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ORIGINAL RESEARCH

Ajmaline-Induced Abnormalities in Brugada Syndrome: Evaluation With ECG Imaging

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BACKGROUND: The rate of sudden cardiac death (SCD) in Brugada syndrome (BrS) is ≈1%/y. Noninvasive electrocardiographic imaging is a noninvasive mapping system that has a role in assessing BrS depolarization and repolarization abnormalities. This study aimed to analyze electrocardiographic imaging parameters during ajmaline test (AJT).

METHODS AND RESULTS: All consecutive epicardial maps of the right ventricle outflow tract (RVOT-EPI) in BrS with CardioInsight were retrospectively analyzed. (1) RVOT-EPI activation time (RVOT-AT); (2) RVOT-EPI recovery time, and (3) RVOT-EPI activation-recovery interval (RVOT-ARI) were calculated. ΔRVOT-AT, ΔRVOT-EPI recovery time, and ΔRVOT-ARI were defined as the difference in parameters before and after AJT. SCD-BrS patients were defined as individuals presenting a history of aborted SCD. Thirty-nine patients with BrS were retrospectively analyzed and 12 patients (30.8%) were SCD-BrS. After AJT, an increase in both RVOT-AT [105.9 milliseconds versus 65.8 milliseconds, $P<0.001$] and RVOT-EPI recovery time [403.4 milliseconds versus 365.7 milliseconds, $P<0.001$] was observed. No changes occurred in RVOT-ARI [297.5 milliseconds versus 299.9 milliseconds, $P=0.7$]. Before AJT no differences were observed between SCD-BrS and non SCD-BrS in RVOT-AT, RVOT-EPI recovery time, and RVOT-ARI ($P=0.9$, $P=0.91$, $P=0.86$, respectively). Following AJT, SCD-BrS patients showed higher RVOT-AT, higher ΔRVOT-AT, lower RVOT-ARI, and lower ΔRVOT-ARI ($P<0.001$, $P<0.001$, $P=0.007$, $P=0.002$, respectively). At the univariate logistic regression, predictors of SCD-BrS were the following: RVOT-AT after AJT (specificity: 0.74, sensitivity 1.00, area under the curve 0.92); ΔRVOT-AT (specificity: 0.74, sensitivity 0.92, area under the curve 0.86); RVOT-ARI after AJT (specificity 0.96, sensitivity 0.58, area under the curve 0.79), and ΔRVOT-ARI (specificity 0.85, sensitivity 0.67, area under the curve 0.76).

CONCLUSIONS: Noninvasive electrocardiographic imaging can be useful in evaluating the results of AJT in BrS.

Key Words: Brugada syndrome ■ ECG imaging ■ sudden cardiac death

Brugada syndrome (BrS) was first described as a "right bundle-branch block, persistent ST-segment elevation, and sudden death syndrome."[1] The rate of sudden cardiac death (SCD) in Brugada syndrome (BrS) is ≈1%/year, and it is 100- to 1000-times higher compared with the matched general population.[2,3] The implanted cardioverter defibrillator (ICD) has been demonstrated to reduce mortality

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CLINICAL PERSPECTIVE

What Is New?

- Electrocardiographic imaging (ECGI) can be used in patients with Brugada syndrome (BrS) during ajmaline test (AJT) to assess the severity of substrate in the right ventricular outflow tract (RVOT); at ECGI, RVOT activation time (RVOT-AT) and RVOT recovery time (RVOT-RT) increase after AJT.
- Patients with BrS and a history of aborted sudden cardiac death exhibit the following findings at the ECGI: higher RVOT-AT after AJT, higher ΔRVOT-AT, lower RVOT activation-recovery interval after AJT, and lower ΔRVOT-activation-recovery interval.
- ECGI parameters, including: RVOT-AT, ΔRVOT-AT, RVOT-activation-recovery interval and ΔRVOT-activation-recovery interval are predictors of previous history of aborted sudden cardiac death in BrS.

What Are the Clinical Implications?

- In the current guidelines and clinical practice there is lack of consensus on the optimal clinical management of patients presenting ajmaline-induced BrS. ECGI may be used to stratify the risk of sudden cardiac death in BrS during AJT in addition to clinical scores.
- Given the low number of patients included in our study, results should not be generalized. Further multicenter prospective studies with larger cohorts of patients are warranted in order to confirm our findings.

Nonstandard Abbreviations and Acronyms

AJT	Ajmaline test
BrS	Brugada syndrome
ECGI	non-invasive ECG imaging
RVOT-ARI	right ventricular outflow tract activation-recovery interval
RVOT-AT	right ventricular outflow tract activation time
RVOT-EPI	epicardium of the right ventricle outflow tract
RVOT-RT	right ventricular outflow tract recovery time
SCD	sudden cardiac death

in patients with BrS.[4–6] However, ICD implantation is not without risks since 24% of BrS patients experience inappropriate shocks.[5] Different clinical variables were described as SCD predictors[7–9] and are included in the current guidelines for risk stratification of SCD.[10] Indeed, up to 25% of patients with BrS presenting with ventricular arrhythmias (VA) did not meet guidelines criteria for ICD implantation.[11]

Electrocardiographic imaging (ECGI) is a novel noninvasive mapping system that has a demonstrated role in assessing BrS depolarization and repolarization substrate[12]; its role during ajmaline test (AJT) has never been evaluated.

The aim of this study is to analyze ECGI parameters before and after ajmaline infusion with a standard protocol.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Population

All consecutive patients who underwent ECGI for BrS at Universitair Ziekenhuis Brussel, between April 2018 and May 2021 were retrospectively analyzed and included in the study. The inclusion criteria were the following: (1) BrS diagnosed following current recommendations[13]; and (2) ECGI map performed before and after AJT with the standard protocol of 1 mg/kg in 5 minutes.

Exclusion criteria were the following: (1) Spontaneous BrS type I pattern ECG occurring during ECGI acquisition before AJT; (2) other diagnosis different from BrS syndrome or overlap syndrome diagnosis by means of genetic analysis, transthoracic echocardiography, computed tomography, or magnetic resonance imaging; (3) active treatment with drugs known to affect AJT, including quinidine; and (4) history of previous BrS substrate ablation. Patients were included if they had a history of spontaneous BrS type I but no spontaneous type I before AJT and ECGI.

SCD-BrS patients were defined as patients with a history of aborted SCD (documented resuscitated ventricular tachycardia or ventricular fibrillation). Genetic analysis was performed in all patients with Roche SeqCap EZ Human Exome Probes v3.0 for BrS. For all patients the risk assessment of events at 5 years was calculated according to the scoring system described by Sieira et al.[9]

All patients signed an informed consent previously approved by our institutional review board. All data were collected and updated in the registry of the Universitair Ziekenhuis Brussel, dedicated to BrS, which has been approved by the ethics committee of our hospital. The study complied with the Declaration of Helsinki; the ethics committee approved the study.

Noninvasive ECGI Mapping and Analysis

ECGI methodology with CardioInsight Noninvasive 3D Mapping System technology (Medtronic Inc,

Minneapolis, MN) has been previously described.[12,14–17] Briefly, all patients had the 252 electrodes CardioInsight Vest positioned on the chest. A computed tomography 120 kV scan protocol with high-resolution 64 slices CT Revolution scan system (GE Healthcare, IL, USA) was used to acquire the images. The patient's chest, neck, and all the electrodes were included in the scan protocol. Segmentation of the computed tomography scan was performed by an experienced operator creating a detailed 3-D shell of the heart. The computed tomography scan was thereafter merged with CardioInsight Vest electrodes with an automatic software on the CardioInsight workstation and 3-D geometry was subsequently modeled to add the atrioventricular valves and left anterior descending coronary artery. Based on the computed tomography scan reconstruction, the different anatomical regions were defined as follows: (1) the right ventricle (RV) and left ventricle separated by the left anterior descending artery and (2) epicardium of the right ventricle outflow tract (RVOT-EPI) defined as the region within the RV 4 cm below the pulmonary valve as previously described.[16]

Maps of RVOT-EPI activation based on unipolar electrograms local activation time were thereafter constructed. Local activation time (referenced to the beginning of QRS in ECG lead II) was determined by the maximal negative slope (maximum negative dV/dT) of the electrogram. The steepest negative dV/dT was automatically calculated on the offline map analysis. If the unipolar ECGI signal showed fractionation, defined as at least 2 positive deflections,[18] the activation was automatically annotated on the steepest negative component. Activation maps were checked for 3 consecutive beats to ensure consistency. Analysis of ECGI activation and repolarization maps were performed offline by 2 independent physicians (L.P. and C.M.) blinded to SCD-BrS history, and in case of a discrepancy of interpretation, a third reviewer, also blinded to SCD-BrS history, arbitrated (C.d.A.).

The following parameters were analyzed on ECGI: (1) maximum right ventricular outflow tract activation time (RVOT-AT); (2) maximum RVOT-EPI recovery time (RVOT-RT); and (3) maximum RVOT-EPI activation-recovery interval (RVOT-ARI), as previously described.[12] Maximum RVOT-AT was defined as the local activation time of the latest RVOT-EPI point on each ECGI map. ΔRVOT-AT was defined as the difference between maximum RVOT-AT before and after ajmaline administration; maximum RVOT-RT was defined as the time from the surface ECG reference to the latest RVOT-EPI maximal positive dV/dT of the electrogram T wave. ΔRVOT-RT was defined as the difference between RVOT-RT before and after ajmaline administration; maximum RVOT-ARI was defined as the difference between RVOT-RT and RVOT-AT. ΔRVOT-ARI was defined as the difference between RVOT-ARI before and after ajmaline administration. Every ECGI map was acquired at baseline and after AJT and the analysis was performed for each map before and after ajmaline infusion. In patients undergoing hybrid epicardial BrS substrate ablation, ECGI map was also acquired after the ablation to assess the complete abolition of epicardial substrate.

Follow-Up

Patients were followed up in the outpatient clinic every 6 months and by remote monitoring. Patients implanted with an ICD underwent device interrogations every 6 months. Patients without ICD underwent 24-hour Holter-ECG every 6 months. The primary outcome was VA occurrence, defined as sustained ventricular tachycardia (at least 30 seconds) or ventricular fibrillation.

Statistical Analysis

All variables were tested for normality with Shapiro–Wilk test. Normally distributed variables were described as mean±SD and the groups were compared through paired or unpaired *t* test as appropriate, while the non-normally distributed variables were described as median (interquartile range) and compared by Mann–Whitney test or Wilcoxon signed-rank test as appropriate. The categorical variables were described as frequencies (percentages) and compared by χ^2 test or Fisher exact test as appropriate. Cohen's kappa statistic was used to assess interobserver agreement in ECGI analysis.

A univariate logistic regression analysis was performed to predict SCD-BrS. The minimum number of events per predictor variable was set at 10 as recommended to avoid an overfitting problem[19]; based on the number of observed events (12 SCD-BrS patients), multivariate logistic regression was not performed.

The variables included in the univariate logistic regression analysis were RVOT-AT before ajmaline, RVOT-AT after ajmaline, ΔRVOT-AT, RVOT-RT before ajmaline, RVOT-RT after ajmaline, ΔRVOT-RT, RVOT-ARI before ajmaline, RVOT-ARI after ajmaline, ΔRVOT-ARI, Sieira score. Odds ratio (OR) and relative 95% CI and receiver operating characteristic curve for each significant predictor were calculated. The receiver operating characteristic curve shows the trade-off between sensitivity and specificity as one changes the cutoff value. The best cutoff was obtained using the Youden's method. The Youden's method (or index) maximizes the vertical line between receiver operating characteristic curve and the diagonal line (ie, chance level).[20] Sensitivity and specificity were calculated at the best cutoff derived by Youden's method. Discrimination was measured by area under the receiver operating characteristic curve measure (AUC). DeLong test was used to compare AUCs between logistic regression models. The bootstrapping method was used for internal

validation with 100 repetitions (B=100) as previously described.[21] Bootstrapping was performed with rms package on R software.[22] Calibration was assessed with rms package on R software using a calibration plot obtained with bootstrapping method (B=100).

A *P* value <0.05 was considered statistically significant.

The analysis was performed using R software version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Study Population Characteristics

Thirty-nine consecutive patients with BrS met the inclusion criteria and were retrospectively analyzed. One patient was excluded because of occurrence of spontaneous BrS type I during ECGI. Thirty-five patients (89.7%) were screened with ECGI before epicardial ablation because they were considered at high risk according to the Sieira score; all 35 patients (100%) received an ICD. Four patients (10.3%) were screened with ECGI in the context of family screening. The latter did not undergo any invasive treatment (nor ICD, nor epicardial ablation), because they were deemed at low risk. Twelve patients (30.8%) had a history of aborted SCD. Non SCD-BrS patients had no history of previous spontaneous VA or ICD intervention. Eight patients (20.5%) presented with a mutation of SCN5A. Compared with non SCD-BrS patients, SCD-BrS patients showed more frequent history of spontaneous type I ECG (6 patients [50.0%] versus 3 patients [11.1%], *P*=0.014), a higher rate of inducibility of VA at the electrophysiological study (5 patients [41.7%] versus 1 patient [3.7%], *P*=0.007) and a higher mean Sieira score (7.2 points±1.3 versus 2.2 points±1.2, *P*<0.001). All patients developed BrS ECG type I after ajmaline infusion (test positive at a mean time of 4.2 min±0.7). No VA were induced during AJT. Patient characteristics are summarized in Table 1 and in Table S1.

Noninvasive Mapping Analysis

At baseline, mean RVOT-AT was 65.8 milliseconds, mean RVOT-RT was 365.7 milliseconds, and mean RVOT-ARI was 299.9 milliseconds, with no difference between SCD-BrS and non SCD-BrS (*P*=0.9, *P*=0.91, *P*=0.86, respectively). After ajmaline administration there was an increase in both RVOT-AT (105.9 milliseconds±31.4 versus 65.8 milliseconds±25.2, *P*<0.001) and RVOT-RT (403.4 milliseconds±34.7 versus 365.7 milliseconds±27.1, *P*<0.001) but not in RVOT-ARI (297.5 milliseconds±42.6 versus 299.9 milliseconds±36.1, *P*=0.7).

Compared with non SCD-BrS patients, SCD-BrS patients showed higher RVOT-AT after AJT (138.1 milliseconds±17.7 versus 91.6 milliseconds±24.9, *P*<0.001), higher ΔRVOT-AT (73.1 milliseconds±35.9 versus 25.4 milliseconds±23.0, *P*<0.001), lower RVOT-ARI after AJT (270.7 milliseconds±32.3 versus 309.4 milliseconds±41.6, *P*=0.007), and lower ΔRVOT-ARI (–30.8 milliseconds±44.2 versus 10.2 milliseconds±29.6, *P*=0.002), Figures 1 and 2. There was no difference between SCD-BrS patients and non SCD-BrS in RVOT-RT following AJT (*P*=0.52) and ΔRVOT-RT (*P*=0.45). Complete ECGI analysis is summarized in Table 2. Good interobserver agreement was observed for ECGI analysis (κ=0.95).

Table 1. Clinical Characteristics of Patients With Brugada Syndrome With and Without History of Sudden Cardiac Death

	No SCD-BrS (N=27)	SCD-BrS (N=12)	Total (N=39)	*P* value
Age, y	39.3±14.9	42.8±12.6	40.3±14.2	0.48
Sex (male)	16 (59.3%)	7 (58.3%)	23 (59.0%)	1.00
History of syncope (n, %)	19 (70.4%)	8 (66.7%)	27 (69.2%)	1.00
Spontaneous BrS 1 pattern (n, %)	2 (7.4%)	6 (50.0%)	8 (20.5%)	0.006
SCD family history (n, %)	5 (18.5%)	3 (25.0%)	8 (20.5%)	0.68
SND (n, %)	4 (14.8%)	1 (8.3%)	5 (12.8%)	1.000
VA inducibility at EPS (n, %)	1 (3.7%)	5 (41.7%)	6 (15.4%)	0.007
Sieira score (points)	2.2±1.2	7.2±1.3	3.7±2.6	<0.001
ICD (n, %)	23 (85.2%)	12 (100%)	35 (89.7%)	0.29
ECG RBBB (n, %)	3 (11.1%)	3 (25.0%)	6 (15.4%)	0.63
ECG Incomplete RBBB (n, %)	7 (25.9%)	3 (25.0%)	10 (25.6%)	1.00
ECG PQ (ms)	173.2±30.7	175.7±30.2	174.0±30.2	0.82
ECG QRS (ms)	102.8±20.0	115.0±36.3	106.5±26.2	0.18
ECG HV (ms)	49.8±11.8	46.2±6.8	49.1±10.9	0.58

BrS indicates Brugada syndrome; EPS, electrophysiological study; HV (His-Ventricle); ICD, implanted cardioverter defibrillator; RBBB, right bundle-branch block; SCD, sudden cardiac death; SCD-BrS patients, patients with a history of aborted SCD; SND, sinus node dysfunction; and VA, ventricular arrhythmias.

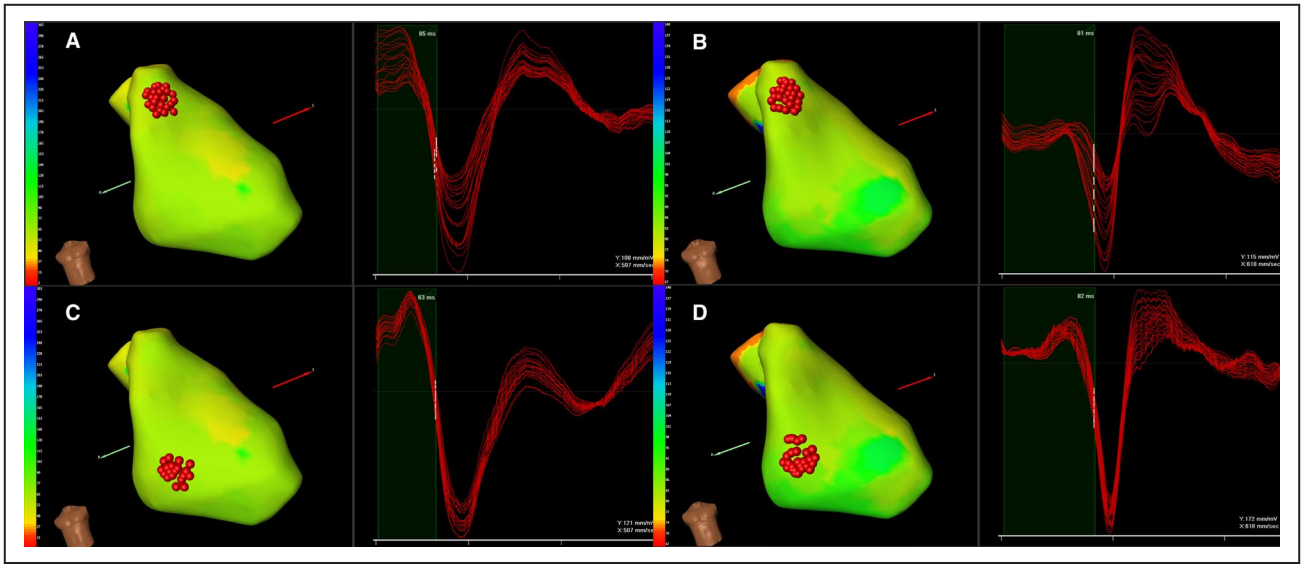

Figure 1. ECG imaging in patient with Brugada syndrome without history of aborted sudden cardiac death.
Patient 9 activation map with CardioInsight Noninvasive 3D ECGI before and after ajmaline. Each red point on the activation map (left) corresponds to 1 unipolar electrogram (right). **A**, ECGI map of RVOT-EPI before ajmaline: Left side: activation map with ECGI. Right side: RVOT-EPI unipolar signals (RVOT-AT 65 milliseconds). **B**, ECGI map of RVOT-EPI after ajmaline: Left side: activation map with ECGI. Right side: RVOT-EPI unipolar signals (RVOT-AT 81 milliseconds). RVOT-AT is increased after ajmaline. For comparison, right ventricular free wall ECGI map is shown. **C**, ECGI map of right ventricular free wall before ajmaline: Left side: activation map with ECGI. Right side: unipolar signals (activation time 63 milliseconds). **D**, ECGI map of right ventricular free wall after ajmaline: Left side: activation map with ECGI. Right side: unipolar signals (activation time 82 milliseconds). ECGI indicates noninvasive electrocardiographic imaging; RVOT-AT, right ventricular outflow tract activation time; and RVOT-EPI, epicardium of the right ventricle outflow tract.

SCD-BrS Prediction Model

At the univariate logistic regression analysis, predictors of SCD-BrS were as follows: RVOT-AT after AJT (OR per 1 milliseconds increase, 1.09 [95% CI, 1.03–1.15], *P*=0.002), ΔRVOT-AT (OR per 1 milliseconds increase, 1.05 [95% CI, 1.02–1.09], *P*=0.002), RVOT-ARI after AJT (OR per 1 milliseconds increase, 0.97 [95% CI, 0.95–0.99], *P*=0.018), and ΔRVOT-ARI (OR per 1 milliseconds increase, 0.97 [95% CI, 0.95–0.99], *P*=0.007).

The best cutoffs to predict SCD-BrS were the following: (1) RVOT-AT after AJT>110.5 milliseconds (specificity: 0.74, sensitivity 1.00, AUC 0.92); (2) ΔRVOT-AT>40.3 milliseconds (specificity: 0.74, sensitivity 0.92, AUC 0.86); (3) RVOT-ARI after AJT<267.5 milliseconds (specificity 0.96, sensitivity 0.58, AUC 0.79); and (4) ΔRVOT-ARI<–18 milliseconds (specificity 0.85, sensitivity 0.67, AUC 0.76), Figure 3.

At the internal bootstrapping validation, optimism-corrected performance was as follows: (1) RVOT-AT after AJT (AUC 0.92); (2) ΔRVOT-AT (AUC 0.85); (3) RVOT-ARI after AJT (AUC 0.77); and (4) ΔRVOT-ARI (AUC 0.76), Figure S1.

Sieira score ≥2 yielded a specificity of 0.22, sensitivity of 1.00, and an AUC of 0.61 in predicting SCD-BrS. At DeLong test there was no significant difference between AUCs of different logistic regression models.

Follow-Up

Following ECGI mapping, 35 patients (89.7%) underwent hybrid epicardial BrS substrate ablation. ECGI map performed after ablation confirmed complete epicardial substrate abolition in 33 patients (94.3%). In 2 patients (5.7%), complete abolition of the epicardial substrate was not possible because of right coronary artery proximity in the area of interest and because of the vicinity of a small branch of the left anterior descending coronary artery in the anterior RVOT-EPI. At a mean follow-up of 69.2 months±22.5, no deaths were observed. Two SCD-BrS patients (5.1%) experienced VA after a mean follow-up of 16.3 months±12.2, 1 patient experienced ventricular tachycardia, and the other patient experienced ventricular tachycardia and ventricular fibrillation. All VA were detected and treated appropriately by the ICD.

DISCUSSION

The main findings of this study are as follows: (1) an increase in both RVOT-AT and RVOT-RT but not in RVOT-ARI can be observed on the ECGI after AJT in patients with BrS; (2) SCD-BrS patients compared with individuals without history of SCD had higher RVOT-AT after AJT, higher ΔRVOT-AT, lower RVOT-ARI after AJT, and lower ΔRVOT-ARI; (3) ECGI parameters: RVOT-AT,

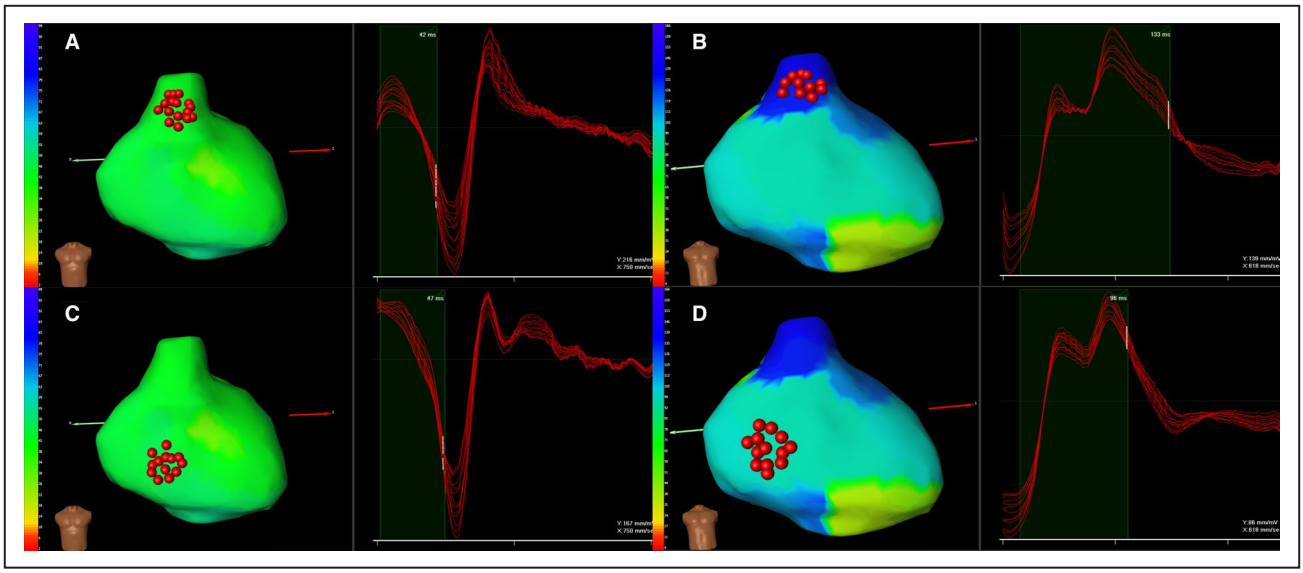

Figure 2. ECG imaging in patient with Brugada syndrome with history of aborted sudden cardiac death.
Patient 33 activation map with CardioInsight Noninvasive 3D ECGI before and after ajmaline. Each red point on the activation map (left) corresponds to 1 unipolar electrogram (right). **A**, ECGI map of RVOT-EPI before ajmaline: Left side: activation map with ECGI. Right side: RVOT-EPI unipolar signals (RVOT-AT 42 milliseconds). **B**, ECGI map of RVOT-EPI after ajmaline: Left side: activation map with ECGI. Right side: RVOT-EPI unipolar signals (RVOT-AT 133 milliseconds). RVOT-AT is increased after ajmaline. The unipolar signal is fragmented and the activation time is annotated on the maximum negative dV/dT on the second component of unipolar signal. For comparison, right ventricular free wall ECGI map is shown. **C**, ECGI map of right ventricular free wall before ajmaline: Left side: activation map with ECGI. Right side: unipolar signals (activation time 47 milliseconds). **D**, ECGI map of right ventricular free wall after ajmaline: Left side: activation map with ECGI. Right side: unipolar signals (activation time 96 milliseconds). ECGI indicates noninvasive electrocardiographic imaging; RVOT-AT, right ventricular outflow tract activation time; and RVOT-EPI, epicardium of the right ventricle outflow tract.

ΔRVOT-AT, RVOT-ARI, and ΔRVOT-ARI were predictors of SCD history; and (4) RVOT-AT after AJT showed the best prognostic accuracy in predicting history of SCD.

Clinical Role of ECGI in Brugada Syndrome

The current study is the first to report ECGI use with AJT in patients with BrS. In a recent article, Zhang et al[12] first demonstrated the role of ECGI technology in assessing the electrophysiological substrate in this patient population. Although our results are consistent with the latter at baseline, a difference in ECGI parameters between SCD-BrS and non SCD-BrS patients could only be observed after ajmaline infusion.

RVOT-AT is a measure of delayed depolarization that has been demonstrated to be a substrate of VA in BrS.[23] Indeed, previous studies involving epicardial electroanatomic mapping showed the presence of

Table 2. ECGI Analysis in Patients With Brugada Syndrome With and Without History of Sudden Cardiac Death

	No SCD-BrS (N=27)	SCD-BrS (N=12)	Total (N=39)	*P* value
RVOT-AT before ajmaline, ms	66.2±22.2	65.0±31.9	65.8±25.2	0.90
RVOT-AT after ajmaline, ms	91.6±24.9	138.1±17.7	105.9±31.4	<0.001
ΔRVOT-AT, ms	25.4±23.0	73.1±35.9	40.1±35.1	<0.001
RVOT-RT before ajmaline, ms	365.4±29.3	366.5±22.4	365.7±27.1	0.91
RVOT-RT after ajmaline, ms	401.0±35.5	408.8±33.6	403.4±34.7	0.52
ΔRVOT-RT, ms	35.6±24.1	42.2±26.8	37.6±24.8	0.45
RVOT-ARI before ajmaline, ms	299.2±38.7	301.5±31.2	299.9±36.1	0.86
RVOT-ARI after ajmaline, ms	309.4±41.6	270.7±32.3	297.5±42.6	0.007
ΔRVOT-ARI, ms	10.2±29.6	−30.8±44.2	−2.4±39.1	0.002

ΔRVOT-ARI indicates difference between RVOT-ARI before and after ajmaline administration; ΔRVOT-AT, difference between RVOT-AT before and after ajmaline administration; ΔRVOT-RT, difference between RVOT-RT before and after ajmaline administration; RVOT-ARI, right ventricular outflow tract activation-recovery interval; RVOT-AT, right ventricular outflow tract activation time; RVOT-RT, right ventricular outflow tract recovery time; and SCD-BrS patients, patients with a history of aborted SCD.

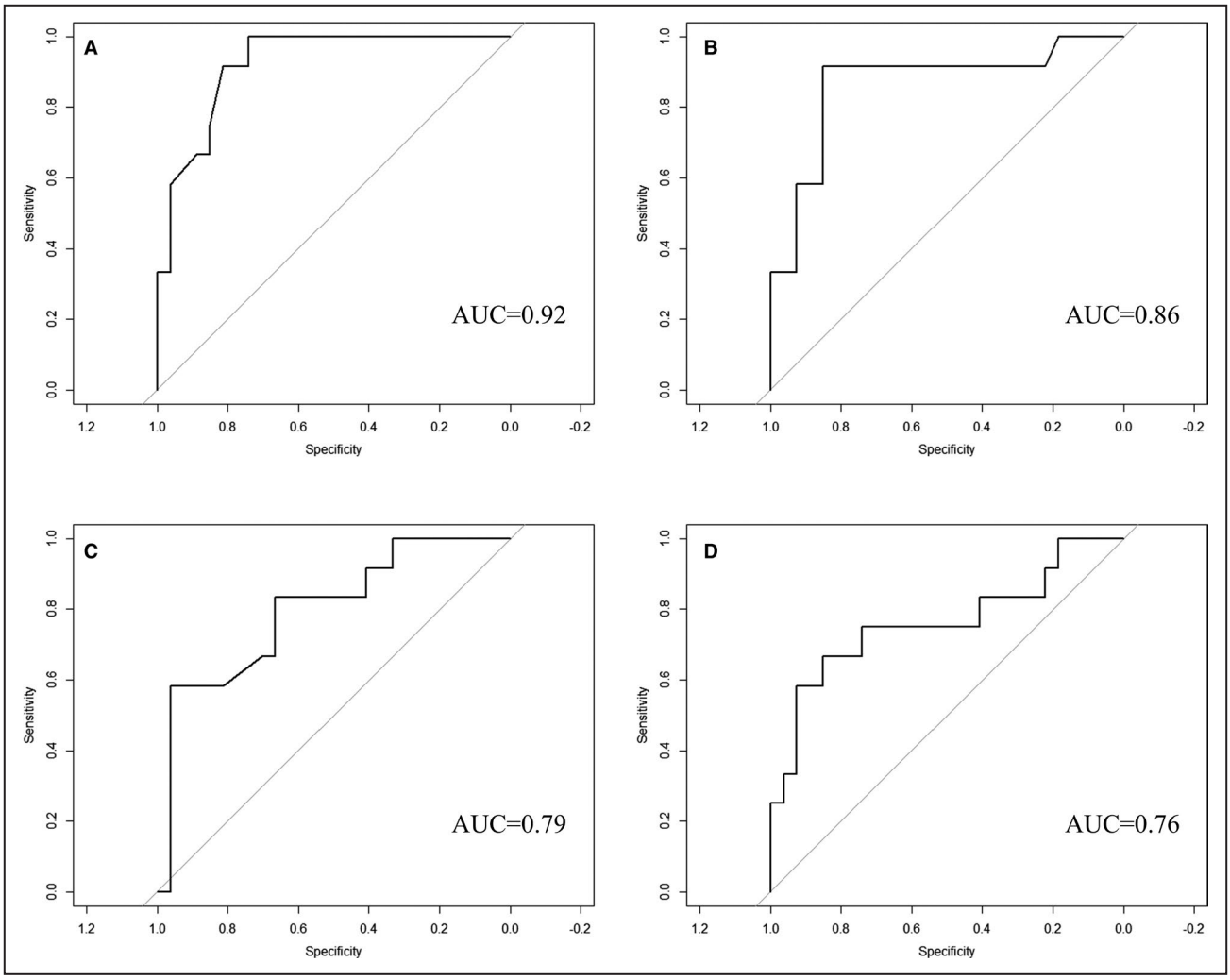

Figure 3. ROC curves of univariate logistic regression analysis.
All curves refer to univariate logistic regression analysis using SCD-BrS as dependent variable. **A**, ROC curve for RVOT-AT after ajmaline administration (AUC 0.92). **B**, ROC curve for ΔRVOT-AT (AUC 0.86). **C**, ROC curve for RVOT-ARI after ajmaline administration (AUC 0.79). **D**, ROC curve for ΔRVOT-ARI (AUC 0.76). AUC indicates area under the curve; ROC, receiver operating characteristic; SCD-BrS, sudden cardiac death Brugada syndrome; RVOT-ARI, right ventricular outflow tract activation-recovery interval; and RVOT-AT, right ventricular outflow tract activation time.

fractionated and late potentials on RVOT-EPI as the electrical expression of slow conduction.[24] Importantly, AJT helped to unmask the electrical substrate both in terms of area and duration of fragmentation.[25] Noticeably, our group demonstrated that SCD-BrS patients had longer fragmented potentials during high-density electroanatomic mapping, only after AJT[26]; furthermore, we found a significant correlation between RVOT-AT and abnormal fragmented potentials activation time, both before (ρ=0.76) and after (ρ=0.82) ajmaline infusion.[26] RVOT-AT might be a noninvasive measure of delayed fragmented epicardial potentials, and this may explain the higher RVOT-AT observed in SCD-BrS patients after AJT.

RVOT-RT is a measure of repolarization while RVOT-ARI is considered to be a measure of the action potential duration; delayed repolarization and prolonged epicardial action potential duration in patients with BrS, compared with controls, has been previously demonstrated with ECGI.[12] In particular, longer RVOT-ARI was observed in the epicardium than in the endocardium, indicating a prolongation of epicardial action potential duration. Also, steep epicardial action potential duration gradients were demonstrated to be contributing to the arrhythmogenesis in an optical coherence model of BrS.[27]

SCD Risk Stratification in Brugada Syndrome

SCD risk stratification in BrS is still a matter of debate. Clinical predictors[7,8] appear as an appealing and

pragmatic solution, especially if combined within risk assessment scores. Sieira et al[9] recently proposed a reliable risk score model with the aim of predicting the occurrence of SCD in this patient population. Similarly, the Shanghai score, initially defined for BrS diagnosis[28], has been later validated for SCD risk stratification.[29] However, its prognostic value has been demonstrated only in patients without previous ventricular fibrillation.

The performance of a risk score depends on the number of events per analyzed variable to avoid overadjustment. In the current study, 12 events per variable were used, yielding an AUC of 0.76 to 0.92 for different ECGI parameters. This was higher than previous studies. However, the prognostic value of the ECGI in our study has only been validated in patients with BrS with previously aborted SCD.

Clinical scores have been shown to help in guiding the decision towards an ICD implantation in patients with BrS.[2] However, these might be hampered by a certain number of limitations. Probst et al[30] found that, in an independent cohort validation, both Shanghai and Sieira scores had moderate performance to predict SCD in BrS (AUC Sieira=0.71 [0.61–0.81], AUC Shanghai=0.73 [0.67–0.79]). Also, clinical scores showed worse performance in patients with a history of previous SCD and a low predictive value in intermediate risk.[30] The clinical problem is not negligible since guidelines are already clear on the management of high-risk patients and of low-risk patients. However, there is a lack of consensus on intermediate risk and ajmaline-induced BrS treatment.[13] Furthermore, in a recent study including only drug-induced BrS, a decision to implant ICD based on syncope or electrophysiological study inducibility led to an annual rate of 0.38% appropriate interventions and a deceiving rate of ICD-related complication rate of 14.8% including a 4.9% rate of inappropriate shocks.[31]

Limitations

The main limitation of the study lies in its retrospective nature. SCD events could not be analyzed prospectively but only retrospectively because 35 patients (89.7%) underwent hybrid epicardial BrS substrate ablation after ECGI. The number of patients included is relatively small. The low sample size does not enable adjustment for confounding factors; the reported unadjusted relationships may include bias. Limitations also include referral bias because of the inclusion of study patients from a tertiary center specialized in BrS. Patients included in the presented cohort had a mean Sieira score of 3.7, and thus were deemed at high risk. Validation of ECGI parameters, prospectively and in a large cohort, also including patients at lower risk, would add value to their clinical utility. ECGI parameters are not validated for BrS patients with spontaneous type I ECG during ECGI acquisition.

CONCLUSIONS

ECGI parameters after ajmaline, including RVOT-AT, ΔRVOT-AT, RVOT-ARI, and ΔRVOT-ARI, are predictors of SCD history in patients with BrS. Use of ECGI in risk stratification of SCD in BrS might be useful in addition to clinical scores. The current study should be considered as hypothesis generating and further prospective cohort studies are eagerly awaited.

ARTICLE INFORMATION

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Supplemental Material

Table S1
Figure S1

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SUPPLEMENTAL MATERIAL

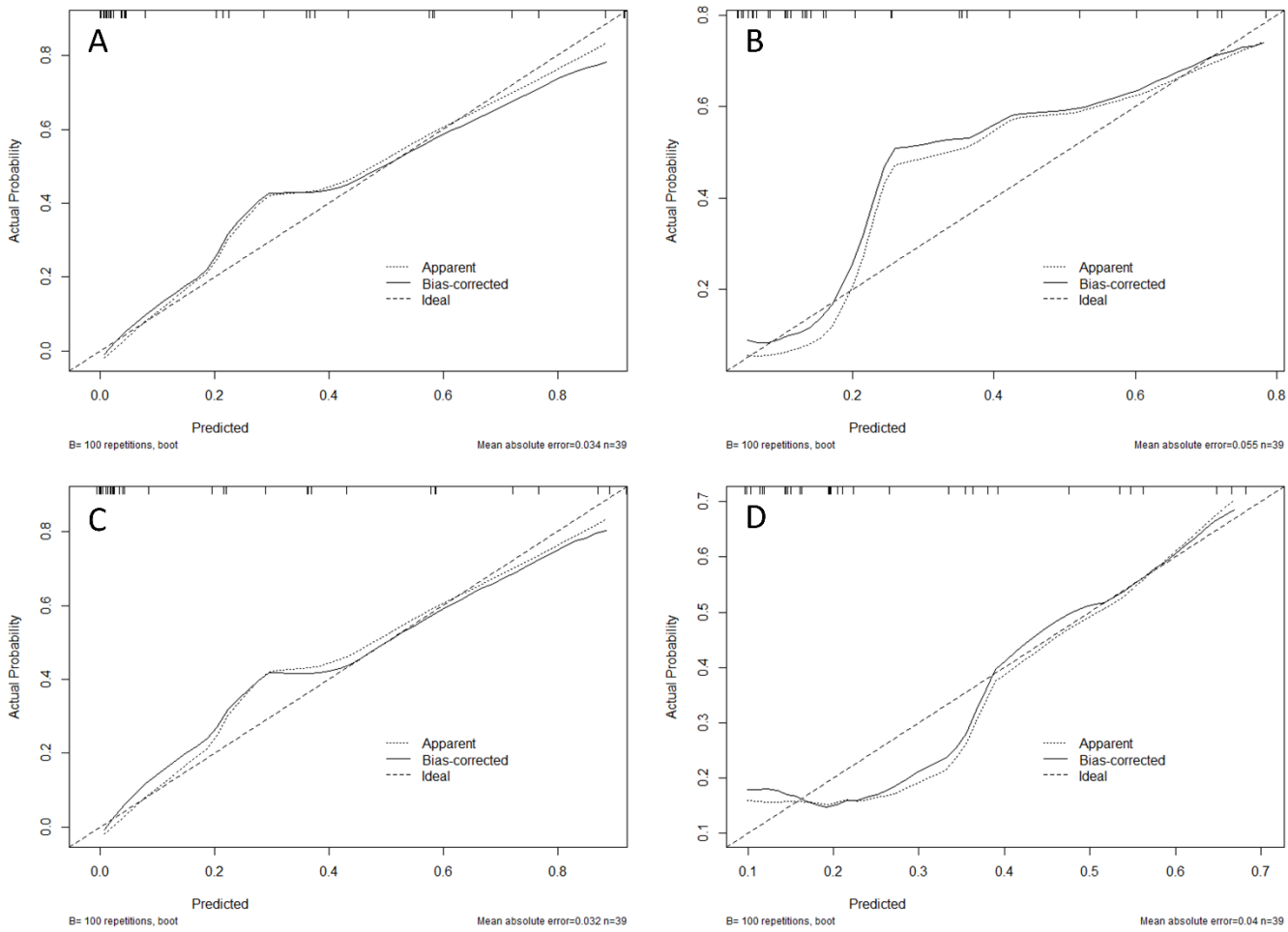
Table S1. Complete clinical characteristics of study population.

Patient	Age	Sex (Male)	Ablation	Gene mutation	ECG QRS	ECG PQ	ECG HV	ECG RBBB	ECG Incomplete RBBB	Syncope	History of spontaneous BrS type I	SCD family history	SND	VA at EPS	Aborted SCD	Sieira Score
1	22	+	+	none	100	130	40	-	+	+	-	-	-	-	-	**2**
2	63	+	+	none	200	120	55	+	-	-	+	+	-	+	+	**8**
3	64	-	+	SCN5A	142	188		+	-	+	-	+	-	-	-	**3**
4	44	+	+	none	118	170		-	-	+	+	-	-	+	+	**9**
5	38	-	+	SCN5A	82	180		-	+	-	-	-	+	-	+	**7**
6	58	-	+	none	78	140	40	-	-	+	-	-	-	+	+	**8**
7	36	-	+	SCN5A + ANK2	118	222		-	-	+	+	-	-	-	+	**7**
8	48	-	+	none	80	154	35	-	-	+	-	-	-	-	-	**2**
9	37	+	+	none	132	200		-	-	+	-	-	-	-	-	**2**
10	38	+	+	SCN5A	112	160	48	-	+	+	-	-	-	-	+	**6**
11	47	-	+	CTNNA3 + DPP6 + TTN	74	135		-	-	+	-	-	-	-	-	**2**
12	58	-	+	SCN5A	118	198	58	-	+	+	-	-	-	-	-	**2**
13	69	-	+	AKAP9	96	218	53	-	-	+	-	-	-	-	-	**2**
14	15	+	+	SNTA1	100	158	49	-	-	-	-	-	+	-	-	**3**
15	17	+	+	KCND3	104	170		-	+	+	-	-	-	-	+	**6**
16	46	-	-	none	80	180		-	-	+	-	-	-	-	-	**2**
17	44	-	-	none	85	200		-	-	-	-	-	-	-	-	**0**
18	51	-	+	none	82	162		-	-	+	-	+	-	+	+	**9**
19	29	+	-	none	80	150		-	-	-	-	+	-	-	-	**1**
20	38	+	+	none	120	230		-	-	+	+	-	-	-	-	**3**
21	56	+	+	none	114	168		-	-	+	+	-	-	-	+	**7**
22	10	+	+	none	102	154	70	-	-	+	-	-	+	-	-	**5**
23	33	+	+	none	102	170	40	-	-	+	-	-	+	-	-	**5**
24	36	+	-	SCN5A	146	220	77	+	-	-	-	-	+	-	-	**3**
25	41	+	+	none	80	196	42	-	-	-	-	-	-	+	+	**6**
26	44	-	+	none	84	170	43	-	-	-	-	-	-	-	-	**0**
27	53	+	+	none	116	206		-	-	-	+	-	-	-	-	**1**
28	61	+	+	none	126	188		+	-	+	-	-	-	-	-	**2**

29	46	+	+	none	90	188		-	-	+	-	-	-	+	-	**4**
30	35	+	+	SCN5A	160	220		+	-	+	+	+	-	-	+	**8**
31	50	+	+	SCN5A	118	218		-	+	+	-	+	-	-	-	**3**
32	20	-	+	SCN2B	102	146	45	-	-	-	-	+	-	-	-	**1**
33	36	-	+	none	132	200		+	-	-	+	-	-	-	+	**5**
34	22	+	+	none	80	162	50	-	+	+	-	-	-	-	-	**2**
35	28	-	+	SCN4B	92	130	40	-	+	-	-	+	-	-	-	**1**
36	41	+	+	none	114	152	59	-	+	+	-	-	-	-	-	**2**
37	40	-	+	none	80	144		-	+	+	-	-	-	-	-	**2**
38	30	+	+	none	110	162	42	-	-	+	-	-	-	-	-	**2**
39	29	+	+	none	106	126	46	-	-	+	-	-	-	-	-	**2**

EPS: electrophysiological study; BrS: Brugada syndrome; HV (His-Ventricle); RBBB: right bundle branch block; SCD: sudden cardiac death; SND: sinus node dysfunction; VA: ventricular arrhythmias.

Figure S1. Calibration plots obtained with bootstrapping method.



All curves refer to univariate logistic regression analysis using SCD-BrS as dependent variable. Panel A: calibration plot curve for RVOT-AT after ajmaline administration. Panel B: calibration plot curve for ΔRVOT-AT. Panel C: calibration plot curve for RVOT-ARI after ajmaline administration. Panel D: calibration plot curve for ΔRVOT-ARI.