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Viewpoint

Brugada Phenocopies: Consideration of Morphologic Criteria and Early Findings From an International Registry

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Brugada syndrome (BrS) is an inherited sudden cardiac death syndrome characterized by type 1 or type 2 electrocardiographic (ECG) patterns in precordial leads V_1-V_3 that predispose individuals to malignant ventricular arrhythmias and sudden cardiac death.[1] Brugada phenocopies (BrPs) are clinical entities that have ECG patterns that are identical to true congenital BrS but are elicited by various other clinical or technical factors such as myocardial ischemia, metabolic abnormalities, mechanical mediastinal compression, or poor electrocardiographic (ECG) filters.[2]

This article discusses the conceptual emergence of BrP as a new ECG phenomenon, reviews the current BrP diagnostic criteria, and provides a new morphologic classification that more precisely categorizes future BrP cases. Preliminary results from the International Registry of Brugada Phenocopies (www.brugadaphenocopy.com)[3] are also discussed.

Conceptual Emergence of the BrP

BrS is characterized by 2 ECG patterns found in leads V_1-V_3: the typical type 1 "coved" pattern or the type 2 "saddleback" pattern. The type 1 pattern has a high take-off ST-segment elevation that is $\geq$ 2 mm followed by a downsloping concave or rectilinear ST segment with a negative symmetrical T wave (Fig. 1A).[1] The type 2 pattern is defined as a high take-off (r') that is $\geq$ 2 mm from the isoelectric baseline, followed by ST-segment elevation that is convex with respect to the isoelectric baseline, with elevation $\geq$ 0.05 mV, with a variable T wave in lead V_1 and positive or flat T wave in lead V_2 (Fig. 2A).[1]

In true congenital BrS, these ECG patterns are often dynamic and are sometimes concealed; however, various clinical circumstances such as vagal stimulation, febrile states, and electrolyte imbalances can *unmask* true BrS. In these patients, there is an inherited congenital abnormality that predisposes individuals to malignant ventricular arrhythmias.[4,5] This dysfunction can be elicited with a positive provocative challenge using sodium channel blockers such as flecainide, ajmaline, or procainamide.[1]

More recently, the concept of BrP emerged with numerous observations of Brugada ECG patterns arising in the absence of true congenital BrS.[2] Type 1 Brugada ECG patterns were observed in the context of hypokalemia in a patient with congenital hypokalemic periodic paralysis (Fig. 1B)[6]; acute inferior ST-elevation myocardial infarction with right ventricular involvement (Fig. 1C)[7]; concurrent hyperkalemia, hyponatremia, and acidosis (Fig. 1D)[8]; and acute pulmonary embolism (Fig. 1E).[9] Similarly, type 2 Brugada ECG patterns were observed in the context of congenital pectus excavatum causing mechanical mediastinal compression (Fig. 2B)[10]; acute pericarditis (Fig. 2C)[11]; after accidental electrocution injury (Fig. 2D)[12]; and as a result of using inappropriate high-pass ECG filters (Fig. 2E).[13] Once these clinical/technical abnormalities resolved, there was subsequent normalization of the electrocardiogram. Importantly, these patients have no personal or family history of sudden cardiac death and have a negative result on provocative challenge with sodium channel blockers, when applicable.

Initially, various terms such as Brugada-like ECG patterns, acquired Brugada syndrome, and Brugada syndrome mimicry were used to describe these phenomena. This lack of consensus regarding terminology created confusion and uncertainty when differentiating true congenital BrS with other acquired Brugada-like ECG patterns. As such, we consolidated the terminology with the term "Brugada phenocopy."[2] It is of note is that the term "phenocopy" was chosen because it was previously used to describe an environmental condition that imitates one produced by a gene; therefore, it served as a reasonable and succinct description for all acquired Brugada-like ECG manifestations.[14] Subsequently, after an extensive literature review,[2] we grouped these case reports into 6 etiologic categories and established a systematic BrP diagnostic approach (Table 1).[15,16]

BrP Clinical Reproducibility

In all previous BrP case reports, the Brugada ECG pattern was observed in the context of a singular inciting clinical event such as a metabolic derangement or myocardial ischemia. Recently, the concept of BrP was serendipitously advanced by demonstrating clinical reproducibility in the setting of

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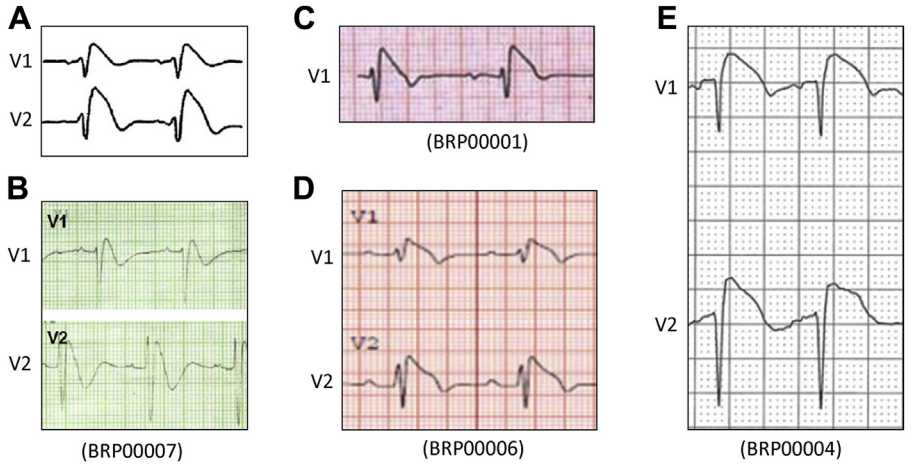

Figure 1. Comparison of various type 1 Brugada phenocopies. (**A**) True congenital type 1 Brugada syndrome electrocardiogram shown in comparison to (**B**) congenital hypokalemic periodic paralysis (type 1B BrP); (**C**) acute inferior ST-elevation myocardial infarction with right ventricular involvement (type 1A BrP); (**D**) concurrent hyperkalemia, hyponatremia, and acidosis (type 1A BrP); and (**E**) acute pulmonary embolism (type 1B BrP). Numbers under figures are International Registry of Brugada Phenocopies identification numbers. BrP, Brugada phenocopy.

recurrent hypokalemia.[17] Briefly, a young patient with diarrhea was admitted to the hospital because of severe hypokalemia (potassium, 1.5 mEq/L) with concurrent metabolic acidosis (pH, 7.22). The ECG was consistent with a typical type 1 Brugada ECG pattern (Fig. 3A). The patient's metabolic abnormalities were corrected, resulting in subsequent normalization of the electrocardiogram (Fig. 3B). During the same hospitalization period, the patient again became hypokalemic (potassium, 2.6 mEq/L); however, without concurrent acidosis (pH 7.45). The corresponding electrocardiogram was again consistent with a typical type 1 Brugada ECG pattern (Fig. 3C) that resolved after correction of the metabolic abnormality (Fig. 3D). Importantly, this patient had no personal or family history of sudden cardiac death and had a negative result on flecainide provocative challenge.

Diagnostic Dilemma

Establishing a clear diagnostic distinction between true congenital BrS and BrP remains an ongoing challenge. BrS can occur spontaneously in the absence of a personal or family history of malignant ventricular arrhythmias and in the absence of defined genetic abnormalities.[1,18] Currently, clinical decisions regarding diagnosis and intervention with implantable cardioverter-defibrillator (ICD) therapy relies on a combination of (1) clinical factors (presence of family or personal history, or both, of malignant ventricular arrhythmias), (2) ECG morphologic characteristics (spontaneous type 1 or intermittent type 1 unmasked by sodium channel blockers or febrile states), (3) positive results on provocative testing with ajmaline, flecainide, or procainamide, and (4) positive genetic markers (many of which are currently undefined or neither sensitive nor specific).[16]

With BrP the same approach applies. The clinical diagnosis of BrP is suggested by (1) clinical factors (an identifiable underlying condition that triggers the ECG pattern and complete absence of personal or family history of syncope or malignant ventricular arrhythmias); (2) ECG morphologic characteristics (identical to true BrS but disappear on resolution of the triggering underlying condition), (3) negative

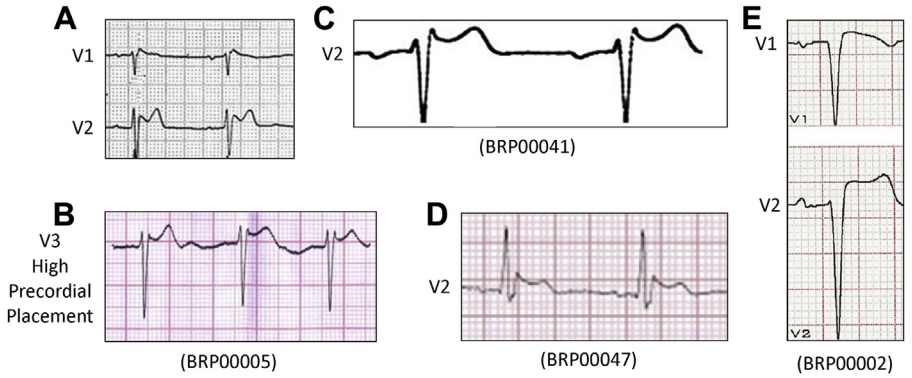

Figure 2. Comparison of various type 2 Brugada phenocopies. (**A**) True congenital type 2 Brugada syndrome shown in comparison to (**B**) congenital pectus excavatum causing mechanical mediastinal compression (type 2A BrP), (**C**) acute pericarditis (type 2A BrP), (**D**) after accidental electrocution injury (type 2A BrP), and (**E**) as a result of using inappropriate high-pass electrocardiographic filters (type 2C BrP). Numbers under figures are International Registry of Brugada Phenocopies identification numbers. BrP, Brugada phenocopy.