Defining Repolarization Dispersion Substrate in Patients with Type-1 Brugada Phenotype: a New Algorithm for Automated Mapping of Activation Recovery Interval.

Abstract (249 words)

Background

Repolarization heterogeneity in right ventricular outflow tract (RVOT) contribute to type-1 electrocardiographic (ECG) phenotype of Brugada syndrome (BrS), though data on feasibility of repolarization dispersion mapping are scarce.

Objective

We aimed to assess repolarization patterns through an automated calculation of activation recovery interval (ARI) estimated on unipolar electrograms (UEGs) in subjects with spontaneous type-1 BrS phenotype and controls. We also investigated the relation between ARI and right ventricle activation time (RVAT) and ARI and T-wave peak-to-end interval (Tpe) in BrS patients.

Methods

Patients underwent endocardial high-density electroanatomical mapping (HDEAM); BrS showing an overt type-1 ECG were defined OType1, while those without (latent type-1 ECG, LType1) received ajmaline infusion. BrS patients only underwent programmed ventricular stimulation (PVS). Data were elaborated to obtain ARI corrected with the Bazett formula (ARIc). Activation maps provided RVAT.

Results

39 BrS subjects (24 OType1 and 15 LTtype1) and 4 controls were enrolled. OType1 and post-ajmaline LType1 showed longer mean ARIc than controls (306±27.3 ms vs. 281.7±10.3 ms, $p=0.05$; and 333.3±16.3 ms, $p<0.001$, respectively). Ajmaline induced a significant prolongation of ARIc compared both to pre-ajmaline LTtype1 (333.3±16.3 vs 303.4±20.7 ms, $p<0.001$) and OType1 (306±27.3 ms, $p<0.001$). In patients with type-1 ECG (OTtype1 and post-ajmaline LType1) there was a correlation between ARIc and RVAT ($r=0.34$, $p=0.04$) and between ARIc and Tpec ($r=0.60$, $p<0.001$), especially if considering OType1 subjects ($r=0.55$, $p=0.008$ and $r=0.65$ $p<0.001$, respectively).

Conclusion

ARIc mapping demonstrates increased local repolarization dispersion in RVOT in BrS. ARIc positively correlates with RVAT and Tpec, especially in OType1.

Keywords

Brugada syndrome; repolarization; activation recovery interval; Tpeak-Tend interval; electroanatomic substrate.

Abbreviation list

ARI	Activation Recovery Interval
ARIc	Activation Recovery Interval corrected for the Bazett formula
ARIQ3	Activation Recovery Interval at the 75% of the distribution corrected for the Bazett formula
BrS	Brugada Syndrome
EAM	Electroanatomical mapping
ECG	Electrocardiogram
EPS	Electrophysiological study
HDEAM	High density right ventricular electroanatomical mapping
ICD	Implantable cardioverter defibrillator
LAT	Local Activation Time
LType1	Latent type-1 electrocardiographic pattern at the time of electrophysiological study
OType1	Overt type-1 electrocardiographic pattern at the time of electrophysiological study
PVS	Programmed ventricular stimulation
PVS+	Ventricular tachycardia/fibrillation inducible during programmed ventricular stimulation
PVS-	Ventricular tachycardia/fibrillation not inducible during programmed ventricular stimulation
ROI	Region of interest
RV	Right ventricle

RVAT	Right ventricular activation time
RVOT	Right ventricular outflow tract
SCD	Sudden cardiac death
Tpe	Tpeak-Tend interval
Tpec	Tpeak-Tend interval corrected for the Bazett formula
UEG	Unipolar electrogram
VGD	Voltage Gradient dispersion
VF	Ventricular Fibrillation
VT	Ventricular Tachycardia

Introduction

Brugada Syndrome (BrS) is characterized by the presence of a coved-type J-point elevation in right precordial leads on surface electrocardiogram (ECG) and by an increased risk of sudden cardiac death (SCD)[1]. Both depolarization and repolarization abnormalities have been described in BrS patient and their interplay on explaining the electrophysiological basis of the disease is reported in the literature[3]. Previous clinical studies suggested that the varying degree of J-point elevation observed within different BrS subjects may reflect different conduction abnormalities and repolarization heterogeneity in right ventricular outflow tract (RVOT)[4].

The repolarization hypothesis states that ECG phenotype and arrhythmogenesis of BrS might be due to transmural and epicardial repolarization dispersion[5]. Tpeak-Tend (Tpe) interval is widely used as an index of transmural dispersion of repolarization[6]. A recent meta-analysis has shown that a prolongation of Tpe is associated with higher arrhythmic risk in BrS patients, although a cut-off value to identify high-risk patients still needs to be defined[7]. Activation Recovery Interval (ARI) estimates action potential duration[8] and has previously been used to evaluate spatial repolarization dispersion in BrS[9-13].

This study aimed to assess the reliability of repolarization dispersion mapping using an automated calculation of ARI from endocardial unipolar electrograms

(UEGs) derived from RV high-density electroanatomic mapping (RV-HDEAM) in BrS patients and controls. We also investigated the relation between ARI distribution and RV activation, as well as Tpeak-Tend interval (Tpe) in BrS patients with type-1 phenotype.

Methods

Study population

Thirty-nine consecutive BrS patients with previously documented spontaneous type-1 pattern were enrolled. Four healthy patients provided control data. Exclusion criteria were: presence of overt cardiac structural disease, age less than 16 years or informed consent denial. The diagnosis of BrS was based on current recommendations[14,15]. Genetic testing was performed using next generation sequencing analysis (Illumina NextSeq 500/550). All patients underwent an electrophysiological study (EPS) without sedation with RV endocardial high-density electroanatomical mapping (HDEAM) using the CARTO®3 system (Biosense Webster Inc.). Patients showing an overt type-1 ECG during EPS were defined OType1; those without were defined LType1 and received ajmaline challenge[15] during HDEAM. All BrS subjects underwent PVS after RV-HDEAM (in the LType1 subgroup PVS was performed after complete recovery of ECG modifications

induced by ajmaline). The induction protocol was carried out from RV apex and RVOT at two drive trains (8 stimuli at 600 and 400 ms) with up to two extrastimuli until refractoriness or a 200 ms coupling interval was reached[16]. PVS was considered positive (PVS+) in case the patient developed VF, VT lasting more than 30s or requiring direct current shock because of hemodynamic instability. Noninducible patients were defined as PVS-.

All participants provided written informed consent for the study. The study was conducted following the 2013 Helsinki Declaration and was approved by the Hospitals' Review Boards.

High-density electroanatomical mapping (HDEAM)

RV-HDEAM was performed during sinus rhythm using the CARTO®3 (Biosense Webster Inc., CA, USA) mapping system, as previously described[17]. A linear multipolar DecaNav® catheter with 2-8-2 interelectrode spacing and ablation catheter with a contact-force sensor (SmartTouch™® or SmartTouch SF™®) was used for RV mapping. The Wilson Central Terminal on surface ECG or the 11th electrode of DecaNav® catheter was used as unipolar reference. The ablation catheter was used to validate the points having adequate contact with heart surface. Confidense® mapping software (Biosense Webster Inc., CA, USA) was set to acquire exclusively points having position stability ≤ 6 mm, LAT stability ≤ 6 ms,

pattern matching with sinus rhythm pattern and contact force 5-25 g. The Fill&Color® interpolation threshold for electroanatomical mapping was set at 6 mm. A minimum of 700 points were acquired.

Bipolar signals were filtered at 30–500 Hz, while UEGs at 1–240 Hz. Amplitude, duration, relation to surface QRS, multiple components of the signals were simultaneously analyzed. For each patient, local activation maps (LATs) were used to calculate right ventricular activation time (RVAT), defined as the interval between the beginning of surface QRS and the latest depolarizing point in RV.

HDEAM data export and ARI calculation

Data acquired during RV-HDEAM were exported and OpenEP software[18] was used to convert data into MatLab® (MathWorks Inc.) format. Paraview software provided the selection of a specific region of interest (ROI) in RVOT[19]. MatLab® was used to create an automated algorithm for ARI calculation using endocardial UEGs in each point of the ROI. ARI was calculated starting from the minimum dV/dt of the unipolar QRS to the maximum dV/dt of the following T wave, as previously described by Wyatt et al[8]. In case of noise, presence of a premature ventricular beat, or abnormal T-wave morphologies, the UEG was discarded.

For each patient, mean ARI and mean ARI corrected for heart rate based on the Bazett formula (ARIc) were calculated. ARIQ3 refers to the ARIc value at 75% of

ARIc distribution; the ARIQ3 extension (as the percentage respect with the whole ROI) was also calculated. ARI values of each point were interpolated using Paraview[20] on a three-dimensional mesh. A color code was set for a specific ARI duration to create ARIc maps. A two-color map was created by setting the threshold at ARIQ3 to visualize the spatial extension of ARIQ3 for each patient.

Tpeak-Tend interval calculation

Tpeak-Tend interval (Tpe) was calculated only in BrS with type-1 ECG phenotype (OType1 and post-ajmaline LType1). Tpe was measured on 20 low-noise beats recorded during the procedure using a multi-stage, dedicated automated algorithm. For Tpe calculation, data was exported from the CARTO®3 system to MatLab® as previously described. Using MatLab®, heartbeat detection on surface ECG was first performed, and heart rate was determined. Non-sinus beats were discarded through morphological clustering. Twenty low-noise sinus beats were then extracted and averaged, obtaining an average beat for each lead. Tpe was calculated on V1, V2 and V3 with an algorithm based on the tangent method[21]. An operator checked the accuracy of the calculation of each Tpe value with a custom graphic user interface, correcting the starting and ending point of the interval if needed or discarding the lead if Tpe was not measurable due to abnormal T wave morphology. For each

patient, the mean value of Tpe of V1, V2 and V3 was calculated. Mean corrected Tpe (Tpec) was determined using the Bazett formula.

Treatment and Follow-up

ICD implantation for primary prevention was proposed to PVS+ and to selected high-risk PVS- patients. Patients underwent a follow-up with ECG monitoring and half-yearly ICD check (in ICD recipients) unless symptoms appearance, arrhythmias documentation or ICD interventions.

Statistical analysis

Continuous variables were reported as mean ± standard deviation or median and interquartile range according to the data distribution, assessed with the Shapiro test. Discrete variables were expressed as numbers and/or percentages.

For comparison between two groups, unpaired t-test or nonparametric Mann-Whitney U test was used depending on the variable distribution. ANOVA or Kruskal-Wallis, with Tukey's range test, was used to compare more than two groups. For the comparison of a group before and after ajmaline injection, paired t-test or Wilcoxon test was used as appropriate. Correlation between continuous variables was tested using Pearson R correlation coefficient or Spearman coefficient, as appropriate.

Differences were considered significant in case of p-value ≤ 0.05. Statistical analysis and graphs were performed using R software (version R 2023.03.1+446, *R Development Core Team*, Vienna, Austria).

Results

Study population

Study population included 39 BrS patients and 4 healthy controls. Clinical data of the study population is summarized in **Table 1**. BrS population included 24 OType1 patients (62%) and 15 LType1 (38%). Nine patients (23%) had VT/VF inducible at PVS, of which 7 (29%) were OType1 and 2 (13%) LType1 (p=0.06). Genetic testing was performed on 30 patients; of them, 2 (7%) carried a *SCN5A* pathogenic mutation.

Endocardial mapping analysis, ARI and Tpe calculation

ARI analyses are summarized in **Table 2**. BrS patients during type-1 ECG pattern (post-ajmaline LType1 and OType1) showed longer mean ARIc values with respect to controls (333.3±16.3 ms vs 281.7±10.3; p=0.02 and 306±27.3 ms vs 281.7±10.3 ms, p=0.05, respectively). Ajmaline induced a significant prolongation of ARIc both compared to pre-ajmaline LType1 (303.4±20.7 ms vs 333.3±16.3 ms, p<0.001) and

to OType1 (306±27.3 ms vs 333.3±16.3 ms, p=0.001) subjects. Ajmaline administration determined a prolongation of mean ARIc in all but one patient. Through the interpolation of ARIc values, ARIc maps were reconstructed (**Figure 1**).

ARIQ3 analysis is reported in **Table 2**. ARIQ3 analysis revealed localized longer ARIc mainly in the anterior and subpulmonary portion of RVOT (**Figure 2**). In controls, ARIQ3 zones had shorter ARIc values with respect to BrS subjects (312.7±15.1 ms vs 347.1±29.5 ms, p=0.03). In OType1 subjects, mean ARIQ3 was 335.1±28.3 ms and the ARIQ3 area was 23.1% of the whole ROI. In LType1 patients, ajmaline induced significant prolongation of ARIQ3 (331.7±20.2 ms vs 366.2±20.2 ms, p=0.002) but the extension of ARIQ3 values did not differ between pre and post ajmaline administration (22.1% vs 21.9%, p=0.85).

PVS- patients had an average ARIc of 318.5±24.3 ms and an average ARIQ3 of 349.2±26.4 ms; PVS+ patients had an average ARIc of 309.8±35.5 and an average ARIQ3 of 339.8±39.1 ms. There were no differences for ARIc nor for ARIQ3 between these two groups (p=0.48 and p=0.61, respectively).

RVAT values are summarized in **Table 2**. No significant differences in RVAT between OType1 and pre-ajmaline LType1 (p=0.19) were found. Considering LType1 subjects, ajmaline administration induced a significant prolongation of RVAT (89±13 vs 101±22.5 ms, p=0.02).

Tpec values, assessed in patients with type-1 ECG pattern (OType1 and post-ajmaline LType1), are summarized in **Table 2**. In OType1 patients average Tpe was 74±9.5 ms while average Tpec was 78.3±12.8 ms. Post-ajmaline LType1 patients had an average Tpe 86.5±11.7 ms and Tpec of 98.3±12.9 ms. A significant difference between groups was present both for Tpe and Tpec ($p=0.002$ and $p<0.001$, respectively).

Correlation analysis

Correlation plots are reported in **Figure 4** and in **Figure 5**. In the whole type-1 ECG BrS population a significant linear correlation was found between median ARIc and RVAT ($r=0.34$; $p=0.04$) (**Figure 4)** and between median ARIc and Tpec ($r=0.60$; $p<0.001$) (**Figure 5**). The correlation between ARIc and RVAT was weak but its significance increased considering OType1 patients ($r=0.55$; $p=0.008$).

The correlation between median ARIc and Tpec was even more significant considering OType1 patients ($r=0.65$ with $p<0.001$). Interestingly, in this population, a strong correlation was found between ARIQ3 values and Tpec ($r=0.73$; $p<0.001$).

Discussion

In this study we present a novel automated algorithm to evaluate repolarization maps through high-density point-by-point ARI analysis on endocardial UEGs in a BrS population. The main findings are the following:

1. BrS subjects, both with latent and overt type-1 phenotype, exhibited zones of marked repolarization dispersion in RVOT, highlighted by longer ARIc values than controls;

2. Type-1 phenotype evoked by sodium channel blockade was associated with a marked increase of repolarization dispersion coherently with a remarkable mean ARIc prolongation;

3. BrS type-1 phenotype showed prolonged ARIc values mainly in the anterior wall of RVOT;

4. A linear correlation was present between mean ARIc and RVAT and between mean ARIc and Tpe interval in BrS patients with type-1 ECG, especially in those with overt rather than ajmaline-induced type-1 phenotype.

Activation Recovery Interval

The repolarization hypothesis has been demonstrated on animal models[22], while data supporting this hypothesis in BrS patients are scarce. ARI evaluated by UEGs estimates local action potential duration[8,23] and represents a measure of repolarization properties of local myocardium. Previous studies have demonstrated

the existence of dispersion of repolarization in BrS patients with type-1 ECG phenotype[11,12,24]. By creating high-density ARI maps, we found differences in spatial repolarization in RVOT among healthy control subjects, BrS patients with an overt type-1 pattern and those with a latent type-1 pattern. It is known that in the healthy heart, the normal propagation of the impulse generates a gradient of ARIs from the apex to the base, with the early activating regions having the longest ARI and the late activating regions having the shortest. This enables a spatial synchronization of repolarization time which prevents reentry phenomena[25]. ARI maps in controls (**Figure 1**) revealed a relatively homogenous distribution, with zones of longer ARI in the anterior part of RVOT. BrS subjects exhibited mean ARIc and localized ARIQ3 values significantly longer than controls, both in OType1 and LType1. Ajmaline administration induced a significant prolongation of mean ARIc and a marked increase of localized ARIc as represented by ARIQ3 analysis. Our data are in line with other studies, demonstrating an impact of RVOT repolarization dispersion on the genesis of type-1 phenotype in BrS[11,23]. Nagase et al.[11] assessed ARIc from UEGs in the endocardial and epicardial RVOT of 19 BrS subjects undergoing pilsicainide; they reported a prolongation of ARIc after pilsicainide administration specifically in epicardial RVOT rather than in the endocardium. We found, instead, a significant impact of ajmaline administration in endocardial ARI dispersion. This could be explained by the high density of points analyzed,

which allows a detailed repolarization map enhancing even small differences between RVOT and nearby zones. Furthermore, a possible aggregation of action potentials in the epi-endocardial layers may create a sort of "averaging effect".

Comparing type-1 phenotype populations, we observed that patients undergoing ajmaline infusion presented significantly longer ARIc values than those with spontaneous BrS pattern. It is known that a prolongation of ARIc may be due to the presence of an increase in transient potassium outward current, which produces a deep phase-1 notch and a preferential epicardial prolongation of action potentials (depending on the extent of the phase-0 depolarization upstroke). Such current is mainly expressed in RVOT rather than other RV or left ventricle zones in BrS subjects[11]. A possible explanation of this impact of sodium-channel blockade in inducing greater prolongation of ARIs with respect to OType1 could be due to the extent of the sodium channels blocked inducing a variable degree of repolarization of RVOT wall and a consequent different impact on the transient potassium outward current: while in spontaneous type-1 subjects only a part of these channels might be inactive, in ajmaline-induced type-1 pattern all sodium channels available might be virtually blocked provoking a sort of "extremization response".

Correlation analysis

Considering BrS population with type-1 ECG (OType1 and post-ajmaline LType1 subjects), a linear correlation was found between ARIc and RVAT (r=0.34; p=0.038). The significance of this correlation increased considering patients with spontaneous type-1 phenotype (r=0.54; p=0.008). No correlation between ARIc and RVAT was found in post-ajmaline LType1 subjects. The relationship between RV conduction abnormalities and repolarization dispersion in BrS is scarcely investigated in literature. Some studies supported the conclusion that BrS phenotype was generated by conduction delay in RVOT, as depolarization dispersion assessed through localized ARI prolongation in RVOT was not related to J-point elevation on ECG[13]. The authors concluded that the presence of localized conduction slowing, late and fragmented potentials in the epicardial RVOT were secondary to conduction delays, supporting the "depolarization hypothesis"[26,27]. Other authors observed a predominant role of repolarization abnormalities: the association of localized "loss of dome" during in phase-1 and prolongation of action potential in other zones may induce a concealed phase-2 reentry, which accounted for epicardial fractionated and late potentials[28,29]. Our data confirm the relationship between repolarization dispersion and RV conduction, mostly in OTtype1 patients. No correlation was observed between ARIc and RVAT in post-ajmaline LType1.

This study shows a significant linear correlation between ARIc and Tpec (r=0.60; p<0.001) in the whole type-1 ECG BrS population. This correlation is

mainly driven by OType1 patients ($r=0.65$ with $p<0.001$) while no relationship between ARIc and Tpe was seen in post-ajmaline LType-1 subjects. Yan and Antzelevitch were the first to suggest the use of the Tpe interval as a measure of transmural dispersion of repolarization[30]. Given that Tpe interval is an accepted marker of repolarization dispersion, the good linear correlation between Tpec and ARIc observed in our study confirms the reliability of our model in the high-density repolarization mapping. This concept is furthermore supported by the good correlation between ARIQ3 and Tpec ($r=0.73$; $p<0.001$).

Clinical studies have demonstrated that Tpe prolongation was significantly associated with a high risk of ventricular tachyarrhythmias and/or SCD in BrS[31,32]. Moreover, a recent meta-analysis including 1740 BrS patients demonstrated that high-risk BrS individuals present longer Tpe intervals[21,22]. Interestingly, the presence of a linear correlation between ARIc and Tpec especially in OType1 patients seems coherent with the known prognostic role of spontaneous type-1 ECG pattern.

Finally, differences in ARIc were seen when considering PVS+ and PVS- patients. Both patients of our cohort who experienced arrhythmic events were PVS- and presented a spontaneous type-1 ECG. This observation is in line with previous studies that questioned the role of PVS alone in the prognostic evaluation of BrS patients[33,34] paving the way to a multiparametric model of risk stratification

considering clinical and electrophyiological parameters, especially in asymptomatic BrS with a spontaneous type-1 ECG.

Study limitations

This study has relevant limitations. Firstly, we did not perform epicardial mapping and ARIs were estimated from endocardial unipolar electrograms. ARIc and Tpec calculations were automatized, however they required the inspection of an operator to recognize signals that could not be analyzed or errors committed by the code (mostly because of the variable morphologies of T wave). Background noise was responsible for discarding 1 lead in 8 cases for Tpe calculation. Moreover, this study is limited by the low number of arrhythmic events at follow-up, which prevented us from directly evaluating the prognostic value of ARI mapping. Lastly, the low rate of SCN5A mutation carriers did not allow an evaluation of ARIs selectively in this group.

Conclusion

ARIc mapping through a high-density endocardial UEG analysis demonstrates an increase in local repolarization dispersion in RVOT of BrS subjects. In BrS patients with type-1 ECG, especially in OType1, ARIc positively correlates with abnormal RV depolarization and repolarization dispersion on surface

ECG (through Tpe analysis), unveiling the abnormal electrical substrate. Further studies are needed to evaluate the prognostic impact of ARI mapping in a multiparametric model including other clinical and electrophysiological parameters, especially in asymptomatic BrS patients.

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Table 1

	BrS (n=39)	OType1 (n=24)	LType1 (n=15)
Age	41±11	41±11	41±12
Male	33 (85%)	21 (88%)	12 (80%)
Family history of BrS	6 (13%)	3 (13%)	2 (13%)
Family history of SCD	7 (18%)	4 (17%)	3 (20%)
Symptoms	22 (56%)	13 (54%)	9 (60%)
VT/VF during follow-up	2 (5%)	1 (4%)	1 (7%)
Syncope	12 (31%)	6 (25%)	6 (40%)
ICD	19 (49%)	13 (54%)	6 (40%)
Appropriate shock	1 (3%)	–	1 (7%)
Inappropriate shock	1 (3%)	1 (4%)	–
Infection	1 (3%)	1 (4%)	–

Table 2

	Controls (n=4)	OType1 (n=24)	Pre-ajmaline LType1 (n=15)	Post-ajmaline LType1 (n=15)
Mean ARIc	281.7±10.3 ms	306±27.3 ms	303.4±20.7 ms	333.3±16.3 ms
Mean ARIQ3	312.7±15.1 ms	335.1±28.3 ms	331.7±23.3 ms	366.2±20.2 ms
Thrid quartile (% ROI)	22.8%	23.1%	22.1%	21.9%
RVAT	75±7.5 ms	111±44.3 ms	89±13 ms	101±22.5 ms
Tpec	–	78.3±12.8 ms	–	98.4±12.9 ms

Figure 1. ARIc maps.
Examples of ARIc maps of **(A)** subject 8 (control, mean ARIc 275.2 ms), **(B)** subject 6 (OType1 with an arryhthmic event at follow-up, mean ARIc 323.9 ms), **(C)** subject 28 (OType1, mean ARIc 320.4 ms) and subject 52 (**(D)** pre-ajmaline LType1 and **(E)** post-ajmaline LType1, mean ARIc 301 ms and 340.7 ms). The control patient presents shorter and more omogeneous ARIc values compared to BrS patients. Ajmaline administration determines a prolongation of ARIc in subject 52. Zones of dispersion of repolarization are present in subject 6, subject 28 and subject 52 (pointed by the black arrows).
Ajm = ajmaline. ARIc = Activation Recovery Interval corrected for the Bazett formula. BrS = Brugada Syndrome. LType1 = latent type-1 BrS patient. OType1= overt type-1 BrS patient.

Figure 2. ARIQ3 maps.
Example of ARIQ3 maps of subject 6 (OType1with an arryhthmic event at follow-up), **(C)** subject 28 (OType1) and subject 52 (**(D)** pre-ajmaline LType1 and **(E)** post-ajmaline LType1). ARIQ3 zones are specifically located in the anterior and subpulmonary portion of RVOT.
Ajm = ajmaline. ARIQ3 = Activation Recovery Interval at 75% of the ARI distribution corrected for the Bazett formula. BrS = Brugada Syndrome. LType1 = latent type-1 BrS patient. OType1= overt type-1 BrS patient.

Figure 3. Boxplot of ARIc differences between groups.
Boxplot showing the differences of ARIc between controls, pre-ajmaline LType1 and OType1 (left panel), and pre-ajmaline and post-ajmaline LType1 patients (right panel). OType1 patients had significantly longer ARIc values compared to controls ($p=0.05$). No significant differences were observed between pre-ajmaline LType1 and controls ($p=0.07$), nor between OType1 and LType ($p=0.83$). Ajmaline administration determined a significant prolongation of ARIc in LType1 patients ($p<0.001$).
For statistical analysis between groups ANOVA test with Tukey's range test for *post-hoc* analysis was used. To compare ARIc values between pre-ajmaline and post-ajmaline LType1 paired t-test test was used.
Ajm = ajmaline. ARIc = Activation Recovery Interval corrected for the Bazett formula. LType1 = latent type-1 BrS patient. OType1= overt type-1 BrS patient.

Figure 4. Correlation plots between RVAT and ARIc.
Graphs showing the correlation between RVAT and ARIc in **(A)** patients with BrS pattern (OType + post-ajmaline LType patients), **(B)** OType patients, **(C)** pre-ajmaline LType patients and **(D)** post-ajmaline LType patients. A significant correlation between these variables was seen both in BrS ($p=0.04$) and in OType1 patients ($p<0.008$). For correlation analysis the Spearman coefficient was used.
Ajm = ajmaline. ARIc = Activation Recovery Interval corrected for the Bazett formula. BrS = Brugada Syndrome. LType1 = latent type-1 BrS patient. OType1= overt type-1 BrS patient. RVAT = right ventricular activation time.

Figure 5. Correlation plots between Tpec and ARIc.
Graphs showing the correlation between Tpec and ARIc in **(A)** patients with BrS pattern (OType + post-ajmaline LType patients), **(B)** OType patients, and **(C)** post-ajmaline LType patients. A significant correlation between the variables was seen both in BrS ($p<0.001$) and in OType1 patients ($p<0.008$).
For correlation analysis the Pearson R coefficient was used.
Ajm = ajmaline. ARIc = Activation Recovery Interval corrected for the Bazett formula. BrS = Brugada Syndrome. LType1 = latent type-1 BrS patient. OType1= overt type-1 BrS patient. Tpec= Tpeak-Tend interval corrected for the Bazett formula.

Supplemental materials

Figure 6. Boxplot of ARIc differences based on PVS results.

Comparison of ARIc values between controls, PVS+ and PVS- patients. PVS- have significantly longer ARIc compared to controls (p=0.01).

For statistical analysis Kruskal-Wallis test with Fisher test for *post-hoc* analysis was used.

ARIc = Activation Recovery Interval corrected for the Bazett formula. PVS: programmed ventricular stimulation.