

Catecholaminergic Polymorphic Ventricular Tachycardia



Marwan M. Refaat, MD, FHRS, FESC^{a,b,*},
Sylvana Hassanieh, BS^b, Melvin Scheinman, MD^c

KEYWORDS

• Cardiac • Catecholaminergic • Polymorphic • Ventricular tachycardia

KEY POINTS

- Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a challenging and serious disease with a high incidence of sudden cardiac deaths.
- Patients with CPVT should not be exposed to physical or emotional exertion that might induce ventricular tachycardia.
- This article presents a case with CPVT and discusses the clinical features of the disease, its genetic background, and the management of CPVT.

CASE PRESENTATION

A 25-year-old woman presented for evaluation in 2005 in the cardiac electrophysiology clinic after several episodes of exercise-induced syncope. Syncope can sometimes be aborted with cessation of activity and rest. The patient's first episode occurred at the age of 18 years in 1998. From 1998 to 2005, she had 1 episode per year, each with strenuous exercise. Her baseline electrocardiogram (ECG) shows a normal sinus rhythm. An exercise treadmill test showed a normal QT response to exercise and in recovery, singlet PVCs, and occasional couplets that occurred with exercise with multifocal non-short-coupled PVCs (predominantly right bundle branch block, inferior axis) **Fig. 1**. A β -blocker was initiated for empiric suppression of the PVCs. The patient had several additional episodes of syncope after

she stopped the β -blocker. Genetic testing identified a novel RYR2 mutation. The patient refused transvenous implantable cardioverter-defibrillator (ICD) placement. She was started on flecainide, which controlled the ventricular arrhythmias and her syncopal episodes. She was not eligible for the subcutaneous ICD after failing the screening test designed to identify susceptibility to T-wave oversensing during stress but not rest.

DISCUSSION

The patient had catecholaminergic polymorphic ventricular tachycardia (CPVT).

The disease was first described in 1975 and it was termed CPVT by Coumel in 1978. CPVT is characterized by polymorphic premature ventricular contractions or polymorphic ventricular tachyarrhythmias in genetically predisposed

Disclosure: None.

^a Cardiology, Department of Internal Medicine, American University of Beirut Faculty of Medicine and Medical Center, PO Box 11-0236, Riad El-Solh, Beirut 1107 2020, Lebanon; ^b Department of Biochemistry and Molecular Genetics, American University of Beirut Medical Center, Beirut, Lebanon; ^c Division of Cardiology, Department of Medicine, University of California San Francisco Medical Center, San Francisco, CA, USA

* Corresponding author. Cardiology, Department of Internal Medicine, American University of Beirut Faculty of Medicine and Medical Center, PO Box 11-0236, Riad El-Solh, Beirut 1107 2020, Lebanon.

E-mail address: mr48@aub.edu.lb

Card Electrophysiol Clin 8 (2016) 233–237

<http://dx.doi.org/10.1016/j.ccep.2015.10.035>

1877-9182/16/\$ – see front matter © 2016 Elsevier Inc. All rights reserved.

Downloaded for Anonymous User (n/a) at American University of Beirut from ClinicalKey.com by Elsevier on September 17, 2024. For personal use only. No other uses without permission. Copyright ©2024. Elsevier Inc. All rights reserved.

Patient ID044971062
27-Oct-2005
3:42:10pm

157 bpm

EXERCISE
STAGE 4
09:06

BRUCE
4.2 mph
16.0 %

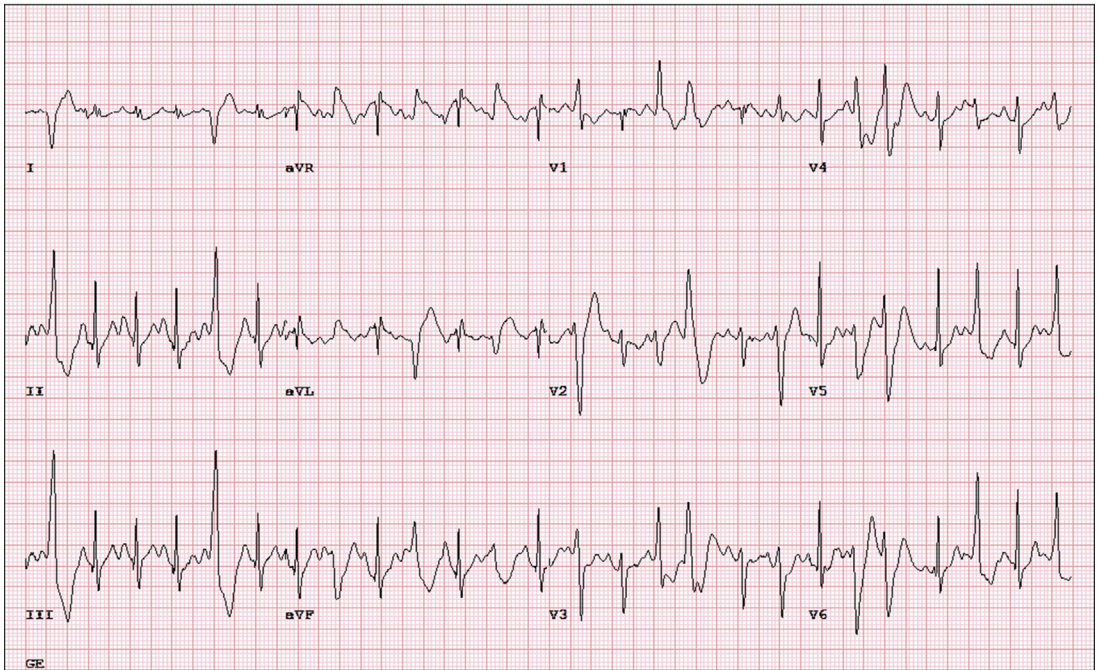


Fig. 1. Electrocardiogram of the patient with catecholaminergic polymorphic ventricular tachycardia after treadmill stress test (Bruce protocol). The recording shows sinus tachycardia with polymorphic ventricular beats.

individuals on physical or emotional stress.¹ Most of the CPVT mutations are in the gene encoding the ryanodine receptor (*RyR2*).² Also, researchers have shown mutations in cardiac calsequestrin (*CASQ2*) to result in CPVT.³ Recently alterations in triadin^{4,5} and calmodulin,⁶ which regulate *RyR2* channel openings, were found to cause CPVT. Classic CPVT is manifested in dysregulated calcium handling. On exercise or emotional stress, the release of catecholamines increases diastolic calcium leak from the sarcoplasmic reticulum and causes intracellular calcium overload, which triggers the sodium/calcium pumps to restore homeostasis by importing sodium inside the cell and extruding calcium ions.⁷ The sodium current induces depolarization of the cell membrane in the myocyte, which is visualized at late diastole (transient inward current) and is responsible for delayed afterdepolarization (DAD).⁷⁻⁹

CLINICAL CHARACTERISTICS AND DIAGNOSIS

The first clinical manifestation of CPVT is syncope induced by physical or emotional stress.¹ Less prevalent signs and symptoms are dizziness or palpitations. There is generally a 2-year delay between the first and second syncope episode

observed in patients with CPVT. In some cases the first incidence is sudden cardiac arrest or death. The age at presentation is between 7 and 11 years.¹⁰ The prevalence of the disease is not exactly reported but is estimated to be 1:10,000.¹¹

Exercise ECG unmasks features diagnostic of CPVT.¹² This develops at a heart rate of 110 to 130 beats per minute.¹⁰ On continuation of exercise, premature ventricular complexes progress to polymorphic ventricular tachyarrhythmia.¹³ Patients with CPVT might present with bidirectional ventricular tachycardia (VT), which is evident in an alternating QRS axis morphology with a rotation of 180° on a beat-to-beat basis.

RyR2 mutation was associated with postpacing abnormal repolarization in CPVT. An *RyR2* mutation in the C-terminal channel-forming domain has an increased risk of nonsustained VT compared with N-terminal domain. The first VT complex in CPVT commonly originates from the right ventricular outflow tract.

GENETICS OF CATECHOLAMINERGIC POLYMORPHIC VENTRICULAR TACHYCARDIA

The dominant mutation in cardiac ryanodine receptor (*RyR2*) accounts for CPVT type 1,¹⁰ and

for most cases (55%–65%), with the CPVT locus linked to the long arm of chromosome 1 (1q42–q43) for this mutation.¹⁴ The *RyR2* is a channel located in the membrane of the sarcoplasmic reticulum that is responsible for the control of calcium release. The other type of CPVT is confined to the autosomal recessive mutation in the cardiac calsequestrin (*CASQ2*)¹⁵ and this variant is linked to chromosome 1 (1p13–p21),¹⁶ accounting to 3% to 5% of cases¹⁷ (Table 1). Calsequestrin is the major calcium storage protein in the sarcoplasmic reticulum and forms, along with *RyR2*, triadin, and junctin, a major regulatory unit that strictly regulates intracellular calcium.¹⁸

More than 100 mutations in *RyR2* have been documented in CPVT1. These mutations are single base pair substitutions with many of them affecting the *FKBP12.6*-binding domain.^{19,20} Most of the *RyR2* mutations are in the transmembrane segments (cluster IV). One of the proposed mechanism of the most common mutation reported (*R4497C-RyR2*) to cause CPVT is by reducing the binding affinity of *RyR2* to the regulatory protein *FKBP12.6* (calstabin 2) under basal conditions, and such reduced binding is further exaggerated after protein kinase A phosphorylation of *RyR2* during adrenergic activation.²¹ Mice knockout for *FKBP12.6* develop arrhythmias that are typical for CPVT. On administration of a derivative of 1,4-benzothiazepine called K201, which enhances the binding of *FKBP12.6* to *RyR2*, the arrhythmias disappear.²¹ Another proposed mechanism is that *RyR2* mutations that cause CPVT increase the sensitivity of *RyR2* to luminal calcium activation, which causes spontaneous calcium release from the sarcoplasmic reticulum. Those events caused by store overload–induced Ca^{2+} release lead to DADs that consequently induce arrhythmias and thus explain how the mutations increase the susceptibility to adrenergically mediated arrhythmias on exercise or emotional stress.^{22,23} A third proposed mechanism is that *RyR2* mutations impair the interdomain interactions and the proper folding

controlling channel gating and thus lead to unzipping of the 2 domains and sarcoplasmic reticulum calcium leakage.

Only 12 CPVT mutations and 3 nonsynonymous polymorphisms pertaining to calsequestrin have been reported.¹⁷ The major recessive mutation in this group is *D307H* mutation.¹⁵ Another mutation that has been reported, and shows the possibility of interaction of *CASQ2* with *RyR2*, is *R33Q*. Adult rat myocytes carrying this mutation showed an increase in excitation-contraction coupling gain along with repetitive consecutive spontaneous propagating calcium waves and local calcium signals compared with cells expressing wild-type *CASQ2*. It was concluded that the *R33Q* mutation disrupts interactions of *CASQ2* with the *RyR2* channel complex and impairs regulation of *RyR2* by luminal calcium.²⁴ *CASQ2* has a recessive mode of inheritance but some investigators have reported heterozygosity cases in nonconsanguineous families.²⁵

Genetic testing for patients with CPVT with clinical diagnosis aids in identifying mutations in 65% of cases.²⁶ The high incidence of sudden cardiac death as the primary outcome makes CPVT a serious cardiac channelopathy disorder (30% of cases).¹⁰ Thus genetic testing for patients showing a clinical picture (such as bidirectional VT) is cost-effective, whereas, in patients with no clinical correlation, genetic testing is less often performed.²⁶ Because of the large size of the *RyR2* gene, critical exons have been selected for screening; typically a set of 105 translated exons is available for the purpose of the test.¹⁷ Because *CASQ2* inheritance is still suspected, recommendations are to screen *CASQ2* in *RyR2*-negative index cases.

Other genes have been reported to cause CPVT-like phenotype. These genes include *KCNJ2* encoding the Kir2.1 potassium channel²⁷ and *ANK2* encoding for ankyrin-B,²⁸ a cytoskeletal protein. No genetic tests are performed for the genes mentioned earlier except when there is a clinical diagnosis linked to negative *RyR2* mutation.

Table 1
Causative genes in CPVT

Gene	Protein	Frequency (%)	Transmission Mode	Chromosome
<i>RYR2</i>	Ryanodine receptor	60	Autosomal dominant	1q42.1
<i>CASQ2</i>	Calsequestrin isoform 2	1–3	Autosomal recessive	1p13.3-p11
<i>KCNJ2</i>	Inward rectifier (I_{K1}) K ⁺ channel, Kir 2.1	5–10	Autosomal dominant	17q24.3
<i>CALM1</i>	Calmodulin 1	Rare	Autosomal dominant	14q32.11
<i>TRDN</i>	Triadin	Rare	Autosomal recessive	6q22.31
<i>ANK2</i>	Ankyrin-B	Rare	Autosomal dominant	4q25

Because CPVT is a genetic disease, first-degree family screening is required whenever a mutation is identified in an affected patient for *RyR2* and *CASQ2* genes. First-degree and second-degree families are to be evaluated clinically and genetically in identified cases of CPVT mutation.¹⁷

MANAGEMENT

Because sudden cardiac death might be the first manifestation in patients with CPVT, genetic screening of relatives is crucial. This presymptomatic diagnosis with proper counseling and medication administration is important in CPVT management.²⁹ Patients with a previous episode of ventricular fibrillation, those with unstable VT while they are on β -blockers, and those with a younger age at diagnosis are all considered at high risk.¹⁰

Patients with CPVT should not be exposed to physical or emotional exertion that might induce VT. Thus no vigorous physical activity is allowed, along with control of emotional challenges and triggers.³⁰ Usually, β -blockers are indicated then increased until an appropriate dose has been achieved, on exercise testing and Holter monitoring.^{31,32} Targeted therapy to *RyR2*-mediated calcium release has been promising with flecainide in combination with β -blockers.³³ Alpha-blockade has been shown to potentiate CPVT therapy in a calsequestrin-mutant mice model of CPVT.³⁴ Ongoing studies are assessing the protection from cardiac arrhythmia through ryanodine receptor-stabilizing protein calstabin 2 (Rycals). CaMKII (Ca²⁺/calmodulin-dependent protein kinase II) inhibition has been shown to rectify arrhythmic phenotype in a patient-specific induced pluripotent stem cell model of CPVT.³⁵

ICD implantation is indicated for patients with CPVT who have survived a cardiac arrest (class I indication).³¹ ICD might also be the selected choice in high-risk patients having a strong family history of sudden death.

SUMMARY

CPVT is a challenging and serious disease with a high incidence of sudden cardiac deaths. This article presents a case with CPVT and discusses the clinical features of the disease, its genetic background, and the management of CPVT.

REFERENCES

1. Leenhardt A, Lucet V, Denjoy I, et al. Catecholaminergic polymorphic ventricular tachycardia in children. A 7-year follow-up of 21 patients. *Circulation* 1995;91(5):1512–9.
2. Priori SG, Napolitano C, Tiso N, et al. Mutations in the cardiac ryanodine receptor gene (hRyR2) underlie catecholaminergic polymorphic ventricular tachycardia. *Circulation* 2001;103(2):196–200.
3. Postma AV, Denjoy I, Hoorntje TM, et al. Absence of calsequestrin 2 causes severe forms of catecholaminergic polymorphic ventricular tachycardia. *Circ Res* 2002;91(8):e21–6.
4. Chopra N, Knollmann BC. Triadin regulates cardiac muscle couplon structure and microdomain Ca²⁺ signalling: a path towards ventricular arrhythmias. *Cardiovasc Res* 2013;98(2):187–91.
5. Roux-Buisson N, Cacheux M, Fourest-Lieuvain A, et al. Absence of triadin, a protein of the calcium release complex, is responsible for cardiac arrhythmia with sudden death in human. *Hum Mol Genet* 2012;21:2759–67.
6. Nyegaard M, Overgaard MT, Sondergaard MT, et al. Mutations in calmodulin cause ventricular tachycardia and sudden cardiac death. *Am J Hum Genet* 2012;91:703–12.
7. Faggioni M, van der Werf C, Knollmann BC. Sinus node dysfunction in catecholaminergic polymorphic ventricular tachycardia: risk factor and potential therapeutic target? *Trends Cardiovasc Med* 2014; 24(7):273–8.
8. Fabiato A. Time and calcium dependence of activation and inactivation of calcium-induced release of calcium from the sarcoplasmic reticulum of a skinned canine cardiac Purkinje cell. *J Gen Physiol* 1985;85:247–89.
9. Liu N, Colombi B, Memmi M, et al. Arrhythmogenesis in catecholaminergic polymorphic ventricular tachycardia: Insights from a RyR2 R4496C knock-in mouse model. *Circ Res* 2006;99:292–8.
10. Priori SG, Napolitano C, Memmi M, et al. Clinical and molecular characterization of patients with catecholaminergic polymorphic ventricular tachycardia. *Circulation* 2002;106:69–74.
11. Napolitano C, Priori SG. Diagnosis and treatment of catecholaminergic polymorphic ventricular tachycardia. *Heart Rhythm* 2007;4:675–8.
12. Refaat MM, Hotait M, Tseng ZH. Utility of the exercise electrocardiogram testing in sudden cardiac death risk stratification. *Ann Noninvasive Electrocardiol* 2014;19(4):311–8.
13. Liu N, Ruan Y, Priori SG. Catecholaminergic polymorphic ventricular tachycardia. *Prog Cardiovasc Disease* 2008;51(1):23–30.
14. Swan H, Piippo K, Viitasalo M, et al. Arrhythmic disorder mapped to chromosome 1q42-q43 causes malignant polymorphic ventricular tachycardia in structurally normal hearts. *J Am Coll Cardiol* 1999; 34:2035–42.
15. Lahat H, Pras E, Olender T, et al. A missense mutation in a highly conserved region of *CASQ2* is associated with autosomal recessive catecholamine-induced

- polymorphic ventricular tachycardia in Bedouin families from Israel. *Am J Hum Genet* 2001;69:1378–84.
16. Lahat H, Eldar M, Levy-Nissenbaum E, et al. Autosomal recessive catecholamine- or exercise-induced polymorphic ventricular tachycardia: clinical features and assignment of the disease gene to chromosome 1p13-21. *Circulation* 2001;103:2822–7.
 17. Ackerman MJ, Priori SG, Willems 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;8:1308–39.
 18. Mohamed U, Napolitano C, Priori SG. Molecular and electrophysiological bases of catecholaminergic polymorphic ventricular tachycardia. *J Cardiovasc Electrophysiol* 2007;18(7):791–7.
 19. Medeiros-Domingo A, Bhuiyan ZA, Tester DJ, et al. The RYR2-encoded ryanodine receptor/calcium release channel in patients diagnosed previously with either catecholaminergic polymorphic ventricular tachycardia or genotype negative, exercise-induced long QT syndrome: a comprehensive open reading frame mutational analysis. *J Am Coll Cardiol* 2009;54:2065–74.
 20. Priori SG, Napolitano C. Cardiac and skeletal muscle disorders caused by mutations in the intracellular Ca²⁺ release channels. *J Clin Invest* 2005;115:2033–8.
 21. Wehrens XH, Lehnart SE, Huang F, et al. FKBP12.6 deficiency and defective calcium release channel (ryanodine receptor) function linked to exercise-induced sudden cardiac death. *Cell* 2003;113:829–40.
 22. Jiang D, Wang R, Xiao B, et al. Enhanced store overload-induced Ca²⁺ release and channel sensitivity to luminal Ca²⁺ activation are common defects of RyR2 mutations linked to ventricular tachycardia and sudden death. *Circ Res* 2005;97:1173–81.
 23. Jiang D, Xiao B, Yang D, et al. RyR2 mutations linked to ventricular tachycardia and sudden death reduce the threshold for store-overload-induced Ca²⁺ release (SOICR). *Proc Natl Acad Sci U S A* 2004;101:13062–7.
 24. Terentyev D, Nori A, Santoro M, et al. Abnormal interactions of calsequestrin with the ryanodine receptor calcium release channel complex linked to exercise-induced sudden cardiac death. *Circ Res* 2006;98:1151–8.
 25. Raffaele di Barletta M, Viatchenko-Karpinski S, Nori A, et al. Clinical phenotype and functional characterization of CASQ2 mutations associated with catecholaminergic polymorphic ventricular tachycardia. *Circulation* 2006;114:1012–9.
 26. Bai R, Napolitano C, Bloise R, et al. Yield of genetic screening in inherited cardiac channelopathies: how to prioritize access to genetic testing. *Circ Arrhythm Electrophysiol* 2009;2:6–15.
 27. Tristani-Firouzi M, Jensen JL, Donaldson MR, et al. Functional and clinical characterization of KCNJ2 mutations associated with LQT7 (Andersen syndrome). *J Clin Invest* 2002;110(3):381–8.
 28. Mohler PJ, Splawski I, Napolitano C, et al. A cardiac arrhythmia syndrome caused by loss of ankyrin-B function. *Proc Natl Acad Sci U S A* 2004;101:9137–42.
 29. Pflaumer A, Davis AM. Guidelines for the diagnosis and management of catecholaminergic polymorphic ventricular tachycardia. *Heart Lung Circ* 2012;21(2):96–100.
 30. Maron BJ, Chaitman BR, Ackerman MJ, et al. Recommendations for physical activity and recreational sports participation for young patients with genetic cardiovascular diseases. *Circulation* 2004;109:2807–16.
 31. Zipes DP, Camm AJ, Borggrefe M, et al. ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Circulation* 2006;114:e385–484.
 32. Hayashi M, Denjoy I, Extramiana F, et al. Incidence and risk factors of arrhythmic events in catecholaminergic polymorphic ventricular tachycardia. *Circulation* 2009;119:2426–34.
 33. Watanabe N, Chopra D, Laver HS, et al. Flecainide prevents catecholaminergic polymorphic ventricular tachycardia in mice and humans. *Nat Med* 2009;15:380–3.
 34. Kurtzwald-Josefson E, Hochhauser E, Bogachenko K, et al. Alpha blockade potentiates CPVT therapy in calsequestrin-mutant mice. *Heart Rhythm* 2014;11:1471–9.
 35. Di Pasquale E, Lodola F, Miragoli M, et al. CaMKII inhibition rectifies arrhythmic phenotype in a patient-specific model of catecholaminergic polymorphic ventricular tachycardia. *Cell Death Dis* 2013;4:e843.