



CPVT

Catecholaminergic Polymorphic Ventricular Tachycardia

A Guide for Clinicians



Catecholaminergic Polymorphic Ventricular Tachycardia

Introduction

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a potentially fatal cardiac arrhythmia in individuals with a structurally normal heart. The disorder is characterized by syncope, typically beginning in the first decade of life, which may be triggered by physical activity or intense emotion. In patients with CPVT, stress-induced releases of catecholamines cause a dysfunction of calcium-ion channels in myocytes. The ion channel dysfunction induces ventricular arrhythmias, which can lead to syncope or sudden cardiac death. Spontaneous recovery from the arrhythmia is possible, but the ventricular tachycardia can progress to ventricular fibrillation and sudden death.

CPVT is most commonly an autosomal-dominant genetic disorder with mutations affecting calcium regulation within the heart. A less frequent autosomal recessive disorder is clinically identical. Almost 30 % of patients with CPVT have a relative who died suddenly prior to age 40 (Priori et al. 2002). CPVT affects men and women equally. The incidence of CPVT within the population is not precisely known, but is estimated to be 1:10,000 (Liu et al. 2008).

Clinical Presentation

In many cases, the first clinical manifestation of CPVT is syncope triggered by acute emotional or physical stress. The average age of symptom onset is between seven and nine years (Priori et al. 2002; Leenhardt et al. 1995), but symptoms have been observed in patients of a wide range of ages. The diagnosis of CPVT is often not obvious because resting electrocardiograms (ECGs) appear normal, without QT prolongation, atrioventricular and intraventricular conduction defects, and Brugada-like ST-segment pattern. Furthermore, cardiac imaging exams are normal. The CPVT diagnosis is frequently missed unless an exercise stress test or Holter is performed to document ventricular arrhythmias. In some cases, sudden death can be the first symptom. Approximately 30 % of probands present with a family history of stress-related syncope, seizure, or sudden death; therefore, a detailed family history may help in establishing the proper diagnosis.

Symptoms of CPVT, which may occur without warning, include heart palpitations, dizziness, and syncope occurring during physical activity or acute emotion. It is not possible to diagnose CPVT with a standard resting 12-lead electrocardiogram; an exercise stress test is required. Exercise intensity can be increased gradually to evaluate whether VT can be induced. As exercise intensity increases further, VT may be sustained. The distinguishing characteristic of CPVT is an alternating QRS axis morphology with rotation of 180° on a beat-to-beat basis (Liu et al. 2008). Bidirectional ventricular tachycardia is typical of CPVT but is present in less than half of cases. When the typical bidirectional VT is not observed, progressive worsening of arrhythmias with increasing exercise workload may help establish the diagnosis (see Figure 1). Some patients exhibit polymorphic VT or ventricular fibrillation (Liu et al. 2008).

Clinical Diagnosis

The diagnosis is based on reproducibly elicited ventricular arrhythmias during exercise stress testing. The clinical diagnosis of CPVT includes the following features (adapted from Napolitano et al. 2009):

- Exercise-induced polymorphic ventricular arrhythmias
 - ECGs during exercise stress test reproducibly elicit arrhythmias in the majority of affected individuals.
 - Complexity of arrhythmias increases progressively with increase in workload, from isolated premature beats to bigeminy and runs of non-sustained ventricular tachycardia (VT) to longer runs of VT and even sustained ventricular tachycardia.
 - Alternating 180° QRS axis on a beat-to-beat basis (bidirectional VT).
 - Some CPVT patients may present with irregular polymorphic VT.
 - Some CPVT patients exhibit supraventricular arrhythmias.
- Syncope during exercise or acute emotion
- History of exercise or emotion-related palpitations and dizziness in the absence of structural cardiac abnormalities

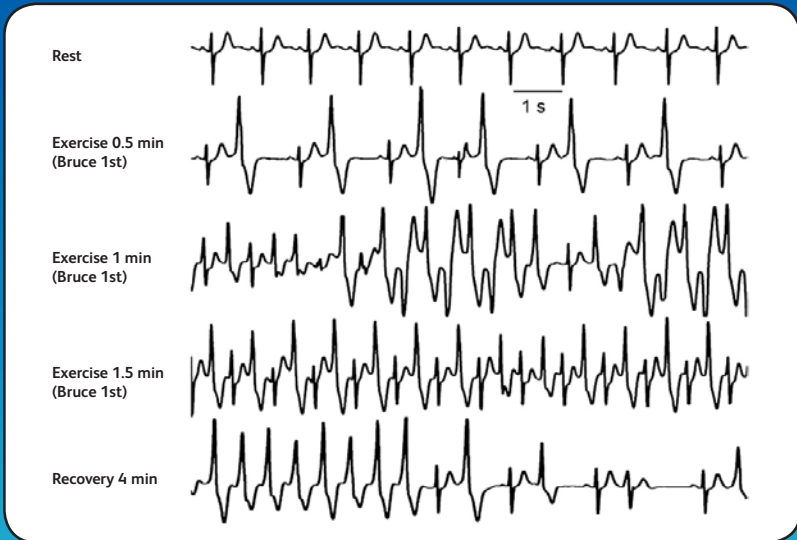


Figure 1. Exercise stress test in a patient with polymorphic VT and RYR2 mutation. Ventricular arrhythmias are observed with a progressive worsening during exercise. Typical bidirectional VT develops after one minute of exercise, with a sinus heart rate of approximately 120 beats per minute. Arrhythmias rapidly recede during recovery. (Image from Liu et al. 2008)

Management

Several management strategies exist for CPVT:

Drugs—Beta-adrenergic blockers are indicated for primary prevention in all clinically affected individuals with CPVT (Napolitano et al. 2009). Although no quantitative data are available on actual risk of a cardiac arrest as the first manifestation of the disease, beta blocker treatment has been recommended for individuals with an RYR2 mutation and neither a history of cardiac events (syncope) nor ventricular arrhythmias on exercise stress testing (Napolitano et al. 2009). In symptomatic patients with CPVT, the maximum dose that is tolerated should be maintained. The reproducible induction of arrhythmia during exercise allows effective dose titration and monitoring. Efficacy of β -blockers on long-term follow-up seems to be variable, however, and is not sufficient to prevent CPVT symptoms in all cases.

ICD—In cases in which β -blocker therapy is not fully effective, implantable cardioverter defibrillator (ICD) devices can be used. For example, in cases in which the highest tolerated dose of β -blockers fails to control arrhythmias sufficiently, an ICD should be considered.

Lifestyle changes—CPVT-affected patients who show exercise-induced arrhythmias should avoid competitive sports and intense physical activity.

Surveillance—CPVT patients should be monitored for effectiveness of therapy. Follow-up visits should occur every six to twelve months, based on the severity of clinical symptoms. Follow-up monitoring should include resting ECG, Holter monitoring, and an exercise stress test performed at the maximum age-predicted heart rate (Napolitano et al. 2009).

Genetics of CPVT

Mutations in at least two genes have been associated with CPVT—RYR2, which codes for the cardiac ryanodine receptor channel, and CASQ2, which encodes calsequestrin, a calcium-buffering protein in the sarcoplasmic reticulum (SR) (Priori et al. 2002). Mutations in these two genes account for 50 % - 70 % (Liu et al. 2008) of CPVT cases. The majority of identifiable mutations occur in the RYR2 gene, which is inherited in an autosomal-dominant manner. Each child of an individual with autosomal-dominant, RYR2-associated CPVT has a 50 % chance of inheriting the mutation. De novo mutations have been observed and may account for half of autosomal-dominant CPVT cases, likely due to the high rate of premature death (Napolitano et al 2009). Less frequent are mutations in the CASQ2 gene, causing an autosomal-recessive genetic disorder. Parents of an affected child are unaffected carriers, while full siblings of the proband have a 25 % chance of also having CPVT.

Indications and Utility of Genetic Testing

Genetic testing in a clinically affected patient with CPVT can clarify the diagnosis and assist in the management of family members. Identification of a mutation in the family can lead to genetic identification of at-risk family members who are clinically asymptomatic. A negative genetic test result for the familial mutation could obviate the need for repeated follow-up examinations.

Since treatment and surveillance are available and can help reduce morbidity and mortality, first-degree relatives of individuals with RYR2-associated CPVT and siblings of CASQ2-associated CPVT should be offered molecular genetic testing if the family-specific mutation is known. If the family-specific mutation is not known, first-degree relatives of an affected individual should be evaluated with resting ECG, Holter monitoring, and stress test (Napolitano et al. 2009).

Genetic Testing Results and What They Mean

Diagnostic genetic testing can be considered for patients who clinically manifest with symptoms of CPVT and for patients who are asymptomatic but are from a family with a known mutation. Testing should be performed first on the family member who is symptomatic—i.e., has clinical manifestations of CPVT. Preferably, the youngest of the most severely affected family members should be tested first. The three possible outcomes of genetic testing are: positive, negative, and variant of unknown clinical significance (VOUS). All patients who undergo genetic testing should receive pre-test and post-test genetic counseling so that they can understand the implications of testing. Information about genetic counseling services can be found at www.nsgc.org.

- **Positive result:**

A positive test result indicates that one or more disease-causing mutations were identified in that individual. This finding can help confirm the diagnosis of CPVT and provides valuable information to family members. Relatives (children, siblings, and parents for RYR2-associated CPVT, and siblings for CASQ2-associated CPVT) of the proband can then be offered predictive genetic testing to determine their risk for CPVT. If a family member is found to be positive for the familial mutation(s), this individual is considered to be at risk for CPVT and is a candidate for beta-blocker therapy and monitoring every six to twelve months (Napolitano et al. 2009).

- **Negative result:**

A negative result in an affected individual does not rule out CPVT, and the patient should be managed according to his or her clinical symptoms. Possible reasons for a negative result could be: (1) patient may have a mutation in a gene not covered in the testing panel, or (2) patient may have a mutation in a part of a CPVT-associated gene that was not covered in the test. Predictive genetic testing of family members when the affected family member's test is negative is neither informative nor warranted. Family members of a clinically affected individual with negative test results may still be at risk for CPVT and thus should be regularly screened by a cardiologist. In addition, cardiac clearance prior to participation in competitive sports is highly recommended. If an asymptomatic individual is negative for a mutation identified in a family member, this person is considered a true negative and is not at increased genetic risk for familial CPVT.

- **Variant of Unknown Clinical Significance (VOUS)**

A VOUS result indicates that the pathogenicity of the genetic variant cannot clearly be established. The VOUS has been tested in a panel of normal individuals and was not identified in any of the normal individuals. To further clarify the clinical significance of this variant, testing of family members is helpful. If an affected adult relative is found to have the same variant, it is more likely that the variant is disease-causing. The greater the number of affected family members who carry the VOUS, the greater the likelihood that the VOUS is pathogenic. With consistent linkage of the VOUS with symptomatic family members, the variant found would be reclassified as a family-specific mutation, and extended family members could be offered predictive genetic testing.

References

1. Napolitano C, Priori SG and Bloise R. Catecholaminergic polymorphic ventricular tachycardia. *GeneReviews*. NCBI/NIH. Initial posting 2004, last update 2009.
2. Liu N, Ruan Y, Priori SG. Catecholaminergic polymorphic ventricular tachycardia. *Progress in Cardiovascular Diseases*. 51(1); 2008. 23-30.
3. Leenhardt A, Lucet V, Denjoy I et al. Catecholaminergic polymorphic ventricular tachycardia in children: a seven-year follow-up of 21 patients. *Circulation* 91: 1512-1519. 1995.
4. Priori SG, Napolitano C, Memmi M et al. Clinical and molecular characterization of patients with catecholaminergic polymorphic ventricular tachycardia. *Circulation* 106; 69-74. 2002.

About GeneDx

GeneDx was founded in 2000 by two scientists from the National Institutes of Health (NIH) to address the needs of patients and clinicians in diagnosing rare inherited disorders. Currently, GeneDx offers testing for more than 200 rare Mendelian disorders, oligonucleotide-microarray-based testing for detection of chromosomal abnormalities, testing for autism spectrum disorders, and gene panels for testing various forms of inherited cardiac disorders. Our highly trained and experienced physicians, geneticists, and genetic counselors work as a team to bring gene discoveries to clinical medicine for use in direct patient care. We invite you to visit our website, www.genedx.com, to learn more about us and the services we offer.

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