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REVIEW ARTICLE

Exercise Stress Test in The Assessment of Brugada Syndrome Patients

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Abstract

Brugada syndrome (BS) is a genetic channelopathy, clinically characterized by an increased risk of sudden cardiac death. The diagnosis requires a typical electrocardiographic pattern, and data on risk stratification are limited in the literature. The aim of this study was to conduct a review on the importance of exercise stress test (EST) in risk stratification in BS. Articles were searched in the PubMed, Scielo and Google Scholar databases. From the 200 articles retrieved, eight were included, with a total of 712 patients (95% men) aged between 35 and 60 years. Severe symptoms and ventricular arrhythmias were reported by 256 patients before the EST, with syncope being reported in 70% of cases. The reviewed articles suggest that the EST is a safe method that can help in the diagnosis and risk stratification for malignant arrhythmias in patients with BS. Potential predictors of poor prognosis were: augmentation in ST-segment elevation > 0.5 mV in V1, V2 or V3 in early recovery; J-point elevation in lead > 2mm in aVR in late recovery; heart rate reduction < 40% from maximum heart rate in late recovery and occurrence of ventricular extrasystoles in early recovery.

Introduction

Brugada syndrome (BS) is a genetic channelopathy with a typical electrocardiogram (ECG) and an increased risk of sudden cardiac death (SCD), secondary to polymorphic ventricular tachycardia in the absence of gross structural heart disease.[1] BS is one of the most common channelopathies, with a worldwide prevalence of 0.05%,[2] and higher prevalence among Asian populations. A Japanese study showed characteristic echocardiographic features of BS in 0.12-0.14% of the population,[3] whereas the prevalence of BS was 0.01-0.03% among Europeans and North-Americans.[4] BS is more prevalent among men, with mean age of 41± 15 years, of Japanese descent, and from the Southeast Asia. It is estimated that BS accounts for 4% of all SCDs, and most patients are diagnosed only after the arrhythmic event.[4]

The electrocardiographic pattern, called type 1 pattern, is characterized by J-point elevation and ST-segment elevation ≥2 mm, with a coved morphology in one or more right precordial leads (V1 and V2), followed by a symmetric negative T wave. Either spontaneous or drug-induced, this is the only definite pattern for the diagnosis of BS. The type 2 pattern is defined by a saddleback-type ST-segment elevation ≥2 mm, followed by a positive or biphasic T-wave. This pattern has diagnostic value when conversion to the type 1 pattern occurs either spontaneously or after administration of class 1 sodium channel blocker according to the Vaughn- Williams classification.[5]

Brugada ECG patterns may present in a continuous, intermittent or concealed manner, and be unmasked by modulating factors that affect transmembrane ionic currents, such as vagal tone, elevation of body temperature, male sex hormones, and some drugs.[6]

Lower ventricular arrhythmia rates are seen in asymptomatic patients, especially in those without previous history of arrhythmia. Recent studies have shown arrhythmia rates of 0.8-1.2% a year in asymptomatic patients,[6] and up to four times higher in the presence of syncope. However, despite having a

Keywords

Brugada Syndrome/complications; Atrial Fibrillation; Bundle Branch Block; Exercise Test/methods; Diagnosis; Prognosis.

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more benign course, many patients with BS and history of aborted SCD had been asymptomatic and classified as low risk for arrhythmic events. Besides, the risk seems to be cumulative with time, achieving up to 10% at ten years. Thus, risk stratification of SCD in BS must improve.[7]

In this context, exercise stress test (EST), a low-morbidity, low-cost test, has been shown to be potentially useful in the diagnosis of patients with type 1 electrocardiographic pattern, either intermittently present or concealed, and in risk stratification of ventricular arrhythmic events in these individuals. This study aimed to conduct a comprehensive literature review on the importance of EST in risk stratification in BS.

Methods

The articles were searched in the PubMed, Scielo and Google Scholar databases, using the search terms *((exercise [Title/Abstract]) OR (treadmill [Title/Abstract])) AND (Brugada [Title/Abstract])*.

The abstracts were read and full texts of articles addressing EST in the diagnosis or in risk stratification of BS patients were reviewed. Articles published in Portuguese, English or Spanish between 1992 and 2021 were retrieved. Case reports, duplicates, different articles from the same population, review articles, articles that had not been published in scientific papers and articles for which only the abstract was available were excluded. Articles in which EST was performed using different analysis parameters from the ones used in clinical practice were also excluded.

Results

The initial search identified 137 articles in *PubMed*. After analysis of the titles, the number of articles possibly related to the search topic was reduced to 33 articles. After full text reading, 25 articles met the exclusion criteria, and eight were included for analysis.

From the Google Scholar database, 59 articles were retrieved and assessed; 51 met the exclusion criteria, and then eight were included for analysis, which were the same as those identified in PubMed (Figure 1 and Table 1).

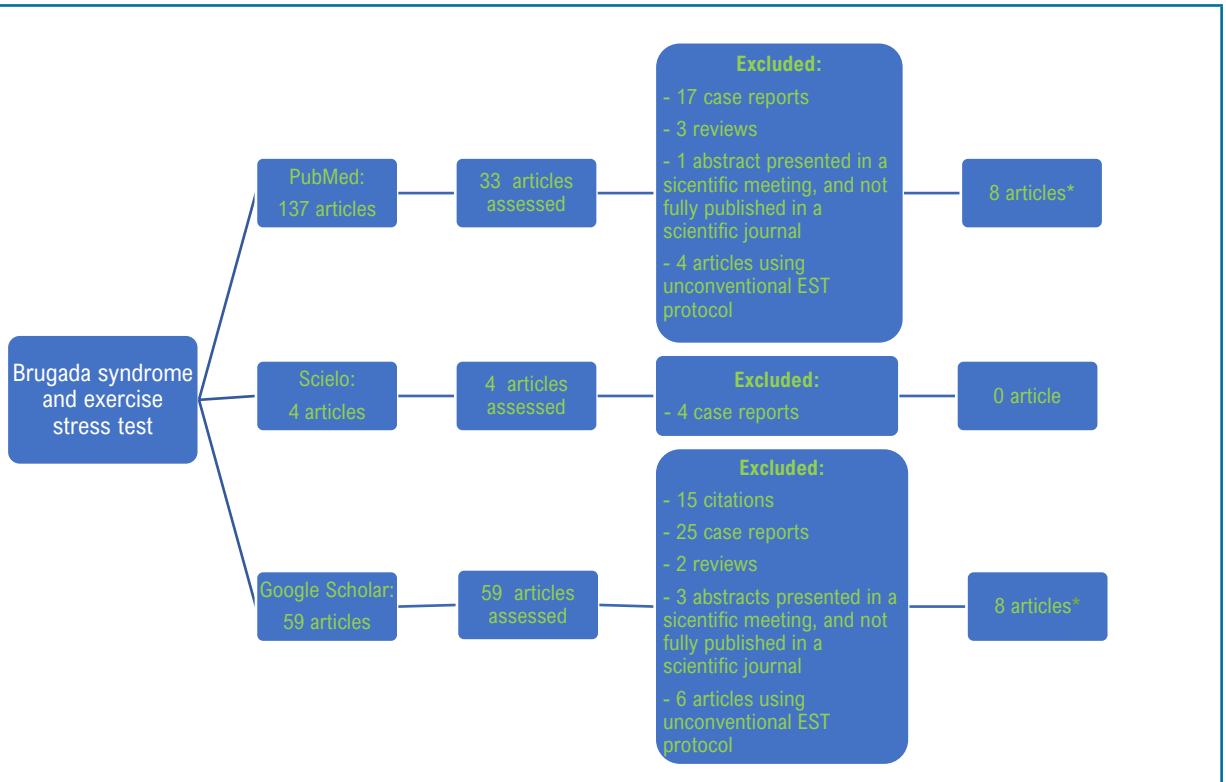

Figure 1 – Flowchart of article selection; *the eight articles identified in PubMed were the same as those identified in Google Scholar.
EST: exercise stress test.

Table 1 – Studies evaluating the effects of exercise stress in Brugada syndrome patients

Authors	Study	N	Sex	Age	Symptoms	Findings/Results***
Amin et al.[8]	Retrospective	35 Controls 25 BS* SCN5A+ 25 SB SCN5A-	Male	SCN5A+: 43+/-3 SCN5A-: 42+/-2	SCN5A+: VF†/VT‡ (1) syncope (6) palpitations (2) SCN5A-: VF/VT (1) syncope (6) palpitations (4)	Exercise accentuated the type 1 Brugada electrocardiographic phenotype in the BS group. Peak J-point amplitude was found in early recovery, with no significant difference (p=0.093). The presence of an SCN5A mutation was associated with higher conduction slowing at fast heart rates (p<0.001)
Chanavirut et al.[9]	Cross-sectional	23 Controls 11 BS com ICD#	Male	50+/-6	SCD survivors**	All patient performed an exercise test on a cycle ergometer, Patients with BS showed higher parasympathetic and lower sympathetic activation during the recovery period (p<0.05)
Makimoto et al.[10]	Prospective	102 Controls 93 BS	91 Men	Controls: 46+/-17 SB: 46+/-14	VF (22) Syncope (35)	Elevation of ST-segment > 0.05mV in V1-V3 during early recovery from exercise testing in 34 patients with BS, During 76 ± 38 months of follow-up, VF occurred in 44% of patients with BS and ST elevation vs. 17% in BS without ST elevation (p=0.004)
Morita et al.[11]	Prospective	307 SB	299 Men	45+/-12	Syncope (75) Aborted SCD (13)	Ventricular extrasystoles occurred in 27% of patients at the time of treadmill exercise test. During 92+/-68 months of follow-up, 30 patients experienced VF; VF was more frequent in those who experienced ventricular extrasystoles early after exercise (1.5-3 minutes) (p<0.05). Multivariate analysis including symptoms, spontaneous type 1 ECG, and ventricular extrasystoles in the early recovery phase showed that these factors were independently associated with VF (p<0.05)
Pospiech et al.[12]	Prospective	46 BS 17 IRBBB	IRBBB‡‡: 13 Men BS: 40 Men	IRBBB: 43+/-13 BS: 49+/-14	Syncope (9) Dizziness (4) Chest pain (3) Palpitations (2)	BS patients showed larger beta angle at rest, exercise and recovery compared to IRBBB patients (p<0.001). Assessment of beta angle at exercise could help discriminate BS patients from healthy individuals
Subramanian et al.[13]	Prospective	82 Controls 75 BS	Controls: 75 Men SBS 68 Men	Controls: 48,5+/-13,7 SB: 49,1 +/-15,4	Asymptomatic	Patients performed exercise testing and were followed up for 77.9+/-28.9 months. Multivariate analysis revealed that increase in S wave upslope duration ratio >30% at peak exercise (HR 1.35, 95% CI 1.08-10.97, P = 0.023), augmentation of J point elevation in lead aVR >2 mm in late recovery (HR 1.88, 95% 1.21-15.67, P = 0.011), and delayed HR recovery (HR 1.14, 95% CI 1.06-18.22, P = 0.042) were correlated with worse outcomes

Tachibana et al.[14]	Cross-sectional	110	108 Men	54+/-13	VF/aborted SCD (13) Syncope (39)	BS patients who were assessed for subcutaneous ICD eligibility were studied. Forty-five patients were considered eligible for ICD implantation using ECG. The presence of complete right bundle branch block was a significant predictor of ineligibility for S-ICD (p=0.03). After exercise stress testing, 11 patients showed ineligibility for S-ICD. ECG during exercise showed higher T-wave voltage and lower R-wave voltage/T-wave voltage ratio (p<0.01). Therefore, exercise stress testing should be considered before subcutaneous ICD implantation.
Von Hafe et al.[15]	Cross-sectional	35	25 Male	53.8+/-12	Syncope (10)	Patients with BS who were assessed for subcutaneous ICD eligibility were studied. Of these, 14.3% were considered ineligible for ICD implantation using ECG at rest. The presence of complete right bundle branch block was associated with subcutaneous ICD ineligibility (p<0.01) After exercise stress testing, the percentage of ineligible patients increased to 16.7%, with no significant difference in ECG variables between eligible and ineligible patients. The study indicates the importance of screening after exercise stress testing in all patients with BS and indication for subcutaneous ICD

BS: Brugada syndrome; VF: Ventricular fibrillation; VT: Ventricular tachycardia; ECG: electrocardiography; ICD: implantable cardioverter; SCD: sudden cardiac death; IRBBB: incomplete right bundle branch block; a p<0.05 was considered statistically significant

Four articles were retrieved from Scielo, and all were excluded as they were all case reports (Figure 1).

In the eight articles included in the analysis, 712 patients with BS were studied for the effects of exercise stress; 95% of them were men, aged from 35 to 60 years. One article, by Morita et al.,[11] accounted for 42% of the patients. Most studies were conducted in Asia.

Symptoms or severe ventricular arrhythmias (ventricular fibrillation/ ventricular tachycardia) were reported by 256 patients before the EST, and syncope was reported by 70% of the cases. Most patients (64%) were asymptomatic.

Regarding the EST, the treadmill exercise test was the most common, while bicycle exercise testing was used in two studies, by Chanavirut et al.,[9] and by Pospiech et al.,[12] One episode of ventricular tachycardia during the exercise test was reported in the article by Subramanian et al.[13]

Discussion

Although BS is a rare disease, it accounts for up to 20% of sudden deaths in young patients with structurally normal hearts. Several studies have tried to determine a more accurate method to diagnose the syndrome and stratify the risk for adverse events.

In the France, Italy, Netherlands, Germany Brugada syndrome Registry (FINGER),[16] in which most patients (64%) were asymptomatic, the role of six risk factors in the prediction of arrhythmic events were assessed – syncope, spontaneous type 1 ECG, male sex, familial history of SCD, inducibility of ventricular tachyarrhythmias during electrophysiological study, and the presence of an SCN5A mutation. Syncope and spontaneous type 1 ECG were the only significant predictors. In the Programmed Electrical Stimulation Predictive Value (PRELUDE) study,[17] 308 patients with type 1 ECG were followed-up for 34 months.

The following predictors of events were identified: history of syncope and spontaneous type 1 ECG, ventricular refractory period < 200 ms and QRS fragmentation.

Insertion of an ICD is the only therapy recommended for cardiac arrest survivors. However, identifying those patients at increased risk for ventricular arrhythmias in primary prevention, and who would potentially benefit from an ICD is still challenging and controversial.[7] ICD insertion is an invasive, expensive approach, and not free of complications including pneumothorax, hematoma, displacement or breakage of the leads, infections and high incidence of inappropriate therapies.[18,19]

In this context, the EST, which is known to be useful in the diagnostic definition of patients with intermittent or even concealed Brugada electrocardiographic pattern due to positive modulating factors (increased vagal tone and decreased adrenergic tone at recovery and increase of body temperature with exercise), has been shown to be relevant in the prognostic stratification of these patients, as suggested in Table 1.

Amin et al.,[8] observed that exercise aggravates the ECG phenotype in BS and the presence of an SCN5A mutation is associated with slower conduction at fast heart rates. The authors also found that an increase in ST-segment elevation in early recovery from EST was a strong predictor of spontaneous ventricular fibrillation.

Subramanian et al.,[13] studied 75 asymptomatic patients with BS, who underwent treadmill exercise testing and followed-up for six years. Of these, 11.1% had a major arrhythmic event (appropriate shock of ICD or CSD). Three independent predictors of major arrhythmic event during exercise testing were identified: (1) increase in S wave upslope (ratio of the duration between the S-wave nadir and the J-point to the duration between the beginning of QRS and the J-point) >30% at peak exercise in precordial leads; (2) J-point elevation in lead aVR of 2 mm in late recovery; and (3) heart rate fall < 40% from maximum heart rate in late recovery. Of patients who had an unfavorable result, 80% had the three predictors. The authors concluded that EST is a simple, safe test, with high predictive accuracy for risk stratification in asymptomatic patients with type 1 BS pattern (Figures 2 and 3).

Makimoto et al.,[10] reported that one third of patients with BS undergoing EST had augmentation of ST-segment elevation in early recovery. This was an independent predictor for ventricular fibrillation during the follow-up. Augmentation of ST-segment elevation was considered when ≥ 0.05mV in early recovery (1 - 4 minutes) compared with ECG at rest, in one or more right precordial leads (V1-V3). Also, the authors observed a higher heart rate recovery in patients with ST-segment elevation at early recovery, suggesting that this response is predominantly vagally mediated.[10]

More recently, Morita et al.,[11] in a study with 307 BS patients, 73% of them asymptomatic, observed that the occurrence of ventricular extrasystoles early after exercise (1.5-3 minutes) was associated with ventricular fibrillation during the 92 +/-68-month follow-up (Table 2).

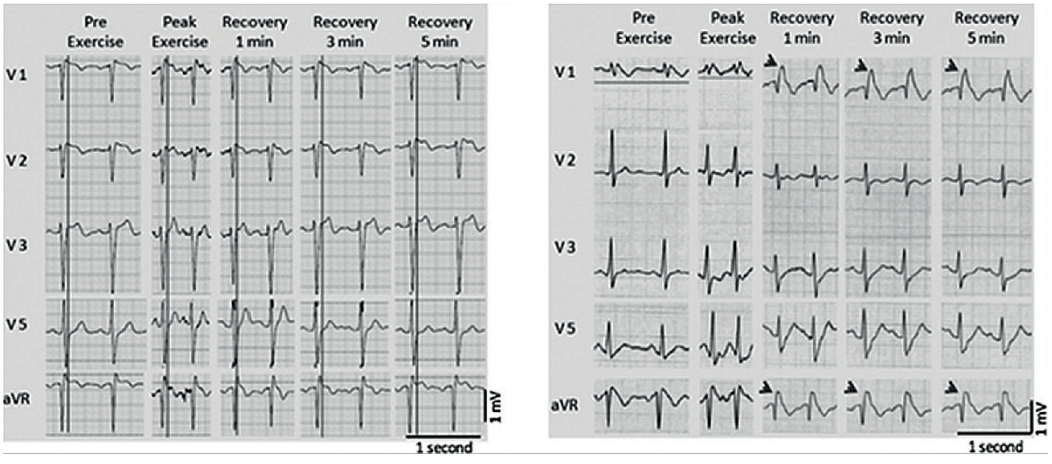

Figure 2 – Electrocardiographic changes during exercise stress test in patients with Brugada syndrome (BS). Left panel: ST-segment elevation in precordial leads and lead aVR during early recovery in a patient with type 1 BS. Vertical lines indicate the end of QRS from the V5 lead, representing the peak St elevation. Right panel: example of J-point elevation (arrows) in precordial leads and aVR during early and late recovery; adapted from Subramanian et al.[13]

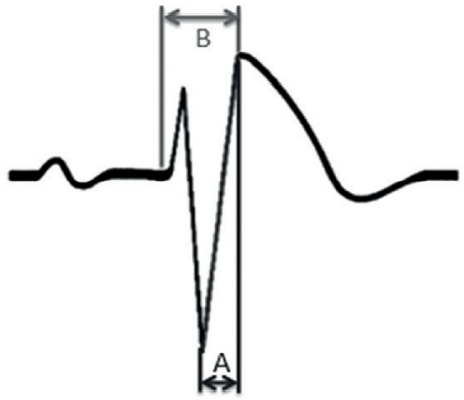

Figure 3 – S-wave slope: ratio between duration of the S-wave upslope and the QRS duration (A/B); A: duration (milliseconds) from S-wave nadir to the J-point. B: duration (milliseconds) from the QRS deflection to the J-point (RJ interval). Adapted from Subramanian et al.[13]

Table 2 – Exercise stress test findings associated with poor prognosis in Brugada syndrome patients

Authors	Findings
Makimoto et al.[10]	ST elevation > 0.05mV in V1, V2 in early recovery compared with baseline electrocardiogram
Morita et al.[11]	Occurrence of ventricular extrasystoles in early recovery (1.5 – 3 minutes)
Subramanian et al.[13]	- Increase > 30% of the ratio – duration of the ascending part of the S-wave /duration of the QRS complex in right precordial leads at peak exertion - J point in aVR > 2 mm at late recovery - Heart rate reduction < 40% at late recovery at peak exertion

With respect to the safety of EST in patients with BS, of the 712 cases reported, one patient (prevalence of 0.1%; 1:1000) had non-sustained ventricular tachycardia, with spontaneous resolution during exercise. The incidence is higher than that of ventricular fibrillation or tachycardia during EST in the general population, 1:5000 tests.[20] It is worth mentioning, however, that the Brazilian Society of Cardiology recommends the presence of a qualified physician in case of cardiological emergencies throughout the EST.[21]

Our group is currently developing a historical prospective study with BS patients in Brail, not only evaluating the electrocardiographic variables described in these previous studies, but also correlating them with prognosis, inducibility in invasive electrophysiological study, and presence of appropriate shocks in patients with ICDs. This is the subject of a Master's thesis in Cardiovascular Sciences at the Federal University of Ceara.

Limitations

The small number of studies available in the literature (mostly case reports) was a limitation of the present study.

Conclusion

The articles reviewed suggest that EST can be help in the diagnosis and risk stratification for malignant arrhythmias. Potential predictors of poor prognosis were: augmentation in ST-segment elevation > 0.5 mV in V1, V2 or V3 in early recovery; J-point elevation in lead > 2mm in aVR in late recovery; heart rate reduction < 40% from maximum heart rate in late recovery and occurrence of ventricular extrasystoles in early recovery.

Author Contributions

Conception and design of the research and writing of the manuscript: Miná CPC, Rocha EA; acquisition of data: Miná CPC, Rocha EAQ; analysis and interpretation of the data: Miná CPC, Rocha EA, Rocha EAQ; statistical analysis and obtaining financing: Miná CPC; critical revision of the manuscript for intellectual content: Mont'Alverne DGB, Rocha EA.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any thesis or dissertation work.

Ethics Approval and Consent to Participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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