

Measurements and Changes in the ECG of Patients Suffering From Brugada Syndrome: a Longitudinal Study

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Abstract

Brugada syndrome (BrS) is an inherited ion channelopathy that predisposes individuals to ventricular arrhythmia and sudden cardiac death. BrS is characterised by specific morphology in the electrocardiogram (ECG) that can be used for non-invasive risk stratification of these patients. In this study we assessed the risk stratification capability of three ECG-derived markers through a longitudinal analysis of 10-second ambulatory 12-lead ECGs from 36 BrS patients, using high precordial lead placement. After preprocessing the ECGs, including noise removal and detecting the start, peak and end of each wave and heartbeat, three markers were computed: corrected QT interval (QTc), average power of QRS (Pavg), and absolute QRS area (AreaQRSabs). Results indicated a significant increase in the median QTc and AreaQRSabs in leads II and aVR between the 2 cohorts. In conclusion, ECG markers were obtained for BrS risk stratification, though further studies with larger populations and control groups are necessary to confirm and validate their diagnostic value.

1. Introduction

Brugada Syndrome (BrS) is an inherited disorder, associated with a significantly elevated risk of sudden cardiac death (SCD) [1], making it of paramount importance for the clinician to be able to accurately identify and manage these patients. Currently, recognized risk factors include a history of resuscitated cardiac arrest or arrhythmogenic syncope. However, most patients are diagnosed in the pre-clinical phase with an annual SCD rate estimated between 0.5% and 1% [2]. Patients suffering from BrS are usually

divided into symptomatic and asymptomatic, based on the presence of syncope or SCD. Despite progressive insights into the underlying mechanisms of BrS, the field lacks robust, reliable indicators for non-invasive continuous monitoring and risk stratification of BrS patients, especially the asymptomatic ones.

BrS is characterized by electrocardiogram (ECG) changes including ST-segment elevation, described as either a coved-shaped (type 1) or saddleback-shaped (type 2) morphology [3]. Nevertheless, the manifestation of these ECG patterns is subtle and may remain latent, posing diagnostic challenges for this condition. Therefore, this study aims to assess the time evolution of well-known ECG-based markers associated with BrS in 10-second-long ambulatory ECGs. For that reason, we performed a longitudinal study including up to 4-year of follow-up. The goal of this study is to identify risk stratification markers to improve BrS diagnosis and prognosis.

2. Materials

A total of 6 symptomatic (age median 60 [56 - 66]) and 30 asymptomatic (age median 46 [38 - 57]), were included in this study. For each patient, two 10-second-long ambulatory ECGs were recorded during the periodical medical check: using the standard electrode position and by placing the electrodes in the Brugada configuration (see Figure 1) [4].

3. Methods

Preprocessing: Pre-processing of each 10-second-long ECG included low-pass filtering (40 Hz cut-off) to remove muscular and power-line noise and high-pass filtering (0.5 Hz cut-off) to attenuate baseline wander. QRS complexes

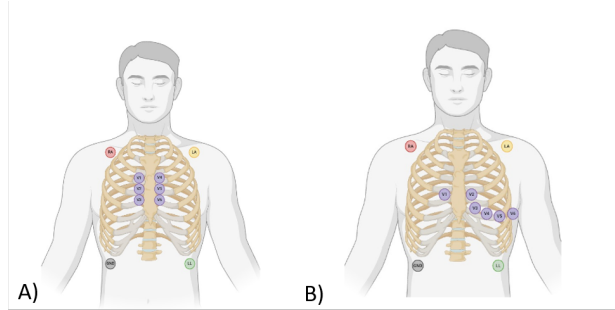


Figure 1: A) Brugada electrode position B) Standard electrode position.

were detected and delineated in each single lead (SL) using a wavelet-based delineation method [5]. Then, the multi-lead delineation (ML) strategy proposed in Martínez *et al.* was also applied to obtain a global delineation [5].

Selected ECG markers: Since BrS causes alteration in the QRS complex [6], 3 ECG-based markers in both SL and ML delineation were computed: the absolute value of the area of the QRS complex (AreaQRSabs), QT corrected according to Bazett's formula (QTc) and average power of QRS complex (Pavg).

Statistical analysis: Kruskal-Wallis test was performed to assess the statistical difference in markers' time progression across all follow-up years within each group (i.e., symptomatic and asymptomatic). Additionally, the Mann-Whitney U test was employed to compare the distributions of markers between symptomatic and asymptomatic individuals in each year of follow-up.

Random Mixed Model: a Random Mixed Model (RMM) analysis was conducted to account for the longitudinal nature of the data and to examine the marker progression along the follow-up in the two cohorts, considering both fixed effects (e.g., symptomatic) and random effects (e.g., markers and leads). Only the significant markers and leads from the Mann-Whitney U test were used.

4. Results

Kruskal-Wallis test showed no significant differences between the ECG progression of symptomatic and asymptomatic patients during the follow-up regardless of the lead configuration (i.e., standard and Brugada) and delineation approach (i.e., SL and ML).

Out of the three proposed ECG markers, only the areaQRSabs and QTc showed statistically significant results. Specifically, just 3 among all possible combinations of markers and leads gave consistent Mann-Whitney U test results. In this regard, Figures 2 (panels a to d), 3 (panels a to d), ?? (panels a to d) show boxplot distribution for the areaQRSabs lead aVR, QTc lead II, and QTc aVR, re-

spectively. In each panel, blue was used for asymptomatic and red for symptomatic, and the P-value from the Mann-Whitney U test for every year was also given.

Figures 2 (panels e to h), 3 (panels e to h), ?? (panels e to h) show results for the areaQRSabs lead aVR, QTc lead II, and QTc aVR, respectively for the RMM. As in the previous figures, blue was used for asymptomatic and red for symptomatic patients.

These figures show higher values of AreaQRSabs aVR in asymptomatic patients than in symptomatic and higher values of QTc in symptomatic patients. Increasing trends of QTc across the follow-up can be observed in symptomatic patients, and approximately stable values can be observed in asymptomatic patients. No specific trends can be appreciated in the AreaQRSabs marker. Moreover, higher differences between the two cohorts are observed in the Brugada configuration and better results are noticed in SL delineation approach.

5. Discussion

In this study, we evaluate the ability of three ECG-derived markers to assess potential differences between symptomatic and asymptomatic BrS patients. All of them were related to the QRS segment, which is particularly important in BrS because of the presence of the type 1 Brugada pattern. However, Pavg performed poorly when compared to areaQRSab and QTc, being QTc already a higher-risk ECG marker. Despite areaQRSabs and Pavg being associated with depolarization, they present different results likely due to areaQRSabs being more sensitive to amplitude and duration variations, while Pavg smooths out these differences, potentially missing subtle relevant changes. Since a wider QRS duration is linked to a higher risk of SCD, areaQRSabs might serve as a more effective marker for stratification [6]. Moreover, these considerable differences could also be associated with the imbalance of the two cohorts, which could blur the underlying changes.

While the type 1 BrS pattern is typically observed in the precordial leads, our study found significant differences in leads II and aVR. This could be because (i) no type 1 patterns were present in the ECGs and (ii) in general, changes in the electrocardiographic repolarization activity due to BrS might be manifested in other leads [1].

Larger changes were observed in the ECGs with Brugada lead configuration, which is consistent with the literature, as it enhances the ECG morphological changes consequence of the BrS.

The results from the Kruskal-Wallis test indicate that there was no statistically significant intra-group difference over the years, probably due to the number of follow-up years, which could be not sufficient to see age changes.

There were notable inter-group differences between the two cohorts at every year, as the Mann-Whitney U test

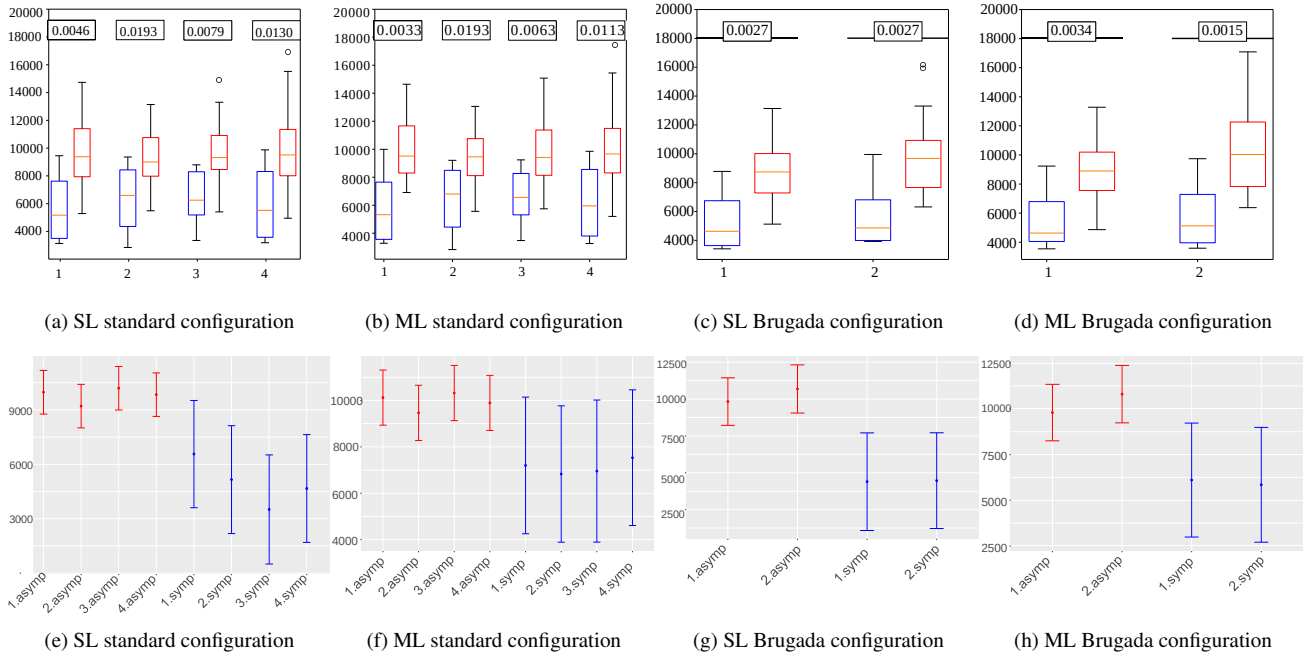


Figure 2: Boxplots distribution with p-value from the Mann-Whitney (panel a to d) and RMM (panel e to h) of the AreaQRSabs in lead aVR across the follow-up between symptomatic (in blue) and asymptomatic patients (in red) in both standard and Brugada lead configuration with the different delineation approaches (ML, SL).

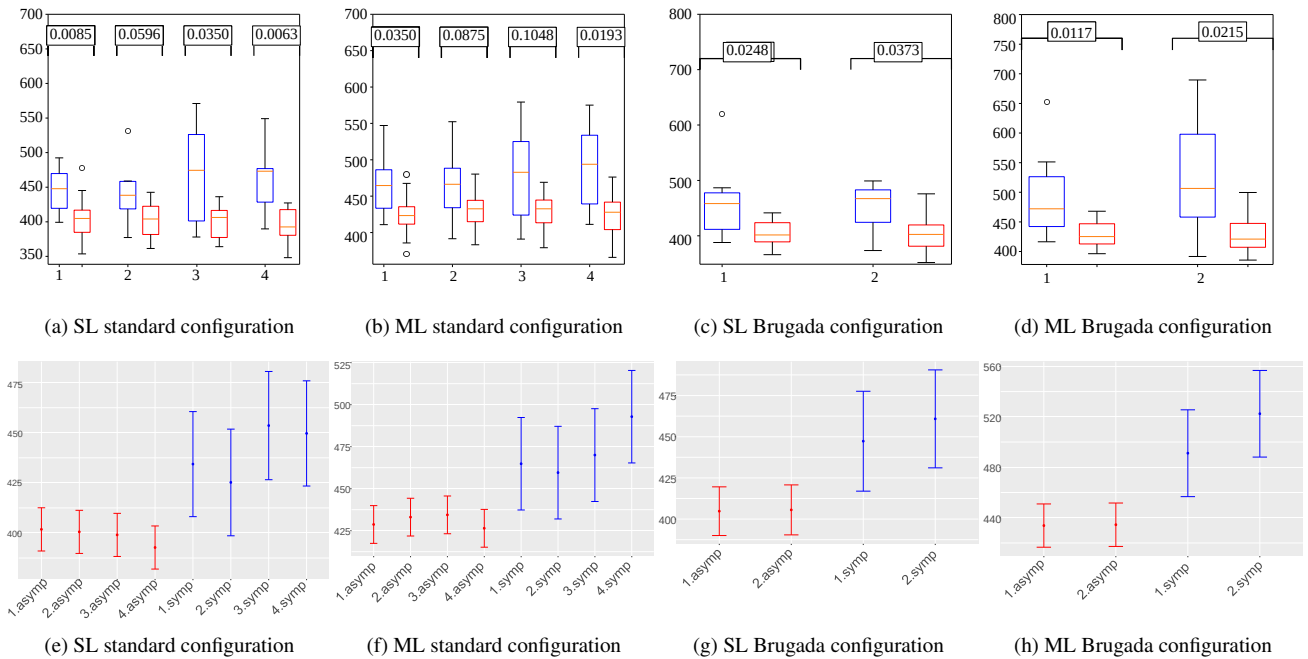


Figure 3: Boxplots distribution with p-value from the Mann-Whitney (panel a to d) and RMM (panel e to h) of the QTc in lead aVR across the follow-up between symptomatic (in blue) and asymptomatic patients (in red) in both standard and Brugada lead configuration with the different delineation approaches (ML, SL).

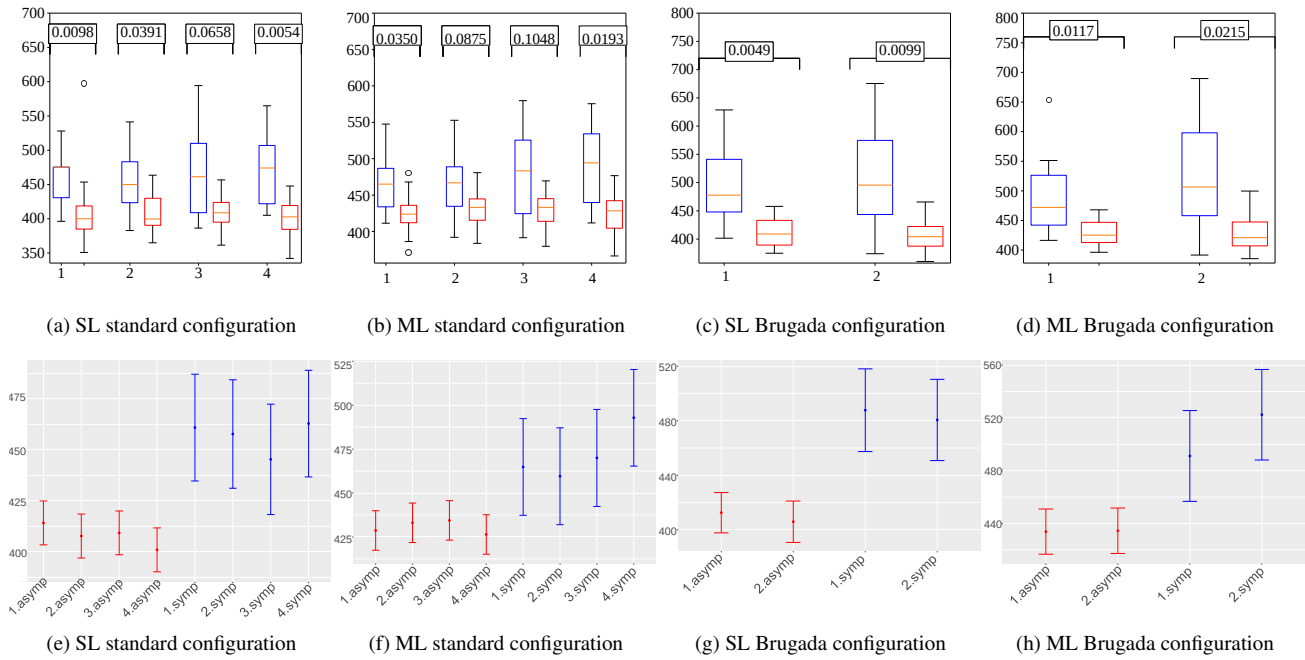


Figure 4: Boxplots distribution with P-value from the Mann-Whitney (panel a to d) and RMM (panel e to h) of the QTc in lead II across the follow-up between symptomatic (in blue) and asymptomatic patients (in red) in both standard and Brugada lead configuration with the different delineation approaches (ML, SL).

showed. These findings were also confirmed by the RMM analysis, exhibiting the existence of ECG marker changes that differentiate the symptomatic and asymptomatic cohorts over time. The results indicate that the markers in symptomatic and asymptomatic groups remain relatively stable over time and may help differentiate between them.

The main limitation of this work is posed by the considerable imbalance in the number of patients in each group as well as the years of follow-up in both electrode configurations as they might have hampered our ability to generalise the results.

6. Conclusion

In conclusion, this study allowed a preliminary identification of ECG-derived markers which can potentially be employed for risk stratification of BrS patients. To validate these results, future works should be carried out with balanced cohorts allowing a better comparison between groups and increasing the number of follow-up years to observe any age-related changes.

Acknowledgments

This study received funding from Fundació La Marató de TV3 (Project 245/U/2020) and the ERN GUARD-Heart. F. P. expresses gratitude for the support received

through the "Juan de la Cierva" fellowship ID JDC2022-049039-I, co-funded by MCIN/AEI and the European Union-NextGenerationEU/PRTR.

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