Analysis of QRS Alterations during Stress Test Recordings on Patients with Brugada Syndrome

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Abstract

Brugada syndrome (BrS) is characterized by the occurrence of syncope and sudden cardiac death due to cardiac arrhythmia, in patients with apparently structural normal heart. A study population of 46 patients with suspected or diagnosed BrS was analyzed. Six patients presented clinical symptoms, 13 patients did not present any clinical symptoms, and 27 were negatively diagnosed of having the syndrome. Stress test ECG recordings were analyzed for all the patients by evaluating a QRS-angle index during the entire duration of the test. Changes in these angles, measured at different stages of the test were statistically compared among the three patient groups. The R-wave angle showed its highest changes in augmented leads aVL (-11.9°$\pm$ 10.9°) and aVR (-7.9°$\pm$ 11.7°) at the time of maximum effort. Similar changes were observed in both asymptomatic and control groups, but slightly different to the symptomatic group, in particular during the active (AR) and passive (PR) recovery phases. Statistically significant differences were found between symptomatic and asymptomatic groups in such phases (AR: p=0.0125, PR: p=0.0194 in aVR), but not between asymptomatic and non-diagnosed BrS subgroups (AR, p=0.2039, PR: p=0.5826). This study shows that morphologic changes during depolarization induced by stress test are associated with the symptomatic BrS, particularly during the recovery phases.

1. Introduction

Brugada syndrome (BrS) is a genetic pathology, firstly described more than 20 years ago, associated with a high risk of sudden cardiac death (SCD) in patients with an apparently normal structural heart [1]. Other clinical features of Brugada syndrome include a typical ECG pattern of right bundle branch block (RBBB) with persistent ST-segment elevation in the right precordial leads V1-V3, being the coved type-1 ECG pattern the diagnostic one in conjunction with at least documented polymorphic ventricular tachycardias (VT) or ventricular fibrillation (VF), family history of SCD or type 1 ECG pattern, inducibility on programmed electrical stimulation (PES), syncope or nocturnal agonal respiration [2].

The main challenges regarding BrS are related to patient risk stratification and the definition of the best treatment approach. The implantation of a cardioverter defibrillator (ICD) is recommended for symptomatic patients. However, the decision of implanting an ICD is more complex on asymptomatic patients, who represent between 60-64% of the patients diagnosed of having this syndrome, since they show a lower risk of arrhythmic events than symptomatic subjects [3]. The difficulty here is to identify which of the asymptomatic patients may benefit from an ICD implantation.

Depolarization disorders have been one of the two main hypotheses underlying the pathophysiology of BrS, together with the hypothesis of repolarization disorders. Basically, depolarization disorders are associated with conduction delays within the right ventricular outflow tract (RVOT), combined with mild structural RV derangements [4]. Based on this particular hypothesis, this study is mainly focused in the analysis of a QRS angle-based method, in order to investigate its ability to unmask potential differences between asymptomatic and symptomatic patients. For this purpose, we analyze ECG recordings acquired during a stress test in a population of patients suffering from BrS.

2. Methods

2.1. Population

The population used for this study comprises 46 patients with suspected or diagnosed Brugada syndrome, enrolled in the Brugada project carried out by the Department of Cardiologie et Maladies Vasculaires du CHU de

Rennes (Rennes, France). From the total population, 6 patients presented clinical symptoms including VF or syncope (symptomatic patients, group S), 13 were diagnosed as having the syndrome, but did not present any clinical symptoms (asymptomatic patients, group A), and in the remaining 27 patients, the coved-type 1 ECG pattern of BrS was not induced under any diagnostic test (non-diagnosed group, group ND).

A standard 12-lead ECG (Cardionics, Webster, Texas) recording with a sampling rate of 1000 Hz was acquired for each patient during an exercise test (stress test), using an ergometer and under the following protocol:
Warm-up: 2 minutes of initial workload pedaling at 50 Watts (30 W for women).
Exercise phase: +30 W (+20 W for women) during 2 minutes followed by subsequent increments of +20 W every 2 minutes and until reaching tiredness.
Active recovery phase (ARP): 3 minutes of exercise with a workload of 50 W.
Passive recovery phase (PRP): 3 minutes at rest.

The mean duration of the exercise test was 13.9 ± 3.9 minutes while exhaustion was expected to be reached by the 85% of the maximum theoretical heart rate.

2.2. Preprocessing

All ECG signals involved in the study were preprocessed before the evaluation of the analyzed indices. This preprocessing step included automatic QRS complexes detection, normal beats selection according to [5], baseline drift attenuation via cubic spline interpolation and wave delineation using a wavelet-based technique [6].

2.3. The R-wave angle

The angle-based method proposed in this study for evaluating QRS alterations during stress test ECG recordings is illustrated in Fig. 1 and it can be calculated by the following general expression:

$$\Phi_{\text{R}} = \arctan\left(\left|\frac{s_{\text{U}} - s_{\text{D}}}{1 + s_{\text{U}} s_{\text{D}}}\right|\right) \quad (1)$$

where s_{U} and s_{D} are the slopes of the lines l_{U} (red lines) and l_{D} (blue lines), respectively, expressed in mm/mm in the case of having a two-dimensional (2D) euclidean space coordinate system. Here, the amplitude of the ECG signal is given in μV and the time in ms, thus, the values of the original slopes $\hat{s}_{\text{U}}$ and $\hat{s}_{\text{D}}$ giving in μV/ms must be reescaled to mm/mm in order to have an angular measurement in a proper scale matching to the conventional ECG tracings in clinical printouts (i.e.; a paper speed of 25 mm/s and a gain of 10 mm/mV). To do that, s_{U} and s_{D} are multiplied by a scale factor of 0.4 for this particular case, resulting in:

$$\Phi_{\text{R}} = \arctan\left(\left|\frac{\hat{s}_{\text{U}} - \hat{s}_{\text{D}}}{0.4(6.25 + \hat{s}_{\text{U}} \hat{s}_{\text{D}}}\right|\right) \quad (2)$$

Further details of the methodology used for evaluation this particular angle-based method are described in [7].

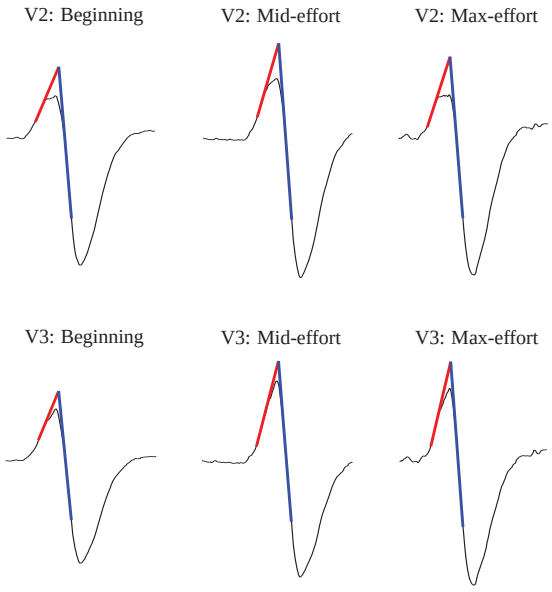

Figure 1. Examples of the QRS angle evaluated in this study. Each column displays representative beats corresponding to the beginning, middle and end of the effort in leads V2 and V3. Red and blue lines represent l_{U} and l_{D}, respectively.

2.4. Statistical analysis

After evaluation of the R-wave angle throughout the entire stress test recording, averaged values $\bar{\Phi}_{\text{R}}$ were obtained at specific time instants, including the beginning of the test (TB), the half time between the effort peak and the beginning of the test (ME), the maximum effort peak (EP), the end of the ARP and the end of the PRP. Each averaged value was calculated in a 30-sec window duration, just before the end of each stage, except for the TB stage where the first 30 seconds of the angle series were used. Subsequently, delta values $\Delta\Phi_{\text{R}}$ between the averaged values obtained at TB and the other different stages (ME, EP, ARP and PRP) were calculated and expressed in mean $\pm$ SD.

To find out whether there are significant differences between the delta values obtained at different stages of the test, and between different groups of patients (S, A and ND groups), the Wilcoxon-Mann-Whitney non-parametric test was applied. The level of significance was set at 0.05.

3. Results

Figure 2 shows the time course of the heart rate (HR) during the stress test, together with the time course of Φ_{R} and R-wave amplitude in lead aVR. It can be seen that Φ_{R}

becomes narrower while Ra and the HR increase. These variables tend to their initial values at the end of the PRP.

On average, the maximum HR achieved at the time of maximum effort peaks and just before starting the recovery phase was 160.6 $\pm$ 26.1 beats/min for the whole study population. For the different groups of patients, the maximum HR achieved was 164.6 $\pm$ 20.9 beats/min in the group A, 156.8 $\pm$ 30.7 beats/min in the group S and 159.6 $\pm$ 27.9 beats/min in the ND group.

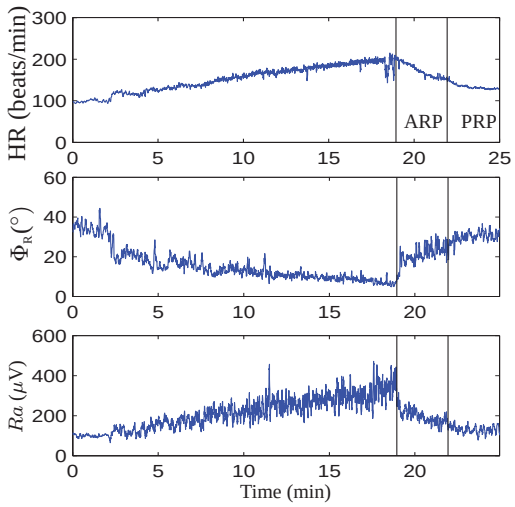

Figure 2. Time course of: (Top) the heart rate during the entire stress test for a particular patient of the study; (Middle) angle Φ_R and (Bottom) R-wave amplitude in lead aVR. Vertical lines mark the beginning of both ARP and PRP.

Delta values of the R wave angle, $\Delta\Phi_R$, evaluated at the time of maximum effort with respect to the beginning of the test, presented the greatest values in augmented leads aVL (-11.9 $\pm$ 10.9°) and aVR (-7.9 $\pm$ 11.7°) rather than in precordial leads V1 (-2.2 $\pm$ 7.8°), V2 (-0.3$\pm$ 4.9°) and V3 (0.2$\pm$ 1.9°). The same behavior was observed when the patients are separated by groups, but with some differences between them. Figure 3 shows the same observation as well as the evolution of the changes throughout the different stages of the test in the leads V1, V2, aVL and aVR. It also shows that the shape of the evolution patterns was found to be similar between asymptomatic and no diagnosed groups, whereas it was slightly different in the symptomatic one, especially during the recovery phases.

Table 1 displays the values as mean $\pm$ SD of $\Delta\Phi_R$ for the three groups of patients at the EP, ARP and PRP stages. Results corresponding to the statistical tests (Wilcoxon-Mann-Whitney test) applied to compare changes in the Φ_R among different groups of patients are also shown. As expected from the results displayed in Fig. 3, differences between symptomatic and asymptomatic groups were found to be statistically significant in such phases (ARP: p =

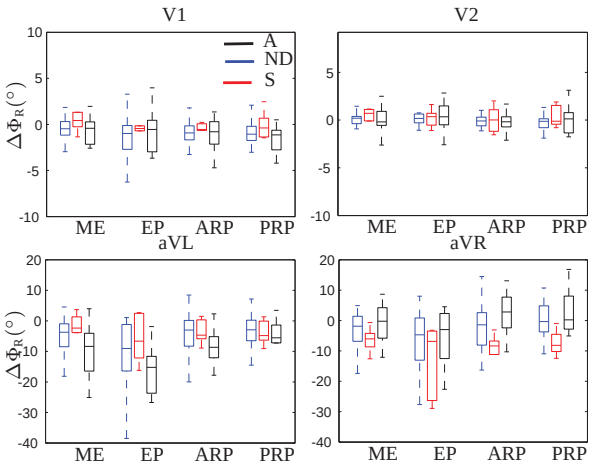

Figure 3. Boxplots of the delta values $\Delta\Phi_R$ evaluated at the stress test stages ME, EP, ARP and PRP for the three group of patients (asymptomatic, symptomatic and non diagnosed) in the precordial leads V1 and V2 and in the augmented leads aVL and aVR.

0.0125, PRP: p = 0.0194 in lead aVR), but not between asymptomatic and non-diagnosed Brugada groups (ARP, p = 0.2039, PRP: p = 0.5826). When comparing symptomatic and non-diagnosed groups, the test was statistically significant only in the passive recovery phase (PRP: p = 0.0168).

4. Discussion and conclusions

In this study we evaluate a QRS angle-based method on a database that includes patients with BrS and patients suspected of having this syndrome. The proposed method was used to determine potential alterations that occur in the ventricular depolarization (QRS complex) during a stress test and to identify differences between asymptomatic and symptomatic Brugada patients, and between the above two and patients who have not been diagnosed with the BrS so far, but have family antecedents.

Globally, the most significant changes of R-wave angle were observed at the peak of maximum effort. It is to note that such changes were more prominent in the augmented leads aVL and aVR and not in the right precordial leads (V1-V3), which are the most commonly used in the clinical diagnosis of this particular syndrome. This finding is clearly reflected in Fig. 3, where one can appreciate that the evolution of the changes, evaluated at different stages of the test, shows very little variation in leads V1 and V2 with respect to that observed in leads aVL and aVR, even when patients are separated into groups. Importantly, although lead aVR has often been categorized as having a negligible clinical relevance, it is evident that, in this study as well as in other ones related to this [8] and other car-

Table 1. Mean±SD of $\Delta\Phi_R$ computed at EP, ARP and PRP in the leads aVL and aVR and for the three groups. P-values of the statistical test applied to compare the different groups of patients are also shown for the two leads.

Lead	EP	ARP	PRP	**Lead**	EP	ARP	PRP
aVL				**aVR**			
S	-6.1 ± 7.6	-3.7 ± 3.9	-3.7 ± 4.1	S	-12.2 ± 11.8	-8.2 ± 3.1	-7.3 ± 4.3
A	-18.0 ± 12.2	-9.7 ± 8.5	-7.1 ± 9.7	A	-6.7 ± 13.0	-0.4 ± 11.7	1.1 ± 10.2
ND	-10.8 ± 10.4	-5.4 ± 8.5	-3.9 ± 7.0	ND	-7.5 ± 11.7	-3.1 ± 8.9	-0.3 ± 8.3
All	-11.9 ± 10.9	-6.6 ± 8.2	-4.9 ± 7.5	All	-7.9 ± 11.7	-3.2 ± 9.5	-0.9 ± 8.6
Comp	p	p	p	**Comp**	p	p	p
S/A	0.0415^*	0.1246	0.5743	S/A	0.1518	0.0125^*	0.0194^*
S/ND	0.3156	0.7974	0.9358	S/ND	0.2936	0.0587	0.0168^*
A/ND	0.0751	0.0856	0.4053	A/ND	0.6649	0.2039	0.5826

diac diseases [9, 10], the analysis of lead aVR has shown to have an important clinical value. In [8], a prominent R wave in lead aVR (aVR sign) was reported in Brugada patients, mostly symptomatic, who suffered a recurrence during the follow-up period (polymorphic VT/VF or syncope). This aVR sign was associated with a delayed RV activation because of a rightward direction of depolarization wave.

The most important outcome of this study is that the differences among groups of patients were found to be significant during the recovery phase (active and passive phases), especially when symptomatic and asymptomatic patients were compared. When comparing these two groups with the non-diagnosed one, only the symptomatic group was statistically different to it at the very last part of the recovery ($p = 0.0168$). Thus, these results suggest that there may be significant differences in the response of the patients, according to their clinical diagnoses, when an increase vagal activity occurs.

This preliminary study showed that QRS angle changes induced by stress test, in particular during the recovery phases, which are characterized by an increased parasympathetic tone, are associated with patients diagnosed with the Brugada syndrome. This finding should be considered in further studies, in combination with the analysis of repolarization changes, to characterize the electrophysiological changes induced by Brugada syndrome. Since the study carried out here is based on dynamic analysis, performing classification analysis between different patients groups would also be of interest.

Acknowledgements

This work was supported by the French Ministry of Health (Programme Hospitalier de Recherche Clinique - PHRC Régional) and by project TIN2013-41998-R from MINECO, Spain. EP acknowledges the financial support of Ramón y Cajal program from MINECO.

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