Diagnosis of Non-Type I Brugada Syndrome Patients by Vectorcardiographic Measurements

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Abstract

Brugada syndrome (BrS) causes sudden death in patients with structurally normal hearts. Manifestation of BrS in the ECG is dynamic and most patients do not show unequivocal signs of the syndrome during ECG screening. We studied the vectorcardiograms (VCG) of 98 BrS patients, 61 of whom did not present type I ECG at the time of the recording and 59 control subjects. The orientation and duration of terminal R waves present in -X and/or –Y orthogonal leads were measured. Terminal R waves were present in 85% BrS patients without a type I ECG, 53% of control subjects and 96% of RBBB patients. Terminal R waves of BrS patients were longer than those of healthy subjects. Orientation of terminal R waves of BrS patients and healthy subjects was similar, but differed in RBBB patients. Identification of BrS patients without a type I ECG can be highly improved by measuring the duration and orientation of terminal R waves.

1. Introduction

Brugada syndrome (BrS) is a heritable arrhythmia syndrome that causes sudden death in young adults with structurally normal hearts. BrS is diagnosed in basis on the clinical and familiar history of the patient and a characteristic electrocardiogram (ECG) pattern displaying a coved-type ST segment ≥ 0.2mV in right precordial leads (referred as type I ECG) [1].

However, this clinical manifestation is often dynamical and shows variations over time, including transient normalization of the ST segment and conversion to a saddleback-type pattern [2]. Only 25 % of ECGs of BrS patients display a type I ECG [3] and thus detection of this disorder is not always possible in absence of previous symptoms or a familiar history of the disease.

Since BrS is reflected only as an electrical disorder, the ECG is the only not invasive technology that allows, up to the date, to diagnose the disease, which does not show any sign in the different modalities of medical image. Our hypothesis is that BrS patients may present special ECG characteristics, even in absence of a type I ECG, such as the presence of terminal R waves in right precordial leads. Terminal R waves are not specific for BrS patients and more often are linked to Right Bundle Branch Block (RBBB). However, terminal R waves of BrS patients and those present in other clinical conditions may present different characteristics that are not easily determined from the standard ECG. In the present study, vectorcardiographic representation of terminal R waves of BrS, RBBB and Healthy patients were compared. The vectorcardiogram (VCG) is a three-dimensional representation of the electrical activity of the heart and thus provides spatial information that may be hidden in the standard ECG. The VCG has been used in evaluation of myocardial infarct size [4], and it shows more sensitivity than the ECG for the diagnosis of multiple infarctions, which are associated with left anterior fascicular block [5]. In this study we aim at the determination of temporal and spatial characteristics of terminal R waves of BrS patients that may allow discrimination from those appearing in non-BrS subjects.

2. Methods

2.1. Patient population

The study group consists of 98 BrS patients and 59 controls. Among all BrS patients included in our study, 37 patients presented Type 1 ECG (BrS-1) whereas 61 patients did not present a type I ECG (BrS-N1). The clinical diagnosis of BrS was established prior to our study based on the presence of a coved-type ST-segment elevation ≥ 0.2 mV in two right precordial leads either spontaneously or after ajmaline or flecainide administration. In our control population we included 25 Right Bundle Branch Block (RBBB) patients and 34 healthy subjects. RBBB was diagnosed based on the presence of terminal R waves in right precordial leads and

slurred S waves on left precordial or standard leads. RBBB patients were classified as complete RBBB (CRBBB) if presented a QRS complex duration longer than 120 ms or as incomplete RBBB (IRBBB) otherwise. Selected control subjects had no history of previous heart disease and a normal resting ECG.

2.2. Signal acquisition

Vectorcardiograms were obtained from 67-lead Body Surface Potential Mapping (BSPM) recordings. A total of 67 chest and back leads were acquired simultaneously for each subject during 2 minutes. Electrodes were mounted as described previously [6] (see Fig.1). Signals were acquired at a sampling rate of 2048 Hz, with a resolution of 1 μV and a bandwidth of 500 Hz.
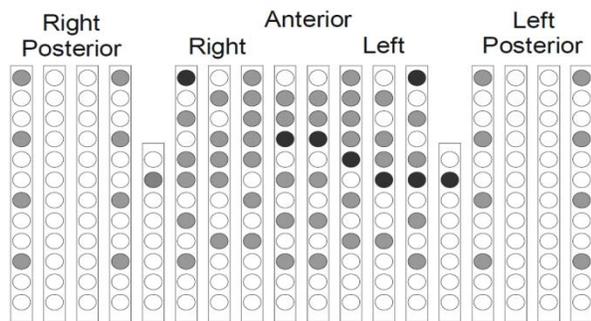

Figure 1. Electrode position in our BSPM system. Black circles correspond to the approximated location of precordial, right and left arm leads.

2.3. ECG signal processing

ECG signals were processed using Matlab 7.10.0 (The Mathworks Inc,). First, baseline was estimated by filtering with a Butterworth 10th order low-pass filter with a cut-off frequency of 0.6 Hz after decimation to a sampling frequency of 51.2 Hz. Baseline was interpolated to 2048 Hz and subtracted to the original recording. Then, ECG signals were filtered with a 10th order, low-pass Butterworth filter with a cut-off frequency of 70 Hz. Power spectral density of all signals was computed by using Welch periodogram with a hamming window of 8 seconds and 50% overlap. Leads presenting more than 0.5% of their spectral content at 50Hz were filtered with a 2nd order IIR notch filter centered at 50 Hz. All leads were visually inspected after filtering and leads with noticeable noise were excluded from further analysis.

QRS complexes were detected by selection of local maxima after steeper slopes in a simplified ECG obtained by polyline splitting [7]. Then, averaged PQRST complexes were obtained by template matching-averaging. Fiducial points in averaged beats were detected by selecting points preceding or following segments with steeper slopes in a simplified beat obtained

by polyline splitting. Fiducial point detection was then manually verified. P_{onset} and T_{offset} served as anchoring points for baseline estimation on the averaged beats and remaining baseline was subtracted.

Orthogonal leads were computed from surface measurements as a linear combination of 7 surface potentials by using the same weightings and electrode locations as proposed by Frank [8]. Potentials at surface locations required for computation of Frank leads but not recorded in our BSPM grid were interpolated by cubic spline interpolation.

2.4. Terminal R waves measurements

Terminal R waves were defined as terminal positive deflections on the QRS complex of X or Y leads larger than 0.1 mV and following a local minimum on the QRS complex. Onset of terminal R waves was defined as either zero voltage crossing of the potential before the terminal R wave maximum value or the time instant of a previous local minimum depending on QRS morphology. Offset of terminal R waves was defined as the time instant with a steeper slope after the terminal R wave maximum value. Duration of terminal R waves was measured as the difference between offset and onset time instants. Amplitude of terminal R waves was defined as the maximum potential within the terminal R wave. The angle of orientation of terminal R waves at the front (φ_{FP}) and horizontal (φ_{HP}) planes were calculated as the arctangent of the values obtained from terminal R wave in lead X and Y, as well as X and Z, respectively.

2.5. Statistical analysis

Numeric values were expressed as mean ± standard deviation or as frequencies and percentages. Comparisons among groups were made using an unpaired Student´s test. A p value lower than 0.05 was considered statistically significant to reject the null hypothesis.

3. Results

3.1. VCG descriptors

General shape of VCG loops of BrS patients was similar to that of healthy subjects, with the QRS loop in the frontal plane (FP) mainly located in the left quadrant (see Fig. 2A Left) and in the left posterior quadrant in HP (see Fig. 2A Right). The last portion of the QRS complex in BrS patients, however, points towards the right half of the torso, both in BrS-1 and BrS-N1 groups giving rise to the terminal R' wave. QRS loops of RBBB patients (both IRBBB and CRBBB) also present a terminal wave directed towards the right (see Fig. 2B and 2C).

Table 1. VCG descriptors

	BrS-1 N=37	BrS-N1 N=61	CRBBB N=13	IRBBB N=12	Healthy N=34
Terminal R wave	27 (73%)	52 (85%)	12 (92%)	12 (100%)	18 (53%)
Terminal R wave φFP (deg)	37 ± 140 [#]	85 ± 107 [#]	160 ± 20 [†]	114 ± 93	62 ± 100
Terminal R wave φHP (deg)	83 ± 109 [+#*]	117 ± 47 [#*]	-39 ± 138 [†]	-82 ± 123 [†]	99 ± 31
Terminal R wave Duration (ms)	194 ± 99 [†]	166 ± 107 [†]	163 ± 78 [†]	145 ± 75	106 ± 38
Terminal R wave Amplitude (µV)	261 ± 122	243 ± 119 [#]	348 ± 165 [†]	247 ± 121	231 ± 87

($p < 0.05$) [+] vs. BrS-N1, [#] vs. CRBBB, [*] vs. IRBBB, [†] vs. healthy

However, terminal waves of RBBB patients point towards the front whereas those of BrS patients point towards the back, as seen on the horizontal plane. Main vectorcardiographic characteristics of groups are summarized in table 1. BrS patients presented more terminal R waves than healthy individuals (80% and 53% respectively). Remarkably, 85% of BrS-N1 patients presented terminal R waves which were longer than those appearing in healthy individuals (166±107 ms vs. 106±38 ms, p<0.05). Terminal R waves of CRBBB patients had a similar duration than those of BrS-N1 patients (163±78 ms vs. 166±107 ms, p<0.05) but higher amplitude (348±165 µV vs. 243±119 µV, p<0.01) and presented a different orientation on the horizontal plane (-39±138° vs. 117±47°, p<0.01). Terminal R waves of IRBBB patients had a similar duration than those of BrS patients (145±75 ms vs. 166±107 ms, p<0.05) but a different orientation on the horizontal plane (-82±123° vs. 117±47, p< 0.01).

3.2. Diagnosis of BrS-N1

Based on the differences observed in the terminal R waves of BrS patients and controls, we defined a diagnostic criterion for terminal R waves in the detection of BrS based on ROC analysis. We defined as diagnostic terminal R waves as those longer than 76 ms and with an orientation in the HP higher than 0°. According to this criterion we achieved a correct detection of BrS in 74% BrS-N1 patients, with sensitivity equal to 73% and specificity equal to 75%.

4. Discussion

Current ECG criterion for the detection of Brugada syndrome has a low sensitivity due to the transient nature of the ECG in BrS patients. Terminal R waves often appear in BrS patients, but they are not diagnostic for Brugada Syndrome because they also appear in RBBB and even in healthy patients. We have shown that orientation and duration of these terminal R waves allow a discrimination of BrS with a higher sensitivity than the presence of a type I ECG.

Terminal R waves of BrS patients show the same orientation than those in healthy subjects and thus the depolarization sequence may be similar in both groups. In both healthy and BrS patients the right ventricular outflow tract (RVOT) may be the last myocardial region to be depolarized. However, terminal R waves of BrS patients are more often present and longer than in healthy individuals. This finding is consistent with the involvement of the RVOT region in the development of arrhythmogenesis in BrS patients. Both a slower activation of the RVOT region or the presence of a deeper notch in phase 1 of the action potential in RVOT region could give rise to these long terminal R waves in BrS patients.

Terminal R waves present in BrS patients, in contrast, have a different spatial orientation than those appearing in RBBB patients, even in incomplete RBBB. This is consistent with an altered activation sequence in RBBB, with a last activation of the anterior region of the right ventricle that is not taking place in BrS patients. Until recently, it was unclear whether BrS patients had right bundle branch block, as it was first postulated [1]. A recent report based on VCG representation demonstrated that activation sequence in type I ECG BrS patients differed from that of RBBB patients [9]. Here we go a step further and we demonstrate that VCG loops of the QRS complex of BrS patients show an activation pattern that does not depend on the presence of a coved-type ST elevation and is easily distinguishable from that of a RBBB patient. Analysis of the orientation of terminal R waves in patients suspected from BrS but without a type I ECG may help in establishing a diagnosis.

5. Conclusion

R' waves of BrS patients are longer than those appearing in healthy subjects and oriented towards the posterior part of the torso, whereas R' waves of RBBB patients are oriented towards the anterior torso. Identification of BrS patients without a type I ECG can be highly improved by measuring terminal R wave parameters.
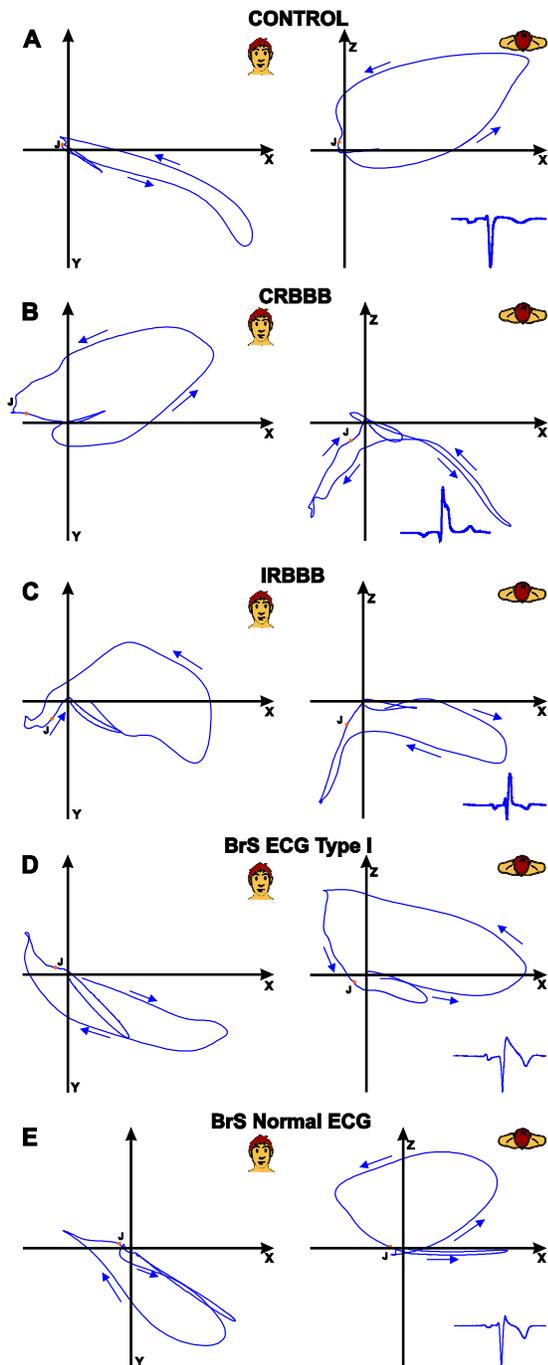
Figure 2. Vectorcardiograms of patients included in our study. Panel A: healthy subject, Panel B: CRBBB patient, Panel C: IRBBB, Panel D: BrS-1, Panel E: BrS-N1 patient. On the left, VCG representation on the frontal plane. On the right, VCG representation on the horizontal plane. Arrows indicate the direction of the inscription of the loop. J point (offset of the QRS complex) as detected in leads X and Y is displayed. For each patient, lead V1 is shown on the rightmost part of each panel.

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