Epsilon-like waves and ventricular conduction abnormalities in subjects with type 1 ECG pattern of Brugada syndrome

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BACKGROUND Previous studies have demonstrated an overlap between the arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) and Brugada syndrome (BS). Conduction delay in the right ventricle has been demonstrated in both entities.

OBJECTIVE This study investigated specific ARVC/D electrocardiographic (ECG) markers in subjects with spontaneous or drug-induced type 1 ECG pattern of BS.

METHODS The study population consisted of 47 apparently healthy individuals (38 men, mean age 44.1 ± 13.3 years) with spontaneous (n = 17) or drug-induced (n = 30) type 1 ECG phenotype of BS. The clinical records of these individuals were retrospectively analyzed.

RESULTS Fifteen subjects (31.9%) were symptomatic, with a history of syncope. A family history of BS or sudden cardiac death was reported in 10 (21.3%) and 8 (17.0%) cases, respectively. Epsilon-like waves in leads V1-V3 were observed in 6 subjects (12.7%). Epsilon-like waves were seen in spontaneous type 1 ECGs in 2 cases and after sodium channel blocking test in 4 cases. In baseline ECGs, localized prolongation (>110 ms) of the QRS complex in leads V1-V3, QRS duration ratio in (V1+V2+V3)/(V4+V5+V6) ≥ 1.2, and prolonged S wave upstroke (>55 ms) in leads V1-V3 were seen in 48.8%, 29.8%, and 40.4% of subjects, respectively. Epsilon-like waves and delayed S wave upstroke were more commonly observed in subjects with family history of BS ($P = .014$ and $P = .038$, respectively).

CONCLUSION Specific ECG markers that reflect ventricular conduction delay in ARVC/D are commonly observed in subjects with spontaneous or drug-induced type 1 ECG pattern of BS as well. These depolarization abnormalities may be related to subtle underlying structural abnormalities.

KEYWORDS: Epsilon waves; Brugada syndrome; Arrhythmogenic right ventricular cardiomyopathy/dysplasia

ABBREVIATIONS **ARVC/D** = arrhythmogenic right ventricular cardiomyopathy/dysplasia; **RV** = right ventricle; **BS** = Brugada syndrome; **ECG** = electrocardiogram; **VT/VF** = ventricular tachycardia/fibrillation; **SCD** = sudden cardiac death; **EPS** = electrophysiological study; **ICD** = implantable cardioverter defibrillator; **MRI** = magnetic resonance imaging

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Introduction

Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D), a genetically determined heart muscle disorder, is characterized histologically by fibrofatty replacement of the myocardium, primarily of the right ventricle (RV), and life-threatening ventricular arrhythmias or sudden cardiac death (SCD).[1] The Brugada syndrome (BS) is considered an electrical disease characterized by the presence of ST-segment elevation in leads V1 through V3 on surface electrocardiogram (ECG), the absence of gross structural heart disease, and a high propensity of ventricular tachycardia/fibrillation (VT/VF) or SCD.[2–4]

Although ARVC/D and BS are distinct clinical entities with respect to both the clinical presentation and genetic predisposition, previous studies have demonstrated an overlap between these diseases.[5–7] Sodium channel blocking tests induced the characteristic coved-type ECG pattern of BS in 16.3% of patients diagnosed with ARVC/D, whereas fibrofatty replacement of cardiac myocytes has been reported in patients diagnosed with BS.[8,9] Furthermore, conduction delay in the RV has been demonstrated in both entities.[1,4] Specifically, ECG markers in patients with ARVC/D including the presence of epsilon waves, localized prolongation of the QRS complex in leads V1–V3, QRS duration ratio in (V1+V2+V3)/(V4+V5+V6) ≥ 1.2, and prolonged S wave upstroke in leads V1–V3 have been proposed to reflect activation delay in the RV.[1,10,11]

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Given that BS may be associated with depolarization abnormalities occurring in the RV,[4] we investigated the afore mentioned ECG markers in subjects with spontaneous or drug-induced type 1 ECG pattern of BS.

Study population

The clinical records of 52 consecutive individuals diagnosed with spontaneous or drug-induced (ajmaline 1 mg/kg, or flecainide 2 mg/kg, or procainamide 10 mg/kg) type 1 ECG pattern of BS from 2000 to 2010 were retrospectively analysed. The ECG diagnosis of BS was strictly based on the recommendations of the Second Consensus Conference on BS.[4] A type 1 ECG pattern was defined as a prominent coved ST-segment elevation displaying J-point elevation $\geq$ 2 mm or 0.2 mV along with a flat or negative T wave in at least 2 leads from V1 through V3. Five individuals with right bundle branch block were excluded from the study. All subjects underwent transthoracic echocardiography to rule out structural heart disease. The following clinical data were collected in all patients: age, gender, family history of SCD (<45 years of age), family history of BS, and indication for implantable cardioverter defibrillator (ICD) implantation. An electrophysiological study (EPS) was performed in 26 subjects. Moreover, screening for *SCN5A* gene mutations was performed in 4 subjects (1 positive proband). Subjects with a previous history of syncope, agonal respiration or seizures at night, and aborted SCD were considered as symptomatic. Patient treatment was based on clinical judgment of the participating centers.

The following parameters that may reflect activation delay of the RV in ARVC/D[10] were evaluated in baseline ECGs (in the absence of any antiarrhythmic medication): (1) the presence of epsilon waves defined as a distinct deflection after the end of the QRS complex in leads V1–V3. However, in certain cases, it is not obvious whether these deflections occur at the end or immediately after the QRS complex. Therefore, in the current study, a broad definition termed epsilon-like waves was used to avoid such discrepancies in ECGs interpretation; (2) localized prolongation of the QRS complex in leads V1–V3 (>110 ms); (3) QRS duration ratio in (V1+V2+V3)/(V4+V5+V6) $\geq$ 1.2; and (4) prolonged S wave upstroke defined from the nadir of the S wave up to the isoelectric line in leads V1–V3 (> 55 ms). Additionally, in patients with drug-induced type 1 ECG pattern, we evaluated the appearance of an epsilon-like wave in leads V1–V3 immediately after drug challenge, because this conduction abnormality has been proposed to reflect the extent of RV involvement in patients with ARVC/D.[11] The ECG strips were recorded at a paper speed of 25 or 50 mm/sec and at a sensitivity of 10 mm/mV. ECG analysis was carried out manually by 2 independent investigators.

The SPSS software package (version 13.0 for Windows, SPSS Inc., Chicago, Illinois) was used for statistical analysis. Data are expressed as mean values $\pm$ standard deviation. The Fisher exact test was used to test for any associations between categorical variables. A value of $P < .05$ was considered to be statistically significant. The study was approved by the medical ethical review committees of the participating hospitals. Informed consent was obtained from all subjects.

Results

The final study population consisted of 47 apparently healthy individuals (38 men, age 44.1 $\pm$ 13.3 years) with spontaneous (n = 17) or drug-induced (n = 30) type 1 ECG phenotype of BS. Two sibling pairs were included in this study population. The clinical characteristics of the study population are shown in Table 1. Fifteen subjects (31.9%) were symptomatic, exhibiting a history of syncope. A family history of BS or SCD was reported in 10 (21.3%) and 8 (17.0%) cases, respectively. An EPS was performed in 26 subjects, and programmed right ventricular stimulation induced VT/VF in 17 of them (65.7%). A single-chamber ICD was implanted in 16 individuals. During a mean follow-up period of 4.9 $\pm$ 3.1 years, 1 subject suffered an appropriate ICD discharge due to sustained polymorphic VT and 1 died due to noncardiac causes. Atrial arrhythmias were seen in 11 subjects (23.4%). There were no inappropriate ICD therapies in our cohort.

Epsilon-like waves were observed in 6 subjects (12.7%). Epsilon-like waves were seen in spontaneous type 1 ECGs in 2 cases (Figure 1, cases 1 and 2) and after sodium channel blocking tests in 4 cases (Figure 2, cases 3 to 6). Cardiac magnetic resonance imaging (MRI) using gadolinium confirmed the absence of structural abnormalities in the 2 cases with spontaneous epsilon-like waves. Two of these subjects displayed a family history of SCD ($P = .267$), and 4 of them a family history of BS ($P = .014$). Of note, 1 couple of siblings presented epsilon-like waves after ajmaline challenge (cases 3 and 4). One positive proband for SCN5A gene mutation (exon 26, 4477-4479delAAG, K1493del) displayed an epsilon-like wave in lead V1 after drug challenge (case 6). As shown in Table 1, localized prolongation (>110 ms) of the QRS complex in leads V1-V3 was noted in 48.8% of subjects, whereas

Table 1 Clinical characteristics of the study population

Variables	Individuals with BS ECG phenotype (n = 47)
Age (yrs)	44.1 $\pm$ 13.3
Men (%)	>38 (80.9)
Spontaneous type 1 ECG phenotype (%)	17 (36.2)
Symptomatic (%)	15 (31.9)
Family history of BS (%)	10 (21.3)
Family history of SCD (%)	8 (17.0)
Epsilon waves (%)	6 (12.7)
QRS duration >110 ms in leads V1-V3 (%)	22 (48.8)
QRS duration ratio (V1+V2+V3)/(V4+V5+V6) > 1.2 (%)	14 (29.8)
S-wave upstroke in leads V1-V3 > 55 ms (%)	19 (40.4)
EPS (%)	26 (55.3)
Inducible VT at EPS (%)	17 of 26 (65.4)
ICD implantation (%)	16 (34)
Follow-up period (yrs)	4.9 $\pm$ 3.1
Atrial arrhythmic events during follow-up (%)	11 (23.4)
Ventricular arrhythmic events during follow-up (%)	1 (2.1)

BS = Brugada syndrome; ECG = electrocardiographic; EPS = electrophysiological study; ICD = implantable cardioverter-defibrillator; SCD = sudden cardiac death; VT = ventricular tachycardia.