ESC European Society of Cardiology

European Heart Journal - Case Reports (2021) **5**(11), 1–5
https://doi.org/10.1093/ehjcr/ytab454

CASE REPORT
Arrhythmias / Electrophysiology

Ventricular fibrillation arrest due to Brugada syndrome in a coronavirus disease 2019 patient with negative procainamide challenge: a case report

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Received 10 June 2021; first decision 5 July 2021; accepted 25 October 2021; online publish-ahead-of-print 8 November 2021

Background Pharmacologic challenge test is often used to diagnose Brugada syndrome (BrS) when spontaneous electrocardiograms (ECG) do not show type I Brugada pattern but reported sensitivity varies. The role of the exercise stress test in diagnosing Brugada syndrome is not well-established.

Case summary A patient had a type I Brugada pattern ECG during the recovery phase of exercise stress test but had a negative procainamide challenge test. He had a loop recorder implanted and later survived a ventricular fibrillation (VF) arrest provoked by coronavirus disease 2019 (COVID-19). Electrocardiogram on arrival showed type 1 Brugada pattern. He was discharged after implantable cardioverter-defibrillator implantation. He later underwent genetic testing and was found to be heterozygous for c.844C>G (p.Arg282Gly) mutation in the SCN5A gene.

Discussion Type 1 Brugada pattern ECG may be unmasked by ST-segment augmentation during recovery from exercise. Exercise stress test may play a role in the diagnosis of Brugada syndrome when suspicion for Brugada syndrome remains after a negative procainamide challenge test or if the patient has exercise-related symptoms. COVID-19 can unmask BrS and trigger a VF cardiac arrest.

Keywords Brugada syndrome • Ventricular fibrillation • COVID-19 • Procainamide challenge • Exercise stress test • Case report

ESC Curriculum 5.1 Palpitations • 5.6 Ventricular arrhythmia

Learning points

- Type 1 Brugada pattern electrocardiogram may be unmasked by ST-segment augmentation during recovery from exercise.
- Exercise stress testing may be considered when suspicion for Brugada syndrome remains after a negative procainamide challenge test, especially if there are exercise-related symptoms.
- Coronavirus disease 2019 can unmask Brugada syndrome and precipitate ventricular fibrillation cardiac arrest.

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Handling Editor: Belinda Gray
Peer-reviewers: Efstatios Papatheodorou; Chris Miles
Compliance Editor: Stefan Simovic
Supplementary Material Editor: Mariame Chakir

Introduction

Brugada syndrome (BrS) is characterized by typical electrocardiogram (ECG) patterns and associated with sudden cardiac death. Though type I Brugada pattern or coved ST-segment elevation ≥0.2 mV followed by inverted T wave in more than one right precordial leads (V1–V3) is considered diagnostic of BrS, the diagnosis can be challenging due to the lack of a 'gold standard' diagnostic test. The Shanghai BrS Score, a scoring system incorporating ECG, clinical history, family history, and genetic test result has been proposed by some experts to facilitate diagnosis and risk stratification.[1] Pharmacologic challenge test is often used to diagnose BrS when spontaneous ECGs do not show type I Brugada pattern. Here, we describe a patient who had a type I Brugada pattern ECG during the recovery phase of exercise stress test but a negative procainamide challenge test. He later survived a ventricular fibrillation arrest provoked by COVID-19.

Timeline

15 months before the presentation	**Patient referred for palpitation and pre-syncope. Unremarkable echocardiogram and 48-h Holter. Type 1 Brugada pattern was seen during recovery phase of exercise stress test.**
13 months before the presentation	Cardiac electrophysiologic test during which ventricular fibrillation (VF) was induced with ventricular triple extra-stimuli but no Brugada pattern was seen with procainamide infusion. Loop recorder implanted and no events on subsequent interrogations.
Current presentation	He survived a VF cardiac arrest in the setting of coronavirus disease 2019. Implantable cardioverter-defibrillator implanted before discharge.
3 months after presentation	Genetic testing came back heterozygous for c.844C>G (p.Arg282Gly) mutation in the SCN5A gene.

Case presentation

A 50-year-old male was referred to the cardiology office for palpitations and pre-syncope while playing ice hockey. He had no history of syncope and no significant past medical history. His father had a history of coronary artery disease, valve replacement surgery and died of 'heart attack' at age 75. His son had episodes of syncope which were thought to be vasovagal. His grandfather had a sudden death in his 50 s. His cardiovascular exam was unremarkable. Labs including complete blood count, comprehensive metabolic panel, and TSH were within normal limits. His echocardiogram did not show any structural heart disease and a 48-h Holter monitoring showed 263 single premature ventricular complexes (PVCs). He then underwent exercise ECG stress test. His baseline ECG showed sinus rhythm with incomplete right bundle branch block (*Figure 1A*). There was no ECG evidence of ischaemia at peak heart rate. However, about 3 min into recovery, his ECG showed type 1 Brugada pattern (*Figure 1B*) which returned to baseline about 5 min into recovery. He also developed multifocal PVCs including couplets and 3 beats of monomorphic ventricular tachycardias (VTs) (*Figure 1C*). The patient was referred to an electrophysiologist. He underwent an electrophysiology (EP) study with procainamide challenge. High lead positioning of V1 and V2 in the second intercostal space was used during the EP study. Ventricular fibrillation was induced with triple ventricular extra-stimuli in the basal state but no Brugada pattern was seen with procainamide infusion (850 mg/10 min). He had a loop recorder implanted after the EP study and was followed by cardiology without a documented arrhythmia. About a year later, he had coronavirus disease 2019 (COVID-19) exposure and felt unwell for 2 days. He then had a cardiac arrest at home and was successfully resuscitated. On exam, he was afebrile, intubated, and non-responsive to pain with reactive pupils. Heart sound was irregular at 122/min without murmurs and he had crackles bilaterally. His ECG on arrival showed atrial fibrillation with type I Brugada pattern (*Figure 2*) and interrogation of his loop recorder showed ventricular fibrillation (VF) at the time of the arrest (*Figure 3*). Initial labs showed leucocytosis of 22.3 × 10^9/L, creatinine of 1.85 mg/dL, high-sensitive troponin T of 3904 ng/L, C-reactive protein of 10.4 mg/L, and D-dimer of 18 440 ng/mL. Electrolytes including calcium and magnesium were normal. A coronary angiogram showed non-obstructive coronary artery disease. PCR for SARS-CoV-2 was positive and his chest X-ray was consistent with COVID-19 pneumonia. Echocardiogram on presentation showed severely reduced left ventricular ejection fraction which recovered to normal in 2 weeks. He had a good neurologic recovery and underwent a dual-chamber implantable cardioverter-defibrillator (ICD) implantation prior to discharge. He later underwent genetic testing and was found to be heterozygous for c.844C>G (p.Arg282Gly) mutation in the SCN5A gene. The patient continued to do well on follow-up 3 months later and underwent genetic counselling with plans to test his children for the same mutation.

Discussion

Brugada syndrome is usually autosomal dominant and is most commonly associated with mutations in SCN5A, the gene coding for the alpha subunit of the cardiac sodium channel. However, mutations in SCN5A were identified in less than 30% of patients.[2]

Although pharmacologic challenge test has traditionally been used to diagnose BrS when spontaneous ECGs do not show typical Brugada pattern, reported sensitivity and reproducibility of the test varies.[3,4] Among the Class I anti-arrhythmics used for provocative testing, procainamide in particular has been associated with a lower sensitivity[4] but is nonetheless the most commonly used one in the United States due to its availability in intravenous form.[5] High ECG lead positioning in the second and third interspaces during provocative testing has been used to increase the sensitivity.[6]

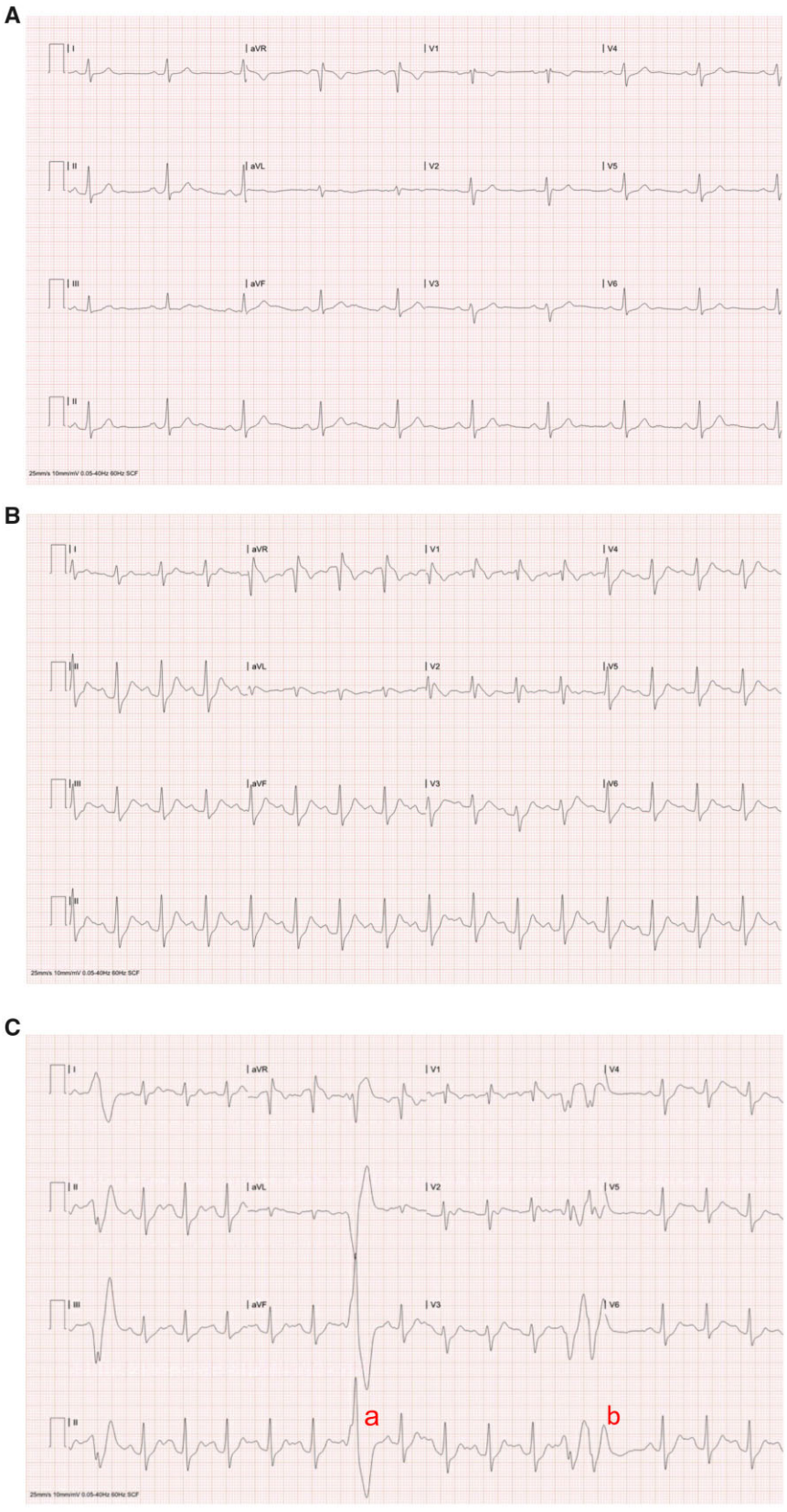

Figure 1 (*A*) Baseline electrocardiogram showing incomplete right bundle brunch block. (*B*) Electrocardiogram 3 min into recovery phase of exercise stress test showing ≥2 mV coved ST-elevation with T-wave inversion in lead V1 and V2 consistent with Brugada type I pattern. Inverse Brugada pattern can be seen in lead III and aVF. (*C*) electrocardiogram 3–4 min into recovery phase of exercise stress test showing premature ventricular complexes of two different morphologies (*A*, *B*). He also had 3-beats of ventricular tachycardias of the second morphology.

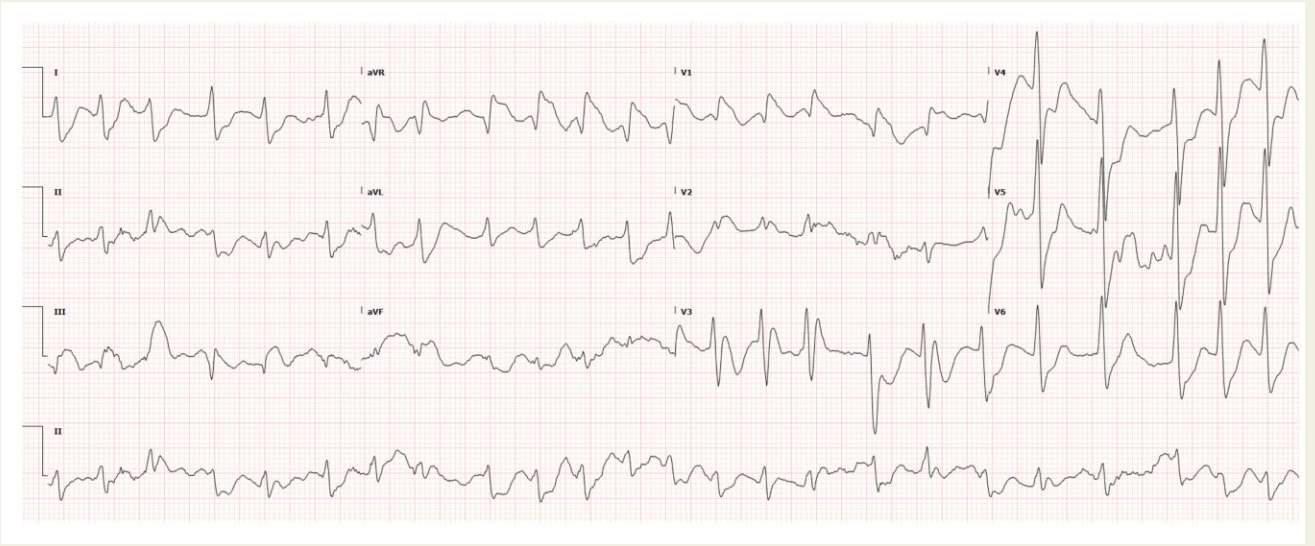

Figure 2 Electrocardiogram on arrival after successful resuscitation of out-of-hospital ventricular fibrillation cardiac arrest showing type I Brugada pattern (coved ST-elevation ≥2 cm with T-wave inversion in lead aVR, V1, and V2).

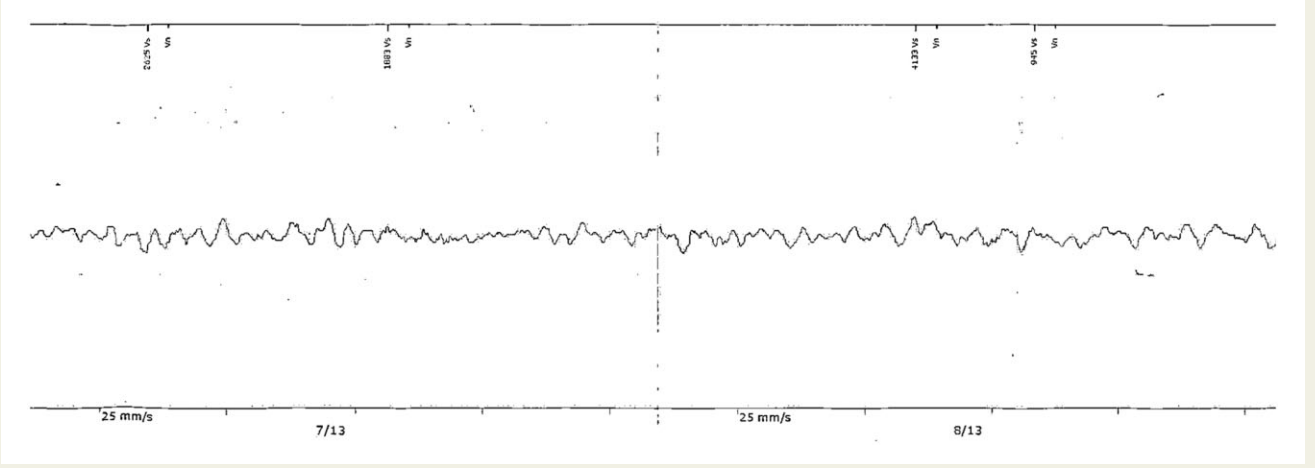

Figure 3 Interrogation of the patient's implanted loop recorder showed ventricular fibrillation at the time of the cardiac arrest.

The role of exercise stress testing in BrS is not clearly defined. Augmentation of ST-segment elevation during the recovery phase of exercise stress test can unmask type I Brudaga pattern ECGs, likely due to increased parasympathetic activity.[7] In one study of a group of 93 BrS patients, ST-segment augmentation of >0.05 mV during recovery from exercise was seen in 34 (37%) but in none of the 102 healthy controls and its presence was predictive of future cardiac events.[8] In our patient, the type 1 Brugada pattern ECG during recovery from exercise could have been considered both diagnostic for BrS and counted as a risk factor for future events. The subsequent negative procainamide infusion test was of unclear significance. Polymorphic PVCs and ventricular triplets seen during recovery from exercise also raise concern that ventricular arrhythmias might have been responsible for the patient's initial symptoms. Given the potential information exercise stress tests can offer, their low cost and wide availability, it may be reasonable to consider exercise stress testing when suspicion for BrS remains after a negative procainamide challenge or if the patient has exercise-related symptoms. More studies are needed on the sensitivity of stress test for the diagnosis of BrS.

Electrophysiology study may help risk-stratify patients with asymptomatic BrS. Inducible polymorphic VT or VF in EP study is associated with a higher risk for sudden cardiac death for patient with BrS, however, the inclusion of triple extra-stimuli decreases the specificity.[6] The 2017 AHA/ACC/HRS guideline-recommended consideration of EP study with programmed ventricular stimulation using single and double extra-stimuli for risk-stratification of patients with asymptomatic BrS and shared decision-making regarding ICD.[6] In our patient, although VF was induced, the fact it was only induced with triple extra-stimuli made the result less specific.

The role of genetic testing in diagnosis and risk stratification of BrS is unclear given limited sensitivity and specificity,[9,10] and poor correlation between genotype and adverse events.[11] The 2017 AHA/ACC/HRS guideline recommended the use of genetic testing for BrS only for cascade screening of relatives.[6]

Fever has been known to trigger ventricular arrhythmias in BrS[12] and COVID-19 has been reported to have unmasked BrS in case reports.[13] Coronavirus disease 2019 or fever likely have triggered the VF cardiac arrest in our patient. Regional registries have showed increased out-of-hospital cardiac arrests coinciding with local COVID-19 outbreaks.[14] More studies are needed to study the relationship between COVID-19 and sudden cardiac death.

Conclusions

Exercise stress testing is widely available and should be considered as an adjunctive test for diagnosis of BrS when pharmacologic challenge test is negative but clinical suspicion remains, especially when the patient has exercise-related symptoms.

Lead author biography

Dr Guangchen Zou obtained both Bachelor of Medicine and Doctor of Medicine degrees at Shanghai Jiao Tong University School of Medicine in Shanghai, China where he worked on research into catheter ablation of cardiac arrhythmias at Shanghai Chest Hospital. He is now an internal medicine resident at Danbury Hospital in Connecticut, USA.

Supplementary material

Supplementary material is available at *European Heart Journal—Case Reports* online.

Slide sets: A fully edited slide set detailing these cases 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.

Conflict of interest: None declared.

Funding : None declared.

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