# ST-Elevation Magnitude Correlates With Right Ventricular Outflow Tract Conduction Delay in Type I Brugada ECG

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**BACKGROUND:** The substrate location and underlying electrophysiological mechanisms that contribute to the characteristic ECG pattern of Brugada syndrome (BrS) are still debated. Using noninvasive electrocardiographical imaging, we studied whole heart conduction and repolarization patterns during ajmaline challenge in BrS individuals.

**METHODS AND RESULTS:** A total of 13 participants (mean age, 44±12 years; 8 men), 11 concealed patients with type I BrS and 2 healthy controls, underwent an ajmaline infusion with electrocardiographical imaging and ECG recordings. Electrocardiographical imaging activation recovery intervals and activation timings across the right ventricle (RV) body, outflow tract (RVOT), and left ventricle were calculated and analyzed at baseline and when type I BrS pattern manifested after ajmaline infusion. Peak J-ST point elevation was calculated from the surface ECG and compared with the electrocardiographical imaging–derived parameters at the same time point. After ajmaline infusion, the RVOT had the greatest increase in conduction delay (5.4±2.8 versus 2.0±2.8 versus 1.1±1.6 ms; $P$=0.007) and activation recovery intervals prolongation (69±32 versus 39±29 versus 21±12 ms; $P$=0.0005) compared with RV or left ventricle. In controls, there was minimal change in J-ST point elevation, conduction delay, or activation recovery intervals at all sites with ajmaline. In patients with BrS, conduction delay in RVOT, but not RV or left ventricle, correlated to the degree of J-ST point elevation (Pearson $R$, 0.81; $P$<0.001). No correlation was found between J-ST point elevation and activation recovery intervals prolongation in the RVOT, RV, or left ventricle.

**CONCLUSIONS:** Magnitude of ST (J point) elevation in the type I BrS pattern is attributed to degree of conduction delay in the RVOT and not prolongation in repolarization time.

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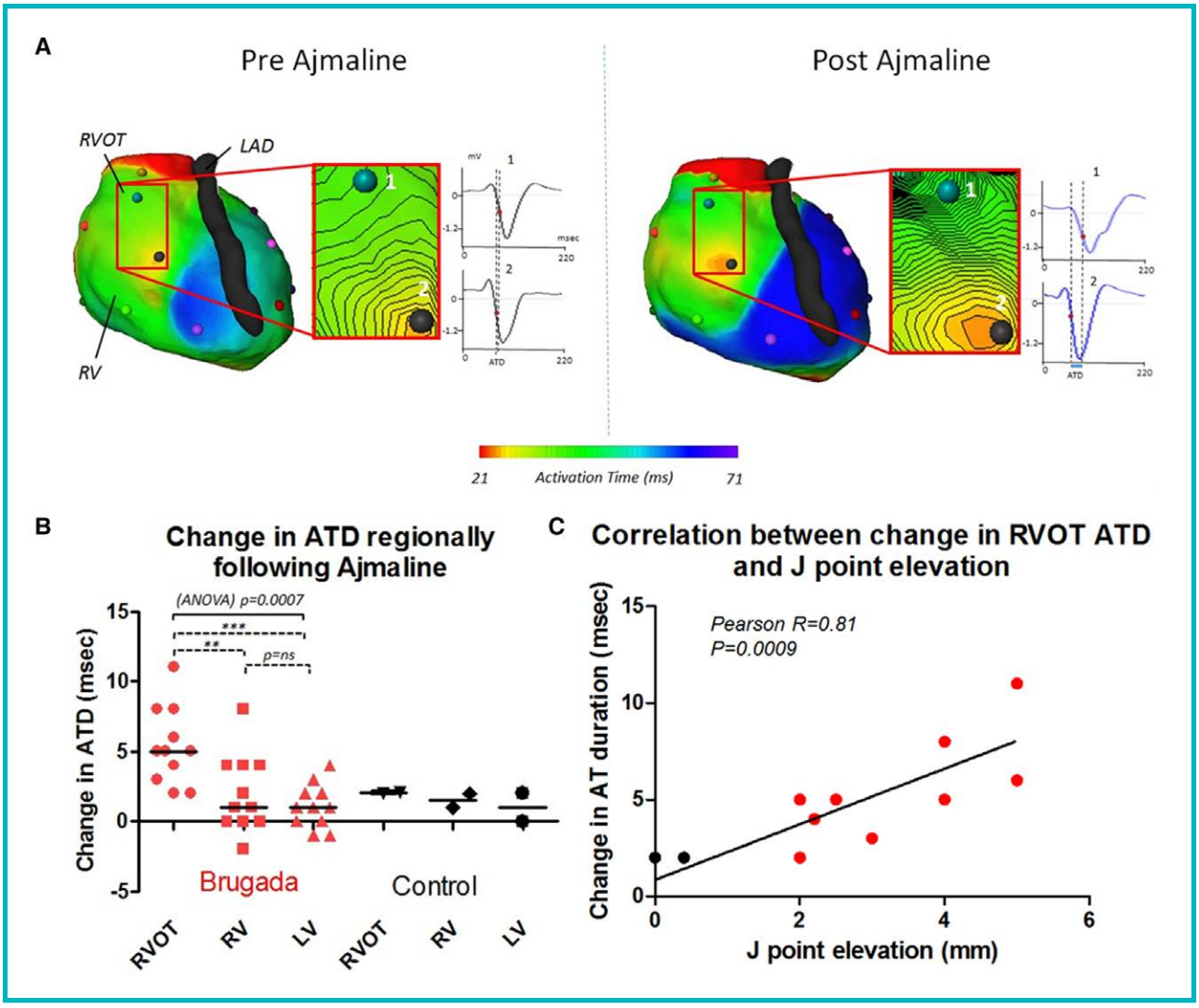


## WHAT IS KNOWN?

- The underlying electrophysiological mechanism that contribute to the Brugada syndrome ECG is still debated.

## WHAT THE STUDY ADDS?

- In patients with Brugada syndrome, changes in both depolarization and repolarization occur after sodium channel blockade in the right ventricle.
- We demonstrate a direct correlation between ST elevation in the Brugada syndrome pattern and conduction slowing, but not repolarization, in the right ventricular outflow tract providing further support for the depolarization hypothesis.

Both abnormalities in repolarization and depolarization have been described in Brugada syndrome (BrS) although which of these mechanisms give rise to the ST-segment elevation (STE) in the type I pattern remain unclear.[1] The varying degree of STE observed within different BrS subjects likely reflects different degrees of conduction and repolarization heterogeneity in the epicardial right ventricular outflow tract (RVOT), as suggested by previous clinical studies.[2–4]

Body surface mapping potential and echocardiographic surrogates of conduction over the right ventricle (RV), but not repolarization, have been found to correlate with STE after sodium channel blockade in BrS.[2,3] In contrast, single contact electrode data from electrophysiological catheters situated in the epicardial and endocardial RVOT demonstrated that STE corresponded to prolongation of repolarization in the epicardial RVOT after pilsicainide infusion.[4] Currently, high-density, epicardial data characterizing the relationship of STE to changes in conduction and repolarization are lacking.

Electrocardiographical imaging (ECGi) is a novel tool that uses body surface potentials from a 252-electrode vest, and using inverse solution mathematics, recon-

structs >1200 unipolar electrograms onto a digitized epicardial heart surface. It is possible to observe patterns of depolarization and repolarization using this method, and it has also been used to study the electrophysiological substrate in a variety of conditions.[5,6]

In this study, we aimed to characterize whole heart electrophysiological conduction and repolarization patterns on the epicardial surfaces of BrS hearts after ajmaline infusion. We also correlated these changes to the degree of J point elevation of the ST segment on the surface ECG to further elucidate the mechanisms that underlie the type I ECG in BrS.

# METHODS

## Subject Enrollment

Patients referred to our center for an ajmaline challenge for suspected BrS were recruited. Individuals were referred for the test as part of a family screen or based on clinical history and ECG findings. All patients were required to withhold all concurrent medications 5 days before the test.

## Study Protocol

ECGi (EcVUE system, Medtronic) and 15-lead surface ECG recordings were simultaneously performed at resting baseline and throughout the ajmaline challenge. The ECGi methodology has been described and validated previously.[7] Briefly, body surface potential data obtained via a 252-electrode vest were combined with patient-specific heart-torso geometry derived from a thoracic computed tomographic scan. Using inverse solution mathematical algorithms, the ECGi system reconstructed epicardial unipolar electrograms (EGM) and panoramic activation maps over a single sinus beat which was visualized on a digitized image of the patient's heart (Figure 1A).

A total ajmaline dose of 1 mg/kg was administered and infused over a period of 5 minutes. The infusion was prematurely stopped in the event of manifestation of the type 1 BrS pattern or prolongation of the QRS interval by 130%. Recordings were discontinued once the 15-lead ECG had returned to baseline or for a period of at least 20 minutes where no ECG changes were observed. The study protocol was reviewed and approved by our institutional review committee (ref: 14/LO/1318). All subjects gave informed consent.

## Changes in Activation Time Duration From ECGi

Three-dimensional activation maps were automatically generated from the ECGi system and are based on local activation timings, defined as the steepest negative deflection (–dV/dt) during the QRS complex, of the unipolar EGM. Activation maps were generated at baseline and after ajmaline infusion (at manifestation of BrS pattern in responders or end of infusion in nonresponders), and the activation timing window of interest was synchronized to allow comparison across phases. Activation maps for 3 consecutive beats were checked at each phase to ensure consistency. Analysis and detection of differences in activation patterns across the phases were performed by 2 of the reviewers, and where interpretation differed, a third reviewer arbitrated. A surrogate for RVOT, RV free wall, and left ventricular (LV) free wall activation time duration (ATD) was derived from the difference in EGM local activation time between 2 points, 3.5 cm apart, in the direction of the activation wavefront within their respective regions preajmaline infusion. This was compared with the RVOT, RV, and LV ATD derived from the same locations postajmaline infusion. Anatomic landmarks on computed tomographic scan were used to define the regions: (1) left anterior descending artery separated the RV and LV, and (2) the outflow tract was defined as the region within the RV 4 cm below the pulmonary valve. An example of ATD measurement in the RVOT is shown in Figure 2.

## Activation Recovery Intervals From ECGi Unipolar EGMs

For each patient, the LVs and RVs were anatomically divided into 15 regions (Figure 1B) from which 45 unipolar EGMs (3 per region) were analyzed during a cardiac cycle at each of the following phases: (1) pre-ajmaline, and (2) post-ajmaline. EGM analysis was performed using an off-line semiautomated custom-made program with Matlab (Mathworks Inc). Activation recovery interval (ARI), a surrogate of action potential (AP) duration, or index of myocardial repolarization time was taken from the local activation timings to the steepest negative deflection (–dV/dt) of a positive T wave or the steepest positive deflection (+dV/dt) of a negative or biphasic T wave of the unipolar EGM (Figure 1B).[8] As ARI vary with heart rate, values were corrected using the Bazett formula (corrected activation recovery interval [ARIc]). Changes in both ARI and ARIc in the RVOT, RV, and LV after ajmaline infusion were subsequently computed. Changes in RVOT transepicardial ARI/ARIc dispersion were also calculated which was defined as the maximum difference between ARI/ARIc values within this region. A detailed ARI map of the RVOT region was also derived to illustrate the changes in response to ajmaline in 1 patient. As such an electroanatomical map could not be automatically produced by the EcVUE version of the ECGi system, ARI was individually derived from >100 points within the RVOT region before and after ajmaline infusion. Contour maps were subsequently created using a graphical software package (Surfer 13, Golden Software LLC, Colorado) with the data obtained.

## 15-Lead Surface ECG Analysis

Tpeak-end duration (Tped) reflects transmural dispersion of repolarization and was calculated in the precordial leads as shown in Figure 1C using digital calipers by a reviewer blinded to patient details.[9] Manifestation of the type I BrS pattern (J point elevation ≥2 mm within the coved ST-segment and negative T wave in ≥1 precordial RV lead) was confirmed by 2 study investigators on the 15-lead ECG.[10] The J point was defined as the junction between the end of the QRS complex and the beginning of the ST segment.[11] J point elevation was the distance in millimeters from the isoelectric baseline determined with digital calipers (Figure 1C). The ST segment at 40 ms ($ST_{40}$) and 80 ms ($ST_{80}$) from this point was also obtained. The time point at which the diagnostic BrS pattern became evident on the 15-lead ECG was noted and simultaneously corroborated on the ECGi system. Changes in conduction (ATD) and repolarization (ARI/ARIc) derived from the ECGi system were studied

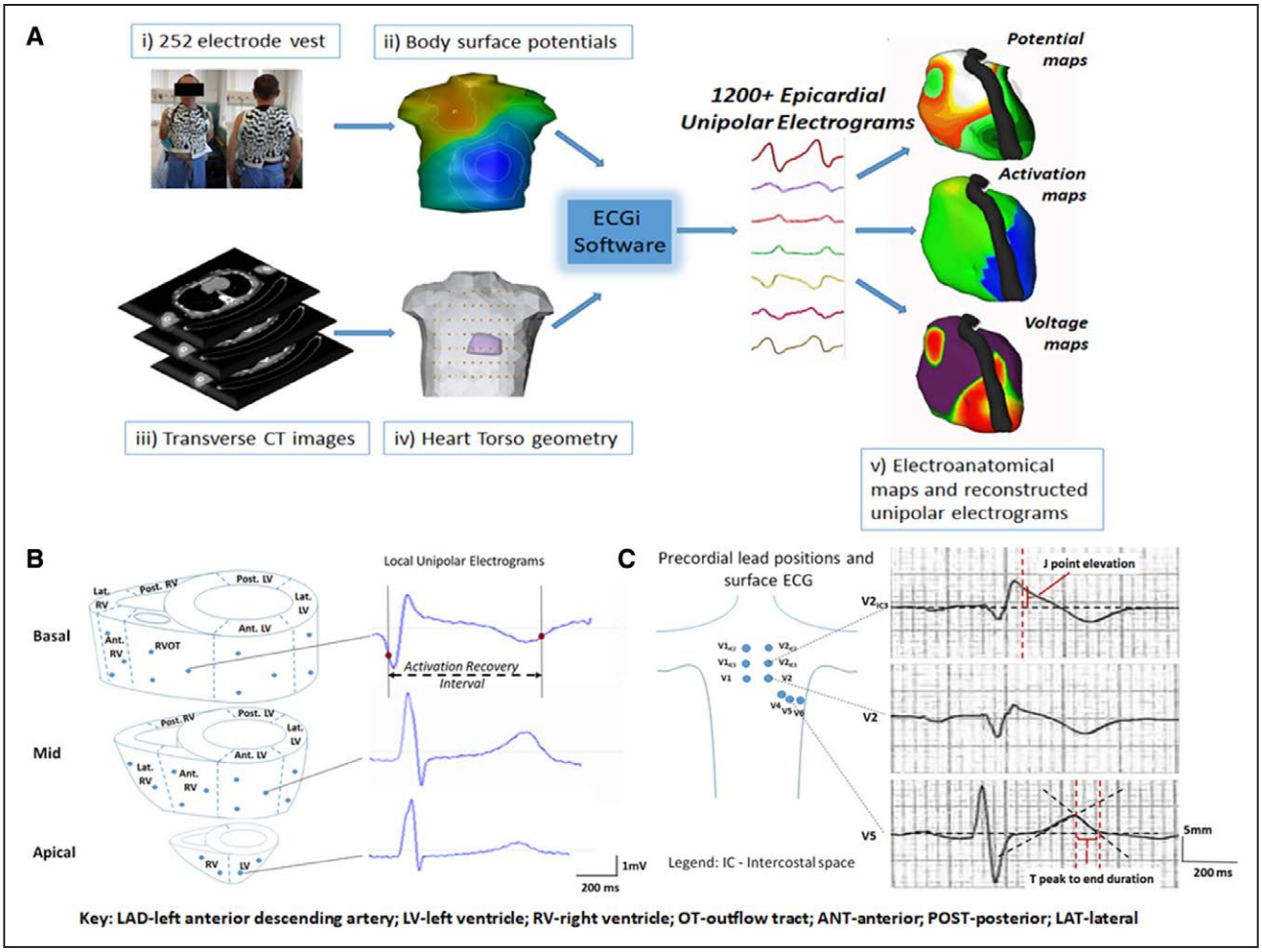


**Figure 1. Reconstruction of unipolar electrograms from body surface potential and measurements derived from unipolar electrograms from the epicardial surface and from the 12 lead body surface ECG.**
**A**, Electrocardiographical imaging (ECGi) system combining body surface potential data from a 252-electrode vest (i and ii) with computed tomographic (CT)–derived heart-torso geometry (iii and iv) to produce epicardial unipolar electrograms and panoramic 3-dimensional electroanatomical maps (v). **B**,The heart is anatomically divided into 15 segments with examples of unipolar electrograms in 3 regions shown. **C**, Position of electrode of 15-lead ECG recording and measurement of J elevation and Tpeak to end duration. LV indicates left ventricle; RV, right ventricle; and RVOT, right ventricular outflow tract.

between the 2 phases: (1) preajmaline infusion, and (2) postajmaline infusion—at the point when type I BrS pattern manifest. In cases where the ajmaline challenge yielded a negative result, the post-ajmaline phase was taken at the 6-minute point after commencement of the infusion. For each patient, the maximal J point and ST (J-ST) elevation from the precordial leads was calculated from the surface ECG using digital calipers. Maximal J-ST point elevation was correlated with the amount of change in ATD, ARI/ARIc, and Tped in each region. Changes in Tped within RV/RVOT region is represented by the lead with maximal J-ST point elevation within V1 and V2 in the second, third, and fourth intercostal spaces and lead V5 for the LV. Because transepicardial dispersion of repolarization also exists in the BrS phenotype, J-ST point elevation was also correlated with the change in RVOT ARI/ARIc transepicardial dispersion.

## Statistical Analysis

Changes in ATD, ARI/ARIc, and Tped from baseline were calculated for the RVOT, RV, and LV in each individual, with pooled mean change and SD presented for each anatomic region. Differences between the 3 regions in mean change in ATD and ARI/ARIc after ajmaline infusion were compared using a 1-way ANOVA. The Newman–Keuls multiple comparison test was used in the post hoc analysis if ANOVA was significant. Where a 2-group comparison of continuous variables was appropriate, the unpaired *t* test was used. Correlation was calculated using Pearson correlation coefficient. Statistical analysis was performed using GraphPad PRISM v5 (Graphpad Software Inc), and a $P<0.05$ was considered significant.

# RESULTS

## Patient Characteristics

Thirteen patients underwent ajmaline challenge with ECGi and 15-lead surface ECG recordings (mean age, 44±12 years; 8 men). Eleven of these had a type I BrS pattern induced on the surface ECG. A positive diag-

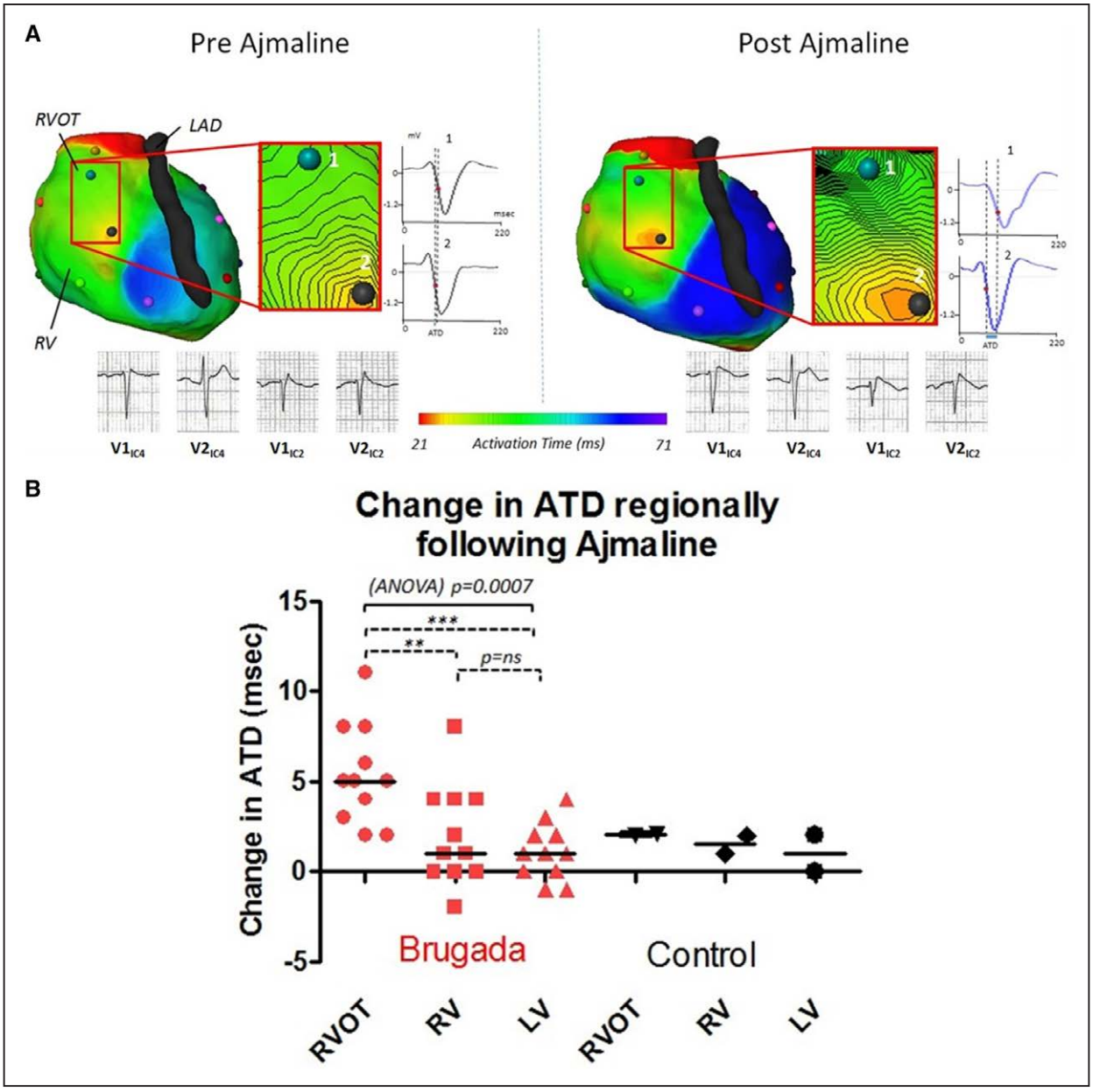


**Figure 2. Changes in whole heart activation time duration with ajmaline.**
**A**, Three-dimensional activation maps of epicardial breakthrough during a sinus beat before and after ajmaline infusion, at maximal J point elevation, in a patient with Brugada syndrome (BrS). Close up of the right ventricular outflow tract (RVOT; red box) shows greater isochronal crowding, with corresponding delay in electrogram local activation timing at site 1, after ajmaline infusion. **B**, Mean±SD changes in activation time duration (ATD) in the RVOT, right ventricle (RV), and left ventricle (LV) are shown with the largest increase in the RVOT after ajmaline infusion in patients with BrS. $^{**}P<0.01$; $^{***}P<0.001$. ns indicates not significant. LAD indicates left anterior descending artery.

nosis was reached between 1.5 and 6 minutes of the ajmaline infusion. Manifestation of the type I pattern occurred within leads V1 and V2 in the second, third, and fourth intercostal spaces. No ventricular arrhythmias were induced during the infusion. Table 1 summarizes the clinical characteristics of all participants. Two patients (12 and 13) had BrS excluded after a negative ajmaline challenge and served as controls in the study.

## Effect of Ajmaline on Whole Heart Activation Pattern

A representative example of 3-dimensional activation map before and after ajmaline infusion in a patient with BrS is shown (Figure 2A). Conduction slowing within the RVOT, as evidenced by greater amount of isochronal crowding or increase in ATD between 2 fixed points, can be observed after the appearance of the type I BrS pat-

**Table 1. Group Characteristics**

| S/No | Gender | Age | Ajmaline Result | Maximal J Point Elevation, mm | Type I Pattern in Lead, s | Previous SCD Event | Time to Positive Ajmaline, min |
|---|---|---|---|---|---|---|---|
| 1 | M | 33 | + | 5 | $V2_{IC3}$ | – | 6 |
| 2 | M | 40 | + | 2.5 | $V1_{IC2}$ | – | 5 |
| 3 | M | 39 | + | 3 | $V1_{IC2}$; $V2_{IC3}$ | + | 6 |
| 4 | F | 69 | + | 2 | V1 | – | 6 |
| 5 | M | 32 | + | 2 | $V1_{IC2}$ | – | 5 |
| 6 | M | 50 | + | 4 | V2 | + | 6 |
| 7 | M | 52 | + | 4 | V2; $V2_{IC3}$ | + | 5 |
| 8 | F | 50 | + | 5 | V2 | – | 5 |
| 9 | F | 60 | + | 2.2 | V1 | – | 6 |
| 10 | M | 36 | + | 4 | $V2_{IC3}$ | – | 1.5 |
| 11 | F | 50 | + | 2 | V1 | – | 5 |
| 12 | M | 38 | – | 0 | V1 | – | n/a |
| 13 | F | 25 | – | 0.4 | V1 | – | n/a |

V1 and V2 are in the right and left fourth intercostal space (IC), respectively. IC2, second intercostal space. IC3, third intercostal space. F indicates female; M, male; n/a, not applicable; and SCD, sudden cardiac death.



tern after ajmaline infusion. In all 11 patients with BrS, an increase in ATD was preferentially seen in the RVOT compared with the RV and LV (5.4±2.8 versus 2.0±2.8 versus 1.1±1.6 ms; ANOVA *P*=0.0007; Figure 2B). In contrast, no significant differences were observed between the RVOT, RV, and LV in the controls (2.1±0.1 versus 1.5±0.7 versus 1.0±1.4 ms; ANOVA *P*=0.58).

## Effect of Ajmaline on EGM Morphology and Whole Heart Repolarization

Alterations in EGM morphology were observed in patient with BrS and not in controls. Representative examples of EGMs are shown before and after ajmaline infusion in a BrS and control patient (Figure 3Ai and 3Aii). Manifestation of coved ST-segment elevation along with negative T wave could be observed in EGMs restricted to the RVOT region (Figure 3Ai) although no such changes were observed in the control patient (Figure 3Aii). ARI was observed to preferentially prolong in the RVOT region in comparison to the RV and LV (39±32 versus 12±30 versus 2±19 ms; ANOVA *P*=0.0056; Figure 3B). A similar picture was observed with ARIc (69±32 versus 39±29 versus 21±12 ms; ANOVA *P*=0.0005). In the controls, no differences in ARI/ARIc prolongation between regions were observable (ANOVA *P*=0.50 and *P*=0.45, respectively).

The mean increase in Tped was similarly larger in leads over the RVOT/RV than LV in the BrS group (19±7 versus 1±2; *P*=0.004; Table 2). Prolongation in Tped in the RV lead, where maximal ST elevation was observed, was larger than the LV lead (V5; 21±18 versus 2±13 ms; *P*=0.013). No significant difference was observed between the RV/RVOT and LV for controls after ajmaline infusion (2±3 versus 1±0.5 ms; *P*=0.512).

## Correlation of ATD, ARI/ARIc, and Tpeak-End Duration With J-ST Point Elevation

To investigate the effect changes in conduction and repolarization within the epicardial RVOT have on J point elevation after ajmaline infusion, we correlated change in ATD and ARI/ARIc with maximal J point elevation. A strong correlation was observed between increase in ATD in the RVOT and J point elevation (Pearson *R*=0.81; *P*=0.0009; Figure 4A) but not in the RV (*R*=0.27; *P*=0.36) and LV (*R*=0.21; *P*=0.49), where a 1-mm increase in J point elevation equated to an increase in ATD by 1.44±0.32 ms in the RVOT. In addition, there was no significant correlation between ARI/ARIc prolongation and J point elevation in any region (ARI-RVOT: *R*=0.33, *P*=0.27; RV: *R*=–0.08, *P*=0.79; LV: *R*=–0.07, *P*=0.82; ARIc-RVOT: *R*=0.51, *P*=0.07; RV: *R*=0.13, *P*=0.66; LV: *R*=0.40, *P*=0.18; Figure 4B). J point elevation was also not observed to correlate with Tped changes in any of the RV/RVOT and LV leads (Table 2). No significant correlation to J elevation was also observed when compared with Tped changes in the RV lead where maximal J elevation was observed (Figure 4C).

Transepicardial heterogeneity of the AP duration, or dispersion of ARI/ARIc, may exist within the RVOT in BrS. At baseline, there was a higher but nonsignificant difference in ARI dispersion in patients with BrS when the BrS ECG was not manifest (35±27 versus 13±5 ms; *P*=0.3). After ajmaline infusion, ARI dispersion within the RVOT was greater in patients with BrS than controls (58±22 versus 17±6 ms; *P*=0.04). This was similar for ARIc dispersion. Figure 5A illustrates the prolongation and increase in ARI gradients within the RVOT in a patient with BrS after ajmaline infusion. We correlated the changes in RVOT dispersion with J point elevation

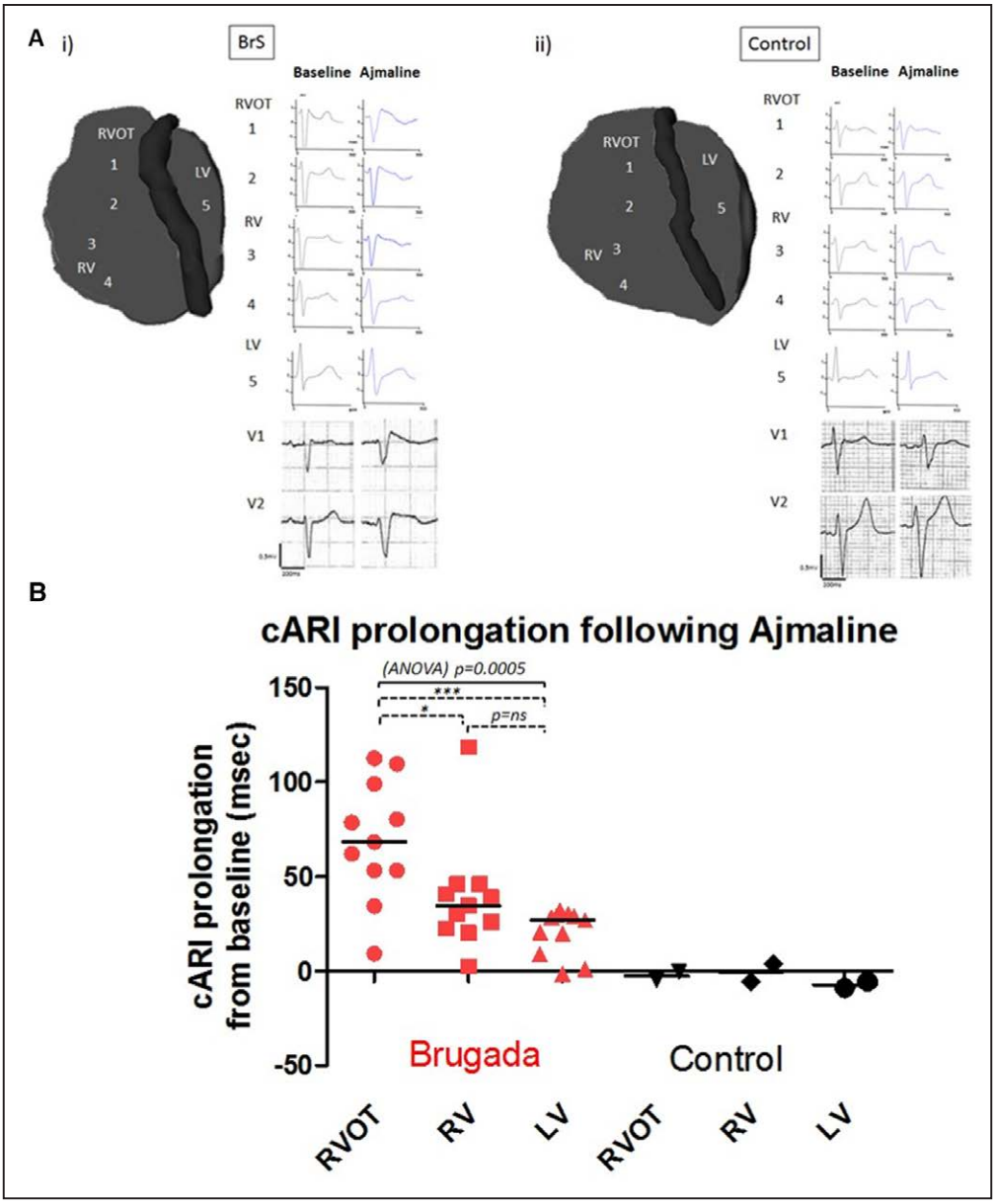


**Figure 3. Changes in whole heart activation recovery interval (ARI) with ajmaline.**
**A**, Changes in unipolar electrogram morphology in a patient with Brugada syndrome (BrS) (i) and control (ii) after ajmaline infusion. In the patient with BrS, there is coving and T wave inversion after ajmaline infusion in EGMs within the right ventricular outflow tract (RVOT) region but no change in EGM morphology in the right ventricle (RV) or left ventricle (LV). ARI in the RVOT region are subsequent prolonged. In contrast, there is little change in morphology or ARI in the control patient despite the full ajmaline dose administered. **B**, Mean ARI prolongation is greatest in the RVOT compared with the RV or LV in patients with BrS. *$P$<0.05; **$P$<0.01. ns indicates not significant.

but did not find a significant relationship using ARI ($R$=0.20; $P$=0.50) or ARIc ($R$=0.20; $P$=0.52; Figure 5B). Similar results were observed when correlated with $ST_{40}$ and $ST_{80}$ elevation (Table 3).

## DISCUSSION

In this study, we describe the changes in conduction and AP duration in nonspontaneous BrS human hearts in vivo after ajmaline infusion. Greater changes were observed in the RVOT than RV or LV reaffirming the site of the pathological substrate in this condition. Importantly, we demonstrated a correlation between J point elevation in the type I BrS pattern and increasing conduction delay in the epicardial RVOT which further supports the depolarization hypothesis as the underlying electrophysiological mechanism of the type I pattern seen.

**Table 2. Tpeak-End Duration at Baseline and After Ajmaline Infusion**

| Region | Leads | Brugada Syndrome | | Control | | Correlation of Tpe Change to J Elevation | |
|---|---|---|---|---|---|---|---|
| | | Baseline, ms | Ajmaline, ms | Baseline, ms | Ajmaline, ms | Pearson *R* | *P* Value |
| RV/RVOT | V1 (IC2) | 82±10 | 104±23 | 81±4 | 84±7 | 0.26 | 0.39 |
| | V2 (IC2) | 93±16 | 98±19 | 79±5 | 82±9 | −0.24 | 0.43 |
| | V1 (IC3) | 83±13 | 107±25 | 74±7 | 79±5 | 0.37 | 0.22 |
| | V2 (IC3) | 90±17 | 110±26 | 86±23 | 91±21 | 0.32 | 0.29 |
| | V1 | 85±16 | 109±18 | 60±11 | 65±9 | 0.57 | 0.06 |
| | V2 | 96±16 | 112±13 | 95±1 | 95±3 | −0.02 | 0.95 |
| | Lead with max J elevation | 85±15 | 106±20 | 60±11 | 61±12 | 0.44 | 0.13 |
| LV | V4 | 95±11 | 95±14 | 75±5 | 77±7 | −0.10 | 0.75 |
| | V5 | 94±11 | 96±14 | 75±5 | 76±6 | −0.01 | 0.99 |
| | V6 | 89±12 | 87±11 | 77±7 | 77±7 | 0.06 | 0.85 |

LV indicates left ventricle; RV, right ventricle; RVOT, right ventricular outflow tract; and Tpe, Tpeak-end.



## Differences in the RVOT, RV, and LV in BrS

Although the genetic abnormalities implicated in BrS affect individual ion channel functioning across the heart uniformly, the RVOT has been shown to be the site of the electrophysiological substrate that gives rise to the BrS phenotype.[12] One explanation likely lies in differences during embryonic development and ion channel expression between the RVOT, RV, and LV.[13] Thus, it is of interest to determine the differential behavior of the RVOT, RV, and LV to sodium channel blockade although few studies have examined the electrophysiological changes in these regions simultaneously in patients with nonspontaneous type I pattern.[2,3,14]

Body surface potential mapping data in patients with BrS after ajmaline infusion have previously shown significant increase in body surface filtered QRS duration in the precordial leads overlying the RV but not the LV.[2] Differences between the RV and RVOT were not commented on because of the methodological limitations in knowing the corresponding body surface potentials of the RV and RVOT. Another whole-heart study using ECGi in patients with a spontaneous type I pattern showed that steeper repolarization gradients and higher mean activation durations were preferentially found in the RVOT compared with RV or LV within BrS subjects at resting baseline.[5] These studies, in addition to previous intracardiac electrophysiological mapping studies restricted to the RV/RVOT, support our findings that changes in conduction and repolarization after ajmaline infusion predominantly affects the RVOT in comparison to RV or LV in the BrS heart.[14–16]

## Changes in Conduction and J-ST Elevation

Increase in ATD was most prominent in the RVOT and did not differ much between the RV and LV free wall (Figure 3) in the patients with BrS. The embryonic RVOT differs in embryological origin to the LV and loses its slow conducting properties much later than the RV and LV during its development. It is purported that remnants of the embryonic outflow tract are present, as supported by findings of fibrosis and the presence of late potentials in the RVOT in a transplanted BrS heart.[17] Combined with genetic defects that alter the current available for AP propagation (eg, inward sodium [$I_{Na}$]), initiation of the AP in the RVOT occurs much later than the RV. The depolarization hypothesis considers that delayed activation in the RVOT, relative to the RV, creates an electrotonic gradient which gives rise to the ST elevation observed on the body surface electrodes over this region. It would thus follow that the magnitude of J-ST point elevation would correlate with the degree of activation delay in the RVOT and not the RV or LV as confirmed in our results. Our findings are also similar to previous studies that have correlated filtered QRS duration from body surface mapping potentials and RV conduction delay from echocardiography to ST elevation on the surface ECG.[2,3] Change in ATD observed in our study is relatively small and seemingly associated with large changes in J-ST elevation. It should be pointed out that these measurements only reflect changes in conduction over a selected epicardial area and may act as a surrogate for larger absolute changes in conduction that occur transmurally or across the entire myocardium.[18]

## Changes in Epicardial Repolarization With J-ST Point Elevation

In the repolarization hypothesis, transmural dispersion created by a more notched AP and longer action potential duration from cells in the epicardium than endocardium is proposed to give rise to the ST elevation seen and is supported mainly by experimental data.[1] In one

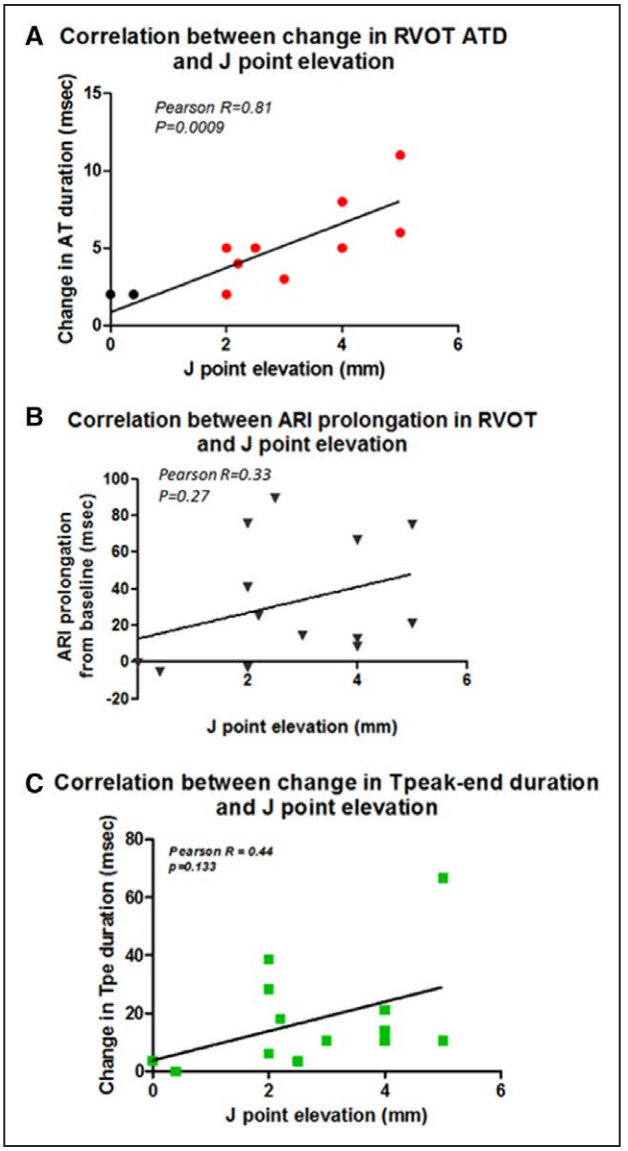


**Figure 4. Correlation between J point elevation and conduction/repolarization measures.**
**A**, Correlation between maximal J point elevation after ajmaline infusion and the corresponding changes in activation time duration (ATD) in the right ventricular outflow tract (RVOT) at the same time point for all patients. **B**, Correlation between maximal J point elevation after ajmaline infusion and the corresponding ARIc prolongation in the RVOT at the same time point for all patients. **C**, Correlation between maximal J point elevation after ajmaline infusion and the Tpeak-end duration (Tped) changes in the RVOT/right ventricle (RV) lead with maximal J elevation at the same time point for all patients. ARI indicates activation recovery interval.

clinical study, ARIc from unipolar EGMs in the endocardial and epicardial RVOT were measured during electrophysiological catheter studies in 19 BrS subjects.[4] After sodium channel blockade with pilsicainide in 9 individuals, Nagase et al[4] reported a prolongation in ARIc in the epicardial RVOT but no change in the endocardium and reported this occurrence on manifestation with the BrS phenotype. In contrast, other studies compared body surface mapping potential and echocardiographic surrogates of repolarization with ST elevation after ajmaline and flecainide infusions, respectively, but found no correlation in either study.[2,3]

Similar to Nagase et al,[4] we have observed prolongation of ARI/ARIc in the epicardial RVOT occurring with the onset of the BrS phenotype. In addition, we demonstrate that ARIc prolongation occurs preferentially over this region compared with the RV and LV. However, we also show that changes in repolarization on the RVOT epicardium do not correlate with the degree of J point and ST elevation after sodium channel blockade. It should be pointed out that ECGi does not provide EGM data from the endocardium, and it is assumed that the changes to transmural dispersion after sodium channel blockade arise mainly from the ARIc prolongation in the RVOT epicardium, as previously shown by Nagase et al.[4]

Another surrogate of transmural dispersion of repolarization is the Tped.[9] Although a preferential increase in Tped occurred over the RV/RVOT region in patients with BrS, there was no significant correlation with J point elevation. However, it has also been suggested that Tped from the surface ECG may reflect regional dispersion rather than transmural which limits the interpretation of our findings.[19]

Prolongation of ARI/ARIc may also be related to the blocking effects of ajmaline on the transient potassium outward current ($I_{to}$).[20] The greater prolongation in the whole RV (including RVOT) of ARI/ARIc than LV is in keeping with there being a smaller $I_{to}$ channel density in the LV (ARI: 25±25 versus −2±19 ms; $P<0.01$; ARIc: 54±20 versus 21±12 ms; $P<0.01$).[13] The differences between the RV and RVOT are less clear and may relate to a differential distribution density of $I_{to}$ channels in these regions. Interestingly, little change was observed within the RVOT and RV in the controls. Nagase et al[4] similarly observed no significant changes in ARIc in the RVOT in their 3 controls after pilsicainide infusion. It is possible that these differences in ARI prolongation observed between BrS and controls may relate to the amount of functioning $I_{to}$ channels available which would support the notion that non-SCN5a genetic mutations are also implicated in this syndrome.[1]

Although we have not observed a correlation between J point or ST elevation with surrogates of transmural or transepicardial ARI dispersion, it may be premature to completely discount the repolarization hypothesis as a fundamental assumption has been made with ARI measurements. ARI derived from the unipolar EGM assumingly reflects a single AP duration as used in several previous studies.[4,5,12,14–16] In a pharmacological wedge preparation model of BrS, Szél and Antzelevitch[21] demonstrate that notching within the ST segment observed in the unipolar EGM signal in

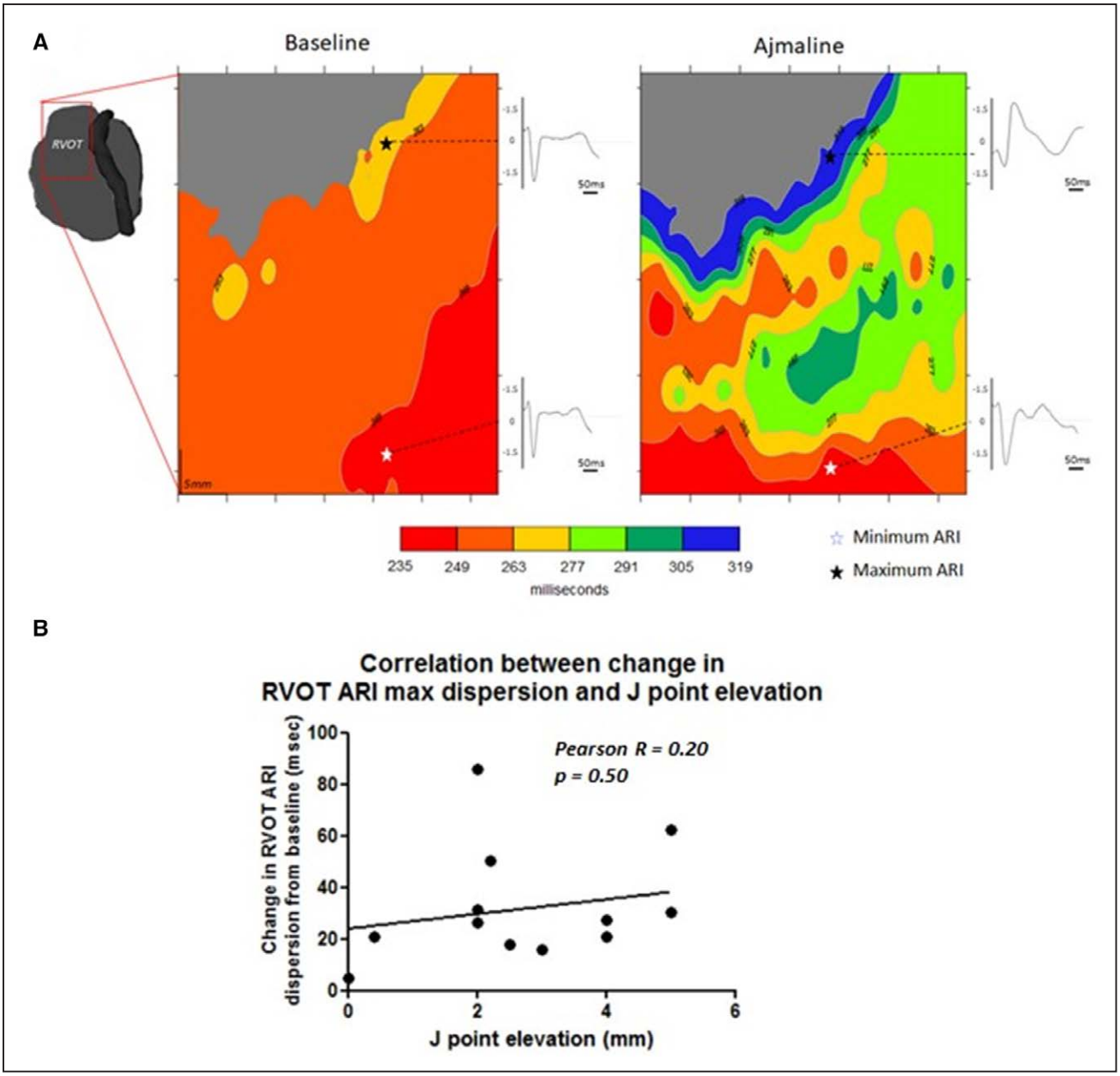


**Figure 5. Change in activation recovery interval (ARI) within the right ventricular outflow tract with ajmaline in a patient with Brugada syndrome.**
**A**, ARI map in the right ventricular outflow tract (RVOT) region of a patient with Brugada syndrome (BrS) at baseline and after manifestation of the BrS pattern with ajmaline. One observes prolongation of ARI within the RVOT and increase in maximal gradient or dispersion of ARI with ajmaline. **B**, Maximal dispersion of ARI is correlated with J point elevation (and ST-segment elevation; Table 3)

BrS could relate to a second AP caused by concealed phase 2 re-entry. In these EGMs, the T wave is proposed to be related to the second depolarization, and ARI measurements may thus produce an erroneous result. In Figure 3Ai, comparison has been made to the notching observed in the coved ST segment of the unipolar ECGi EGM from the RVOT. Although we have no monophasic AP data to determine whether phase 2 re-entry is occurring in our patients, previous work has shown the presence of singular monophasic APs in the RVOT epicardium in BrS human studies.[12,22] We, therefore, assume the validity of using ARI to reflect action potential duration as with other work in the literature.[4,5,12,14–16]

## Limitations

The number of controls in our study is small. However, the aim of this study was to correlate ST elevation and changes in depolarization and repolarization

**Table 3. Correlation to $ST_{40}$ and $ST_{80}$ After Ajmaline Infusion**

| | Correlation to $ST_{40}$ | *P* Value | Correlation to $ST_{80}$ | *P* Value |
|---|---|---|---|---|
| ATD change | | | | |
| RVOT | 0.84 | 0.0003 | 0.91 | 0.0001 |
| RV | 0.27 | 0.37 | 0.25 | 0.41 |
| LV | 0.24 | 0.43 | 0.35 | 0.24 |
| ARI prolongation | | | | |
| RVOT | 0.41 | 0.16 | 0.41 | 0.16 |
| RV | –0.79 | 0.78 | –0.11 | 0.73 |
| LV | 0.05 | 0.87 | 0.12 | 0.69 |
| Change in RVOT ARI dispersion | 0.29 | 0.34 | 0.33 | 0.28 |

ARI indicates activation recovery interval; ATD, activation time duration; LV, left ventricle; RV, right ventricle; and RVOT, right ventricular outflow tract.

rather than to compare differences in BrS and normal hearts. Both our controls did not manifest the type I pattern despite receiving the full weight-adjusted dosage of ajmaline and provide important control points to this correlation study. It is also unclear what effects age, sex, and individual genetic mutations have on this relationship between conduction delay and ST elevation. Evidence exists on the differences in ion channel distribution between the sexes and age has an impact on conduction in SCN5a+ murine hearts.[20,23] The number of BrS cases in this study limits our ability to provide answers to these questions.

The RVOT studied is assumed to be the region encompassing the area 4 cm below the pulmonary valve as identified from the computed tomographic scan and may have possibly included a small part of the RV at the junction of the outflow tract. The ATD examined within the heart only reflects specific areas within the RV and LV free wall. This was limited by being able to obtain the same measurement points along the activation wave fronts at baseline and after ajmaline infusion. We think that main regions of interest were studied, and little additional information would be obtained by breaking the regions down further which are also fraught with other methodological difficulties.

Our study is also restricted to those with a concealed type I BrS pattern and does not include any with a spontaneous type I pattern for comparison. Although we are conducting a separate study in the latter group, an advantage of studying the concealed BrS group with ajmaline allows for each subject to serve as their own baseline control. Interindividual variability in conduction and repolarization at baseline exists and would require a much larger number of patients with a spontaneous type I pattern and varying ST elevation to derive any correlative data.

## Conclusions

The strength of our study is in providing in vivo epicardial whole heart and regional changes in conduction, repolarization, and EGM morphology in response to ajmaline. More importantly, we demonstrate the underlying significance of the magnitude of ST elevation seen in the BrS pattern on the surface ECG. Our findings that conduction delay or excitation failure in the RVOT, and not prolongation of epicardial AP duration, correlates with the BrS pattern provides further support for the depolarization hypothesis.

## AFFILIATIONS

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## DISCLOSURES

Dr Kanagaratnam has received honoraria from CardioInsight Inc. The other authors report no conflicts.

## FOOTNOTES

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# ST-Elevation Magnitude Correlates With Right Ventricular Outflow Tract Conduction Delay in Type I Brugada ECG

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