

Case Report

Exercise Testing With Flecainide Demonstrates Provocable Brugada Syndrome

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ABSTRACT

A young man with baseline early repolarization was initiated on flecainide and diltiazem for symptomatic atrial arrhythmias. A treadmill stress test induced a type 1 Brugada electrocardiogram pattern at higher heart rates. Flecainide was discontinued. Genetic testing revealed no SCN5A mutations, and a 3-generation pedigree revealed no events of concern. In this case report, we review the use-dependent properties of flecainide. We also discuss how this property can be exploited during exercise stress testing to provoke the diagnostic type 1 Brugada pattern at higher heart rates.

RÉSUMÉ

Chez un jeune homme présentant au départ une repolarisation précoce, un traitement à base de flécaïnide et de diltiazem a été instauré pour lutter contre les arythmies auriculaires symptomatiques. Une épreuve d'effort sur tapis roulant a permis d'obtenir un électrocardiogramme caractéristique d'un syndrome de Brugada de type 1 à des fréquences cardiaques plus élevées. Le traitement par le flécaïnide a été arrêté. Des analyses génétiques ont mis en évidence un résultat négatif pour les mutations du gène SCN5A, et un examen de l'arbre généalogique sur 3 générations n'a révélé aucun événement préoccupant. Dans cette étude de cas, nous analysons la propriété du flécaïnide d'avoir une efficacité proportionnelle à son utilisation. Nous évoquons également la possibilité d'exploiter cette propriété lors des épreuves d'effort afin de provoquer l'apparition du profil d'ECG du syndrome de Brugada de type 1 à des fréquences cardiaques plus élevées.

Case

A 46-year-old man was diagnosed with symptomatic atrial arrhythmias. Initial investigations including bloodwork and echocardiogram (ECG) were unremarkable. Baseline supine ECG (Fig. 1) revealed evidence of early repolarization in the anterior precordial leads. Holter monitoring revealed frequent premature supraventricular ectopic heartbeats that were 40.9% of all QRS complexes and that were isolated in pairs and in runs of atrial tachycardia. These were not suppressed with metoprolol or sotalol. The patient declined invasive intervention and was initiated on a combination of 75 mg flecainide twice daily, and 120 mg of diltiazem daily, for atrial arrhythmia suppression and because of suspicion of underlying atrial fibrillation due to the high burden of atrial ectopy.

Upon follow-up, the patient reported significant improvements without drug-related side effects. Because of concern

Novel Teaching Points

- Flecainide use-dependence allows for provocation of the diagnostic type 1 Brugada pattern at higher heart rates.
- Flecainide challenge during an exercise stress test can aid in BrS diagnosis by unmasking the diagnostic type 1 pattern at higher heart rates.

related to Brugada syndrome (BrS) in the context of a baseline ECG with early repolarization in the anterior precordial leads, an exercise treadmill stress test was organized. The patient developed a type 1 Brugada ECG pattern on treadmill exercise stress testing, which was most evident at high heart rates and resolved in recovery (Fig. 2; Supplemental Fig. S2; Supplemental Tables S1 and S2). The patient was asked to discontinue flecainide and meet with a genetic counsellor for SCN5A testing and a detailed family history. The patient was advised to avoid medications on the Brugada “medications to avoid” list (BrugadaDrugs.org).

There were no SCN5A mutations upon genetic testing. A 3-generation pedigree revealed no immediate or extended family history or events of concern. Cascade family screening was initiated. High lead ECG after flecainide discontinuation did not show evidence of BrS in the proband (Supplemental Fig. S1).

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See page 1081 for disclosure information.

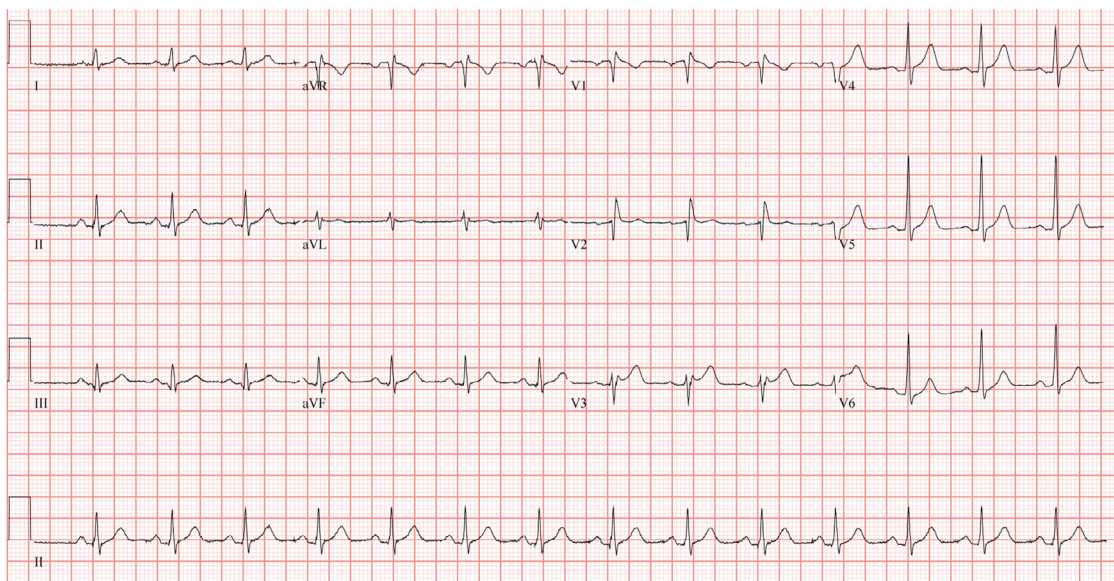


Figure 1. Baseline supine electrocardiogram prior to flecainide therapy onset, suspicious for type 2 Brugada pattern in V₃.

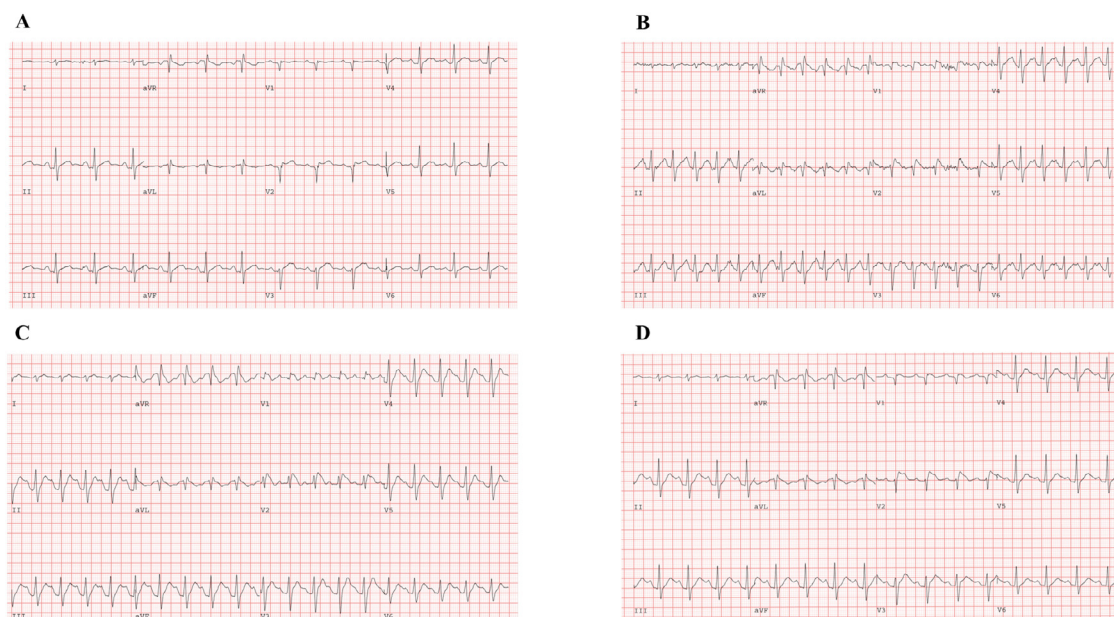


Figure 2. Exercise treadmill stress test electrocardiograms showing development of type 1 Brugada pattern at higher heart rates: (A) pretest; (B) running at 3.4 mph (Stage 3 Bruce protocol); (C) 1 minute, 5 seconds of recovery; and (D) 3 minutes, 5 seconds of recovery. Incomplete resolution of the type 1 pattern is noted at the end of recovery.

Discussion

BrS is characterized by an ECG finding of coved ST-segment elevation followed by a negative T-wave in the right precordial leads.¹ Although some patients present with syncope or sudden cardiac arrest, most will be asymptomatic. Therefore, an important diagnostic tool is a challenge study with a sodium-channel blocker to unmask the diagnostic type 1 ECG pattern.

Flecainide is 1 of 3 sodium-channel blockers used to perform a challenge study. It displays use-dependence whereby it blocks voltage-gated sodium channels at higher rates of

depolarization.^{2,3} This display makes flecainide especially effective at unmasking the Brugada phenotype at higher heart rates, such as during exercise. Clinically, this unmasking could allow for the development of exercise stress test protocols that use flecainide to identify provokable BrS. Clinicians should carefully evaluate for early repolarization before initiating flecainide, as this medication may have tragic consequences in patients with undiagnosed BrS.

The pathophysiology of BrS explains the efficacy of sodium-channel blockade in unmasking characteristic ECG patterns. According to the repolarization theory, the characteristic ST-

segment elevation in BrS results from a transmural voltage gradient between the endo- and epicardium of the right ventricular outflow tract.¹ This gradient is due to an enhanced I_{to} -mediated action potential notch and loss of action potential dome in the epicardium. This loss can result from any underlying mechanism that decreases inward current or increases outward current. Sodium-channel blockers temporarily reduce inward sodium current to unmask BrS ECG patterns. Furthermore, enhanced sodium-channel inactivation is one mechanism of reduced inward current in inherited BrS.⁴ At higher body temperatures, such as during exercise stress testing, inactivation is further accentuated due to channel-gating kinetics.¹ As flecainide blockade normally increases after sodium-channel inactivation, this process becomes enhanced in this case to effectively unmask BrS ECG patterns. It has also been shown that calcium-channel blockade can contribute to unmasking of BrS ECG patterns by reducing inward calcium current.⁵ In this case, it is possible that diltiazem may have further contributed to unmasking the BrS ECG pattern.

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Disclosures

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Supplementary Material

To access the supplementary material accompanying this article, visit *CJC Open* at <https://www.cjcopen.ca/> and at doi:10.1016/j.cjco.2021.04.001.