had an SCN5A mutation with medically treated failure from VF storms, necessitating a heart transplantation surgery.\(^7\) The explanted heart showed no evidence of repolarization abnormality. Instead, the investigators found evidence of interstitial fibrosis causing conduction delay. Thus, one can reasonably conclude that epicardial surface and interstitial fibrosis and reduced gap junction expression in the RVOT are the abnormal myocardial structures that underlie arrhythmogenic substrates, as detected by abnormal low-voltage fractionated late potentials.

**Mapping of BrS substrates**

**Mapping technique**

Armed with knowledge of the BrS arrhythmogenic substrate and its electrogram characteristics and location, one can now straightforwardly map the substrate sites and eliminate them by catheter ablation. To do this, one must gain access into the pericardial space for epicardial mapping. Endocardial and epicardial electroanatomic mapping of the RV as well as epicardial mapping of the left ventricle can then be performed. The choices of mapping catheters and electroanatomic systems can be left to the operator’s discretion as long as they permit high-density electroanatomic mapping. In our laboratory, we prefer to use a 3.5-mm-tip NaviStar ThermoCool SmartTouch catheter and CARTO system ( Biosense Webster, Inc., Diamond Bar, CA). Image integration tools such as CARTO-Merge, CartoUnivu for fluoroscopic/angiographic image integrations, and 2D-Realtime Integration with electroanatomic mapping are helpful in creating the detailed epicardial and endocardial electroanatomic map. Such maps can be displayed based on either voltage or duration of local potentials. Abnormal electrograms are defined as electrograms that have low voltage (<1 mV); split electrograms or fractionated electrograms with multiple potentials with ≥2 distinct components, with >20 ms isoelectric segments between peaks of individual components; and long duration (>80 ms) or late potentials, with distinct potentials extending beyond the end of the QRS complex. These abnormal electrograms are tagged as target sites for ablation procedures.

**Importance of sodium channel blockers in identifying subtle substrate sites**

In our earlier experience of mapping BrS substrates, we did not use a sodium channel blocker such as ajmaline, procainamide, or flecainide during mapping. Even though the outcomes of our mapping and ablation procedures were quite good, we learned subsequently that BrS substrates remained present after ablation in some patients because the initial ablation procedures did not include all substrate sites, as evidenced by the appearance of a Brugada ECG pattern after the ajmaline provocation test. And some of these patients with incomplete substrate ablation had VF recurrences necessitating a repeat ablation procedure. During the
repeat procedure, we found that substrate sites were much larger than those of the first ablation procedure, especially after ajmaline infusion. Over the past 5 years, we have modified our mapping protocol in an effort to better define the BrS substrate sites by a compulsory mapping of the RV epicardium after the administration of a sodium channel blocker with either ajmaline or procainamide (United States).

Twenty-eight symptomatic patients with BrS (all men; median age 32 years) underwent mapping and ablation of BrS substrates under this new protocol: 21 with ajmaline (50–80 mg over 5 minutes) and 7 with procainamide (750–1000 mg over 20–30 minutes) infusion. We found that all patients had anterior RVOT epicardial substrates with typical abnormal electrogram characteristics as mentioned above, confirming our original publication. However, we have observed new additional findings: First, after sodium channel blocker administration, the substrate areas could be quite large. Approximately 20 cm² covered almost the entire RV epicardium and extended to the RV body in 15 of 28 patients (53%). Seven patients also had inferior wall arrhythmogenic substrates (25%), and the map of 1 of these 7 patients is shown in Figure 2. Second, we discovered that ajmaline caused a 2-fold increase in substrate areas from 10.3 ± 8 at baseline to 19.5 ± 5.6 after ajmaline infusion (P < .01); procainamide also increased the substrate areas, but in lesser magnitude. Figure 3 shows an example of the CARTO electroanatomic map before and after ajmaline infusion (50 mg) of another symptomatic patient with BrS. The drug increased the targeted area of the BrS substrate from 14.3 to 20.4 cm², which covers the main part of the anterior RVOT epicardium to the body of the RV epicardium. We performed RFA by targeting the substrate areas that were defined after ajmaline/procainamide infusion. This resulted in the normalization of the Brugada ECG pattern in all patients with standard ECG lead placement. However, with ajmaline challenged and lead placement at the higher second and third ICSs, 5 patients (18%) continued to have type 1 Brugada ECG pattern; 3 of these 5 patients had recurrent VF episodes and required reablation. Interestingly, 4 of these 5 patients whose Brugada ECG pattern remained present after the first ablation underwent the procedure before the SmartTouch NaviStar catheter became available. It is unclear whether poor contact of the epicardial tissue is the reason why we did not quite eliminate the substrates, but one has to speculate that poor contact could be the factor.

Ablation protocol and ablation end points

An irrigated-tip catheter that provides force measurement is recommended. We would not ablate the target site if the contact force is lower than 5 g. With good contact, radiofrequency power between 20 and 45 W is sufficient to create a desirable acute effect of ablation on the substrate site. As shown in Figure 4 (Video 1), if radiofrequency energy is effective in creating the lesion, the recorded electrogram voltage amplitude will be drastically reduced and the mid and late components of the fractionated potentials will disappear, indicating the elimination of the intramyocardial substrate that generated mid and late components of the fractionated potentials of the recorded signals.

As discussed previously, our mapping protocol has been modified by adding a sodium channel blocker as part of defining the targeted substrate areas for ablation. Likewise, we no longer use our old ablation end points from the original publication—either noninducible VT/VF or normalization of the Brugada ECG pattern during the ablation procedure. We believe that the best and only end point is to eliminate all substrate areas that harbor abnormal low-voltage fractionated signals detected after sodium channel blocker challenge, as described above.

Figure 2  Example of the large Brugada syndrome substrate areas of a patient with multiple implantable cardioverter-defibrillator shocks due to recurrent ventricular fibrillation. A: Anterior view of the electroanatomic map of the RV epicardium combined with the RV angiographic image using CartoUnivu software, displaying a large area of the right ventricular outflow tract and RV proper with abnormal fractionated late potentials. Abnormal electrograms are shown in the right panel (pink dots). B: Lateral view of the RV epicardial map highlighting abnormal substrate areas involved at the inferior wall RV epicardium where fractionated late potentials are also recorded after ajmaline infusion, as shown in the left panel. Abl-d = bipolar ablation distal; Abl-p = bipolar ablation proximal; Abl-d-Uni = unipolar ablation distal; RV = right ventricular; V1 ICS3 = lead V1 at the third intercostal space; V2 ICS3 = lead V2 at the third intercostal space.
Complications
In our hands, the complication rate is relatively low. Hemopericardium occurred in 1 patient (2%), but did not prevent the completion of ablation. Mild pericarditis pain is experienced in ~35% of patients, but did not prolong hospitalization. There were no major groin complications that required blood transfusion or surgical intervention.

Conclusion and Future Direction
Epicardial substrate ablation for BrS is effective and a welcome addition to the therapeutic armamentarium. We hypothesize that a certain subset of patients with BrS could be treated with catheter ablation procedures without the need of an ICD. This is the subset of patients with BrS who had no overlapping syndrome i.e combined BrS and early repolarization syndromes and could be treated with extensive substrate ablation alone, provided that the procedure yields normalization of the right precordial ECG at the higher ICS lead positioning after sodium channel blocker challenge.

To test this hypothesis, a multicenter randomized study, Ablation in Brugada Syndrome for the Prevention of VF Episodes (BRAVE study, ClinicalTrials identifier NCT02704416), has been launched. If the study results confirm this hypothesis, we should be able to more confidently treat this subset with RFA without an ICD. And of course one has to balance the benefit of epicardial ablation with the risks of the procedure both acutely and after long-term follow-up. One has to raise the questions: Would extensive ablation of the RVOT, parts of the RV body, and inferior aspect of the RV affect RV function or would the scar from ablation cause monomorphic VT? The answers to these questions remain elusive and need to await further studies such as the newly launched BRAVE study.

Nevertheless, we can confidently conclude that at least for patients with BrS who have suffered from recurrent VF episodes, epicardial ablation of the BrS substrate should be the treatment of choice.

Appendix
Supplementary data
Supplementary data are available in the online version of this article at http://dx.doi.org/10.1016/j.hrthm.2016.12.001
References


