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INVITED REVIEW / DAVETLİ DERLEME

Brugada phenocopies: Current evidence, diagnostic algorithms and a perspective for the future

Brugada fenokopileri: Güncel kanıt, tanı algoritmaları ve geleceğe bakış

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Summary– Brugada syndrome (BrS) is a congenital channelopathy associated with the development of malignant ventricular arrhythmias and sudden cardiac death. The diagnosis of BrS is made based on Brugada ECG pattern and clinical history. Brugada phenocopies (BrP) are clinical entities that are characterized by ECG patterns identical to those of BrS but arise from different underlying conditions such as metabolic abnormalities, myocardial ischemia and mechanical compression. Distinction between the two is important because BrS requires investigations for risk stratification whereas BrP requires appropriate treatment for the underlying conditions. In the present review, we summarized the current data in the literature, systematic diagnostic approach, gaps in the literature and future perspective on BrP.

Özet– Brugada sendromu (BrS) konjenital bir kanalopati olup malign ventriküler aritmi gelişimi ve ani kardiyak ölüm ile ilişkilidir. BrS tanısı elektrokardiyografide (EKG) Brugada paterni ve klinik öykü ile konulmaktadır. Brugada fenokopileri (BrP) ise metabolik bozukluklar, miyokardiyal iskemi ve mekanik bası gibi altta yatan nedenlere bağlı oalrak BrS EKG paterninin görüldüğü durumlardır. BrP ve BrS arasında ayrıcı tanı yapılması BrS hastalarında ani kardiyak ölümü engelemek amacıyla risk değerlendirmesi yapılmasının gerekli olması nedeniyle son derece önemlidir. Bu derlemede BrP ile ilgili güncel kanıtları, tanı kriterlerinin sistematik değerlendirilmesini ve henüz aydınlatılmamış noktaları değerlendireceğiz.

Brugada syndrome (BrS) is a channelopathy that is associated with a higher likelihood of developing malignant ventricular arrhythmias and sudden cardiac death. It is characterized by two types of ECG patterns: a coved ST- segment elevation (≥0.2 mV) and subsequent T-wave inversion in right precordial leads (Type I) and saddleback appearance (Type II).[1] The diagnosis of BrS requires clinical history in the presence of spontaneous or induced Type I ECG pattern.[2] The syndrome is linked to more than 80 mutations in the SCN5A gene. It was originally thought to be a Mendelian disease with an autosomal dominant inheritance pattern with incomplete penetrance.[3] However, given the poor genotype-phenotype correlation, this notion may not be completely true.[4] The ECG pattern in BrS is dynamic and in majority of cases drug challenge with sodium channel blocker or conditions such as fever, vagal state and electrolyte imbalance are required to unmask the distinct ECG pattern.

Abbreviations:

BrP	*Brugada phenocopy*
BrS	*Brugada syndrome*
ECG	*Electrocardiogram*
RCA	*Right coronary artery*
RVOT	*Right ventricular outflow tract*

Over the recent years, there have been cases published in the literature on the presence of Brugada ECG pattern without the syndrome. Initially these cases were defined as "Brugada-like ECG pattern" or "acquired Brugada syndrome". The lack of consistent terminology caused confusion in differential diagnosis in patients who had distinct Brugada ECG pattern but did not have BrS. The concept of Brugada phenocopy

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has emerged to describe those cases. The term "phenocopy" implies there are environmental conditions that imitate Brugada ECG patterns produced by syndromic causes.[5] A recently published consensus report consolidated the definition and terminology of BrP.[6] The diagnosis of BrP is established with a negative drug challenge result.[7] A systematic approach is required for the differential diagnosis between BrP and BrS since patients who are diagnosed with the latter require risk stratification for sudden cardiac death. In the present review, we will discuss current definition and classification of BrP, pathophysiology underlying the occurrence of the distinct ECG pattern, clinical conditions inducing BrP and finally highlight gaps in evidence and future perspectives.

Pathophysiology Underlying ECG Pattern in Brugada Syndrome

There are two major hypothesis proposed for the underlying mechanism of BrS: Repolarization hypothesis, depolarization hypothesis and cardiac neural crest theory that aims to explain depolarization/repolarization abnormalities through embryonic origins.

In repolarization hypothesis there is an outward shift in the balance of transmembrane currents in the right ventricular outflow tract (RVOT) epicardium, due to reduced inward sodium current and prominent transient outward potassium current.[8] Accentuation of action potential notch in the RVOT epicardium is thought to underlie the generation of ST-segment elevation in ECG.[9] Epicardial repolarization dispersion leads to phase 2 reentry generating premature ventricular premature beats.[10] When these triggering beats encounter the substrate generated by increased local or transmural dispersion of repolarization, sustained ventricular arrhythmias can ensue.

Depolarization hypothesis is characterized by the conduction delay in the RVOT relative to the other regions of right ventricle causing voltage gradient and ST-segment elevation.[11] Conduction slowing occurs as a result of reduced sodium channel or gap junction function or myocardial fibrosis and can lead to lower excitation wavelengths for re-entry. Recent studies evaluating the role of catheter ablation in the management of malignant arrhythmias in BrS favored the depolarization hypothesis as radiofrequency ablation of epicardial sites showing late potentials and fragmented electrocardiograms reduced arrhythmia-free interval and ST-segment elevation in BrS patients.[12] These authors suggested that since the late potentials were abolished together ablated areas of conduction, the depolarization hypothesis is an important arrhythmogenic mechanism. Moreover, a current-to-load mismatch phenomenon in the subepicardium was proposed by Hoogendijk and colleagues.[13,14] In such a scheme, reduced sodium currents due to loss-of-function cause subepicardial excitation failure or delayed activation and is responsible for the ST-segment elevation on the ECG.

Cardiac neural crest cell theory is proposed by Elizari et al.,[15] who hypothesized that the RVOT and its nearby structures have different electrophysiolgical and structural characteristics because these sites have different embryogenic origin from the rest of the cardiac tissue. In this theory functional abnormalities of connexin 43 which is a structural protein in gap junctions[16] and has pivotal roles in cardiac neural crest cell migration[17] and cardiac depolarization propagation, cause slow conduction and transmural repolarization heterogeneity in the RVOT. Thus, this theory is not independent from, but attributes depolarization and repolarization abnormalities to embryonic origins.

In BrS electrical abnormalities within the RVOT are caused by congenital ion channel dysfunctions. To date we can only speculate that transient dysfunction in ion channels are precipitated by underlying conditions in genetically susceptible individuals causing ECG changes in BrP.

Definition and Diagnostic Criteria for Brugada Phenocopy

Brugada Phenocopies are clinical entities that are characterized by Brugada ECG pattern type I and type II in the absence of BrS (Fig. 1). Diagnostic criteria for BrP are: *i)* characteristic type I or type II Brugada ECG pattern, *ii)* the presence of an underlying condition inducing Brugada ECG patterns, *iii)* resolution of the ECG patterns after eliminating the underlying condition, *iv)* a low pretest probability for BrS as defined by lack of clinical symptoms, medical history and family history suggestive of BrS, *v)* negative provocative testing with sodium channel blocker drugs (not mandatory if surgical RVOT manipulation has occurred within the last 96 hours), and *vi)* a negative genetic testing for SCN5A (recommended but not

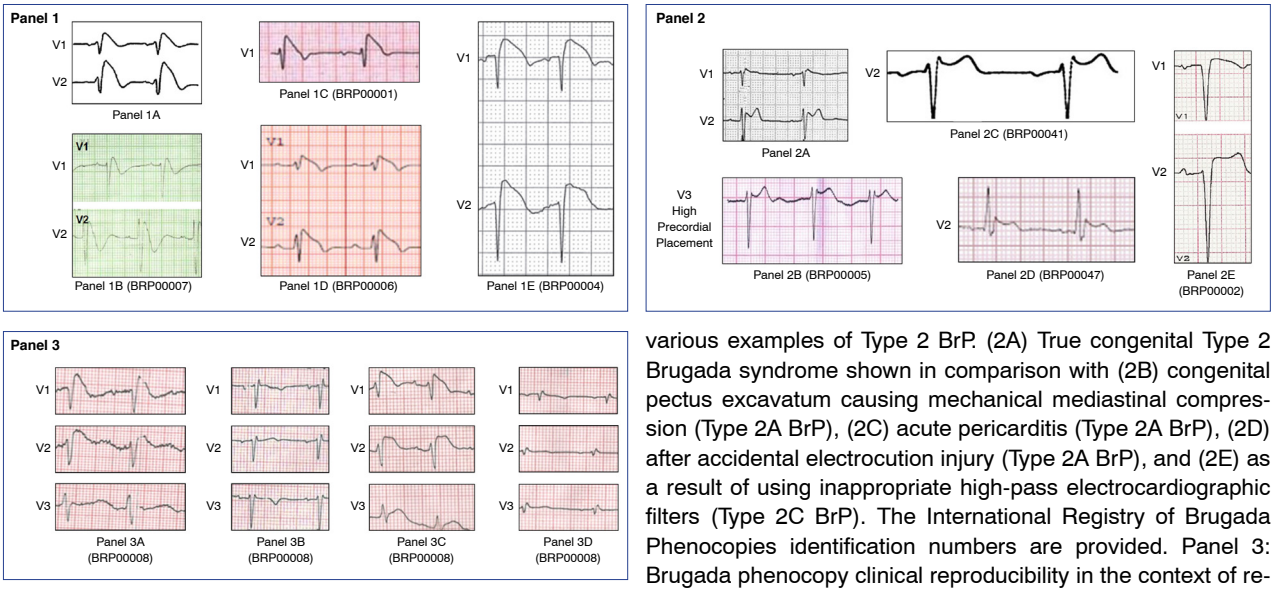

Figure 1. Several electrocardiogram samples from patients with a Brugada phenocopy. Panel 1: Comparison of various examples of a type I Brugada phenocopy (BrP). (1A) True congenital type 1 Brugada syndrome electrocardiogram shown in comparison with (1B) congenital hypokalemic periodic paralysis (Type 1B BrP), (1C) acute inferior ST-elevation myocardial infarction with right ventricular involvement (Type 1A BrP), (1D) concurrent hyperkalemia, hyponatremia, and acidosis (Type 1A BrP), and (1E) acute pulmonary embolism (Type 1B BrP). The International Registry of Brugada Phenocopies identification numbers are provided. Panel 2: Comparison of various examples of Type 2 BrP. (2A) True congenital Type 2 Brugada syndrome shown in comparison with (2B) congenital pectus excavatum causing mechanical mediastinal compression (Type 2A BrP), (2C) acute pericarditis (Type 2A BrP), (2D) after accidental electrocution injury (Type 2A BrP), and (2E) as a result of using inappropriate high-pass electrocardiographic filters (Type 2C BrP). The International Registry of Brugada Phenocopies identification numbers are provided. Panel 3: Brugada phenocopy clinical reproducibility in the context of recurrent hypokalemia. A patient with recurrent Type 1A BrP. (3A) Electrocardiogram on presentation, when the patient was hypokalemic, consistent with a Type 1 Brugada ECG pattern; (3B) After intravenous correction of the serum potassium level, the ECG normalized; (3C) During the same hospitalization period, the patient again became hypokalemic with a recurrence of the Type 1 Brugada ECG pattern; (3D) Subsequent normalization of the electrocardiogram after the serum potassium level was corrected. The International Registry of Brugada Phenocopies identification numbers are provided. Modified from Serra G, et al.[22] BrP: Brugada phenocopy; ECG: Electrocardiogram.

mandatory as it is possible to identify mutation only in 20%-30% of probands that are known to have BrS) [6] (Table 1).

Systematic approach is required for correct diagnosis of BrP. Provocative drug challenge testing is an important step for differentiating BrS and BrP. A negative test supports the diagnosis of BrP. However, it should be emphasized that false negative results were reported up to 23% and cases with delayed diagnosis of BrS were described previously in the literature.[18,19] Repeated drug challenge should be pursued whenever possible in the context of contradictory findings. It is important to note that there are two subgroups which are excluded from the classification of BrP: Fever induced Brugada pattern and Brugada pattern induced by drugs that are known to have sodium channel blocking properties. Individuals within these subgroups should not be diagnosed with BrP even

Table 1. Diagnostic criteria for Brugada phenocopy (First 4 criteria are mandatory)

1. ECG pattern has type 1 or type 2 Brugada morphologic criteria
2. Presence of an underlying condition that is identifiable and reversible
3. Resolution of the ECG pattern upon elimination of the underlying condition
4. Low pretest probability for Brugada syndrome determined by the lack of symptoms, clinical history, and family history
5. A negative provocative test with a sodium channel blocker drug (e.g., ajmaline, flecainide, or procainamide)*
6. A negative genetic test**

*Provocative testing is not mandatory if surgical right ventricular outflow tract manipulation has occurred within the last 96 hours.
**Desirable, but not mandatory, since the SCN5A mutation has been identified in only 20-30% of probands affected by Brugada syndrome.
ECG: Electrocardiogram.

they fulfill all diagnostic criteria because underlying pathophysiological mechanisms and prognosis might be different from that of BrP.[6]

The ECG patterns in BrP are identical to those in BrS. In their study, Gottschalk et al.[20] asked 10 international experts on BrS to review 12 ECGs without providing clinical history data from six patients with confirmed diagnosis of BrS and 6 with BrP. They found that intra-observer repeatability was moderate (κ:0.56) and inter-observer agreement was only fair (κ:0.36) for the true diagnosis. Even more recent methodologies including β-angle[21] and the base of the triangle[22] which were previously shown to differentiate between Brugada ECG pattern and patterns of similar morphology (incomplete right bundle branch block, athletes etc.) failed to identify accurately ECG patterns of BrS and BrP.[23] These data further supported the notion that the value of ECG in discriminating BrP and BrS is limited and systematic diagnostic approach is indeed warranted.

Recently, Anselm et al.[24] proposed a new classification for describing BrP cases (Table 2). Type 1 BrP and type 2 BrP indicate typical type 1 "coved" and type 2 "saddleback" Brugada ECG patterns respectively.[24] Additional three qualifiers were added within each group to determine whether each case fulfills diagnostic criteria: Class A includes BrP cases that satisfy all mandatory diagnostic criteria including negative provocative drug challenge. Class B includes highly suspected BrP cases but not all diagnostic criteria are fulfilled. Cases in which mandatory provocative testing cannot be performed due to lost to follow up or death are included in this group. Class C includes highly suspected BrP cases in which provocative testing is not clinically justified or indicated. This group encompasses cases with recent intervention to the RVOT region or BrP due to use of inappropriate ECG filters.

Clinical Conditions That Can Give Rise to BrP

It is important to identify underlying condition triggering Brugada ECG pattern. Currently these conditions are grouped into 6 categories: *i)* metabolic conditions, *ii)* mechanical compression, *iii)* ischemia and pulmonary embolism, *iv)* myocardial and pericardial disease, *v)* ECG modulation, *vi)* miscellaneous. According to latest data from an international registry[25] there are more than 100 cases of BrP recorded to the online portal (Table 3).

Metabolic conditions

Metabolic conditions causing BrP constitute almost half of cases (63 out of 135) enrolled into the international registry, with a mean age of 48 ± 18 and male predominance (47 male vs 14 female, 2 unknown). In 51 cases, type I Brugada pattern was observed in the ECG and type II pattern was observed in the remaining 12 cases. Metabolic conditions causing BrP included hyponatremia,[26] hypokalemia,[27] hyperkalemia,[28,29] hypophosphatemia,[30] hypothermia,[31] diabetic ketoacidosis[32] and hypopituitarism.[33] Electrolyte disturbances are thought to induce BrP by causing transient outward potassium current leading to the amplification of action potential notch which

Table 2. Morphologic classification system for Brugada phenocopy

Type	
Type 1	BrP with a coved Brugada ECG pattern
Type 2	BrP with a saddleback Brugada ECG pattern
Class	
Class A	All mandatory BrP diagnostic criteria are satisfied, including positive results from a provocative drug challenge with sodium channel blockers
Class B	Highly suspected BrP: Not all mandatory criteria are complete*
Class C	Highly suspected BrP: Provocative drug challenge is not indicated and/or justified**

*This group includes cases in which a provocative drug challenge is pending or it is not possible to perform due to various factors, such as the patient is lost to follow-up or deceased.
**This group includes cases in which a provocative drug challenge is not clinically indicated, such as patients with recent surgical right ventricular outflow tract manipulation or BrP secondary to the use of inappropriate high-pass ECG filtering.
BrP: Brugada phenocopy; ECG: Electrocardiogram.

Table 3. Etiologic classification for Brugada phenocopy

Categories	Number of cases	Brugada phenocopy Type
Metabolic conditions	63	Type 1A:15 Type 2A:1
		Type 1B:35 Type 2B:11
		Type 1C:1 Type 2C: 0
Mechanical compression	18	Type 1A:6 Type 2A:1
		Type 1B:7 Type 2B:2
		Type 1C:2 Type 2C:0
Ischemia and pulmonary embolism	27	Type 1A:7 Type 2A:0
		Type 1B:15 Type 2B:3
		Type 1C:2 Type 2C:0
Myocardial and pericardial disease	12	Type 1A:3 Type 2A:1
		Type 1B:6 Type 2B:2
		Type 1C:0 Type 2C:0
Electrocardiogram modulation	3	Type 1A:0 Type 2A:1
		Type 1B:0 Type 2B:0
		Type 1C:0 Type 2C:2
Miscellaneous	12	Type 1A:0 Type 2A:2
		Type 1B:7 Type 2B:1
		Type 1C:2 Type 2C:0

Updated from www.brugadaphenocopy.com on November 25, 2019.

facilitates loss of action potential dome in the epicardium of the RVOT. These transient abnormalities generate voltage gradient between endocardium and epicardium of the RVOT which is manifested as Brugada pattern in the ECG. Importantly Brugada ECG pattern was resolved upon the elimination of the triggering metabolic condition.

Xu et al.[34] reported the analysis of patients with hyperkalemia induced BrP from the international registry. Their findings indicated that hyperkalemia was a common cause of BrP (27 cases) and the ECG pattern was resolved within hours (mean time to resolution was 7 ± 3 hours). Brugada ECG pattern occurred at high serum potassium concentrations (mean serum potassium level was 7.45 ± 0.89 mmol/L). Provocative drug challenge was performed in 28% of cases and all failed to reproduce the type I ECG pattern. No sudden cardiac death or ventricular arrhythmic events were reported during follow up.

Two cases are worth discussing in more detail for further understanding the concept of BrP by providing more evidence on its reproducibility. Genaro et al.[35] reported a patient with severe hypokalemia due to gastrointestinal loss. A Type 1 Brugada pattern was present in the 12-lead surface ECG. Resolution of the ECG pattern was observed upon intravenous potassium replacement. The patient underwent provocative drug challenge which was negative. During the hospital stay, the ECG pattern reoccurred as the patient became hypokalemic again. The patient had no personal or family history of symptoms suggestive of BrS. Another case reported a patient that developed recurrent Brugada ECG pattern that was considered to be due to hyperkalemia.[36] The ECG pattern normalized after resolution of hyperkalemia. These cases were important as they highlighted the reproducibility of the ECG pattern, thereby advancing the concept of BrP.

Mechanical compression

Several cases reported patients with BrP induced by mechanical compression due to tumoral mass.[37-39] The common characteristic of all cases was the involvement of the RVOT by either mediastinal mass, intrcardiac tumors or metastatic carcinomas. ECG pattern was resolved upon the removal of tumor which supported that the mechanical compression

was the cause of BrP. Perez-Riera et al.[37] reported a 79 years old female with type I Brugada ECG pattern.The patient was diagnosed with an anterior mediastinal Non-Hodgkin lymphoma extending into the RVOT. The provocative drug challenge with sodium channel blocker was negative and ECG pattern was resolved following the treatment with immunotherapy and chemotherapy. Another clinical entity that was previously shown causing BrP is pectus excavatum.[40] Surgical correction of this anterior chest wall deformity normalized the ECG abnormality. Transmural repolarization heterogeneity induced by direct mechanical compression of the RVOT may cause Brugada ECG pattern in these patients. In addition, ischemia caused by the lesion pressure over the RVOT can induce transient ion channel dysfunction and the occurrence of BrP.

Ischemia and pulmonary embolism

Myocardial ischemia is considered as a common cause of BrP and currently there are 27 cases submitted to the international registry.[25] Proposed mechanism through which ischemia induces Brugada ECG pattern is the ischemia-induced transient ion channel dysfunction generating increased outward potassium current and decreased inward sodium current. Anatomically, the RVOT is supplied by the conus branch of the right coronary artery (RCA). Previous case reports described occurrence of BrP in the context of the acute occlusion of the RCA causing transient ischemia of the RVOT.[41,42] Interestingly, a Brugada ECG pattern was identified in a patient with acute mid RCA occlusion sparing the coronary flow in the conus branch.[43] These authors proposed that delayed depolarization in the Purkinje fibers of the right ventricle might be the cause of BrP in this case. In addition, BrP is not restricted to the right precordial leads. Cases describing Brugada ECG pattern in the inferior leads[44] and anterolateral leads[45] have been published recently.

Using data from the international registry, Xu et al.[46] investigated BrP in the context of myocardial ischemia. They found that ECG pattern was transient and resolved upon the correction of the ischemia in all of the included cases. There was no specific coronary artery involvement as BrP was identified in 29% and 65% of cases with left anterior descending artery and RCA obstruction respectively. No arrhythmic event occurred during the acute phase or on follow-up.

It is important to note that ischemia can also unmask BrS, thus; a systematic approach is needed for the differential diagnosis between BrS and BrP. Application of the provocative drug challenge test using sodium channel blockers may cause harm during the acute phase of ischemia but it is recommended that patients should undergo drug challenge as soon as the ischemia is resolved.

In a similar fashion pulmonary embolism may induce BrP due to ischemia caused by the acute pressure overload on the right side of the heart. Zhan et al.[47] reported two cases with acute pulmonary embolism and presenting with hypotension. Brugada ECG pattern was present in the right precordial leads which resolved promptly following thrombolytic infusion.[47]

Myocardial and pericardial disease

Myocardial and pericardial diseases that were previously reported to cause BrP include Chagas myopathy,[48] acute and chronic myocarditis,[49,50] acute pericarditis[51] and myotonic dystrophy.[52] Inflammation-induced ischemia and fibrotic changes in the myocardium inducing slow depolarization and repolarization heterogeneity are proposed as the potential mechanisms causing BrP in this group.

ECG modulation

Another underlying condition for BrP is the improper application of high-pass filtering. Normally a high-pass filter is used for eliminating low frequency noises during ECG recording which are most likely resulted from movement of ECG electrodes on the skin, physicochemical skin-electrode changes and body movement related to normal breathing. Low frequency components of normal ECG such as ST segment can be distorted in case applying non-recommended cutoff frequency values. Importantly, although the change in the ST segment by applying improper high-pass filter depends on the baseline ECG characteristics, it is more common in the right precordial leads. Recently, Garcia-Niebla et al.[53] reported a 55 years old female in whom application of a non-standard high-pass filter of 0.5 Hz produced Brugada ECG pattern.

Miscellaneous

There are several cases in the literature describing BrP in the context of some underlying conditions that could not be classified into other five groups. These include

BrP in patients with Ebstein anomaly,[54] intracranial hemorrhage[55] and following biphasic synchronized electrical cardioversion for atrial fibrillation.[56]

Gaps in the Evidence and a Perspective for the Future

Sodium channel blockers, such as ajmaline, procainamide, flecainide and pilsicainide, are used for induce a Brugada type I ECG pattern and diagnose true BrS. Other agents that are known to block sodium channels may serve a similar role at appropriate dose in unmasking the ECG pattern. Individuals presenting with Brugada ECG pattern while on agents that are known to have sodium channel blocking activity constitutes a challenge for differential diagnosis between BrP and BrS.[6] In addition, several reports describing Brugada ECG pattern in the context of overdose of drugs that have sodium channel blocking properties which are considered to induce artificial sodium channel dysfunction in the absence of BrS.[57] However, the terminology BrP does not cover ECG patterns induced by sodium channel blocker agents both in the context of appropriate and over dosage. Future research is needed before classifying those cases either as BrS or BrP.

Currently, it is unclear why some patients present with BrP and some do not in the same environmental conditions. It is most likely that in response to environmental stimuli, transient functional and structural alterations of electrolyte channels located in the RVOT region occur among patients that are predisposed to ECG changes due to genetic susceptibility. However, this yet to be proven with experimental validation models. Although patients with BrS are at increased risk of sudden cardiac death due to malignant arrhythmic episodes, it is yet to be evaluated that whether arrhythmic risk of patients with BrP is increased or not during long-term. Up to 25th November 2019 there has been no registered case to the online portal related to sudden cardiac death in patients with BrP. To date only recommendation for the treatment of BrP is the elimination of the underlying condition. Finally, we strongly encourage researchers that are currently working on this pattern to use the terminology BrP for consistency and consolidating this emerging concept. In addition, we recommend you submitting your cases to the international registry at http://www.brugadaphenocopy.com/.

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