# Recurrent exercise-induced ventricular tachycardia in a patient with Brugada syndrome

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## Introduction

Brugada syndrome (BS) is an inherited arrhythmia syndrome with an increased risk of sudden cardiac death.[1] Polymorphic ventricular tachycardia (VT) triggered by high vagal tone, particularly during sleep, is considered the primary mechanism of sudden death in these patients. Although some BS patients may present with monomorphic VT, its relation to exercise remains unknown.[2] Accordingly, there are limited recommendations to restrict exercise in BS owing to lack of evidence of provocation of ventricular arrhythmia by exercise.[3,4] We present a case of a patient with BS due to an *SCN5A* mutation with recurrent exercise-induced monomorphic VT.

## Case report

The patient is a 19-year-old man with a history of asymptomatic BS who first presented to our hospital following successful resuscitation for an out of hospital cardiac arrest. He was diagnosed with BS at age 11 when cascade family genetic testing prompted by his father's diagnosis of BS revealed a pathologic *SCN5A* mutation (R282C). He has a history of spontaneous type I Brugada pattern on electrocardiogram (ECG), which is more prominent when leads $V_1$-$V_2$ are placed 1–2 intercostal spaces higher. He underwent an initial work-up at age 11 with an echocardiogram, treadmill stress test, and 48-hour Holter monitor. His echocardiogram revealed normal biventricular size, function, and wall motion. His treadmill stress test revealed normal exercise capacity without arrhythmia, and his 48-hour Holter monitor showed sinus rhythm without arrhythmia. He followed up with cardiology annually until age 18 with treadmill stress test, ECG, and Holter monitor that were normal except for spontaneous type I Brugada pattern and occasional ventricular ectopy during Holter and stress test after age 16. Electrophysiology study and cardiac magnetic resonance (CMR) imaging were not performed. Notably, his father's CMR imaging was remarkable for midmyocardial late gadolinium enhancement (LGE) of the basal inferolateral wall with normal left and right ventricle (LV and RV) size and function. No regional wall motion abnormalities, aneurysmal changes, or fatty infiltration were noted. The patient had no family history of sudden death or personal history of syncope or sustained ventricular arrhythmia. Although his father received a

### KEY TEACHING POINTS

- Sudden cardiac death in Brugada syndrome (BS) is usually attributed to vagally mediated polymorphic ventricular tachycardia (VT), but implantable cardioverter-defibrillator studies show high prevalence of monomorphic VT. Currently, guidelines provide limited guidance on exercise counseling.
- There is growing evidence that BS is part of the spectrum of "sodium channelopathy" and may phenotypically overlap with arrhythmogenic cardiomyopathy, which is strongly associated with sudden cardiac death during exercise.
- Our case suggests that some BS patients with overlap features of arrhythmogenic cardiomyopathy are at risk for exercise-induced ventricular arrhythmia.
- Cardiac magnetic resonance is a valuable tool for identifying arrhythmogenic substrate in patients with cardiomyopathies. Whether the presence of structural cardiac abnormalities increases the risk of exercise-induced ventricular arrhythmia in BS patients requires further study.

**KEYWORDS** Arrhythmogenic cardiomyopathy; Brugada syndrome; Cardiac magnetic resonance; Exercise; Late gadolinium enhancement; Ventricular tachycardia

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Conflict of Interest: None relevant to this manuscript for all authors. **Address reprint requests and correspondence:** Dr Alexander Mazur, Division of Cardiovascular Medicine and Abboud Cardiovascular Research Center, University of Iowa Hospitals and Clinics, 318E GH, 200 Hawkins Dr, Iowa City, IA 52242. E-mail address: alexander-mazur@uiowa.edu.



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primary prevention implantable cardioverter-defibrillator (ICD), the patient was deemed low risk for sudden death.

The patient was participating in a basketball practice when he suddenly developed lightheadedness, attempted to sit, and subsequently lost consciousness. An athletic trainer started cardiopulmonary resuscitation. The automatic external defibrillator advised shock, which successfully converted him to sinus rhythm on the first attempt. The stored automatic external defibrillator electrogram during the event showed polymorphic VT degenerating to ventricular fibrillation (Figure 1A). His admission ECG revealed nonspecific intraventricular conduction abnormalities and ST-segment elevation consistent with early repolarization pattern. A repeat ECG with precordial leads placed 1 intercostal space higher revealed a right bundle branch/left anterior fascicular block QRS pattern with J-point/ST-segment elevation in leads $V_1$ and $V_2$, consistent with a Brugada type I ECG pattern (Figure 1B). Echocardiogram the following morning showed normal-sized LV with a mildly reduced LV ejection fraction (LVEF) of 48% and normal RV size and function. A CMR image obtained 24 hours post arrest demonstrated normal wall thickness, a mildly enlarged LV with reduced LVEF of 47%, and a mildly enlarged RV with mildly decreased RVEF of 44.5%. There were no regional wall motion abnormalities or aneurysmal changes. Delayed gadolinium enhancement imaging demonstrated subepicardial enhancement involving the basal inferior and inferolateral walls (Figure 2). He underwent implantation of an ICD and was discharged home. At his 3-week follow-up outpatient visit, his ECG showed type 2 Brugada pattern and repeat echocardiogram revealed a persistently depressed LVEF of 45%, so he was started on metoprolol succinate 25 mg daily. One week

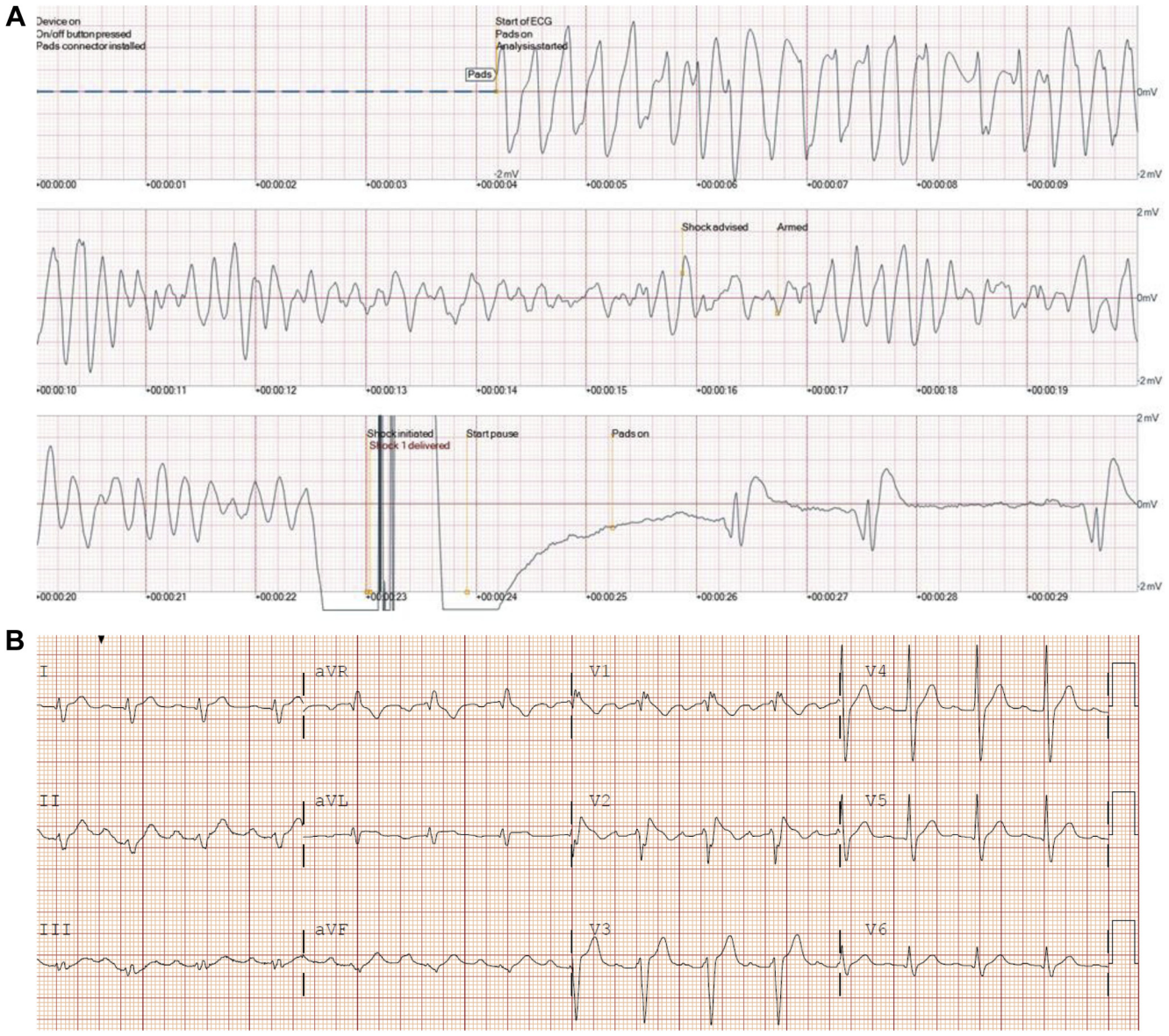


**Figure 1** **A:** Stored automatic external defibrillator electrogram during cardiac arrest. **B:** Twelve-lead electrocardiogram (ECG) with leads $V_1$ and $V_2$ moved up 1 intercostal space.

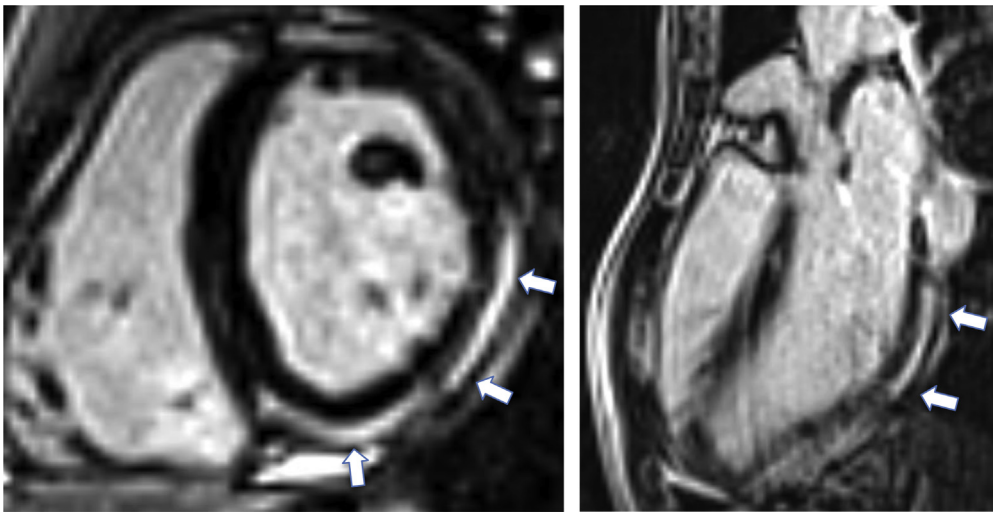

**Figure 2** Delayed-enhancement cardiac magnetic resonance sequences with subepicardial enhancement involving the basal inferior and inferolateral walls (*arrows*).

later, he went on a work trip and left his metoprolol at home. Approximately 48 hours after his last dose of metoprolol while engaging in rigorous physical activity, he had 2 spells of lightheadedness. Remote interrogation of his ICD revealed 2 episodes of monomorphic VT at a rate of 245 beats per minute (bpm) during periods of sinus tachycardia with rates 153 bpm and 130 bpm that were successfully treated with antitachycardia pacing (Figure 3). The patient's metoprolol was subsequently increased to 50 mg daily, he was counseled on the importance of medication compliance, and he was advised against rigorous exercise. In the following 6 months, his device recorded 1 self-terminating 6-beat episode of nonsustained monomorphic VT that occurred at a sinus rate of 118 bpm. Given his cardiomyopathy and monomorphic VT, repeat genetic testing was performed using Arrhythmia and Cardiomyopathy Comprehensive Panel and add-on Preliminary-evidence Genes for Arrhythmia and Cardiomyopathy Panel (114 genes; Invitae Corporation, San Francisco, CA). No relevant pathogenic variants were detected beyond his known *SCN5A* mutation.

## Discussion

Although BS is classically considered a vagally mediated arrhythmia syndrome in which exercise plays no provocative role, our case suggests that in some BS patients, exercise may be an important trigger of ventricular arrhythmia. In this case, a young man with a history of BS deemed low risk by conventional risk stratification methods had aborted sudden death in the setting of exercise and subsequently had recurrent episodes of exertional monomorphic VT terminated by antitachycardia pacing. Taken in conjunction with the finding of LV LGE, he appears to have exercise-induced ventricular arrhythmia owing to a phenotypic overlap between BS and arrhythmogenic cardiomyopathy (AC), most likely caused by the *SCN5A* mutation.

Although BS is traditionally considered a primary arrhythmogenic syndrome, clinical and bench research suggests that BS may be part of a spectrum of sodium channelopathies in which variants in proteins involving the connexome, including SCN5A, can cause changes in sodium current along with histopathologic changes and structural cardiac

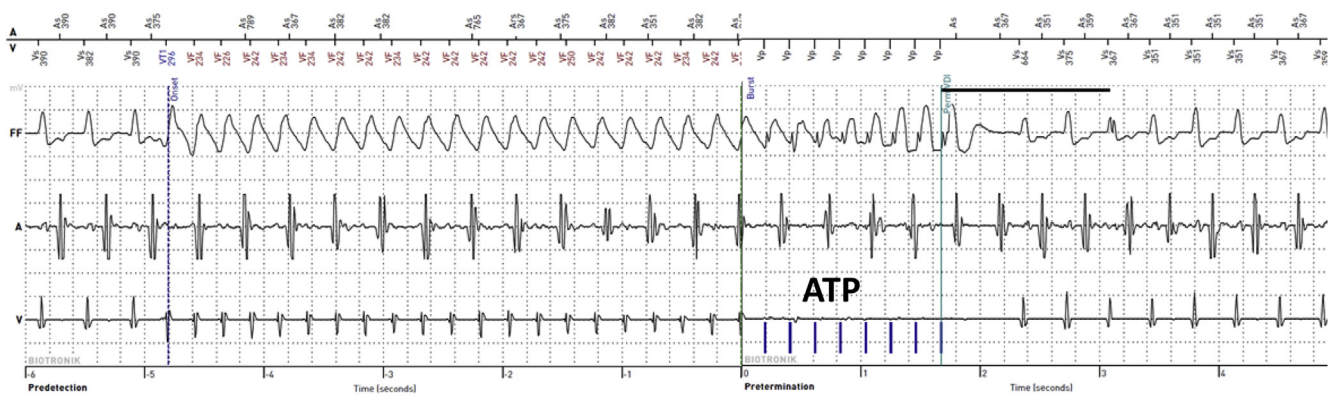


**Figure 3** Stored implantable cardioverter-defibrillator electrogram during an episode of exertional lightheadedness shows monomorphic ventricular tachycardia terminated with antitachycardia pacing (ATP). Note sinus tachycardia preceding the event. FF, A, and V indicate far-field ventricular, atrial, and near-field bipolar ventricular electrograms, respectively.

abnormalities.[5–7] Histopathologic studies in patients with BS found evidence of subtle structural abnormalities of the RV outflow tract myocardium manifested as interstitial fibrosis with increased collagen deposition and reduced gap junction redistribution.[8] On the other hand, some data suggest that approximately 15% of AC patients develop a BS ECG pattern during challenge with a sodium channel blocker.[9,10] As an integral part of the connexome, numerous *SCN5A* mutations have been linked to AC and dilated cardiomyopathy.[11] Although the prevalence of *SCN5A* as the etiology of AC or dilated cardiomyopathy is unknown, whole exome sequencing of a cohort of 281 AC patients revealed 1.8% prevalence of putative pathologic loss-of-function *SCN5A* mutations, which were associated with severe structural disease and a high risk of ventricular arrhythmia.[12]

CMR studies in BS patients have yielded mixed results. While some studies have demonstrated either decreased RV systolic function or increased RV dimensions, others have found no increased prevalence of abnormal findings as compared to a control population.[13,14] Evidence of LGE was noted in 1 of 2 studies with 8% in BS patients vs 0% in matched controls ($P = .028$).[13,14] Furthermore, 1 study of T1 mapping showed 20% prevalence of elevated T1 signal consistent with fat signal, a marker of AC, in BS patients vs none in controls.[15] Nevertheless, the clinical significance of LGE on CMR imaging in BS is not well understood. Further studies are needed to better understand the role of advanced cardiac imaging in risk stratification of BS patients.

In conclusion, our case suggests that in some patients with BS, exercise may trigger life-threatening ventricular arrhythmia. Identifying patients at risk of exercise-induced ventricular arrhythmia may have important implications for counseling regarding participation in athletic and recreational activities. Whether the presence of structural cardiac abnormalities increases the risk of exercise-induced ventricular arrhythmia in BS patients requires further study.

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