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Brugada phenocopy: Mechanisms, diagnosis, and implications

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ABSTRACT

Brugada phenocopies are Brugada-like ECG patterns induced by reversible clinical conditions. Baranchuk and colleagues characterized this condition in 2012, and since then the phenomenon has been increasingly reported. It has the same pattern classification of Brugada syndrome (i.e., types 1 and 2), but differs substantially regarding etiology and prognosis. Awareness of Brugada phenocopies must be sought to help understanding the mechanisms of ion channel dysfunction and to avoid misdiagnosis and mistreatment of Brugada syndrome.

Introduction

The Brugada brothers described in 1992 a "clinical and electrocardiographic syndrome" which later received their name [1]. It is an autosomal dominant heart disease caused by dysfunctional ion channels whose carriers have a classical ECG pattern and a predisposition to malignant ventricular arrhythmias. ECG alterations can be dynamic and sometimes are unmasked by acquired conditions such as fever and electrolyte abnormalities, which may complicate the diagnosis [2]. In fact, reports of atypical ECG consistent with Brugada pattern exist since 1953 [3], but the syndrome remained elusive for almost 4 decades.

However, Brugada-like ECG findings may be incited even in the absence of congenital dysfunction of ion channels. These cases have spread some confusion on the terminology around the pattern, with some authors referring them as "acquired Brugada syndrome", "Brugada syndrome mimicry" and "Brugada-like ST segment abnormalities", among many other terms. Riera and colleagues [5] proposed the description "Brugada phenocopy", and Baranchuk and colleagues [6] further characterized the condition. They systematically reviewed reports, established an etiologic classification, and speculated possible mechanisms, making a scientific approach to the phenomenon feasible.

There is a growing interest in understanding Brugada phenocopies. It is unknown whether they pose an increased risk of arrhythmias and sudden death; hence, their optimal management is uncertain [7,8]. They must not be mistaken with Brugada syndrome, for which prognosis and therapeutical approach are standardized [9].

Pathogenesis

Possible mechanisms for Brugada phenocopies are speculative [6–8,10,11]. It is thought that the pattern is induced by an imbalance between ion currents during the phase 1 of the action potential (AP) or by conduction delays in the anterior myocardial wall. This is similar to what occurs in Brugada syndrome according to the repolarization and depolarization theories, respectively [2,10–13].

According to the former explanation, a net outward shift would be created by increased transient outward potassium current (I_{to}) or by decreased inward currents, mainly L-type calcium current and peak sodium channel current. This shift may be most present in tissues with normally prominent I_{to}, such as the epicardium of the right ventricular outflow tract (RVOT). The endocardium presents a lesser I_{to} and therefore would not suffer as many ionic imbalances. The consequent transmural gradient might give rise to the Brugada pattern [10–13]. At late phase 1 of the AP, these shifts cause all-or-none repolarization of some epicardial sites, inducing focal dispersion of repolarization [13]. It leads to local re-excitation and phase 2 reentry arrhythmias.

The depolarization model, nevertheless, states that ionic dysfunction resulting in delayed depolarization of the RVOT would be responsible for creating an electrical gradient with the rest of the RV [10,12,13]. Such delay works similarly in an ischemic zone during an anterior wall myocardial infarction, which may incite a ST segment elevation towards the right precordial leads along with malignant arrhythmias due to afterdepolarizations [10,12,13].

Accordingly, a recent study using simulations of the normal anterior ventricular wall showed that potassium concentration, fibrosis, and I_{to} were implicated in generating Brugada pattern [14]. Hyperkalemia resulted in delayed conduction and unexcitability by increasing the resting potential, which makes the sodium channels unavailable. This finding is facilitated by the presence of fibrosis, thus requiring lower concentrations of potassium to incite characteristic ST-T alterations.

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Finally, an increase in I_{to} resulted in a transmural gradient that was synergistic with the slower conduction generated by hyperkalemia and fibrosis in inducing Brugada Phenocopies [14].

In Brugada syndrome, these alterations stem from congenital ion channel dysfunctions. Interventions in canine hearts decreasing the inward currents or increasing the outward currents during the AP plateau have been shown to incite Brugada-like ST elevation and reentry arrhythmias [8–10]. Reversible clinical conditions may likewise cause ion channel dysfunctions transiently, mimicking the pathogenesis of Brugada syndrome and providing a general explanation for this phenomenon [11–12,15]. Interestingly, tachycardia has been linked to the development of a Brugada phenocopy in the context of hyperkalemia, once again pointing to dynamic ion channel dysfunction as a basis for the phenomenon [16]. However, there are no animal models on Brugada phenocopies, and most existing theories arise from studies on Brugada syndrome.

Causes

There are >100 published cases of Brugada phenocopies [17]. Aiming the clarification of the topic, the International Registry of Brugada phenocopies maintains an online database for the documentation and follow-up of these patients. Based on the standardization proposed by Baranchuk and colleagues [6], they classify causes of phenocopies as shown in Table 1 [7,17].

Most cases of phenocopies are related to metabolic imbalances, ischemia, and pulmonary embolism [17]. Notably, hyper- and hypokalemia represent the only conditions known to cause recurrent Brugada phenocopy; such reports allow greater assurance on the causal relationship between the concurrent condition and the pattern [18,19].

It is intuitive to imagine how metabolic derangements induce Brugada pattern. These conditions are known to affect ionic transport across plasma membrane, which may cause reversible alterations in sodium currents and I_{to} [6,13,18]. Such alterations may be responsible for creating a transmural myocardial gradient or for slowing conduction around RVOT, thereby inducing the ECG pattern. In fact, cases of hyperkalemia are thought to induce transient sodium channel dysfunction, whereas hypokalemia enhances I_{to} directly [6,13]. Ischemia, however, is more elusive: Brugada phenocopies have been seen with either coronary artery as the culprit [20,21]. Most reports include atherosclerotic coronary disease, but fistulae [22] and congenital anomalies [23] have also been linked to development of Brugada pattern. Moreover, in a study with drug induced coronary spasm, ischemia in the right coronary artery area was more likely to be associated with development of Brugada pattern [20]. What exact ionic mechanism elicits the pattern is unknown. It is possible that ischemia in the RVOT play a role, as it may induce ion channel dysfunctions consistent with those accepted for Brugada syndrome [20]. Pulmonary embolism may likewise induce transmural RV ischemia due to acute pressure overload and muscle stretch [24]. Nevertheless, it is unclear how LV ischemia during acute coronary syndromes would also generate Brugada phenocopies. Two cases of atypical ST elevation myocardial infarction leading to Brugada pattern in the anterolateral [21] and inferior [25] walls have been reported. It is plausible that ion channel dysfunctions similar to those of the RVOT in Brugada syndrome happen elsewhere in the heart with corresponding ECG findings.

Table 1
Etiological categories of Brugada Phenocopies as for the International Registry [17].

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

Mechanical compression and peri-myocardial disease, albeit relatively common among Brugada phenocopies, are poorly understood. A non-Hodgkin lymphoma has been reported to compress the RVOT inducing a Brugada phenocopy with ECG normalization after antineoplastic treatment [26]; it is ensuing that the pressure over the RV has induced the appropriate channel dysfunctions to incite Brugada pattern. Correspondingly, pneumothoraxes are also linked to Brugada pattern due to the same mechanism, though they may induce RVOT ischemia as well [27].

The means by which pericarditis and myocarditis might trigger Brugada phenocopies are even more uncertain, but the injury and inflammation may lead to ion channel dysfunction in the RVOT [28]. Additionally, Brugada pattern seems to be rare in Chagas' disease in view of the paucity of reports; the frequent presence of severe intraventricular conduction delays may hinder the detection of classical ECG findings in V1-V3 [29]. Nevertheless, this disorder courses with extensive fibrosis of the basal regions of the heart, which likely predisposes to the occurrence of Brugada phenocopies [14]. Other, more exotic causes, such as aluminum phosphide and yellow phosphorus intoxication, are very little comprehended [30,31].

Finally, ECG modulation has been lately regarded as a cause of Brugada phenocopies. These artifacts are associated with high-pass filter used to attenuate low-frequency interference. As a result, some low-frequency ECG components such as the ST-T may be distorted, thereby mimicking Brugada pattern [32].

Diagnosis

The diagnosis of Brugada phenocopies as currently accepted by the International Registry of Brugada phenocopies lies on a set of criteria (Table 2) that focuses on the main characteristics of the phenomenon; cases are divided based on ECG morphology and number of met criteria [33,34]. A four-step approach has been suggested [17] for making the diagnosis of a suspected case:

1) Identify Brugada ECG pattern;
2) Determine low pretest probability of Brugada syndrome;
3) Undertake drug challenge with a sodium channel blocker:
   a. ajmaline, 1 mg/kg, over 5 min;
   b. flecainide, 2 mg/kg, over 10 min;
   c. procainamide, 10 mg/kg, over 10 min; or
   d. pilsicainide, 1 mg/kg, over 10 min.

4) Do genetic testing (not mandatory).

The ECG pattern is classified as type 1 or type 2 based on leads V1–V3. Type 1 Brugada pattern (Fig. 1) is characterized by ≥2 mm ST elevation followed by concave or rectilinear downsloping ST-segment, with negative and symmetric T wave [2]. Type 2 Brugada pattern (Fig. 2) has a takeoff (r′) ≥ 2 mm and convex ST elevation ≥0.5 mm, with variable T wave in V1 and positive or flat T wave in V2 [2,6,7]. Patterns are further grouped in class A, B, and C [34]. Class A represents cases in which all mandatory criteria were met, including challenge test. Class B includes reports with incomplete mandatory criteria, but still highly

Table 2
Brugada phenocopies diagnostic criteria as for the International Registry [17,34]. Genetic testing is not mandatory since it has sensitivity ≤ 30%.

Diagnostic criteria	Presence of type 1 or type 2 Brugada pattern
	Presence of an indetifiable underlying condition
	Reversal of the pattern upon resolution of the condition
	Low pre-test probability of Brugada syndrome
	Negative provocative testing
	Provocative testing not mandatory if RVOT manipulation within 96 h
	Negative genetic testing

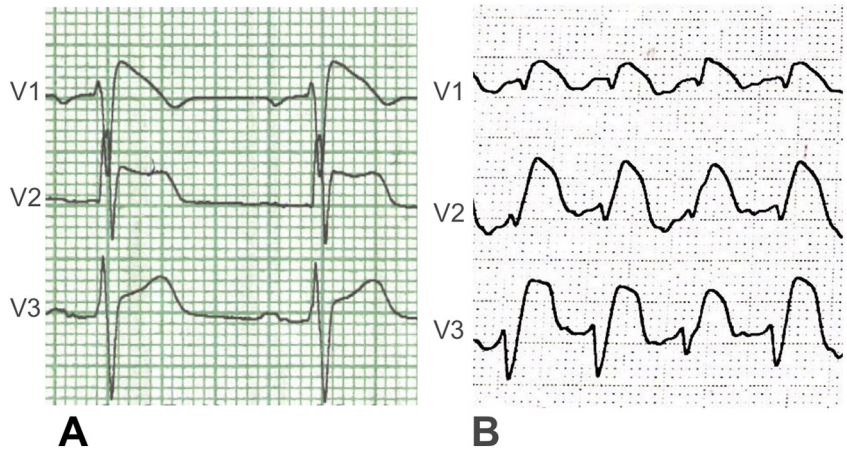

Fig. 1. Cases of Brugada syndrome and Brugada phenocopy with type 1 ECG pattern. A: True congenital Brugada syndrome in a patient with a history of aborted sudden death. B: Brugada henocopy in a patient with hyperkalemia.

suspected of presenting phenocopies. Cases with unjustified provocative testing (e.g., surgical manipulation of RVOT within 48 h) are qualified as class C. It is worth noting that the ECG patterns are the same as for Brugada syndrome, and there is not an electrocardiographic marker to distinguish Brugada phenocopy from Brugada syndrome. It has been shown that expert cardiologists [9] cannot distinguish between both conditions when using only surface ECG, and more recently measures of β-angle and the base of the triangle [35] in V1 and V2 have proved to be similar in Brugada phenocopies and Brugada syndrome. Importantly, ST segment elevation as seen in Brugada pattern can also be confused with ST elevation myocardial infarction, since these conditions may present with similar ECG changes; such distinction might become even more complicated in acutely ill patients [19,36]. The presence of characteristic Brugada-like ST-segment elevation in V1 to V3 which is reversible after the resolution of an underlying clinical condition favors the diagnosis of Brugada phenocopy.

Low pretest probability is determined by patient's symptoms, medical history and family history [17]. Palpitations, syncope, cardiac arrest and thrashing at night should be lacking in cases of Brugada phenocopy, and there may be no sudden death nor unexplained syncope in the patient's family. These findings are associated to Brugada syndrome [37], leading to the supposition that patients who present with them have had unmasked the disease rather than an acquired condition. Such cases simulate the behavior of a Brugada phenocopy; however, even concealed Brugada syndrome may pose an increased risk of malignant arrhythmias and sudden cardiac death [37].

Provocative tests with sodium channel blockers must be done when suspecting of a Brugada phenocopy, since these medications are able to unveil Brugada syndrome. They act by blocking predominantly sodium currents as compared to I_{to}, increasing the already present ionic imbalance at the RVOT of patients with ion channel dysfunctions [38–50]. The challenge should be done with an IV infusion of ajmaline, procainamide, pilsicainide, or flecainide [17]. A continuous ECG monitoring must be undertaken, and depiction of type 1 Brugada pattern constitutes a positive result. It is advisable to provide close medical attention, as ventricular arrhythmias and cardiac arrest might be precipitated by the test, even in asymptomatic patients [38]. Excessive QRS widening and frequent premature ventricular beats indicate high-risk of complications and encourage interruption of the challenge [33]. The used drugs have presented good reproducibility [38], but flecainide has been shown to present significantly lower sensitivity than ajmaline (77% against 100%, respectively) [39,40]. A negative result in the provocative test supports the diagnosis of Brugada phenocopy; nevertheless, it must not be overlooked that there may be up to 23% of false-negatives [39] when using flecainide, and cases of delayed diagnosis of Brugada syndrome have been reported [41]. Of note, it is not required to perform challenges if the patient has had surgical manipulation of the RVOT within 96 h of presenting the pattern [42].

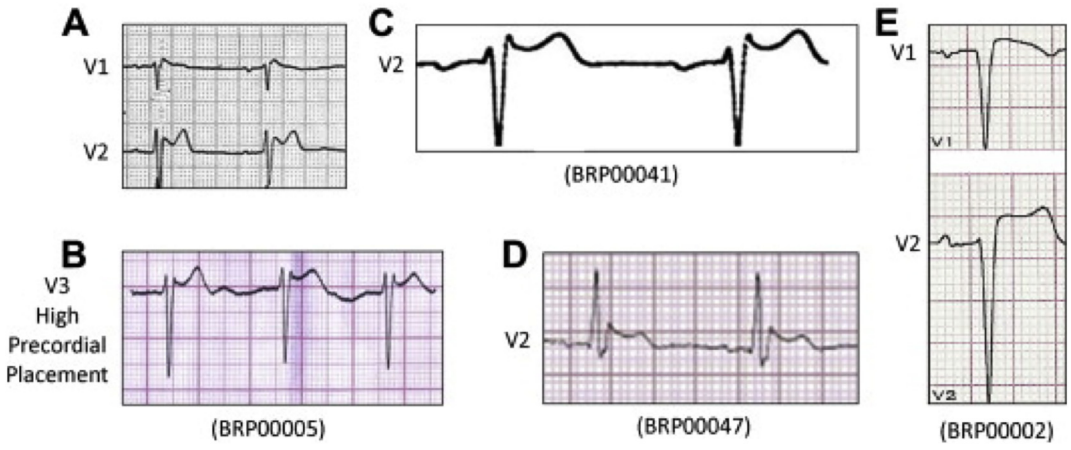

Fig. 2. Cases of Brugada syndrome and Brugada phenocopy with type 2 ECG pattern. A: True congenital Brugada syndrome. B: Brugada phenocopy caused by congenital pectus excavatum with mechanical mediastinal compression. C: Brugada phenocopy incited by acute pericarditis. D: Brugada phenocopy after accidental electrocution injury. E: Brugada phenocopy due to use of high-pass ECG filters. Numbers under figures are International Registry of Brugada Phenocopies identification numbers. (From Anselm DD, Gottschalk BH, Baranchuk A. Brugada phenocopies: consideration of morphologic criteria and early findings from an international registry. Can J Cardiol. 2014 Dec;30[12]:1511-5; with permission of PULSUS GROUP INC.)

Genetic testing for the mutation in the cardiac sodium channel (SCN5A) gene can be performed, being positive in 11% to 28% of patients with Brugada syndrome [43]. Due to its low sensitivity, this test is not mandatory.

Some acquired Brugada patterns are not Brugada phenocopies

Fever-induced Brugada pattern and sodium channel blocker-induced Brugada pattern should not be classified as phenocopies even when fulfilling the aforementioned diagnostic algorithm, since they might present different pathogenesis and prognosis than Brugada phenocopies. Negative provocative challenges for these groups of patients are not appropriate for excluding Brugada syndrome due to the high pre-test probability [7,44].

Other classes of drugs may also incite Brugada pattern, but whether it relates to Brugada phenocopies is debatable [7].

Fever-induced Brugada pattern

A large series reported that up to 2% of patients with fever may develop Brugada pattern, compared to 0,1% of afebrile patients [45]. The patients did not have history of syncope and presented resolution of the pattern after body temperature normalization. This condition may precipitate malignant arrhythmias and sudden death; also, fever increased the risk of cardiac arrest in patients with known Brugada syndrome [46,47].

The mechanisms by which fever induces Brugada pattern are uncertain. Initially the explanation had been that dysfunctional ion channels present in Brugada syndrome were temperature-sensitive. Fever would cause the inward peak sodium channel current to decay, leaving I_{to} unopposed [48].

However, Keller and colleagues [49] demonstrated that even heterozygous patients carrying SCN5A gene mutations with no measurable current exhibited sensitivity to fever. They suggested that temperature-dependent properties of wild-type channels were responsible for the carriers' susceptibility to elevated temperatures.

One way or another, fever-induced Brugada pattern is characterized by an inherited ion channels dysfunction predisposing to malignant arrhythmias. Hence, it is regarded as a form of unmasked Brugada syndrome.

Drug-induced Brugada pattern

Patients with known Brugada syndrome and carrier family members may present Brugada pattern upon use of many commonly prescribed drugs [2–4]. Even asymptomatic patients without family history of Brugada syndrome have been reported to display Brugada pattern after exposure to predisposing agents [50–53]. Postema and colleagues maintain an updated list of drugs related to type 1 Brugada phenotype at their website www.brugadadrugs.org [54], some of which are capable of inducing arrhythmias in patients with Brugada syndrome.

Almost all of those agents are confirmed or believed to block sodium channels. This is the same mechanism by which provocative test medications act, leading to the supposition that most sodium channel blocker-induced Brugada patterns are cases of unmasked Brugada syndrome [7,44]. Nevertheless, the extent to which there is an underlying genetic predisposition or solely an acquired blockade in ion channels at times is uncertain. Of note, cases involving sodium channel blocker overdose in otherwise asymptomatic patients are unlikely to hold a congenital background and thus are being classified as “acquired sodium channel dysfunction” [44].

Regarding drugs with other mechanisms of action, most of the knowledge comes from few interventional studies on patients with Brugada syndrome and some isolated case reports [54–57]. It is also believed that they act by unmasking Brugada syndrome rather than as phenocopies; however, due to the lack of evidence, this distinction is a topic deserving further evaluation [6]. Acetylcholine, edrophonium, ergonovine, alpha-adrenergics, calcium blockers, nitrates, potassium channel openers, alcohol and cannabis are all believed to induce Brugada pattern [6,20,55–57].

Implications and perspectives

The main attributes of any medical phenomenon are [1] description in case reports or case series; [2] speculations about a pathophysiologic basis; [3] evidence of reproducibility; and [4] demonstration on experimental models [18]. Regarding Brugada phenocopies, the first step has been achieved initially in an unstandardized fashion. As the initial reports did not prompt a uniform description, further development of the concept was hindered until Baranchuk and colleagues created diagnostic criteria [6]. Moreover, appropriate mechanisms have been proposed for different etiologies, and more cases are being regularly published. Nevertheless, it was not until 2014 that the first case of reproducible Brugada phenocopy was reported, followed by a second report by our group in 2018 [18,19]. Also, there are few prospective data on Brugada phenocopy, and its clinical meaning is uncertain.

Recently, Xu and colleagues [58] reviewed 27 cases of patients with hyperkalemia-induced Brugada phenocopy and found no episode of malignant arrhythmia or sudden death. Nonetheless, Rivera-Juárez and colleagues [14] observed hyperkalemia admissions during a 6-year period and found 15 patients with Brugada ECG findings and low pretest probability of having Brugada syndrome. In-hospital mortality was similar in patients with and without development of Brugada pattern (40% and 43%, respectively; $P = .85$), being driven primarily by severity of the underlying condition. However, 40% of patients with hyperkalemia and Brugada pattern had malignant arrhythmias in the short- and mid-term, against 25% of those with others ECG manifestations. It is likely that patients with hyperkalemia-induced Brugada phenocopy represent a high-risk group that should be cautiously managed; nevertheless, the investigators performed provocative tests in only 5 patients, one of which had a positive result. Accurate diagnosis of unmasked Brugada syndrome must not be overlooked, as this group of patients is already known to present increased risk for malignant arrhythmias and sudden cardiac death.

The prognosis of Brugada phenocopies with other etiologies is even cloudier, as the literature is mainly composed by case reports. Therefore, neither specific treatments nor standardized approaches exist; reversal of inciting factors and a detailed family screening may be attempted, undertaking provocative tests if necessary. Diagnostic criteria for Brugada phenocopies must evolve to present better sensitivity, specificity and feasibility, thereby making possible more accurate differentiation between phenocopies and Brugada syndrome.

Future directions

Experimental models of Brugada phenocopy are needed to further validate the concept of the phenomenon and to uncover its exact mechanism [7,59,60]. They should distinguish between transient abnormalities in sodium channels that are not elicited by provocative tests and alterations of other ion channels [60]. It is worth noting that each inciting factor may act by a particular means, which possibly will lead to improvements in the classification system of phenocopies by the time these differences are understood [6]. Additionally, Anselm and colleagues [34] have proposed that Brugada syndrome and Brugada phenocopies may constitute ends of a shared disease spectrum, at least in some cases involving electrolyte imbalances. This supposition arises from the fact that such conditions are reported to unmask Brugada syndrome as well as to incite Brugada phenocopies. Nevertheless, the mechanisms by which these cases would respond differently to challenge tests are unknown [34]. Exposing genetic models of Brugada syndrome to triggers of Brugada phenocopies would help clarify if

both conditions could represent distinct manifestations of the same ion channel abnormalities [34,59].

Future research must simulate an environment in which the ECG pattern is induced by appropriate ion channel dysfunctions [59]. Nishida and colleagues [61] have found that localized cooling of the canine RVOT caused ECG findings and ionic channel changes consistent with Brugada syndrome. As hypothermia is linked to Brugada phenocopies [62], a model with cooling of the entire myocardium could help to understand the pathophysiology underlying the phenomenon. Nevertheless, potassium disorders are commoner causes of phenocopies and have already shown reproducibility of the pattern in the same patient [17–19]. The mechanisms by which hyper- and hypokalemia provoke imbalances in ion currents are more comprehended than those of any other reported cause of Brugada phenocopy [61]. Thus, various groups are relying on potassium imbalances as an experimental basis for the phenomenon [63].

Declarations of interest

None.

References

[1] Brugada P, Brugada J. Right bundle branch block, persistent ST segment elevation and sudden cardiac death: a distinct clinical and electrocardiographic syndrome. J Am Coll Cardiol 1992;20:1391–6.
[2] Bayés de Luna A, Brugada J, Baranchuk A, Borggrefe M, Breithardt G, Goldwasser D, et al. Current electrocardiographic criteria for diagnosis of Brugada pattern: a consensus report. J Electrocardiol 2012;45:433–42.
[3] Osher HL, Wolff L. Electrocardiographic pattern simulating acute myocardial injury. Am J Med Sci 1953;226(5):541–5 Nov.
[4] Pilz B, Luft FC. Acquired Brugada syndrome. Am J Cardiol 2003;92(6):771 Sep 15.
[5] Riera ARP, Uchida AH, Schapochnik E, Dubner S, Filho CF, Ferreira C. Propofol infusion syndrome and Brugada syndrome electrocardiographic phenocopy. Cardiol J 2010;17:130–5.
[6] Baranchuk A, Nguyen T, Ryu MH, Femenía F, Zareba W, Wilde AA, et al. Brugada phenocopy: new terminology and proposed classification. Ann Noninvasive Electrocardiol 2012;17:299–314.
[7] Anselm DD, Evans J, Baranchuk A. Brugada phenocopy: a new electrocardiogram phenomenon. World J Cardiol 2014;6:81–6.
[8] Kataoka H. Electrocardiographic patterns of the Brugada syndrome in right ventricular infarction/ischemia. Am J Cardiol 2000;86(9):1056 Nov 1.
[9] Gottschalk BH, Anselm DD, Brugada J, Brugada P, Wilde AA, Chiale PA, et al. Expert cardiologists cannot distinguish between Brugada phenocopy and Brugada syndrome electrocardiogram patterns. Europace 2016;18:1095–100.
[10] Yan GX, Antzelevitch C. Cellular basis for the Brugada syndrome and other mechanisms of arrhythmogenesis associated with ST segment elevation. Circulation 1999;100:1660.
[11] Shimizu W. Acquired forms of the Brugada syndrome. J Electrocardiol 2005;38:22–5.
[12] Szél T, Antzelevitch C. Abnormal repolarization as the basis for late potentials and fractionated electrograms recorded from epicardium in experimental models of Brugada syndrome. J Am Coll Cardiol 2014;63(19):2037–45 May 20.
[13] Wilde AA, Postema PG, Di Diego JM, Viskin S, Morita H, Fish JM, et al. The pathophysiological mechanism underlying Brugada syndrome. Depolarization versus repolarization. J Mol Cell Cardiol 2010;49(4):543–53.
[14] Rivera-Juárez A, Hernández-Romero I, Puertas C, Zhang-Wang S, Sánchez-Álamo B, Martins R, et al. Clinical characteristics and electrophysiological mechanisms underlying Brugada ECG in patients with severe hyperkalemia. J Am Heart Assoc 2019;8(3) Feb 5. (e010115).
[15] Tomé G, Freitas J. Induced Brugada syndrome: possible sources of arrhythmogenesis. Rev Port Cardiol 2017;36:945–56.
[16] Abu Shama R, Bayes de Luna A, Baranchuk A. Tachycardia-dependent Brugada phenocopy due to hyperkalemia. J Cardiovasc Electrophysiol 2017;28:1084–5.
[17] Gottschalk BH, Anselm DD, Baranchuk A. Brugada Phenocopy international registry and online educational portal. http://www.brugadaphenocopy.com; 2014, Accessed date: 4 February 2019.
[18] Genaro NR, Anselm DD, Cervino N, Estevez AO, Perona C, Villamil AM, et al. Brugada phenocopy clinical reproducibility demonstrated by recurrent hypokalemia. Ann Noninvasive Electrocardiol 2014;19(4):387–90 Jul.
[19] Neto NO, Pilla L, Oliveira WS, Velloso RN, Maia FG, do Nascimento AL, et al. Brugada Phenocopy induced by recurrent hyperkalemia: more evidence for the reproducibility of a new phenomenon. J Electrocardiol 2018;51(3):402–4 May-Jun.
[20] Noda T, Shimizu W, Taguchi A, Satomi K, Suyama K, Kurita T, et al. ST-segment elevation and ventricular fibrillation without coronary spasm by intracoronary injection of acetylcholine and/or ergonovine maleate in patients with Brugada syndrome. J Am Coll Cardiol 2002;40(10):1841–7.
[21] Pérez-Riera AR, Barbosa-Barros R, Daminello-Raimundo R, de Abreu LC, Baranchuk A. Unusual ST-segment elevation in the anterolateral precordial leads: ischemia, Brugada phenocopy, Brugada syndrome, all, or none? Circulation 2017;136(20):1976–8 Nov 14.
[22] Dendramis G, Paleologo C, Piraino D, Assennato P. Coronary artery fistulas and Brugada ECG pattern, a random association? Int J Cardiol 2015;197:78–80 Oct 15.
[23] Dendramis G. Coronary anomalies and Brugada Phenocopy, the first documented case in the world. Int J Cardiol 2015;199:335–6 Nov 15.
[24] Zhang N, Liu T, Tse G, Yu S, Fu H, Xu G, et al. Brugada phenocopy in a patient with acute pulmonary embolism presenting with recurrent syncope. Oxf med case reports 2017 May 30; 2017 [5:omx014].
[25] Alper AT, Tekkesin AI, Çinier G, Turkkan C, Baranchuk A. First description of a Brugada phenocopy in the inferior leads in the context of an acute inferior myocardial infarction. Europace 2017;19(7):1219 Jul 1.
[26] Pérez-Riera AR, Barbosa Barros R, Daminello-Raimundo R, Resende Barbosa MPC, de Abreu LC. Brugada phenocopy caused by a compressive mediastinal tumor. Ann Noninvasive Electrocardiol 2018;23(3) May. (e12509).
[27] Barcos JC, Tello Santacruz IA, Monié CC, Fernández Recalde ML, Humphreys JD. Brugada phenocopy induced by severe pneumothorax. J Electrocardiol 2018;51(2):343–5 Mar-Apr.
[28] Yu M, Zhang Q, Huang X, Zhao X. Type 1 Brugada phenocopy in a patient with acute pericarditis. J Electrocardiol 2018;51(6):1121–3 Nov-Dec.
[29] Brito MR, Miranda CE, Rabelo W, Marino RL. Type 1 electrocardiographic Brugada pattern in a woman with Chagas disease: a case report. Europace 2010;12(9):1345–6 Sep.
[30] Nayyar S, Nair M. Brugada pattern in toxic myocarditis due to severe aluminum phosphide poisoning. Pacing Clin Electrophysiol 2009;32(11):e16–7 Nov.
[31] Dharanipradab M, Viswanathan S, Kumar GR, Krishnamurthy V, Stanley DD. Yellow phosphorus-induced Brugada phenocopy. J Electrocardiol 2018;51(1):129–31 Jan-Feb.
[32] García-Niebla J, Serra-Autonell G, Bayés de Luna A. Brugada syndrome electrocardiographic pattern as a result of improper application of a high pass filter. Cardiol 2012;110:318–20.
[33] Anselm DD, Baranchuk A. Brugada phenocopy: redefinition and updated classification. Am J Cardiol 2013;111(3):453 Feb 1.
[34] Anselm DD, Gottschalk BH, Baranchuk A. Brugada phenocopies: consideration of morphologic criteria and early findings from an international registry. Can J Cardiol 2014;30(12):1511–5 Dec.
[35] Gottschalk BH, Garcia-Niebla J, Anselm DD, Jaidka A, De Luna AB, Baranchuk A. New methodologies for measuring Brugada ECG patterns cannot differentiate the ECG pattern of Brugada syndrome from Brugada phenocopy. J Electrocardiol 2016;49(2):187–91 Mar-Apr.
[36] Campistol JM, Almirall J, Montoliu J, Revert L. Electrographic alterations induced by hyperkalaemia simulating acute myocardial infarction. Nephrol Dial Transplant 1989;4(3):233–5.
[37] Brugada J, Campuzano O, Arbelo E, Sarquella-Brugada G, Brugada R. Present status of Brugada syndrome. JACC State-of-the-Art Review J Am Coll Cardiol 2018;72(9):1046–59 Aug 28.
[38] Gasparini M, Priori SG, Mantica M, Napolitano C, Galimberti P, Ceriotti C, et al. Flecainide test in Brugada syndrome: a reproducible but risky tool. Pacing Clin Electrophysiol 2003;26(1 Pt 2):338–41 Jan.
[39] Therasse D, Sacher F, Babuty D, Mabo P, Mansourati J, Kyndt F, et al. Value of the sodium-channel blocker challenge in Brugada syndrome. Int J Cardiol 2017;245:178–80 Oct 15.
[40] Wolpert C, Echternach C, Veltmann C, et al. Intravenous drug challenge using flecainide and ajmaline in patients with Brugada syndrome. Heart Rhythm 2005;2(3):254–60 Mar.
[41] Chauveau S, Le Vavasseur O, Chevalier P. Delayed diagnosis of Brugada syndrome in a patient with aborted sudden cardiac death and initial negative flecainide challenge. Clin Case Rep 2017;5(12):2022–4 Oct 31.
[42] Anselm DD, Pérez-Riera AR, Femenia F, Baranchuk A. Brugada Phenocopy in a patient with surgically repaired Pentalogy of Fallot. RIA 2012;3(1):20–4.
[43] Probst V, Wilde AA, Barc J, et al. SCN5A mutations and the role of genetic background in the pathophysiology of Brugada syndrome. Circulation: Cardiovasc Genet 2009;2(6):552–7.
[44] Xu G, Gottschalk BH, Kocabaş U, Baranchuk A. Not all Brugada electrocardiogram patterns are Brugada syndrome or Brugada phenocopy. Balkan Med J 2017;34(6):593 Dec.
[45] Adler A, Topaz G, Heller K, et al. Fever-induced Brugada pattern: how common is it and what does it mean? Heart Rhythm 2013;10:1375–82.
[46] Amin AS, Meregalli PG, Bardai A, Wilde AA, Tan HL. Fever increases the risk of cardiac arrest in the Brugada syndrome. Ann Int Medicine 2008;149:216–8.
[47] Junttila MJ, Gonzalez M, Lizotte E, Benito B, Vernooy K, Sarkozy A, et al. Induced Brugada-type electrocardiogram, a sign for imminent malignant arrhythmias. Circulation 2008;117:1890–3.
[48] Dumaine R, Towbin JA, Brugada P, Vatta M, Nesterenko DV, Nesterenko VV, et al. Ionic mechanisms responsible for the electrocardiographic phenotype of the Brugada syndrome are temperature dependent. Circ Res 1999;85:803–9.
[49] Keller DI, Rougier JS, Kucera JP, Benammar N, Fressart V, Guicheney P, et al. Brugada syndrome and fever: genetic and molecular characterization of patients carrying SCN5A mutations. Cardiovasc Res 2005;67:510–9.
[50] Palaniswamy C, Selvaraj DR, Chugh T, et al. Brugada electrocardiographic pattern induced by amitriptyline overdose. Am J Ther 2010;17:529–32.
[51] Tada H, Sticherling C, Oral H, Morady F. Brugada syndrome mimicked by tricyclic antidepressants overdose. J Cardiovasc Electrophysiol 2001;12:275.
[52] Pirotte MJ, Mueller JG, Poprawski T. A case report of Brugada-type electrocardiographic changes in a patient taking lithium. Am J Emerg Med 2008;26:e1–3.
[53] Arı ME, Ekici F. Brugada-phenocopy induced by propafenone overdose and successful treatment: a case report. Balkan Med J 2017;5:458–63.

[54] Postema PG, Wolpert C, Amin AS, Probst V, Borggrefe M, Roden DM, et al. Drugs and Brugada syndrome patients: review of the literature, recommendations and an up-to-date website (www.brugadadrugs.org). Heart Rhythm 2009;6:1335–41.
[55] Miyazaki T, Mitamura H, Miyoshi S, Soejima K, Aizawa Y, Ogawa S. Autonomic and antiarrhythmic drug modulation of ST segment elevation in patients with Brugada syndrome. J Am Coll Cardiol 1996;27:1061–70.
[56] Romero-Puche AJ, Trigueros-Ruiz N, Cerdán-Sánchez MC, Pérez-Lorente F, Roldán D, Vicente-Vera T. Brugada electrocardiogram pattern induced by cannabis. Rev Esp Cardiol (Engl Ed) 2012;65(9):856–8 Sep.
[57] Shimada M, Miyazaki T, Miyoshi S, Soejima K, Hori S, Mitamura H, et al. Sustained monomorphic ventricular tachycardia in a patient with Brugada syndrome. Jpn Circ J 1996;60:364–70.
[58] . Xu G, Gottschalk BH, Anselm DD3, Benditt DG, Maheshwari A, Sreenivasan S, Shama RA, Dendramis G, Barajas-Martínez H, Rubio Campal JM, Aznaurov SG, Baranchuk A. Relation of the Brugada phenocopy to hyperkalemia (from the International Registry on Brugada Phenocopy). Am J Cardiol. 2018 Mar 15;121(6):715–717.
[59] Baranchuk A, Gottshalk B, Anselm DD. Brugada phenocopy: update 2014. Proceedings of the 41st International Congress on Electrocardiology. Bratislava, Slovakia; June 2014.
[60] Barajas-Martínez H, Hu D. The future is here: experimental models and genetics in Brugada phenocopy. Brugada phenocopy: The art of recognizing the Brugada ECG pattern. London, UK: Academic Press; 2018. p. 125–32.
[61] Nishida K, Fujiki A, Mizumaki K, Sakabe M, Sugao M, Tsuneda T, et al. Canine model of Brugada syndrome using regional epicardial cooling of the right ventricular outflow tract. J Cardiovasc Electrophysiol 2004;15(8):936–41 Aug.
[62] Gottschalk B, Anselm DD, Baranchuk A. Suspected Brugada phenocopy in the context of hypothermia. Acta Cardiol 2014;69(4):454–5 Aug.
[63] Baranchuk A, Maheshwari A, Sreenivasan S, Benditt DG. Specific Brugada phenocopies: electrolyte and metabolic disorders. Brugada phenocopy: the art of recognizing the Brugada ECG pattern. London, UK: Academic Press; 2018. p. 87–92.