Spontaneous electrocardiogram alterations predict ventricular fibrillation in Brugada syndrome

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BACKGROUND Patients with Brugada syndrome (BS) often have spontaneous changes in their electrocardiogram (ECG).

OBJECTIVE To evaluate the significance of ECG alterations, we investigated the relationships between the ECG and the occurrence of ventricular fibrillation (VF) in both patients and an experimental model of BS.

METHODS In study 1, we evaluated ECG alterations in BS patients with (VF+, n = 33) and without (VF−, n = 41) spontaneous VF. We defined type 0 ECG as coved-type ST elevation without a negative T wave, which represents the existence of loss-of-dome (LOD) type action potentials (APs). In study 2, we optically mapped epicardial APs and recorded transmural ECGs in 34 canine right ventricular tissues with a drug-induced BS model by a combination of pinacidil and pilsicainide.

RESULTS In study 1, changes in ST level ≥0.2 mV were more frequent in the VF+ group than in the VF− group ($P < .01$). Spontaneous ECG alterations and appearances of types 1 and 0 ECGs were more frequent in the VF+ group than in the VF− group ($P < .01$). In study 2, BS model with spike-and-dome (SAD) epicardial APs exhibited type 1 ECG. Deepening of the phase 1 notch of the APs induced heterogeneous conversion of the APs (SAD→LOD) and resulted in ECG conversion from type 1 to type 0. Significant AP heterogeneity often appeared during AP alterations and initiated phase 2 reentry. Tissues having ventricular tachycardia (VT; n = 20) had more frequent alterations in APs and ECG than in tissues without VT (n = 14; $P < .01$).

CONCLUSION ECG alterations, especially conversion between types 0 and 1, are associated with significant AP heterogeneity that can initiate VF in BS.

KEYWORDS: Sudden death; Electrocardiography; Ventricular fibrillation; Brugada syndrome

ABBREVIATIONS **AP** = action potential; **APD** = action potential duration; **BS** = Brugada syndrome; **CL** = cycle length; **ECG** = electrocardiogram; **f-QRS** = fragmented QRS; **ICD** = implantable cardioverter-defibrillator; **LOD** = loss-of-dome; **LP** = late potential; **LV** = left ventricle; **RBBB** = right bundle branch block; **RV** = right ventricle; **SAD** = spike-and-dome; **VF** = ventricular fibrillation; **VT** = ventricular tachycardia

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Introduction

Brugada syndrome (BS) is characterized by ST elevation in the right precordial leads, episodes of ventricular fibrillation (VF),[1] and sudden cardiac death in patients generally 30–50 years old.[2,3] Type 1 electrocardiogram (ECG), with ≥0.2 mV coved-type ST elevation followed by a negative T wave, as defined by the Report of the Second Consensus Conference of Brugada Syndrome, is the only ECG type diagnostic of BS.[4] Although detection of type 1 ECG is important to predict patient prognosis,[2,5] ECGs in patients with BS often vary spontaneously between normal and type 1, making it difficult to assess the risk of VF.[3,4,6] Repetitive recordings are necessary to detect and verify the presence of type 1 ECG.[6,7] ECG alterations are also associated with frequent implantable cardioverter-defibrillator (ICD) discharges.[7]

Experimental studies have shown that type 1 ECG reflects spike-and-dome (SAD) type action potentials (APs)[8–11] and that a shallow or absent negative T wave reflects loss-of-dome (LOD) type AP in the right ventricular (RV) epicardium.[9–11] Although some clinical studies reported coved ST elevation without negative T waves in the ECGs of patients with BS,[10] the significance of that particular ECG variation and its prediction of VF risk are unknown.

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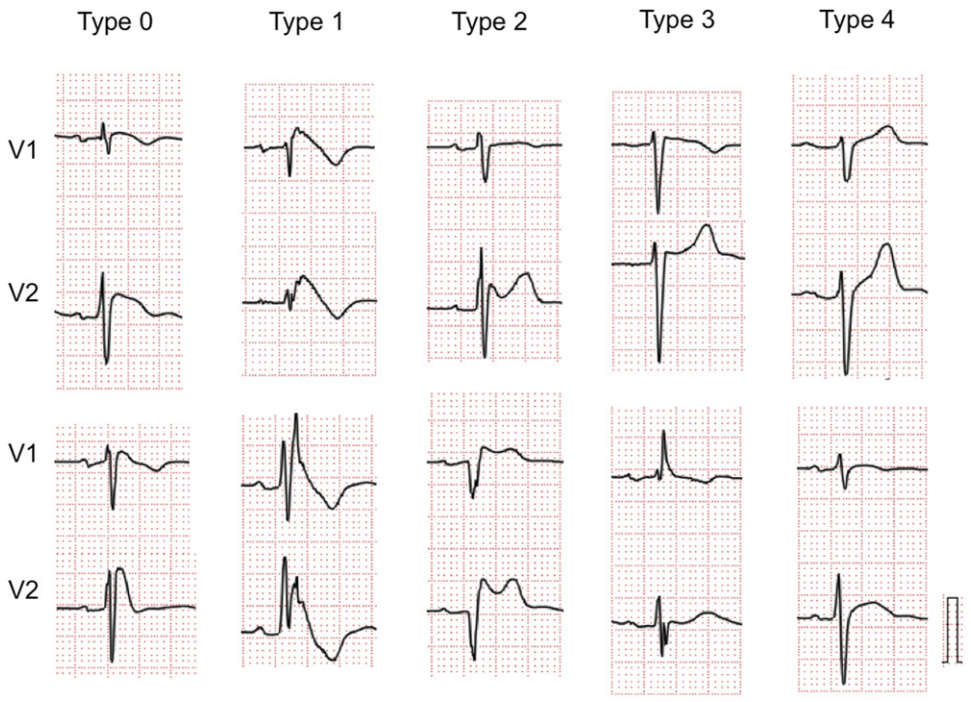

Figure 1 Classification of ECG types. Two typical ECGs are shown in each type. Type 0 is defined as an ECG with coved-type ST elevation ≥2 mm and a shallow negative T wave (≤1 mm) or having no negative T wave. Type 1–3 ECGs are defined by the Consensus Reports of Brugada Syndrome. Normal ECG is defined as normal-appearance ECG with or without early repolarization.

In the present study, we evaluated spontaneous alterations in the ECGs and in the ST level during follow-up in BS patients with and without VF and the underlying mechanism and impact of ECG alterations on the occurrence of ventricular arrhythmias in an *in vitro* experimental model of BS.

Methods

Clinical studies

The study groups comprised 70 males and four females with Brugada-type ECGs (mean age 59 ± 13 years), divided into those with (VF+ group) and without (VF− group) documented VF. To minimize the inclusion of patients with new onset of VF in the future, the VF−group consisted of elderly patients (≥60 years old at their first visit), because new-onset VF is rare in this population and we wished to minimize this additional variable.[2,3] Naturally, conclusions from our study can only be directed to the specific population we studied. All patients had type 1 ECG (54 spontaneous and 20 pilsicainide-induced[10]). Of the 20 patients with pilsicainide-induced type 1 ECG, 17 were in the VF− group and three in the VF+ group. No patients were from the same family. Echocardiography and chest X-ray were performed in all patients, and no abnormalities were found. All patients underwent an electrophysiological study after risks were explained and written informed consent obtained.

Standard 12-lead ECGs (0–150 Hz filter) and additional V1–V3 at the third intercostal space were recorded simultaneously. To evaluate the alterations in ECG type and ST level, we acquired ECGs during the initial and at each scheduled (3–6 months of follow-up) and any unscheduled visits and during any in-hospital stay. We evaluated the alterations in the ECG at rest (usually 2 hours before or after meal) and excluded the ECGs recorded with any stress (such as exercise test, drug challenge test, full stomach, and febrile illness).

We evaluated RR, PQ, and QRS intervals in lead II and QT interval, ST level at J point, and existence of fragmented QRS (fQRS)[12,13] in leads V1–V3 and V5 of the 12-lead ECG at their first visit. ECGs during follow-up were classified as type 0, 1, 2, 3, or normal. Types 2 and 3 ECGs were defined as in the Reports of the Second Consensus Conference of Brugada Syndrome.[4] We defined type 1 as in the Consensus Report, that is, having ST elevation with negative T wave, but added the criterion of T-wave depth >1 mm. We defined type 0 ECG as having coved ST elevation ≥2 mm and a shallow or absent negative T wave (depth ≤1 mm). Our previous experimental studies showed that type 0 ECG represented the existence of LOD type APs in the RV epicardium[9–11] (Figure 1). When multiple ECG types were observed, for example, when leads V1, V2, and V3 showed type 1, 0, and 2 ECGs, respectively, we classified the ECG as the type with the lowest number, type 0 in this example. We realize that the addition of new ECG categories complicates the BS classification, but the existing classification does not include the type 0 ECG.

The electrophysiological study, as we reported previously,[12] was performed in 54 patients. Induction of ventricular arrhythmia was attempted without antiarrhythmic drugs. The criterion for ventricular arrhythmia was induction of sustained polymorphic ventricular tachycardia (VT) or VF by programmed electrical stimulation from the RV apex, RV outflow tract, or left ventricle, using a maximum of two extra stimuli shortened to intervals reaching ventricular refractoriness at two cycle lengths (CLs).