

Brugada Phenocopy: Update 2014

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Abstract. *Brugada Phenocopies (BrP) continue to emerge as clinical entities that are distinct from true congenital Brugada Syndrome (BrS). BrP are characterized by type 1 and type 2 Brugada ECG patterns in leads V1-V3; however, BrP are elicited by various underlying associated conditions. A new ECG classification is proposed and a launching of an international website is discussed. We will also review the progress made to-date regarding BrP.*

Keywords: *Brugada Syndrome, Brugada Phenocopy, Genetics, Ion Channels*

1. Introduction

Brugada Syndrome (BrS) is an inherited cardiac channelopathy characterized by type 1 and type 2 ECG patterns in leads V1-V3 which predispose individuals to malignant ventricular arrhythmias and sudden cardiac death (Figure 1, Panel A) (1). Brugada Phenocopies (BrP), however, are clinical entities that have ECG patterns that are identical to true congenital BrS but are elicited by various factors such as electrolyte disturbances, mechanical compression, poor ECG filters, and myocardial ischemia (Figure 1, Panel B) (2). The current BrP etiological categories are depicted in Table 1 and the diagnostic criteria in Table 2.

The term *Phenocopy* was chosen because it describes 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 (3). In this paper, we review the progress made to-date regarding BrP, discuss areas of ongoing controversy, and identify opportunities for further investigation.

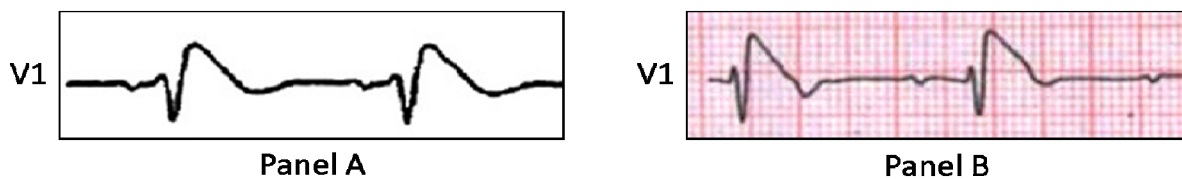


Fig. 1. Comparison of true congenital Brugada Syndrome and Brugada Phenocopy. Classical congenital type 1 "coved" Brugada ECG pattern (Panel A) (1). Brugada Phenocopy in a patient presenting with an acute inferior ST-segment elevation myocardial infarction with right ventricular involvement (Panel B) (5). Lead V1 is identical to the type 1 Brugada ECG pattern. Reproduced with permission (1,5).

Table 1. Brugada Phenocopy Etiological Categories

Etiological Category	
i.	Metabolic Conditions
ii.	Mechanical Compression
iii.	Ischemia & Pulmonary Embolism
iv.	Myocardial & Pericardial Disease
v.	ECG Modulation
vi.	Miscellaneous

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Table 2. Clarification of Brugada ECG Pattern, Brugada Phenocopy, and True Congenital Brugada Syndrome

Brugada ECG Pattern

- i. 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 Brugada Phenocopy (2-12)

- i. The ECG pattern has a type 1 or type 2 Brugada morphology
- ii. The patient has an underlying condition that is identifiable
- iii. The ECG pattern resolves after resolution of the underlying condition
- iv. There is a low clinical pretest probability of true Brugada Syndrome determined by lack of symptoms, medical history, and family history
- v. Negative provocative testing with sodium channel blockers such as ajmaline, flecainide, or procainamide
- vi. Provocative testing not mandatory if surgical RVOT manipulation has occurred within the last 96 hours
- vii. 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 Brugada Syndrome)

Features that suggest true congenital Brugada Syndrome

- i. The ECG pattern has a type 1 or type 2 Brugada morphology
- ii. There is a high clinical pretest probability of true congenital Brugada Syndrome determined by presence of symptoms, medical history, and family history
- iii. Positive provocative testing with sodium channel blockers such as ajmaline, flecainide, or procainamide. This indicates sodium channel dysfunction consistent with true Brugada Syndrome
- iv. The results of genetic testing are positive (desirable but not mandatory because the SCN5A mutation is identified in only 20% to 30% of probands affected by true Brugada Syndrome)

ECG indicates electrocardiogram; RVOT, right ventricular outflow tract; and SCN5A; sodium channel voltage-gated type V alpha subunit.

2. Discussion

The diagnostic distinction between BrP and true congenital BrS focuses on a few key features. The first is that patients with BrP have a reversible underlying condition such as adrenal insufficiency, hypokalemia, or myocardial ischemia which elicits the Brugada ECG pattern. Once this underlying condition resolves, there is normalization of the ECG. Second, patients with BrP have a low clinical pretest probability of true BrS as opposed to a high pretest probability in patients with true BrS (4-9). Third, patients with BrP have a negative provocative challenge with a sodium channel blocker, while those with true BrS have a positive provocative challenge (Table 2). Additionally, while patients with high-risk true congenital BrS are candidates for ICD implantation, the clinical implications of patients with BrP remain unknown. Therefore, the only BrP treatment recommendations at this time would be to focus on resolution of the underlying condition as further intervention has not yet been investigated or validated.

Brugada Phenocopy – Genetics

The inclusion of genetic testing regarding BrP continues to be an area of discussion and will undoubtedly evolve. We have not included genetics as a mandatory diagnostic criterion since only 20-30% of probands with true congenital BrS have positive genetic tests (2, 10-12). Therefore, the vast majority of patients with BrS will have negative genetic testing at this

time. Additionally, even within families known to carry genetic mutations consistent with BrS, there is a poor correlation between genetic testing, ECG manifestations, and clinical outcomes (1). Furthermore, the presence of genetic mutations in true congenital BrS has been shown to be a poor predictor of arrhythmic events and is not a cost effective method of risk stratification in unselected patients diagnosed with BrS.

We also acknowledge that not all patients with exposure to various underlying conditions such as hypokalemia, hyperkalemia, adrenal insufficiency or myocardial ischemia will develop a Brugada ECG pattern. This suggests a possible genetic predisposition for these ECG phenomena. However, looking into the same genes that are associated with true congenital BrS may not be of diagnostic yield.

Brugada Phenocopy – Clinical Reproducibility

The chronological emergence of new ECG phenomena should include: (i) phenomenological observation; (ii) speculation on pathophysiological mechanisms; (iii) clinical reproducibility; and (iv) experimental model validation.

Speculations on the pathophysiological mechanisms of BrP were published elsewhere (2-17) and finally, clinical reproducibility was demonstrated in the context of recurrent severe hypokalemia (13). Briefly, a young patient with diarrhea was admitted to hospital due to severe hypokalemia (K 1.5 mmol/L) with acidosis. The ECG depicted a typical type 1 Brugada ECG pattern. Upon resolution of the metabolic disorder, the ECG returned to normal. A flecainide test did not induce a Brugada type 1 pattern. Before diarrhea completely resolved, the patient presented with a second episode of hypokalemia (K 2.6 mmol/L) without acidosis. The ECG again depicted a typical type 1 Brugada ECG pattern which resolved after correction of the metabolic abnormality. This case confirms *clinical reproducibility*, which as suggested above, is the third step in the validation model of new ECG phenomenon.

3. Future Directions

The key to completely understanding the mechanisms behind BrP is to reproduce these phenomena under strictly controlled environmental conditions (18). The development of experimental validation models will help us determine whether BrP are transient alterations of the sodium channels that are not reproducible with a sodium channel blocking test, or alternatively, a malfunction of other ion channels. Similarly, a model that induces genetic modifications to reproduce the conditions of true BrS and exposing this model to the well described conditions of BrP would help us to understand whether they are entities that belong to the same spectrum or completely different entities.

In order to learn about the natural history of BrP, we are developing an international online database at www.brugadaphenocopy.com which will allow for longitudinal follow-up. 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.

Finally, we would like to comment on a morphological classification that we are about to launch. As different congenital or acquired QT prolongations can be classified based on their morphology, we propose the BrP to be classified according to:

1. **Type-1 BrP**: it is represented by a BrP that is identical to a type-1 “true” Brugada ECG pattern.

2. **Type-2 BrP**: it is represented by a BrP that is identical to a type-2 “true” Brugada ECG pattern.

Each category is divided into:

1. **Sub-type A**: all components of the definition for a BrP have been met as per Table 2
2. **Sub-type B**: not all components of the definition for a BrP have been met as per Table 2 (after completion of our website, we will submit letters-emails- to all authors that have published possible BrP that are considered to be type-1 or type-2 sub-type B; in order for them to run all tests that are necessary to become a sub-type A.
3. **Sub-type C**: not all components of the definition for a BrP have been met as per Table 2; however, no additional tests are needed (i.e. ECG modulation, see Table 1).

3. Final Remarks

The field of BrP continues to evolve as more cases are being published. The major advances in the last 18 months could be summarized as follows:

- Acceptance of the terminology by the scientific community
- Clinical reproducibility (once the “injury” is re-introduce, the ECG patterns re-appears
- New morphological classification (explained above)
- Completion of the international database that will allow for a better long-term follow-up and determination of the natural history of this condition
- Progressive utilization of the new ECG techniques to determine the presence of a Brugada pattern (19) (Beta and Alfa angles; base of the triangle). These measurements will help us to distinguish Brugada ECG patterns from other causes of r’ in leads V1-V2. Once one has decided that this is not a Brugada ECG pattern, then both “true” congenital BrS and BrP have been ruled out. The systematic application of these techniques, will necessary reduced the number and categories of currently existent BrP, as in the case of Pectus Excavatum (9) and others.

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