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EDITORIAL

Brugada phenocopy: A new electrocardiogram phenomenon

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Abstract

Brugada phenocopies (BrP) are clinical entities that are etiologically distinct from true congenital Brugada syndrome. BrP are characterized by type 1 or type 2 Brugada electrocardiogram (ECG) patterns in precordial leads V1-V3. However, BrP are elicited by various underlying clinical conditions such as myocardial ischemia, pulmonary embolism, electrolyte abnormalities, or poor ECG filters. Upon resolution of the inciting underlying pathological condition, the BrP ECG subsequently normalizes. To date, reports have documented BrP in the context of singular clinical events. More recently, recurrent BrP has been demonstrated in the context of recurrent hypokalemia. This demonstrates clinical reproducibility, thereby advancing the concept of this new ECG phenomenon. The key to further understanding the pathophysiological mechanisms behind BrP requires experimental model validation in which these phenomena are reproduced under strictly controlled environmental conditions. The development of these validation models will help us determine whether BrP are transient alterations of sodium channels that are not reproducible with a sodium channel provocative test or alternatively, a malfunction of other ion channels. In this editorial, we discuss the conceptual emergence of BrP as a new ECG phenomenon, review the progress made to date and identify opportunities for further investigation. In addition, we also encourage investigators that are currently reporting on these cases to use the term BrP in order to facilitate literature searches and to help establish this emerging concept.

Key words: Brugada phenocopy; Brugada syndrome; Electrolytes; Myocardial ischemia; Pulmonary embolism; Cardiomyopathy; Electrocardiogram filters

Core tip: Diagnostic distinctions between Brugada phenocopies (BrP) and Brugada syndrome (BrS) are: (1) BrP patients have a reversible underlying condition and upon resolution of this condition, the electrocardiogram normalizes; (2) BrP patients have a low pretest probability of BrS as opposed to a high pretest probability in patients with true congenital BrS; and (3) BrP patients have a negative sodium channel blocker test, while patients with BrS have a positive test. The different electrocardiographic response to the provocative challenge highlights a pathophysiological divergence when comparing BrP and BrS. This suggests alternative underlying mechanisms with various genetic, structural and environmental interactions yet to be elucidated.

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INTRODUCTION

Brugada syndrome (BrS) is a congenitally inherited car-

diac channelopathy characterized by type 1 and type 2 electrocardiogram (ECG) patterns in leads V1-V3 that predisposes individuals to malignant ventricular arrhythmias and sudden cardiac death[1]. Brugada phenocopies (BrP) are clinical entities that have ECG patterns that are identical to true congenital BrS but are elicited by various other factors, such as myocardial ischemia, metabolic abnormalities, mechanical mediastinal compression and poor ECG filters[2,3]. In this editorial, we discuss the conceptual emergence of BrP as a new ECG phenomenon, review the progress made to date and identify opportunities for further investigation.

THE BRUGADA ECG PATTERN

True congenital BrS is characterized by two ECG patterns in leads V1-V3: The typical type 1 "coved" or the type 2 "saddleback" patterns. The type 1 pattern has a high take-off ST-segment elevation that is ⩾ 2 mm followed by a down-sloping concave or rectilinear ST-segment with a negative symmetric T-wave (Figure 1A)[1]. The type 2 pattern is defined as a high take-off (r') that is ⩾ 2 mm from the isoelectric baseline, followed by ST-segment elevation that is convex with respect to the isoelectric baseline with elevation ⩾ 0.05 mV, with variable T-wave in lead V1 and positive or flat T-wave in lead V2 (Figure 2A)[1].

THE BRUGADA PHENOCOPY

BrP are clinical entities that are etiologically distinct from true congenital BrS. BrP are defined by ECG patterns that are identical to BrS but are elicited by various clinical circumstances. 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[4].

Since the initial reports, type 1 BrP have been reported in the context of an acute inferior ST-segment elevation myocardial infarction with right ventricular involvement (Figure 1B)[5]; concurrent hyperkalemia, hyponatremia and acidosis (Figure 1C)[6,7]; acute pulmonary embolism (Figure 1D)[8,9]; and hypokalemia in the context of congenital hypokalemic periodic paralysis (Figure 1E)[10,11]. Similarly, type 2 BrP have been reported immediately post-electrocution accidental injury (Figure 2B)[12]; in the context of congenital pectus excavatum causing mechanical mediastinal compression (Figure 2C)[13]; and as a result of an inappropriate high-pass ECG filter (Figure 3)[14].

In each of these prior reports, the BrP was observed in the context of a singular inciting clinical event such as myocardial ischemia or metabolic derangement. Finally, the BrP concept was advanced by demonstrating clinical reproducibility in the context of recurrent hypokalemia[15]. Briefly, a young patient with diarrhea was admitted to hospital due to severe hypokalemia (K 1.5 mEq/L) with concurrent acidosis. The ECG depicted a typical type 1 Brugada ECG pattern (Figure 3A). Upon correction of the metabolic abnormalities, the ECG promptly

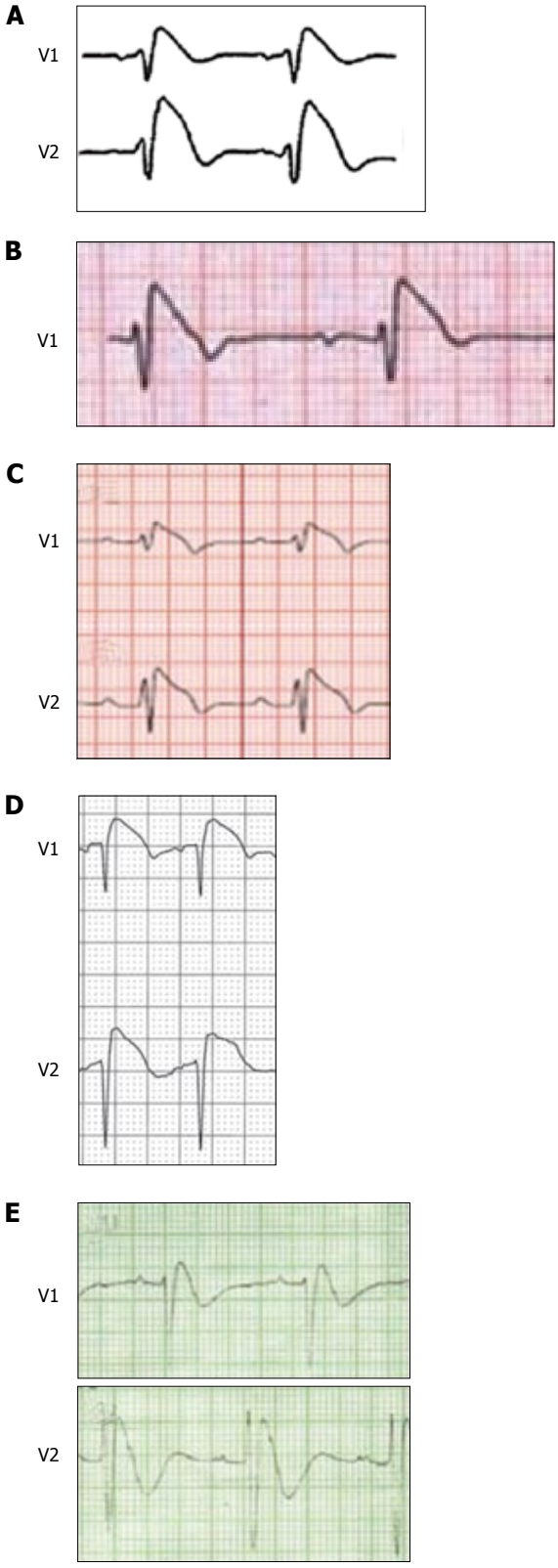

Figure 1 Type 1 Brugada phenocopies. A: True congenital type 1 Brugada electrocardiogram (ECG) pattern; B: Type 1 Brugada phenocopies (BrP) in a patient with an acute inferior ST-segment elevation myocardial infarction with right ventricular involvement; C: Type 1 BrP in a patient with concurrent hyperkalemia, hyponatremia and acidosis; D: Type 1 BrP in a patient with an acute pulmonary embolism; E: Type 1 BrP in a patient with hypokalemia in the context of congenital hypokalemic periodic paralysis.

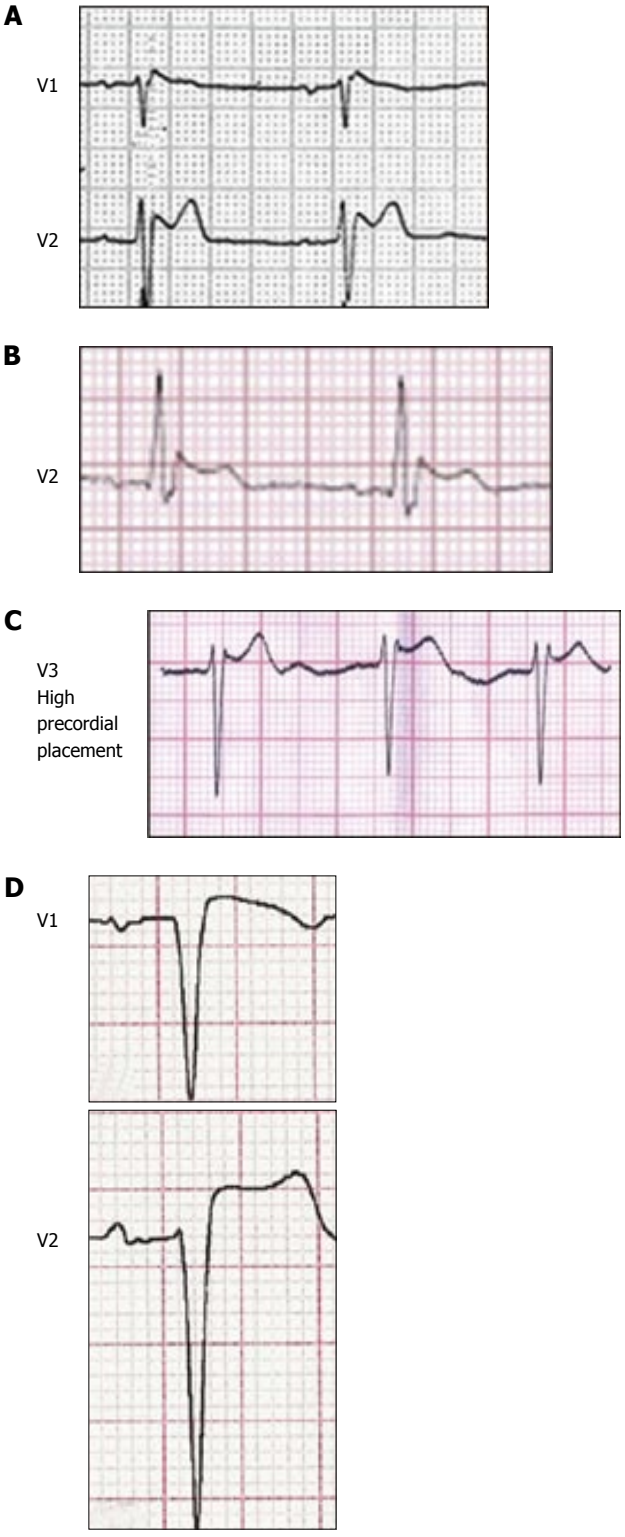

Figure 2 Type 2 Brugada phenocopies. A: True congenital type 2 Brugada electrocardiogram (ECG) pattern; B: Type 2 Brugada phenocopies (BrP) in a patient with an accidental electrocution injury; C: Type 2 BrP in a patient with congenital pectus excavatum causing mechanical mediastinal compression; D: Type 2 BrP as a result of an inappropriate high pass ECG filter.

returned to normal (Figure 3B). A subsequent flecainide provocative challenge did not induce a type 1 Brugada ECG pattern, thereby excluding myocardial sodium channel dysfunction. During the same hospitalization period, the patient experienced ongoing diarrhea with a second episode of hypokalemia (K 2.6 mEq/L); however, without concurrent acidosis. The ECG again depicted a typical type 1 Brugada ECG pattern (Figure 3C) which resolved after correction of the metabolic abnormality (Figure 3D). This case report is important because it was the first to demonstrate clinical reproducibility of the BrP.

Table 1 Brugada phenocopy etiological categories

Etiological category
Metabolic conditions
Mechanical compression
Ischemia and pulmonary embolism
Myocardial and pericardial disease
ECG modulation
Miscellaneous

Reproduced with permission[9]. ECG: Electrocardiogram.

DIFFERENTIATING BRUGADA PHENOCOPY FROM BrS

Currently, a total of 55 case reports, editorials, letters, abstracts and book chapters have been published that discuss the etiology, pathophysiology and conceptual evolution of BrP[16]. This has led to the current BrP etiological categories (Table 1) and diagnostic criteria (Table 2).

The diagnostic distinction between BrP and true congenital BrS focuses on a few key features. First, patients with BrP have a reversible underlying condition such as adrenal insufficiency, hypokalemia or myocardial ischemia that elicits or induces the Brugada ECG pattern. Once this underlying condition resolves there is prompt normalization of the ECG. This is contrary to true congenital BrS where the ECG manifestations are unmasked by sodium channel blockers, vagotonic agents, febrile states and various metabolic conditions. Second, patients with BrP have a low clinical pretest probability of true congenital BrS as opposed to a high clinical pretest probability in patients with true congenital BrS who have a documented personal history of cardiac arrest, nonvagal syncope or a family history of sudden cardiac death[1]. Third, patients with BrP have a negative provocative challenge with a sodium channel blocker, while those with true congenital BrS have a positive provocative challenge (Table 2).

The different response to a sodium channel provocative challenge highlights a fundamental pathophysiological divergence when comparing BrP and BrS patients who are exposed to similar environmental stimulus. For example, Postema *et al*[17] reported a case of true congenital BrS in the context of hyperkalemia and acidosis. This patient presented with a type 1 Brugada ECG pattern and underwent a positive provocative challenge with ajmaline and negative sodium channel voltage-gated type V alpha subunit genetic testing. Interestingly, Recasens *et al*[6] and Anselm *et al*[7] reported a similar case where the patient presented with a type 1 Brugada ECG pattern in the context of hyperkalemia, hyponatremia and acidosis.

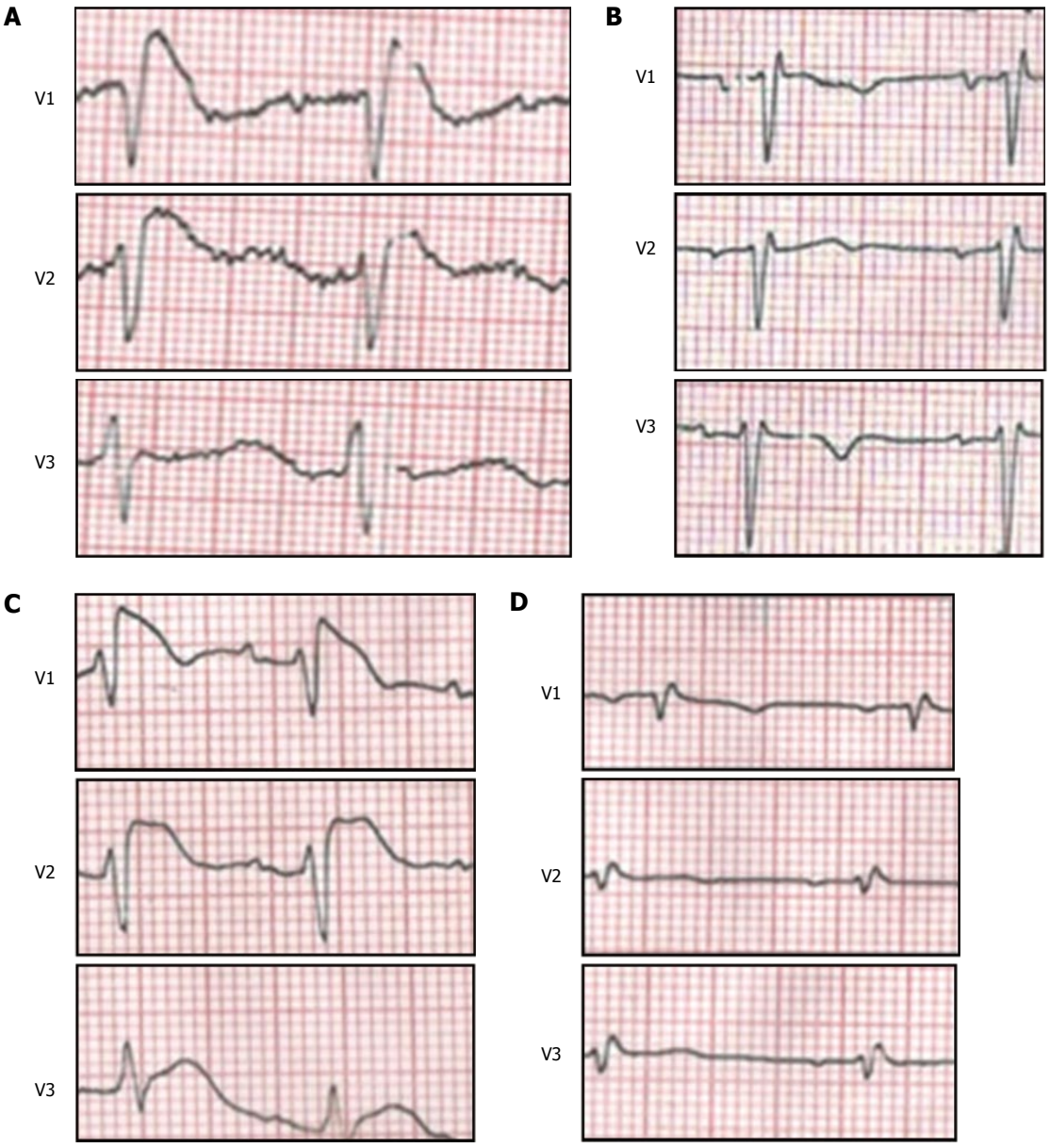

Figure 3 Brugada phenocopy clinical reproducibility. A: Electrocardiogram (ECG) on presentation while the patient is hypokalemic consistent with a type 1 Brugada ECG pattern; B: After correction of the electrolyte abnormality, the ECG normalizes; C: While in hospital, the patient again becomes hypokalemic with recurrence of the type 1 Brugada ECG pattern; D: Subsequent normalization of the ECG pattern after potassium is corrected.

This patient had a negative flecainide provocative challenge. Given the negative sodium channel provocative test, this suggests alternative underlying mechanisms with various genetic, structural and environmental interactions that are yet to be elucidated[18].

Additionally, while patients with high-risk true congenital BrS are candidates for cardioverter-defibrillator implantation, the clinical implications of patients with BrP remain unknown. Therefore, BrP treatment recommendations at this time would suggest focusing on the resolution of the underlying condition as further intervention has not yet been investigated or validated.

BRUGADA PHENOCOPY: FUTURE DIRECTIONS

The chronological emergence of new ECG phenomena should include: (1) phenomenological observation; (2) speculation on pathophysiological mechanisms; (3) clinical reproducibility; and (4) experimental model validation. The literature to date has demonstrated steps (1), (2) and (3); however, the key to further understanding the mechanisms behind BrP requires that these phenomena be reproduced under strictly controlled environmental conditions[19-21]. The development of experimental validation models will help us determine whether BrP are transient alterations of the sodium channels that cannot be reproduced with a provocative sodium channel blocking test, or if they are a malfunction of other myocardial ion channels. Similarly, exposing a genetic model of true congenital BrS to the common conditions that elicit BrP would aid in understanding whether BrP and BrS are entities that belong to the same spectrum of disease, or are completely different entities. In that sense, the model that

Table 2 Criteria to differentiate the Brugada electrocardiogram pattern, Brugada phenocopy and true congenital Brugada syndrome

Brugada ECG pattern
The ECG pattern has a type 1 or type 2 Brugada morphology as currently defined by Bayés de Luna *et al*[1]
Diagnostic criteria for BrP
The ECG pattern has a type 1 or type 2 Brugada morphology
The patient has an underlying condition that is identifiable
The ECG pattern resolves after resolution of the underlying condition
There is a low clinical pretest probability of true BrS determined by lack of symptoms, medical history and family history
Negative provocative testing with sodium channel blockers such as ajmaline, flecainide or procainamide
Provocative testing not mandatory if surgical RVOT manipulation has occurred within the last 96 h
The results of genetic testing are negative (desirable but not mandatory because the SCN5A mutation is identified in only 20% to 30% of probands affected by true BrS)
Features that suggest true congenital BrS
The ECG pattern has a type 1 or type 2 Brugada morphology
There is a high clinical pretest probability of true congenital BrS determined by presence of symptoms, medical history and family history
Positive provocative testing with sodium channel blockers such as ajmaline, flecainide or procainamide. This indicates sodium channel dysfunction consistent with true BrS
Genetic testing is positive in about 20% to 30% of probands

Reproduced with permission[16]. RVOT: Right ventricular outflow tract; SCN5A: Sodium channel voltage-gated type V alpha subunit; BrP: Brugada phenocopies; BrS: Brugada syndrome.

discovered genetic alterations in patients with acquired long QT[22] should serve as inspiration to develop the BrP experimental model.

In order to learn about the natural history of BrP, an international online database that allows for longitudinal follow-up is in development at www.brugadaphenocopy.com. We encourage all investigators that are currently reporting on these cases to use the term Brugada phenocopy in order to facilitate literature searches and to help establish this emerging concept[23,24].

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