Int J Cardiovasc Sci. 2023; 36:e20230053

EDITORIAL

Adding the Exercise Test as a Tool in the Medical Decision-Making Process in Brugada Syndrome

Luiz Eduardo Mastrocola,[1] Fábio Mastrocola[1]

Hospital do Coração,[1] São Paulo, SP – Brazil

Editorial referring to the article: Exercise Stress Test in The Assessment of Brugada Syndrome Patients

Introduction

Most cases of sudden cardiac arrest (SCA) and sudden cardiac death (SCD) are caused by ventricular tachyarrhythmias, with most of these associated with structural heart disease, particularly coronary heart disease. SCA is an uncommon occurrence in the apparently normal heart and accounts for only 5 to 10 percent of total cases.

Genetics and Appearance

Brugada syndrome (BrS) is an inherited arrhythmogenic condition initially described in 1992, characterized by a peculiar rest 12 lead ECG morphology, absence of structural cardiomyopathy, high incidence of ventricular arrhythmias, and fatal cardiac arrest.[1,2] Typically, the ECG findings consist of a pseudo-right bundle branch block and persistent ST-segment elevation, primarily in leads V1 to V2, although isolated cases have described similar findings involving the inferior ECG leads.[3] Three types of Brugada ECG patterns have been described: **type 1** ECG is characterized by a coved ST elevation of ≥2 mm in V1-V3, followed by negative T waves; **type 2** ECG has >2 mm of saddleback-shaped ST elevation; and **type 3** has the morphology of either type 1 or type 2, but with <2 mm ST elevation.[4] However, considering very subtle differences and a lack of clinical implication in distinguishing between types 2 and 3, these should currently be considered as type 2.[5] More recently, the phenomenon of Brugada phenocopies has also been described (similar ECG pattern), which appears in such situations as pulmonary embolism, myocardial ischemia, and hyperkalemia.[6]

Despite the latest hypothesis of additional inheritance pathways, BrS is still considered a Mendelian condition inherited in an autosomal dominant manner with incomplete penetrance.[7] But even with a large body of information acquired on its clinical presentation and genetic features to date, in addition to some similarities with other inheritable arrhythmogenic diseases (Long QT Syndrome, Arrhythmogenic Cardiomyopathy), there are still several controversial aspects on its pathophysiology, limiting the availability of risk stratification and diagnostic algorithms, as well as effective and definitively established treatment options. It is considered to be responsible for approximately 4% of all sudden cardiac deaths (SCDs) and nearly 20% of all SCDs in individuals with structurally normal hearts.[8] Currently, the sodium channel protein type V subunit α gene (SCN5A) is the primary gene linked to BrS, and roughly 30% of all documented cases are imputable to one of the gene's more than 350 genetic variants.[9] Since the first description of genetic mutation related to BrS (1998), around 500 sporadic mutations in more than 40 genes have been described as likely related to BrS. These genes mainly encode sodium, potassium, and calcium channels, as well as related proteins.[10] The discovery of additional genes that may be linked to BrS has enabled genetic screening in clinical assessment. Nonetheless, an extensive study of all probable BrS-associated genes has shown a disorder mutation in less than 40% of all confirmed cases; thus, the genetic origin of the condition remains undiscovered in most families.[11]

Keywords

Exercise; Decision Clinical, Brugada Syndrome; Genetic; Electrocardiograhy/methods; Cardiac, Arrhythmia; Cardiac Syncope; Heart Failure.

Mailing Address: Luiz Eduardo Mastrocola
Hospital do Coração. Rua Maria Figueiredo, 633, ap 61. Postal code: 04002-003. São Paulo, SP, Brazil.
E-mail: luizeduardo.mastrocolla@gmail.com

DOI: https://doi.org/10.36660/ijcs.20230053

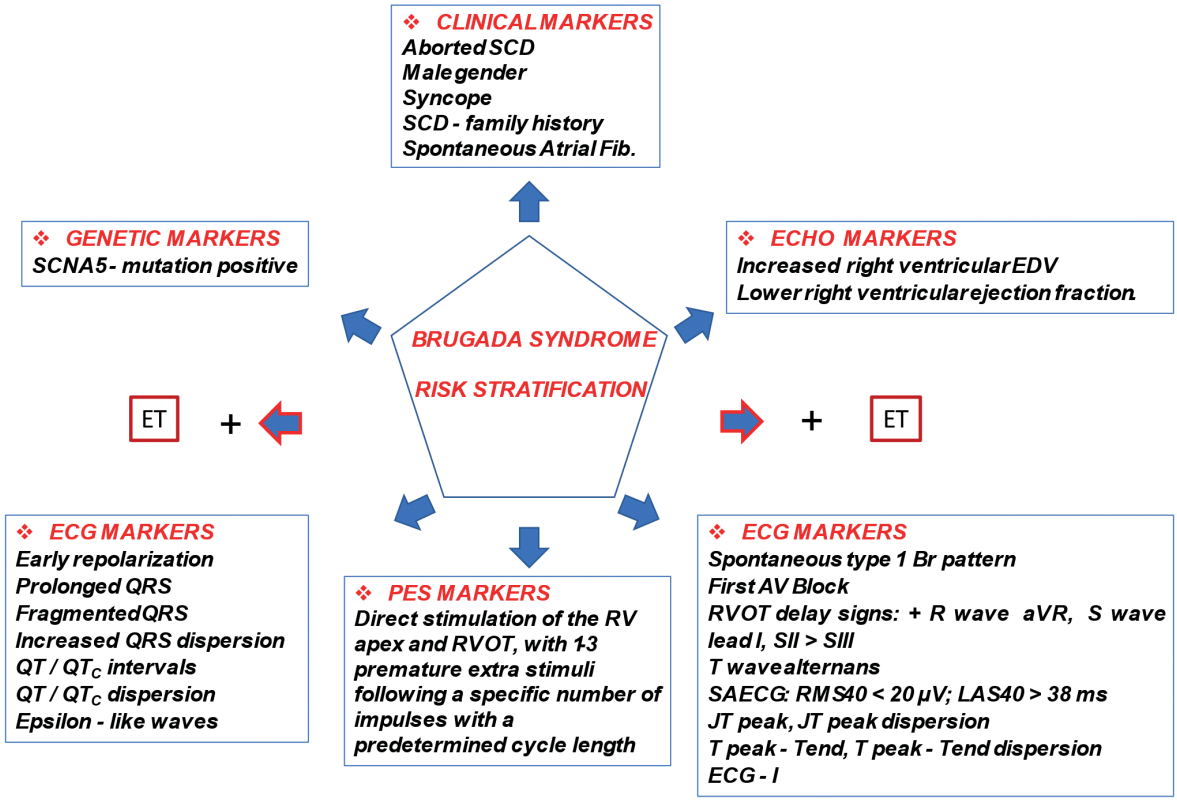

Figure 1 – Suggested markers for risk stratification in Brugada syndrome.
SCD – sudden cardiac death; Fib. – fibrillation; BrS – Brugada syndrome; Br – Brugada; SCN5A – sodium channel protein type V subunit α gene; RV – right ventricle; RVOT – right ventricle outflow tract; PES – programmed electrical stimulation; ET – adding exercise testing data (prognostic markers) from Miná et al.,[3] (https://doi.org/10.36660/ijcs.20220079); AV – atrioventricular; SAECG – signal-averaged ECG; RMS40 – root mean square voltage of the QRS complex terminal 40 ms; LAS40 – duration of low amplitude signals <40 µV of the QRS complex; ECG I – electrocardiographic imaging

Sudden Cardiac Death Risk Stratification in BrS

The primary challenge in individuals with a BrS type 1 ECG is to identify those who are at risk for sudden death and those who are not.[12] Researchers have proposed identifying these individuals who are at risk for SCD by applying a multiparametric clinical strategy, including a family history of SD, a syncope of presumed cardiac origin, an abnormal electrophysiology study (contradictory findings on the prognostic significance in asymptomatic BrS), among others. Their findings indicate that individuals with several risk factors are at the greatest risk (**Figure 1**).[3,13,14]

In this important and intriguing review by Miná et al,[3] on the relevance of exercise testing (ET) in risk stratification in BrS, made through extensive research of many well-known search platforms and databases, 712 patients (95% male) were selected from eight articles. Before the ET, symptoms and/or severe ventricular arrhythmias (ventricular fibrillation / ventricular polymorphic tachycardia) were reported by 256 patients (35.9%), with syncope documented in 70% of the cases. Additionally, the prognostic markers derived from ET were: **a)** an increase in ST-segment elevation of greater than 0.5mV in early recovery in V1, V2, or V3; **b)** an increase in the S-wave slope in the right precordial leads of greater than 30%; **c)** a J-point elevation in AVR of greater than 2 mm in late recovery; **d)** a decreased heart rate in late recovery of less than 40% of the peak heart rate; and **e)** an appearance of ventricular ectopic beats in early recovery. In the final comments, the authors suggest that the ET is a safe test to be performed in patients with BrS and possibly infers that the method can be added as a new proposed tool in the medical decision-making process in BrS, helping to clarify the diagnosis in doubtful cases as well to stratify the risk of future malignant arrhythmias.[15]

Indeed, in an era in which regular physical exercise is recommended for as many people as possible, from childhood to old age, acting as a stronger protecting factor against all-cause and cardiovascular morbidity and mortality, in addition to promoting a better quality of life, many guidelines and recommendations from medical societies have been published in order to guide healthy individuals and those with comorbidities[16-19], highlighting the role of exercise tests for the cardiovascular evaluation and exercise prescription. Moreover, knowing that there is an increasing trend towards a sedentary lifestyle and a rising prevalence of obesity and associated cardiovascular diseases (CVDs), the promotion of physical activity (PA) and regular exercise is more crucial than ever and at the forefront of priorities for all scientific CV societies.

Exercise tests have not been included on a regular basis as a tool in BrS evaluation algorithms, considering that there is some controversial evidence that showing an aggravating phenotype during exercise or early recovery, or electrophysiology (EP) study, is effective in detecting individuals at risk of SCD.[16] However, since there is a greater risk of events related to parasympathetic activity in this syndrome, arrhythmias can occur after exercise, a point in which there is vagal recovery and sympathetic withdrawal, perhaps reinforcing the role of ET as an auxiliary method in risk stratification, as mentioned in the current review.[3] It is noteworthy that in two studies included in the discussion of the article in question, namely "France, Italy, Netherlands, Germany Brugada syndrome Registry (FINGER)" and "Programmed Electrical Stimulation Predictive Value (PRELUDE)" (references on the original text) did not include data from ET as risk markers or predictors, with further studies needed. However, sports have not been described as an SCD risk factor in BrS,[16] and in asymptomatic patients with only an inducible type 1 Brugada ECG pattern, preventive measures are recommended, such as the avoidance of triggering drugs, electrolyte imbalance, and increases in core temperature > 39 degrees Celsius (avoidance of febrile illness, saunas, steam rooms, sports in humid / warm environments, and prolonged endurance events).[20,21] Similar rules apply to asymptomatic genotype positive/phenotype-negative individuals and those with the concealed form of BrS. However, no reports directly link exercise or sports training to cardiac events, and no large prospective studies have evaluated the impacts of exercise and sports on BrS.

Finally, the aspects addressed in the discussion of the present article by Miná et al.,[3] are well conducted, with conceptual highlights based on evidence from the literature, but the possibilities and limitations, not only of the method, but also of the type of the study conducted, the different casuistry and methodology employed, as well as variable follow-up and end points should be carefully analyzed in order to understand the resulting biases. The current review opens an important field of research geared toward improving risk stratification in BrS.

References

1. Cerrone M. Editorial commentary: Non-invasive tools for risk stratification and treatment in Brugada syndrome: Less is more? Trends Cardiovasc Med. 2021 Jul;31(5):330-1. doi: 10.1016/j.tcm.2020.06.010. Epub 2020 Jul 9. PMID: 32653528.

2. Brugada P, Brugada J. Right bundle branch block, persistent ST-segment elevation and sudden cardiac death: a distinct clinical and electrocardiographic syndrome. A multicenter report. J Am Coll Cardiol. 1992;20(6):1391-6. doi: 10.1016/0735-1097(92)90253-j.

3. Miná CP, Rocha EA, Mont'Alverne DG, Rocha EA. Exercise Stress Test in The Assessment of Brugada Syndrome Patients. Int J Cardiovasc Sci. 2023;36: e20220079. doi: 10.36660/ijcs.20220079

4. Popa IP, Șerban DN, Mărănducă MA, Șerban IL, Tamba BI, Tudorancea I. Brugada Syndrome: From Molecular Mechanisms and Genetics to Risk Stratification. Int J Mol Sci. 2023 Feb 7;24(4):3328. doi: 10.3390/ijms24043328. PMID: 36834739; PMCID: PMC9967917.

5. Li KH, Lee S, Yin C, Liu T, Ngarmukos T, Conte G, et al. Brugada syndrome: A comprehensive review of pathophysiological mechanisms and risk stratification strategies. Int J Cardiol Heart Vasc. 2020. 26;100468. doi: 10.1016/j.ijcha.2020.100468

6. Maia FS, Mastrocola F, Veronese P. Ventricular pre-excitation and genetically determined arrhythmias. In: Santos ECL, Mastrocola F (Eds.) Cardiology CardioPapers. 2nd ed. Rio de Janeiro/São Paulo: Atheneu; 2019. Chap.7, p. 64-85.

7. Oliveira Neto NR, de Oliveira WS, Mastrocola F, Sacilotto L. Brugada phenocopy: Mechanisms, diagnosis, and implications. J Electrocardiol. 2019 Jul-Aug; 55:45-50. doi: 10.1016/j.jelectrocard.2019.04.017. Epub 2019 Apr 30. PMID: 31078108.

8. Juang JM, Huang SK. Brugada syndrome - An under-recognized electrical disease in patients with sudden cardiac death. Cardiology. 2004;101(4):157-69. doi: 10.1159/000076693.

9. Khan A, Mittal S, Sherrid MV. Current review of Brugada syndrome: From epidemiology to treatment. Anadolu Kardiyol Derg. 2009;9(Suppl. 2):12-6. PMID: 20089482.

10. Brugada J, Campuzano O, Arbelo E, Brugada G, Brugada R. Present Status of Brugada Syndrome: JACC State-of-the-Art Review. J Am Coll Cardiol. 2018;72(9): 1046-59. doi: 10.1016/j.jacc.2018.06.037.

11. Campuzano O, Brugada G, Falgueras A, Cesar S, Coll M, Mates J, et al. Genetic interpretation and clinical translation of minor genes related to Brugada syndrome. Hum Mutat. 2019;40(6):749-64. doi: 10.1002/humu.23730.

12. Coppola G, Corrado E, Curnis A, Maglia G, Oriente D, Mignano A, et al. Update on brugada syndrome 2019. Curr Probl Cardiol. 2021;46(3):100454. doi: 10.1016/j.cpcardiol.2019.100454.

13. Priori SG, Gasparini M, Napolitano C, Bella P, Ottonelli AG, Sassone B, et al. Risk stratification in Brugada syndrome: Results of the PRELUDE (PRogrammed ELectrical stimUlation preDictive valuE) registry. J Am Coll Cardiol. 2012;59(1):37- 45. doi: 10.1016/j.jacc.2011.08.064.

14. Delise P, Allocca G, Marras E, Giustetto C, Gaita F, Sciarra L, et al. Risk stratification in individuals with the Brugada type 1 ECG pattern without previous cardiac arrest: Usefulness of a combined clinical and electrophysiologic approach. Eur Heart J. 2011;32(2):169-76. doi: 10.1093/eurheartj/ehq381.

15. Okamura H, Kamakura T, Morita H, Tokioka K, Nakajima I, Wada M, et al. Risk stratification in patients with Brugada syndrome without previous cardiac arrest–prognostic value of combined risk factors. Circ J. 2015;79(2):310-7. doi: 10.1253/circj.CJ-14-1059.

16. Pelliccia A, Sharma S, Gati S, Bäck M, Börjesson M, Caselli S, et al. ESC Scientific Document Group, 2020 ESC Guidelines on sports cardiology and exercise in patients with cardiovascular disease: The Task Force on sports cardiology and exercise in patients with cardiovascular disease of the European Society of Cardiology (ESC). Eur Heart J. 2021;42(1):17-96. doi:10.1093/eurheartj/ehaa605.

17. Ghorayeb N, Stein R, Daher DJ, Silveira AD, Ritt LEF, Santos, DF et al. The Brazilian Society of Cardiology and Brazilian Society of Exercise and Sports Medicine's Updated Guidelines for Sports and Exercise Cardiology - 2019. Arq Bras Cardiol. 2019; 112(3):326-68. doi: 10.5935/abc.20190048.

18. Kanaley JA, Colberg SR, Corcoran MH, Malin SK, Rodriguez NR, Crespo CJ, Kirwan JP, et al. Exercise/Physical Activity in Individuals with Type 2 Diabetes: A Consensus Statement from the American College of Sports Medicine. Med Sci Sports Exerc. 2022 Feb 1;54(2):353-68. doi: 10.1249/MSS.0000000000002800.

19. Carvalho T, Milani M, Ferraz AS, Silveira AD, Herdy AH, Hossri CA, et al. Brazilian Cardiovascular Rehabilitation Guideline - 2020. Arq Bras Cardiol. 2020;114(5):943-87. doi: 10.36660/abc.20200407.

20. Priori SG, 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 (ESC). EP Europace. 2015;17(11):1601-87. doi: 10.1093/europace/euv319.

21. Al-Khatib SM, Stevenson WG, Ackerman MJ, Bryant WJ, Callans DJ, Curtis AB, et al. 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. Heart Rhythm. 2018;15(10):e190-e252. doi: 10.1016/j.hrthm.2017.10.035.