Assessment of the Dynamic Response of Cardiac Depolarization During StressTest Recovery Evaluated in Patients with Brugada Syndrome

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Abstract

Brugada syndrome is a genetic disease that may cause sudden cardiac death in patients with structurally normal heart. This study aims to assess dynamic response of cardiac depolarization to physical exercise, and particularlly, during recovery phase. Several ECG depolarization features were studied including the R and S waves amplitude (Ra and Sa), the up-stroke and down-stroke of the R and S waves (S_U, S_D and S_S) and their respective angles (α_R and α_S). Standard 12-lead ECG recordings were acquired during physical exercise test in 23 Brugada patients (11 symptomatic). By using a three-constant S-shaped function, we assessed the dynamics of the ECG markers by modeling their response during the recovery period. Brugada syndrome patients who were asymptomatic presented higher change values and faster change speed than symptomatic patients in several evaluated markers, especially in left precordial leads. On the other hand, symptomatic patients presented larger lag values as compared with asymptomatic patients. We concluded that dynamics of depolarization features, assessed during periods of increased parasympathetic tone, seems to be linked with the presence of symptoms in Brugada patients.

1. Introduction

Brugada syndrome (BrS) is a genetic pathology, firstly described more than 20 years ago, and associated with a high risk of sudden cardiac death (SCD) in patients with an apparently normal structural heart. The coved type-1 ECG pattern (ST elevation $\geq$ 2mm, negative symmetric T wave) in $\geq$ 1 lead of the precordial leads V1-V3 is the main electrophysiological diagnostic marker in BrS [1].

The major challenges today regarding the management of BrS patients are related to risk stratification and the definition of the best treatment approach. The implantation of a cardioverter defibrillator (ICD) is the only validated treatment, recommended for symptomatic patients who have experienced syncope, ventricular fibrillation or an aborted SCD. However, therapeutic strategies are more complex on asymptomatic patients, representing about 60% of BrS patients. The difficulty is thus to identify asymptomatic patients that may benefit from an ICD implantation.

Depolarization disorders have been one of the two main hypotheses underlying the pathophysiology of BrS, associated with slowing conduction within the right ventricular outflow tract (RVOT) [2]. Moreover, the role of the autonomic modulation seems to have an important component in this pathology. In this study, we investigate the cardiac depolarization response to exercise in BrS. A set classical and more refined features extracted from the ECG within the depolarization phase are analyzed, in order to assess potential differences between symptomatic and asymptomatic BrS patients. Both the original ECG features and their heart rate corrected versions were analyzed for this purpose.

2. Materials and methods

2.1. Population

The dataset comprises 23 patients suffering from Brugada syndrome enrolled in a French multi-center clinical project led by Centre de Maladies Cardiovasculaires at CHU Rennes. Eleven patients were diagnosed as symptomatic. The remaining 12 patients were classified as asymptomatic. For each patient, a standard 12-lead ECG recording sampled at 1kHz was acquired during an exercise stress test. The clinical protocol used for this test is described below:

- Heating phase: 2 minutes of initial workload by pedaling at 50 Watts (30 Watts for women).
- Exercise phase: an initial increment of 30 W (20 W for women) during 2 minutes until reaching at least 80% of the maximal theoretical heart rate, defined by the expression $HR_{\max}$ = 220 -age.
- Active recovery (AR) phase: 3 minutes pedaling with the initial workload of 50 W.
- Passive recovery (PR) phase: 3 minutes at rest.

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2.2. Calculation of ECG parameters

All ECG signals were preprocessed before the automatic extraction of the analyzed indices. This included automatic QRS detection and subsequent visual inspection, baseline drift attenuation via cubic spline interpolation, 4-th order Butterworth low pass filtering at 45 Hz to remove muscular noise and wave delineation using an evolutionary optimization approach [3].

Several depolarization markers were extracted from each QRS during the entire exercise stress test and for each lead: $i)$ the amplitudes of the R and S waves (Ra and Sa); $ii)$ their respective slopes ($\mathcal{S}_{\mathcal{U}}$ and $\mathcal{S}_{\mathcal{D}}$), defined as the up-stroke and down-stroke of the R wave and the up-stroke of the S wave $\mathcal{S}_{\mathcal{S}}$ [4], and $iii)$ the angles formed by joining the lines associated with slopes S_U and S_D for the angle R (ϕ_R), as well as the slopes S_D and S_S for the angle S (ϕ_S) [5].

RR time-series were also computed along the entire test. Then, heart rate-corrected markers were obtained by computing the ratio between each ECG marker and the corresponding instantaneous heart rate (HR), $\frac{\mathcal{Y}}{HR}$, where $\mathcal{Y} = \{Ra, Sa, \mathcal{S}_{\mathcal{U}}, \mathcal{S}_{\mathcal{D}}, \mathcal{S}_{\mathcal{S}}, \phi_{\mathcal{R}}, \phi_{\mathcal{S}}\}$.

2.3. Modelisation of the ECG response

After comparing with two other potential functions when investigating depolarization dynamic, the three-constant S-shaped curve (sigmoidal function) known as Gomperzt function [6] was finally selected for modeling the ECG markers response, particularly during the active phase of recovery period (i.e., the first three minutes immediately after the effort peak):

$$f_G(x) = \alpha \cdot e^{-e^{c-bx}} \qquad (1)$$

The above equation is characterized by three parameters defining the shape of the sigmoid, where α is an asymptote while b and c are positive numbers indicating the growth rate (y scaling) and the displacement along the x axis. The parameter α can be interpreted as the delta change achieved by the ECG marker during the study interval, whereas parameters b and c can be seen as the change *speed* and *lag*, respectively.

Normalization process: Before fitting the three sigmoidal models to the different time series, a normalization process was performed, in order to evaluate the fitting error (obtained as the root mean squared error, rmse) in a suitable way, thus compensating the differences existing among different leads and units of measures associated with each marker. Subsequently, baseline values, obtained as the averaged value during the first 5 beats in each time-series were subtracted, so as to obtain all ECG series starting from zero and representing a relative change in each marker.

In addition to the fitting error evaluation purpose, the normalized series were also used, together with the original ones, to further evaluate the dynamics properties of cardiac depolarization. Using normalized series, the group differences owed to the change achieved by the markers during recovery is reduced, while maintaining changes owed only to those parameters accounting for changes speed and lag.

In this paper, the analysis is focused on the active recovery phase. Therefore, a time support starting 15 s before the effort peak EP (maximum heart rate) and ending 15 s after completion of the active recovery phase AR$_{end}$ of each patient was defined, in order to construct each time-series (see Fig. 1 a) and b)). To attenuate the error effect related to both the initial and final 15-s segments, a Tukey's window, also known as the *tapered cosine window*, was used as the weight vector during the fitting process [7]. The N-point Tukey's window is defined as follows:

$$w(x) = \begin{cases} \frac{1}{2}\{1 + cos(\frac{2*\pi}{r}[x - r/2])\}, & 0 \leq x < \frac{r}{2} \\ 1 & \frac{r}{2} \leq 1 - \frac{r}{2} \\ \frac{1}{2}\{1 + cos(\frac{2*\pi}{r}[x - 1 + r/2])\}, & 1 - \frac{r}{2} \leq x \leq 1 \end{cases} \qquad (2)$$

where parameter r represents the ratio of "cosine-tapered" section length to the total window length with $0 \leq r \leq 1$. When setting $r \leq 0$, an N-point rectangular window is returned. On the contrary, if setting $r \geq 1$, an N-point von Hann's window is returned instead. Figure 1 c) illustrates the shape of the Tukey's window for a particular r value between 0 and 1.

The Tukey's window described above will serve as the initial weights to be used in the robust regression *bisquare* strategy. This strategy minimizes the influence of outliers on the fit, providing an effective alternative to the deletion of specific data values. Extreme outliers farther from the fitted line than would be expected get a lower weight, while points close to the fitted model get full weight. To estimate the model parameters, the nonlinear regression procedure was used. The Marquardt iterative method was chosen since it represents a compromise between the linearization method and the steepest descent method. However, fitting results (see green line in Fig. 1) strongly depend on the definition of the initial values of the model parameters to be estimated.

2.3.1. Initial values for the parameters

Specification of the starting values is one of the most difficult issues when estimating parameters of nonlinear models. However, the problem can be simplified by exploiting domain-specific knowledge. Unsuitable initial values may result in longer iterations, greater execution time, non-convergence of the estimation method, and possibly con-

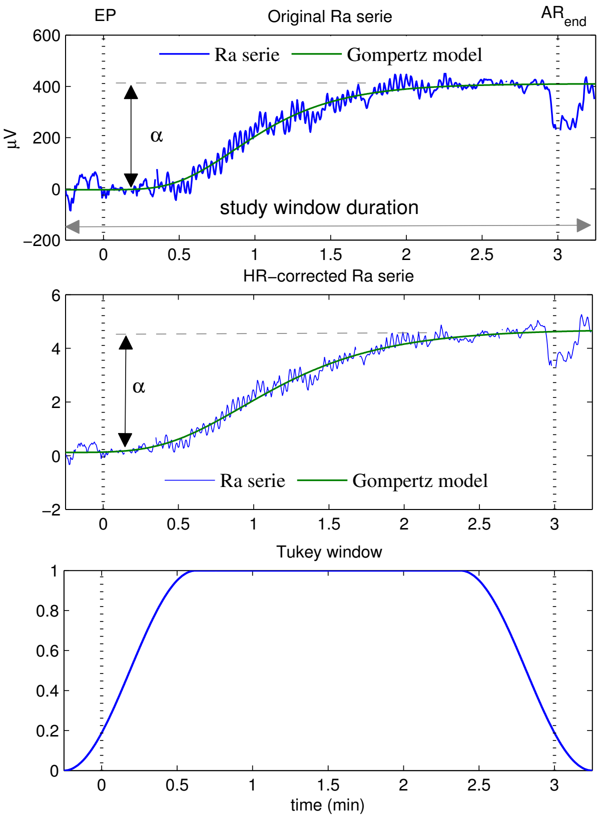

Figure 1. A real example of Gompertz model fitted on the Ra serie evaluated in lead V5: a) Original Ra serie; b), Ra serie corrected by HR; c): initial weights (Tukey window).

vergence to local minima. In the case of the Gompertz model, initial parameter values are set as recommended in [8].

2.4. Statistical analysis

The fitting procedure was applied to all series corresponding to the different markers evaluated in the 12 available leads. Both the heart rate-corrected versions and the original ones were used. The three shape-related parameters estimated from the fitting process were then compared by separating patients in two groups according to symptomatology. The Mann-Whitney non-parametric test was applied and the level of significance was set to 0.05.

3. Results and conclusions

Table 1 presents the leads whose corresponding fitting error values were smaller among the 12 leads for each analyzed ECG marker. It can be observed that left precordial leads V4-V6 are the most addecuated leads when fitting the model on the Ra, α_R and $\mathcal{S}_\mathcal{U}$ series, while leads V1-V3 are instead when fitting the model on the Sa, α_S and $\mathcal{S}_\mathcal{S}$ series, which can be related to the QRS morphology in these leads. Similar results were obtained if the model is fitted on HR-corrected versions of the same markers.

Table 1. Best leads in terms of fitting error.

Marker	**Leads (error, RMSE)**
Ra	V4= 0.0258, V5= 0.0247, V6= 0.0246, II = 0.0273
Sa	V1= 0.0281, V2=0.0295, V3= 0.0249, V4= 0.0251
$\mathcal{S}_\mathcal{U}$	V4= 0.0259, V5= 0.0240, V6= 0.0234, II = 0.0245
$\mathcal{S}_\mathcal{D}$	V3= 0.0218, V4= 0.0200, V5= 0.0198, V6= 0.0219
$\mathcal{S}_\mathcal{S}$	aVL= 0.0227, V4= 0.0266, V5= 0.0310, V6= 0.0258
ϕ_R	V4= 0.0233, V5= 0.0204, V6= 0.0204, II = 0.0211
ϕ_S	V1= 0.0236, V2=0.0236, V3= 0.0242, V4= 0.0255

3.1. Parameters differences among groups

One of the most significant difference observed when comparing the two BrS groups was found to be in the parameter α, indicating a remarkable dynamic in terms of changes occurring during the active recovery period. Figure 2 shows boxplot graphs associated with the markers Ra, $\mathcal{S}_\mathcal{U}$, $\mathcal{S}_\mathcal{D}$, ϕ_R in leads V4-V6. The p-values concerning each group comparison are also displayed. From these results, the main observation we can highlight is that patients who were diagnosed as asymptomatic developed larger delta values than symptomatic patients during the studied period. The same comparison regard of α was found to be no significant for most of the HR-corrected markers.

The other two parameters b and c characterizing both the change speed and lag, respectively, of dynamic depolarization, presented significant differences in the slope $\mathcal{S}_\mathcal{U}$ and in both the ϕ_R and ϕ_S angles, specially in their HR-corrected versions. In the case of $\frac{\mathcal{S}_\mathcal{U}}{HR}$, the parameter c was found to be significant in leads V4 (p = 0.021) and V6 ($p = 0.039$) whereas it happened in lead II (p = 0.029) for $\frac{\phi_R}{HR}$ and in leads V5 (p = 0.005) and V6 (p = 0.037) for ϕ_S. In all cases, the symptomatic group presented greater values, indicating the presence of larger lags in the changes occurring in these markers. Regarding the change speed given by b, no significant difference were found between groups.

3.1.1. Normalized time-series

Results obtained for normalized time-series confirmed thet symptomatic patients present larger lag values, supported by the outcomes obtained for Ra in lead aVF (p= 0.002), for $\frac{\mathcal{S}_\mathcal{U}}{HR}$ in the leads V4 (p= 0.021) and V6 (p= 0.039) and for both $\mathcal{S}_\mathcal{S}$ and α_S in lead V6 (p= 0.016 and p= 0.015, respectively). The change speed (b) values were greater in asymptomatic patients for the slopes $\mathcal{S}_\mathcal{D}$ (p= 0.004) and $\mathcal{S}_\mathcal{S}$ (p= 0.027) in leads III and lead V6, respectively, as well as for the markers α_R in lead II (p= 0.039) and $\frac{\alpha_S}{HR}$ in lead V1 (p= 0.021).

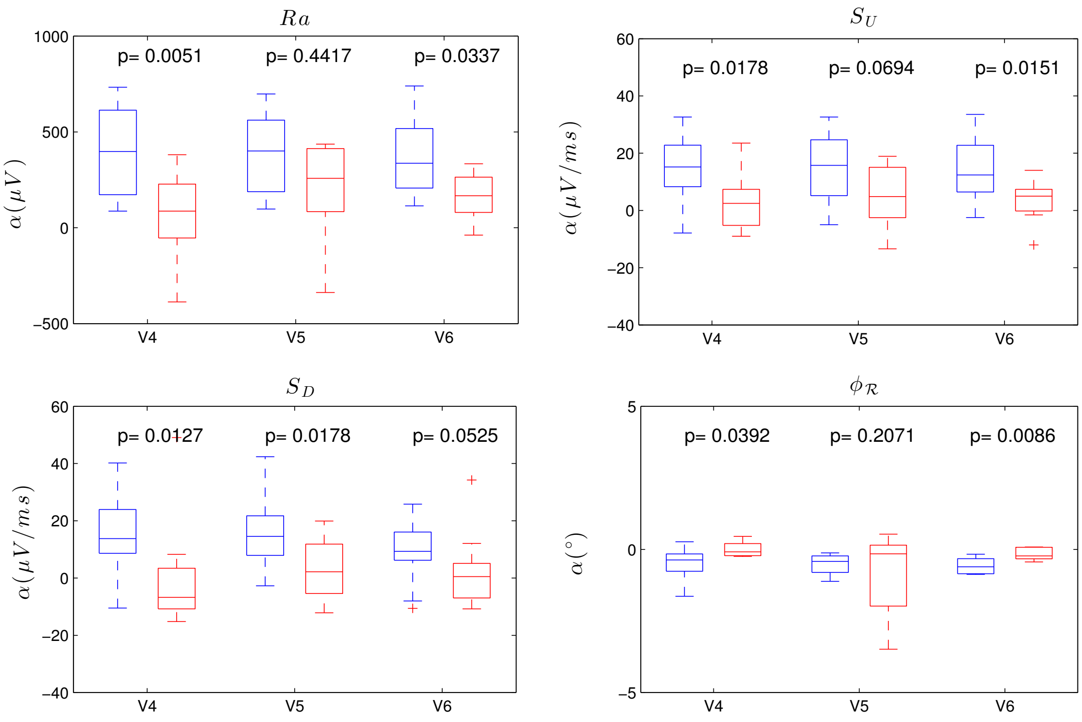

Figure 2. Comparison of parameter α between Brugada groups in leads V4-V6 for the markers Ra, $\mathcal{S}_{\mathcal{U}}$, $\mathcal{S}_{\mathcal{D}}$ and $\alpha_{\mathcal{R}}$.

4. Conclusions

Results obtained in this study showed that significant differences between symptomatic and asymptomatic Brugada patients can be found, when comparing the amount of change achieved during the first three minutes immediately after the exercise cessation (recovery period), as evaluated by depolarization ECG markers. Normalization of the studied markers allowed a better understanding of their dynamics, showing that symptomatic patients present larger lag and lower change speed values than asymptomatic patients. Also, the influence of the HR over was found to be negligible when distinguishing between groups.

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