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# Association between the number of altered late potential criteria and increased arrhythmic risk in Brugada syndrome patients

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## Abstract

**Background** Brugada syndrome (BrS) is associated with abnormal electrophysiological properties at right ventricular epicardium, consisting of fragmented electrograms extending well beyond QRS termination. We aimed to evaluate the utility of signal-averaged electrocardiogram (SA-ECG) for the noninvasive assessment of late potentials (LP) and risk stratification of BrS patients.

**Methods** A prospective, observational, single-center study of BrS patients is submitted to SA-ECG with the determination of the total filtered QRS duration (fQRS), root mean square voltage of the 40 ms terminal portion of the QRS (RMS40), and duration of the low-amplitude electric potential component of the terminal portion of the QRS (LAS40). LP were considered positive when above standard cut-offs: fQRS > 114 ms, RMS40 < 20 μV, and LAS40 > 38 ms. The rates of malignant arrhythmic events (MAEs), defined as sudden death or appropriate shocks, were compared in relation to clinical characteristics and SA-ECG findings.

**Results** A total of 106 BrS patients (mean age, 48 ± 12 years, 67.9% male) were studied, 49% with type-1 spontaneous pattern and 81% asymptomatic. During a median follow up of 4.7 years, 10 patients (7.1%) suffered MAEs, including 4 sudden deaths. The presence of LP was significantly associated with the arrhythmic risk, which increased with the number of altered LP criteria. In comparison to the patients who had none or 1 altered LP criterium, MAE risk was 4.7 times higher in those with 2 altered criteria and 9.4 times higher in those with 3 altered LP criteria.

**Conclusions** SA-ECG may be a useful tool for risk stratification in BrS. The presence of 2 or 3 abnormal LP criteria could identify a subset of asymptomatic patients at high risk of arrhythmic events.

**Keywords** Brugada syndrome · Late potentials · Signal-averaged ECG

## Abbreviations

| | |
|---|---|
| BrS | Brugada syndrome |
| fQRS | Total filtered QRS duration |
| ICD | Implantable cardiac defibrillator |
| LP | Late potentials |
| $LAS_{4o}$ | Low amplitude electric potential component of the terminal portion of the QRS |
| MAE | Malignant arrhythmic events |
| $RMS_{40}$ | Root mean square voltage of the 40 ms terminal portion of the QRS |
| RVOT | Right ventricular outflow tract |
| SA-ECG | Signal-averaged electrocardiography |
| SCD | Sudden cardiac arrest |

## 1 Introduction

Brugada syndrome (BrS) is a channelopathy associated with an increased risk of sudden cardiac death (SCD) in young adults, diagnosed by a coved ST-segment elevation on right precordial leads [1].

Current guidelines recommend implantation of an implantable cardiac defibrillator (ICD) in patients with prior cardiac

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arrest or documented ventricular arrhythmia and may be considered after a suspected arrhythmogenic syncope [2]. In opposition, the management of asymptomatic patients is still undefined. Acknowledging that the first symptomatic presentation may occur with fatal dysrhythmic event emphasizes the importance of improving BrS risk stratification [3].

Over the last decade, evidence from mapping studies suggested that BrS substrate relies on the abnormal electrophysiological properties of right ventricular epicardium, particularly in the right ventricle outflow tract (RVOT) and anterior free wall regions [4–8]. In these areas, abnormal electrograms have been consistently described, characterized by low voltage, fragmentation, and long duration, lasting far longer than the surface QRS complex [4–8]. The degree of electrogram fragmentation [5] and extent of substrate area were correlated with the exuberance of the type 1 pattern [7], and their elimination has shown to both normalize the baseline ECG pattern, as well to significantly reduce arrhythmic events on long-term follow-up [4, 7–9].

Considering the pathophysiological relevance of the abnormal electrophysiological properties of right ventricular epicardium, different techniques are being explored for their noninvasive detection and quantification. Signal-averaged electrocardiography (SA-ECG) is a signal-processing technique that allows the detection of subtle abnormalities in the surface ECG, including low-amplitude signals at the terminus of the QRS complex, usually referred to as "late potentials" (LP). SA-ECG has been explored to identify patients at risk of SCD, particularly in the context of coronary heart disease [10] or arrhythmogenic right ventricular cardiomyopathy [11].

In patients with BrS, the presence of LP evaluated with SA-ECG was found to be correlated with the extent of the arrhythmogenic substrate determined by invasive epicardial mapping [12].

In addition, the documentation of LP was suggested to be associated with an increased risk of arrhythmic events in BrS patients [13–15]. However, the role of SA-ECG in BrS risk stratification remains undefined.

In this study, our primary goal is to clarify the value of LP evaluated with SA-ECG for risk stratification in BrS. Additionally, we aim to test whether the assessment of LP using an adapted location of the surface leads, focused on the RVOT region, has the potential to improve the non-invasive detection of abnormal signals in the context of BrS.

## 2 Methods

### 2.1 Study design

Single-center, prospective, observational cohort study of BrS patients followed in the Santa Maria University Hospital fulfilling the following criteria (1) type 1 Brugada ECG pattern, either spontaneous or drug induced; (2) SA-ECG performed before antiarrhythmic treatment, namely quinidine therapy or epicardial RV ablation (3) minimum follow up of 12 months.

BrS was defined according to current guidelines, considered either the presence of a spontaneous type-1 pattern documented on conventional or modified right precordial leads, or a positive provocative test with intravenous administration of a sodium channel blocker, namely ajmaline or flecainide [2, 16]. Patients were classified as having a spontaneous type 1 pattern if such electrocardiographic pattern was recognized at inclusion or during follow-up.

All patients underwent a standardized evaluation, which included clinical interview, family history characterization, genetic testing, exclusion of overt underlying structural heart disease by transthoracic echocardiogram, exercise stress testing, and 24-h Holter. Additionally, patients with history of syncope suggestive of a vasovagal etiology were submitted to Tilt test.

Up to 2021, programmed ventricular stimulation with up to 2 extra beats both at right ventricular apex and RVOT was performed to patients with unclear symptoms or high-risk familial history. Since 2021, it was also offered to all asymptomatic patients with spontaneous type-1 pattern. A positive result was considered if ventricular fibrillation was induced, and an ICD was subsequently implanted. Decision to implant an ICD was based on the European Society of Cardiology guidelines [2, 17] and a shared decision-making process.

In any circumstances, the decision to implant an ICD to perform programmed ventricular stimulation or to conduct any other diagnostic exams was modified because of the SA-ECG result, which was always approached as a research tool.

### 2.2 Late potentials

LP were analyzed using a SA-ECG system (SpiderView™ recorder, MicroPort®, China), from signals acquired during 30 min in the supine position. The analysis was based on the quantitative time domain measurements of the filtered vector magnitude of orthogonal Frank X, Y, and Z leads. Additionally, surface ECG signals were simultaneously acquired from modified leads, focusing on the RVOT area (Supplemental Fig. 1). A total of 300 beats with noise < 1 μV were amplified, digitized, averaged, and filtered with a high pass filter (40 Hz). Three parameters were assessed via a computer algorithm: (1) the filtered QRS duration (fQRS), (2) the root mean square voltage of the 40 ms terminal portion in the filtered QRS complex ($RMS_{40}$), and (3) the duration of the low-amplitude signals < 40 μV in the terminal filtered QRS complex ($LAS_{40}$). The SA-ECG analysis was performed blinded to the clinical data.

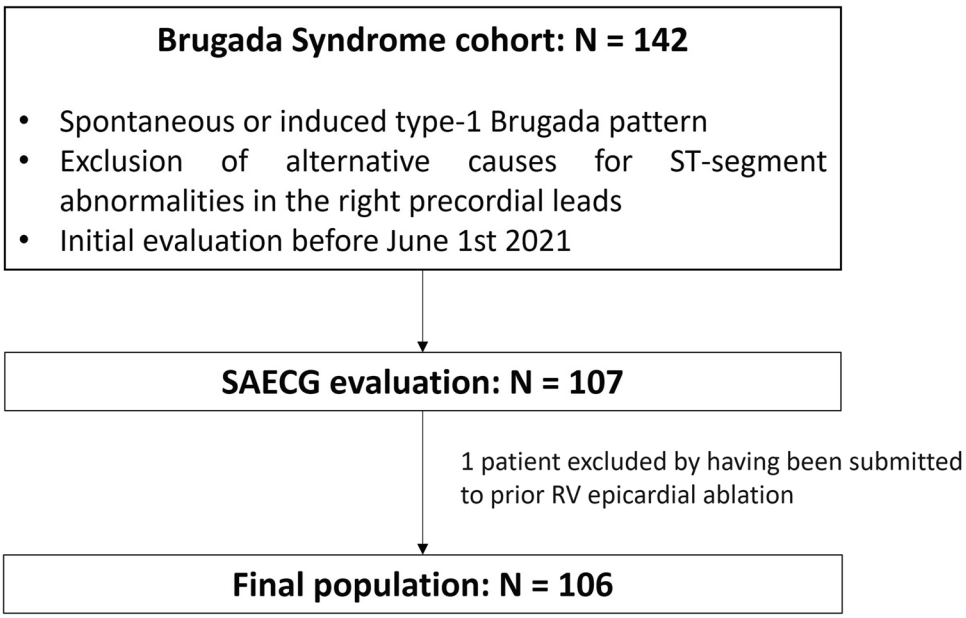



**Fig. 1** Population flow chart

### 2.3 Study endpoints

The study primary endpoint was the occurrence of malignant arrhythmic events (MAE), defined as a composite of SCD or appropriate ICD shocks due to polymorphic ventricular tachycardia or ventricular fibrillation.

### 2.4 Statistical analysis

Continuous variables were described by the mean and standard deviation for normally distributed data or median and interquartile range (IQR) for non-normally distributed data, and categorical variables were expressed as counts or percentages.

Survival analyses were performed to estimate the risk of MAEs considering the full duration of follow up, as well as the adjusted event-rate at 5 years. Univariate Cox regression survival analyses were performed to determine the association between MAE and relevant risk factors based on prior studies, namely, prior malignant arrhythmia, prior syncope, prior syncope presumably of arrhythmic cause, spontaneous type 1 pattern, male gender, family history of SCD and SCN5A mutation, presence of right bundle branch block, and SA-ECG parameters analyzed both as continuous variables and as categorical variables—tested with the following pre-specified thresholds: tertile distribution and standard cut-offs classically applied for risk stratification in the context of structural heart disease (fQRS > 114 ms, RMS40 < 20 µV, LAS40 > 38 ms). Multicollinearity between LPs was assessed with regression analysis. The impact of the number of altered LP criteria in the arrhythmic risk and its usefulness for prognostic stratification was explored using Kaplan Meier survival analysis. For this analysis, positive LP criteria were defined by the standard cut-offs, using the recordings in conventional leads.

All analyses were 2-sided and a $P$-value < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS 26.0 (SPSS, Inc., Chicago, IL, USA).

## 3 Results

### 3.1 Population characterization

A total of 106 patients fulfilled the prespecified inclusion criteria, out of a population of 142 patients—Fig. 1. Table 1 summarizes the baseline characteristics of patients. The mean age was 48 ± 12 years, and there was a male predominance of 67.9%. A spontaneous type 1 pattern was recognized in 48 patients (45.3%). At inclusion, 81.1% were asymptomatic; 13 (12.3%) had prior syncope; 3 (2.8%) had suffered cardiac arrest; and 4 (3.8%) had other symptoms such as presyncope, nocturnal agonal respiration, or seizures. An ICD was implanted at initial evaluation in 7 patients, 3 due to aborted cardiac arrest, and in 4 due to suspected arrhythmogenic syncope.

Of note, 12.3% of patients had family history of BrS and 14.2% presented family history of SCA. The results of genetic tests were available in 99 patients, by direct sequencing of the SCN5A gene in 77 patients (72.6%) and by a 110 gene panel in 22 patients (20.8%), and a pathogenic or likely pathogenic mutation was documented in 11 (10.4%).

**Table 1** Characterization of the population

| Population characteristics | $N=106$ |
|---|---|
| Age, years (mean ± SD) | 48 ± 12 |
| Male gender, *n* (%) | 72 (67.9) |
| Symptomatic status | |
| Asymptomatic, n (%) | 86 (81.1) |
| Prior syncope, n (%) | 13 (12.3) |
| Suspected arrhythmogenic, n (%) | 8 (7.5) |
| Likely vasovagal, n (%) | 5 (4.7) |
| Prior malignant arrhythmic event, n (%)* | 3 (2.8) |
| Other BrS-related symptoms, n (%) | 4 (3.8) |
| Brugada pattern | |
| Spontaneous type 1, *n* (%) | 48 (45.3) |
| Drug-induced type 1, *n* (%) | 58 (54.7) |
| Intraventricular conduction disturbances | |
| QRS duration > 120 ms, *n* (%) | 19 (17.9) |
| Familial and genetic background | |
| Familial history of Brugada syndrome, *n* (%) | 13 (12.3) |
| Familial history of SCA, *n* (%) | 15 (14.2) |
| Pathogenic or likely pathogenic SCN5A mutation, *n* (%)** | 11 (10.4) |
| Programmed ventricular stimulation | 51 (48.1) |
| Induction of VT/VF, *n* (%) | 21/51 (41.2) |
| No induction of VT/VF, *n* (%) | 30/51 (58.8) |
| ICD at study inclusion, *n* (%) | 7 (6.6) |
| Aborted cardiac arrest, *n* (%) | 3 (2.8) |
| Suspected arrhythmogenic syncope, n (%) | 4 (3.8) |

*Malignant arrhythmic event defined as a composite of sudden cardiac death and appropriate ICD shocks due to VT or VF

**Genetic testing performed in 99 patients by direct sequencing of the SCN5A gene (77; 72.6%) or by a 110 genes panel (22; 20.8%)

*ICD* implantable cardiac defibrillator, *SCA* sudden cardiac arrhythmia, *SD* standard deviation, *VT* ventricular tachycardia, *VF* ventricular fibrillation

## 3.2 Clinical outcomes

The median follow-up was 4.7 years (95%CI: 3.9–5.5 years). A total of 10 patients (7.1%) suffered malignant arrhythmic events during follow-up, 4 (3.7%) with SCD, and 6 (5.6%) with appropriate ICD shocks—Table 2. All the 4 patients who died were previously asymptomatic, 1 had a spontaneous type-1 pattern, and 3 had a drug-induced pattern.

In addition to the 7 patients who were submitted to ICD implantation at the time of initial evaluation, 18 patients received an ICD during follow-up. Table 3 presents the indications for ICD implantation.

Three patients with recurrent MAE were treated with quinidine and 2 of them underwent epicardial right ventricular ablation. The 2 patients submitted to ablation had no further arrhythmic recurrences.

**Table 2** Clinical outcomes during long-term follow up

| Events | Total | Estimated 5-year event rate |
|---|---|---|
| Malignant arrhythmic events, *n* (%) | 10 (9.4) | 7.4% |
| Sudden cardiac death, *n* (%) | 4 (3.7) | 2% |
| Appropriate ICD shock, *n* (%) | 6 (5.6) | 5.4% |
| Suspected arrhythmogenic syncope | 2 (1.9) | |

*ICD* implantable cardiac defibrillator

## 3.3 Impact of risk factors on malignant arrhythmic events

A significantly higher risk of MAE was observed in patients with a spontaneous type 1 pattern (HR, 4.759; 95% CI, 1.025–22.091; $p=0.046$). Nevertheless, the risk of MAE did not differ in relation with gender ($p=0.624$), prior syncope ($p=0.212$), likely arrhythmogenic syncope ($p=0.357$) or existence of a pathogenic SCN5A mutation ($p=0.616$)—Supplemental Fig. 2.

The risk of events differed significantly in relation to SA-ECG parameters—Table 4 and Fig. 2, and all LP variables either on conventional or modified leads were significant predictors of MAE in univariate analyses, with the single exception for $RMS_{40}$ evaluated on conventional leads, which nearly reached statistical significance ($p=0.054$). Furthermore, all the standard LP cut-offs (fQRS > 114 ms, $RMS_{40}$ < 20 μV, $LAS_{40}$ > 38 ms), either on conventional or modified leads, were significantly associated with an increased risk of MAE during follow-up—Fig. 3. No differences were observed regarding the SA-ECG characteristics comparing the evaluations performed on conventional or modified thoracic leads ($p=$ NS). Additionally, LP did not present significant multicollinearity.

Presence of right bundle branch block was observed in 19 patients (17.9%), who were at increased risk of MAE (HR, 6.97; 95% CI, 1.86–26.16; $p=0.004$)—Supplemental Fig. 2. These patients often presented positive LP criteria, namely fQRS > 114 ms (73.7% versus 22.4%, $p<0.001$) and RMS < 20 μV (89.5% versus 57.6%, $p=0.009$).

The risk of MAE during follow-up was 4.7 higher in the presence of 2 altered LP criteria (observed in 37 patients) and increased 9.4 times in the 31 patients who had 3 positive LP criteria—Fig. 4. The presence of at least 2 positive LP criteria and prior history of arrhythmic events were the only independent predictors of MAE in an exploratory multivariate Cox regression analysis, remaining significant after adjustment for the presence of spontaneous type 1 BrS pattern, syncope, or positive genetic test—Supplemental Table 1.

Considering the presence of at least 2 positive LP criteria as an indication for ICD implantation would result in a 100% sensitivity to prevent SCD, but the specificity would

**Table 3** Reasons for implantable cardiac defibrillator implantation (at initial evaluation or during follow up)

| Events | At initial evaluation ($N=7$) | During follow up ($N=20$) | Total population ($N=106$) |
|---|---|---|---|
| Aborted cardiac arrest, *n* (%) | 3 (2.8) | | 3 (2.8) |
| Suspected arrhythmic syncope, *n* (%) | 4 (3.8) | 2 (1.6) | 6 (5.7) |
| Type 1 pattern, unexplained syncope, and inducible ventricular fibrillation during programmed ventricular stimulation, *n* (%) | - | 4 (3.8) | 4 (3.8) |
| Type 1 pattern, no symptoms, but inducible ventricular fibrillation during programmed ventricular stimulation, *n* (%) | - | 12 (11.3) | 12 (11.3) |

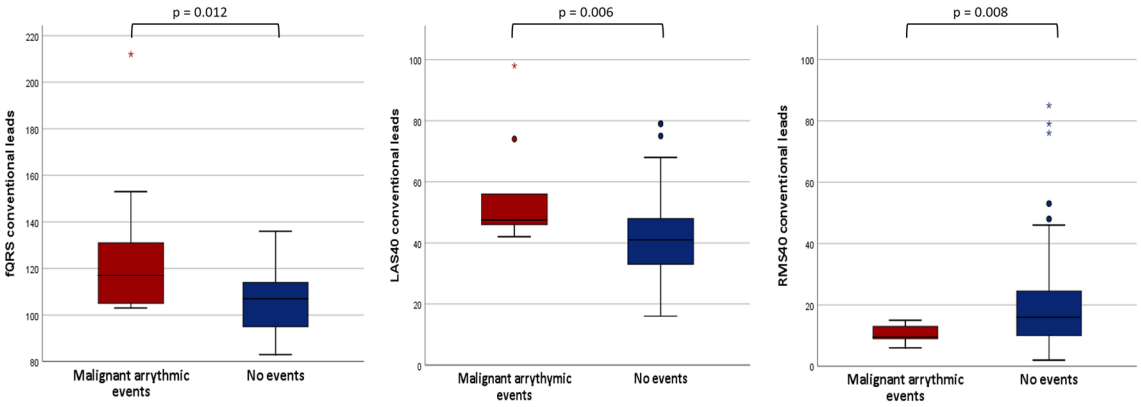



**Fig. 2** Distribution of the signal-averaged ECG characteristics according to the occurrence of malignant arrhythmic events during follow-up

be of only 39.6%, whereas 3 altered LP criteria presented a sensitivity of 70% and a specificity of 75% in identifying patients at risk of MAE. If the decision-making process for ICD implantation would have included the presence of 3 positive LP criteria on top of current recommendations, a 2.8% absolute risk reduction and a 75% relative risk reduction in the chances of SCD would have occurred, due to the prevention of SCD in three patients. This benefit would occur at the expense of an increased device implantation rate of 24 to 38% (15 patients) and thus would reflect one life saved per each five additional ICDs implanted—Fig. 5

## 4 Discussion

The main finding of this study is that the determination of LP by non-invasive assessment with SA-ECG is useful for prognostic stratification in BrS patients. Confirming prior studies [12, 15], the presence of LP, defined by fQRS > 114 ms, $RMS_{40}$ < 20 µV or $LAS_{40}$ > 38 ms, was significantly associated with MAE during follow-up. For the first time, we demonstrated that the arrhythmic risk increased with the number of altered LP criteria, reflecting a stepwise 4.7-fold incremental risk. Furthermore, the presence of ≥ 2 altered LP was found to be an independent risk predictor, and incorporating the presence of 3 positive LP in the decision-making process for ICD implantation on top of current recommendations would have decreased by 75% the occurrence of SCD (absolute risk reduction of 2.8%), meaning one life saved per each five additional implanted ICDs.

Over the last decade, several studies involving high-resolution epicardial mapping have expanded the understanding of BrS pathophysiology, with the documentation of abnormalities in the electrophysiological properties of the subepicardial cardiomyocytes at RVOT and anterior RV free wall. These manifest as fragmented electrograms, with low voltage and very prolonged duration, extending well beyond the QRS complex termination [4, 6]. Such arrhythmogenic substrate was found to be dynamic, being exacerbated in response to BrS triggers, such as fever or ajmaline infusion [5, 6, 18]. Furthermore, the arrhythmogenic substrate area dimensions were larger in the presence of a type-1 ECG pattern [7], in the patients with prior arrhythmic symptoms [7] and in the ones in whom programmed ventricular stimulation induced ventricular fibrillation [18, 19]. Pappone and collaborators have also correlated the extent of the arrhythmogenic substrate with the RV ejection dysfunction evaluated by 3D echo after ajmaline infusion [20]. Furthermore, radiofrequency ablation resulted in abolishment of the fragmental electrograms, normalization

**Table 4** Association of demographic, clinical, and signal-averaged ECG characteristics with the occurrence of malignant arrhythmic events during follow up

| Risk factor | Arrhythmic events ($N=10$) | No arrhythmic events ($N=96$) | Univariate Cox regression analysis | |
|---|---|---|---|---|
| | | | Hazard ratio (95% CI) | *P*-value |
| Male gender, *n* (%) | 8 (80) | 64 (66.7) | 1.48 (0.31–7.06) | 0.624 |
| Prior syncope, *n* (%) | 2 (20) | 11 (11.5) | 0.02 (0.00–9.51) | 0.212 |
| Suspected arrhythmogenic, *n* (%) | 2 (20) | 6 (6.3) | 2.063 (0.431–9.861) | 0.364 |
| Prior malignant arrhythmic event*, *n* (%) | 3 (30) | 0 | 43.34 (8.60–218.29) | < 0.001 |
| Spontaneous type 1, *n* (%) | 7 (70) | 41 (42.7) | 4.759 (1.025–22.091) | 0.046 |
| Familial history of Brugada syndrome, *n* (%) | 0 | 14 (14.6) | 26.03 (0.14–47,283.74) | 0.395 |
| Familial history of SCA, *n* (%) | 1 (10) | 13 (13.5) | 0.58 (0.08–4.51) | 0.606 |
| SCN5A mutation, *n* (%)** | 1 (10) | 10 (10.4) | 0.58 (0.07–4.94) | 0.616 |
| RBBB, *n* (%) | 5 (50) | 5 (5.2) | 6.969 (1.857–26.159) | 0.004 |
| SAECG evaluation | | | | |
| fQRS conventional leads, median (IQR) | 117 (105–147) | 107 (95–114) | 1.04 (1.02–1.06) | < 0.001 |
| $RMS_{40}$ conventional leads, median (IQR) | 9 (7–12) | 17 (12–26) | 0.87 (0.76–1.002) | 0.054 |
| $LAS_{40}$ conventional leads, median (IQR) | 47 (45–50) | 39 (32–47) | 1.09 (1.04–1.14) | 0.001 |
| QRSf modified leads, median (IQR) | 118 (11–153) | 107 (96–113) | 1.03 (1.02–1.05) | < 0.001 |
| $RMS_{40}$ modified leads, median (IQR) | 8 (7–10) | 18 (11–27) | 0.85 (0.73–0.99) | 0.031 |
| $LAS_{40}$ modified leads, median (IQR) | 48 (44–68) | 40 (31–49) | 1.09 (1.05–1.15) | < 0.001 |
| fQRS conventional leads > 114 ms | 7 (70) | 28 (29.2) | 4.995 (1.289–19.355) | 0.020 |
| $RMS_{40}$ conventional leads < 20 µV | 10 (100) | 58 (60.4) | 42.984 (0.178–10,342.452) | 0.179 |
| $LAS_{40}$ conventional leads > 38 ms | 10 (100) | 61 (63.5) | 39.965 (0.148–10,813.758) | 0.197 |
| $RMS_{40}$ modified leads > 114 ms | 7 (70) | 26 (28) | 4.924 (1.260–19.246) | 0.022 |
| $RMS_{40}$ modified leads < 20 µV | 10 (100) | 57 (61.3) | 40.551 (0.119–13,843.577) | 0.213 |
| $LAS_{40}$ modified leads > 38 ms | 10 (100) | 52 (55.9) | 44.435 (0.185–10,684.583) | 0.175 |

*fQRS* total filtered QRS duration, *IQR* interquartile range, $LAS_{40}$ low amplitude electric potential component of the terminal portion of the QRS, *RBBB* right bundle branch block, $RMS_{40}$ root mean square voltage of the 40 ms terminal portion of the QRS, *SAECG* signal-averaged electrocardiography

* Malignant arrhythmic event defined as a composite of sudden cardiac death and appropriate ICD shocks due to VT or VF

** Genetic testing performed in 99 patients by direct sequencing of the SCN5A gene (77; 72.6%) or by a 110 genes panel (22; 20.8%)

of surface ECG, and reduced arrhythmic risk during follow-up [4–7, 18]. Therefore, it has been hypothesized that the magnitude of these electrophysiological abnormalities may be correlated with the risk of SCD in BrS patients.

Electroanatomical mapping is the optimum method to evaluate the electrophysiological abnormalities at RVOT and anterior free wall epicardium. However, such invasive procedure implies epicardial access, which is associated with a relevant risk of serious and sometimes even deadly complications [21, 22]. Establishing a non-invasive method to detect and quantify such abnormal electrophysiological properties fulfills a clear unmet need, potentially improving the risk stratification in a population that is mostly asymptomatic.

In a prior study, Ciconte et al. [12] compared the SA-ECG findings with the arrhythmogenic substrate on electrophysiology study. They observed a strong association between the presence of LP on SA-ECG and the arrhythmogenic substrate extension and hypothesized that LP documented by SA-ECG may eventually identify the BrS patients who benefit from epicardial ablation [12].

We studied 106 BrS patients and followed them during a median of 4.7 years. Our population was predominantly composed by low-risk, asymptomatic (81%), with drug-induced type 1 pattern (55%), and without familiar history of SCD (86%) nor SCN5A mutations (90%). Nevertheless, 10 of them (9.4%) suffered MAE and 4 died due to sudden cardiac arrest. None of the 4 patients who died qualified for ICD implantation based on current guidelines [2], highlighting how suboptimal current stratification is in asymptomatic patients and the urgent need for additional diagnostic methods.

In our population, patients with prior cardiac arrest or documented arrhythmic events were at high risk of MAE, which is in accordance with many prior studies [23]. Similarly, patients with spontaneous type-1 pattern were at higher arrhythmic risk, and such ECG pattern was present in 7 out of the 10 patients who suffered arrhythmic events.

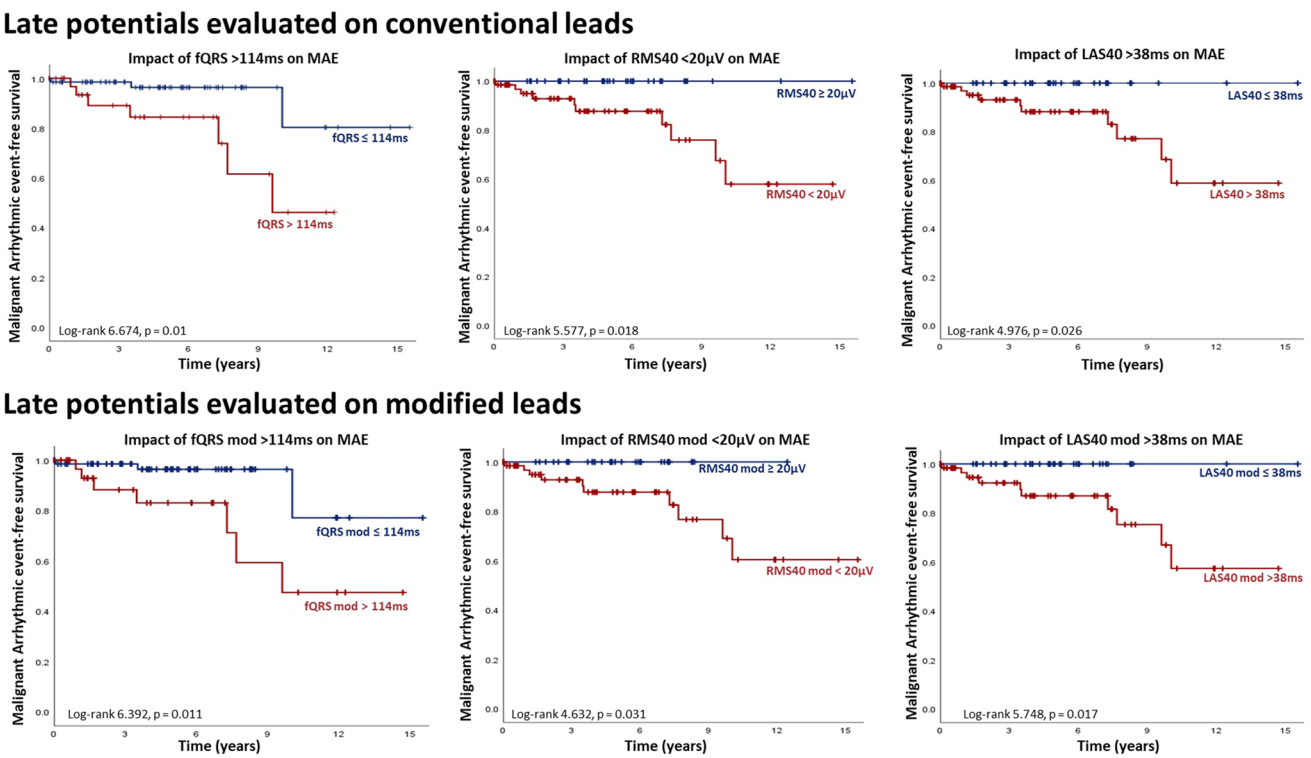



**Fig. 3** Long-term survival free from malignant arrhythmic events in relation to the presence of late potentials on signal-averaged ECG

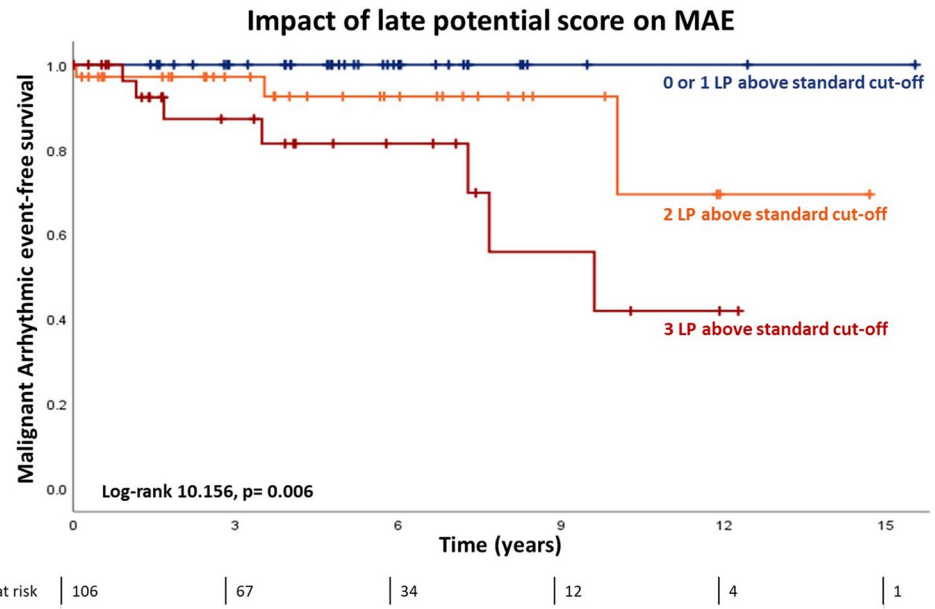
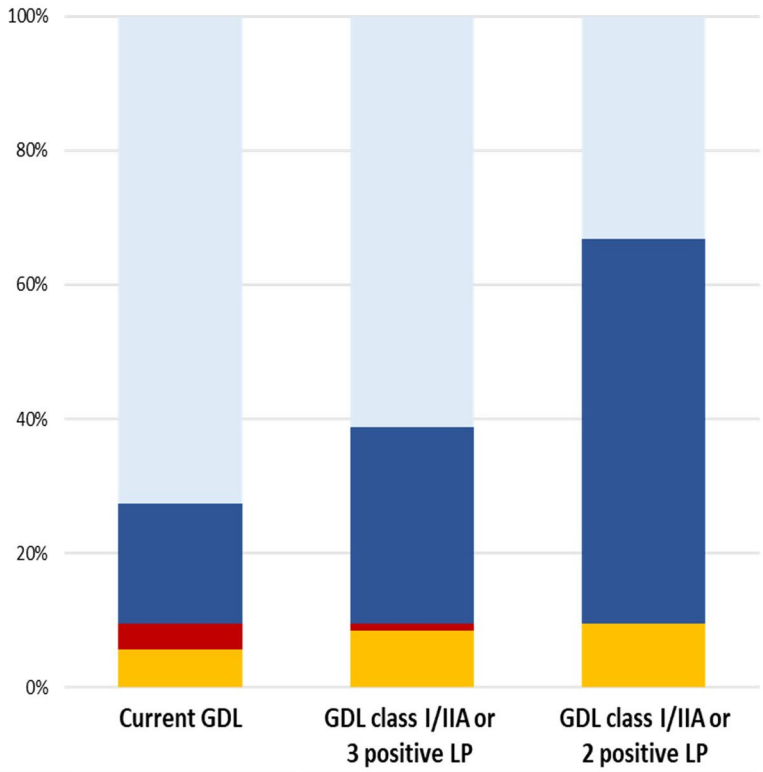



**Fig. 4** Long-term survival free from malignant arrhythmic events in relation to the presence of positive LP, defined by standard cut-offs, as assessed by signal-averaged ECG

Overall, syncope of suspected arrhythmic origin occurred at a low incidence in our population. Only 2 out of the 10 patients who suffered arrhythmic events had a prior syncope of suspected arrhythmic origin. The frequency of MAE was numerically higher in patients with a prior suspected arrhythmogenic syncope (25% versus 6.1%), but the difference did not reach statistical significance. The non-significancy of such difference, in contrast with many other studies [23–25], is likely explained by limitations in terms of event rates and population size. In fact, our population was included in the multicenter BRUGADA-RISK study, where a spontaneous type 1 pattern, arrhythmogenic syncope, presence of early repolarization on peripheral leads, and type 1 in peripheral




| | | | |
|---|---|---|---|
| **ICD + MAE**, n (%) | 6 (5.7) | 9 (8.5) | 10 (9.4) |
| **No ICD + MAE**, n (%) | 4 (3.8) | 1 (0.9) | 0 |
| **ICD + no MAE**, n (%) | 19 (17.9) | 31 (29.2) | 61 (57.5) |
| **No ICD + no MAE**, n (%) | 77 (72.6) | 65 (61.3) | 35 (33.0) |

| | ICD implantation based on current GDL | ICD implantation based on 3 positive LP criteria | ICD implantation based on 2 positive LP criteria | ICD implantation incorporating GDL class I/IIA and 3 positive LP | ICD implantation incorporating GDL class I/IIA and 2 positive LP |
|---|---|---|---|---|---|
| **Sensitivity**, % (95% CI) | 60 (26.2-87.8) | 70 (34.8-93.3) | 100 (69.2-100) | 90 (55-50-99.75) | 100 (69.15-100) |
| **Specificity**, % (95% CI) | 80.2 (70.8-87.6) | 75 (65.1-83.3) | 39.6 (29.8-50.0) | 67.71 (57.39-76.90) | 36.46 (36.87-46.91) |
| **Positive predictive value**, % (95% CI) | 24.0 (14.2-37.6) | 22.6 (14.6-33.2) | 14.7 (12.8-16.9) | 22.50 (16.90-29.30) | 14.08 (12.35-16.02) |
| **Negative predictive value**, % (95% CI) | 95.1 (90.0-97.6) | 96 (90.2-98.4) | 100 | 98.48 (90.97-99.76) | 100 |
| **Accuracy**, % (95% CI) | 78.3 (69.2-85.7) | 74.53 (65.1-82.5) | 45.28 (35.6-55.3) | 69.81 (60.13-78.35) | 42.45 (32.91-52.43) |

ICD: implantable cardiac defibrillator; GDL: guidelines; LP: late potential; MAE: malignant arrhythmic event

**Fig. 5** Utility of incorporating positive LP in the decision for ICD implantation. Comparison of the ICD implantation and MAE rates during follow-up in the study population submitted to ICD implantation according to current guidelines with the ones that would result from incorporating the presence of > 2 and 3 LP above standard cut-offs in the decision-making process

leads were found associated with the MAE and incorporated into a predictive score [24]. However, SA-ECG findings were not explored in that study [24].

In our study, 4 patients suffered from SCD. All of them were asymptomatic, and only 1 had a spontaneous type 1 ECG pattern. In fact, since the patients with spontaneous type 1 pattern and risk factors are receiving ICDs, a paradox is becoming frequently recognized in BrS studies: MAE are more common in the high-risk individuals, manifesting as appropriate ICD shocks, but most of the SCD are occurring in the low-risk individuals, who are not benefiting from ICD. Accordingly, Pappone et al. reported that the patients with worst outcomes did not manifest a spontaneous type 1 pattern [7]. In this context, the observation that SA-ECG might be useful for risk stratification in this population seems particularly relevant.

Due to the relatively small number of events in the study population, a multivariate analysis should be interpreted carefully due to risk of overfitting and as an exploratory analysis. However, we highlight that the association between the presence of LP on SA-ECG and the risk of MAE was independent of the symptomatic status, history of prior arrhythmic events, or ECG pattern.

Takahashi et al. performed SA-ECG evaluation using conventional and modified leads in 41 patients and found significantly lower RMS40 values in modified leads in symptomatic compared to asymptomatic patients. Remarkably, the median RMS40 values in modified leads observed were exceptionally low in both groups ($5.5 \pm 0.8$ μV and $8.2 \pm 0.8$ μV) [26]. Likewise, we explored if the SA-ECG evaluation performed in modified leads, focused on the RVOT, would increase the accuracy for the BrS electrophysiological substrate assessment. We did not observe meaningful differences between the SA-ECG results comparing the orthogonal Frank leads and the modified leads. Nonetheless, the concordance of the SA-ECG findings obtained by these two distinct but simultaneous evaluations corroborates the consistency of the analyses.

Altered LP are observed more commonly in BrS patients comparing to healthy controls [14, 27–29], and these findings seem to be applicable also to children with BrS [30]. Interestingly, 24-h Holter SA-ECG assessment of LP may provide valuable information in BrS, as LP dynamic fluctuations have been shown with LP reaching more frequently positivity during night periods considering standard cut-offs [27, 28, 31].

Moreover, previous studies have suggested that symptomatic BrS presents more frequently altered LP in comparison to asymptomatic patients [13–15]. Particularly, an association between 2 altered LP and ventricular fibrillation was documented by Ikeda et al. [14], by Yoshioka et al. using Night Time LP [28] and in type-2 BrS pattern patients [32]. Considering these results, cumulating evidence seems to point towards a role for LP in BrS arrhythmic risk assessment. In fact, in a prospective study with 43 patients, Huang et al. [15] demonstrated that both altered RMS40 and LAS40 correlated with arrhythmic events during follow-up. Finally, a correlation between 2 altered LP and the likelihood of sustained VT induction in programmed ventricular stimulation has been reported [13, 14, 33].

Supporting previous findings, in our study, the risk of MAE increased with the number of altered LP. The presence of 3 positive LP criteria was observed in 31 patients, and 7 of them (22.6%) suffered MAE during follow up. In comparison to the patients with $\leq 1$ positive LP criterium, the MAE risk was 4.7 times higher in those presenting 2 altered LP criteria and 9.4 times higher in those with 3 positive LP criteria. Noticeably, of the four asymptomatic patients with a spontaneous type 2 pattern who died, three presented 3 positive LP, and the remaining patient had 2 positive LP criteria. Therefore, the non-invasive evaluation of LP by SA-ECG seems a very promising tool for risk stratification. Obviously, our findings need to be confirmed in larger patient cohorts.

The most important limitation of our study is the small rate of events, which demands caution in the assumption of conclusions. Our observations need to be confirmed in larger BrS populations so that the use of SA-ECG may be indicated for risk stratification in this setting. Additionally, arrhythmic events in BrS patients without implanted devices may have been under-reported, and the proportion of patients who received implanted loop recorders was low. However, that is unlikely as all patients suffering from suspected arrhythmogenic syncope received an ICD.

## 5 Conclusion

Our study demonstrates the potential role of non-invasive assessment of LP on SA-ECG for prognostic stratification in BrS patients. The presence of 3 abnormal LP criteria identified a subset of asymptomatic patients at high risk of arrhythmic events, in whom a new individualized management strategy may be desirable.

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s10840-023-01685-8.

**Data availability** The data generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Declarations

**Ethics approval and consent to participate** All patients provided written informed consent. The Institutional Ethics Committee on human research at our institution approved the collection and review of these data.

**Conflict of interest** Drs. Cortez-Dias and Sousa received travel and consulting fees from Biosense Webster, Boston Scientific and Abott Medical. All other authors have reported that they have no relationships relevant to the contents of this paper to disclosure.

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