ECG Wavelet Analysis for the Detection of Gene Mutations in Patients with Brugada Syndrome

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Abstract

We applied wavelet transform (WT) to digital electrocardiograms (ECG) acquired during positive ajmaline test for Brugada syndrome (BrS) in 12 patients (pts) with and 14 pts without gene mutations. Continuous WT was applied to the QRS complex and the ST-T wave on leads V1 to V3 in 4th and 3rd intercostal space (i.c.s.) (Group A, 13 pts) and leads V1 and V2 from 4th, 3rd and 2nd i.c.s. (Group B, 13 pts) using 256 levels.

In group A, there was significantly higher QRS energy at high frequencies in pts with mutations (n=4) both at baseline and during maximum drug effect. In group B, patients with mutations (n=7) had higher QRS energy at low frequencies and higher ST-T energy at low frequencies at baseline and during drug effect.

Continuous WT can help identify carriers of gene mutations among patients with BrS, especially when applied to leads V1 and V2 from the 4th to 2nd i.c. s.

1.   Introduction

The Brugada syndrome (BrS) is an inherited ion chanelopathy characterised by a typical electrocardiographic (ECG) pattern of J point and ST segment elevation in the right precordial leads and predisposition towards malignant ventricular arrhythmias [1]. Risk stratification of patients with BrS is currently an unresolved issue. Gene mutations are currently identified in only $\approx$ 20% of the index cases [2]. However, BS patients with SCN5A mutations might be at a higher risk of ventricular fibrillation compared to those without mutations [3].

Both depolarisation and repolarisation abnormalities contribute to the arrhythmia substrate and arrhythmia genesis in the BrS [4]. Conduction abnormalities in the BrS are currently detected mainly by visual assessment (QRS widening, fragmentation, notching, multiple spikes, etc.) and presence of late potentials on the signal-averaged ECG. In patients with BrS, the presence of fragmented QRS has been reported to predict occurrence of spontaneous ventricular arrhythmias and cardiac arrest [5]. Recently we reported that in patients with the BrS, conduction abnormalities detected by principal component analysis of the QRS are related to previous history of arrhythmia-related symptoms [6].

Wavelet analysis is a form of time-frequency transformation that has long been used in non-invasive electrocardiology for detection of characteristic ECG components, heart rate variability, analysis of ischaemic ST changes, ventricular repolarisation and others [7]. Wavelet analysis of the QRS has been shown to be superior to the standard time-domain signal-averaged ECG for detection of conduction abnormalities related to the arrhythmia risk [8, 9].

In this study, we hypothesised that continuous wavelet transform (WT) applied to the QRS and ST-T wave can help to identify carriers of SCN5A mutations among patients with the BrS. We analysed digital 15-lead ECGs previously recorded during positive diagnostic ajmaline test for BrS with simultaneous acquisition of the right precordial leads in both standard, as well as "high" electrode positions.

2.   Methods

2.1.   Study population and data acquisition

The study population consisted of 26 patients (age 42.0±17.8 years, 13 men, 13 women, age 41.6±19.1 and 42.4±17.2, respectively, p=0.92 for men vs women) with suspected BrS 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 [10]. Following appropriate genetic counselling, all patients underwent mutation analysis of the cardiac sodium channel gene (SCN5A).

Ajmaline was administered intravenously in dose 1 mg/kg for 5 minutes under constant ECG monitoring in

hospital setting [1]. Digital 10-second ECGs with simultaneous acquisition of 15 leads (12 standard leads plus leads V1 and V2 or V1 to V3 from higher positions, see below) 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, MAC5500 or PC-based CardioSoft 6.1 ECG recorder (GE Medical, Milwaukee, WI, USA, 500 Hz, 4.88 µV).

In 13 patients (group A, 6 men, age 46.9±15.7 years) leads V1 to V3 from one intercostal space (i.c.s.) higher (leads V1, V2, V3, $V1_3$, $V2_3$ and $V3_3$) were acquired, whereas in 13 patients (group B, 7 men, age 37.1±19.0 years) leads V1 and V2 from the 4th, 3rd and 2nd i.c.s., without recording of lead V3 (leads V1, V2, $V1_3$, $V2_3$, $V1_2$ and $V2_2$) were acquired. All ECGs were converted into XML text files for subsequent analysis (see below). A test was considered positive if any two or more of the right precordial leads recorded from standard or higher electrode positions demonstrated type 1 Brugada ECG pattern during the test [1].

2.2. ECG preprocessing

No processing of the ECG signals to eliminate or suppress the powerline interference, drift and electromyographic noise has been performed prior to the wavelet transform.

2.3. QRS onset and offset delineation

All QRS onset and offset delineations were performed on a combined lead simulating the spatial vector [11]. The transform to orthogonal XYZ leads was performed using 'primary leads', i.e. the 8 potential differences referred to the left leg electrode F [11]. They were obtained from the 12-lead ECG recordings, following the conversion formulae in the [12]:
$R_F = -II$;
$L_F = -III$;
$Ci_F = Vi – (II+III)/3$, 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:
$CL=0.5(X+Y+Z+0.25(abs(X-Y)+abs(X-Z)+abs(Y-Z)))$;
In ECGs with manifested type 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 QRS offset (J-point) before the occurrence of type 1 Brugada pattern. The QRS onset and offset of the remaining ECGs were subsequently automatically delineated by the 'best matching' or the best correlation with the manually established QRS templates.

The duration of the interval for searching of the best matching is very important. If the interval is too large the algorithm can miss the current QRS complex and T wave and mark 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. Therefore a 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 verified and corrected if necessary. Premature ventricular contractions and noisy heart beats were manually excluded from the analysis.

2.4. Continuous Wavelet Transform

Continuous Wavelet Transform (CWT) was applied to the QRS complex and ST-T-wave. The Biorthogonal wavelet was used, which is a compactly supported spline wavelet, with the symmetry and exact reconstruction characteristics. In particular, the reconstruction and the decomposition order were 2 and 8, and the center frequency was 0.88 Hz. [14]. This analysis was performed considering scales in the range [4-256] for ECG signals of 500 Hz. In particular, the first scale (n=4) corresponds to a pseudo-frequency of 110.3 Hz, while the 256th corresponds to 1.7 Hz.

Wavelet analysis on both the QRS complex and the ST-T wave was performed on one beat selected from the 10 s recordings of leads V1, V2, V3, $V1_3$, $V2_3$ and $V3_3$ (group A) and leads V1, V2, $V1_3$, $V2_3$, $V1_2$, $V2_2$ (group B). The time-frequency density energy function was considered for the analysis, and an example of a patient of group A is reported in Figure. 1.
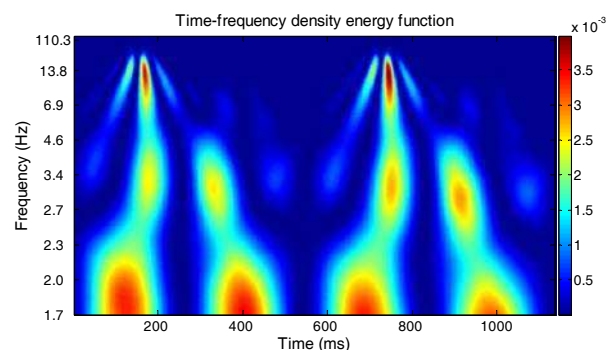

Figure 1. Time-frequency density function obtained by Continuous Wavelet Transform considering scales in the range 4 (110.3 Hz) : 256 (1.7 Hz). Two QRS-T intervals have been considered from one ECG recording acquired at baseline in a patient with a SCN5A mutation.

3. Results

In 4 patients of group A (30.8%) and 7 patients of group B (53.8%) SCN5A mutations were found (p=0.23, chi-square test), whereas 9 patients in group A and 6

patients in group B had no SCN5A mutations.

3.1. Wavelet Transform of the QRS complex and ST-T wave

The results of the wavelet transform (WT) of the QRS complex and ST-T wave of both patient groups are presented in Table 1 and Table 2, respectively.

In group A, patients with SCN5A mutations had increased QRS energy at scales corresponding to higher frequencies compared to those without mutations both at baseline, as well as during maximum drug effect (Table 1). In group B, patients with mutations also had increased QRS energy compared to those without mutations, both at baseline as well as during peak drug effect but at scales corresponding to lower frequencies compared to patients of group A.

With continuous WT of the ST-T wave, only patients of group B demonstrated increased ST-T wave energy in those with mutations compared to those without SCN5A mutations, both at baseline as well as during maximum effect of the drug (Table 2).

Table 1. Increase of QRS energy in patients with compared to patients without SCN5A mutations

QRS Energy	Frequency [Hz]	P value
Group A		
Pre-test	26.7 – 110.3	0.013 – 0.040
Maximum drug effect	18 – 110.3	0.012 – 0.025
Group B		
Pre-test	6.1 – 26.0	0.007 – 0.045
Maximum drug effect	1.7 – 3.4	0.003 – 0.023
	7.9 – 26.0	0.032 – 0.045

Table 2. Increase of ST-T energy in patients with compared to those without SCN5A mutations

ST-T energy	Frequency [Hz]	P value
Group A		
Pre-test	-	-
Maximum drug effect	-	-
Group B		
Pre-test	1.8 – 5.0	0.018 – 0.045
Maximum drug effect	1.8 – 3.6	0.009 – 0.046

4. Discussion and conclusions

The main finding of this study is that among patients with positive diagnostic ajmaline test for the BrS, those with identified mutations of the cardiac sodium channel gene (SCN5A) have greater depolarisation and repolarisation abnormalities compared to those without SCN5A mutations. These differences can be detected by continuous wavelet analysis of the QRS complex and ST-T wave. Importantly, the differences were present already in baseline (i.e. non-diagnostic) ECGs and persisted during the development of drug-induced diagnostic type 1 Brugada ECG pattern.

Although the BrS is considered to be a genetic disorder with autosomal dominant transmission, mutations of the SCN5A gene are currently found in only approximately 20% of the index cases [15]. Therefore currently the diagnosis of the BrS is based on a combination clinical data and electrocardiographic findings rather than on genetic data. The link between a positive genotype and the arrhythmic risk is also not firmly established yet [2]. However, a recent report suggested that such a link might exist [3]. The type of mutation has also been shown to influence the phenotype and risk in a spectrum of SCN5A channelopathies [16]. Hence, it is likely that the genotype – ECG phenotype relation will play an increasing role both for the diagnosis as well as for the development of novel markers of arrhythmic risk in the BrS. The development of such markers especially targeting asymptomatic patients with BrS who until recently were considered to be at low risk is an urgent task [17].

Unlike Fourier analysis, wavelet analysis is particularly suitable for detection and quantification of sharp discontinuities and localised irregularities [7] such as those frequently observed in the QRS and beginning of ST segment in BrS which are related to the arrhythmic risk [5, 6]. Currently such conduction abnormalities are assessed mainly visually, i.e. by the presence of QRS notches, spikes, fractionation, etc., or by the presence of late potentials on the standard time-domain signal-averaged ECG. The latter, however, cannot detect conduction disturbances buried within the QRS [18]. Recently we reported that principal component analysis of the QRS can detect conduction abnormalities related to previous history of arrhythmia-related symptoms in the BrS [6]. Unlike wavelet analysis, however, principal component analysis requires simultaneous processing of several independent leads. In addition, the results obtained with this method highly depend on the dissimilarities between the processed leads, i.e. analysis of several leads displaying highly abnormal but very similar patterns would render results likely to be observed in normal ECGs (e.g. low ratio between the 2nd to 1st eigenvalue).

The set of 6 leads including V1 and V2 recorded from 3 neighbouring intercostal spaces (4th to 2nd) seems to be more sensitive for detection of QRS and ST-T wave abnormalities linked to presence of mutations than leads V1 to V3 recorded from the 4th and 3rd i.c.s. It is widely recognised that recording leads V1 and V2 from the 3rd or 2nd i.c.s. increases their sensitivity to detect type 1 Brugada ECG pattern. Traditionally, however, the ECG

diagnosis of BrS is based on leads V1 to V3 [1, 19]. Recent studies have shown that lead V3 is of little diagnostic value in BrS [20] and the current diagnostic ECG criteria [1] most likely will be revised soon. Our results with principal component analysis of the QRS in BrS [6] are also in concert with the findings of the present study. Visible signs of conduction abnormalities (QRS notching, fractionation, etc.) are also more frequently observed when leads V1 and V2 are recorded in higher than standard electrode positions (3rd and 2nd instead of 4th i.c.s.) (our unpublished observations).

In conclusion, continuous wavelet analysis of the QRS and ST-T wave especially when applied to a set of leads overlying the right ventricular outflow tract (leads V1 and V2 from the 4th to 2nd intercostal space) seems able to identify carriers of SCN5A mutations among patients with the BrS. The method needs to be further tested for improved diagnosis and especially assessment of the arrhythmic risk of patients with the BrS and asymptomatic carriers of Brugada ECG pattern.

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