Original Article

Prevalence and Pattern of Brugada Syndrome: A Five-Year Cohort Registry of 4000 Patients

Hossein Fatemian[1], PhD; Mansour Rezaei[1], PhD; Mehrdad Rabiei Rad[2], MD; Sarvin Dahmardeh[3], MD; Mahdi Khorsand Ghaffari[4], PhD; Mohammad Hossein Nikoo[1*], PhD; Fatemeh Rezaei-Tazangi[5], PhD

ABSTRACT

Background: Patients with Brugada syndrome and a history of sudden cardiac death are at an increased risk for arrhythmias, necessitating the potential use of an implantable cardioverter defibrillator. Diagnostic procedures involve identifying a specific ECG pattern either spontaneously or during a sodium channel blocker test.

Methods: This cohort study examined patients' records from 2015 through 2020 in Shiraz. A random sample of 4000 individuals was selected, and their clinical records were assessed. After registering participants' baseline information, including age, sex, family history, and disease status, ECGs were taken to investigate Brugada syndrome. ECG findings were then reviewed by cardiologists.

Results: Among the 4000 participants, 16 had suspicious ECG findings or a family history of sudden death. Of these, 12 patients exhibited Brugada patterns (types 2 and 3), while 4 were diagnosed with Brugada syndrome (type 1). During the 5-year follow-up period, none of the patients experienced any adverse events. Patients diagnosed with Brugada syndrome were predominantly between 18 and 49 years old.

Conclusions: The prevalence of Brugada patterns and syndrome in Iran was found to be similar to the global average and lower than in Southeast Asia. Additionally, the syndrome's prevalence was significantly higher in men than in women. The highest prevalence was observed in individuals aged 18 to 49 years, indicating a trend toward earlier disease manifestation. No echocardiographic findings specific to Brugada syndrome were identified in this study, and the patients had a favorable 5-year prognosis. ***(Iranian Heart Journal 2024; 25(4): 22-30)***

KEYWORDS: Brugada syndrome, Brugada pattern, Prevalence, Cohort study

[1] Non-Communicable Disease Research Center, Shiraz University of Medical Sciences, Shiraz, IR Iran.
[2] Isfahan University of Medical Sciences, Isfahan, IR Iran.
[3] Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, IR Iran.
[4] Department of Emergency Medicine, Crisis Management and Emergency Medical Services of Markazi Province, Arak University of Medical Sciences, Arak, IR Iran.
[5] Department of Anatomy, School of Medicine, Fasa University of Medical Sciences, Fasa, IR Iran.

***Corresponding Author:** Mohammad Hossein Nikoo, PhD; Non-Communicable Disease Research Center, Shiraz University of Medical Sciences, Shiraz, IR Iran.
Email: m.nikoo@yahoo.com **Tel:** +989177390428

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Brugada syndrome (BrS) is a hereditary arrhythmic disorder associated with ventricular fibrillation, sudden premature arrhythmic death syndrome, and sudden cardiac death. [1, 2] This syndrome is characterized by cardiac conduction abnormalities, such as a high risk for ventricular arrhythmias and ST-segment abnormalities in leads V_1–V_3 on ECG. Although BrS can affect individuals of various ages, ranging from infancy to late adulthood, it is primarily observed in adults. [3] Sudden death resulting from this condition commonly occurs around the age of 40 years. BrS follows an autosomal dominant inheritance pattern with variable penetrance. [4] It is a combination of the Brugada heart rhythm pattern in the ECG with clinical manifestations related to life-threatening ventricular arrhythmias. Specific features of BrS include ST-segment elevation in the right precordial leads on ECG without evidence of ischemia, electrolyte imbalance, and other structural heart diseases. [5, 6] To date, over 100 types of genetic mutations have been associated with BrS, with the most common being the loss-of-function genetic mutation in SCN5A. [7] This mutation is characterized by sodium channel inactivation and has been reported in approximately 20% of BrS cases. BrS predominantly manifests as sudden cardiac arrest in young men with structurally normal hearts. ECG findings in BrS are dynamic; thus, they may not be apparent on a standard 12-lead ECG. In such cases, masked BrS can be revealed using pharmacological agents such as disopyramide, propafenone, ajmaline, pilsicainide, and procainamide. Additionally, masked BrS can manifest in response to various triggers, including tricyclic antidepressants, vagotonic drugs (eg, cocaine), fever, and pneumonia. [8] The prevalence of the asymptomatic Brugada ECG pattern (BrEP) has been evaluated in diverse populations, with reported rates ranging from 0.1% to 1%, depending on the study population. [4] A 2016 meta-analysis reported an average prevalence of BrEP at 0.2%. Furthermore, the average prevalence was found to be 0.9% in men and 0.1% in women. The risk ratio (RR) for all-cause mortality and cardiac death in BrEP has been estimated at 0.78 and 0.92, respectively. [9] Diagnostic approaches for BrS rely on the identification of a specific ECG pattern, which may be observed spontaneously or during a sodium channel blocker test. [10] The ECG criteria for diagnosing Brugada syndrome, including the different types of BrEPs, are summarized in Table 1. [11, 12]

Table 1: ECG Variations in Different Types of Brugada Syndrome

ECG	Type 1	Type 2	Type 3
J-wave amplitude	≤ 2 mm	≤ 2 mm	≤ 2 mm
T wave	Negative	Positive or biphasic	Positive
ST-T configuration	Coved type	Saddleback	Saddleback
ST segment (terminal portion)	Gradually descending	Elevated ≥1 mm	Elevated <1 mm

Patients with BrS and a history of sudden cardiac death or syncope are at a higher risk for arrhythmias and should be considered for an implantable cardioverter-defibrillator (ICD). Managing asymptomatic cases with device-based approaches can be challenging, as high rates of inappropriate shocks and device-related complications can adversely affect ICD therapy. The management of asymptomatic individuals with BrS and induced arrhythmias remains a critical concern. The potential efficacy of antiarrhythmic drugs in BrS has been suggested in the literature. [13] A study demonstrated that hydroquinidine prevented the induction of ventricular tachycardia/ventricular fibrillation (VT/VF) in 76% of asymptomatic patients who underwent electrophysiological therapy. Among patients receiving long-term hydroquinidine therapy (17 ± 13 mon), syncope occurred in 2 out of 21 individuals.

(One case involved syncope associated with QT prolongation, and the other was unexplained.) For asymptomatic patients who received an ICD (n = 10), an appropriate shock was administered during a follow-up period of 13 ± 8 months. In patients experiencing multiple ICD shocks, hydroquinidine effectively prevented VT/VF recurrence in all cases during a mean follow-up of 14 ± 8 months. These findings suggest that prophylactic treatment with hydroquinidine could serve as an alternative to ICD placement in asymptomatic individuals with BrS and inducible arrhythmias. [14]

BrS is recognized as a significant cause of sudden cardiac death in relatively young individuals worldwide. Numerous medications have been reported to induce ECG abnormalities and potentially fatal ventricular tachyarrhythmias associated with BrS. Further, various drugs have been linked to adverse side effects in patients with BrS. [15] Given the scarcity of information on BrS in our geographical region and its potentially life-threatening implications, we aimed to assess the prevalence of BrS among patients in Shiraz over the past 5 years.

METHODS

This retrospective cohort study, conducted with a 5-year follow-up, analyzed the records of patients referred to family doctors in Shiraz between 2014 and 2019. The study was approved by the Shiraz University of Medical Sciences (ethics code: IR.SUMS.MED.REC.1401.070). A random sample of 4000 individuals was selected from 7500 patients who visited family doctors across Shiraz during the years 1395 through 1400. Clinical records of these participants were examined as part of the study. Initially, the selected patients had no underlying health issues or risk factors; they had only visited medical centers for general examinations and check-ups. From the 4000 participants, basic information, including age, sex, and family history, was recorded. Subsequently, an ECG was performed to screen for BrS. Patients were also questioned about their family history of sudden death and the use of an ICD. For those with a family history of sudden cardiac arrest or ICD use, an ECG was additionally conducted on their first-degree relatives to assess the presence or absence of BrS as a potential causative factor. All ECGs were reviewed by a cardiologist, and the prevalence of BrS, along with other significant epidemiological and demographic factors, was investigated. Patients were contacted via phone and asked to visit the clinic for further testing.

Diagnosis of BrS in the ECG of the Studied Patients

BrS is a genetic condition associated with sudden cardiac arrest and death. This syndrome presents in 3 distinct types. The BrEP type 1 is characterized by an elevated ST segment (≥ 2 mm) with upward convexity, followed by an inverted T wave.

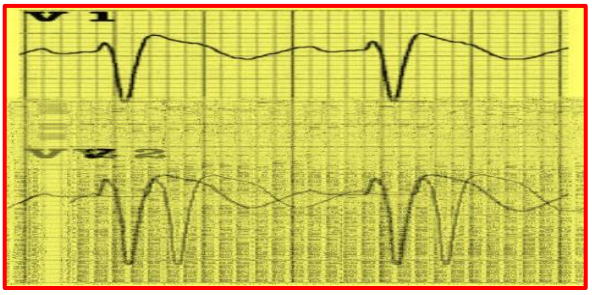

Figure 1: The image showcases Brugada ECG pattern type 1.

BrEP type 2 exhibits a saddle-shaped ST-T waveform. In this pattern, the ascending ST segment descends toward the baseline; then, it rises again to form an upright or biphasic T-wave.

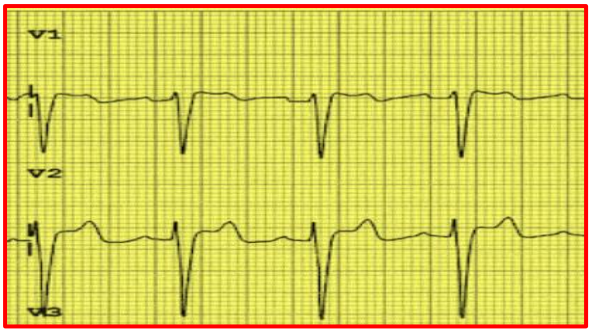

Figure 2: The image illustrates Brugada ECG pattern type 2.

In BrEP type 3, the morphology can resemble either type 1 or type 2 patterns. Nonetheless, it is distinguished by an ST-segment elevation that is less than 2 mm.

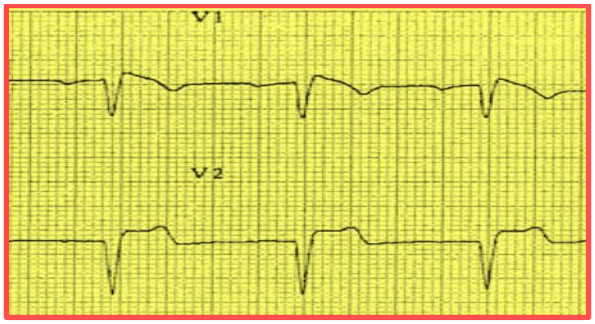

Figure 3: The image demonstrates Brugada ECG pattern type 3.

A definitive diagnosis of BrS is established when an elevated ST segment in a type-1 pattern is observed in more than 1 right precordial lead (V_1–V_3) either spontaneously or following the administration of a sodium channel blocking agent, along with 1 or more of the following criteria:

1. Documented ventricular fibrillation
2. Polymorphic ventricular tachycardia
3. A family history of sudden cardiac death in individuals under 45 years of age
4. Presence of coved-type ECG patterns in family members
5. Inducibility of VT upon programmed electrical stimulation
6. Episodes of syncope or nocturnal agonal breathing

However, the diagnosis of BrS based on type-2 and type-3 ECG patterns requires confirmation by converting the observed pattern to a type-1 pattern following a challenge with a sodium channel-blocking agent. In this study, a BrS diagnosis was considered positive only when both cardiologists agreed on the classification of ECG abnormalities. Patients with a positive diagnosis were contacted by phone and requested to visit the clinic for further relevant testing. Transthoracic echocardiography was performed for all patients to evaluate the presence of structural heart disease.

For patients exhibiting a Brugada type-2 or 3 pattern on a standard 12-lead ECG, an intravenous infusion of 1 mg/kg procainamide was administered over 15 minutes. Patients were then closely monitored in the ICU for 24 hours. ECG recordings were obtained according to the Brugada protocol at 0, 5, 10, 15, and 20 minutes (5 minutes after completing procainamide administration). The conversion of Brugada type-2 or 3 patterns to a type-1 pattern following procainamide administration was considered a diagnostic indicator of BrS.

Follow-up

For symptomatic patients or those with a family history of sudden death or ICD use, an ICD was implanted as a preventive measure. Asymptomatic patients without a family history of sudden cardiac death or ICD use were followed up for 5 years to monitor the development of symptoms and mortality.

Information Collection Tool and Process

Patient information was accessed through their medical records, and ECGs were evaluated by 2 experts to reach a consensus. Additional information and necessary tests were acquired by contacting patients via

phone and inviting them to visit the clinic. Collected data were initially recorded on paper forms and subsequently transferred to an electronic Excel file for further analysis.

Statistical Analysis

Demographic data and ECG findings were entered into SPSS software, version 24, for analysis. For the assessment of the diagnostic consistency between cardiologists, a κ coefficient analysis was performed for quality assurance and control, focusing on validity, accuracy, reliability, and generalizability. Continuous variables were expressed as mean ± standard deviation, while prevalence values were presented as percentages (%).

RESULTS

In this study, 4000 individuals were enrolled, with 47.7% (n = 1908) being men and 52.3% (n = 2092) being women. Out of the 4000 participants, 16 had a suspicious ECG or a family history of sudden cardiac death. Among these, 12 patients exhibited BrEP types 2 or 3, while 4 had BrEP type 1. The primary outcome of interest in this research was the prevalence of BrS in the population. The prevalence of BrEP was 0.3% (12 out of 4000 individuals), and the prevalence of BrS was 0.1% (4 out of 4000 individuals).

Follow-up of patients with BrEP

The 12 patients identified with BrEP underwent a procainamide challenge test. Those with negative test results (n = 12) were followed up for 5 years. During this period, neither the patients nor their family members exhibited symptoms or experienced sudden cardiac arrest, indicating a mortality risk comparable to the general population. All the patients also underwent transthoracic echocardiography, and no structural heart abnormalities were detected.

Patients with BrS

Among the 4000 patients studied, 4 were diagnosed with BrS. Three of these individuals were male (75%), and 1 was female (25%), suggesting a higher prevalence of BrS among men than among women.

• Patient 1

The first patient was a 44-year-old man with a positive procainamide test. Notably, his brother had passed away at the age of 30, with BrS identified as the cause of death. An ICD was implanted in this patient, who was subsequently followed up for 5 years. During this period, neither the patient nor his family members experienced any complications or adverse events.

• Patient 2

The second patient diagnosed with BrS was an 18-year-old girl whose 50-year-old father also had BrS. At the age of 18, the girl experienced sudden cardiac arrest during sleep, which led to a diagnosis of BrS and subsequent ICD implantation. Throughout the 5-year follow-up period, neither the patient nor her family members reported any complications or adverse events.

• Patient 3

The third patient was a 45-year-old man with an incidental positive test result during the study. As he was asymptomatic, an ICD was not implanted. The patient's family declined to undergo ECG testing. While the patient himself remained problem-free during the follow-up, his family's lack of cooperation precluded any further investigation into their health status.

• Patient 4

The fourth patient was a 49-year-old man who tested positive incidentally during the study. As he was asymptomatic, an ICD was not implanted. Over the 5-year follow-up period, the patient experienced no issues

related to his condition. Nevertheless, his family did not demonstrate significant cooperation, which prevented further investigation into their health status.

Additional Study Findings:

1. All patients remained problem-free during the 5-year follow-up period, leading normal lives without any structural heart abnormalities detected by echocardiography.
2. BrS symptoms tended to manifest at a young age, as observed in the cases of an 18-year-old girl (Patient 2) and a 30-year-old man (brother of Patient 1).
3. In both instances, BrS-related symptoms occurred during youth, with cardiac arrest episodes taking place during sleep and rest.
4. In the 2 patients whose families actively participated in the study, no issues were reported for their family members throughout the 5-year follow-up period. The sole exception was the younger brother of Patient 1, who passed away due to BrS-related complications. Still, the families of the remaining patients did not cooperate fully, which limited the exploration of familial consequences of BrS within the context of this study.
5. Echocardiography results were normal for all the study participants.
6. The age range for individuals diagnosed with BrS in this study was 18 to 49 years old.

DISCUSSION

This study aimed to investigate the prevalence of BrS in the metropolitan area of Shiraz and its associated factors. Our findings indicated a BrEP prevalence of 0.3% and a BrS prevalence of 0.1%. Asymptomatic BrEP prevalence has been examined in various populations, ranging between 0.1% and 1%, aligning with the results of the present study.[16, 17]

In a study conducted by Matsuo et al, [18] the prevalence of the aforementioned ECG pattern was over 1% among the participants. This higher prevalence may be attributed to the study's focus on male subjects, as BrEP is more commonly observed in men. Notably, our study shared a similar sex distribution, with a 3:1 male-to-female ratio, although the overall prevalence of BrEP was

In a study by Miyasaka et al, [19] the prevalence of BrEP was estimated at 0.7%. Methodologically, their study shared several similarities with ours, including the confirmation of BrEP by 2 experts and the enrollment of participants undergoing health examinations at a designated institution in Moriguchi. Still, Miyasaka and colleagues examined a greater number of participants and had a notably lower proportion of subjects under 40 years old (85 out of 13,929 individuals), which may contribute to the differences in findings between the 2 studies.

A Japanese study reported an annual BrEP incidence of 14.2 per 100,000 individuals. Data from multicenter registries suggest that the BrS incidence in men with BrEP is higher among Japanese patients (94%–96%) than among Caucasian patients (72%–80%). [20]

Previous studies have corroborated the higher prevalence of BrS in Asian populations than among those in the Middle East and other regions. One potential contributing factor to this disparity is the role of ethnicity-related genetic polymorphisms. [20]

A 2018 meta-analysis by Vutthikraivit et al [2] examined the global prevalence of BrS across various ethnicities, countries, and regions. The worldwide BrS prevalence was estimated at 0.5 per 1,000 individuals. Notably, BrS was more prevalent in Southeast Asia, particularly in conjunction with BrEP Types 2 and 3. Thailand was

identified as having the highest BrS prevalence globally, approximately 15 times higher than the worldwide estimate, consistent with our study's findings.

Our study revealed a 3:1 male-to-female ratio for the BrS prevalence. However, due to the limited sample size of patients with BrS, these findings are statistically constrained. We recommend conducting further studies with larger sample sizes to facilitate a more robust comparison of the BrS frequency between sexes in Iran. Nonetheless, our results align with previous research indicating a higher prevalence of BrS in men.

A meta-analysis by Quan et al [9] demonstrated that the BrS prevalence in men was 9 times higher than that in women.

To date, research on the echocardiographic factors associated with BrS has been limited. A 2019 study by Scheirlynck et al [21] found that patients with BrS exhibited lower right and left ventricular longitudinal strains, along with higher mechanical dispersion, compared to the control group. Furthermore, BrS patients with a history of life-threatening ventricular arrhythmias demonstrated a higher mechanical dispersion in the left ventricle. In addition to the aforementioned findings, another study established a connection between the left atrial volume index and the occurrence of ventricular fibrillation. [22] Conversely, our study yielded no abnormal echocardiographic results among the participants. This finding chimes with a previous study involving 363 asymptomatic BrS patients, where 96.2% of the individuals remained arrhythmia-free during a 5-year period. [23] Makimoto et al [24] observed that 2 out of 17 patients (12%) who experienced VF triggered by 1 to 2 extrastimuli later developed VF. In contrast, none of the 14 patients who were non-inducible by 3 extrastimuli or the 11 patients with no inducible arrhythmias experienced VF during a 6-year follow-up period.

None of our study participants experienced any cardiac events during the 5-year follow-up period, maintaining a normal life and exhibiting no structural heart abnormalities in echocardiography. In light of previous research, it appears that patients with asymptomatic BrS may still face a higher risk of cardiac events than the general population. However, the limitations of our study, such as the small sample size and lack of long-term follow-up, hinder the accurate assessment of these potential risks.

CONCLUSIONS

Our study revealed that the prevalence of BrEP and BrS in Iran aligns with the global average but is lower than that in Southeast Asia. The syndrome was significantly more prevalent in men, potentially attributable to differences in testosterone levels and body fat percentages. We observed that cardiac arrest and sudden death occurred most frequently in individuals aged between 18 and 49 and that disease onset also tended to manifest at a young age. No distinct echocardiographic findings specific to BrS were identified in this study, and patients exhibited a favorable 5-year prognosis.

REFERENCES

1. Fabbris JL, Mesquita AC, Caldeira S, Carvalho AMP, Carvalho ECd. Anxiety and spiritual well-being in nursing students: A cross-sectional study. Journal of Holistic Nursing. 2017; 35(3):261-70.

2. Vutthikraivit W, Rattanawong P, Putthapiban P, Sukhumthammarat W, Vathesatogkit P, Ngarmukos T, et al. Worldwide Prevalence of Brugada Syndrome: A Systematic Review and Meta-Analysis. Acta Cardiol Sin. 2018; 34(3):267-77.

3. Brugada R, Campuzano O, Sarquella-Brugada G, Brugada P, Brugada J, Hong K. Brugada syndrome. GeneReviews®[Internet]. 2016.

4. Wylie J, Garlitski A. Brugada syndrome: Clinical presentation, diagnosis, and evaluation. Uptodate; 2018.

5. Patocskai B, Antzelevitch C. Novel therapeutic strategies for the management of ventricular arrhythmias associated with the Brugada syndrome. Expert opinion on orphan drugs. 2015; 3(6):633-51.

6. Priori SG, Blomström-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J, et al. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac Death. The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology. Giornale italiano di cardiologia (2006). 2016; 17(2):108-70.

7. Hedley PL, Jørgensen P, Schlamowitz S, Moolman-Smook J, Kanters JK, Corfield VA, et al. The genetic basis of Brugada syndrome: a mutation update. Human mutation. 2009; 30(9):1256-66.

8. MORADI MO, Sedaghat A, Niakan M, Hajiesmaeili M, Seifi S, Soleimanirad R. Sudden cardiac arrest due to Brugada syndrome: a case report and literature review. 2013.

9. Quan X-Q, Li S, Liu R, Zheng K, Wu X-F, Tang Q. A meta-analytic review of prevalence for Brugada ECG patterns and the risk for death. Medicine. 2016; 95(50).

10. Gourraud J-B BJ, Thollet A, Le Marec H, Probst V. . Brugada syndrome: diagnosis, risk stratification and management. Archives of cardiovascular diseases. 2017;110(3):188-95.

11. Nishizaki M, Yamawake N, Sakurada H, Hiraoka M. ECG interpretation in Brugada syndrome. Journal of Arrhythmia. 2013; 29(2):56-64.

12. Othieno AA, Isaacs DJ, Vinson DR, Levis JT. ECG Diagnosis: Brugada Syndrome. Perm J. 2019; 23.

13. Conte G, Sieira J, Ciconte G, De Asmundis C, Chierchia G-B, Baltogiannis G, et al. Implantable cardioverter-defibrillator therapy in Brugada syndrome: a 20-year single-center experience. Journal of the American College of Cardiology. 2015; 65(9):879-88.

14. Hermida J-S, Denjoy I, Clerc J, Extramiana F, Jarry G, Milliez P, et al. Hydroquinidine therapy in Brugada syndrome. Journal of the American College of Cardiology. 2004; 43(10):1853-60.

15. 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(9):1335-41.

16. Priori SG, Wilde AA, Horie M, Cho Y, Behr ER, Berul C, et al. HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes: document endorsed by HRS, EHRA, and APHRS in May 2013 and by ACCF, AHA, PACES, and AEPC in June 2013. Heart Rhythm. 2013; 10(12):1932-63.

17. Patel SS, Anees S, Ferrick KJ. Prevalence of a Brugada pattern electrocardiogram in an urban population in the United States. Pacing Clin Electrophysiol. 2009; 32(6):704-8.

18. Matsuo K AM, Nakashima E, Seto S, Yano K. . Clinical Characteristics of Subjects with the Brugada-Type Electrocardiogram: A Case Control Study. Journal of cardiovascular electrophysiology. 2004; 15(6):653-7.

19. Miyasaka Y TH, Yamada K, Tokunaga S, Saito D, Imuro Y, et al. Prevalence and mortality of the Brugada-type electrocardiogram in one city in Japan. Journal of the American College of Cardiology. 2001; 38(3):771-4.

20. Kamakura S. Epidemiology of Brugada syndrome in Japan and rest of the world. Journal of Arrhythmia. 2013; 29(2):52-5.

21. Scheirlynck E, Van Malderen S, Motoc A, Lie Ø H, de Asmundis C, Sieira J, et al. Speckle tracking echocardiography data in Brugada syndrome patients. Data Brief. 2019; 25:104330.

22. Toh N, Morita H, Nagase S, Taniguchi M, Miura D, Nishii N, et al. Atrial electrophysiological and structural remodeling in high-risk patients with Brugada syndrome: assessment with electrophysiology and echocardiography. Heart Rhythm. 2010; 7(2):218-24.

23. Sieira J, Ciconte G, Conte G, Chierchia G-B, de Asmundis C, Baltogiannis G, et al. Asymptomatic Brugada syndrome: clinical characterization and long-term prognosis. Circulation: Arrhythmia and Electrophysiology. 2015; 8(5):1144-50.

24. Makimoto H, Kamakura S, Aihara N, Noda T, Nakajima I, Yokoyama T, et al. Clinical impact of the number of extrastimuli in programmed electrical stimulation in patients with Brugada type 1 electrocardiogram. Heart Rhythm. 2012;9(2):242-8.