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INTERMEDIATE

CASE REPORT: CLINICAL CASE

Recurrent Cardiac Arrest With Negative Stress Test

An Unusual Presentation of Catecholaminergic Polymorphic Ventricular Tachycardia

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ABSTRACT

Catecholaminergic polymorphic ventricular tachycardia is a genetic disorder that causes ventricular tachyarrhythmias via increased release of intracellular calcium. The standard diagnostic measure is an exercise stress test that reveals ventricular ectopy. We present an extraordinary case marked by a normal stress test and no relation to exertion. (**Level of Difficulty: Intermediate.**) (J Am Coll Cardiol Case Rep 2020;2:1178–81) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

A 19-year-old male budding politician experienced sudden cardiac arrest (SCA) after a speech for student council. He had returned to his seat when he lost consciousness. Bystanders started cardiopulmonary resuscitation, and an automated external defibrillator delivered a shock, which restored circulation. He was transported to a hospital, where he was bradycardic in the 50s. Other vital signs were within normal limits. Examination revealed no acute abnormalities. The patient could not recount the moments surrounding the end of his speech. According to the patient and his family, this was the first occurrence of SCA in his life. He played football in middle school and was engaged in regular strenuous activity at the time, including playing basketball and running every other day. He reported occasional subjective palpitations at rest but had never experienced dizziness, syncope, chest pain, or shortness of breath at rest or during exertion. Family history was also negative.

LEARNING OBJECTIVES

- To recognize that CPVT can occur sporadically. Genetic analysis may be warranted even in the absence of family history.
- To recognize that neither a negative treadmill test nor lack of symptoms upon exertion rule out CPVT.
- To understand that nadolol is the preferred initial medication for the management of CPVT. Add flecainide if the patient has a history of SCA.

MEDICAL HISTORY

The patient had no previously known conditions.

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DIFFERENTIAL DIAGNOSIS

When significant structural abnormalities are excluded, SCA is often due to familial syndromes such as arrhythmogenic right-ventricular cardiomyopathy (ARVC), Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia (CPVT), Wolff-Parkinson-White (WPW) syndrome, and long QT syndrome (LQTS). These can be differentiated though not definitively excluded by electrocardiography (ECG), imaging, and genetic tests.

INVESTIGATIONS

There were no significant electrolyte abnormalities. ECG showed sinus bradycardia with a PR interval of 160 ms and QTC of 420 ms. Results of echocardiography were normal; there was no evidence of hypertrophic cardiomyopathy, dilated cardiomyopathy, valvular disease, or other structural disease. Exercise ECG with nuclear perfusion imaging stress test (maximum heart rate 179 beats/min, total mileage 0.6) did not show significant ventricular arrhythmias or inducible ischemia. Coronary angiogram revealed a small left-anterior descending myocardial bridge. However, it was not seen on cardiac magnetic resonance imaging, which, additionally, did not show delayed enhancement, evidence of infiltrative disease, or ARVC.

MANAGEMENT

Bisoprolol was started, and a dual chamber implantable cardioverter-defibrillator (ICD) was placed. He recovered well and was discharged.

DISEASE COURSE

Seven months later, SCA recurred in similar fashion to the first event. The patient had just spoken at a Model United Nations gathering. He felt palpitations, then experienced cardiac arrest, resuscitated by ICD shock. Device interrogation exposed sinus tachycardia at 150 beats/min, followed by an episode of polymorphic ventricular tachycardia (VT)/ventricular fibrillation (VF) as shown in **Figure 1**, appropriately aborted by the ICD. Treadmill testing was repeated. As before, there were no QT prolongation, ischemia, or high premature ventricular contraction (PVC) burden. Maximum heart rate achieved was 128 beats/min. Medical management was adjusted from bisoprolol to nadolol and flecainide. Genetic analysis unveiled a heterozygous p. R420W mutation in the RYR2 gene, diagnostic of CPVT.

DISCUSSION

In CPVT, a gain of function mutation in myocardial calcium release channels results in excess intracellular calcium in response to catecholamines (**Figure 2**). This can cause ventricular after-depolarizations, with subsequent VF or VT (polymorphic and bidirectional). Syncope and SCA most often occur with exertion, less often with emotional stress; in up to 27% of cases normal activity is the trigger (1,2). Indeed, the preferred diagnostic modality is an exercise stress test, which shows PVCs and or VT with increasing effort in up to 80% of symptomatic patients (3). In the pursuit of a diagnosis, an electrophysiology study with epinephrine was not used because it was unlikely to provide additional information. This patient achieved heart rates above that at which PVCs were expected to be seen. Current guidelines advise that electrophysiology studies are not indicated in these patients (4).

The possible myocardial bridge was considered as a potential cause of SCA, but this was considered unlikely given his asymptomatic historical and ongoing athletic history, lack of inducible ischemia on the treadmill, and the clinically low association of myocardial bridging with ischemia in general. The demonstrated RYR2 mutation suggests CPVT as the likely etiology of recurrent SCA in this case despite the lack of family history and negative results of the treadmill test.

Although arrhythmogenic genetic disorders such as CPVT are often thought of as familial illnesses, studies show that mutations sporadically occur in the RYR2 gene in about 20% to 50% of cases (2). Furthermore, incomplete penetrance and expressivity have been noted, including with the RYR2-R420W variant of CPVT, which this patient had (1). Therefore, lack of family history of palpitations, exertional syncope, or cardiac arrest does not preclude this diagnosis or render genetic analysis unnecessary. A positive family history is only found in 30% of cases (2).

Current scientific knowledge supports the management of CPVT with medications and, in some cases, placement of ICD. Beta blockers are the mainstay of medical therapy (5). Nadolol is known to be superior to beta-1 selective blockers (5). Leren et al. found that, compared with no treatment and beta-1 selective blockers, nadolol reduces both the occurrence and severity of ventricular arrythmias. Beta-1

ABBREVIATIONS AND ACRONYMS

ARVC = arrhythmogenic right ventricular cardiomyopathy

CPVT = catecholaminergic polymorphic ventricular tachycardia

ECG = electrocardiography

ICD = implantable cardioverter defibrillator

LQTS = long QT syndrome

PVC = premature ventricular contraction

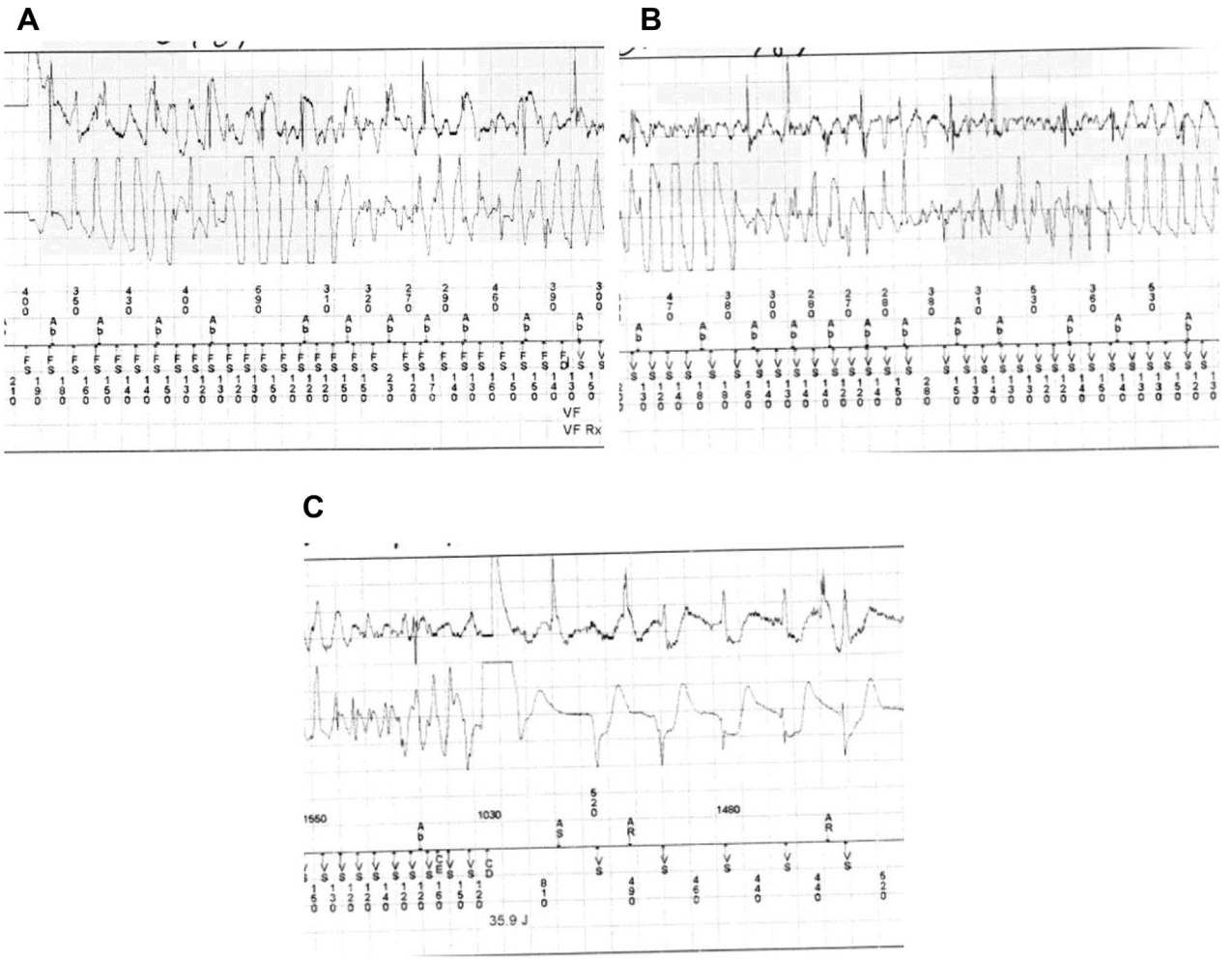
SCA = sudden cardiac arrest

VF = ventricular fibrillation

VT = ventricular tachycardia

WPW = Wolff-Parkinson-White

FIGURE 1 Rhythm Strip



(A to C) Polymorphic VT/VF terminated by a 36 Joule shock

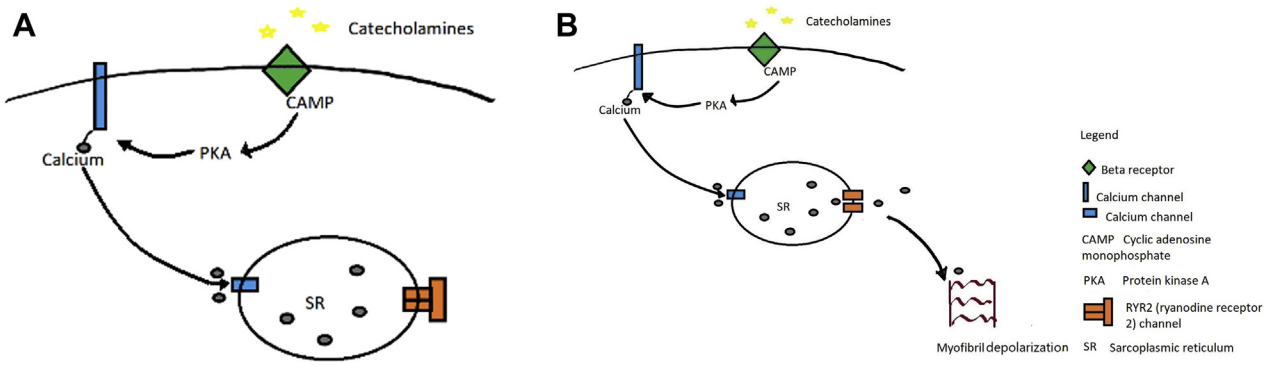
selective blockers, on the other hand, did not demonstrate a significant difference in events when compared with no treatment (6). Flecainide, which suppresses the release of excess calcium, can be used as additional therapy (7). When added to a beta-blocker, it has been shown to decrease exercise-induced ventricular arrythmias in patients with CPVT (7,8). The 2013 Heart Rhythm Society/European Heart Rhythm Society/Asia Pacific Heart Rhythm Society expert consensus statement recommends nadolol, flecainide, and ICD placement in patients who present with SCA. The 2017 guideline for syncope recommends the use of verapamil and left cardiac sympathetic denervation in refractory CPVT (9).

Placement of an ICD is also warranted in patients who fail medical therapy (2). This patient received a dual-chamber transvenous ICD because of his resting bradycardia, anticipated to worsen with medical treatment. He paces 94% of the time in the atrium. Despite concerns about infectious and mechanical complications, this approach is safer than subcutaneous ICD in light of the heavy beta blockade.

FOLLOW-UP

After the change in therapy, the patient has had no more incidents of SCA in a year. He was encouraged to employ yoga and meditation and avoid competitive sports. He remains interested in politics and currently plays noncompetitive sports. Despite counseling, his family is yet to pursue screening.

FIGURE 2 Function of the RYR2 Channel During Diastole



(A) Catecholamines bind to the beta receptor, which then activates calcium release into the sarcoplasmic reticulum. A normal RYR2 channel does not allow calcium release from the SR into the cytosol during diastole. **(B)** A mutated, leaky RYR2 channel allows calcium release and depolarization.

CONCLUSIONS

The diagnosis and management of CPVT require an exhaustive approach, especially in patients who do not present with classical syncope upon exertion. When strongly suspected, genetic analysis is appropriate, even if family history and traditional treadmill testing results are negative. Nadolol has been shown to be superior to beta-1 selective blockers. The addition of flecainide to nadolol is even more effective and should be considered as an option for first-line therapy.

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REFERENCES

1. Roston TM, Yuchi Z, Kannankeril PJ, et al. The clinical and genetic spectrum of catecholaminergic polymorphic ventricular tachycardia: findings from an international multicenter registry. Eurospace 2018;20:541–7.

2. Leenhardt A, Denjoy I, Guicheney P. Arrhythmogenic disorders of genetic origin. Circ Arrhythm Electrophysiol 2012;5:1044–52.

3. Sy R, Krahn A. Exercise testing: the catecholaminergic polymorphic ventricular tachycardia crystal ball? EP Europace 2012;14:1225–7.

4. Muresan L, Cismaru G, Martins RP, et al. Recommendations for the use of electrophysiological study: update 2018. Hellenic J Cardiol 2019;60:82–100.

5. Priori SG, Wilde AA, Horie M, et al. HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes. Heart Rhythm 2013;10:1932–51.

6. Leren IS, Saberniak J, Majid E, Haland TF, Edvardsen T, Haugaa KH. Nadolol decreases the incidence and severity of ventricular arrhythmias during exercise stress testing compared with β1-selective β-blockers in patients with catecholaminergic polymorphic ventricular tachycardia. Heart Rhythm 2016;13:433–40.

7. Van der Werf C, Kannankeril PJ, Sacher F, et al. Flecainide therapy reduces exercise-induced ventricular arrhythmias in patients with catecholaminergic polymorphic ventricular tachycardia. J Am Coll Cardiol 2011;57:2244–54.

8. Kannankeril PJ, Moore JP, Cerrone M, et al. Efficacy of flecainide in the treatment of catecholaminergic polymorphic ventricular tachycardia: a randomized clinical trial. JAMA Cardiol 2017;2:759–66.

9. Shen WK, Sheldon RS, Benditt DG, et al. 2017 ACC/AHA/HRS Guideline for the evaluation and management of patients with syncope. J Am Coll Cardiol 2017;70:e41–110.

KEY WORDS beta-blockers, electrophysiology, exercise, genetic disorders, palpitations, ventricular fibrillation