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Concealed abnormal atrial phenotype in patients with Brugada syndrome and no history of atrial fibrillation

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ABSTRACT

Objectives: The electrocardiogram (ECG) of patients with BrS in sinus rhythm might reflect intrinsic atrial electrical abnormalities independent from any previous atrial fibrillation (AF). Aim of this study is to investigate the presence of P-wave abnormalities in patients with BrS and no history of AF, and to compare them with those displayed by patients with documented paroxysmal AF and by healthy subjects.
Methods: Continuous 5-min 16-lead ECG recordings in sinus rhythm were obtained from 72 participants: 32 patients with a type 1 Brugada ECG, 20 patients with a history of paroxysmal AF and 20 age-matched healthy subjects. Different ECG-based features were computed on the P-wave first principal component representing the predominant morphology across leads and containing the maximal information on atrial depolarization: duration, full width half maximum (FWHM), area under the curve and number of peaks in the wave.
Results: Patients with BrS and no history of AF (mean age: 53 ± 12 years; males: 28 pts., spontaneous type 1 ECG: 20 pts., *SCN5A* mutation: 10 pts) presented with longer P-wave duration, higher FWHM and wider area under the curve in comparison with the other two groups. Although P-wave features were abnormal in BrS patients, no significant difference was found between patients with spontaneous type 1 ECG and ajmaline-induced type 1 ECG, symptomatic and asymptomatic ones, and between patients with a pathogenic *SCNA5* mutation and patients without a known gene mutation.
Conclusions: Patients with BrS without previous occurrence of AF present with a concealed abnormal atrial phenotype. In these patients atrial electrical abnormalities can be detected even in the absence of an overt ECG ventricular phenotype, symptoms and a *SCN5A* mutation.

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1. Background

Brugada syndrome (BrS) is an inherited ion channel cardiac disease characterized by a peculiar electrocardiographic (ECG) ventricular phenotype, the coved-type ST-segment elevation in the right precordial leads, and an increased risk of sudden cardiac death in the absence of overt structural cardiac abnormalities [1–3].

Patients with BrS have also a higher incidence of paroxysmal atrial fibrillation (AF) that approximates 20% of cases: the presence of spontaneous AF in BrS characterizes patients with a more severe phenotype as far as syncope, spontaneous type 1 ECG, and sustained ventricular arrhythmias is concerned [3–5]. Although a full understanding of the pathophysiological mechanisms leading to AF in these patients is still missing, the putative mechanism is thought to be related to ion channel dysfunction equally presenting at the atrial and ventricular level, thus leading to occurrence of atrial arrhythmias [5,6]. Indeed, the presence of a *SCN5A* gene mutation has been associated with enhanced atrial electrical abnormalities [5].

Patients with BrS present with an increased intra-atrial conduction time when compared to healthy subjects [5–7]. These electrophysiological abnormalities have been documented at the time of invasive electrophysiological (EP) study in patients with an overt BrS phenotype, some of them also presenting with AF [5–7]. However, non-invasive assessment of P-wave abnormalities using resting ECG would be clinically more relevant, be significantly more cost-effective, and would avoid risk-related invasive procedure. The resting ECG of BrS patients might reflect atrial electrical abnormalities despite the absence of documented AF

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and be very useful for screening purpose. To date, limited information is available on the assessment of P wave parameters in BrS patients [7,8]. Advanced post-processing ECG signal analysis is nowadays available that allows non-invasive identification of patients prone to paroxysmal AF which are usually characterized by long P-wave duration and high beat-to-beat morphology variability [9]. Conversely, no information is available on beat-to-beat P-wave morphological variability in BrS patients.

The aims of this study were to: 1) Investigate the presence of P-wave abnormalities in BrS patients without history of AF; 2) Compare measurement of atrial abnormalities of BrS patients without known history of AF with healthy subjects as well as with patients with history of paroxysmal AF; 3) Evaluate whether BrS patients presenting with a spontaneous type 1 ECG had more severe atrial abnormalities than patients with drug-induced type 1 pattern; 4) Evaluate whether atrial abnormalities were more pronounced in symptomatic patients or in patients with a known *SCN5A* gene mutation.

2. Methods

2.1. Study population

A total of 72 subjects were included from 2 different European Institutions (Fondazione Cardiocentro Ticino, FCCT, Lugano, Switzerland and Maastricht University Medical Center, The Netherlands). Thirty-two consecutive patients (Group 1) were diagnosed with BrS: 22 patients with an unknown genotype at FCCT and 10 patients with an established *SCN5A* gene mutation at Maastricht University Medical Center. All patients had either a spontaneous or drug-induced Brugada type 1 ECG, no documented episodes of paroxysmal AF, and continuous follow-up at each respective enrolling Institution. Moreover, 20 healthy age-matched individuals referred for suspected coronary artery disease without any history of AF and no structural heart disease (Group 2) and 20 patients with documented recurrent episodes of paroxysmal AF referred for non-pharmacological therapy (Group 3) were included at FCCT.

The diagnosis of BrS was determined using the recommendations of the Brugada consensus report [3]. Accordingly, ECGs were classified as Brugada coved-type (type 1) or saddleback (type 2) or normal. An ECG was considered diagnostic of BrS if a coved type ST elevation ≥2 mm was documented in ≥1 lead from V1 to V3 in the presence or absence of a sodium-channel blocker agent. Ajmaline (1 mg/kg) was administered intravenously over a 5 min period to unmask the diagnostic ECG pattern of BrS in case of non-diagnostic basal ECG. All baseline and drug-induced 16 lead ECGs were recorded at a paper speed of 25 mm/s and amplitude of 10 mm/mV with the right precordial leads positioned at the sternal margin of the third and fourth intercostal space.

Paroxysmal AF was defined on the frequent occurrence of recurrent episodes of AF self-terminating within 7 days. Medical history, physical examination, bi-dimensional transthoracic echocardiogram and cardiac magnetic resonance imaging were performed in all cases in order to rule-out underlying structural cardiac abnormalities and to assess cardiac dimensions and function.

Electrophysiologic study (EPS) was performed in case of palpitations, syncope potentially related to a supraventricular arrhythmia or for risk stratification purposes. Atrioventricular conduction intervals (AH, HV) and sinus node function were assessed in any case. To establish sustained ventricular arrhythmias inducibility, a maximum of 3 ventricular extrastimuli with a minimal coupling interval of 200 ms was delivered from at least one ventricular site unless ventricular fibrillation or sustained ventricular tachycardia was induced. Continuous atrial pacing and pacing with atrial extrastimuli from a catheter placed in the right atrial appendage or coronary sinus was performed to assess the presence of repetitive atrial firing (defined as occurrence of 2 or more premature atrial complexes after atrial stimulation) and induced AF (defined as AF induced by extrastimuli and persisting for >30 s). Indication to implantable cardioverter-defibrillator (ICD) was determined according to the recommendations of the 2nd Brugada consensus conference [3].

Clinical follow-up consisted of physical examinations, 5-min ECG recording, and 24-h Holter recording, or implantable cardioverter-defibrillator controls performed every 6 months.

2.2. ECG analysis

2.2.1. ECG acquisition

All patients underwent a 16 leads ECG recording obtained by a high-resolution ECG machine (CARDIOVIT CS-200 Excellence; Schiller) having a sampling frequency of 1 KHz and a band-pass filter with cut-off frequencies set at 0.05–350 Hz. All recordings lasted 5 min.

2.2.2. Data analysis

Unidentified ECGs were electronically transferred to the Politecnico di Milano (Milan, Italy) and the Swiss Federal Institute of Technology (EPFL, Lausanne, Switzerland) for advanced signal analysis. Analysis was conducted at each laboratory and both groups were blinded to clinical baseline characteristics and history of arrhythmic episodes.

2.2.3. Assessment of P-wave features by principal component analysis (PCA)

Every lead signal was preprocessed at Politecnico of Milan (Italy) and analyzed to extract the average P-wave. To isolate the P-waves, first R-waves were detected using an algorithm similar to that proposed by Pan and Tompkins, which acts as a high-pass filter on the ECG signals, enhancing the high-frequency QRS complexes. P-waves were then extracted in a 300-ms long window starting from 350 ms before the R-wave. Ectopic atrial signals or P-waves with excessive noise were excluded by computing the cross-correlation function between each P-wave and a P-wave template. All P-waves were tested as P-wave template, and the one providing the highest average cross-correlation was used as final P-wave template. Finally, before the averaging procedure, P-waves were aligned according to the lag at which the cross-correlation function between the P-wave template and each single P-wave shows its maximum.

Principal component analysis (PCA), implemented through an algorithm based on Singular Value Decomposition, was performed on average P-waves [10]. The first principal components, containing the maximal information on atrial depolarization, were analyzed (Fig. 1). The following morphological parameters were computed on the first principal components: duration, full width half maximum (FWHM), and area under the curve. In addition, a beat-to-beat analysis was performed: the principal component analysis was computed on each beat and the Euclidean distance between the average morphology over all the beats acquired and the morphology identified on each beat for the first principal components was assessed. Four similarity indexes, based on the vector distance, were computed (normalized between 0 and 1): s1: similarity between each first principal component and the next one; s2: similarity between each first principal component and all the other beats; s3: similarity between each first principal component and the mean of all the beats; s4: similarity between each first principal component and the median of all the beats.

2.2.4. Assessment of beat-to-beat P-wave morphological variability

Additional analysis on beat-to-beat P-wave morphology on a single lead was performed at EPFL (Lausanne, Switzerland). Lead II was used because it exhibited the highest P-wave amplitude. Baseline wandering was removed using two consecutive median filters. Finally, high frequency noise and power line interference were reduced by using a fifth-order low-pass Butterworth filter with a cut-off frequency of 40 Hz. After the detection of R-peaks and the removal of premature beats, a search window (fixed for all beats but dependent on the subject) prior to each R-peak was created to extract P-waves. The onsets and offsets of P-waves were then obtained using first and second derivative estimates of the ECG signal. Subsequently, beat-to-beat Euclidean distance between P-waves (a numerical index of P-wave stability over time) was assessed and computed as:

$$EDist_i = \frac{\sqrt{\sum_{k=1}^{N}(P_{i+1}[k]-P_i[k])^2}}{\sqrt{\sum_{k=1}^{N}(P_{i+1}[k])^2}}, \text{ for } i = 1, 2, \cdots, L-1$$

where P_i and P_{i+1} represent P-waves resynchronized with regard to their center of gravity. N is the length in samples of each P-wave. L is the number of P-waves extracted from the lead II ECG. For each subject, the morphological variability of P-wave over time was quantified by using mean and standard deviation of the beat-to-beat Euclidean distance.

2.2.5. Statistical analysis

Data are presented as mean ± SD or as median (25–75 percentiles), or as absolute values and percentages where appropriate. The statistical comparison between the two groups was performed by using the nonparametric Mann-Whitney *U* test for unpaired data. Statistical significance was set at $p < 0.05$.

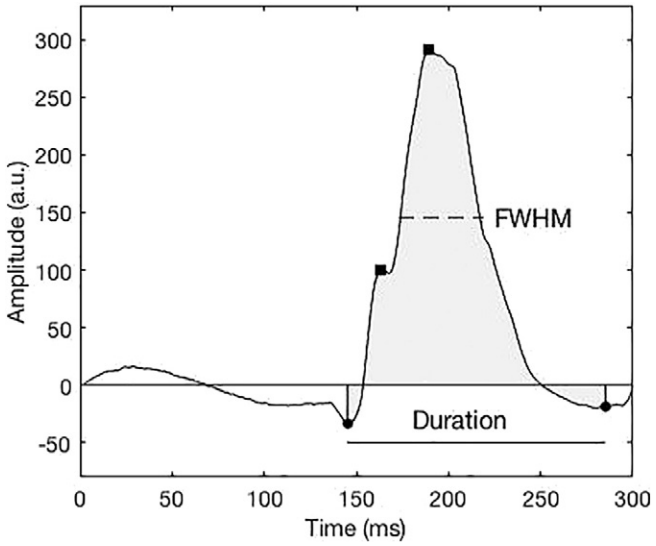

Fig. 1. Principal component analysis.

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