Temporal Variability of Ventricular Activation in Brugada Syndrome Patients

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Abstract

In Brugada Syndrome (BrS), ventricular fibrillation events peak during night. This temporal pattern suggests that circadianity may modulate arrhythmogenesis. The present work evaluates the circadianity of ventricular activation in BrS patients from 24-hour ECGs with the high-precordial leads. Lead-dependent propagation progression times, $\mathcal{T}_l^p(h)$, are computed every h-th half hour in each l-th lead as the time instant along the QRS complex when the QRS energy reaches a percentage, p, of the total QRS energy. $\mathcal{T}_l^p(h)$ is characterized by median and standard deviation over 24 hours, as well as the MESOR and amplitude of the cosinor analysis. The median and MESOR of $\mathcal{T}_l^{70}(h)$ are longer by more than 10 ms in BrS patients than in controls. In particular, the median and standard deviation of $\mathcal{T}_l^p(h)$ at different energy percent can distinguish between BrS vs controls (AUC≥ 0.8), and BrS-I vs BrS-II (AUC$= 0.78$). Cosinor analysis indicates that $\mathcal{T}_l^p(h)$ is less influenced by circadianity than heart rate. The Spearman correlation of $\mathcal{T}_l^p(h)$ with heart rate is lower than 0.5 in each lead for both BrS and controls. These findings suggest that intra-day variability in propagation progression times is not primarily driven by circadianity or heart rate. Furthermore, the temporal variability of $\mathcal{T}_l^p(h)$ is higher in symptomatic BrS patients supporting its potential role as risk stratification marker in BrS.

1. Introduction

Brugada syndrome (BrS) is a genetic disease responsible for up to 28% of sudden cardiac deaths (SCD), and 10% of resuscitated cardiac arrests in subjects with structurally normal hearts [1]. Currently, the implantable cardioverter defibrillator (ICD) is the only established effective treatment. Risk stratification of BrS patients is based on the arrhythmogenic history and the presence of the spontaneous BrS type-I pattern in the ECG at rest. The BrS type-I pattern shows a coved-type ST segment $\geq$0.2 mV, followed by a negative T wave in at least one right-precordial lead placed in the second, third, or fourth intercostal space (IC) [2]. However, this method of risk stratification lacks sensitivity due to the variability of the coved-type ST-segment elevation, which depends on many clinical and environmental conditions. Indeed, up to 40% of BrS patients have a non-diagnostic ECG at rest [3, 4]. The dynamics of ventricular conduction in BrS patients can be captured by a 24-hour Holter ECG with high-precordial lead configuration that allows monitoring the right ventricular outflow tract (RVOT), a region especially affected by slowed cardiac conduction in BrS [5].

A distinct circadian pattern has been observed in BrS, with ventricular fibrillation (VF) events peaking during the night, and the type-I ECG pattern appearing predominantly from the afternoon through midnight [6]. Additionally, an increased incidence of cardiogenic syncope and cardiac arrest has been reported predominantly during sleep [1]. These temporal patterns suggest that circadian rhythms may modulate arrhythmogenic susceptibility in BrS.

In previous studies [7, 8], we introduced a method to assess the temporal dispersion of ventricular activation by computing lead-specific propagation progression times from 24-hour ECGs. Using this approach, BrS patients exhibited significantly greater temporal dispersion of ventricular activation compared to controls. However, their circadian variation has yet to be systematically analyzed.

Consequently, this work aims: (1) to quantify the circadian variation of lead-dependent propagation progression times using cosinor analysis; (2) to assess the prognostic value of these parameters for risk stratification in BrS.

2. Study population

Holter ECGs from 102 BrS patients (age $53[42; 64]$ years old, 66% male, 30% BrS symptomatic (BrS-S), 28%

BrS spontaneous type-I pattern (BrS-I)) and 44 controls (age $25[23;52]$ years old, 41% male) were collected using a 12-lead ECG recorder (Spiderview Plus, Livanova-Sorin group, ELA Medical) with sampling frequency of 1000 Hz. ECGs last at least 19 hours. High precordial leads were recorded simultaneously at the second, third and fourth IC at the right ($V1_{2IC}$,$V1_{3IC}$,$V1_{4IC}$) and left ($V2_{2IC}$,$V2_{3IC}$,$V2_{4IC}$) sides of the sternum. Data collection was approved by the ethical committee of Hospital Clínic de Barcelona (Reg. HCB/2020/0306).

The BrS population was grouped in BrS-I (N=29, age 58[52;66] years old, 58% male, 52% BrS-S) or drug-induced type-I pattern (BrS-II, N=73, age 51[42;61] years old, 86% male, 22% BrS-S). BrS-S patients (N=31, age 53[43;67] years old, 71% male, 48% BrS-I) were those who: (1) experienced cardiogenic syncope, SCD, VF and/or ventricular tachiarrhythmic events before the ECG recording; (2) were eligible for ICD implantation. Otherwise patients were considered asymptomatic (BrS-A, N=71, age 53[42;61] years old, 63% male, 20% BrS-I).

3. Methods

3.1. ECG signal processing

Each l-th high-precordial ECG lead is segmented into h-th consecutive windows, 30-minute long. Powerline noise is filtered by a notch filter with cut-off frequencies $[49.5-50.5]$ Hz. In addition, each ECG window is band-pass filtered between 0.3 Hz and 45 Hz. A median cardiac beat, $x_{l,h}(n)$, representative of each ECG window is computed [7]. The onset ($\mathrm{QRS_o}$) and end ($\mathrm{QRS_e}$) samples of the QRS complex in the median cardiac beat are identified by a multi-lead wavelet-based delineator [9].

For each h-th window, mean heart rate, $\mathrm{HR}(h)$, and QRS duration, $\mathrm{QRS_d}(h)$, are computed. The median and standard deviation of $\mathrm{HR}(h)$ and $\mathrm{QRS_d}(h)$ are calculated in the 24 hours obtaining $\mathrm{m_{HR}}$, σ_{HR}, $\mathrm{m_{QRS_d}}$ and $\sigma_{\mathrm{QRS_d}}$.

3.2. Propagation progression time

Propagation progression times relative to QRS onset, $\mathcal{T}_l^p(h)$, are estimated for $p \in \{30, 50, 70\}$ percent of the total QRS energy [7] as:

$$\mathcal{T}_l^p(h) = \arg\min_m \left| \sum_{n=n_o}^{m} x_{l,h}^2(n) - \frac{p}{100} \sum_{n=n_o}^{n_e} x_{l,h}^2(n) \right| \quad (1)$$

with $l \in \{V1_{2IC}, V1_{3IC}, V1_{4IC}, V2_{2IC}, V2_{3IC}, V2_{4IC}\}$, and time window $h \in \{1, ..., 48\}$. The median ($m_{\mathcal{T}_l^p}$) is computed in each lead over 24 hours, and the temporal variability of the propagation progression time in each lead, $\sigma_{\mathcal{T}_l^p}$, is estimated as the standard deviation of propagation progression times over 24 hours [7]:

$$m_{\mathcal{T}_l^p} = \underset{h}{\mathrm{median}}\{\mathcal{T}_l^p(h)\}; \qquad \sigma_{\mathcal{T}_l^p} = \underset{h}{\mathrm{std}}\{\mathcal{T}_l^p(h)\}. \quad (2)$$

3.3. Cosinor analysis

The circadianity of propagation progression times is evaluated through the cosinor analysis, which fits a generic series $y(h)$ to a sinusoidal function based on a least squares approach [10]. The cosinor regression model is defined as:

$$y(h) = M + A\cos\left(\frac{2\pi h}{\tau} + \phi\right) + e(h) \quad (3)$$

where M (also called MESOR, acronym of midline estimating statistic of rhythm) represents the mean of the adjusted sinusoid, A is the amplitude, ϕ is the acrophase (timing of the peak value within the cycle), τ is the period (24 hours in this case) and $e(h)$ is the residual error to be minimized (Figure 1). Cosinor fit is considered representative of circadian rhythm if the p-value from the test differentiating A from zero-amplitude is < 0.05.

3.4. Statistics

Continuous variables are shown as median[IQR]. Group comparisons are performed using the Mann-Whitney U test (significance $p < 0.05$) for: BrS vs Controls; BrS-I vs BrS-II; BrS-S vs BrS-A. The association between $\mathcal{T}_l^p(h)$, HR and $\mathrm{QRS_d}$ is estimated by Spearman correlation. To evaluate the discriminative power of the proposed metrics, a multivariate logistic regression is conducted with the leads considered as variables. Classification performance is assessed by the Area Under the Curve (AUC).

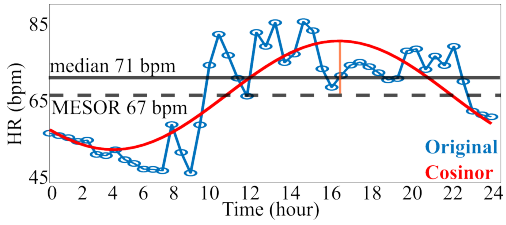

Figure 1. Fitted cosinor (red) to $\mathrm{HR}(h)$ series (blue). Orange line=cosinor amplitude; black dashed line=MESOR.

4. Results

In both BrS patients and controls, $\mathrm{HR}(h)$ follows a biphasic oscillatory pattern, reaching its minimum during the night (BrS 57[50;61] bpm; control 53[47;60] bpm), and maximum from 14:00 to 18:00 pm (BrS 96[86;104] bpm; control 100[91;106] bpm). While $\mathrm{QRS_d}(h)$ is higher at night with maximum values from 2:00 to 3:00 am (BrS 131[119;149] ms; control 111[100;117] ms, p-value=3.021×10^{-12}). Based on the zero-amplitude test (Table 1), $\mathrm{QRS_d}(h)$ is less affected by circadian rhythm than $\mathrm{HR}(h)$, especially in BrS. The Spearman correlation between $\mathrm{HR}(h)$ and $\mathrm{QRS_d}(h)$

is: BrS -0.4[-0.7;0.0], control -0.6[-0.7;-0.3]. BrS patients have significantly higher values of $\mathrm{m}_{\mathrm{QRS_d}}$, $\sigma_{\mathrm{QRS_d}}$, MESOR and amplitude of $\mathrm{QRS_d}(h)$ cosinor fit than controls (Table 1). The median value and the MESOR of $\mathcal{T}_l^{70}(h)$ are at least 10 ms longer in BrS patients than controls across leads in the second IC (Figure 2). Additionally, BrS patients exhibit significantly greater intrasubject temporal variability $\sigma_{\mathcal{T}_l^p}$ across all leads compared to controls. The variability $\sigma_{\mathcal{T}_l^p}$ exceeds that of the corresponding cosinor amplitude (Figure 2). The cosinor fit of $\mathcal{T}_l^p(h)$ reveals a maximum peak during day hours, with a high intersubject variability. The latter is inferable from the high IQR of the cosinor acrophase of $\mathcal{T}_l^p(h)$, which is significantly different from acrophase of $HR(h)$ for both Brs and control groups. On average, the Spearman correlations of $\mathcal{T}_l^p(h)$ with $\mathrm{HR}(h)$ and $\mathrm{QRS_d}(h)$ are lower than 0.5 and 0.8, respectively, for both the BrS and control groups.

BrS-I patients have longer $\mathrm{m}_{\mathrm{QRS_d}}$ (Table 1), delayed propagation time $\mathcal{T}_l^p(h)$, and higher intrasubject variability $\sigma_{\mathcal{T}_l^p}$ than BrS-II ones (Figure 2). Although the cosinor amplitude of $\mathcal{T}_l^p(h)$ does not show differences between the two groups, and the variability $\sigma_{\mathcal{T}_l^p}$ is a more distinguishing characteristic, resulting higher in BrS-I than BrS-II.

In the comparison between BrS-S and BrS-A patients, BrS-S group has higher variability in activation times across multiple leads. Specifically, $\sigma_{\mathcal{T}^{70}_{V1_{4IC}}}$ (BrS-S 4.0[2.4;7.1] ms, BrS-A 2.9[1.9;4.9] ms) $\sigma_{\mathcal{T}^{70}_{V2_{3IC}}}$ (BrS-S 5.9[3.3;8.6] ms, BrS-A 3.4[2.1;7.2] ms), and $\sigma_{\mathcal{T}^{50}_{V1_{3IC}}}$ (BrS-S 3.9[2.4;7.9] ms, BrS-A 2.3[1.8;5.3] ms) are significantly higher in BrS-S than BrS-A group (p-value< 0.05). Notably, $\sigma_{\mathcal{T}^{70}_{V2_{3IC}}}$ is higher for BrS-S patients with implanted ICD (N=25) than BrS-S patients without ICD (6.9 [4.1;9.3] ms vs 2.7 [1.9;4.9] ms, p-value=0.012).

In the multivariate logistic regression analysis, $\mathrm{m}_{\mathcal{T}_l^{70}}$ and $\sigma_{\mathcal{T}_l^{50}}$ are the most effective features distinguishing between BrS vs controls ($\mathrm{AUC}_{\mathrm{m}_{\mathcal{T}_l^{70}}}$=0.81, $\mathrm{AUC}_{\sigma_{\mathcal{T}_l^{50}}}$=0.80). While $\mathrm{m}_{\mathcal{T}_l^{30}}$ is the most effective feature distinguishing between BrS-I and BrS-II ($\mathrm{AUC}_{\mathrm{m}_{\mathcal{T}_l^{30}}}$=0.78). In contrast, for the comparison between BrS-S and BrS-A patients, the AUC is ≤ 0.7 for all features.

5. Discussion

The work evaluates the circadianity of lead-dependent global propagation progression times, which quantify the delay in ventricular conduction in the RVOT [7].

While the MESOR and amplitude of the cosinor model theoretically correspond to the median and standard deviation of $\mathcal{T}_l^p(h)$ under circadian influence, our findings suggest that daily variations of $\mathcal{T}_l^p(h)$ are not strongly associated with either circadian rhythm or HR. In particular, the cosinor amplitude underestimates the variability of $\mathcal{T}_l^p(h)$, indicating that standard deviation is a more reliable metric for capturing pathophysiological variations. Furthermore, the timing of maximum values of the cosinor fit for $\mathcal{T}_l^p(h)$ does not correlate with the maximum value of $\mathrm{QRS}_d(h)$, suggesting that increases in activation times $\mathcal{T}_l^p(h)$ and their variability may stem from morphological changes in the QRS complex rather than QRS prolongation.

Delayed ventricular conduction in the RVOT constitutes a substrate for VF in BrS, and it may be reflected by longer $\mathrm{QRS_d}(h)$ [5]. As expected, BrS patients present significantly longer $\mathrm{m}_{\mathrm{QRS_d}}$ than controls, especially at night when BrS patients are more vulnerable to VF. When characterizing the BrS population, the patients with spontaneous type-I pattern have longer $\mathrm{QRS_d}$ than the BrS-II group. The slowed ventricular activation in BrS population and its BrS-I subgroup is also represented by the higher values of $\mathrm{m}_{\mathcal{T}_l^p}$ than controls and Brs-II group respectively. However, BrS-S patients, who are considered to have high cardiac risk, have comparable $\mathrm{m}_{\mathrm{QRS_d}}$ with BrS-A group. BrS-S patients, specifically those with implanted ICD, show significantly higher daily variability in lead-dependent activation times. This result may indicate that high risk BrS-S patients have higher daily intra-subject variability in QRS complex morphology than BrS-A ones.

The metrics $\mathrm{m}_{\mathcal{T}_l^{70}}$ and $\sigma_{\mathcal{T}_l^{50}}$, are able to separate between BrS patients and controls, whereas $\mathrm{m}_{\mathcal{T}_l^{30}}$ between BrS-I and BrS-II. Although, spatial differences of $\mathrm{m}_{\mathcal{T}_l^p(h)}$ among leads affect regression coefficient. The characterization of ventricular conduction through directionality, speed and pattern of variation in propagation progresison times may aid in the development of the classification model. These aspects along with validation of classification model will be addressed in a future study.

Age differences between controls and BrS patients may have influenced group comparisons. Additionally, the effect of sex on cardiac conduction and the characterization of symptomatic patients will be explored in future studies.

6. Conclusion

The daily variability in propagation progression times seems to depend on the pathophysiological state of the subject rather than the circadian rhythm or heart rate. This variability is more accurately captured by the standard deviation of lead-dependent propagation times than by cosinor-based measures. Notably, the variability is higher in symptomatic patients, confirming its potential use as an ECG risk stratification marker in BrS.

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Table 1. Distribution (m[IQR]) of m_{HR}, σ_{HR}, m_{QRS_d} and σ_{QRS_d}, MESOR and cosinor amplitude of HR(h) (M_{HR}, A_{HR}) and QRS_d(h) (M_{QRS_d}, A_{QRS_d}). %p<0.05 is the subjects percentage with significant non-zero amplitude test (HR | QRS_d, left side for HR and right side for QRS_d). BrS vs control (Con), BrS-I vs BrS-II, BrS-S vs BrS-A: $*p < 0.01$, $**p < 0.001$.

	m_{HR} (bpm)	σ_{HR} (bpm)	m_{QRS_d} (ms)	σ_{QRS_d} (ms)	M_{HR} (bpm)	A_{HR} (bpm)	M_{QRS_d} (ms)	A_{QRS_d} (ms)	%p<0.05
Con	72[68;80]	12.4[10.1;14.5]	102[95;109]	3.7[2.7;4.4]	73[69;85]	11.2[8.7;15.1]	102[94;109]	3.0[1.9;4.0]	98 | 86
BrS	72[66;78]	10.4[8.1;12.5]*	119[107;130]**	5.8[4.0;8.8]**	72[67;79]	10.3[7.4;12.5]	118[108;131]**	4.0[2.3;5.6]*	95 | 68
BrS-I	72[66;76]	9.3[8.0;11.0]	132[106;150]	8.6[4.7;11.7]	71[65;77]	10.1[6.9;11.9]	131[108;148]	4.3[2.8;6.2]	93 | 55
BrS-II	73[66;79]	10.8[8.3;12.6]	116[108;125]*	5.1[3.7;7.4]	72[67;79]	10.5[7.8;12.9]	116[108;125]*	3.8[2.2;5.2]	96 | 73
BrS-S	71[65;78]	9.2[7.7;11.4]	116[105;133]	7.3[4.9;9.5]	71[65;78]	10.1[6.0;11.8]	117[107;133]	4.0[2.9;6.2]	94 | 74
BrS-A	73[67;78]	10.9[8.3;12.8]	119[108;127]	5.0[3.9;8.1]	72[68;80]	10.5[7.8;13.0]	118[108;127]	3.9[2.0;5.5]	96 | 75

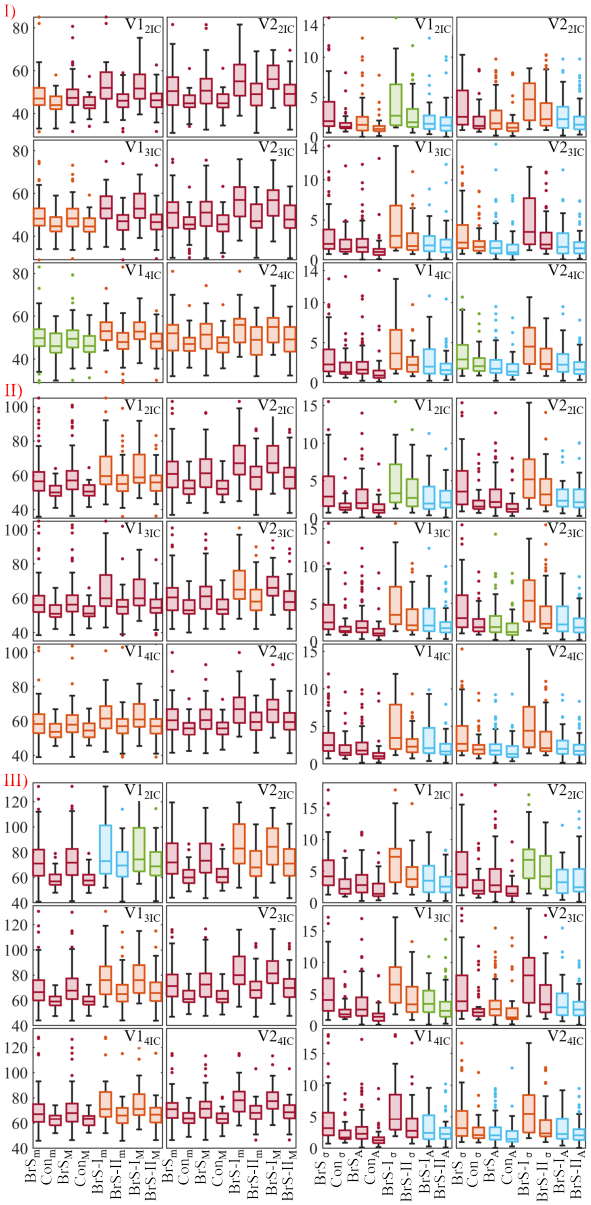

Figure 2. Boxplots of median (m), MESOR (M), standard deviation (σ) and cosinor amplitude (A) of $\mathcal{T}_l^{30}(h)$ in I), $\mathcal{T}_l^{50}(h)$ in II), and $\mathcal{T}_l^{70}(h)$ in III) for high precordial leads. Statistical significance of Mann-Whitney U test: p-value$\geq$0.05 in blue, 0.01$\leq p$-value$<$0.05 in green, 0.001$\leq p$-value$<$0.01 in orange, p-value$<$0.001 in red.

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