

Exercise-induced Brugada syndrome type 1 pattern



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Introduction

Brugada syndrome (BrS) is an inherited disorder usually affecting patients with otherwise structurally normal hearts. Many triggers have been identified that can result in the phenotypic expression of the higher-risk BrS type 1 pattern. These triggers include but are not limited to fever, heightened vagal tone, and sodium (Na) channel blocking agents. Conversion to the type 1 pattern during exercise is unusual and in fact isoproterenol is a treatment for ventricular tachycardia (VT) storm in Brugada syndrome. We describe a case of a patient who exhibited BrS type 1 pattern during an exercise stress evaluation.

Case report

This is a case of a 24-year-old man who presented to the emergency department with complaints of chest pain. The pain was described as right-sided, sharp in nature, and which did not worsen with ambulation. His past medical history was unremarkable, and he denied any recent febrile illness. He also denied use of supplements, alcohol, or illicit drugs, and a toxicology screen confirmed no illicit drug use. Family history was notable for a brother who died suddenly while working as a grocery clerk, in his early 20s, in Mexico. The brother was in good health and had no prior cardiovascular history. Although the details surrounding the events of his brother's demise are unclear, the patient recalls that the "brother was stacking heavy boxes" when he collapsed and died.

On presentation, the patient was afebrile and hemodynamically stable with a normal oxygen saturation on room air. His chest radiograph and lab work were all unremarkable. Incidentally, the initial 12-lead electrocardiogram (ECG) revealed a type 2 Brugada pattern (Figure 1A) with

KEYWORDS Brugada syndrome; Stress testing; Channelopathy; Sudden cardiac death; Ventricular arrhythmia; Type 1 pattern; Inherited disorder (Heart Rhythm Case Reports 2022;8:288–291)

Funding Support: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. Disclosures: All listed authors have no conflicts to disclose. **Address reprint requests and correspondence:** Dr John Kassotis, Rutgers, Robert Wood Johnson Medical School, 125 Paterson St, Medical Education Building 5th Floor, Room 582, New Brunswick, NJ 08901. E-mail address: JK1585@rwjms.rutgers.edu.

KEY TEACHING POINTS

- This is an important case of exercise-induced type 1 Brugada syndrome (BrS) in a patient who presented with atypical chest pain and a type 2 Brugada pattern.
- The patient had a brother who died suddenly during exertion in his early 20s, suggestive of an inherited channelopathy.
- This may represent a genetic variant with phenotypic expression during exertion. This is an important consideration when patients present with ventricular tachycardia or ventricular fibrillation storm, since isoproterenol may result in a worsening of the condition.
- This is an unusual form of BrS and suggests that stress testing may be an important consideration in the evaluation of patients with BrS using a risk stratification tool.

saddleback ST elevations in leads V₁ and V₂. His echocardiogram revealed a preserved left ventricular ejection fraction without any valvular or other structural abnormalities. The emergency department then ordered an exercise nuclear stress test for further evaluation.

The myocardial perfusion imaging was normal; however, during exercise it was noted that there were dynamic ECG changes, with a gradual onset, beginning at a heart rate of 146 beats per minute (bpm). The ECG changes were most pronounced during peak exercise at a heart rate of 184 bpm. During peak exercise the ST segments in V₁-V₂, which were placed in the standard fourth intercostal position, became more pronounced and converted to a coved pattern consistent with a BrS type 1 pattern (Figure 1E). During recovery, the ST segments gradually reverted to baseline (Figure 1J). Prior to exercise testing, leads V₁ and V₂ were moved from the fourth to the second intercostal space to ensure that there was no preexisting type 1 pattern. The patient completed stage 4 of a standard Bruce protocol without

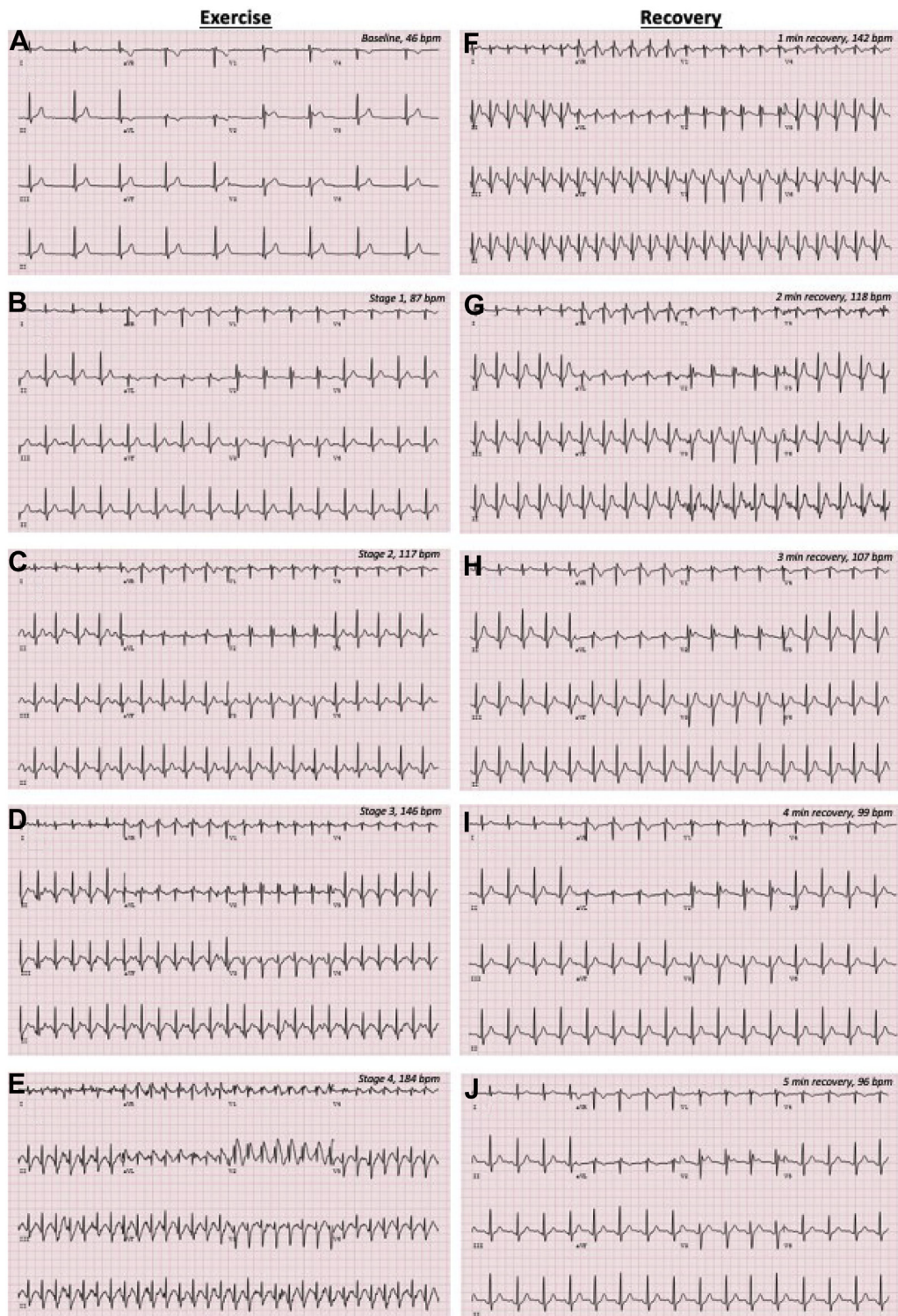


Figure 1 A–E: Electrocardiogram (ECG) results representing the exercise portion of the stress test. **A:** Baseline ECG with saddle-back ST-segment elevations in V₁-V₂, consistent with the Brugada type 2 pattern. **B–E:** Stages 1–4 of the standard Bruce protocol, respectively. Note the gradual augmentation of ST segments in leads V₁ and V₂, which become noticeable at a heart rate of 146 beats per minute (bpm) (**D**). Furthermore, maximum ST-segment augmentation along with transition to the type 1 pattern occurs during peak exercise at a heart rate of 184 bpm (**E**). **F–J:** ECGs representing 1-minute intervals into the recovery portion of exercise stress testing, through termination of testing, 5 minutes into recovery (**J**). Note the gradual decrease in the ST segments along with the transition back to the type 2 pattern.

experiencing chest pain or arrhythmias during exercise or throughout recovery.

Discussion

Ventricular arrhythmias in BrS typically occur in states of rest and bradycardia, especially during nighttime or sleep. This suggests that vagal activity may play an important role in the arrhythmogenesis of BrS. It is also well established that the extent of ST-segment change is a function of autonomic tone.¹⁻⁴ Both laboratory and clinical studies have shown an association between ST-segment augmentation and parasympathetic activity. Conversely, ST-segment reduction has been observed in association with sympathetic activity.^{1,5,6} This explains the use of isoproterenol in BrS with VT storm and the avoidance of medications with beta-blocking properties.

ST-segment augmentation with phenotypic expression of BrS type 1 during exercise stress testing has been previously reported. Masrur and colleagues⁷ performed a systematic review describing the effects of exercise stress testing on BrS patients. Of the 166 patients undergoing a stress evaluation, 95 (57%) exhibited ST-segment augmentation, with the vast majority (93) occurring during the recovery phase. Furthermore, only 2 patients manifested ST-segment augmentation during the exercise portion of the stress evaluation,^{8,9} which are findings similar to the present case. It is important to note that the presenting ECGs were different, when compared to the present case, with 1 patient having a BrS Type 1 pattern and the other having a normal ECG. Although these findings are rare, this suggests that there is a subset phenotype where an increase in sympathetic activity, or at least one of its downstream effects such as an increase in heart rate, may be a trigger for the more malignant type 1 pattern.

In addition, there has also been a unique genetic mutation described in a group of BrS patients with ST-segment augmentation occurring at rapid heart rates.¹⁰ Veldkamp and colleagues¹⁰ identified a specific *SCN5A* mutation involving the C-terminal portion of the Na channel that augments slow inactivation and delays recovery of Na channel availability. This may explain exercise as a trigger for the BrS type 1 pattern in this subset of patients. It is also worth noting that affected individuals with this mutation also manifested QT prolongation at slower heart rates.

In contrast, there have been reports of ST-segment reduction in BrS patients occurring at rapid heart rates. Zhang and colleagues¹¹ had observed a decrease in ST-segment elevation on reconstructed electrograms from the right ventricular outflow tract at increased heart rates using noninvasive ECG imaging. Additionally, there was also an increase in fractionated potentials at higher heart rates, which suggests a perturbation in depolarization as a contributor to the BrS ECG pattern. In comparison to our case, however, exercise was limited in this study and there was a reported mean increase in heart rate from 71 to 133 bpm. This distinction is important because ST augmentation did not occur in our case until

around 146 bpm and gradually peaked at the maximum achieved heart rate of 184 bpm. It may be that exercise intensity and peak heart rate play a role in the expression of the type 1 pattern.

Although no genetic testing was done owing to loss of follow-up, the unusual response during exercise that was observed in our case may be mutation specific. Genetic testing would have been invaluable, allowing us the ability to describe the mutation. Like the findings by Veldkamp and colleagues, this could be explained by a mutation that affects the time-dependent properties of the Na channel. If the kinetics of the Na channel were altered to where there is enhanced slow inactivation, it would be expected to see a decrease in inward Na currents at rapid heart rates. This reduction in Na current would result in a relative increase of early repolarization forces through the Ito channel. Given the increased expression of Ito channel in the epicardium and right ventricular outflow tract, a voltage gradient would be expected to occur at rapid heart rates that would manifest as J-point augmentation on the overlying ECG leads. Furthermore, there would also be fewer Na channels in the recovered state with each successive beat, leading to slowed conduction and altered wavefront propagation, which was observed by Zhang and colleagues. The result would be a decrease in conduction velocity, as well as a relative increase in the early repolarization force driven by the Ito channel. This model would support an abnormality involving both conduction and repolarization.

Although there was no indication for stress testing in this patient presenting with noncardiac chest pain and a type 2 BrS pattern, this case demonstrated an example of exercise provoking the phenotypic expression of the BrS type 1 pattern. Fortunately for our patient, he did not develop a potentially lethal arrhythmia during either exercise or recovery. Batra and colleagues¹² reported a case of an 18-year-old patient who presented with exertional symptoms and a baseline ECG revealing a BrS type 1 pattern. The patient developed VT during exercise. Considering the limited data regarding the use of exercise testing and BrS, this may represent a useful tool in risk-stratifying a subset of patients at risk for exertional arrhythmias.

Our case adds to the rare findings that ST-segment augmentation can occur during exercise, which could be explained by an unusual mutation of BrS. This has significant clinical implications in that there may exist a subset of BrS patients that may not respond, or even possibly have an adverse outcome, to isoproterenol in the treatment of VT storm.

References

1. Kasanuki H, Ohnishi S, Ohtuka M, et al. Idiopathic ventricular fibrillation induced with vagal activity in patients without obvious heart disease. *Circulation* 1997;95:2277-2285.
2. 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;27:1061-1070.
3. Noda T, Shimizu W, Taguchi A, 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;40:1841–1847.
4. Mizumaki K, Fujiki A, Tsuneda T, et al. Vagal activity modulates spontaneous augmentation of ST elevation in the daily life of patients with Brugada syndrome. *J Cardiovasc Electrophysiol* 2004;15:667–673.
 5. Tanaka H, Kinoshita O, Uchikawa S, et al. Successful prevention of recurrent ventricular fibrillation by intravenous isoproterenol in a patient with Brugada syndrome. *Pacing Clin Electrophysiol* 2001;24:1293–1294.
 6. Litovsky SH, Antzelevitch C. Differences in the electrophysiological response of canine ventricular subendocardium and subepicardium to acetylcholine and isoproterenol. A direct effect of acetylcholine in ventricular myocardium. *Circ Res* 1990;67:615–627.
 7. Masrur S, Memon S, Thompson P. Brugada Syndrome, exercise, and exercise stress testing. *Clin. Cardiol* 2015;38:323–326.
 8. Cho JH, Cho DK, Choi JY, et al. An unusual case of exercise induced idiopathic Brugada electrocardiographic pattern. *Korean Cir J* 2007;37:517–519.
 9. Guevara-Valdivia M, Micheli A, Iturralde P, et al. Infrequent electrocardiographic changes during exercise stress test in a patient with Brugada syndrome. *Arch Cardiol Mex* 2003;73:212–217.
 10. Veldkamp M, Viswanathan P, Bezzina C, Baartscheer A, Wilde A, Balse J. Two distinct congenital arrhythmias evoked by a multidysfunctional Na⁺ channel. *Circ Res* 2000;86:e91–e97.
 11. Zhang Z, Sacher F, Hoffmayer K, et al. Cardiac electrophysiological substrate underlying the ECG phenotype and electrogram abnormalities in Brugada syndrome patients. *Circulation* 2015;131:1950–1959.
 12. Batra A, Watson R, McCantra A. Exercise-induced syncope and Brugada syndrome. *Ann Pediatr Cardiol* 2019;12:292–294.