REVIEW

Insights into the Clinical Spectrum of Catecholaminergic Polymorphic Ventricular Tachycardia

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Abstract

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is induced by stress or exertion especially in young individuals with normal baseline ECG and without any structural heart disease. The most common type of ventricular tachycardia (VT) in these patients is bidirectional VT but could also be polymorphic VT or ventricular fibrillation. These two main types of CPVT are caused by mutations on the ryanodine (RyR2) or calsequestrin (CASQ2) receptor, with an autosomal dominant and recessive inheritance pattern respectively. The prognosis is dismal without treatment and the main therapeutic approach consists of administration of beta blocker, flecainide, calcium channel blockers or ICD implantation. Genetic testing is important for all family members of CPVT probands in order to identify asymptomatic carriers. ***Rhythmos*** 2018;13(1):6-8.

Keywords: catecholaminergic polymorphic ventricular tachycardia; sudden cardiac death; genetic testing; channelopathies

Abbreviations: CASQ2 = calsequestrin receptor, CPVT = catecholaminergic polymorphic ventricular tachycardia, DADs = delayed after – depolarizations, ICD = implantable cardiac defibrillator, RyR2 = ryanodine receptor, SCD = sudden cardiac death

Introduction

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a rare inherited potentially lethal cardiac arrhythmia, first described by Reid in 1975 and more systematically by Coumel in 1978.[1,2] It is induced by emotional stress or exercise usually during the first or second decade of life in patients without structural heart disease and may be either polymorphic or bidirectional ventricular tachycardia (VT) or ventricular fibrillation (**Fig**. 1). Common clinical manifestations of CPVT are syncope or sudden cardiac death (SCD). [3]

Genetic basis of CPVT

About 5 types of CPVT have been described, but the most common type accounting for 50-60% of the cases in an autosomal dominant form, is caused by a mutation on the hRyR2 gene that encodes for the cardiac ryanodine receptor (RyR2). The RyR2 is involved in the regulation of cardiac calcium (Ca^{+2}) homeostasis controlling its release from the sarcoplasmic reticulum to the cytosol in response to the Ca^{+2} entry during the plateau phase of the action potential.[4] The second most common type of CPVT is caused by a mutation on the CASQ2 gene, encoding for calsequestrin and the rate of SCD is higher than that observed in the first type.[5] Mutations on the KCNJ2 gene have been described in individuals presented with exercise induced bidirectional VT without QTc prolongation. These patients do not have the phenotypic abnormalities related to Andersen-Tawil syndrome which is also caused by mutations in the same gene.[6,7]

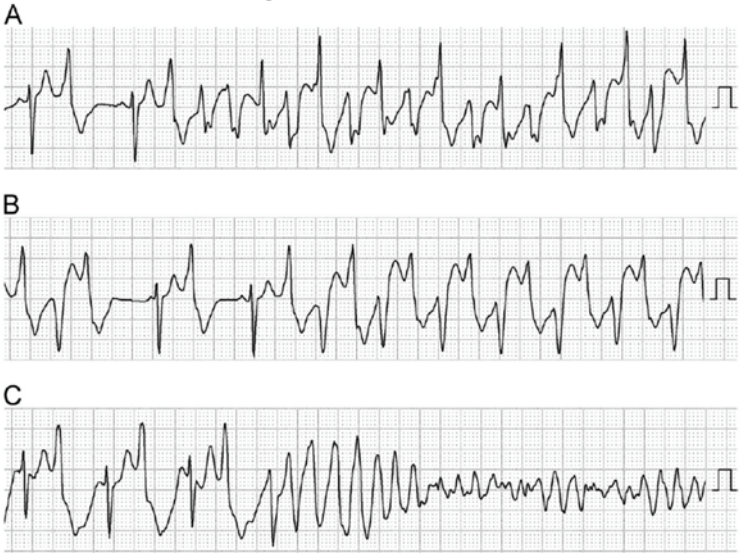

Figure 1. Clinical and ECG types of catecholaminergic polymorphic ventricular tachycardia (CPVT), A: Polymorphic VT, B: Bidirectional VT, C: Ventricular Fibrillation

Natural history and clinical presentation

The prevalence of CPVT is estimated ~1:10,000 but due to the nature of the syndrome it is not easy to know the exact prevalence since the first clinical presentation could be SCD.[2] CPVT is a familial cardiac arrhythmia and about 30% of probands have a family history of SCD before the age of 40 years.[8] Patients have their first symptoms in early childhood but the mean age of the onset of syncope is 12 years.[9] The resting ECG and the echocardiogram are usually normal and patients have syncopal episodes during stress which could be easily ascribed to neurologic disorders. Thus, diagnosis is usually delayed which may lead to a fatal outcome. Some patients have sinus bradycardia or prominent U waves in the resting ECG. Bradycardia may be due to the impaired handling of Ca^{+2} by the mutant RyR2 channel in the sinoatrial nodal cells.[10] Also, in some cases a mild prolongation of the QT interval has been reported, thus implicating long QT syndrome in the differential diagnosis of the syncope. [11,12]

The most important clinical test to diagnose CPVT is the *exercise stress test* and this should be performed in all patients with adrenergically driven – syncope. The typical pattern consists of the appearance of premature ventricular beats, isolated or in couplets, usually polymorphic, when the heart rate is >100 bpm followed by runs of VT at upper

heart rate values.[8,13] As mentioned above, the tachycardia could be either polymorphic or bidirectional which is the typical characteristic pattern of CPVT. Bidirectional VT is characterized by an 180^0 beat to beat change of the frontal QRS axis and is caused by delayed after – depolarizations (DADs) – induced triggered activity due to excessive Ca^{+2} diastolic release.[8,14] Although this pattern is typical for the majority of patients, CPVT could also be manifested either as polymorphic VT or ventricular fibrillation (VF).[8]

Additionally, supraventricular tachyarrhythmias may occur in patients with CPVT. Sustained or non – sustained atrial tachycardias and atrial fibrillation are sometimes observed during exercise. The Ca^{+2} overload caused by those supraventricular tachycardias could in turn promote triggered activity in the ventricle.[15] It must be noted that the origin of CPVT VTs could be in the right and/or left ventricular outflow tract area or even at the right ventricular apex, suggesting a multifocal origin.[16]

Exercise testing remains the cornerstone of clinical tools to reproduce the VT patterns of CPVT. VT is not inducible during an electrophysiology study with programmed ventricular stimulation, and such study does not have any prognostic value. Contrariwise, heart rhythm monitoring, either with ambulatory Holter recording or with implantable loop recorders, is very useful to diagnose CPVT especially in patients with emotional stress. [17]

Management of patients with CPVT

The mortality rate for untreated individuals with CPVT may reach 50% by 20 years of age.[11] Current treatment includes curtailed exercise, avoidance of stressful situations, and β-blocker therapy. Beta blockers, and specifically those without intrinsic sympathomimetic activity, are considered the first line treatment option in patients with CPVT.[17] The recommended beta blocker is nadolol, which is a long-acting drug, at a dose of 1-2 mg/kg.[2] Propranolol is an alternative beta blocker since nadolol is not available in several countries. Dosage titration and follow up with beta blocker therapy require repeated exercise tests and Holter recordings. The annual rate of arrhythmic events on beta-blockers ranges between 3% and 11% per year.[18] In the Italian CPVT registry ~30% of patients had recurrent arrhythmia episodes treated with the maximal tolerated dose of beta blockers.[8,19]

Flecainide seems to have a beneficial effect in the suppression of ventricular arrhythmia events and it was initially tested in a CASQ2 knock-out mouse model.[20] The exact mechanism is not yet clearly defined and small case series have been reported. Flecainide add-on therapy in patients already receiving beta blocker without complete suppression of ventricular arrhythmias is recommended.[17] According to a first small randomized cross-over study, in 13 patients with CPVT receiving background beta-blocker therapy and fitted with an implantable cardioverter defibrillator (ICD), the median ventricular arrhythmia score during exercise was significantly reduced by flecainide (0 vs 2.5 for placebo; $P < .01$), with complete suppression observed in 11 of 13 patients (85%) with no difference in the overall and serious adverse events between the flecainide and placebo arms. [21]

In addition to medical therapy, an ICD should be implanted in patients with aborted SCD. Painful ICD shocks can increase sympathetic tone leading to electrical storm and repeated ICD discharges which could be potentially fatal. Hence, it is crucial to carefully program the ICD parameters with long delays and high cut off rates taking also into account the high incidence of supra-ventricular arrhythmias in these patients.[22,23] In a 2-year follow up ~50% of patients with implanted ICD received appropriate therapy despite medical therapy. Also, in the same cohort, patients without secondary prevention indication also received appropriate ICD discharges.[19]

Calcium channel blockers, mainly verapamil, have also been studied in patients with CPVT.[24] Rosso et al reported a reduction in the arrhythmic events in patients who received verapamil plus beta blocker.[25]

Left cervical sympathectomy is indicated for patients in whom beta blockers are contraindicated or cases with an ICD who continue having recurrent VT episodes despite maximal drug therapy.[26] Nevertheless, this therapy should not be considered as an alternative to ICD implantation as it has not proved the elimination of ventricular arrhythmias during long-term follow up. Moreover, it requires well trained surgeons in order to avoid complications, like Horner syndrome which is rare in experienced centers.[27]

Screening is useful for patients who suffer from CPVT and their family members. Both clinical evaluation and genetic testing are required to identify undiagnosed and asymptomatic family members in the presence of CPVT probands. To date, over 130 mutations have been reported showing a high degree of genetic heterogeneity.[28] The autosomal dominant variant, which is related to RyR2 mutations, is by far more frequent (50%-55% of patients with CPVT).[4] Because RyR2 is one of the largest genes in the human genome, with 105 exons, many laboratories have limited the test only on selected regions (about 66 exons) which have been related to CPVT, with a lower detection sensitivity.[29] Screening should be performed in all definitive CPVT probands and considered in subjects with idiopathic VF when an adrenergic trigger is identified. On the other hand, screening for CASQ2 mutation concerns subjects in whom a recessive pattern of inheritance has been observed or when the RyR2 screening

is negative. In total, the yield of genetic testing is about 55 – 60% and when clinical diagnosis is clear it shows a good cost – effectiveness ratio.[30]

New modes of therapy, such as gene therapy for CPVT caused by *CASQ2* loss-of-function variants,[31] are currently being explored and may hopefully become available in the future for this potentially lethal form of inherited channelopathy.

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