Catecholaminergic Polymorphic Ventricular Tachycardia

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Abstract: Catecholaminergic polymorphic ventricular tachycardia is a rare cause of exercise-induced arrhythmia and sudden cardiac death in the pediatric patient. This arrhythmia is difficult to diagnose in the emergency department, given the range of presentations; thus, a familiarity with and high index of suspicion for this pathology are crucial. Furthermore, recognition of the characteristic electrocardiogram findings and knowledge of the management of the symptomatic patient are necessary, given the risk of arrhythmia recurrence and cardiac arrest. In this review, we discuss the presentation, differential diagnosis, and management of catecholaminergic polymorphic ventricular tachycardia for the emergency care provider.

Key Words: catecholaminergic polymorphic ventricular tachycardia, sudden cardiac arrest

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TARGET AUDIENCE
This CME activity is intended for pediatric emergency medicine physicians, emergency medicine physicians, and pediatricians.

LEARNING OBJECTIVES
After completion of this article, the reader should be able to:
1. Define catecholaminergic polymorphic ventricular tachycardia
2. Review pathophysiology of catecholaminergic polymorphic ventricular tachycardia;
3. Review presentation and diagnosis of catecholaminergic polymorphic ventricular tachycardia;
4. Review electrocardiogram findings indicative of catecholaminergic polymorphic ventricular tachycardia; and
5. Discuss current consensus guidelines for the acute and chronic management strategies catecholaminergic polymorphic ventricular tachycardia.

A 13-year-old child presents to the emergency department after collapsing while running in a soccer game. He required cardiopulmonary resuscitation and 1 defibrillation by an automated external defibrillator prior to emergency medical services arrival. His parents report that he has collapsed previously, but he always recovered within a few minutes. The paramedics show you the electrocardiogram (ECG) (Fig. 1) obtained en route to the emergency department. What is the likely diagnosis, and what is your management in the emergency department?

DEFINITION AND EPIDEMIOLOGY
Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a cardiac arrhythmia characterized by an emotion- or exercise-induced polymorphic ventricular tachycardia.1 Although previously described in case reports in 1975,2 CPVT was defined by Leenhardt et al1 in 1995 as an etiology of polymorphic ventricular tachycardia with exercise in patients with an otherwise normal resting ECG and structurally normal heart. The characteristic ECG finding when symptomatic is bidirectional ventricular tachycardia, as seen in Figure 2. While the exact incidence of CPVT is unknown, it is estimated to be 1 in 10,000.3,4 When left untreated, symptomatic CPVT has a mortality of 30% by the age of 40 years.5,6 Typical age at presentation ranges from early childhood to early adulthood, with an average between 11 and 21 years; however, incident symptomatic cases have been reported in adults up to 40 years old.1,5,7 Furthermore, CPVT is often misdiagnosed initially as vasovagal syncope, seizure disorder, and other arrhythmias such as long QT syndrome (LQTS), resulting in an average delay to diagnosis of up to 2 years.7

PATHOPHYSIOLOGY AND GENETICS
While the overarching mechanism of CPVT is related to an increase in the release of calcium (Ca2+) from the junctional sarcoplasmic reticulum (SR) into the cytoplasm of the cardiac myocyte, there are multiple mechanisms and concomitant gene mutations associated with this pathology.5 Understanding the regulation of Ca2+ release in a myocyte is crucial to understanding this pathophysiology (Fig. 3). In response to the action potential propagating throughout the myocardium, calcium enters the cell through the voltage-gated Ca2+ channel (L-type channels). Once in the cell, the elevated Ca2+ level induces the ryanodine (RyR2) channel located in the junctional SR to release calcium from the SR into the cytoplasm of the cell, so-called “Ca2+-induced Ca2+ release.” The resultant elevation in intracellular Ca2+ induces contraction of the sarcomere by binding to troponin in the myofilaments. The RyR2 channel is additionally activated by stimulation from β-adrenergic receptors via a cAMP mechanism, increasing Ca2+ in the SR. The Ca2+ is then removed from the cytoplasm by Ca2+-ATPase and sodium-dependent mechanisms transporting it back into the SR and the extracellular space.8–10

There are 4 genes that have been directly linked to CPVT, all of which affect Ca2+ release in the cardiac myocyte. Currently, only 60% of cases of CPVT are found to have a genetic mutation, and additional genes are currently under investigation.11 The first identified genetic mutation was described in the cardiac ryanodine receptor (RYR2 or CPVT1) gene, which accounts for 50% to 55% of CPVT cases.1,2,12,13 This mutation is autosomal dominant and results in diastolic “leak” of Ca2+ into the SR leading to elevated Ca2+ levels in the cytoplasm. This effect is noted to be more pronounced in high β-adrenergic states and hence the association of arrhythmias with exercise.2,12,13 The second genetic mutation identified in CPVT patients is the CASQ2 (CPVT2) gene, which encodes cardiac calsequestrin, a Ca2+-buffering protein in the SR.
that inhibits the RYR2 protein.\textsuperscript{1,14} This mutation is autosomal recessive and accounts for only 2% to 5% of CPVT patients.\textsuperscript{3,4} The third gene identified in association with CPVT is CALM1, which is autosomal dominant and encodes calmodulin, a protein that binds calcium and stabilizes the RYR2 channel and accounts for less than 1% of cases.\textsuperscript{3,5,6,15} Finally, in 2012, the gene TRDN was identified in 2 families with CPVT.\textsuperscript{1,5,7,16} TRDN encodes triadin, a protein that links RYR2 and calsequestrin in the SR.

**PRESENTATION AND DIAGNOSIS**

The most common clinical presentation of CPVT is syncope, followed by cardiac arrest as in our case presentation. However, it should be noted that given the ability to test for genetic mutations associated with this pathology, asymptomatic patients (especially relatives of affected patients) are now being identified in up to 19% of cases.\textsuperscript{1,5,7,17} In the largest cohort study to date, 64% of patients presented with syncope, 33% with cardiac arrest, 7% with palpitations, and 4% with chest pain.\textsuperscript{7–10} The average age at presentation is approximately 11 years old.\textsuperscript{7,11}

Clinical diagnosis is based on the documentation of a polymorphic ventricular tachycardia that is induced by adrenergic stimuli (emotion or exercise) without any additional structural or electrical cardiac abnormality.\textsuperscript{4} Catecholaminergic polymorphic ventricular tachycardia can be diagnosed further via genetic testing in the absence of symptoms at the time of presentation.\textsuperscript{4,18} A family history of sudden unexpected death in a relative younger than 40 years, an ECG showing exercise-induced ventricular ectopy, or a seizure during exercise (common misdiagnosis in CPVT) should also raise suspicion of CPVT.

While genetic testing has become a standard in diagnosis for CPVT, Holter monitoring, exercise stress testing (EST), and isoproterenol or epinephrine challenge may be useful in making the diagnosis and differentiating from LQTS. The baseline ECG in a CPVT patient typically is normal, occasionally marked by mild bradycardia.\textsuperscript{19} Progressive ventricular ectopy during EST may be a hallmark for diagnosing these patients. Appearance of premature ventricular beats (PVCs), bigeminy or trigeminy, polymorphic PVCs, and finally nonsustained to sustained bidirectional ventricular tachycardia have been described in CPVT.\textsuperscript{1,3,20} The characteristic bidirectional ventricular tachycardia is rarely found on ECG; more common are polymorphic PVCs; thus, careful attention to the ECG and telemetry is necessary for clinical diagnosis.

Current guidelines recommend genetic testing for CPVT genes in patients who exhibit symptoms or if there is a suspicious family history. In addition, once a pathogenic mutation is identified, given the high risk to family members, complete cardiac evaluation and testing including mutation-specific genetic testing are recommended in relatives of the index case.\textsuperscript{11}

For the emergency provider, the basis for diagnosis of CPVT is heightened clinical awareness of the pathology and attention to the history of presentation. In general, patients who present at younger than 18 years with exertional syncope have a likelihood of a cardiac etiology of approximately 50%.\textsuperscript{21} Table 1 summarizes findings concerning for cardiac etiology and CPVT of patients presenting to the emergency department.\textsuperscript{7}

**ACUTE MANAGEMENT STRATEGIES**

At the outset, it is important to distinguish benign syncope (such as vasovagal syncope) from the arrhythmogenic syncope induced by exercise in conditions such as CPVT and LQTS. This can be done by taking a detailed history of the event with particular inquiry of prodromal symptoms (such as dizziness, lightheadedness, or visual or auditory stimuli) that may suggest a more benign etiology. Emergency management of symptomatic CPVT with ongoing arrhythmia is guided by the presentation and stability of the patient. Polymorphic ventricular tachycardia of any etiology should be differentiated into pulseless patients and patients with a pulse, which can further be subdivided into stable and unstable based on signs of hemodynamic compromise.
Pulseless

Pulseless patients, as in our introductory case, should be treated following Pediatric Advanced Life Support and Advanced Cardiac Life Support guidelines. Specific therapies for polymorphic ventricular tachycardia include defibrillation (2–4 J/kg), magnesium administration (20–50 mg/kg), intravenous β-blocker therapy (esmolol 500 μg/kg bolus followed by a drip of 50–300 μg/kg per minute), and amiodarone (5 mg/kg, may be repeated twice up to 15 mg/kg, maximum dose 300 mg).

With a Pulse

Polymorphic ventricular tachycardia likely associated with CPVT with a pulse should be managed with removal of catecholamine stimulus (such as pain or anxiety), β-blocker therapy, and sedation to decrease catecholamine release when stable. The basis of this management strategy is to neutralize the adrenergic stimulation from the RyR2 channel resulting in the abnormal Ca²⁺ release. Thus, it is imperative to reduce pain, treat anxiety/ agitation, and provide sedation for painful procedures to reduce the adrenergic surge that will potentiate the arrhythmia.

In patients who are unstable and nearing pulseless arrest, management is targeted at immediate cessation of the rhythm, including synchronized cardioversion/defibrillation (polymorphic ventricular tachycardia may not permit identification of the QRS for cardioversion; thus, defibrillation may be necessary), magnesium administration (20–50 mg/kg), intravenous β-blocker therapy (propranolol 0.1 mg/kg up to 3 mg over 10 minutes or esmolol 500-μg/kg bolus followed by a drip of 50–300 μg/kg per minute), and amiodarone (5 mg/kg over 20–60 minutes).

Exercise-Related Syncope

Approximately half of pediatric patients who present with exercise-related syncope are found to have a cardiac etiology. The differential diagnoses for syncope with exertion include LQTS, Wolff-Parkinson-White syndrome, hypertrophic cardiomyopathy, pulmonary hypertension, Brugada, intermittent heart block, arrhythmogenic right ventricular dysplasia, CPVT, and rarely neurocardiogenic syncope when all other etiologies have been ruled out. Tretter and Kavey proposed screening for exercise-related syncope with family history of cardiac events or sudden unexplained death, abnormal physical examination, and abnormal ECG. If 1 or more of these parameters is positive in a child with syncope, screening for underlying cardiac disease should be undertaken. The etiology of exertional syncope may not be elucidated in the emergency department, given limited testing; however, these patients should be further investigated with an exercise stress test, echocardiography, and cardiology referral.

CHRONIC MANAGEMENT STRATEGIES

Long-term management of CPVT is targeted at reduction in adrenergic stimulation to the RyR2 channel with β-blockers and lifestyle modifications. In patients who continue to be at risk of ventricular arrhythmia, an implantable defibrillator can be placed to prevent sudden cardiac arrest.

Lifestyle modification is the first tenant of management in CPVT patients with the modification or cessation of exercise.
Initial pharmacologic intervention includes β-blocker therapy with propranolol or nadolol; however, there is a 25% treatment failure with this intervention.2–7,18 In the setting of incomplete control of the ventricular arrhythmia or intolerance of β-blocker therapy, flecainide, which is a direct RyR2-channel blocker, may be added. In the past, the calcium-channel blocker verapamil was included in the pharmacologic management of CPVT, but effectiveness is controversial.4,18

Implantable cardiac defibrillator (ICD) placement is a class I recommendation for CPVT patients with a history of cardiac arrest, recurrent syncope, or polymorphic ventricular tachycardia despite pharmacologic therapy.18,31 Even after placement of an ICD, pharmacologic management needs to be optimized to reduce the number of shocks a patient experiences. The last line of therapy for CVVT is left cardiac sympathetic denervation, which has been shown to be effective in patients who continue to experience syncope, polymorphic ventricular tachycardia, and/or several appropriate shocks from an ICD despite maximal pharmacologic therapy.1,18,32

Current research involving gene therapy in a mouse CASQ2 CPVT model has shown promise putting a new treatment on the horizon with implications such as not only CPVT but also heart failure–associated arrhythmias.33,34

CONCLUSIONS

For our introductory case, he converted to a normal sinus rhythm with intravenous β-blockade and anxiolyis. He was started on chronic β-blocker therapy with lifestyle modifications to limit intense physical activity, but was able to return to recreational sports with an automated external defibrillator available at all times. Genetic testing was done for prognostication and to aid in the screening of his immediate family members.

Catecholaminergic polymorphic ventricular tachycardia is a rare but life-threatening genetic condition characterized by ventricular arrhythmias that can progress to polymorphic ventricular tachycardia in high adrenergic states. The emergency provider should have a high index of suspicion for this pathology in patients presenting with exercise-induced syncope or seizure-like activity in the presence of a normal examination, echocardiogram, and baseline ECG.

REFERENCES

11. Ackerman MJ, Priori SG, Willem's S, et al. HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies: this document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA). Heart Rhythm. 2011;8:1308–1339.


CME EXAMINATION
JUNE 2017

Please mark your answers on the ANSWER SHEET.

Catecholaminergic Polymorphic Ventricular Tachycardia, Wall and Iyer.

1. What is the initial therapy for symptomatic catecholaminergic polymorphic ventricular tachycardia (CPVT) with a pulse in the emergency department?
   a. treatment of pain and/or anxiety
   b. synchronized cardioversion
   c. intravenous amiodarone
   d. external pacing

2. Which enzyme is not associated with pathway leading to CPVT?
   a. triadin
   b. calmodulin
   c. troponin
   d. calsequestrin

3. When asymptomatic, what electrocardiogram (ECG) finding is most characteristic of CPVT?
   a. ST elevation in the precordial leads
   b. prolongation of the QT segment
   c. normal sinus rhythm
   d. first-degree atrioventricular block

4. What presentation is concerning for CPVT?
   a. first-time seizure with minimal tonic-clonic activity
   b. syncope
   c. palpitations with exercise
   d. family history of CPVT
   e. all of the above

5. What is the key to diagnosis of CPVT?
   a. high index of suspicion and thorough history
   b. abnormal ECG
   c. echocardiogram
   d. cardiac magnetic resonance imaging
ANSWER SHEET FOR THE PEDIATRIC EMERGENCY CARE
CME PROGRAM EXAM
June 2017

Please answer the questions on page 432 by filling in the appropriate circles on the answer sheet below. Please mark the one best answer and fill in the circle until the letter is no longer visible. To process your exam, you must also provide the following information:

Name (please print): ___________________________________________________________________________________________
Street Address _______________________________________________________________________________________________
City/State/Zip _______________________________________________________________________________________________
Daytime Phone ______________________________________________________________________________________________
Specialty ___________________________________________________________________________________________________

Your completion of this activity includes evaluating them. Please respond to the following questions below.

Please rate this activity (1 – minimally, 5 – completely)

Was effective in meeting the educational objectives
Was appropriately evidence-based
Was relevant to my practice

Please rate your ability to achieve the following objectives, both before this activity and after it:
1 (minimally) to 5 (completely)

1. Define catecholaminergic polymorphic ventricular tachycardia.
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4. Review electrocardiogram findings indicative of catecholaminergic polymorphic ventricular tachycardia.
5. Discuss current consensus guidelines for the acute and chronic management strategies catecholaminergic polymorphic ventricular tachycardia.

How many of your patients are likely to be impacted by what you learned from these activities?
○ <20%  ○ 20%-40%  ○ 40%-60%  ○ 60%-80%  ○ >80%

Do you expect that these activities will help you improve your skill or judgment within the next 6 months? (1 - definitely will not change, 5 - definitely will change)
1 2 3 4 5

How will you apply what you learned from these activities (mark all that apply):
In diagnosing patients  ○  In making treatment decisions  ○
In monitoring patients  ○  As a foundation to learn more  ○
In educating students and colleagues  ○  In educating patients and their caregivers  ○
As part of a quality or performance improvement project  ○  To confirm current practice  ○
For maintenance of board certification  ○  For maintenance of licensure  ○
To consider enrolling patients in clinical trials  ○
Other ______________________________________________________________________________________________________

Please list at least one strategy you learned from this activity that you will apply in practice:

Please list at least one (1) change you will make to your practice as a result of this activity:

Did you perceive any bias for or against any commercial products or devices?
Yes  No

If yes, please explain:

How long did it take you to complete these activities? _____ hours _____ minutes

What are your biggest clinical challenges related to pediatric emergency care?

[ ] Yes! I am interested in receiving future CME programs from Lippincott CME Institute! (Please place a check mark in the box)