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Electrocardiographic evidence of abnormal atrial phenotype in Brugada syndrome

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ABSTRACT

Background: Brugada syndrome (BrS) is an inherited ion channelopathy that may predispose affected individuals to atrial cardiomyopathy. We tested the hypothesis that BrS patients have higher degrees of atrial electrophysiological abnormalities compared to controls, and these can be reflected by changes in P-wave parameters determined on the electrocardiogram (ECG).

Methods: This was a single-center retrospective study comparing BrS patients to age- and gender-matched control subjects. Mean P-wave duration (PWD_{mean}), maximum PWD (PWD_{max}) and minimum PWD (PWD_{min}), P-wave dispersion (PWD_{max} – PWD_{min}), and P-wave terminal force in V1 (PTFV1) were measured. PWD_{max} ≥ 120 ms, in the presence and absence of biphasic P-waves in the inferior leads, were termed advanced and partial inter-atrial block (IAB), respectively.

Results: The proportion of IAB was significantly higher in BrS patients (28/51; 55%) than in control subjects (14/51; 27%; Fisher's Exact test; $P < 0.01$). Advanced IAB was observed in two BrS patients but none of the control subjects ($P = 0.50$). Compared to controls, BrS patients showed higher PWD_{mean} (107 [98–113] vs. 97 [90–108] ms; KWANOVA, $P < 0.01$), PWD_{max} (123 [110–132] vs. 113 [107–121] ms; $P < 0.001$) but statistically indistinguishable PWD_{min} (82 [72–92] vs. 77 [69–85]; $P = 0.09$), and P-wave dispersion (38 [26–52] vs. 37 [23–45] ms; $P = 0.14$). PTFV1 was significantly higher in BrS patients than in control subjects (24 [0–40] vs. 0 [0–27] mm. ms; $P < 0.05$).

Conclusion: Atrial conduction abnormalities are frequently observed in BrS. These patients may require monitoring for future development of atrial fibrillation and stroke.

Introduction

Brugada syndrome (BrS) is a cardiac ion channel disease that can lead to ventricular tachycardia, ventricular fibrillation, and/or sudden cardiac death (SCD). Abnormalities in ventricular depolarization and repolarization have been extensively studied in BrS; however, the accompanying changes in the atria have been less well studied. In a cohort of Japanese BrS patients, P-wave durations (PWDs) were significantly prolonged and were associated with atrial arrhythmia inducibility [1]. In another cohort, BrS patients showed longer PWDs and greater P-wave dispersion when compared with control subjects [2]. It was recently reported that BrS patients had greater atrial electrophysiological abnormalities than non-BrS patients with paroxysmal atrial fibrillation (AF) [3]. In this study, we tested the hypothesis that BrS patients have higher degrees of atrial electrophysiological abnormalities compared to controls, and these can be reflected by changes in P-wave parameters determined on the electrocardiogram (ECG).

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Methods

Study subjects

This retrospective study received ethics approval from the NTEC-CUHK Clinical Research Ethics Committee. The inclusion criteria were subjects diagnosed with BrS who presented to the Prince of Wales Hospital – a teaching hospital based in Hong Kong, China. Diagnosis of BrS was made in accordance with the 2012 consensus published in the Journal of Electrocardiology, the 2013 HRS/EHRA/APHRS expert consensus statement, and the 2015 ESC Guidelines [4–6]. The baseline characteristics of age, sex, comorbidities (hypertension, hypercholesterolemia,

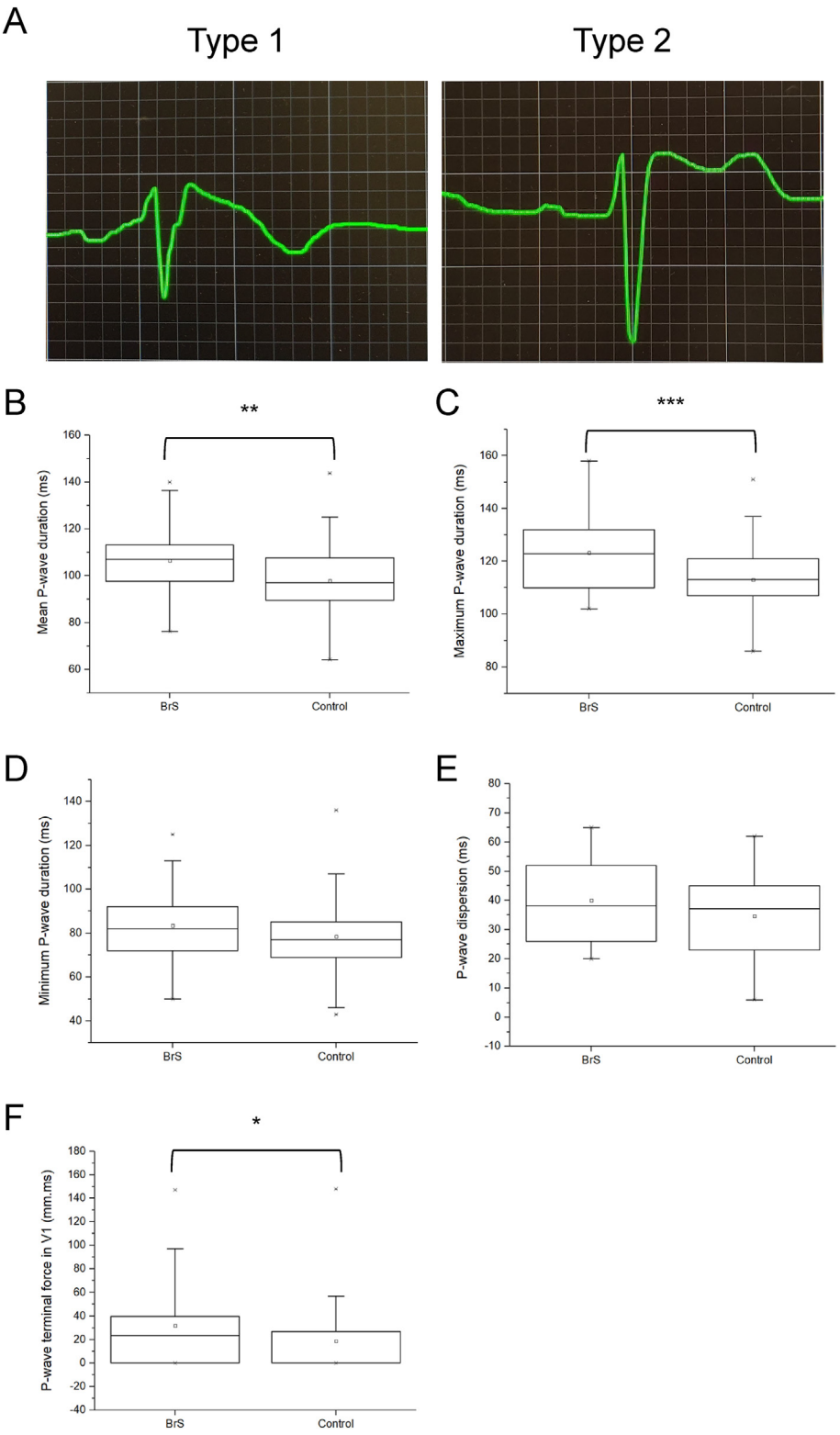

Fig. 1. Screenshot of the ECG analysis program (A). The first and second white lines indicate the onset and end of the P-wave, respectively. Mean P-wave duration (B), maximum P-wave duration (C), minimum P-wave duration (D), P-wave dispersion (E) and P-wave terminal force in V1 (PTFV1) (F) in Brugada patients versus control subjects. *P*-value were obtained from Kruskal-Wallis ANOVA. *, ** and *** used to denote $P < 0.05$, 0.01 and 0.001, respectively.

ischemic heart disease, diabetes mellitus), type of Brugada pattern, syncopal symptoms, and spontaneous VT or VF were recorded. For the control group, age- and sex-matched patients who were admitted to the internal medicine ward over the same time period were included. Patients who suffered from previous or current episode of myocardial infarction were excluded.

Electrocardiographic measurements

The following parameters were obtained from 12-lead ECGs recorded from leads V1, II, III and aVF. These leads were chosen because V1 is one of the better leads for assessing P-wave morphology and the inferior leads are assessed for the presence or absence of inter-atrial block. Measurements were made using Phillips ECG Vue (Standard Edition). The first ten measurements were validated by clinical electrophysiologists (T.L., K.P.L.). The mean P-wave duration (PWD_{mean}) was calculated from values obtained from leads V1, II, III and aVF (Fig. 1). The maximum and minimum PWD were determined (PWD_{max} and PWD_{min}). Partial and advanced inter-atrial block (IAB) were defined in accordance with the 2012 consensus statement as $PWD_{max} \geq 120$ ms in the absence and presence of biphasic P-waves in the inferior leads, respectively [7]. P-wave dispersion was defined as $PWD_{max} - PWD_{min}$. P-wave terminal force in V1 (PTFV1) was defined as the area subtended by the terminal negative component of a biphasic P-wave in lead V_1, with the area calculated by multiplication of the duration and depth of the waveform [8].

Statistical analysis

Data were expressed as median [lower quartile - upper quartile]. Categorical data were analysed by Fisher's exact test. Differences between study groups were tested using ANOVA or Kruskal-Wallis ANOVA. $P < 0.05$ was considered statistically significant.

Results

Clinical characteristics

This study included a total of 51 Chinese patients with BrS and 51 age- and sex-matched control subjects. The baseline characteristics are shown in Table 1. The method of measurement of the ECGs and examples of spontaneous type 1 and non-type 1 Brugada pattern are shown in Fig. 1A. The positions of the start and end of the P-wave are represented by the two vertical lines. A detailed analysis on ventricular depolarization and repolarization indices of this cohort was previously reported by our group [9]. This is a follow-up study comparing different P-wave parameters between BrS patients and control subjects.

Table 1
Demographic and clinical characteristics of Brugada syndrome patients and control subjects included in this study.

Characteristics	BrS ($n = 51$)	Controls (n = 51)	P-value
Male sex	46 (90%)	46 (90%)	1.00
Age (years)	56 ± 17	57 ± 11	0.78
ICD insertion	21 (41%)	0 (0%)	<0.0001
Appropriate ICD shocks	4 (8%)	–	–
Syncope	25 (49%)	0 (0%)	<0.0001
Spontaneous VT	7 (14%)	0 (0%)	0.01
Diabetes mellitus	2 (4%)	4 (8%)	0.68
Hypertension	18 (35%)	18 (35%)	1.00
Hypercholesterolemia	4 (8%)	21 (41%)	0.0002

Data were presented as number (%) or mean ± standard deviation. P-value were obtained from Fisher's exact test (for frequency data) or ANOVA (for continuous data).
Abbreviations: BrS: Brugada Syndrome, ICD: implantable cardioverter defibrillator, VT: ventricular tachycardia.

Brugada patients show greater degrees of atrial electrophysiological abnormalities than control subjects

The proportion of IAB was significantly higher in BrS patients (28/51; 55%) than in control subjects (14/51; 27%; Fisher's exact test; $P < 0.01$). Advanced IAB was observed in two BrS patients but in none of the control subjects ($P = 0.50$). When compared with control subjects, BrS patients showed a higher PWD_{mean} (107 [98–113] vs. 97 [90–108] ms; KWANOVA, $P < 0.01$; Fig. 1B) and PWD_{max} (123 [110–132] vs. 113 [107–121] ms; $P < 0.001$; Fig. 1C) but statistically indistinguishable PWD_{min} (82 [72–92] vs. 77 [69–85]; $P = 0.09$; Fig. 1D) and P-wave dispersion (38 [26–52] vs. 37 [23–45] ms; $P = 0.14$; Fig. 1E). Nevertheless, PTFV1 was significantly higher in BrS patients than in control subjects (24 [0–40] vs. 0 [0–27] mm.ms; $P < 0.05$; Fig. 1F).

Spontaneous type 1 and non-type 1 Brugada patients show similar degrees of atrial electrophysiological abnormalities

The proportion of IAB was similar between type 1 (15/22; 68%) and non-type 1 BrS patients (13/29; 45%; Fisher's exact test; $P = 0.15$). Both cases of advanced IAB were seen in non-type 1 subjects ($P = 0.50$). When compared with non-type 1 BrS patients, those with spontaneous type 1 patterns showed similar PWD_{mean} (112 [101–116] vs. 103 [97–112] ms; KWANOVA, $P = 0.14$; Fig. 2A) and PWD_{max} (127 [116–138] vs. 118 [110–131] ms; $P = 0.37$; Fig. 2B), longer PWD_{min} (88 [79–95] vs. 78 [68–90]; $P < 0.05$; Fig. 2C), and similar P-wave dispersion (35 [25–51] vs. 40 [31–58] ms; $P = 0.35$; Fig. 2D) and PTFV1 (25 [0–48] vs. 17 [3–38] mm.ms; $P = 0.69$; Fig. 2E).

Discussion

This study includes the largest cohort to-date specifically examining P-wave indices in BrS patients. The most important finding is that Brugada patients showed greater degrees of atrial electrophysiological abnormalities when compared with age- and sex-matched controls. BrS patients showed a higher incidence of IAB, longer mean and maximum PWDs, larger PTFV1 but similar minimum PWD and P-wave dispersion. There were no apparent differences observed in P-wave indices between spontaneous type 1 and non-type 1 BrS patients, except for the minimum P-wave duration, which was longer in patients with spontaneous type 1 Brugada pattern.

BrS patients have an increased risk of developing ventricular arrhythmias [10], potentially leading to SCD [11]. BrS patients with a type 1 pattern are thought to have a higher risk of developing such adverse events compared with those with non-type 1 patterns [12–14]; although those with non-type 1 patterns are also at risk [15]. BrS patients have an elevated risk of developing atrial arrhythmias, specifically AF [16,17]. The presence of AF may promote a more severe phenotype, such as manifestation of a spontaneous type 1 pattern and syncope [18–20]. Moreover, BrS patients have been found to have an abnormally high incidence of AF-related stroke [21]. There is also some evidence of atrial conduction abnormalities in BrS that can be detected invasively during electrophysiological studies [22]. There are several reasons as to why BrS patients develop abnormal atrial electrophysiology. Genetic mutations in different ion channel genes found in BrS can be expressed in both atrial and ventricular cardiomyocytes, leading to alterations in the gating or distribution in the cardiac ion channels [23], in turn promoting the development of atrial as well as ventricular arrhythmias [24]. Moreover, atrial fibrosis has been reported in BrS, indicating the additional presence of a structural substrate.

Various ECG markers have been used for the risk stratification in BrS. These have mainly focused on ventricular depolarization or repolarization, but not on atrial ECG markers. Atrial electrophysiological abnormalities can manifest as partial and advanced IAB, which has been extensively studied in other conditions [25–33]. However, there are only a few studies to date evaluating P-wave indices in BrS. In 15

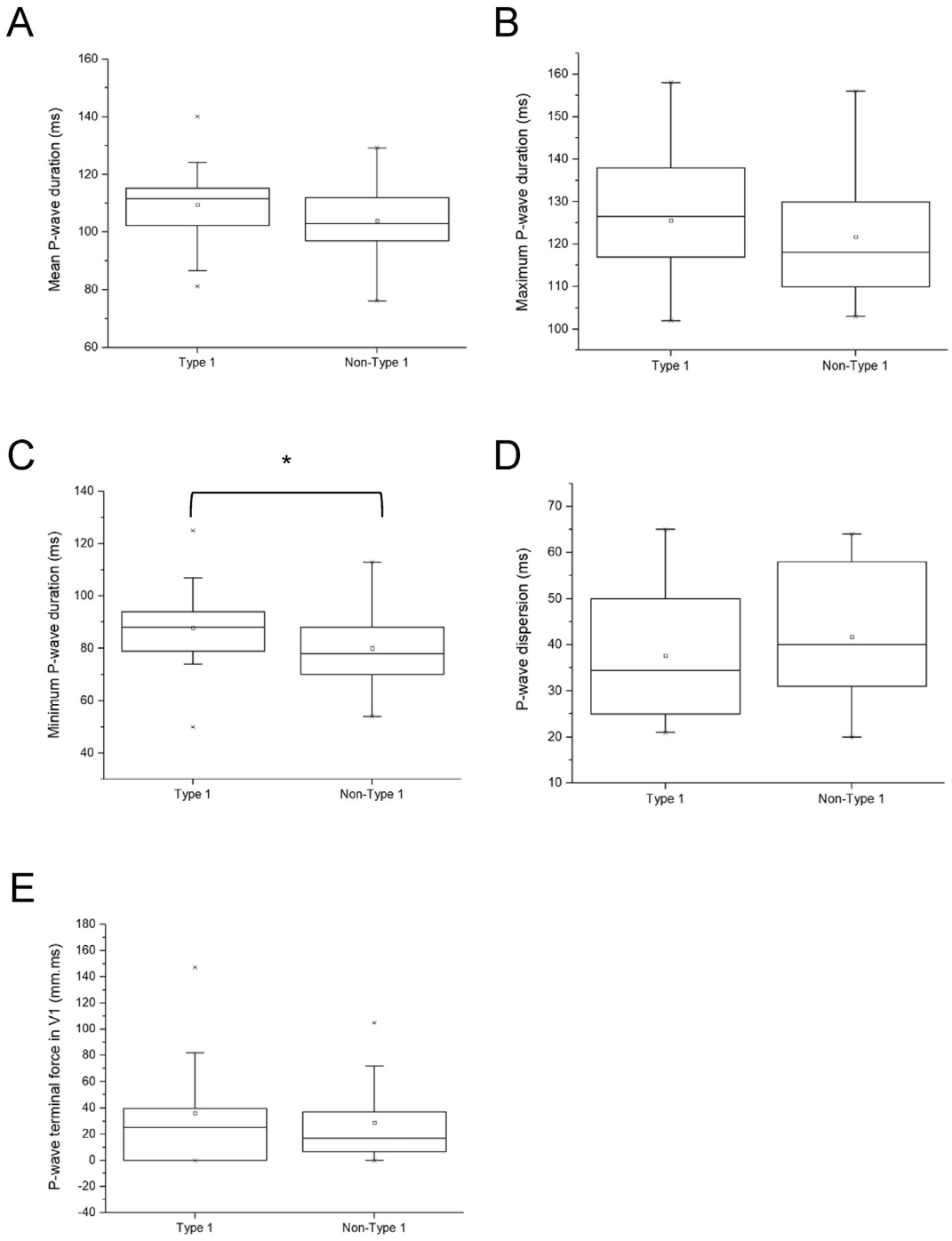

Fig. 2. Mean P-wave duration (A), maximum P-wave duration (B), minimum P-wave duration (C), P-wave dispersion (D) and P-wave terminal force in V1 (PTFV1) (E) in spontaneous type 1 and non-type 1 Brugada patients. P-value were obtained from Kruskal-Wallis ANOVA. *, ** and *** used to denote $P < 0.05$, 0.01 and 0.001, respectively.

patients with BrS and Brugada-type ECG, longer PWDs were observed when compared with controls, and this was associated with atrial arrhythmia inducibility [1]. In another cohort of 20 patients with BrS, longer PWDs and greater P-wave dispersion were observed when compared with control subjects [2]. Another study found that in 38 patients with BrS, those with atrial tachyarrhythmias exhibited increased values of PWDs and P-wave dispersion than those without atrial tachyarrhythmias [34]. Recently, a study found higher degrees of atrial electrophysiological abnormalities in 32 BrS patients when compared to 20 non-BrS patients with paroxysmal AF [3]. Indeed, BrS patients have demonstrated longer PWDs on signal-averaged electrogram recordings when compared to controls, but shorter PWDs when compared to those with paroxysmal AF [35]. In another cohort, programmed electrical stimulation induced sustained AF in the patients with Brugada-type ECGs [36], supporting the hypothesis that there are electrophysiological and structural substrates in the atria for arrhythmogenesis. Our study provides further evidence that abnormal atrial electrophysiological changes are found in Brugada patients which are detectable through simple ECG measurements.

Limitations

Several limitations of this study are recognized. Firstly, this included a small cohort from a single center. These findings should be confirmed

in larger studies. Secondly, this was a retrospective study that did not examine hard outcomes. Given that IAB is independently associated with the occurrence of both AF and stroke in other cohorts [8,37,38], future studies are needed to determine whether P-wave indices would similarly predict such outcomes in BrS. Thirdly, our definition of IAB slightly differed from the 2012 consensus statement [7] in that we were not able to align the cursors such that we would measure the P-wave onset and offset simultaneously in different leads. Therefore, we had made a compromise of measuring the P-wave duration separately in each lead and take the mean value across the leads. Fourthly, as this was a retrospective study of previously recorded ECGs from the local hospital database intended for clinical use, it did not precisely record where the V1 electrodes were placed. Nevertheless, our hospital guidelines recommend the electrodes to be placed according to agreed standards. To fully control for variations in P-wave morphology due to electrode positioning, a prospective research study is needed to precisely place and record the locations of different ECG electrodes. Fifthly, genetic testing for possible mutations in different ion channel genes is not routinely performed, and therefore we did not have a sufficient sample size to conduct a subgroup analysis to make comparisons of the P-wave indices between SCN5A positive and SCN5A negative BrS subjects.

Conclusions

This study provides electrocardiographic evidence that atrial conduction abnormalities are frequently observed in BrS. These patients may require monitoring for future development of atrial fibrillation and stroke.

Acknowledgements

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