

Catecholaminergic Polymorphic Ventricular Tachycardia in a Patient With Recurrent Exertional Syncope

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A 16-year-old male with a prior history of recurrent syncope was referred to our hospital after being resuscitated from cardiac arrest developed while playing volleyball. His electrocardiogram (ECG) demonstrated ventricular fibrillation at a local emergency department. After referral, an ECG showed bidirectional ventricular tachycardia (VT) and nonsustained Torsade de Pointes. Two days later, his heart rate became regular, and no additional episodes of VT were observed. His ECG showed sinus rhythm with a corrected QT interval of 423 msec, and two-dimensional echocardiography was unremarkable. We made the diagnosis of a catecholaminergic polymorphic VT. However, only premature ventricular complex bigeminy was induced on exercise ECG and epinephrine infusion tests, and the patient showed no episodes of syncope. His father and mother had different missense mutations in the cardiac ryanodine receptor on genetic testing. The proband had both mutations in different alleles and was symptomatic. It was recommended that the patient avoid competitive physical activities, and a β -blocker was prescribed. (**Korean Circ J 2012;42:129-132**)

KEY WORDS: Catecholamines; Tachycardia, ventricular; Genetics; Syncope; Exercise.

Introduction

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is an inherited arrhythmogenic disease that can cause syncope or sudden cardiac death during emotional or physical stress in the absence of detectable structural heart disease and a prolonged QT interval on an electrocardiogram (ECG). Mutations in two genes, the cardiac ryanodine receptor gene (*RyR2*) and calsequestrin 2 gene (*CASQ2*), have been identified in patients with CPVT. These mutations lead to an increase in intracellular Ca^{++} concentration, resulting in life-threatening ventricular arrhythmias, possibly via delayed depolariz-

ations. Molecular genetic testing for *RyR2* and *CASQ2* is clinically available. Here, we report a case of CPVT with the identified genetic mutations.

Case

A 16-year-old male, who had suffered from recurrent episodes of syncope triggered by physical exertion was referred to our hospital after undergoing defibrillation at a local emergency department (ED). He had lost consciousness at school during a volleyball test that was also emotionally stressful. Paramedics found him pulseless and started cardiopulmonary resuscitation. An initial ECG at a local ED revealed ventricular fibrillation. Although his arrhythmia was converted to sinus rhythm after defibrillation, the patient was stuporous and had repeated episodes of nonsustained ventricular tachycardia (VT). After referral to our hospital, ECG monitoring in the ED and intensive care unit showed intermittent nonsustained VT and bidirectional VT (Fig. 1). When the patient became agitated, his heart rate increased, and the ECG showed nonsustained polymorphic VT despite intravenous administration of a β -blocker. He was sedated and placed on mechanical ventilation. Two days later, his heart rate was regular, and no additional episodes of VT were observed. Sedation was stopped, and the patient was weaned from the ventilator.

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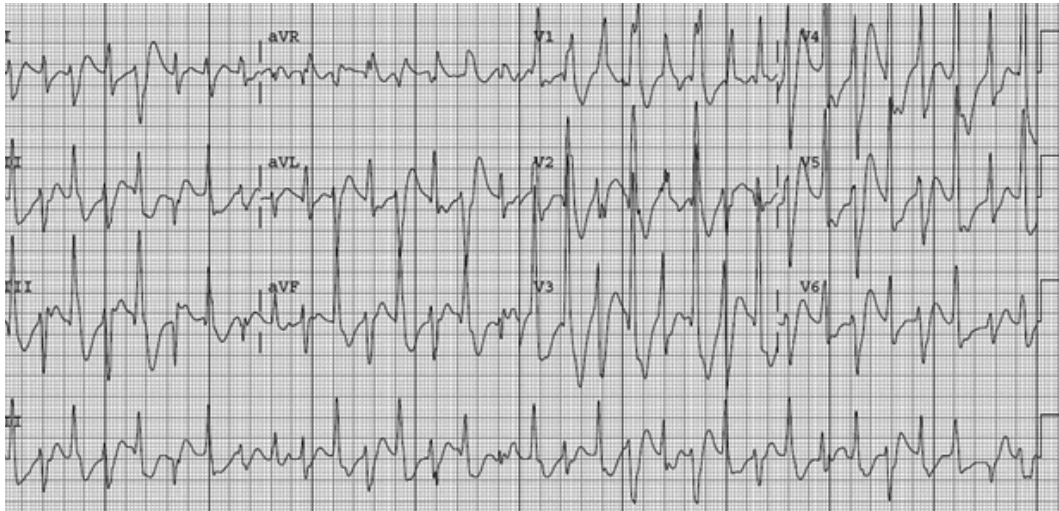


Fig. 1. Twelve-lead electrocardiogram in the coronary care unit shows bidirectional ventricular tachycardia.

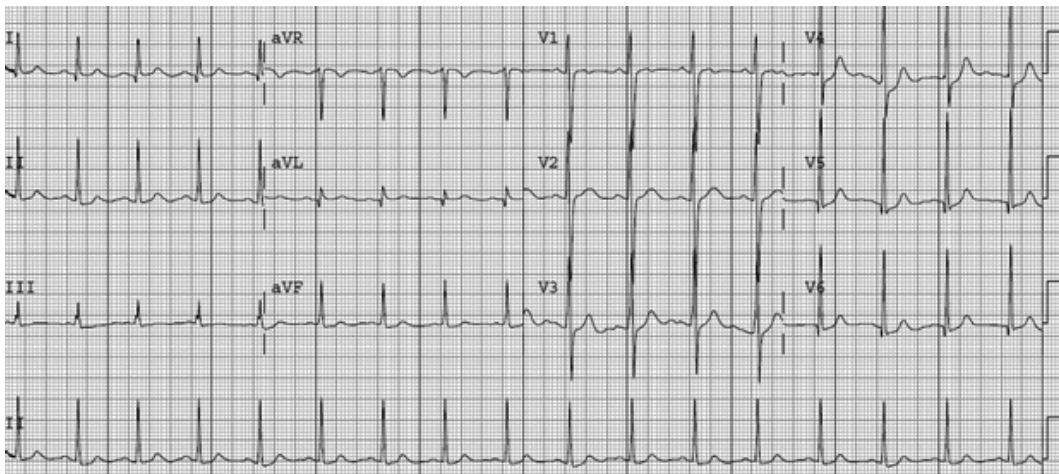


Fig. 2. Baseline electrocardiogram shows a normal sinus rhythm with a normal QT interval.

His ECG showed a sinus rhythm with a corrected QT interval of 423 msec (Fig. 2). Routine laboratory findings, including electrolytes and two-dimensional echocardiography, were unremarkable. A detailed history of the patient included several episodes of syncope since the age of 8 years associated with physical activities, such as sprinting, playing football, and fighting with a sibling. His father also experienced an episode of syncope associated with sprinting at the age of 9 years. No other family members had histories of syncope or sudden cardiac death. The patient and his family underwent a genetic analysis, and his father and mother each had one different *de novo* missense mutation in *RyR2* (exon 97 c.14009T>A p.L4670H in the father and exon 37 c.5428G>C p.V1810L in the mother). The symptomatic proband inherited both mutations. As his episodes of syncope were associated with sympathetic activation, an exercise ECG test and epinephrine infusion test (intravenous bolus of 0.1 $\mu\text{g}/\text{kg}$ followed by continuous infusion at rates of 0.1 $\mu\text{g}/\text{kg}$ per minute) were performed. However, only premature ventricular complex (PVC) bige-

miny was induced with no episodes of syncope during the exercise ECG test (Fig. 3) and epinephrine only increased his heart rate without an arrhythmia. With these clinical features, we made the diagnosis of CPVT. Atenolol (37.5 mg bid; 1.9 mg/kg/day) was prescribed, and a follow-up exercise ECG test while on the β -blocker was performed 3 days later. During the follow-up exercise ECG test, fewer PVCs were seen at peak exercise. The patient remains on 50 mg bid atenolol (2.3 mg/kg/day) and is being followed. To date, he has been free of episodes of syncope.

Discussion

Catecholaminergic polymorphic ventricular tachycardia, arrhythmogenic right ventricular cardiomyopathy, and long QT syndrome are well known causes of exercise-induced syncope that commonly manifest normal baseline ECGs.^{1,2)} Therefore, many provocation tests, including VT induction, an exercise ECG test, and epinephrine infu-

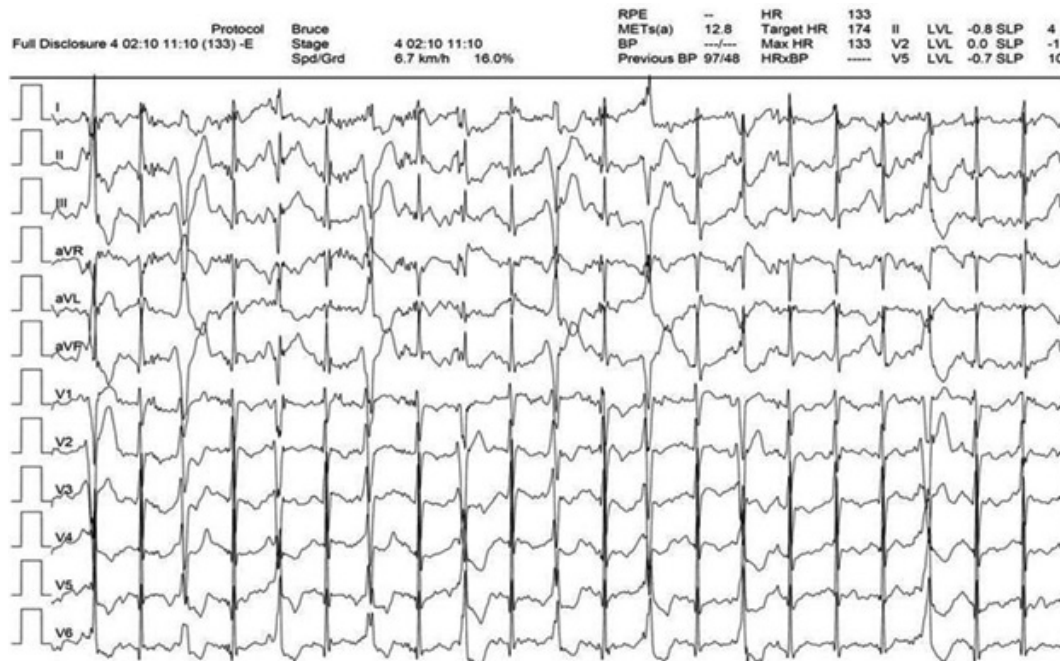


Fig. 3. Ventricular bigeminy was seen at the peak heart rate during exercise electrocardiogram testing after the patient was administered propranolol.

sion tests, have been used to diagnose exercise-induced syncope.¹⁾²⁾ Exercise-induced bidirectional VT has been considered the hallmark of CPVT for many years. However, recent studies¹⁾²⁾ have shown that ventricular bigeminy is the most common exercise-induced arrhythmia among patients with CPVT, and serious arrhythmias such as bidirectional VT and polymorphic VT are rarely induced. Therefore, exercise-induced ventricular bigeminy no longer should be considered an innocent arrhythmia, at least in suspicious cases of CPVT. Therefore, exercise ECG testing for diagnosing CPVT may be suboptimal.

Catecholaminergic polymorphic ventricular tachycardia may have both an autosomal dominant and an autosomal recessive pattern of inheritance. The more common type 1 autosomal dominant CPVT is caused by mutations in *RyR2* on chromosome 1q42-q42 and results from defective calcium release from the sarcoplasmic reticulum, which is required for myocardial contraction.³⁾ A mutation in *RyR2* can increase calcium release and cause life-threatening ventricular arrhythmias. Patients with *RyR2* mutations become symptomatic at an early age, and men are at higher risk for cardiac events.⁴⁾ In the autosomal recessive variant, type 2 CPVT, the causative gene is *CASQ2*, located on chromosome 1p13-21.⁵⁾ *CASQ2* encodes calsequestrin, a calcium buffering protein in the sarcoplasmic reticulum, which binds a large amount of calcium. While the mechanism by which this mutation causes ventricular arrhythmias has not been clearly established, the mutated protein may be associated with the following: loss of polymerization of CASQ monomers, loss of calcium buffering capability, or indirect destabilization of the ryanodine receptor channel.⁶⁾⁷⁾

Patients with CPVT, in which many forms of exercise are associat-

ed with catecholamine release that triggers VT, should be cautioned against virtually all forms of vigorous and/or competitive physical activity.⁸⁾ Since the early reports on CPVT, β -blockers have been used as primary therapy for CPVT,⁹⁾¹⁰⁾ and they are indicated for both chronic treatment and acute therapy for sustained VT. Other antiarrhythmic drugs such as amiodarone and class I drugs have proved to be ineffective.¹¹⁾ However, these issues were addressed in a study that evaluated both the molecular mechanisms and clinical efficacy of flecainide in mice and humans.¹²⁾ Implantable cardioverter defibrillators can be considered for primary prevention despite the potential drawbacks in young patients and concerns about provoking arrhythmic storms. Left cardiac sympathetic denervation has been reported effective in patients whose symptoms were not adequately controlled by β -blockers.¹³⁾ This approach may also be considered for individuals with intractable arrhythmic storms to reduce the number of implantable cardioverter-defibrillator shocks.

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