Quantification of Delayed Activation in Right Ventricular Outflow Tract in Brugada Patients

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Abstract

Brugada syndrome is a genetic disease associated with increased incidence of sudden cardiac death. Brugada patients have demonstrated delayed and heterogeneous conduction localized in the epicardial right ventricular outflow tract. Ventricular dyssynchrony in the right ventricular outflow tract constitutes a substrate of ventricular fibrillation. The present work aims to identify delays in the ventricular activation in Brugada patients from 24-hour electrocardiographic monitoring with the high precordial leads configuration. A lead-dependent global activation time is computed, every half hour in each lead, as the time instant along the QRS complex at which 50% *of its total energy is reached. The spatial dispersion in activation,* $\Delta\mathcal{T}$*, is defined as the difference between maximum and minimum global activation time values across leads, and it is evaluated every half hour. Brugada patients, especially the symptomatic ones, showed higher spatio-temporal dispersion over the 24 hours in global activation time than controls, indicating delayed and variable ventricular conduction (BrS:* $\Delta\mathcal{T}$=$13[9;28]$*ms; Controls:* $\Delta\mathcal{T}$=$8[6;9]$*ms,* $p < 0.01$*). In conclusion, this metric for quantifying spatial dispersion of ventricular activation not only distinguishes BrS patients but also holds potential for enhancing risk stratification in individuals with conduction disorders through 24-hour electrocardiographic monitoring.*

1. Introduction

Brugada syndrome (BrS) is a genetic disease associated to an increased incidence of sudden cardiac death (SCD) [1]. The penetrance of BrS is age- and sex-dependent and most lethal events occur in men over 40 years old [2]. BrS is diagnosed based on the clinical and family history of the patient along with a characteristic electrocardiographic pattern. This pattern displays a coved-type ST segment $\geq 0.2mV$, followed by a negative T wave in at least one right precordial lead placed at the second, third, or fourth intercostal space. This electrocardiographic pattern, referred to as type I BrS pattern, is required for diagnosing BrS [3, 4]. However, this pattern changes over time, displaying different morphologies of ST-segment elevation such as the "saddleback" pattern. Although, saddleback-type ST segments are not considered diagnostic for BrS, they may convert into a type I BrS pattern during pharmacological testing [4]. The temporal variability of the BrS patterns depends on many clinical and environmental conditions: temperature, age, hormones, metabolic factors and electrolytes, neuromuscular diseases, toxin or poison, mechanical compression, vascular factors, myocardial and pericardial diseases [2, 4].

Mutations in the SCN5A gene are the most commonly associated to BrS [2]. The reduction of inward Na^+ current in BrS patients leads to slowed cardiac conduction, especially affecting the right ventricular outflow tract (RVOT), resulting in a delayed electrical activation [2]. The ventricular dyssynchrony in the RVOT can promote reentrant arrhythmias and create voltage gradients, constituting a substrate for ventricular fibrillation [5]. Altered conduction may be reflected in the ECG by longer QRS duration, fragmented QRS complex and ST segment elevation [6].

The spontaneous dynamics of ventricular conduction in BrS patients can be captured by the 24-hour Holter ECG monitoring with high precordial leads configuration (Figure 1.A) that allows to monitor the RVOT area and demonstrated to be useful in the diagnosis of BrS [4, 6]. Risk stratification is one of the main clinical issues in BrS. In fact, among patients with the BrS who have died suddenly, 68% had no previous history of arrhythmia-related symptoms and therefore had not been protected by implantable cardioverter defibrillator (ICD) [6]. Apart from the spontaneous BrS type I pattern, no other ECG feature has shown an indication for increased arrhythmic risk [6]. In addition, diagnosis of BrS patients based on the standard ECG pattern lacks sensitivity due to the dynamical nature of coved-type ST-segment elevation [4]. Indeed, up to 40% of BrS patients present with non-diagnostic ECG at rest.

The present work aims to quantify the dispersion of global ventricular activation times measured from high precordial leads (Figure 1.A) for the identification of: 1) patients with BrS, and, among them, 2) symptomatic BrS patients who suffered arrhythmic events, (BrS-S). We hypothesise that BrS patients exhibit delayed conduction in the RVOT, which can be observed using 24-hour ECG Holter monitoring with a high precordial lead configuration. In addition, we hypothesize that BrS-S patients exhibit a greater dispersion of ventricular activation compared to asymptomatic BrS patients (BrS-A).

2. Methods

2.1. Electrocardiographic recordings

44 ECGs from BrS patients (median age $54[46; 62]$ years old, 75% male, 18% symptomatic, 55% BrS type-I) and 15 controls (median age $26[24, 56]$ years old, 60% male) were collected using a continuous 12-lead ECG recorder (Spiderview Plus, Livanova-Sorin group, ELA Medical, Montrouge, France) with 2.5 µV of voltage amplitude resolution (16 bits) and sampling frequency of 1000 Hz. Data collection was approved by the ethical committee of Hospital Clínic de Barcelona (Reg. HCB/2020/0306).

Symptomatic patients (N=12) were considered as those who experienced syncope of cardiac origin and/or SCD before ECG recording, who was eligible for ICD implantation and who suffered major events during follow up.

2.2. ECG signal processing

Each l-th high precordial ECG lead was segmented into h-th consecutive windows, 30-minute long. Each ECG window was band-pass filtered between 0.3Hz and 40Hz to reduce baseline wandering and high-frequency noise. A median cardiac beat representative of each ECG window was computed. The cardiac beats used to compute the median cardiac beat were those having a correlation coefficient greater than 0.9 when compared to the template beat. Each of these selected beats was aligned to the template beat, constructed by computing the median of the 10 beats that showed the highest correlation with each other.

The onset (n_o) and end sample (n_e) of the QRS complex in the median cardiac beat ($x_{l,h}(n)$) were identified using a multi-lead wavelet-based delineator [7].

2.3. Estimation of lead-dependent global ventricular activation time

The ventricular activation time $\mathcal{T}_{l,h}$ was measured for each l-th lead in every h-th ECG half-hour window as the time instant within the QRS complex, $x_{l,h}(n)$, at which it reaches 50% of its total energy:

$$\mathcal{T}_{l,h} = \arg\min_{m} \left| \sum_{n=n_o}^{m} x_{l,h}^2(n) - 1/2 \sum_{n=n_o}^{n_e} x_{l,h}^2(n) \right| \quad (1)$$

with $l \in \{V1_{2IC}, V1_{3IC}, V1_{4IC}, V2_{2IC}, V2_{3IC}, V2_{4IC}\}$ (see high lead configuration in Figure 1) and time window $h \in \{1, ..., 48\}$ corresponding to 24 hours.

The global activation time for each lead is computed as the median $\mathcal{T}_{l,h}$ over 24 hours:

$$\mathcal{T}_l = \underset{h}{\text{median}}\{\mathcal{T}_{l,h}\}. \quad (2)$$

The temporal variability of the ventricular activation time in each lead, $\sigma_{\mathcal{T}_l}$, is defined as the standard deviation of ventricular activation times over a 24-hour period:

$$\sigma_{\mathcal{T}_l} = \underset{h}{\text{std}}\{\mathcal{T}_{l,h}\}. \quad (3)$$

The spatial dispersion in the activation time for each h-th half-hour signal excerpt, ($\Delta\mathcal{T}_h$) is estimated as the maximum difference in global activation times across all leads:

$$\Delta\mathcal{T}_h = \max_{l}\{\mathcal{T}_{l,h}\} - \min_{l}\{\mathcal{T}_{l,h}\}. \quad (4)$$

Finally, the median value ($\Delta\mathcal{T}$) and the standard deviation ($\sigma_{\Delta\mathcal{T}}$) of $\Delta\mathcal{T}_h$ over the 24-hour period were computed to characterize the daily spatial dispersion and its temporal variability of ventricular activation for each subject:

$$\Delta\mathcal{T} = \text{median}\{\Delta\mathcal{T}_h\} \quad (5)$$

$$\sigma_{\Delta\mathcal{T}} = \text{std}\{\Delta\mathcal{T}_h\}. \quad (6)$$

For each subject, the earliest and latest leads in reaching 50% of ventricular activation were identified as those with the most frequently observed minimum and maximum global ventricular activation time over the 24-hour period.

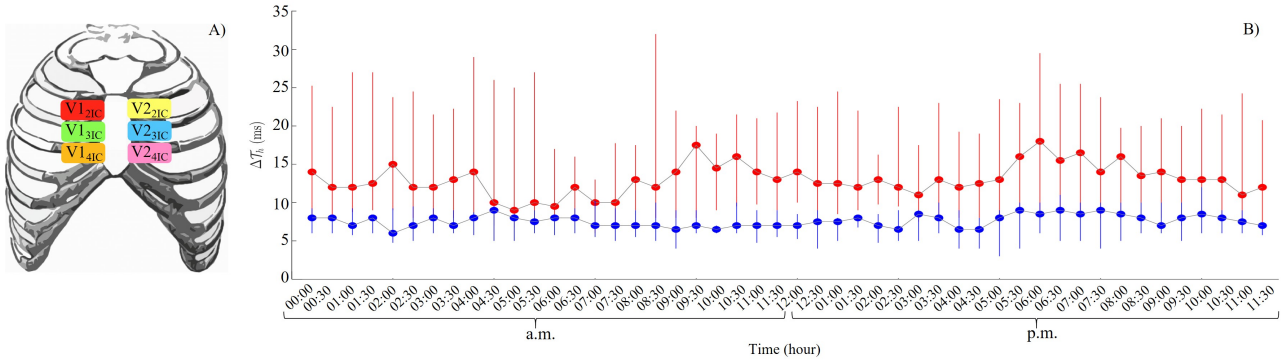

Figure 1. A) High precordial lead configuration. B) Spatial dispersion $\Delta\mathcal{T}_h$ over 24 hours (median[IQR]). BrS in red; Controls in blue.

2.4. Statistics

Mann-Whitney U test was used to compare the metrics regarding spatial dispersion and temporal dispersion of activation between BrS patients and controls. Additionally, these metrics will be evaluated to distinguish between BrS-S and BrS-A. Significance levels were set at 0.01.

3. Results

BrS patients showed a global ventricular activation time, $\mathcal{T}_l$, approximately 10 ms longer than controls in all leads (Table 1). Additionally, BrS patients exhibit a significantly larger spatial dispersion of ventricular activation (around 5 ms on average) when compared to controls (see $\Delta\mathcal{T}$ in Table 1). These differences are further highlighted by the inter-subject variability, as quantified by the interquartile range (IQR), which is 19 ms for BrS patients compared to 3 ms for controls. Figure 1 B) illustrates the spatial dispersion $\Delta\mathcal{T}_h$ over time for BrS patients and controls. Regarding the intrasubject temporal variability over the 24 hours, BrS patients displayed significantly higher values of $\sigma_{\Delta\mathcal{T}}$ (almost 5 fold) than controls (Table 1).

When distinguishing between BrS-S and BrS-A patients, BrS-S patients exhibited higher median global activation times compared to BrS-A patients in most leads (Table 1). Further, BrS-S patients exhibited greater median spatial dispersion of activation than BrS-A patients ($\Delta\mathcal{T}$ = 17ms vs 12ms) with comparable IQR values (17ms vs 19ms), as shown in Table 1.

Among controls, the earliest lead to reach the global activation time was $V1_{2IC}$ in 67% of the cases, while the latest was $V2_{4IC}$ in 60% of the cases. In contrast, BrS patients showed larger variability with $V1_{2IC}$ being the first activating lead in 47% of patients while the remaining patients were equally distributed across the remaining leads. For the majority of BrS patients, the latest activating leads were $V2_{2IC}$ (28%) and $V2_{4IC}$ (28%).

Table 2 shows that BrS patients exhibited significantly greater intrasubject temporal variability $\sigma_{\mathcal{T}_l}$ in the ventricular activation delay relative to the QRS onset across all leads over a 24-hour period compared to controls. Additionally, BrS-S patients displayed higher intrasubject variability in most leads compared to BrS-A patients.

4. Discussion

In this work, we introduced a novel metric to characterize the spatial dispersion of ventricular activation in BrS patients during 24-hour electrocardiographic monitoring with high precordial lead configuration. Our findings indicate that BrS patients show delayed activation compared to controls. Additionally, we observed greater delay of activation in symptomatic patients, which suggests the presence of delayed conduction in the RVOT area.

The high values of $\mathcal{T}_l$, $\Delta\mathcal{T}$, $\sigma_{\mathcal{T}_l}$ and $\sigma_{\Delta\mathcal{T}}$ observed in BrS patients indicate a greater spatial and temporal variability in conduction than in controls. This enhanced conduction variability supports the presence of delayed conduction in the RVOT, as detected through high precordial leads. These results are in agreement with previous studies suggesting a delayed conduction in the RVOT area [4,8,9].

BrS-S patients exhibited greater global activation time and spatial variability in activation time compared to asymptomatic ones (BrS-A). In terms of temporal variability, BrS-S patients showed higher values across most precordial leads. This aligns with findings showing that spatial and temporal heterogeneity in conduction facilitates arrhythmic events [5].

$V2_{2IC}$ and $V2_{4IC}$ were identified as the latest activating leads in BrS patients with 28% of occurrences. This variability in the identification of the latest lead in reaching 50% of QRS complex energy can be linked to inter-subject anatomical differences of the RVOT area.

The different distribution of the first and last leads in reaching 50% of QRS complex energy may depend on the anatomic relation between the right ventricle and the positions of electrodes, which is subject-specific, and any of

Table 1. Distribution (median[25^{th};75^{th}]) of global activation time $\mathcal{T}_l$ (ms) along with the spatial dispersion of ventricular activation time, $\Delta\mathcal{T}$ and $\sigma_{\Delta\mathcal{T}}$ (ms). BrS vs Control: $^*p < 0.01$.

Population	$V1_{2IC}$	$V1_{3IC}$	$V1_{4IC}$	$V2_{2IC}$	$V2_{3IC}$	$V2_{4IC}$	$\Delta\mathcal{T}$	$\sigma_{\Delta\mathcal{T}}$
Control	52[49;57]	53[50;58]	54[50;59]	57[51;62]	59[52;62]	57[53;62]	8[6; 9]	1.2[0.9;2.5]
BrS	62[54;75]*	63[55;72]*	61[55;73]*	66[57;79]*	67[57;81]*	68[60;77]*	13[9;28]*	5.6[3.0;7.6]*
BrS-S	61[56;75]	68[55;72]	66[54;75]	65[57;81]	73[55;84]	74[60;81]	15[12;29]	5.5[2.8;6.7]
BrS-A	62[54;75]	61[55;72]	60[56;71]	66[57;79]	66[58;77]	68[60;74]	12[8;27]	5.6[2.9;8.1]

Table 2. Distribution (median[25^{th};75^{th}]) of temporal variability of ventricular activation time, $\sigma_{\mathcal{T}_l}$ (ms). BrS vs Control: $^*p < 0.01$.

Population	$V1_{2IC}$	$V1_{3IC}$	$V1_{4IC}$	$V2_{2IC}$	$V2_{3IC}$	$V2_{4IC}$
Control	1.3[1.2;1.7]	1.3[1.1;1.5]	1.4[1.3;1.8]	1.3[1.2;2.6]	1.5[1.2;3.2]	1.6[1.3;2.2]
BrS	4.5[2.3;7.9]*	4.5[2.3;8.1]*	3.7[2.7;7.0]*	6.5[3.4;8.0]*	5.1[3.2;7.2]*	4.8[3.0;6.9]*
BrS-S	4.0[1.7;7.1]	5.6[1.9;8.5]	4.2[2.8;7.6]	4.3[2.4;7.9]	5.4[3.9;5.8]	6.1[4.0;8.2]
BrS-A	4.5[2.6;8.5]	4.2[2.5;7.5]	3.4[2.7;6.4]	7.0[3.7;8.1]	4.7[2.8;9.0]	4.2[3.0;6.3]

the intercostal spaces could be closest to the RVOT [6].

This methodology could be applied to standard 12-lead ECG for patients with various clinical conditions affecting ventricular depolarization. Future studies involving patients with conditions such as arrhythmogenic right ventricular cardiomyopathy, early repolarization, infarction or bundle branch block could explore the specificity of the proposed metric for quantifying ventricular activation dispersion.

5. Conclusion

This study introduces a novel method for quantifying the spatial dispersion of ventricular activation. BrS patients, who typically show delayed activation times in the RVOT area, exhibited significantly higher spatial dispersion of ventricular activation using this metric compared to controls. Eventually, this metric could help in risk stratification for patients with conduction disorders through 24-hour electrocardiographic monitoring.

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