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CASE SERIES
Arrhythmias/electrophysiology

Provocative testing using low dose oral flecainide for diagnosis of Brugada syndrome: a report of two cases

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Background Brugada syndrome (BrS) is a genetic disease characterized by coved ST-segment elevation in the right precordial leads that predispose to life-threatening ventricular tachyarrhythmia. The electrocardiographic signature is dynamic and often concealed but can be unmasked by potent sodium channel blockers such as Flecainide. Some studies have evaluated the effectivity of oral Flecainide 400 mg for provocative testing, but clinical utility of lower dose Flecainide (300 mg) has never been documented.

Case summary These two cases illustrate the effectiveness of low dose oral Flecainide to unmask Brugada electrocardiographic pattern. In our patients, diagnostic type 1 electrocardiography started to develop 30 min after drug administration and reached maximal positivity at 3.5–4.5 h. No atrioventricular block or ventricular arrhythmia was observed during the procedures.

Discussion A potent sodium channel blocker facilitates marked reduction of the right ventricle epicardial action potential, which creates a transmural voltage dispersion and manifests as an ST elevation in the right precordial leads. Time to positivity was comparably rapid, and time to maximal ST-elevation appeared close to peak plasma level of Flecainide (ranging from 1 to 6 h). Although asymptomatic patients have a low rate of adverse cardiac events, it is crucial to inform patients to avoid various modulators and precipitating factors that could trigger malignant arrhythmias.

Keywords Brugada syndrome • Flecainide challenge test • electrocardiogram • case series

ESC Curriculum 5.8 Cardiac ion channel dysfunction • 5.6 Ventricular arrhythmia

Learning points

- Electrocardiographic pattern of Brugada syndrome is often concealed and can be unmasked by potent sodium channel blocker.
- Drug challenge using low dose oral Flecainide (300 mg) is a reasonable alternative method for diagnosing Brugada syndrome.

Introduction

Brugada syndrome (BrS) is a genetic disease characterized by coved ST-segment elevation (STE) in the right precordial leads (V1 to V2) that predispose to life-threatening ventricular tachyarrhythmia and sudden cardiac death. The electrocardiographic signature is dynamic and often concealed but can be unmasked by potent sodium channel blockers such as intravenous Ajmaline and Flecainide.[1] However, usage of these drugs is limited due to their non-availability, including in our country. The second consensus of BrS recommended that the

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only oral drug for this test was Flecainide 400 mg but with limited evidence.[2] Dubner *et al.*[3] reported that typical coved-type electrocardiography (ECG) was unmasked in 7 of 14 patients (50%) who underwent a Flecainide challenge test (FCT). Similarly, Prasad *et al.*[4] (2016) performed the test on 25 patients, and 14 patients (56%) were positive. Recent consensus recommended a lower dose of oral Flecainide (200–300 mg) for provocative testing in patients suggestive of BrS.[5] However, their clinical utility has never been reported in the literature, and there has been no standard protocol for FCT using oral preparation. This report presents two asymptomatic young males suspected with BrS who underwent drug challenge using oral Flecainide 300 mg with serial ECG changes during the test.

Timeline

Patient	1	2
Symptoms	Asymptomatic	Asymptomatic
Family history of sudden cardiac death	None	None
Baseline ECG	Saddleback ST-elevation (Type 2 Brugada)	Mild coved ST-elevation
ECG changes during Flecainide challenge test	Coved ST-elevation developed in lead V1–V3 30 min after drug administration Maximal ST elevation (11 mm) in V1 was attained at 3.5 h	Coved ST-elevation generated in lead V1 30 min after drug delivery Maximal ST elevation (3 mm) in V1 was displayed at 4.5 h
Test Interpretation	Positive	Positive
Adverse event during Flecainide challenge test	None	None

Case presentation

Patient 1

A 21-year-old asymptomatic man was referred to the outpatient clinic for evaluation of his ECG. He had no history of palpitations, dizziness, or syncope and was not receiving any drugs. There was no history of heart disease or sudden cardiac death (SCD) among the patient's family members. The physical examination was unremarkable, with a body weight of 57 kg. Blood count, biochemistry, electrolytes, and echocardiography were normal. Standard 12-lead ECG displayed saddle-back type STE in lead V2 suggestive of Brugada type 2 pattern with a PR interval of 160 ms, QRS duration of 80 ms, and corrected QT interval (cQT) (Bazett formula) of 398 ms (*Figure 1*).

We performed provocative testing using oral Flecainide to clarify the diagnosis (the oral FCT protocol is available in the Supplementary material online). The test was conducted in the hospital in a setting fully equipped for cardiopulmonary resuscitation. A single oral dose of Flecainide 300 mg was administered, and isoprenaline was prepared as an antidote. The test was closely monitored with continuous ECG monitoring over 24 h. Resting 12-lead ECG with standard lead [typically placed 12-lead ECG with V1 and V2 located in the 4th intercostal (ICS)] and upper right lead (one ICS above normal with V1 and V2 placed in the 3rd ICS) (*Figure 2*) were performed at 15, 30, 60, and 90 min, hourly (first 6 h), and then every 2 h until the end of the procedure (24 h). The test result was positive with coved STE developed in leads V1–V3 30 min after drug administration and reached maximal positivity at 3.5 h with ST-elevation 11 mm in V1 with a PR interval of 180 ms, QRS duration of 124 ms, and cQT interval of 525 ms (*Figure 3*). The patient did not have any symptoms during the procedure, and no episode of major atrioventricular (AV) block or atrial or ventricular tachyarrhythmia was observed. After 24 h, he was discharged from the hospital.

The patient had a dynamic ECG at the basal condition with a type 2 Brugada pattern found at the first visit (*Figure 1*) but disappeared at the second visit (0 min in *Figure 3*). An inducible type 1 was exhibited in V1 and V2 after administration of oral Flecainide and thus met the diagnostic criteria of BrS. Asymptomatic patients with type 1 ECG appeared only after drug challenge do not need any specific treatment.[5] The patient was educated on lifestyle modifications to prevent arrhythmia, including avoidance of drugs that can trigger arrhythmia, the importance of seeking prompt treatment during febrile illness, and avoidance of excessive alcohol intake. Competitive sport is not prohibited, but exercise-related hyperthermia, dehydration, and electrolyte disturbances should be avoided. All his first-degree relatives were encouraged to undergo family screening, including at least a clinical evaluation and ECG examination. Genetic testing is unavailable in our country. The patient did not report any symptoms until now (3 months later).

Patient 2

A 28-year-old asymptomatic man came to our clinic for a medical checkup. He did not consume any drugs and had no family history of sudden death or cardiac disease. Physical examination was normal, with a body weight of 62 kg. Blood analysis, biochemistry, and echocardiography revealed no abnormalities. Baseline ECG showed mild coved STE (1.5 mm) in lead V1 suggestive of the Brugada pattern with a PR interval of 180 ms, QRS duration of 100 ms, and cQT interval of 412 ms (*Figure 4*). We performed FCT to confirm the diagnosis with a similar protocol demonstrated in the first patient. After Flecainide administration, coved STE developed in lead V1 at 30 min and reached maximal positivity at 4.5 h with ECG displaying STE 3 mm in V1, PR interval of 200 ms, QRS duration of 120 ms, and cQT of 436 ms. The coved STE pattern was more prominent in the upper right-sided lead (*Figure 5*). The patient did not have any symptoms during the test, and there were no episodes of AV block or tachyarrhythmia. He was discharged after 24 h and did not report any cardiac events during follow-up (2 months after the test).

During the test, a typical ECG pattern was demonstrated only in lead V1 in the standard position (4th ICS). It became more significant in the upper-right lead position (3rd ICS), demonstrating that superior lead placement could increase the sensitivity of detecting a typical Brugada ECG pattern. Lifestyle modification and family screening were also instructed to the patient.

Discussion

Provocative testing using sodium channel blocker is indicated in patients displaying abnormal ECG suggestive of Brugada pattern but not spontaneous coved type 1 under baseline conditions.[6] Ajmaline, a class IA antiarrhythmic agent, is recommended the first option when performing the test,[7] but the main problem is its availability. Our centre does not have intravenous ajmaline and Flecainide, and therefore, we started to use oral Flecainide 300 mg as recommended by the current expert consensus.

Flecainide is an antiarrhythmic drug class IC that strongly inhibits peak inward sodium current (I_{Na}). In addition, Flecainide also inhibits the late

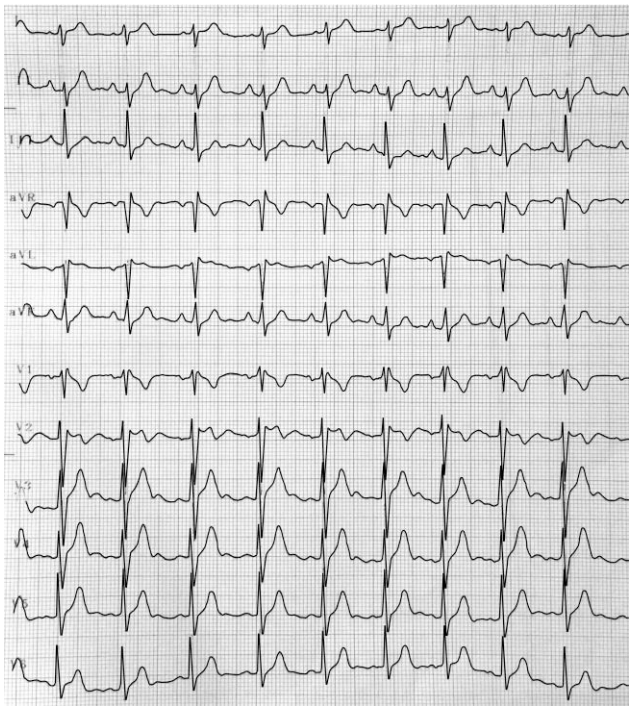

Figure 1 Baseline electrocardiography of the first patient. Baseline electrocardiography revealed a type 2 Brugada pattern. Electrocardiography leads were placed in a normal position.

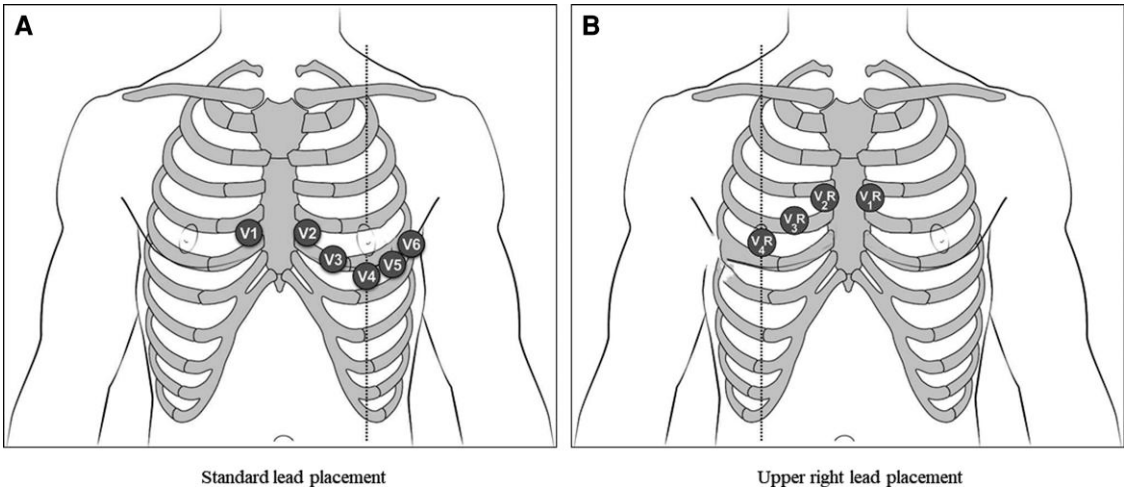

Figure 2 Precordial lead placements. Precordial lead placements in standard position (typically placed 12-lead electrocardiography with V1 and V2 located in the 4th intercostal) (*A*), and upper right lead (one intercostal space above normal with V1 and V2 placed in the 3rd intercostal) (*B*).

I_{Na}, delayed rectifier potassium (K+) current, transient outward current I_{to}, and the ryanodine receptor. Potent sodium channel blocker mediates the loss of epicardial action dome and marked reduction of the epicardial action potential, creating a transmural voltage gradient in the right ventricle and manifesting as an STE in the right precordial leads.[1,8]

We attained ECG recording in the regular and upper right lead (one ICS above normal) to increase the test's sensitivity. Provocative testing is considered positive when coved type ST elevation at least 2 mm developed in at least one right precordial lead (V1 and V2) positioned in the 2nd, 3rd or 4th ICS.[5] In our patients, coved ST elevation developed at 30 min after drug administration, which was relatively rapid compared to the time to positivity of provocative testing using intravenous Flecainide reported by Calvo *et al.*,[9] who demonstrated that majority of induced type I ECG

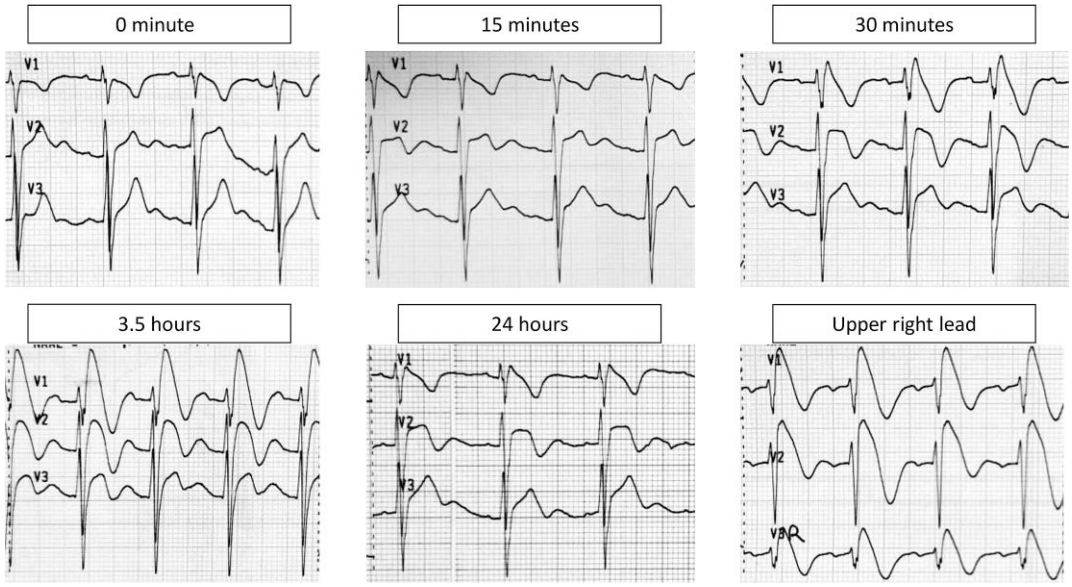

Figure 3 Serial electrocardiography of the first patient during drug challenge. Electrocardiography changes recorded at a standard lead position were shown. Coved ST-elevation developed at 30 min after drug administration and reached maximal positivity at 3.5 h. The typical Brugada pattern was more prominent at the upper right placement, as shown in the last picture.

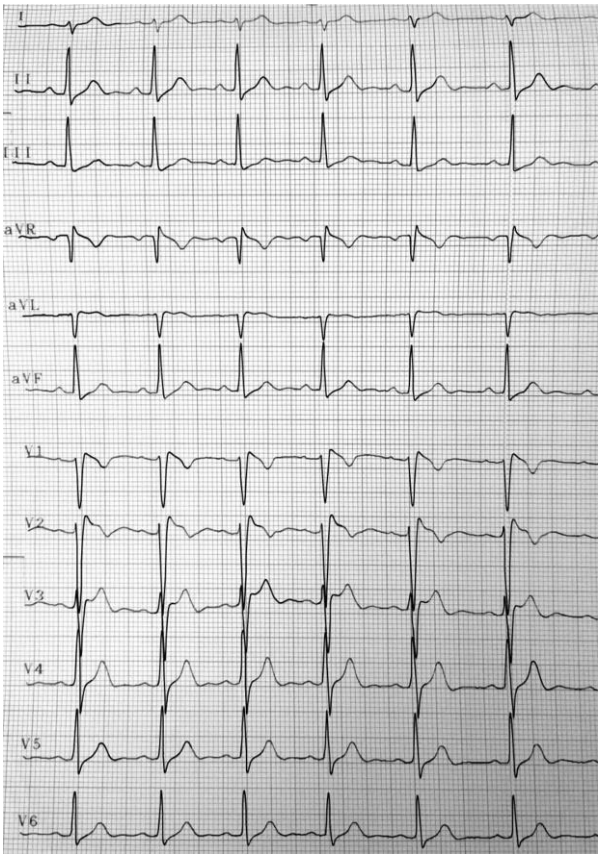

Figure 4 Baseline electrocardiography of the second patient. Baseline electrocardiography showed mild coved ST elevation in lead V1. Electrocardiography leads were placed in a normal position.

pattern was observed during the first 30 min of the test (ranging from 10 to 90 min). Maximal ST elevation was identified at 3.5 h in the first patient and 4.5 h in the second patient, which seemed close to Flecainide peak plasma level (between 1 and 6 h).[10]

Regarding elimination half-life, oral Flecainide has a longer plasma half-life than intravenous preparation, with a mean half-life of 13 h (range 7 to 22 h) and 11 h (range 7 to 15 h), respectively.[10,11] Earlier study of provocative testing with oral Flecainide 400 mg proposed ECG monitoring for 24 h after drug administration, and there were no adverse events reported in the study.[3] We adopted the protocol and performed monitoring for ECG changes, arrhythmias and hemodynamic parameters over 24 h. At the end of the test, the ECG of both patients showed that coved ST elevation in V1 did not completely resolve, implying that oral Flecainide (300 mg) may have a relatively rapid onset (30 min) but a longer offset compared to intravenous preparation. However, there were no episodes of AV block or tachyarrhythmia observed during the procedure, and patients were discharged without symptoms during follow-up. Previous studies of the intravenous Flecainide test indicate that the incidence of adverse events during the test is low and emerges during drug infusion. No late-onset arrhythmic events were observed.[12,13]

There have been no clear-cut recommendations for risk stratification in asymptomatic patients and only displaying type 1 Brugada ECG after drug challenge. The risk of an arrhythmic event in asymptomatic patients is low, with an annual incidence rate of 0.5% per year and higher arrhythmic events in men than in women.[14] Long-term follow-ups should be considered in patients with BrS as symptoms and SCD usually occur later in life (age ± 40 years) with >300 times higher risk of SCD than in matched population.[15]

Lifestyle changes for the prevention of arrhythmias are essential. All BrS patients should be informed of the various modulators and precipitating factors that could induce malignant arrhythmias, including fever and excessive alcohol intake. Several drugs may aggravate ST elevation and provoke arrhythmic events (as described at www.brugadadrugs.org) and should be avoided. Regarding family members, all patient's first

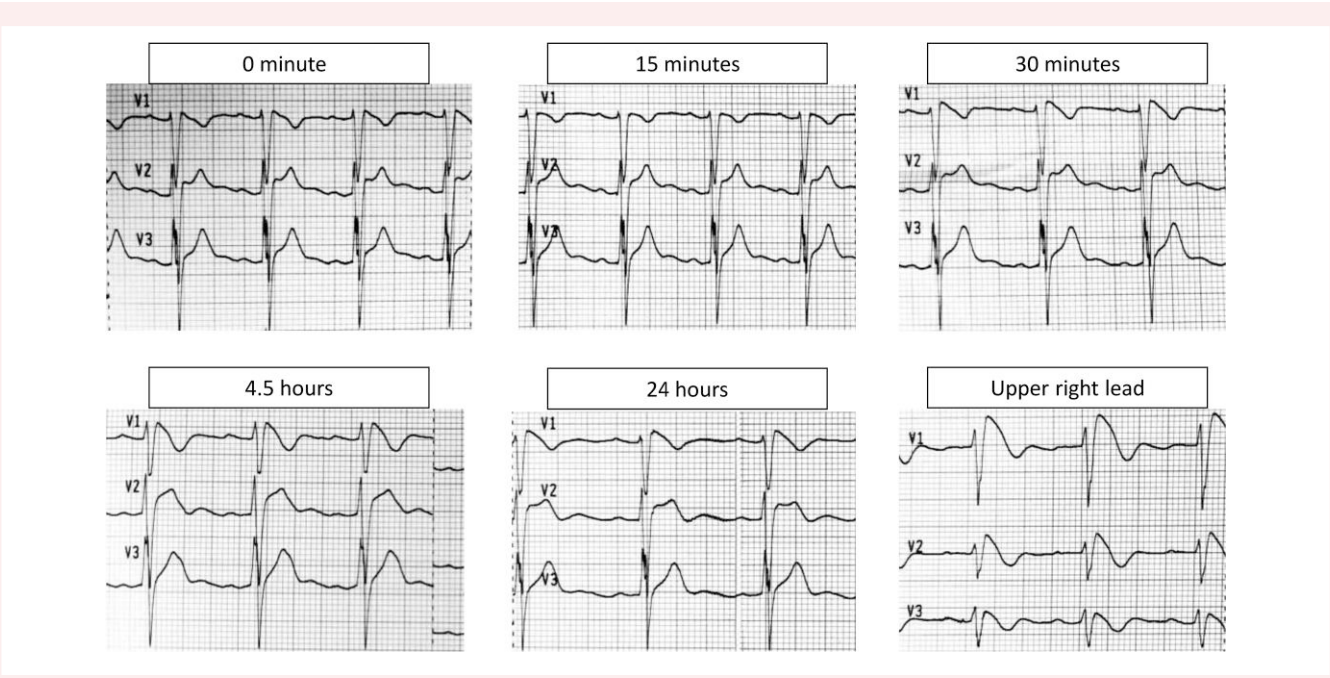

Figure 5 Serial electrocardiography of the second patient during drug challenge. Serial electrocardiography changes recorded at the standard lead position were displayed. Coved ST elevation was appeared in V1 at 30 min after drug administration and reached peak positivity at 4.5 h. The last picture showed that the electrocardiography pattern was more significant during lead placement at the upper right position.

degree relatives should undergo a clinical evaluation, ECG examination, and genetic testing if feasible.[5,15]

Conclusions

This case series supports using low dose oral Flecainide (300 mg) as an effective alternative method to unmask type 1 Brugada electrocardiographic pattern when intravenous drug preparations are not available. We recommend conducting the test under full supervision and continuous 24 h ECG monitoring.

Lead author biography

Muzakkir Amir was born on 10 August 1971. He has been working as a cardiac electrophysiologist since 2014 at cardiac centre Dr Wahidin Sudirohusodo hospital, Makassar, Indonesia. He also gained fellowship in interventional cardiology at Chongqing medical university China in 2011. Currently, he is a director of Cardiology Training Program at Medical Faculty of Hasanuddin University, Indonesia.

Supplementary material

Supplementary material (oral flecainide challenge test protocol) is available at *European Heart Journal—Case Reports* online.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The authors confirm that written consent for submission and publication of this case report, including images and associated text, has been obtained from the patient in line with COPE guidance.

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