

“Fever vs. Drug: Battling with the Brugada syndrome substrate.”

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1500

Fever vs. Drug: Battling with the Brugada syndrome substrate

Brugada syndrome (BrS) and associated life threatening ventricular arrhythmias (VA) are a leading cause of sudden cardiac death (SCD) in the young, especially in South East Asia (1). The presence of the Type 1 Brugada ECG pattern in the ECG leads overlying the right ventricular outflow tract (RVOT), spontaneously or provoked by sodium channel blockers or by fever, is essential for the diagnosis (2). The specificity of the type 1 pattern induced by pyrexia or sodium channel provocation is uncertain. A 2% prevalence of the type 1 pattern was noted in consecutive patients presenting to an Israeli ED with fever (3), whilst 4% of healthy Turkish controls undergoing ajmaline provocation developed the type 1 pattern (4). This has led to refinements in the diagnostic criteria for BrS, including a diagnostic scoring system, the Shanghai Score (1). Fever or drug-induced Type 1 pattern alone are no longer diagnostic without evidence of further clinical or familial features although fever was given a greater weighting in the scoring system.

There are electrocardiographic differences between fever-induced and drug-induced type 1 patterns. A drug-induced pattern was reproduced in only 81% of cases presenting with an initial fever-induced pattern. The drug-induced pattern was associated with significant PR and QRS prolongation, whilst the PR interval was shortened by fever (5). The same study suggested a higher risk associated with a fever-induced pattern although Adler et al. had found a good prognosis (3). It seems that provoked type 1 patterns are a relatively common finding.

Understanding the pathophysiology of BrS is therefore critical to understanding these differences. Counter to the perception of BrS as a disease devoid of any structural features, there now exists significant evidence in favor of subtle abnormalities within the RVOT. Nademanee studied a group of BrS patients with recurrent VF, undertaking electromagnetic mapping of the right ventricular (RV) epicardium and endocardium demonstrating fractionated and late low voltage potentials within the RVOT epicardium. Radiofrequency catheter ablation (RFCA) within this region resulted in: elimination of the type 1 Brugada ECG pattern; non-inducibility of VF; and low recurrence rates (6). In BrS patients undergoing open thoracotomy and RVOT RFCA, these epicardial fractionated late potentials correlated

with epicardial and intramyocardial fibrosis on biopsy. Ablation at these sites was effective in eliminating the type 1 pattern and reducing event rates. The same arrangement of subtle epicardial RVOT fibrosis, coupled with altered expression of the gap junction protein Connexin-43, was detected in sudden cardiac death cases in whom surviving first degree relatives were found to have BrS (7).

Brugada *et al* (8) analyzed the effect of flecainide on the epicardial substrate in a group of BrS patients with ICDs who were symptomatic with syncope or dizziness and were inducible at EP studies, and then underwent RFCA. Flecainide was shown to increase the area of low voltage fractionated signals within the RVOT and RV free wall. RFCA within these regions was effective in eliminating the BrS phenotype and inducibility.

Enter the fascinating study by Chung *et al* published in this issue of the journal (9), who sought to explore the substrate of BrS further. Warm water was instilled into the epicardial space to induce local hyperthermia and mimic the effect of fever. Flecainide's effects on the substrate and enhancement of epicardial premature ventricular complex (PVC) triggers were also examined with the hypothesis that this would allow a more efficacious strategy for RFCA encompassing PVC trigger ablation and substrate modification. This incorporated the original observations of Haissaguerre *et al* (10) who described the successful ablation of PVCs originating from the RVOT or right Purkinje conducting system, responsible for triggering VAs in specific patients with BrS.

Fifteen BrS patients with a history of an aborted cardiac arrest (n=10) or VA with syncope (n=5) were recruited: eight patients had a spontaneous Type 1 pattern at baseline, with the remaining demonstrating a type 1 pattern with flecainide. All patients underwent flecainide administration to assess the effect on PVC burden. Two patients demonstrated an increase in PVC density whilst three patients had documented PVCs at baseline. PVCs originated from the RVOT (n=3) and left ventricular papillary muscle (n=2), the latter being a novel association in BrS. Targeted RFCA resulted in successful elimination of these triggers. Substrate mapping identified abnormal epicardial electrograms and scar in the anterior RV free wall and RVOT in 11 patients who then went on to have successful epicardial substrate modification with immediate elimination of the BrS phenotype in five patients and then a

further two patients during follow up. All cases were rendered non-inducible with elimination of VA recurrences except in one subject. Chung *et al* have added further to the weight of evidence in favor of ablation as a valid therapeutic modality in high risk BrS patients (9).

Warm water instillation was undertaken in six patients and resulted in a significant increase in the area of functional scar over the epicardial surface. Whilst there was little observed differences in abnormal electrograms, in contrast with Brugada *et al*'s findings of significant effects on electrogram morphology caused by flecainide (8), there were significant alterations of epicardial conduction velocities. These were reduced in areas in which functional scar was identified, whereas an increase in activation velocity was seen in epicardial areas devoid of scar, as well as the endocardium. Furthermore all these individuals were rendered inducible during warm water instillation when only one was inducible at baseline. This observed enhancement of heterogeneity in conduction within the RV and RVOT therefore suggests a primary mechanism for VF of epicardial reentry in patients with BrS with fever and may have implications for arrhythmogenesis in BrS in general. The specific effect of fever was also comparable to that described by Mizusawa *et al* (5) where the fever-induced type 1 pattern was accompanied by shortening of the PR interval in contrast with the more widespread impact of sodium channel blockers on conduction.

Several clinical questions remain. Does fever-induced type 1 pattern indicate a higher long term risk than a drug-induced pattern? What is the place of trigger ablation in ablation strategies? given that more recent studies have included less severely affected patients, are we convinced about the role of RVOT RFCA in patients without VT storm and/or recurrent VAs? A first logical step is a robust and systematic randomized control trial of patients with sufficiently high event rates to permit a successful study over a reasonable length of time. The BRAVE Study (11) aims to investigate the efficacy and prognostic value of RVOT RFCA in symptomatic BrS patients compared to current therapy of ICD alone. This will provide valuable insight into the potential role for RFCA in long term risk reduction and whether in the future it may offer value for primary prevention in the asymptomatic patient.

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