A novel method to enhance phenotype, epicardial functional substrates, and ventricular tachyarrhythmias in Brugada syndrome

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BACKGROUND Fever is associated with the manifestation of Brugada phenotype and ventricular tachycardia/ventricular fibrillation (VT/VF) in patients with Brugada syndrome (BrS). The thermal effect on the pathogenesis of functional substrates in BrS remains unknown.

OBJECTIVE This study aimed to elucidate the thermal effect on BrS phenotype, VT/VF, and electrophysiological characteristics of epicardial functional substrates in BrS.

METHODS We consecutively studied 15 patients with BrS receiving radiofrequency catheter ablation for drug-refractory ventricular tachyarrhythmias. Baseline characteristics, electrocardiographic features, and changes in epicardial functional substrates before and after epicardial warm water instillation (n = 6) were recorded and analyzed.

RESULTS A total of 15 male patients (mean age 41.3 ± 10.3 years) with type 1 BrS presenting with ventricular tachyarrhythmias were consecutively enrolled. Epicardial mapping in 11 patients demonstrated a significantly larger epicardial scar/low-voltage zone (LVZ) area within the right ventricular outflow tract and anterior right ventricular free wall than within the endocardium (6.32 ± 12.74 cm² vs 52.91 ± 45.25 cm²; P = .007). Epicardial warm water instillation in 6 patients led to a significant enlargement of the functional scar/LVZ area (123.83 ± 35.26 cm² vs 63.53 ± 40.57 cm²; P = .03), accelerated conduction velocity of the endocardium and epicardium without scar/LVZ area, and increased VT/VF inducibility (16.7% vs 100%; P = .02). Ablation by targeting premature ventricular complexes and/or epicardial abnormal substrates rendered noninducibility of VT/VF and prevented the recurrences of VT/VF.

CONCLUSION Epicardial warm water instillation enhanced functional epicardial substrates, which contributed to the increased inducibility of ventricular tachyarrhythmias in BrS. Ablation by targeting the triggers and abnormal epicardial substrates provided an effective strategy for preventing ventricular tachyarrhythmia recurrences in BrS.

KEYWORDS Brugada syndrome; Catheter ablation; Epicardial warm water instillation; Functional substrates; Ventricular tachyarrhythmias

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Introduction

Brugada syndrome (BrS) is one of the leading causes of ventricular tachycardia/ventricular fibrillation (VT/VF) and sudden cardiac death (SCD) in young adults in the East and Southeast Asia. The loss-of-function autosomal dominant mutations in 1 copy of the SCN5A gene accounts for the etiology in 20%–30% of patients with BrS. Three subtype electrocardiographic features have been recognized to facilitate the diagnosis and are characterized by the elevation of ST segment in right precordial leads either spontaneously or after a provocative drug test with the administration of a sodium channel blocking agent. Both repolarization and depolarization abnormalities have been proposed as the...
etiology of precordial lead electrocardiographic phenotype and the potential arrhythmogenesis.\(^4\) Owing to the risk of recurrences of ventricular tachyarrhythmias and SCD, an implantable cardioverter-defibrillator (ICD) implantation is recommended for patients with BrS who have experienced cardiac arrest and those who have documented spontaneous sustained VT with or without syncope.\(^3\) In spite of the role of ICDs in the prevention of SCD, current strategies for ameliorating occurrences of ventricular tachyarrhythmias are limited. Given the disappointing efficacy and adverse effects of antiarrhythmic drugs, catheter ablation offers an alternative therapeutic strategy for patients with BrS presenting with SCD and frequent ventricular tachyarrhythmias.

A previous study demonstrated that the onset of ventricular tachyarrhythmias in patients with BrS was frequently triggered by specific premature ventricular complexes (PVCs).\(^5\) There is also evidence that radiofrequency catheter ablation (RFCA) targeting the triggers originating from the arborization of the right ventricular (RV) Purkinje system and right ventricular outflow tract (RVOT) could be an effective strategy for preventing the recurrence of further tachyarrhythmias.\(^6\) In addition, Nademanee et al\(^7\) demonstrated the effectiveness of ablating the arrhythmogenic substrate at the RVOT epicardium on decreasing the VT/VF burden. A recent study also reported that RFCA of enhanced epicardial abnormal substrates at the anterior free wall of the RV and RVOT after flecainide testing could eliminate BrS phenotype.\(^8\) However, whether these enhanced functional epicardial substrates contributed to ventricular arrhythmogenesis clinically remains unknown.

Fever is the most common trigger of BrS phenotype and the associated occurrences of ventricular tachyarrhythmias.\(^9,10\) This is supported by the fact that hot baths, particularly in Japan, contribute to syncope or SCD in patients with BrS.\(^11\) However, the regulatory mechanisms of increased temperature on the clinical manifestation of BrS phenotype and the associated ventricular tachyarrhythmias remain to be elucidated.

In the present study, we investigated (1) consecutive patients with BrS and drug-refractory ventricular tachyarrhythmias treated with RFCA for triggers and arrhythmogenic substrates and (2) the thermal effects on the manifestation of electrophysiological features, endocardial/epicardial substrates, and the inducibility of ventricular tachyarrhythmias in BrS were assessed using a novel method of epicardial warm water instillation. We postulated that our results could bring new insight into the understanding of epicardial functional substrates and the association between thermal effect and ventricular arrhythmogenicity.

## Methods

### Study population

From 2011 to 2015, 15 patients with documented spontaneous or flecainide-induced type 1 BrS electrocardiogram (ECG) who had aborted SCD or episodes of VT/VF were consecutively enrolled. Detailed medical and family history, 12-lead ECG, 24-hour Holter monitoring, signal-averaged ECG, and transthoracic 2-dimensional echocardiography was performed. This study was conducted at the Taipei Veterans General Hospital in Taiwan and was approved by the institutional review board of the Taipei Veterans General Hospital (IRB no. 2015-12-006AC) and Department of Health, Taiwan. Written informed consent was obtained from all patients.

### Provocation of Brugada phenotype

1. **Flecainide provocative test:** The ECG features before and after flecainide testing were obtained. For patients with PVCs before or after flecainide testing, the density of PVCs was calculated.

2. **Epicardial warm water instillation:** After obtaining the epicardial access and epicardial substrates, 60 mL of warm water (0.9% saline) with a temperature of 39°C – 40°C was infused into the epicardial space for 10 minutes. The changes in ECG features were quantified after warm water instillation.

### Electrophysiology study and substrate mapping

1. **Baseline electrophysiology study:** The baseline electrophysiology study was performed as described previously.\(^12\) For detailed information, see Online Supplemental Materials.

2. **Epicardial warm water instillation, remapping, and repeated electrophysiology study:** After epicardial warm water instillation, the instilled warm water was drained to prevent inadequate contact during remapping. Repeated endocardial and epicardial substrate mapping was achieved using a multipolar mapping catheter, with continuous warm water irrigation at a rate of 2 mL/min. The ECG was continuously recorded during remapping. The substrate characteristics regarding the changes in the scar, low-voltage zone (LVZ), area with abnormal electrograms and conduction velocity were compared with those before warm water instillation. The comparison of point-to-point electrogram properties regarding the local ventricular activity was performed by selecting corresponding points with an anatomical distance of <3 mm. Finally, repeated induction of VT/VF with and without the infusion of isoproterenol was performed by using the same programmed electrical stimulation protocol.

### Strategies of RFCA

For patients with spontaneous or flecainide-induced PVCs that have been documented to be responsible for the arrhythmogenesis of ventricular tachyarrhythmias (Online Supplemental Figure 1), RFCA by targeting the PVCs was performed. After ablation of arrhythmogenic triggers, VT/VF inducibility was assessed. Epicardial approach with substrate modification was performed for patients with...
positive VT/VF inducibility. Substrate modification and ablation energy were similar as described previously (Online Supplemental Material). After substrate modification, repeated substrate mapping was performed to confirm the complete elimination of abnormal electrograms. Finally, testing for inducibility of VT/VF was performed repeatedly with and without isoproterenol by using the same stimulation protocol.

Clinical follow-up
The patients were examined with ECG, 24-hour Holter ECG, and signal-averaged ECG monitoring after the procedure and during clinical visits every 3–6 months. For detailed follow-up methods, see Online Supplemental Materials.

Statistical analysis
Data are expressed as mean ± standard deviation for normally distributed continuous variables and proportions for categorical variables. Continuous variables were analyzed using a 2-tailed t test. Discrete variables were compared using the χ² test. The differences in substrate characteristics before and after epicardial warm water instillation were compared using the Wilcoxon signed-rank test and χ² test. The point-to-point comparisons of the local ventricular activity before and after epicardial warm water instillation were performed using a paired t test. All statistical significances were set at P < .05, and all statistical analyses were carried out using SPSS 20.0 (IBM Corporation, Armonk, NY).

Results
Baseline characteristics of patients with BrS
A total of 15 patients [mean age 41.3 ± 10.3 years; 15 men (100%)] with BrS were consecutively enrolled. The baseline ECG demonstrated type 1 BrS pattern in 8 patients and type 2 BrS pattern in 2 patients (Table 1). Of them, 10 patients had an initial presentation with aborted SCD, and syncope was noted for the remaining 5 patients. The characteristics of ventricular tachyarrhythmias consisted of VF in 9 patients, nonsustained VT in 3, sustained VT in 2, and sustained VT and VF in 1. The family history of SCD was recognized in 2 patients. Echocardiographic examination confirmed structurally normal hearts in all patients with a mean left ventricular ejection fraction of 59.9% ± 5.3%. A genetic mutation of SCN5A was identified in 3 patients.

Provocation of BrS phenotype
Flecainide provocative test
The flecainide provocative test resulted in type 1 BrS ECG in all study patients. Baseline PVCs were documented in 3 patients, while the flecainide test led to frequent PVCs in additional 2 patients. Furthermore, the PVC density 1 hour after the provocative test increased from 1.62% ± 2.22% to 8.20% ± 3.56% (P = .01). Electrocardiographic features of PVCs were left bundle branch block with inferior axis in 3 patients and right bundle branch block with intermediate or superior axis in 2 (Online Supplemental Figure 2).

Epicardial warm water instillation
Epicardial warm water instillation was performed in 6 patients. One of them underwent a second procedure owing to ICD interventions during follow-up. After epicardial warm water instillation, BrS phenotype was augmented or unmasked in all patients (Figures 1A and 1B and Online Supplemental Figure 3).

Electrophysiological characteristics and substrate properties
BrS phenotype was identified in 8 patients at the beginning of the electrophysiology study. Endocardial bipolar mapping of the RV was performed in all patients with an average scar/LVZ area of 6.32 ± 12.74 cm², while epicardial mapping in 11 patients demonstrated a significantly larger scar/LVZ area located within the RVOT and anterior RV free wall (52.91 ± 45.25 cm²; P = .007). Baseline programmed electrical stimulation induced ventricular tachyarrhythmias in 6 patients with BrS, including VF in 4 patients, VT in 1, and VF/VF in 1.

Effect of epicardial warm water instillation on the enhancement of functional substrates
Electroanatomic mapping demonstrated that the endocardial bipolar and unipolar scar/LVZ areas were similar before and after epicardial warm water instillation (Table 2), while epicardial functional scar, scar/LVZ, and unipolar LVZ areas significantly increased after instillation (80.70 ± 34.67 cm² vs 26.87 ± 17.43 cm², P = .03; 123.83 ± 35.26 cm² vs 63.53 ± 40.57 cm², P = .03; 91.35 ± 26.54 cm² vs 71.48 ± 35.78 cm², P = .03, respectively; Online Supplemental Table 1 and Figures 2 and 3). However, the areas with abnormal electrograms were similar before and after epicardial warm water instillation (10.35 ± 3.47 cm² vs 14.53 ± 8.98 cm²; P = .25; Figure 3).

Notably, the total activation time of the epicardial RV also lengthened from 212.50 ± 70.79 to 236.83 ± 63.81 ms (P = .03; Table 2) after epicardial warm water instillation. The analysis of the regional conduction heterogeneity demonstrated that epicardial warm water instillation significantly accelerated the endocardial activation velocity (2.45 ± 0.42 cm/ms vs 1.25 ± 0.35 cm/ms; P = .03). The epicardial activation velocity in the area without functional scar/LVZ was accelerated with warm water instillation (2.38 ± 0.22 cm/ms vs 1.44 ± 0.18 cm/ms; P = .03; Figure 4), while the conduction velocity was reduced within the epicardial functional scar/LVZ areas (3.18 ± 0.28 cm/ms vs 2.26 ± 0.21 cm/ms; P = .03; Figure 4 and Online Supplemental Figure 4).

A total of 813 paired points with a mean distance of 1.8 ± 0.6 mm before and after epicardial warm water instillation were selected. The results of the point-to-point comparisons of the local ventricular activities before and after epicardial warm water instillation were found to be similar (66.45 ± 32.32 ms vs 65.21 ± 35.30 ms; P = .16; Figure 5).

Furthermore, in 6 patients with BrS receiving epicardial warm water instillation, the VT/VF inducibility with and without isoproterenol by the same stimulation protocol
No periprocedural complications were noted.

The patient underwent repeat RFCA for drug-refractory VF, and 1 patient experienced recurrences of VF episodes and received appropriate ICD interventions (Online Supplemental Figure 5).

During a mean follow-up period of 18.2 months of follow-up. RFCA rendered VT/VF noninducible for all patients by targeting the triggers or substrate modification. Immedi-

### RFCA of triggers and abnormal substrates in BrS

Catheter ablation eliminated the triggers in 5 patients with BrS, including 3 originating from the RVOT and 2 from the left ventricular papillary muscle. Epicardial substrate modification was performed by targeting the identifiable abnormal electrograms in 11 patients during a mean radiofrequency application duration of 27.5 ± 10.5 minutes (Figure 6). The complete elimination of abnormal electrograms after substrate modification was confirmed by repeated substrate mapping. Immediately after the procedure, BrS phenotype was eliminated after substrate modification in 5 of 11 patients while it was attenuated or changed in the remaining 6 patients. Disappearance of BrS phenotype was observed in an additional 2 patients during 3–6 months of follow-up. RFCA rendered VT/VF noninducible for all patients by targeting the triggers or substrate modification. No periprocedural complications were noted.

### Follow-up

After RFCA, none of the patients took antiarrhythmic drugs. During a mean follow-up period of 18.2 ± 9.0 months, only 1 patient experienced recurrences of VF episodes and received appropriate ICD interventions (Online Supplemental Figure 5). The patient underwent repeat RFCA for drug-refractory VF, and there was no further recurrence of ventricular tachyarrhythmias during a follow-up period of 12 months.

### Discussion

#### Main findings

The present study demonstrated several new pivotal findings regarding the clinical characteristics and electrophysiological properties in patients with BrS. First, flecainide testing could enhance triggers that were responsible for the development of ventricular tachyarrhythmias in patients with BrS; those triggers arising from papillary muscle were important for initiating ventricular tachyarrhythmias in certain patients with BrS. Second, epicardial warm water instillation in patients with BrS could result in the augmentation or the presence of electrocardiographic phenotype, enhance epicardial functional substrates owing to the heterogeneous variation in conduction velocity, and facilitate ventricular arrhythmogenesis. Third, catheter ablation, by targeting the triggers or epicardial substrates, can provide an alternative and effective method for the prevention of ventricular tachyarrhythmia recurrences.

#### Triggers of ventricular tachyarrhythmias in patients with BrS

A previous study demonstrated that the occurrences of VF episodes in patients with BrS were frequently preceded by PVCs, which were almost identical to the initiating PVCs of VF according to the electrocardiographic features of ICDs or ECG monitoring. This finding was also corroborated by the fact that the elimination of PVCs that triggered ventricular

### Table 1  Baseline characteristics of patients with BrS

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>Sex</th>
<th>Baseline ECG</th>
<th>PVCs at baseline</th>
<th>Family SCD</th>
<th>Initial manifestation</th>
<th>Clinical documented VT/VF</th>
<th>Flecainide testing</th>
<th>PVC after flecainide testing</th>
<th>Epicardial warm water instillation</th>
<th>SVT</th>
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<tbody>
<tr>
<td>49 M</td>
<td>Type 1</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>SCD</td>
<td>VF</td>
<td>Type 1</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>51 M</td>
<td>Type 1</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>SCD</td>
<td>VF</td>
<td>Type 1</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>24 M</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>Syncope</td>
<td>Nonsustained PMVT</td>
<td>Type 1</td>
<td>+</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>48 M</td>
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<td>+</td>
<td>−</td>
<td>SCD</td>
<td>VF</td>
<td>Type 1</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>35 M</td>
<td>Type 2</td>
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<td>+</td>
<td>−</td>
<td>Syncope</td>
<td>Nonsustained PMVT</td>
<td>Type 1</td>
<td>+</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>48 M</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>SCD</td>
<td>VF</td>
<td>Type 1</td>
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<td>−</td>
<td>−</td>
<td>SCD</td>
<td>VF</td>
<td>Type 1</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>49 M</td>
<td>Type 1</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td>SCD</td>
<td>VF</td>
<td>Type 1</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>56 M</td>
<td>Type 1</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>SCD</td>
<td>Sustained PMVT/VF</td>
<td>Type 1</td>
<td>+</td>
<td>−</td>
<td>−</td>
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<td>−</td>
<td>−</td>
<td>SCD</td>
<td>VF</td>
<td>Type 1</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
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<td>22 M</td>
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<td>−</td>
<td>−</td>
<td>Syncope</td>
<td>Sustained PMVT</td>
<td>Type 1</td>
<td>+</td>
<td>−</td>
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<td>38 M</td>
<td>Type 1</td>
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<td>−</td>
<td>−</td>
<td>SCD</td>
<td>VF</td>
<td>Type 1</td>
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<td>+</td>
<td>−</td>
<td>SCD</td>
<td>VF</td>
<td>Type 1</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>33 M</td>
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<td>−</td>
<td>−</td>
<td>−</td>
<td>Syncope</td>
<td>Sustained PMVT/VF</td>
<td>Type 1</td>
<td>+</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>52 M</td>
<td>Type 1</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>Syncope</td>
<td>Nonsustained PMVT</td>
<td>Type 1</td>
<td>+</td>
<td>−</td>
<td>−</td>
</tr>
</tbody>
</table>

AF = atrial fibrillation; AFL = atrial flutter; AVNRT = atioventricular nodal reentrant tachycardia; BrS = Brugada syndrome; ECG = electrocardiogram; M = male; MMVT = monomorphic ventricular tachycardia; PMVT = polymorphic ventricular tachycardia; PVC = premature ventricular complex; RBBB = right bundle branch block; SCD = sudden cardiac death; SVT = supraventricular tachycardia; VF = ventricular fibrillation; VT = ventricular tachycardia. + = the presence of ECG phenotype, with positive family history of SCD and receiving epicardial warm water instillation; − = the absence of ECG phenotype, no family history of SCD and without receiving epicardial warm water instillation.

*Performed in the second procedure.

Significantly increased from 16.7% to 100% (P = .02; Figures 1C and 6) after warm water instillation. Repeated epicardial mapping after the washout of epicardial warm water demonstrated the regression and attenuation of the epicardial functional scar.
tachyarrhythmias in patients with BrS could effectively prevent further recurrences of ventricular tachyarrhythmias.\textsuperscript{6} The present study results echoed the above findings, suggesting that the ablation of PVCs by RFCA could be a pivotal strategy in BrS. Notably, the present study also demonstrated that PVCs that are responsible for ventricular arrhythmogenesis could be enhanced or unmasked by flecainide testing in certain patients with BrS.

Moreover, the literature has reported that PVCs in BrS usually arise from the RVOT, which was concordant with the present findings.\textsuperscript{6} Our study also identified that, in addition to those from the RVOT, PVCs originating from the papillary muscle could be important triggers for the development of ventricular tachyarrhythmias and could be abolished through RFCA.

**Functional substrates after epicardial warm water instillation**

The present study provided pivotal insights on the potential mechanisms of fever-associated ventricular arrhythmogenicity in patients with BrS. Morita et al\textsuperscript{13} demonstrated that alteration of the tissue temperature contributed to the changes in action potential durations (APDs) and spatial dispersion in BrS.
animal model; this elevation of temperature in BrS could abbreviate APDs, accelerate the conduction velocity, and reduce the dispersion of APDs in the RV epicardium, which was consistent with our findings. We found that the epicardial warm water instillation led to the acceleration of conduction velocity of the epicardium without functional substrates, which

Table 2  Comparisons of substrate characteristics between baseline and after epicardial warm water instillation in patients with BrS (n = 6)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Baseline</th>
<th>Epicardial warm water instillation</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>82.3 ± 19.4</td>
<td>85.2 ± 11.1</td>
<td>.72</td>
</tr>
<tr>
<td>Endocardial mapping</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scar (cm²)</td>
<td>0.00 ± 0.00</td>
<td>0.42 ± 0.48</td>
<td>.11</td>
</tr>
<tr>
<td>Scar (%)</td>
<td>0.00 ± 0.00</td>
<td>0.22 ± 0.26</td>
<td>.11</td>
</tr>
<tr>
<td>Scar + LVZ (cm²)</td>
<td>1.08 ± 1.50</td>
<td>1.90 ± 2.20</td>
<td>.47</td>
</tr>
<tr>
<td>Scar + LVZ (%)</td>
<td>0.37 ± 0.50</td>
<td>0.95 ± 1.13</td>
<td>.14</td>
</tr>
<tr>
<td>Unipolar LVZ (cm²)</td>
<td>9.25 ± 7.70</td>
<td>22.00 ± 36.24</td>
<td>.75</td>
</tr>
<tr>
<td>Unipolar LVZ (%)</td>
<td>3.93 ± 3.08</td>
<td>8.68 ± 13.15</td>
<td>.60</td>
</tr>
<tr>
<td>Epicardial mapping</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scar (cm²)</td>
<td>26.87 ± 17.43</td>
<td>80.70 ± 34.67</td>
<td>.03</td>
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<tr>
<td>Scar (%)</td>
<td>5.02 ± 2.50</td>
<td>14.08 ± 4.65</td>
<td>.03</td>
</tr>
<tr>
<td>Scar + LVZ (cm²)</td>
<td>63.53 ± 40.57</td>
<td>123.83 ± 35.26</td>
<td>.03</td>
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<tr>
<td>Scar + LVZ (%)</td>
<td>11.70 ± 5.57</td>
<td>21.53 ± 3.96</td>
<td>.03</td>
</tr>
<tr>
<td>Unipolar LVZ (cm²)</td>
<td>71.48 ± 35.78</td>
<td>91.35 ± 26.54</td>
<td>.03</td>
</tr>
<tr>
<td>Unipolar LVZ (%)</td>
<td>13.20 ± 4.76</td>
<td>15.78 ± 2.78</td>
<td>.08</td>
</tr>
<tr>
<td>Area with abnormal electrograms (cm²)</td>
<td>10.35 ± 3.47</td>
<td>14.53 ± 8.98</td>
<td>.25</td>
</tr>
<tr>
<td>Area with abnormal electrograms (%)</td>
<td>2.15 ± 0.84</td>
<td>3.05 ± 2.11</td>
<td>.18</td>
</tr>
<tr>
<td>Total activation time (ms)</td>
<td>212.50 ± 70.79</td>
<td>236.83 ± 63.81</td>
<td>.03</td>
</tr>
</tbody>
</table>

BrS = Brugada syndrome; LVZ = low-voltage zone.

Figure 2  Examples of electroanatomic endocardial and epicardial mapping before and after epicardial warm water instillation in 2 patients with BrS. Neither endocardial bipolar voltage mapping (panels A1–D1) nor unipolar voltage mapping (panels A2–D2) shows significant changes in scar/LVZ areas before and after epicardial warm water instillation. However, after epicardial warm water instillation, the size of bipolar scar/LVZ extending from the RVOT to the RV free wall is significantly increased (panel B3 vs panel A3 and panel D3 vs panel C3). Similarly, the epicardial area with abnormal unipolar voltage mapping extending from the RVOT to the RV free wall after epicardial warm water instillation is larger than that before instillation (panel B4 vs panel A4 and panel D4 vs panel C4).
therefore resulted in functional conduction block. As a consequence, epicardial functional substrates were enhanced and conduction velocity of epicardial functional substrates was reduced. This heterogeneity of substrate conduction properties explains the causal depolarization mechanism of BrS and the VT/VF vulnerability by elevated temperature. The above findings were also echoed by the fact that impulse propagation from regions with shorter APDs to those with longer APDs after local refractory period could lead to reentry and promote ventricular arrhythmogenesis mediated by transient potassium outward current at high temperature.

Another recent study reported that epicardial functional substrates and BrS phenotype could be enhanced after the administration of flecainide, which could be eliminated by epicardial substrate modification.8 This conclusion was drawn on the basis of the fact that the LVZ area within the epicardium was expanded from 17.6 to 28.5 cm² after flecainide testing, which was comparable to the present findings. In contrast with the results of epicardial warm water instillation, a larger area of abnormal epicardial electrograms with the longer ventricular activity were identified by flecainide testing, implying a different pathophysiological mechanism for each of the above 2 situations. Fever was associated with decreased membrane density and alteration of voltage dependency of the mutated sodium channels,14,15 while flecainide blocks the Na⁺,1.5 sodium channels and slows the upstroke of action potentials. Moreover, higher incidence of inducible ventricular tachyarrhythmias after epicardial warm water instillation could reflect the pivotal role of enhanced epicardial functional substrates on the development of ventricular tachyarrhythmias. The difference between the flecainide and temperature elevation methods in identifying the critical functional substrates responsible for the arrhythmogenesis of VT/VF and the associated clinical implications require future investigation.

Catheter ablation and Brugada phenotype

There are still debates about the pathophysiology of ECG phenotype in BrS, and both repolarization and depolarization mechanisms have been postulated.4 Similar to previous findings, abnormal substrates were identifiable within the epicardium in BrS and abolition of the potential arrhythmogenic epicardial substrates contributed to the elimination of or changes in ECG phenotype, with the prevention of further inducibility of ventricular tachyarrhythmias; this supports the importance of abnormal depolarization in entity.7,8 In contrast, heterogeneity of epicardial functional substrates and areas with abnormal electrograms between spontaneous BrS phenotype and the epicardial warm water instillation–induced phenotype shown in the present study implies complex interactions between depolarization abnormalities and electrocardiographic features in BrS. Despite the fact that BrS phenotype after the provocative test can be eliminated by RFCA, future studies are warranted to identify the appropriate epicardial substrates for ablation.
In contrast, epicardial substrate modification was performed for patients without triggers or with inducible ventricular tachyarrhythmias after trigger elimination in the present study. On the basis of the above-mentioned strategies, the present study also demonstrated the promising effectiveness of RFCA for the prevention of future VT/VF recurrences. However, whether routine epicardial approach should be performed in BrS needs to be elucidated.

Study limitations
There were several limitations in the present study. First, in spite of continuous warm water instillation, the real-time epicardial temperature during repeated mapping was not measured. Second, given the nature of the rare disease, the clinical prognosis and effectiveness of ventricular tachyarrhythmias prevention were not compared between patients undergoing trigger elimination and those undergoing epicardial substrate modification. Third, the appropriate voltage criteria for the identification of exact
Epicardial fibrosis in patients with BrS remain unknown. The identified scar/LVZ may not reflect the true scar tissue by histopathological examination. In addition, the epicardial fat might result in false scar/LVZ within electroanatomic mapping. However, despite these limitations, the novel method for the enhancement of epicardial functional substrates provided a better understanding of the mechanisms of ventricular tachyarrhythmias. Finally, both PVC elimination and substrate modification have been used in the present study. Future investigation will be warranted for elucidating the appropriate ablation strategy in patients with BrS.

Conclusion
Epicardial warm water instillation is a novel method for the enhancement of functional substrates and the increase in inducibility of ventricular tachyarrhythmias in patients with BrS. RFCA by targeting the triggers and abnormal epicardial substrates provided an effective and promising strategy in the prevention of recurrences of ventricular tachyarrhythmia in BrS.

Appendix
Supplementary data
Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.hrthm.2017.01.006.

References


