

Mechanism of the effects of sodium channel blockade on the arrhythmogenic substrate of Brugada syndrome



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BACKGROUND The mechanisms by which sodium channel blockade and high-rate pacing modify electrogram (EGM) substrates of Brugada syndrome (BrS) have not been elucidated.

OBJECTIVE The purpose of this study was to determine the effect of ajmaline and high pacing rate on the BrS substrates.

METHODS Thirty-two patients with BrS (mean age 40 ± 12 years) and frequent ventricular fibrillation episodes underwent right ventricular outflow tract substrate electroanatomical and electrocardiographic imaging (ECGI) mapping before and after ajmaline administration and during high-rate atrial pacing. In 4 patients, epicardial mapping was performed using open thoracotomy with targeted biopsies.

RESULTS Ajmaline increased the activation time delay in the substrate (33%; $P = .002$), ST-segment elevation in the right precordial leads (74%; $P < .0001$), and the area of delayed activation (170%; $P < .0001$), coinciding with the increased substrate size (75%; $P < .0001$). High atrial pacing rate increased the abnormal EGM duration at the right ventricular outflow tract areas from 112 ± 48 to $143 \pm$

66 ms ($P = .003$) and produced intermittent conduction block and/or excitation failure at the substrate sites, especially after ajmaline administration. Biopsies from the 4 patients with thoracotomy showed epicardial fibrosis where EGMs were normal at baseline but became fractionated after ajmaline administration. In some areas, local activation was absent and unipolar EGMs had a monophasic morphology resembling the shape of the action potential.

CONCLUSION Sodium current reduction with ajmaline severely compromises impulse conduction at the BrS fibrotic substrates by producing fractionated EGMs, conduction block, or excitation failure, leading to the Brugada ECG pattern and favoring ventricular fibrillation genesis.

KEYWORDS Brugada syndrome; Catheter ablation; Fibrosis; Sodium channel blocker; Ventricular fibrillation

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Introduction

Sodium channel blockers (eg, ajmaline, procainamide, and flecainide) can unmask the typical coved type of ST-segment elevation (STE) in the right precordial leads in patients with BrS.¹ However, how these drugs unmask the Brugada pattern

and adversely affect the BrS substrate has not been clearly elucidated. An in silico model has demonstrated that sodium current (I_{Na}) reduction creates activation block at sites of the current to load mismatch, leading to distal activation failure, local monophasic electrograms (EGMs), and typical

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ST-segment changes.² This study aimed to determine the effect of I_{Na} reduction by ajmaline and/or high pacing rate on the right ventricular outflow tract (RVOT) epicardial substrates of symptomatic patients with BrS.

Methods

Study patients

Patients with BrS who had recurrent implantable cardioverter-defibrillator (ICD) discharges due to ventricular fibrillation (VF) episodes were enrolled in the study. All patients provided written informed consent, which had been approved by the internal ethics review board.

Study protocol

Patients first underwent electroanatomic mapping of the BrS epicardial substrates by using a ThermoCool (Biosense Webster, Inc., Diamond Bar, CA) mapping/ablation catheters during sinus rhythm before and after ajmaline administration followed by electrophysiology studies including programmed stimulation for VF induction, as previously described.³ A subset of study patients also underwent atrial pacing, either from the coronary sinus or from the high right atrium, with a decremental interval of 750, 600, 500, and 450 or 400 ms for 30 seconds or until Wenckebach periodicity or second-degree atrioventricular block occurred. During pacing, the mapping catheter was positioned at the RVOT substrate sites where fractionated EGM durations and late potentials were measured at baseline, during pacing, and after ajmaline administration.

When noninvasive electrocardiogram imaging (ECGI; CardioInsight System, Medtronic, Inc., Minneapolis, MN) became available in our institutions, we added ECGI mapping for the arrhythmogenic substrates in our study protocol at baseline and after ajmaline administration.

Mapping

Detailed epicardial and endocardial mapping of the arrhythmogenic substrate of the right ventricle (RV) as well as epicardial mapping of the left ventricle were performed during sinus rhythm. First, epicardial and endocardial electroanatomic mapping was performed using the voltage map software on the CARTO Navigation System (Biosense Webster, Inc.). An abnormal BrS substrate area was characterized by abnormal fractionated EGMs. Once identified, these areas were tagged on the electroanatomic map. After the baseline map was obtained, intravenous ajmaline was administered (10 mg/min) up to a maximum target dose of 100 mg. Mapping of the BrS substrates was then repeated. We defined *arrhythmogenic substrate sites* as areas that harbored *fractionated EGMs*, which were defined as ECGs that had (1) low voltage (≤ 1 mV); (2) multiple potentials with ≥ 2 distinct components, with >20 ms isoelectric segments between peaks of individual components; and (3) wide duration (≥ 70 ms) of late potentials, with distinct potentials extending beyond the end of the QRS complex. The tissue area (in square centimeters) with abnormal fractionated

EGMs was computed before and after ajmaline administration.

Four patients underwent the study during open thoracotomy because they had pericardial adhesion precluding percutaneous access into the pericardium. After the anterior RVOT epicardium was exposed and clearly visualized, point-to-point mapping was used over these areas, in which numbers were assigned over a grid of the anterior RVOT and RV epicardium. A ThermoCool catheter was used for mapping and ablation. Mapping was performed at baseline and after ajmaline administration during both sinus rhythm and atrial pacing at the left atrial appendage. A biopsy was also performed at the sites where fractionated EGMs were recorded.

ECGI mapping

ECGI methodology has been described previously⁴⁻⁶ and is presented in detail in Online [Supplemental Text I](#). Activation mapping was performed during sinus rhythm at baseline and after ajmaline administration. The method of reconstruction of the epicardial activation pattern is also detailed in Online [Supplemental Text I](#) and Online [Supplemental Figure 1](#). We measured maximum STE and minimum voltage of the unipolar ECG within the late activation zone before and after ajmaline administration.

Radiofrequency ablation

Radiofrequency ablation procedures were performed with power from 20 to 50 W, and the maximum temperature was set at 45°C. The primary end point during ablation was the elimination of the arrhythmogenic fractionated ECGs that were identified both at baseline and after ajmaline administration.

Clinical end points and follow-up

All patients were followed up at 1 month after the ablation session and every 3 months thereafter. Ajmaline provocative testing was performed after the 3-month follow-up period. The long-term end points were death and VF episode(s), as detected by ICD interrogation and presence of the Brugada ECG pattern.

Data and statistical analysis

The paired student *t* test was used to compare baseline and ajmaline conditions. The Fisher exact test or χ^2 test was used for categorical data, wherever appropriate. All data were analyzed with SAS version 9.2 (SAS Corp, Cary, NC).

Results

Our 32 study patients were highly symptomatic with frequent ICD discharges due to VF ([Table 1](#)); 28 underwent mapping and ablation percutaneously and the remaining 4 via thoracotomy.

Table 1 Patient clinical characteristics

Characteristic	Value
No. of patients	32
Age (y)	40 ± 12 (median 37)
Gender	Male
Symptoms	Aborted cardiac arrests/VF: 30 (94) Syncope: 2 (6)
Family history	10 (31)
Spontaneous Brugada ECG pattern	28 (88)
Distribution of patients according to the total number of VF episodes on ICD	No episode: 4 (12) 1–4 episodes: 6 (19) 5–9 episodes: 2 (6) 10–20 episodes: 5 (16) >20 episodes: 15 (47)
SCN5A mutation (only 29 had completed the genetic study)	1 of 29 (3)
Sustained VT/VF by PES at baseline	Positive: 31 (97) Negative: 1 (3)

Values are presented as mean ± SD or n (%).

ECG = electrocardiogram; ICD = implantable cardioverter-defibrillator; PES = programmed electrical stimulation; VF = ventricular fibrillation; VT = ventricular tachycardia.

Effects of pacing and ajmaline on ECG variables, ECG duration, and conduction

Fractionated EGMs were recorded in all patients at the anterior RVOT epicardium and in 12 of 32 patients (37%) in both the anterior and the inferior RV epicardium. Ajmaline increased the substrate size from 13.8 ± 6.2 to 24.2 ± 8.6 cm² ($P = .0012$).

In general, higher atrial pacing rate uniformly increased the EGM duration but the effect was moderate in the majority of patients and quite large in the 2 patients (Online Supplemental Figure 2) who had the longest baseline EGM durations. The fractionated EGM duration increased at a higher atrial pacing rate: At 750 ms, the fractionated EGM duration was 112 ± 48 ms and increased to 143 ± 66 ms ($P = .003$), measured during the shortest cycle length pacing that produced 1-to-1 atrioventricular conduction. Figure 1 shows an example of the effect of the pacing cycle length on the fractionated EGM characteristics, comparing coronary sinus pacing of 600 and 450 ms at baseline (Figure 1A) and between 600 ms pacing at baseline and after ajmaline administration (Figure 1B). The bipolar EGMs recorded from the distal (ABLd) and proximal (ABLp) pair electrodes of the ablation catheter at the RVOT epicardium show fractionated EGM potentials beyond the QRS complex; at baseline, the duration of the fractionated EGMs recorded from ABLd increased from 181 ms during pacing at 600 ms to 280 ms during pacing at 450 ms. Even during these remarkable changes in the EGM fractionation, there was no Brugada ECG pattern appearance until ajmaline administration (50 mg) and pacing at 600 ms cycle length (Figure 1B), which shows a profound effect of ajmaline on conduction: The bipolar EGMs recorded at the same RVOT epicardial site show that the drug caused a further marked increase in conduction delay and conduction block, as shown by prolonged fractionated EGMs

beyond the T wave, resulting in a variable increase in EGM duration ranging from 230 to 320 ms. The loss of amplitude of the bipolar EGMs of the last 3 complexes recorded from both ABLd and ABLp pairs (vertical arrows) is compatible with local activation failure (a long recording of 600 ms pacing after ajmaline is shown in Online Supplemental Videos 1A and 1B to authenticate that the loss of EGM amplitude was due to loss of excitation and not due to the loss of mapping catheter's contact). Note that lead V₂ shows alteration of the ST-segment amplitude in such a way that the higher amplitude of the ST segment was related to excitation failure and absence of local activation. The loss of amplitude of fractionated EGMs after ajmaline administration and high rate pacing was observed in 11 of 15 patients (73%).

Table 2 summarizes the effect of ajmaline on the ECG variables: Ajmaline increased the QRS duration by 22% (95% confidence interval [CI] 7.5%–37.7%; $P < .0001$), PR interval by 18% (95% CI 12.5%–24%; $P < .0001$), corrected QT interval by 8% (95% CI 3%–12.6%; $P = .001$), and ST segment in the right precordial leads by 74% (95% CI 74%–161%; $P < .0001$).

ECGI substrate mapping

Figure 2A shows an example of ECGI maps from one of our patients and compares 4 ECGI variables in the late activation zone—activation time, STE, voltage, and area of the late activation zone—at baseline and after ajmaline administration during sinus rhythm in 20 patients. Figure 2A demonstrates that ajmaline increases the activation time, STE, and area of the late activation zone while reducing the EGM voltage in one of the study patients. In aggregate (Figure 2B), ajmaline delayed the activation time (33%; $P = .003$) and increased local unipolar STE (70%; $P = .002$) while significantly reducing the voltage (unipolar) in the late activation zone (33.5%; $P = .016$).

Fibrosis and fractionated EGMs in direct epicardial mapping

Figure 3 shows an example of how ajmaline unmasked the arrhythmogenic substrate areas on the underlying anterior RVOT epicardium in a patient who underwent epicardial mapping during a thoracotomy. Ajmaline (30 mg intravenously) caused changes in bipolar and unipolar EGMs of areas 3, 8, and 13 from relatively normal EGMs to markedly abnormal fractionated EGMs, coinciding with an appearance of STE in the unipolar EGMs in these areas. In particular, the unipolar EGMs after ajmaline administration have a monophasic morphology (resembling an action potential), especially in Figures 3B, 3E, and 3G. This is a sign of absence of local activation (similar to that recorded from a monophasic action potential catheter).⁷ This phenomenon is present at sites 3, 8, and 13. Biopsies at sites 8 and 13 and their histology demonstrate marked epicardial fibrosis (Figure 3D).

All 4 patients, whose mapping and ablation were done under open thoracotomy, had localized epicardial and interstitial fibrosis, which is associated with abnormal fractionated

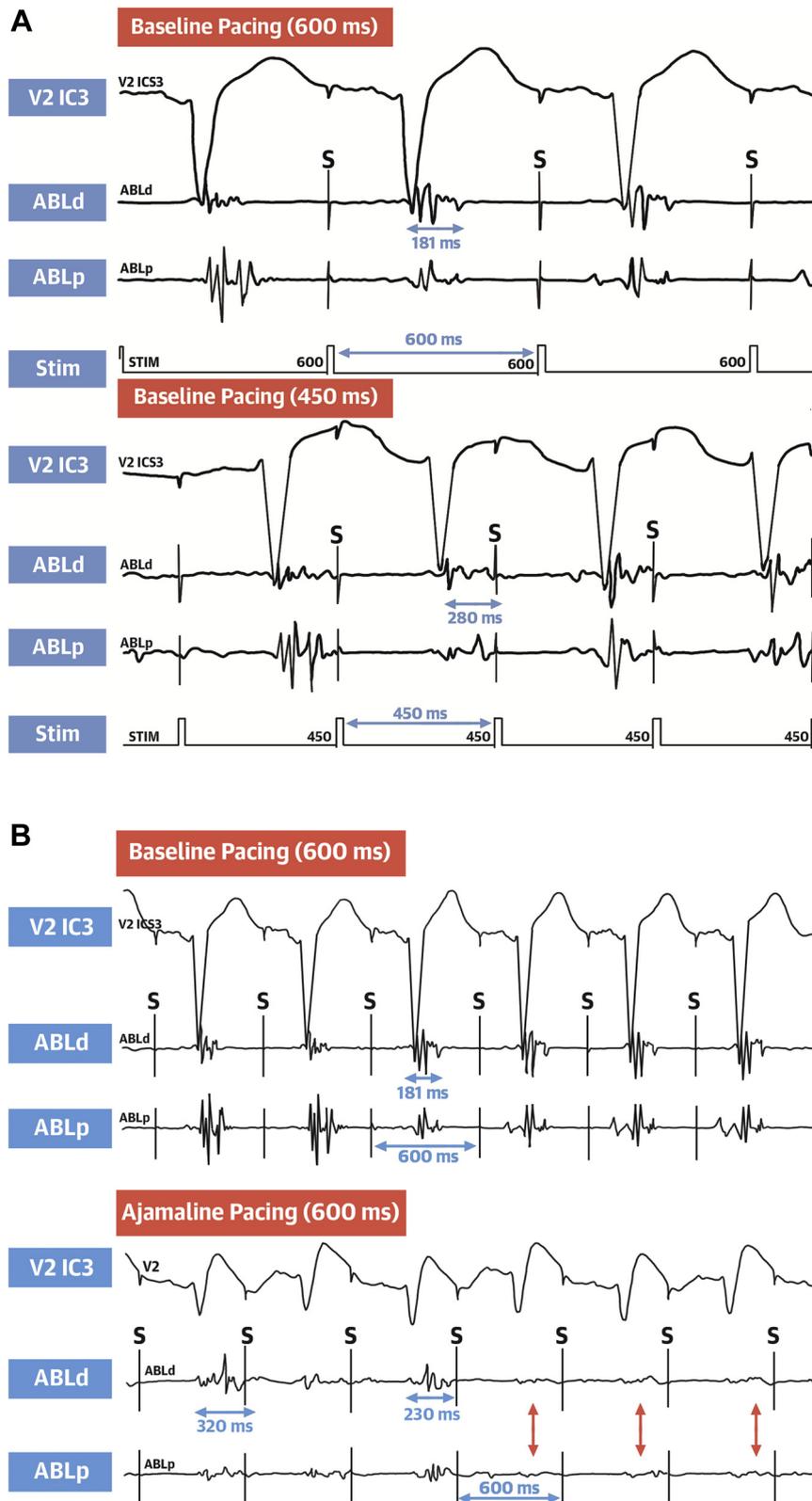


Figure 1 Effects of pacing and ajmaline on the Brugada syndrome substrate sites are illustrated (see text for details). **A:** Effect of the shortening of the pacing cycle length from 600 to 450 ms (coronary sinus pacing) on the electrogram duration at the right ventricular outflow tract epicardial substrate site. **B:** Conduction block at the same site as in panel A after ajmaline administration during pacing at 600 ms. ABLd = ablation distal pair electrode; ABLp = ablation proximal pair electrode; Stim = stimulation artifact; V2 IC3 = lead V₂ at the third intercostal space.

Table 2 Effect of ajmaline on the ECG parameters and RVOT substrate size

Variable	Baseline	Ajmaline	% Difference from baseline (95% CI)	P
CCL (ms)	923 ± 180	884 ± 171	-4.2% (-3% to 11.5%)	.241
PR interval (ms)	176 ± 31	208 ± 38	18% (12.5% to 24%)	<.0001
QRS duration (ms)	106 ± 22	130 ± 44	22.6% (8% to 38%)	.005
QTc interval (ms)	415 ± 44	449 ± 49	8% (3% to 12.6%)	.001
ST-segment voltage (mV)	0.31 ± 0.19	0.54 ± 0.26	74% (45% to 161%)	<.0001
RVOT substrate size (cm ²)	13.7 ± 5.9	23.9 ± 8.2	74% (58% to 91%)	<.0001

Values are presented as mean ± SD unless otherwise indicated.

CCL = cycle length; CI = confidence interval; ECG = electrocardiographic; QTc = corrected QT; RVOT = right ventricular outflow tract.

EGMs. Ajmaline not only unmasks the arrhythmogenic areas that might have been otherwise thought to be a normal area of the RVOT epicardium because of a normal EGM at baseline, but the drug could also cause excitation failure and asynchronous conduction in the substrate areas, as shown in [Figure 4](#).

[Figure 4A](#) shows lead avF and the local bipolar and unipolar EGMs recorded from the RVOT epicardium of another patient who underwent open thoracotomy. The bipolar EGMs recorded from the distal and proximal pair electrodes (ABLd and ABLp) and the unipolar EGM recorded from the distal electrode of the ablation catheter (ABLd uni) show prolonged fractionated EGMs at baseline. After ajmaline administration, the EGM duration drastically changed and became markedly delayed with multiple components and with the EGM duration of 350 and 305 ms at the ABLd and ABLp recording sites, respectively. The unipolar recording of the distal electrode of the first complex also showed multiple potentials, suggesting zigzag conduction at the subepicardial tissue below the recording epicardial site. These late potentials were absent in the second complex, indicating conduction block at the subepicardial site; as a result, the ABLd uni of this complex also had a monophasic component (indicated in red).

[Figure 4B](#) shows the recording of another RVOT substrate site of the same patient. At this site, delayed conduction, asynchronous activation, and intermittent conduction blocks were demonstrated. The duration of fractionated EGMs at these sites was variably and markedly lengthened with intermittent conduction block, causing a significant degree of dispersion of conduction between the distal and proximal pairs. Excitation failure was also seen between the distal and proximal pairs. When conduction blocks occurred in the distal pair of bipolar recording, monophasic components emerged in the unipolar EGMs. Biopsy at this site revealed thick epicardial fibrosis and fibrotic replacement in the subepicardium ([Figure 4C](#)).

Long-term outcomes

After 1 ablation procedure, the type 1 Brugada ECG pattern disappeared in all but 2 patients who had a Brugada ECG pattern after ajmaline administration. After a mean follow-up period of 50 ± 18 months (median 48 months), 31 of 32 patients had no VF recurrence; the remaining patient with VF recurrence had concomitant J-wave elevation in the inferior leads and hence a combined syndrome of BrS and the

early repolarization pattern. The patient is expected to be scheduled for repeat ablation. The 2 patients who continued to have the type 1 Brugada ECG pattern had no VF recurrence.

Discussion

Our study provides new insights into how ajmaline unmasks the Brugada ECG pattern: The drug, by reducing I_{Na} , markedly delays impulse conduction in these RVOT substrate sites that have underlying fibrosis, thereby increasing the areas of late activation and in turn increasing STE over the right precordial ECG leads. This is associated with local STE and local loss of amplitude of the unipolar EGMs, as detected by ECGI. Furthermore, ajmaline unmasks the substrate by creating excitation failure, showing as the genesis of monophasic EGMs or as late monophasic components of unipolar EGMs in the fibrotic tissue ([Figure 3](#)). In short, when I_{Na} is reduced by rapid pacing or ajmaline administration, impulse conduction in the RVOT epicardial fibrotic substrate sites is severely compromised. This causes asynchronous conduction, conduction block, and/or excitation failure, leading to loss of local activation at these sites. These electrophysiological derangements are the underlying mechanism of STE in the right precordial leads and VF genesis in BrS.

Conduction abnormalities during high-rate atrial pacing

The duration of fractionated EGMs was significantly prolonged further when the atrial rate increased in all patients. The increased EGM duration after shortening of the pacing cycle length suggests a further increase in conduction abnormality, a well-known frequency-dependent response of conduction in the diseased tissue.^{8,9}

Unmasking the Brugada ECG by ajmaline

Epicardial and interstitial fibrosis was found in all 4 patients who underwent open thoracotomy for mapping, surgical radiofrequency ablation, and subsequent study of the biopsies. The EGMs at the sites where fibrosis was present could be relatively normal, as shown in [Figure 3](#); they only became markedly abnormal after ajmaline. In some areas, conduction block or asynchronous conduction occurred along with the appearance of the Brugada ECG pattern. Remarkably,

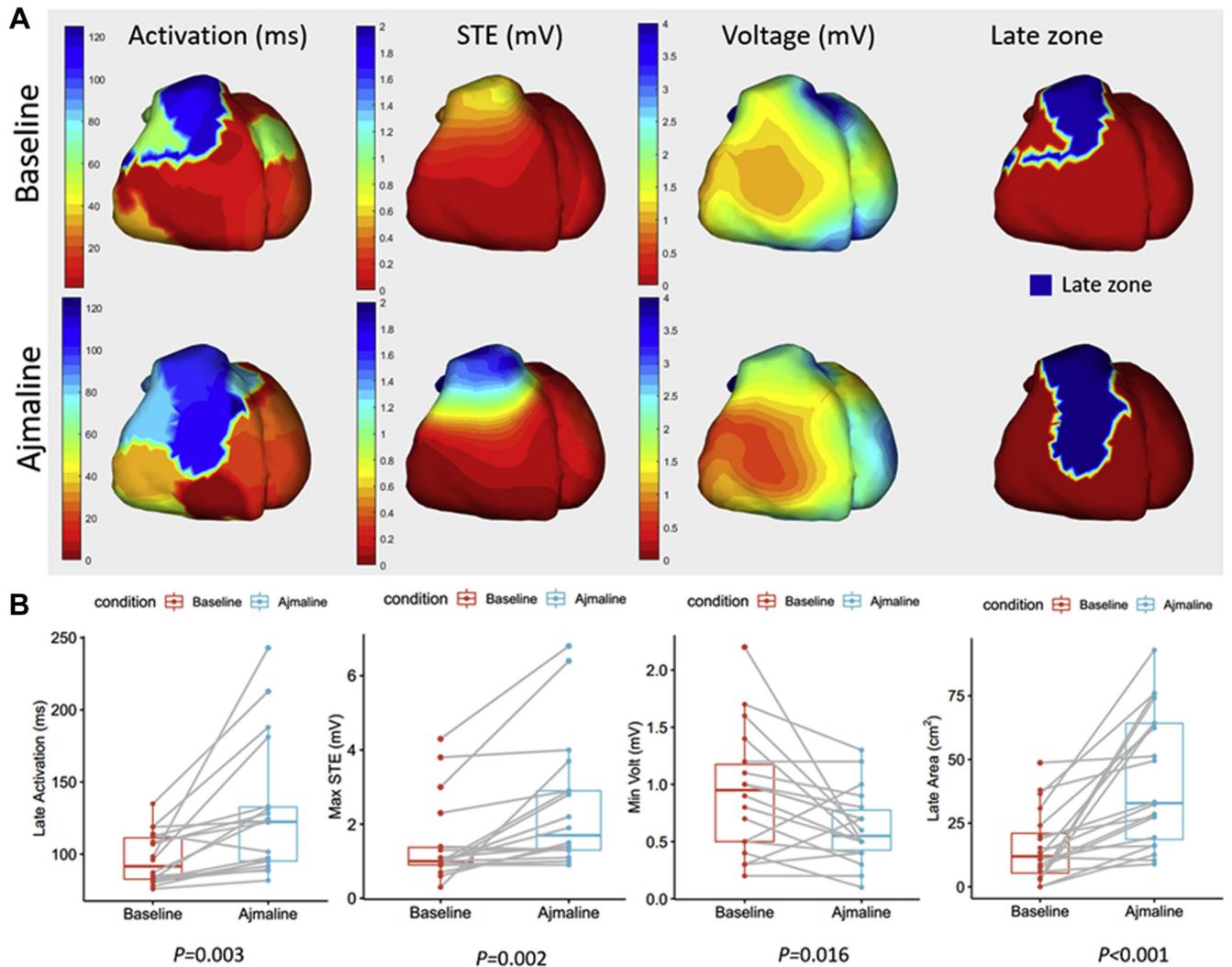


Figure 2 A: Example of electrocardiographic imaging maps from one of the study patients, displaying activation time, ST-segment elevation (STE), voltage, and areas of the late-activated area before and after ajmaline administration during sinus rhythm. B: Results of the analyses of all patients within the late activation zone.

monophasic unipolar EGMs were recorded after ajmaline administration as a sign of absence of activation, even though the tissue was intrinsically excitable. This is in line with the *in silico* and experimental observations of Hoogendijk et al¹⁰ and those of Vigmond et al,¹¹ who show that monophasic-like local EGMs at the epicardial side of the RVOT could be recorded as a result of the current-to-load mismatch owing to structural abnormalities.

Figure 5 displays the mechanisms causing monophasic EGMs during excitation failure. The figure duplicates the first 2 complexes from Figure 4. Complex 1 shows a local fractionated unipolar EGM with local STE in ABLd uni with an appearance of a small monophasic complex. This is caused by the myocardium under ABLd uni that was not activated, leaving the membrane potentials at the resting potential. Since this myocardium is electrically coupled to the surrounding myocardium, it will become a current sink (intracellular) when the surrounding myocardium depolarizes. This means the myocardium at ABLd uni will receive

intracellular current that is transferred to the extracellular space where it can be recorded as a positive potential (monophasic action potential) with the shape of the transmembrane potential of the surrounding myocardium. In complex 1, the amplitude of the local unipolar EGM (or monophasic complex) is small, but still looks like a lead V₁ of the type 1 Brugada pattern. In complex 2, a larger part of the myocardium located at ABLd uni is not activated during the first activation wave “a” but the myocardium under the proximal pair is activated late by the activation wave “d.” The late activated myocardium at ablation proximal unipolar and ablation distal unipolar will provide the intracellular current that flows to the myocardium at ABLd uni and give rise to a monophasic complex in the extracellular space recorded at ABLd uni.

Even though abnormal fractionated EGMs were present at the anterior RVOT in all our patients, many patients initially did not have a spontaneous type 1 Brugada ECG pattern. Thus, localized fractionation and late conduction at the RVOT alone may not be enough to cause the type 1 Brugada

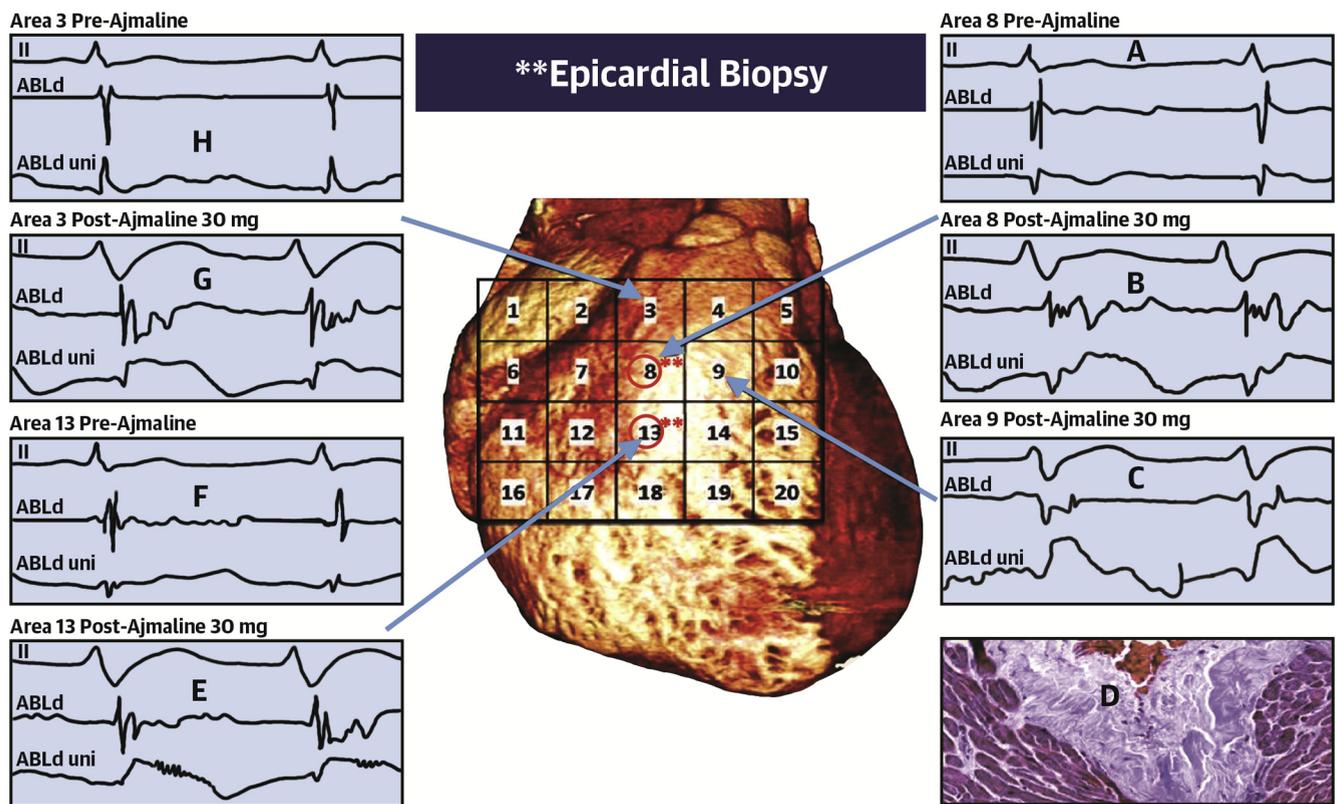


Figure 3 Computed tomography scan of the heart (*center*) from 1 of the 4 patients with Brugada syndrome undergoing open thoracotomy mapping and ablation showing a right ventricular anatomical grid. Electrocardiogram lead II and distal bipolar (0.4 mV/cm voltage scale at the filter 30–300 Hz) and unipolar (5 mV/cm voltage scale at the filter 0.05–300 Hz) electrograms are displayed in insets of the surrounding panels. **A and B:** Electrograms from site 8 at baseline and after ajmaline administration. **C:** Electrograms recorded from site 9 after ajmaline administration. **D:** Histology of the biopsy specimen (Masson's trichrome stain) from site 8 showing epicardial fibrosis. **E–H:** Electrograms recorded from sites 13 and 3 after ajmaline administration and at baseline, respectively (see text for details). ABLd = ablation distal pair electrode; ABLd uni = ablation distal unipolar.

ECG pattern. The signature Brugada ECG pattern appeared only after ajmaline was administered in many of our patients, and monophasic unipolar EGMs were recorded. This was associated with further prolongation of these abnormal epicardial EGMs and conduction block or excitation failure, as shown in Figure 1. Clearly, conduction block in various areas of the anterior RVOT epicardial substrate sites was instrumental in unmasking the type 1 Brugada ECG pattern. This is supported by the observation that small changes in activation contributed to subtle changes in the ECG ST segment.

These findings support those of Hoogendijk et al¹⁰ as well as those of ten Sande et al,¹² which suggest that subepicardial structural abnormalities (in our study patients with BrS, subtle fibrosis in the epicardium and subepicardium) are present in patients with BrS and likely serve as the barriers that create the tortuous path through which the propagating impulses have to go and in turn create fractionated EGMs and late potentials; these fibrotic tissues may also create a narrow isthmus for the depolarizing current to travel through and then reach the area of large expansion of the myocardium mass where a “current-to-load mismatch” occurs, especially in the presence of reduced I_{Na} by ajmaline, causing excitation failure. Excitation failure can be

intermittent or cycle length dependent, resulting in intermittent loss of local activation. The combined tissue discontinuity, excitation failure, and loss of local activation lead to the presence of STE in the right precordial leads because of the electronic current generated by activation of the proximal site through the isthmus.

This observation is therefore consistent with previous studies. In a study of an explanted heart of a patient with BrS who had recalcitrant electrical storms necessitating heart transplantation surgery, Coronel et al¹³ found abundant fibrous and adipose tissue in the RV associated with marked activation delay in the RV. Our recent collaborative multi-center study unequivocally demonstrated epicardial and interstitial fibrosis and reduced gap junction expressions in the RVOT patients who died suddenly with BrS family history and negative routine autopsy.¹⁴ In the same study, we also found epicardial and interstitial fibrosis from the biopsies taken from patients with BrS during open heart ablation from RVOT epicardial sites; at these sites, abnormal, fragmented, and delayed conduction was also found.¹⁴ Thus, the above observation incontrovertibly support that RV epicardium is the main substrate site where fractionated late ventricular EGMs are present in patients with BrS as an expression of structural abnormalities.^{3,14,15}

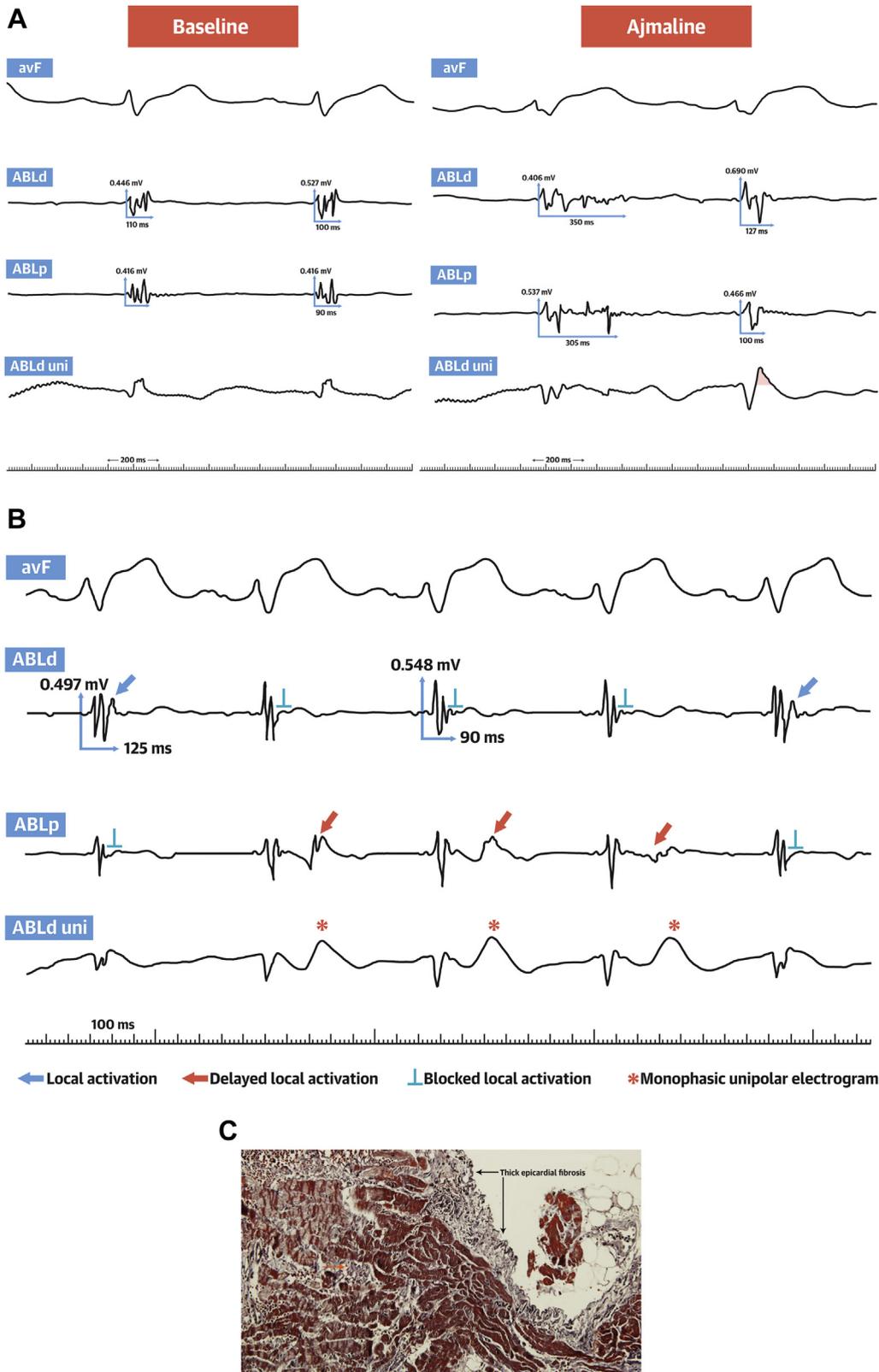


Figure 4 **A and B:** Ajmaline produced delayed conduction, asynchronous activation, and conduction block causing monophasic appearance of the unipolar recording at that site (*pink shade* on the ABLd-uni). **C:** Hematoxylin and eosin stain of the biopsy from this recording site and shows marked epicardial fibrosis and early fibrotic replacement of the myocardium at this site (*orange arrow*). ABLd = ablation distal pair electrode; ABLd-uni = ablation distal electrode unipolar electrogram; ABLp = ablation proximal pair electrode.

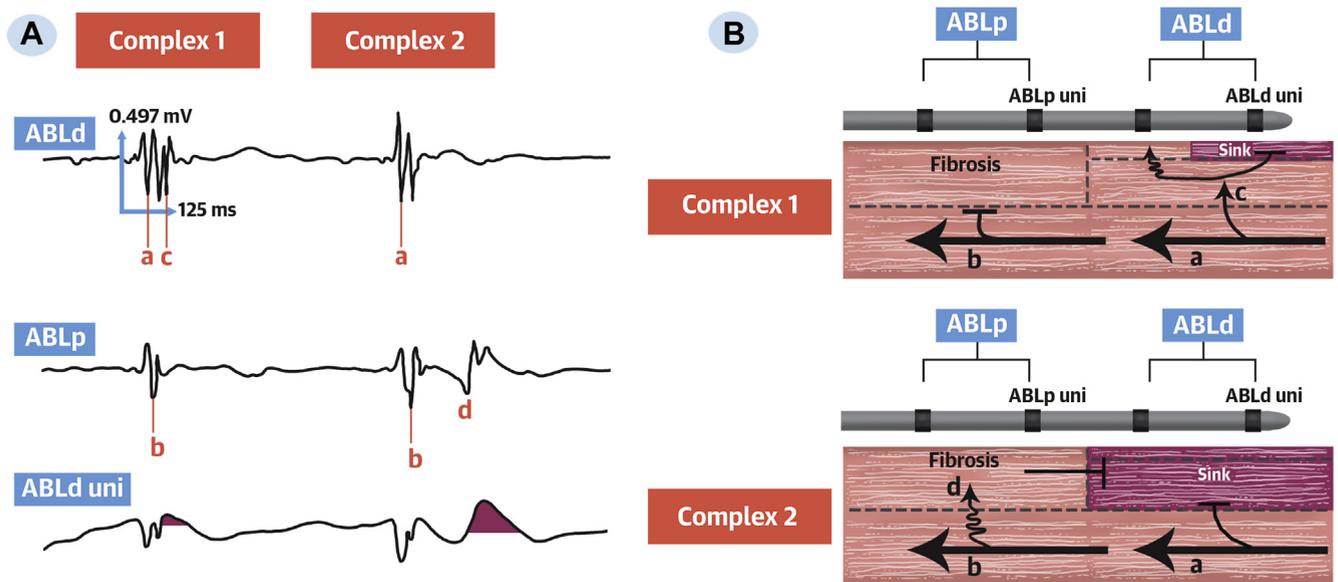


Figure 5 Schema to explain how ajmaline delayed conduction and caused excitation failure of the first 2 impulses in Figure 4B, producing a monophasic unipolar electrocardiographic pattern (see text for details). ABLd = ablation distal pair electrode; ABLp = ablation proximal pair electrode; ABLd uni = ablation distal unipolar; ABLp uni = ablation proximal unipolar.

Study limitations

Our study patients were highly selective of symptomatic patients, and only 3% of our patients had *SCN5A* pathogenic variants; thus, our study population may not be representative of the general population with BrS. Our genome-wide association study shows that *SCN5A* in the Thai population with BrS is only 7%.¹⁶ However, we share the same findings as those of the Europeans and Japanese that BrS phenotype in our population is associated with polygenic variants including *SCN5A*, *Hey2*, and *SCN10A*.¹⁶ Thus, we believe that our population is a not a unique subset.

The number of patients ($n = 4$) in this study who underwent biopsy of the RVOT substrate sites is relatively small. It is conceivable that not all patients with BrS may have extensive fibrosis, as witnessed in our 4 study patients. However, we have so far studied 4 other patients who underwent open thoracotomy (not included in this study); they all had epicardial and subepicardial fibrosis. Thus, it is very likely that most patients with BrS had subtle RV fibrosis as the primary underlying pathology and that our clinical observation of reduced I_{Na} is very likely applicable to BrS. However, since our study patients are highly symptomatic, the degrees of conduction abnormalities and fibrosis in asymptomatic patients may not be as severe as observed in our study patients. Indeed, it would be interesting to carry out studies to determine the relationship between the magnitude/severity of these abnormalities and the incidence and severity of ventricular tachycardia/VF occurrences in patients with BrS.

Conclusion

Our study clearly shows that I_{Na} reduction with ajmaline and/or high-rate pacing severely compromises impulse

conduction in the BrS substrates and can uncover the fibrotic sites by producing fractionated EGMs, conduction block, or excitation failure that create milieu for the current-to-load mismatch phenomenon that leads to VF genesis and the signature Brugada ECG pattern. Ajmaline also is useful in guiding catheter ablation procedures to eliminate all arrhythmogenic areas, as evidenced by a 2-fold increase in the size of the target area for the ablation. Thus, using sodium channel blockers, ajmaline, or pilsicainide is an invaluable tool to guide catheter ablation of the BrS substrates for better long-term outcomes.^{3,17,18}

Appendix Supplementary data

Supplementary data associated with this article can be found in the online version at <https://doi.org/10.1016/j.hrthm.2021.10.031>.

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