

CATECHOLAMINERGIC POLYMORPHIC VENTRICULAR TACHYCARDIA

Definition

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is VT that typically occurs on exercise and episodes of provoked tachycardia are sustained or, usually, non-sustained.^{1,2} CPVT is one of the most lethal inherited channelopathies, with sudden death occurring in up to 30% of patients before age 40 in the absence of antiadrenergic therapy.¹⁻³ The estimated 4- and 8-year cardiac event rates were 33% and 58%, respectively, in a series of patients without β -blockers.¹

Epidemiology

The prevalence of CPVT is virtually unknown, but it is estimated to be in the 1:20,000 range.⁴ There appears to be a similar proportion of male and female patients with CPVT.⁵

Genetics and Pathophysiology

CPVT is mainly due to mutations in the genes encoding the cardiac ryanodine receptor (RyR2) channel (60% of patients - autosomal dominant inheritance), and calsequestrin (autosomal recessive inheritance) that are involved in calcium kinetics (Table 1). A locus on chromosome 7p14–p22 has also been reported, with an early-onset lethal form of recessive CPVT.¹

Triadine is a new gene involved in an autosomal recessive form of CPVT, and three new mutations in the triadin gene (*TRDN*), a protein that links RyR2 and CASQ2, have been identified.¹ Whereas RyR2 gain-of-function variants cause an autosomal dominant form of CPVT, the CASQ2 genetic subtype is considered autosomal recessive and accounts for 2% to 5% of CPVT cases.⁶ Genetic variants in calsequestrin-2 (CASQ2) cause an autosomal recessive form of catecholaminergic polymorphic ventricular tachycardia (CPVT), although isolated reports have identified arrhythmic phenotypes among heterozygotes.⁶

Increased leak of Ca^{2+} from the sarcoplasmic reticulum triggers delayed afterdepolarization and ultimately leads to CPVT.⁷ Arrhythmia in RYR2-mediated CPVT requires both a pathogenic mutation and adrenergic stimulation, which activates downstream kinases such as the Ca^{2+} /calmodulin-dependent protein kinase II (CaMKII), that enhance cardiomyocyte Ca^{2+} handling by phosphorylating numerous targets.⁸ There has been evidence that delayed afterdepolarizations caused by calcium overload are a more common occurrence in Purkinje cells than in ventricular myocytes, and Purkinje cells are probably critical contributors to arrhythmic triggers.¹ Extended clinical phenotypes in patients with RyR2 mutations and CPVT have been described with sinoatrial node and atrioventricular node dysfunction, atrial

fibrillation, atrial standstill, and dilated cardiomyopathy.⁹ Sex-related differences have been described in RYR2 but appear to be minor.⁵

Presentation

QRS morphology suggests an outflow tract origin of the initiating beat in more than 50% of patients, and subsequent beats portray a polymorphic or typically bidirectional VT morphology.¹⁰ They may originate from the LVOT and less frequently from the RVOT or the RV apex.²

Diagnosis

The resting ECG is normal (Table 2). NSVT induced by treadmill exercise testing aimed at evaluating presumed long QT syndrome suggests catecholaminergic polymorphic VT rather than long QT syndrome.¹¹ Catecholaminergic polymorphic ventricular tachycardia patients with a higher heart rate recovery at the first exercise stress test off antiarrhythmic drugs are more likely to have been symptomatic before diagnosis.¹² Polymorphic VT is usually not inducible by programmed ventricular stimulation.¹ Provocative testing with epinephrine (infusion of 0.05 mcg/kg/min and increased every 5 min to 0.1 and 0.2 mcg/kg/min for 5 min at each dose) induces VT in 80% of patients, but a negative test does not exclude the diagnosis.¹³ Care should be taken, since patients diagnosed as CPVT on the basis of the presence of bidirectional ventricular tachycardia on exercise, have been identified as possessing KCNJ2 mutations, which are associated with the rarely lethal Andersen-Tawil syndrome (LQTS 7).¹⁴ **Triadin knockout syndrome (TKOS)** is a rare, inherited arrhythmia syndrome caused by recessive null mutations in *TRDN*-encoded cardiac triadin. It is characterized by extensive T-wave inversions, transient QT prolongation, and severe disease expression of exercise-induced cardiac arrest in early childhood refractory to conventional therapy.¹⁵

Genetic Testing

Indications for genetic testing are presented in Table 3.

Therapy

All phenotypically and/or genotypically diagnosed CPVT patients should receive a **non-selective beta blocker without sympathomimetic activity** in the highest tolerable dose. Nadolol in a dose up to 2 mg/kg/day is the preferred beta blocker.¹⁶⁻¹⁸ Participation in competitive sports is prohibited and the use of sympathomimetic agents is contraindicated. Complete suppression of asymptomatic VPBs may be mandatory, but the presence of

couplets or more successive VPBs during exercise testing is associated with future arrhythmic events, suggesting to intensify the treatment in these cases. A carvedilol analogue in combination with a non-selective beta blocker such as metoprolol or bisoprolol is also under study.¹ **Flecainide** directly blocks RyR2 channels, prevents premature Ca²⁺ release, reduces exercise-induced ventricular arrhythmias in patients with CPVT, and should be probably added to beta blockers as an initial therapy in high-risk patients.^{19,20} **Verapamil** may also be added to beta-blocker therapy.²¹ **ICD** (with beta blockers) is recommended in patients with cardiac arrest or documented VT despite beta blocker therapy (Table 4 and Figure 1). It should be noted that ICD shocks are sometimes ineffective and potentially proarrhythmic, inducing fatal electrical storms by both appropriate and inappropriate ICD shocks.²² In a report by the International CPVT Registry on patients with phenotypic and/or genotypic diagnostic criteria for CPVT who presented with sudden cardiac arrest prior to diagnosis of and treatment for CPVT, the ICD did not confer a survival benefit.²³ Left cardiac sympathetic denervation may also be helpful.²⁴⁻²⁶

Catheter ablation of the bidirectional ventricular premature beats that trigger ventricular fibrillation may become an adjunctive therapy in patients with refractory CPVT,²⁷ but experience is limited. Gene therapy approaches are also evolving. The possibility of viral gene transfer of wild-type *CASQ2* into the heart of R33Q mice has been raised,²⁸ and delivery of a CaMKII inhibitory peptide by adeno-associated virus also represents a novel single-dose gene therapy.⁸

Competitive exercise is not allowed. Only recreational, low-intensity sports are permitted (see relevant Chapters).

Pregnancy

The adrenergic nature of labor and delivery are relevant to catecholaminergic polymorphic ventricular tachycardia.^{29,30} Selective beta blockers are probably less effective than propranolol and nadolol,¹⁷ and flecainide may also be used if needed, although it should be avoided during the first trimester.²⁹ Recommendations are provided in Table 5.

References

1. Leenhardt A, et al. Catecholaminergic polymorphic ventricular tachycardia. *Circ Arrhythm Electrophysiol.* 2012;5:1044-1052. doi: 10.1161/CIRCEP.111.962027
CIRCEP.111.962027 [pii]
2. Sy RW, et al. Arrhythmia characterization and long-term outcomes in catecholaminergic polymorphic ventricular tachycardia. *Heart Rhythm.* 2011;8:864-871. doi: 10.1016/j.hrthm.2011.01.048
S1547-5271(11)00140-8 [pii]
3. Cerrone M, et al. Genetics of sudden death: focus on inherited channelopathies. *Eur Heart J.* 2011;32:2109-2118. doi: 10.1093/eurheartj/ehr082
ehr082 [pii]
4. Wilde AAM, et al. European Heart Rhythm Association (EHRA)/Heart Rhythm Society (HRS)/Asia Pacific Heart Rhythm Society (APHRS)/Latin American Heart Rhythm Society (LAHRS) Expert Consensus Statement on the state of genetic testing for cardiac diseases. *Europace.* 2022. doi: 10.1093/europace/euac030
5. Asatryan B, et al. Sex-Related Differences in Cardiac Channelopathies: Implications for Clinical Practice. *Circulation.* 2021;143:739-752. doi: 10.1161/CIRCULATIONAHA.120.048250
6. Ng K, et al. An International Multicenter Evaluation of Inheritance Patterns, Arrhythmic Risks, and Underlying Mechanisms of CASQ2-Catecholaminergic Polymorphic Ventricular Tachycardia. *Circulation.* 2020;142:932-947. doi: 10.1161/CIRCULATIONAHA.120.045723
7. Suetomi T, et al. Mutation-linked defective interdomain interactions within ryanodine receptor cause aberrant Ca(2+)-release leading to catecholaminergic polymorphic ventricular tachycardia. *Circulation.* 2011;124:682-694. doi: 10.1161/CIRCULATIONAHA.111.023259
CIRCULATIONAHA.111.023259 [pii]
8. Bezzerides VJ, et al. Gene Therapy for Catecholaminergic Polymorphic Ventricular Tachycardia by Inhibition of Ca(2+)/Calmodulin-Dependent Kinase II. *Circulation.* 2019;140:405-419. doi: 10.1161/CIRCULATIONAHA.118.038514
9. Bhuiyan ZA, et al. Expanding spectrum of human RYR2-related disease: new electrocardiographic, structural, and genetic features. *Circulation.* 2007;116:1569-1576. doi: 10.1161/CIRCULATIONAHA.107.711606 [pii]
10.1161/CIRCULATIONAHA.107.711606
10. Napolitano C, et al. Diagnosis and treatment of catecholaminergic polymorphic ventricular tachycardia. *Heart Rhythm.* 2007;4:675-678. doi: S1547-5271(06)02363-0 [pii]
10.1016/j.hrthm.2006.12.048
11. Horner JM, et al. Ventricular ectopy during treadmill exercise stress testing in the evaluation of long QT syndrome. *Heart Rhythm.* 2008;5:1690-1694. doi: 10.1016/j.hrthm.2008.08.038
S1547-5271(08)00869-2 [pii]
12. Lieve KVV, et al. Heart Rate Recovery After Exercise Is Associated With Arrhythmic Events in Patients With Catecholaminergic Polymorphic Ventricular Tachycardia. *Circ Arrhythm Electrophysiol.* 2020;13:e007471. doi: 10.1161/CIRCEP.119.007471
13. Obeyesekere MN, et al. How to perform and interpret provocative testing for the diagnosis of Brugada syndrome, long-QT syndrome, and catecholaminergic polymorphic ventricular tachycardia. *Circ Arrhythm Electrophysiol.* 2011;4:958-964. doi: 10.1161/CIRCEP.111.965947
4/6/958 [pii]
14. Tester DJ, et al. Genetic testing for potentially lethal, highly treatable inherited cardiomyopathies/channelopathies in clinical practice. *Circulation.* 2011;123:1021-1037. doi: 10.1161/CIRCULATIONAHA.109.914838
123/9/1021 [pii]
15. Clemens DJ, et al. International Triadin Knockout Syndrome Registry: The Clinical Phenotype and Treatment Outcomes of Patients with Triadin Knockout Syndrome. *Circulation: Genomic and Precision Medicine.* 2019.
16. Ackerman MJ, et al. Beta-blocker therapy for long QT syndrome and catecholaminergic polymorphic ventricular tachycardia: Are all beta-blockers equivalent? *Heart Rhythm.* 2017;14:e41-e44. doi: 10.1016/j.hrthm.2016.09.012
17. Leren IS, et al. Nadolol decreases the incidence and severity of ventricular arrhythmias during exercise stress testing compared with beta1-selective beta-blockers in patients with catecholaminergic polymorphic ventricular tachycardia. *Heart Rhythm.* 2016;13:433-440. doi: 10.1016/j.hrthm.2015.09.029
18. Peltenburg PJ, et al. An International Multicenter Cohort Study on beta-Blockers for the Treatment of Symptomatic Children With Catecholaminergic Polymorphic Ventricular Tachycardia. *Circulation.* 2022;145:333-344. doi: 10.1161/CIRCULATIONAHA.121.056018
19. Bergeman AT, et al. Flecainide Is Associated With a Lower Incidence of Arrhythmic Events in a Large Cohort of Patients With Catecholaminergic Polymorphic Ventricular Tachycardia. *Circulation.* 2023;148:2029-2037. doi: 10.1161/CIRCULATIONAHA.123.064786

20. Kannankeril PJ, et al. Efficacy of Flecainide in the Treatment of Catecholaminergic Polymorphic Ventricular Tachycardia: A Randomized Clinical Trial. *JAMA Cardiol.* 2017;2:759-766. doi: 10.1001/jamacardio.2017.1320
21. Rosso R, et al. Calcium channel blockers and beta-blockers versus beta-blockers alone for preventing exercise-induced arrhythmias in catecholaminergic polymorphic ventricular tachycardia. *Heart Rhythm.* 2007;4:1149-1154. doi: S1547-5271(07)00559-0 [pii]
10.1016/j.hrthm.2007.05.017
22. Roses-Noguer F, et al. Outcomes of defibrillator therapy in catecholaminergic polymorphic ventricular tachycardia. *Heart Rhythm.* 2014;11:58-66. doi: 10.1016/j.hrthm.2013.10.027
23. van der Werf C, et al. Implantable cardioverter-defibrillators in previously undiagnosed patients with catecholaminergic polymorphic ventricular tachycardia resuscitated from sudden cardiac arrest. *Eur Heart J.* 2019;40:2953-2961. doi: 10.1093/eurheartj/ehz309
24. Wilde AA, et al. Left cardiac sympathetic denervation for catecholaminergic polymorphic ventricular tachycardia. *N Engl J Med.* 2008;358:2024-2029. doi: 10.1056/NEJMoa0708006
358/19/2024 [pii]
25. De Ferrari GM, et al. Clinical Management of Catecholaminergic Polymorphic Ventricular Tachycardia: The Role of Left Cardiac Sympathetic Denervation. *Circulation.* 2015;131:2185-2193. doi: 10.1161/CIRCULATIONAHA.115.015731
26. Waddell-Smith KE, et al. Physical and Psychological Consequences of Left Cardiac Sympathetic Denervation in Long-QT Syndrome and Catecholaminergic Polymorphic Ventricular Tachycardia. *Circ Arrhythm Electrophysiol.* 2015;8:1151-1158. doi: 10.1161/CIRCEP.115.003159
27. Kaneshiro T, et al. Successful catheter ablation of bidirectional ventricular premature contractions triggering ventricular fibrillation in catecholaminergic polymorphic ventricular tachycardia with RyR2 mutation. *Circ Arrhythm Electrophysiol.* 2012;5:e14-17. doi: 10.1161/CIRCEP.111.966549
5/1/e14 [pii]
28. Denegri M, et al. Single delivery of an adeno-associated viral construct to transfer the CASQ2 gene to knock-in mice affected by catecholaminergic polymorphic ventricular tachycardia is able to cure the disease from birth to advanced age. *Circulation.* 2014;129:2673-2681. doi: 10.1161/CIRCULATIONAHA.113.006901
29. Roston TM, et al. Caring for the pregnant woman with an inherited arrhythmia syndrome. *Heart Rhythm.* 2019. doi: 10.1016/j.hrthm.2019.08.004
30. De Backer J, et al. 2025 ESC Guidelines for the management of cardiovascular disease and pregnancy. *Eur Heart J.* 2025. doi: 10.1093/eurheartj/ehaf193