

# QRS&T Wave Alternans and Beat-to-Beat Ventricular Repolarization Variability Assessed from 12-Lead Holters in Patients with Suspected Brugada Syndrome

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## Abstract

*Microvolt 2:1 T wave alternans (TWA) and increased beat-to-beat repolarization variability have been reported in Brugada syndrome (BS) and could be related to increased arrhythmic risk. We hypothesized that among patients (pts) with suspected BS, those with positive diagnostic ajmaline test (i.e. likely carriers of BS mutations) have greater TWA or beat-to-beat repolarization variability on 24-hour Holter recordings than those with negative tests. Six 5-minute night-time ECGs in 14 pts with suspected BS and positive (n=7, 4 male) and negative (n=7, 3 male) ajmaline tests were analyzed for a) 2:1 alternans of the QRS and T using Principal Component Analysis (PCA) of QRS and T waves b) PCA variability measured as standard deviation of PCA of all QRS and T waves. Beat-to-beat repolarization variability, but not 2:1 TWA is increased in pts with positive ajmaline tests. Regular QRS alternans is increased in pts with positive ajmaline tests.*

## 1. Introduction

Macroscopic (visible) and increased microscopic (of the order of microvolts) regular 2:1 T wave alternans (TWA) reflect temporal instability of ventricular repolarization and are predictors of increased risk of ventricular arrhythmias in patients with different cardiac abnormalities [1]. In patients with Brugada syndrome (BS), both macroscopic [2,3] and microscopic TWA [4,5] have been described, although their value for prediction of the arrhythmic risk in BS is still unclear [2,4,5]. Increased irregular beat-to-beat variability of the ST-T segment has also been reported in patients with BS during diagnostic pharmacologic testing [6].

Currently, microscopic TWA is predominantly assessed during exercise testing or atrial pacing [7,8]. Only few studies have tried to investigate TWA from ambulatory Holter recordings using the so-called

modified moving average (MMA) method [9] and none of them has addressed patients with BS.

In this study, we used a previously reported and validated method for TWA detection based on principal component analysis (PCA) [10] to assess beat-to-beat variability of the QRS and ST-T wave from ambulatory Holter recordings acquired in patients who previously had undergone diagnostic ajmaline test for suspected BS.

## 2. Methods

### 2.1. The ECG database

Ambulatory 24-hour 12-lead Holter recordings (CardioMem CM 3000-12, Getemed, GE Medical Systems, 1000 Hz, 5  $\mu$ V resolution) were acquired in 14 patients with suspected BS (7 men, age 35 $\pm$ 18 years, range 14 – 71 years) who previously had undergone diagnostic ajmaline test [11] for suspected BS. The test was positive according to accepted criteria [11] in 7 patients (4 male) and was negative in 7 patients (3 male). In patients with BS, the arrhythmic risk is increased during rest, predominantly during sleep [12]. Therefore in each patient we selected six 5-minute ECG recordings with visibly low level of noise acquired during nighttime (10pm-6am) (84 ECGs in total). They were exported into XML text files for further analysis.

The following methods of analysis were used:

- 2:1 alternans of the QRS (QRS-WA) and T waves (TWA) using a validated method based on amplitude and PCA-derived parameters [10];
- beat-to-beat variability of ventricular repolarization.

### 2.2. Signal preprocessing

Moving averaging of samples in one period of the powerline interference was performed. This filter is meant to eliminate the power-line interference. Its frequency response has a first zero at the interference frequency 50 Hz (60 Hz).

A smoothing procedure for electromyographic noise

suppression was applied [13]. It uses the least-squares approximation method, applied for defining the weighting coefficients for each sample of the selected smoothing interval of 60 ms.

A high-pass recursive filter for drift suppression with a cutoff frequency of 0.64 Hz has been used [14].

### 2.3. J-point and Tend delineation

QRS detection using combined adaptive thresholding was applied [15]. The delineations of QRSONsets, J-points, Tbegs and Tends were automatically performed [16], and the T amplitude was calculated in a combined lead simulating the spatial vector [14].

The transform to the orthogonal leads (X,Y,Z) was performed using ‘primary leads’, i.e. the 8 potential differences referred to the left leg electrode F [14]. These

primary leads were obtained from the 12-lead ECG recordings, following the conversion formulae [17]:

$$R_F = -II; L_F = -III; C_{iF} = V_i - (II+III)/3, \text{ for } i=1:6$$

The orthogonal leads were evaluated by:

$$X = 0.5 * \text{abs}(C_{4F} - C_{1F});$$

$$Y = \text{abs}(R_F);$$

$$Z = \text{abs}(R_F - C_{2F});$$

The combined lead (CL), which is the spatial vector in this case, is calculated by:

$$CL = 0.5(X+Y+Z+0.25(\text{abs}(X-Y)+\text{abs}(X-Z)+\text{abs}(Y-Z)));$$

All ECG recordings and the delineated boundaries were visually observed, and corrected if necessary. Premature ventricular contractions and noisy heart beats were manually excluded from the analysis (Figure 1).

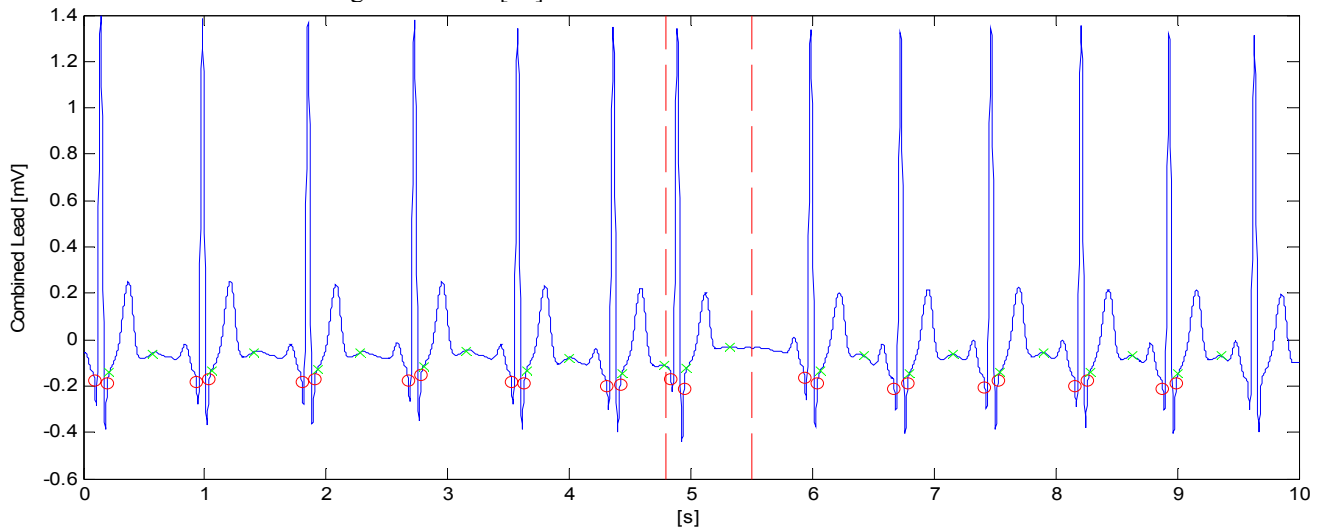


Figure 1. Automatic delineation of QRSONset (red ‘o’), J-point (red ‘o’), Tbeg (green ‘x’) and Tend (green ‘x’) on the Combined Lead. The premature ventricular contraction between the dashed lines is manually excluded from the analysis.

### 2.4. QRS-WA and TWA evaluation

In order to extract a single index for the entire ECG recording, a multi-lead approach for wave alternans detection was adopted. The following time domain parameters were considered for analysis of QRS-WA and TWA:

- Amplitude of the T waves in the combined lead (T\_amp);
- Complexity index of the T waves (PCA\_T);
- Amplitude of the QRS complex in the combined lead (QRS\_amp);
- Complexity index of the QRS waves (PCA\_QRS).

The complexity index of the QRS and T waves was defined as the ratio of the 2<sup>nd</sup>/1<sup>st</sup> PCA-derived eigenvalues. A detailed description of the 2:1 alternans detection method can be found in [10].

The intervals used for searching of QRS-WA and TWA were selected with the help of two methods. Firstly, the entire 5-minute ECG recording was processed, producing a unique time series, which was fed into the detection block (global method). Secondly, a window of 120 consecutive RR intervals was shifted through the entire 5-minute recording and parameter extraction was performed in each window (local method).

The detection block separated the parameters from the series of odd and even RR intervals, following which the 2 series of parameters were compared for statistically significant difference using the non parametric paired-sampled Wilcoxon signed rank test.

With the global methods, the statistical test produces a single binary index, which represents the presence or absence of TWA/QWA. With the local methods, the comparison is repeated for every interval, producing a set

of binary indices, which are either positive (i.e. signifying statistically significant difference between the odd and even series of parameters) or negative. QRS-WA/TWA is considered to be present in case a) there is at least one interval with positive index or b) there are more than one interval with positive index (i.e.  $loc\_PCA\_QRS > 1$ ).

### 2.5. Beat-to-beat variability

The beat-to-beat variability of ventricular depolarization and repolarization was quantified as the standard deviation of PCA of all QRS and T waves in leads V1, V2 and V3 ( $PCA\_QRS_{var}$  and  $PCA\_T_{var}$ ).

## 3. Results

Patients with positive tests were older although not statistically significantly ( $41 \pm 20$  vs  $29 \pm 16$ ,  $p=0.24$ ) and were more frequently symptomatic ( $3/7$  (43%) vs  $0/7$  (0%),  $p=0.051$ , chi-square test) than those with negative tests.

There were no significant differences in regular 2:1 QRS-WA or TWA assessed by the wave amplitudes ( $QRS\_amp$  and  $T\_amp$ ) between patients with positive and those with negative tests, either with global or local indices (Tables 1 and 2). Similarly, there was no significant correlation between the  $QRS\_amp$  and  $T\_amp$  parameters of 2:1 alternans and the outcome of the ajmaline test (Tables 3 and 4).

Table 1. Global (glb) and local (loc) classification indices for QRS-WA:  $QRS\_amp$ ,  $PCA\_QRS$ .

Ajmaline test	Pos		Neg		p
	+	-	+	-	
QRS-WA classification					
glb $QRS\_amp$	0	42	1	41	0.320
glb $PCA\_QRS$	4	38	2	40	0.403
loc $QRS\_amp$	10	32	6	36	0.272
loc $QRS\_amp > 1$	7	35	2	40	0.079
loc $PCA\_QRS$	15	27	4	38	0.004
loc $PCA\_QRS > 1$	11	31	2	40	0.006

Table 2. Global (glb) and local (loc) classification indices for TWA:  $T\_amp$  and  $PCA\_T$ .

Ajmaline test	Pos		Neg		p
	+	-	+	-	
TWA classification					
glb $T\_amp$	0	42	1	41	0.320
glb $PCA\_T$	2	40	4	38	0.403
loc $T\_amp$	8	34	9	33	0.789
loc $PCA\_T$	16	26	11	31	0.248

Regular QRS-WA assessed by PCA ( $PCA\_QRS$ ) using local indices was significantly more frequently present in patients with positive compared to those with negative tests ( $15/42$  (36%) vs.  $4/42$  (9.5%),  $p=0.004$ , Table 1) with a

correlation coefficient  $r=0.27$  and  $p=0.013$  (Table 3). On the other hand, there were no significant differences between the 2 groups in TWA using  $PCA\_T$ , either with global or local indices ( $16/42$  (38.1%) vs.  $11/42$  (26.2%), in patients with positive and negative tests, respectively,  $p=0.24$ , Table 3, with a correlation coefficient  $r=0.13$  and  $p=0.21$  (Table 4).

Table 3. Coefficient correlation for QRS-WA

	coeff. corr	p
loc $QRS\_amp$	0.146	0.1846
loc $QRS\_amp > 1$	0.192	0.0795
loc $PCA\_QRS$	0.267	0.0137
loc $PCA\_QRS > 1$	0.296	0.0062

Table 4. Coefficient correlation for T-WA

	coeff. corr	p
glb $T\_amp$	0.1098	0.3203
glb $PCA\_T$	0.0925	0.4029
Loc $T\_amp$	0.0940	0.3950
Loc $PCA\_T$	0.1368	0.2147

The beat -to-beat variability of the T wave ( $PCA\_T_{var}$ ) was significantly higher in patients with positive compared to those with negative tests, whereas the beat-to-beat QRS variability ( $PCA\_QRS_{var}$ ) was not significantly different between the 2 groups (Table 5).

Table 5. Statistical analysis of the two groups of suspected BS with positive (B+) and negative (B-) ajmaline test considering PCA on QRS and T waves from 3 ECG leads (V1-V2-V3).

Ajmaline test	Pos.		Neg.		p
	mean $\pm$ sd		mean $\pm$ sd		
$PCA\_QRS$	0.177 $\pm$ 0.1223	0.238 $\pm$ 0.2151	0.1150		
$PCA\_T$	0.147 $\pm$ 0.2153	0.063 $\pm$ 0.0592	0.0181		
$PCA\_QRS_{var}$	0.023 $\pm$ 0.0142	0.026 $\pm$ 0.0281	0.5178		
$PCA\_T_{var}$	0.032 $\pm$ 0.0482	0.015 $\pm$ 0.0134	0.0294		

## 4. Discussion and conclusions

This study on a small group of patients with suspected BS demonstrated that those with positive ajmaline test (i.e. likely carriers of mutations for BS) have increased beat-to-beat ST-T wave variability on night-time ambulatory ECG recordings compared to those with negative tests. Importantly, this variability does not follow 2:1 pattern and cannot be detected by amplitude measurements, which form the basis for most current algorithms for detection of 2:1 microvolt TWA. It is also noteworthy that patients with positive tests and increased ST-T variability had more frequently symptoms than those with negative tests and low ST-T variability, which suggests a possible role of increased repolarization

variability in arrhythmogenesis.

Patients with positive ajmaline tests also had increased 2:1 QRS alternans (detected by PCA, but not by amplitude measurements). This has not been reported so far but is not unexpected in light of recent studies which demonstrated the role of depolarization abnormalities in the genesis of arrhythmias in BS [18].

These preliminary results, if confirmed by larger studies on clinically and genetically defined groups of patients with BS and their relatives and analysis of longer recordings acquired under various conditions, might have clinical implications. The diagnosis of BS is likely to be improved by analysis of ST-T variability and 2:1 QRS alternans. Ambulatory Holter recordings are more cost-effective than pharmacologic testing for BS which carries small but definite risk of inducing malignant arrhythmias and can only be performed in hospital setting [11]. The link between beat-to-beat repolarisation variability and 2:1 QRS alternans, on the one hand, and symptoms, on the other, suggests that these methods could help risk stratification in BS. This is important in view of recent studies which failed to demonstrate predictive value for arrhythmic events in BS of 2:1 microvolt TWA [4,5].

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