# Principal Component Analysis of the QRS Complex During Diagnostic Ajmaline Test for Suspected Brugada Syndrome

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## Abstract

*We used principal component analysis (PCA) of the QRS complex to assess depolarisation heterogeity during ajmaline test in 96 patients with suspected Brugada Syndrome (BS). PCA was performed on 15-lead ECGs (12 leads +V1, V2 and V3 from 3rd intercostal space, V1h to V3h using a) V1, V2 and V3 (QRS-PCAstand), b) V1h, V2h and V3h (QRS-PCAhigh), and c) V1 to V3, V1h to V3h (QRS-PCAtotal). Among patients with positive tests (n=23), those with symptoms (n=6) had higher QRS-PCAhigh before (p=0.003) and during maximum drug effect (p=0.001) than those without symptoms (n=17). Following ajmaline, QRS-PCA decreased significantly in patients with negative (n=73) (p=0.00004), but not in those with positive tests (p=0.098). Symptomatic patients with non-diagnostic resting ECGs have increased depolarisation heterogeneity. PCA could detect depolarisation heterogeity and thus help the diagnosis and risk stratification of patients with BS.*

## 1. Introduction

Conduction abnormalities provide an arrhythmic substrate for the development of malignant ventricular arrhythmias and sudden cardiac death in various cardiac diseases such as ischaemic cardiac diseases (IHD), cardiomyopathies and others. Conduction abnormalities are detected electrocardiographically by widening and morphological changes in the QRS and by the presence of late potentials in the signal-averaged ECG. Recently, fragmentation of the QRS was shown to be a marker of a prior myocardial infarction (MI) [1], and increased arrhythmic risk in patients with IHD [2] and dilated cardiomyopathy [3]. In patients with Brugada syndrome (BS), the presence of fragmented QRS was shown to predict occurrence of spontaneous ventricular arrhythmias and cardiac arrest [4].

All studies published so far have assessed the presence of intraventricular conduction disturbances in BS by the duration of the QRS complex, presence of late potentials on the signal-averaged ECG (SAECG) or visible signs of QRS fragmentation, such as notching, multiple spikes, rSr' or similar QRS morphologies, etc. [4-7] Other methods which previously have been used to analyse the QRS complex, such as analysis of the high-frequency components of the QRS [8], wavelet transform [9] and principal component analysis (PCA) [10], have not been applied to the study of intraventricular conduction defects in BS so far.

In this study, we used PCA to analyse the dynamic changes in the QRS complex during diagnostic testing with a sodium-channel blocker (ajmaline) in patients with suspected BS. We used a previously recorded digital ECG database with simultaneous acquisition of the right precordial leads in both standard, as well as "high" positions.

## 2. Methods

### 2.1. Study population and data acquisition

The study population consisted of 96 patients (age 39.4±16.7 years, 62 men, 36 women, age 39.8±17.6 and 38.6±15.2, respectively, age men vs. age women – p=0.74) with suspected BS who underwent diagnostic ajmaline test as part of their standard clinical management. All patients had either normal or non-diagnostic (i.e. not displaying type 1 Brugada ECG pattern) resting ECGs before the test. Details about this patient population have been partially described in previous publications [11].

Ajmaline was administered intravenously in dose 1 mg/kg for 5 minutes under constant ECG monitoring in hospital setting [12]. Digital 10-second ECGs with simultaneous acquisition of 15 leads (standard 12-leads plus leads V1 and V2 from the 3rd intercostal (i.c.) space, and lead V3 with the same cranial displacement – leads V1h to V3h) were acquired before, at short intervals (3 – 5 ECGs per minute) during and up to 10 minutes after the end of drug infusion or until the ECG changes completely subsided using MAC 5000 recorder (GE Medical, Milwaukee, WI, USA, 500 Hz, 4.88 µV).

All ECGs were subsequently converted into XML text

files to be analysed with a custom-developed programme (see below). A test was considered positive if any two (or more) of the 6 leads (V1 to V3 plus V1h to V3h) demonstrated type 1 ECG pattern during the test [12].

## 2.2. ECG preprocessing

In order to eliminate powerline interference, moving averaging of samples in one period of the powerline interference was performed. 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. For drift suppression, a high-pass recursive filter with a cutoff frequency of 0.64 Hz was used [14].

## 2.3. QRS onset and offset delineation

All QRS onset and offset delineations were performed on a combined lead simulating the spatial vector [14]. The transform to orthogonal XYZ leads was performed using 'primary leads', i.e. the 8 potential differences referred to the left leg electrode F [14]. They were obtained from the 12-lead ECG recordings, following the conversion formulae in the [15]:

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

The orthogonal leads were evaluated by:
$X=0.5*abs(C4_F-C1_F)$; $Y=abs(R_F)$; $Z=abs(R_F -C2_F)$;

The combined lead (CL), which is the spatial vector in this case, is calculated by:
$CL=0.5(X+Y+Z+0.25(abs(X-Y)+abs(X-Z)+abs(Y-Z)))$;

In ECGs with manifested Brugada pattern, such as those developing during a positive ajmaline test, the delineation of the J point is difficult. Therefore, as previously reported, we manually determined the QRS onset and offset (J-point) before the occurrence of type 1 pattern. The QRS onset and offset of the remaining ECGs were subsequently automatically delineated by the 'best matching' or the best correlation with the QRS templates.

The duration of the interval for searching the best matching is very important. If it is too large the algorithm can miss a QRS complex and T wave and mark the following ones, whereas if it is too small the algorithm can delineate noise artefacts resembling the QRS complex and T wave. Therefore a QRS detection was performed [16] and the search interval was made dynamically variable to the RR interval.

All ECG recordings and the delineated boundaries were visually verified and corrected if necessary. Premature ventricular contractions and noisy heart beats were manually excluded from the analysis.

## 2.4. PCA analysis

PCA analysis was previously utilised by some of the authors on QRS and T waves for detection of microscopic 2:1 T wave alternans (Physionet/Computers in Cardiology Challenge 2008) [17,18]. In the present study PCA was implemented in a method for characterization of QRS complex.

PCA was performed on a beat-to-beat basis on the automatically delineated QRS onset to QRS offset (J-point) interval using 3 different sets of leads: a) V1, V2 and V3 (QRS-PCAstand), b) V1h, V2h and V3h (QRS-PCAhigh), and c) V1, V2, V3 plus V1h, V2h and V3h (QRS-PCAtotal). PCA (ratio of $2^{nd}$ to $1^{st}$ eigenvalue) was expressed as mean value of PCA of all individual complexes within a 10-s ECG.

Data are presented as mean±standard error (SE). Values were compared using paired and unpaired two-tailed t-test, as appropriate. P value of <0.05 was considered statistically significant.

## 3. Results

There were 23 patients with positive (14 men, age 42.3±16.5 years) and 73 with negative tests (46 men, age 38.3±16.8 years). Among patients with positive tests, 6 had previous history of arrhythmia-related symptoms (2 with syncope and 4 with aborted cardiac arrest), whereas 17 were asymptomatic.

Table 1. QRS-PCA in leads V1 to V3 (QRS-PCAstand)

| QRS-PCAstand (%) | Pre-test | Maximum effect |
|---|---|---|
| Negative tests (n=73) | 0.150±0.017 | 0.081±0.009 |
| Positive tests (n=23) | 0.206±0.040 | 0.167±0.033 |
| P value | 0.15 | 0.29 |
| (+) tests, with symptoms (n=6) | 0.221±0.077 | 0.228±0.084 |
| (+) tests, no symptoms (n=17) | 0.200±0.049 | 0.145±0.034 |
| P value | 0.82 | 0.001 |

In the pre-test ECGs, QRS-PCA was not significantly different between patients with positive compared to those with negative tests (Tables 1 to 3). Following ajmaline QRS-PCAhigh and QRS-PCAtotal became significantly higher in patients with positive compared to those with negative tests (Tables 1 to 3). QRS-PCA decreased significantly during maximum drug effect compared to baseline in patients with negative tests (p=0.0001, p=0.07, p=0.0004 for QRS-PCAstand, QRS-PCAhigh and QRS-PCA-total, respectively), but not in those with positive tests (p=0.15, p=0.97 and p=0.21 QRS-PCAstand, QRS-PCAhigh and QRS-PCA-total, respectively).

Table 2. QRS-PCA in leads V1h to V3h (QRS-PCAhigh)

| QRS-PCAhigh (%) | Pre-test | Maximum effect |
|---|---|---|
| Negative tests (n=73) | 0.150±0.018 | 0.112±0.016 |
| Positive tests (n=23) | 0.199±0.041 | 0.201±0.031 |
| P value | 0.22 | 0.008 |
| (+) tests, with symptoms (n=6) | 0.391±0.111 | 0.308±0.080 |
| (+) tests, no symptoms (n=17) | 0.132±0.028 | 0.163±0.028 |
| P value | 0.003 | 0.039 |

Table 3. QRS-PCA in all 6 leads (QRS-PCAtotal)

| QRS-PCAtotal (%) | Pre-test | Maximum effect |
|---|---|---|
| Negative tests (n=73) | 0.153±0.017 | 0.096±0.01 |
| Positive tests (n=23) | 0.216±0.037 | 0.183±0.024 |
| P value | 0.086 | 0.0002 |
| (+) tests, with symptoms (n=6) | 0.278±0.072 | 0.249±0.063 |
| (+) tests, no symptoms (n=17) | 0.193±0.044 | 0.160±0.023 |
| P value | 0.33 | 0.111 |

In symptomatic patients with positive tests (n=6), QRS-PCAhigh was significantly higher than in asymptomatic patients with positive tests, both at baseline (p=0.003) as well as during maximum effect of the drug (p=0.039) (Table 2). QRS-PCAstand was significantly higher in symptomatic patients during maximum drug effect but not at baseline (Table 1), whereas the differences in QRS-PCAtotal between the two groups were not statistically significant (Table 3).

Table 4. QRS duration

| QRS duration [ms] | Pre-test | Maximum effect |
|---|---|---|
| Negative tests (n=73) | 94±12.1 | 132±20.5 |
| Positive tests (n=23) | 104±17.4 | 140±20.2 |
| P value | 0.005 | 0.089 |
| Positive tests with symptoms (n=6) | 119±27.2 | 150±28.8 |
| Positive tests without symptoms (n=17) | 98±8.6 | 137±16.0 |
| P value | 0.011 | 0.19 |

The QRS duration was significantly longer before the test in patients with positive compared to those with negative tests (p= 0.0050), as well as in symptomatic compared to asymptomatic patients with positive tests (p=0.011), but both differences were decreased and became non-significant at the time of maximum drug effect (p=0.089 and p=0.19, respectively) (Table 4).

The dynamic changes of QRS-PCAhigh during ajmaline test are presented graphically in Figure 1.
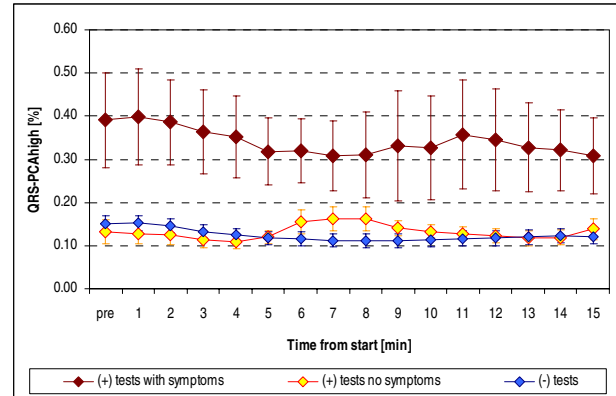


Figure 1 Dynamic changes in QRS-PCAhigh during ajmaline testing. Data are presented as mean±SE. Note that the dynamic profile of QRS-PCAhigh of asymptomatic patients with positive tests (yellow bars) is similar to that of patients with negative tests (blue bars) and is distinctly different from that of patients with positive tests who had history of arrhythmia-related symptoms.

## 4. Discussion and conclusions

The main finding of this study is among patients with positive ajmaline tests. Those with previous history of arrhythmia-related symptoms had significantly increased PCA-QRS compared to those without symptoms, on pre-test ECGs (QRS-PCAhigh) as well as during maximum effect of the drug (both QRS-PCAstand and QRS-PCAhigh). This is in concert with previous reports of low risk of arrhythmic events in asymptomatic patients with a positive test [12].

In addition, the effect of ajmaline on PCA-QRS was distinctly different in patients with positive compared to those with negative tests. While on pre-test ECGs PCA-QRS in both standard and "high" right leads was not significantly different between the two groups, during the test PCA-QRShigh increased significantly in patients with positive but not in those with negative tests.

These finding supports previous reports of a link between increased QRS fragmentation [4,6], prolonged filtered QRS and late potentials on a SAECG [5] and increased arrhythmic risk in BS.

PCA of the QRS seems to be more informative when applied to the "high" (3rd i.c. space) rather than the standard (4th i.c. space) right precordial leads. This corroborates our (unpublished) observations that notching

of the QRS is more frequently observed during positive ajmaline tests in the "high" than in the standard right precordial leads, and further strengthens the role of the "high" leads in the assessment of BS [19-21].

The QRS duration was also significantly longer in patients with positive compared to those with negative tests, as well as in symptomatic compared to asymptomatic patients with positive tests. However, both differences were present only on pre-test ECGs and were considerably diminished following ajmaline administration likely due to a drug-induced non-specific intraventricular conduction delay. This suggests that PCA can add additional diagnostic and prognostic information in BS beyond that provided by the QRS duration. The calculation of PCA depends less on the level of noise and the exact determination of the J-point than the QRS duration.

In conclusion, PCA of the QRS applied to a limited number of "high" right precordial leads is a promising method for detection of intraventricular conduction disturbances and assessment of the arrhythmic risk in patients with the Brugada syndrome.

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