Automatic Assessment of Right Ventricular Repolarisation Dispersion during Diagnostic Ajmaline Test for Suspected Brugada Syndrome

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Abstract

We used principal components analysis (PCA) to quantify right ventricular (RV) repolarisation dispersion during diagnostic ajmaline test for suspected Brugada syndrome (BS). 10-second 15-lead electrocardiograms (ECG) (500 Hz, 12 standard leads + V1 to V3 from 3rd intercostal space, V1h to V3h) were acquired in 61 patients (pts) with suspected BS (38 men, age 39±17 years) during ajmaline administration. PCA (ratio 2nd/1st eigenvalue) was performed on the J-T_{end} interval using a) leads V1 to V3 (PCA_{stand}), b) V1h to V3h (PCA_{high}) and c) V1 to V3 + V1h to V3h (PCA_{total}). Pts with positive tests (n=20) had significantly higher PCA_{high} and PCA_{total}, on pre-test ECGs than those with negative tests. The maximum drug-induced increase of PCA was significantly greater in pts with positive than in those with negative tests (e.g. PCA_{high} 6406±12622% vs 192±350%, p=0.004). Assessment of RV repolarisation dispersion using PCA can help the diagnosis of BS.

1. Introduction

The Brugada Syndrome (BS) is a heritable arrhythmia syndrome manifesting as syncope or sudden cardiac death (SCD) due to polymorphic ventricular tachycardia in the absence of ischemia and/or structural heart disease [1]. Currently the BS is diagnosed when the type 1 ("coved") Brugada electrocardiographic (ECG) pattern, characterised by J-point and ST-segment elevation with a negative T wave, is observed in the right precordial leads V1 to V3 either spontaneously or following administration of sodium channel blockers, in patients who also have a personal or family history of major ventricular arrhythmias (VA) and/or blood relatives carrying the type 1 ECG [2-3]. This pattern is believed to reflect an abnormally magnified right ventricular transmural and regional epicardial dispersion of repolarisation due to the loss of the action potential dome of the epicardial myocytes [4]. Delayed activation of areas in the right ventricular outflow tract has also been shown to play role in the genesis of arrhythmias in BS [5].

Experimental studies have shown that in the BS, the occurrence of ventricular tachycardia or fibrillation via phase 2 reentry and circus movement reentry critically depends on the magnitude of dispersion of repolarisation [6]. Therefore it seems likely that the diagnosis and the assessment of the arrhythmic risk in BS could be facilitated if the visual assessment of the ECG would be supplemented with objective quantitative analysis of repolarisation heterogeneity.

In this study we used principal component analysis applied to a limited set of right precordial leads in order to quantify repolarisation heterogeneity during diagnostic ajmaline test in patients with suspected BS.

2. Methods

2.1. Patient population and data acquisition

Between March 2006 and November 2008, diagnostic ajmaline test was performed in 122 patients with suspected BS (77 men, 45 women, age 36.3±15.0 age 37.0±15.3 years, respectively) as part of their standard clinical management. The indications and the protocol of the test have been reported previously [7,8]. All patients had visibly non-diagnostic for BS (i.e. not displaying type 1 Brugada ECG pattern [2] in lead V1, V2 or V3) resting ECGs. Ajmaline was administered intravenously in dose 1 mg/kg for 5 minutes under constant ECG monitoring. The test was considered positive (and drug administration terminated) if type 1 Brugada pattern developed in any 2 or more of the 6 leads V1 to V3, plus the same 3 leads recorded from one intercostal space higher (see below). There were 21 positive tests (17.2%) and 101 negative tests (82.8%).

Digital 10-second ECGs (500 Hz, 4.88 μV resolution, MAC5000 GE Medical systems) with simultaneous

acquisition of 15 leads (12 standard leads + leads V1, V2 and V3 recorded one intercostal space higher, V1h, V2h and V3h) were recorded at short intervals (3-5 per minute) before, during and up to 10 minutes after the end of drug administration in the case of a negative test, or until the ECG changes completely subsided in case of a positive test.

For the purpose of this study, we selected all 21 positive tests (12 men (57%), age 41.6±16.3 years) and 41 randomly chosen negative tests (26 men (63%), age 36.7±16.6 years, p=0.28 vs positive tests).

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 [9]. 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 [10].

2.3. J-point and T-end delineation

All J and T-end delineations were performed on a combined lead simulating the spatial vector [10]. 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 [10]. These primary leads were obtained from the 12-lead ECG recordings, following the conversion formulae in the [11]:

$R_F = -II$; $L_F = -III$; $Ci_F = Vi - (II+III)/3$, 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)));

Our previously developed method for J and T-end delineation [12] did not work well due to the fact that the type 1 Brugada pattern, provoked by the administration of ajmaline, does not usually manifest a clear J-point and T-end. For that reason we delineated manually QRS-onset, J-point, T-onset, and T-end just once before the occurrence of type 1 Brugada pattern. Then by the 'best matching' or the best correlation with the templates of QRS complex and T wave, all the remaining J-points and T-ends were automatically delineated.

The duration of the interval for searching of the best matching is very important. If the interval is too large the algorithm sometimes misses the current QRS complex and T wave and marks the following ones. On the other hand, if it is too small the algorithm can delineate artefacts resembling the QRS complex and T wave that are due to noise. For that reason QRS detection was performed [13] and the search interval was made dynamically variable to the RR interval.

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.

PCA was performed on a beat-to-beat basis on the automatically delineated J-point to T-end interval using 3 different sets of leads: a) V1, V2 and V3 (PCA_{stand}), b) V1h, V2h and V3h (PCA_{high}), and c) V1, V2, V3 plus V1h, V2h and V3h (PCA_{total}). PCA (ratio of 2nd to 1st eigenvalue) was expressed as mean (PCA(mean)) and maximum (PCA(max)) value of PCA of all individual complexes within a 10-s ECG.

3. Results

Before the administration of ajmaline, the average PCAhigh and PCAtotal was significantly higher in patients with positive compared to those with negative tests, both for PCA(mean) and PCA(max) (Table 1). PCAstand was not significantly different between the 2 groups (Table 1).

Table 1 PCA(mean) and PCA(max) in the two study groups before administration of ajmaline

PCA	PCA_{stand}	PCA_{high}	PCA_{total}
PCA(mean)			
(+) tests	0.087±0.145	0.124±0.130†	0.112±0.150*
(-) tests	0.047±0.074	0.057±0.064	0.052±0.067
PCA(max)			
(+) tests	0.101±0.160	0.147±0.150*	0.130±0.165*
(-) tests	0.060±0.099	0.074±0.084	0.063±0.082

*=p<0.05 vs (-) tests; †=p<0.01 vs (-) tests

Following ajmaline, the 3 groups of PCA parameters increased significantly only in patients with positive tests (Table 2).

Table 2 Increase of PCA(max) during the ajmaline test

PCA(max)	PCA_{stand}	PCA_{high}	PCA_{total}
(+) tests			
Baseline	0.101±0.160	0.147±0.150	0.130±0.165
Max effect	0.391±0.261†	0.501±0.206†	0.458±0.203†
(-) tests			
Baseline	0.060±0.099	0.074±0.084	0.063±0.082
Max effect	0.082±0.130	0.109±0.134	0.084±0.106

†=p<0.01 vs baseline

However, the relative maximum drug-induced increase in PCA was significantly higher in patients with positive compared to those with negative tests (Table 3).

Table 3 Relative maximum increase of PCA (% vs baseline) during the ajmaline test

	PCA_{stand} (%)	PCA_{high} (%)	PCA_{total} (%)
PCA(mean)			
(+) tests	2193±3170†	6406±12622†	3109±4196†
(-) tests	168 ± 420	192 ± 350	137 ± 323

†=p<0.01 vs negative tests

Figure 1 presents an example of the dynamic changes in PCA_{stand} and PCA_{high} (mean±SD) during a positive test in a 15-year-old girl with syncope and a family history of BS (top panel), and during a negative test in a 66-year-old asymptomatic man with family history of BS and SCD (bottom panel). X-axis is the time in minutes after the start of ajmaline injection. At B=0 min is presented the mean of several PCA values just before the start of the injection.

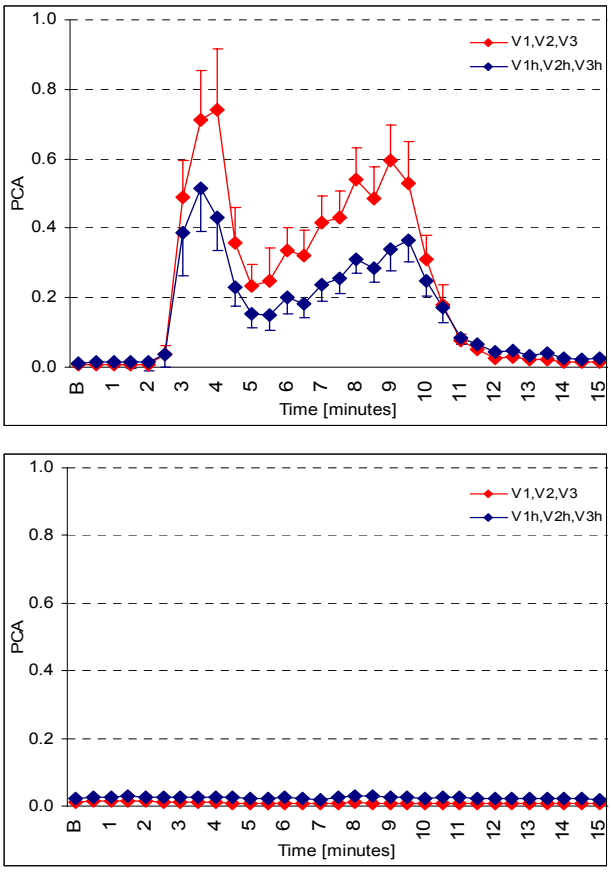

Figure 1 PCA_{stand} and PCA_{high} during a positive test (top panel), and during a negative test (bottom panel). Data are presented as mean±standard deviation (SD). For more clear visibility and in order to avoid overlapping values, only SD+ for PCA_{stand} and SD– for PCA_{high} are shown.

Note the striking difference in the dynamics of PCA_{stand} and PCA_{high} between the 2 tests in Figure 1, whereas the baseline average values of PCA_{stand} and PCA_{high} measured from repeated recordings immediately before the test were higher in the patient with the negative test (PCA_{stand}: 0.013±0.002 vs 0.006±0.001, p<0.0001; PCA_{high}: 0.022±0.003 vs 0.009±0.002, p<0.0001).

Figure 2 presents the dynamic changes in PCA_{high} during the ajmaline test in all patients of the two groups. Note that unlike Figure 1, the values in Figure 2 are presented as mean±standard error (SE). At B=0 min is presented the mean of several PCA values just before the start of the ajmaline injection.

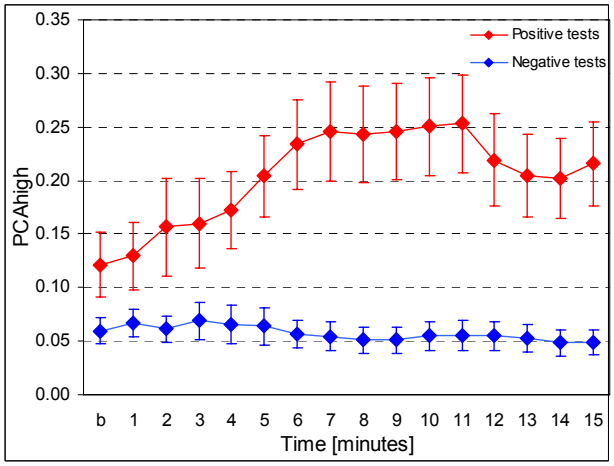

Figure 2 Dynamic changes in PCA_{high} during the ajmaline tests in patients with positive and negative tests. Data are presented as mean±SE.

4. Discussion and conclusions

Currently, the diagnosis of BS is based on visual detection of the so-called "Brugada type 1" pattern defined by descriptive terms ("coved" ST segment elevation). Our results show that the appearance of this signature ECG pattern in the right precordial leads during diagnostic ajmaline testing is accompanied by sharp increase in repolarisation heterogeneity indexed by PCA. Importantly, this can be detected by applying PCA to just 3 right precordial leads.

The results may have practical implications not only for improvement of the interpretation of diagnostic pharmacologic testing in patients with suspected BS. The diagnostic ECG changes in BS often show considerable dynamic variability [14], sometimes even within minutes [15], or appear only under certain physiological conditions (e.g. during fever, after meals, with increased vagal tone, etc.) [16]. The detection of intermittently appearing type 1 Brugada pattern can be important both diagnostically as well as prognostically, because patients with spontaneously appearing Brugada type 1 ECG pattern have higher risk of arrhythmic

events compared to those in whom such ECG changes are elicited only during pharmacological challenge [17]. PCA, applied to a limited number of right praecordial leads, possibly in combination with other automatically assessed parameters (e.g. J-point elevation, T wave inversion) could be used for automatic detection of intermittent Brugada ECG pattern during interpretation of ambulatory Holter recordings or during monitoring with long-term ECG recording devices (event recorders).

Patients with non-diagnostic resting ECGs and positive ajmaline test appear to have increased repolarisation heterogeneity already on their pre-test ECG, compared to those with negative ajmaline test. However, there is large overlap of PCA values between the 2 groups (see Figure 1), which limits the potential usefulness of increased PCA parameters on resting ECGs for supporting the diagnosis of BS. This is consistent with our previous report of considerable inter-individual variation of PCA parameters and their relationship to heart rate changes in healthy subjects [18].

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