VIEWPOINT

Diagnosis and treatment of catecholaminergic polymorphic ventricular tachycardia

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Catecholaminergic polymorphic ventricular tachycardia (VT) was first described by Reid et al[1] in 1975 and by Coumel et al in 1978. The condition was described as a familial cardiac arrhythmia that occurs in patients with structurally normal heart and causes exercise-/emotion-triggered syncope and sudden death with a distinctive pattern of ventricular and supraventricular arrhythmias. Since the first ryanodine receptor mutations were identified in 2001,[2] it appeared evident that catecholaminergic polymorphic VT was caused by uncontrolled Ca^{2+} release from the sarcoplasmic reticulum.[3] Subsequent experimental studies demonstrated that such abnormal calcium handling caused arrhythmias mediated by delayed afterdepolarizations and triggered activity.[4] This article reviews the current knowledge of the diagnosis and therapy for catecholaminergic polymorphic VT and outlines the open issues to be addressed in order to reduce the burden of life-threatening cardiac events in patients with this lethal disorder.

Clinical presentation and diagnosis

Syncope triggered by exercise or emotion often is the initial manifestation of catecholaminergic polymorphic VT.[5,6] The mean age of onset is between 7 and 9 years,[5–7] although later onset has been reported. Approximately 30% of probands have a family history of sudden death before age 40 years,[6] and sudden death can be the first manifestation of the disease in a relevant proportion of cases.[6,8]

The resting ECG of patients with catecholaminergic polymorphic VT usually is normal, although some authors have reported lower-than-normal heart rates,[7] and others have observed prominent U waves.[5,9] Overall, these features are not consistent and are not sufficiently specific for diagnosis. The typical picture of a patient with catecholaminergic polymorphic VT who first presents to a physician is that of a youngster who has experienced one or more syncopal episodes but has a normal ECG and echocardiogram. Because of this presentation, the origin of the syncope may be easily attributed to neurologic disorders, and catecholaminergic polymorphic VT diagnosis may be established only after some delay: 2 ± 0.8 years since the first symptom in our series.[6] Such diagnostic lag should be avoided given the high lethality of the disease.

Arrhythmias in catecholaminergic polymorphic VT

Ventricular arrhythmias in catecholaminergic polymorphic VT typically present with alternating QRS axis with 180° rotation on a beat-to-beat basis, so-called *bidirectional ventricular tachycardia.*

Onset of ectopic activity during exercise stress test is consistently observed at heart rates >110–120 bpm. The complexity and frequency of arrhythmias progressively worsen as workload increases. If exercise is not promptly discontinued, bidirectional VT may degenerate into polymorphic VT and fibrillation. Catecholaminergic polymorphic VT arrhythmias are not inducible during programmed electrical stimulation.[5,6,10]

Catecholaminergic polymorphic VT arrhythmias may originate from both the right and the left ventricular outflow tract (more frequently from the left) as well as the right ventricular apex.[10] In some patients, the initial beat of the tachycardia is not unifocal, suggesting multifocal origin. As a practical consequence, no ECG lead is "best" for detecting the bidirectional pattern of VT.

Supraventricular arrhythmia is part of the catecholaminergic polymorphic VT phenotype. Isolated atrial ectopic beats, nonsustained supraventricular tachycardia, and short runs of atrial fibrillation usually are observed during exercise, with an onset pattern similar to that of ventricular arrhythmias.[5,6,10] In light of the role of triggered activity as a mechanism for arrhythmias in catecholaminergic polymorphic VT,[4] it is interesting to note that the fast supraventricular rate caused by supraventricular tachycardia may act as a trigger for the development of delayed afterdepolarizations and triggered activity in the ventricle.

Catecholaminergic polymorphic VT should be considered in the differential diagnosis of all cases of idiopathic ventricular fibrillation (VF), especially if an adrenergic trigger is present. In 2002, we first reported RyR2 mutations in patients with idiopathic VF.[6] More recently, Krahn

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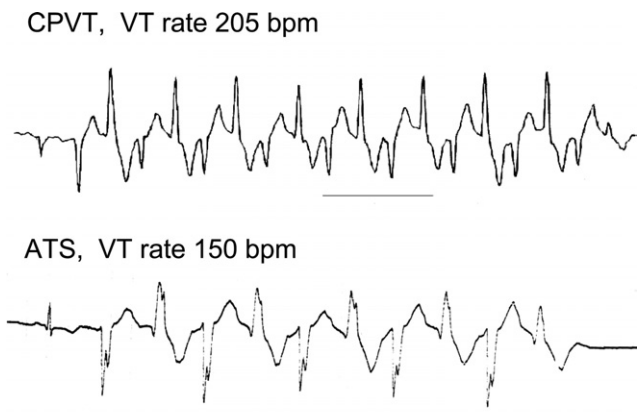

Figure 1 Example of bidirectional ventricular tachycardia (VT) in a patient with RyR2-catecholaminergic polymorphic ventricular tachycardia (CPVT; **top**) and a patient with Andersen-Tawil syndrome (ATS) with a *KCNJ2* mutation **(bottom)**. The rate of tachycardia usually is faster and coupling interval shorter in CPVT-related arrhythmias. An adrenergic trigger invariably is present in catecholaminergic polymorphic VT but often is absent in Andersen-Tawil syndrome.

et al[11] showed that 10 (56%) of 18 patients resuscitated from an unexplained cardiac arrest (normal coronary arteries, normal ventricular function, and normal ECG) can be diagnosed as having catecholaminergic polymorphic VT. Overall, these data seem to support the idea that catecholaminergic polymorphic VT is a relevant cause of adrenergic-triggered (exercise/emotion) idiopathic VF.

Independent of the clinical presentation (syncope or aborted sudden death), the most important step for diagnosis is the ability to reproduce the typical arrhythmic pattern of VT (Figure 1A) by exercise stress test or isoproterenol infusion.[6,10] Holter monitoring also may be important for those patients in whom emotional stress is a major trigger.

Some authors have suggested a possible parallelism between catecholaminergic polymorphic VT and Andersen-Tawil syndrome, an inherited arrhythmogenic disorder caused by mutations in the *KCNJ2* gene.

Andersen-Tawil syndrome is characterized by cardiac (QT prolongation, prominent U waves) and extracardiac (facial dysmorphisms, periodic paralysis) phenotypes.[12] Interestingly, we and others have observed cases of Andersen-Tawil syndrome with bidirectional VT similar to that of catecholaminergic polymorphic VT (Figure 1). Based on these findings, screening for *KCNJ2* as a gene for catecholaminergic polymorphic VT has been proposed.[13]

If *KCNJ2*-related bidirectional VT is considered a catecholaminergic polymorphic VT phenocopy, particularly in patients with Andersen-Tawil syndrome having borderline QT interval prolongation,[14] then *KCNJ2* cannot be considered a gene for catecholaminergic polymorphic VT. Indeed, relevant differences exist between the phenotypes linked with the two genes. Sudden death is exceptional among Andersen-Tawil syndrome and *KCNJ2* mutation carriers.[15] Furthermore, the adrenergic triggers for events and supraventricular arrhythmias are typical in *RyR2*-catecholaminergic polymorphic VT, and careful investigation that includes neurologic assessment and detection of facial dysmorphisms allows the diagnosis of *KCNJ2* Andersen-Tawil syndrome.

Role of genetic testing in catecholaminergic polymorphic VT

Catecholaminergic polymorphic VT may have both an autosomal dominant and an autosomal recessive pattern of inheritance. The autosomal dominant variant is by far more frequent. It is due to mutations in the cardiac ryanodine receptor gene *RyR2*,[2] which causes uncontrolled Ca^{2+} release from the sarcoplasmic reticulum during electrical diastole. Autosomal recessive catecholaminergic polymorphic VT is due to mutations in the cardiac calsequestrin gene *CASQ2*.[16] CASQ2 is a sarcoplasmic reticulum Ca^{2+} buffering protein that plays an active role in the control of calcium release from sarcoplasmic reticulum to cytosol.

Approximately 50%–55% of patients with catecholaminergic polymorphic VT harbor *RyR2* mutations. Because the RyR2-coding region is one of the largest in the human genome, genetic testing is time-consuming and is associated with high cost. However, it is important to emphasize that the entire coding region of the *RyR2* gene should be analyzed, as one study showed that the yield of "targeted screening" (i.e., analysis of exons previously involved in catecholaminergic polymorphic VT) is $<40\%$.[17] Screening should be performed in all definitive catecholaminergic polymorphic VT probands and considered in subjects with idiopathic VF when an adrenergic trigger is identified.

CASQ2 screening is advisable in all pedigrees compatible with a recessive pattern of inheritance but also in all apparently sporadic catecholaminergic polymorphic VT cases with negative RyR2 screening even in the absence of parental consanguinity. Compound heterozygous carriers in nonconsanguineous families may occur.[18] Using a comprehensive screening approach, the percentage of successfully genotyped catecholaminergic polymorphic VT patients is approximately 55%–60%.[19]

The severe clinical manifestations of catecholaminergic polymorphic VT strongly support the use of genetic testing for presymptomatic diagnosis, preventive therapy, and reproductive risk assessment.[20]

Natural history and response to therapy

From an historical perspective, studies assessing the natural history of inherited arrhythmogenic diseases after the initial description of a novel clinical entity consistently report less severe phenotypes over time. This is due to referral bias to international registries; initially the most severe cases are referred/recognized, but once physicians become aware of the disease and diagnostic skills improve, physicians tend to refer larger percentages of asymptomatic patients.[21]

Interestingly, this trend does not appear to be the case with catecholaminergic polymorphic VT. In 2002, we reported data showing that exercise-/emotion-induced syncopal episodes occurred in 67% of patients, and juvenile sudden cardiac death was detectable in 33% of patients from

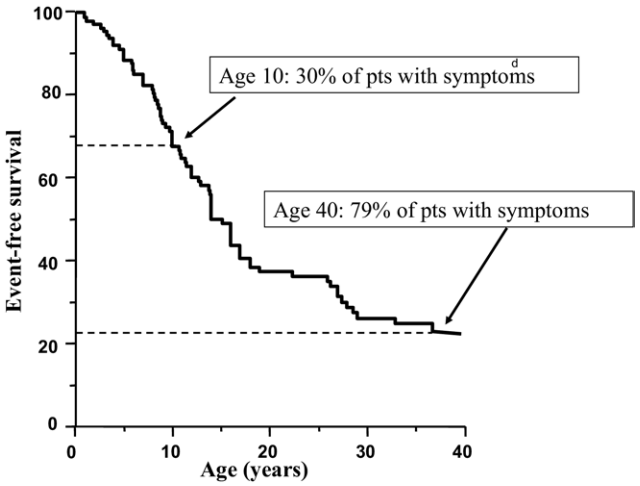

Figure 2 Natural history of catecholaminergic polymorphic ventricular tachycardia in 119 patients. Survival analysis shows time to first cardiac event (syncope, ventricular fibrillation, or sudden death) in the absence of beta-blocker therapy.

among 30 families.[6] These data were substantially confirmed by a Japanese group in 2003,[10] by a European study in 2005,[7] and by a reanalysis of our database of 119 patients, which showed that close to 80% of patients experienced cardiac events before age 40 years (Figure 2).[22] These data on severity are corroborated by the high level of penetrance of the disease (75%–80% according to the largest studies available[6,7]). Therefore, based on current data, catecholaminergic polymorphic VT should be regarded as one of the most severe of the inherited arrhythmogenic disorders.

Therapy

Beta-blockers have been proposed as the mainstay of catecholaminergic polymorphic VT therapy since the early reports[2,5,23] and are indicated for both chronic treatment and acute therapy for sustained VT.

Published reports on the long-term effectiveness of beta-blocking agents have presented conflicting evidence. Whereas Leenhardt et al[5] and Postma et al[7] reported almost complete prevention from recurrence of cardiac events with the exception of noncompliant patients, we[6] and others[10] observed recurrence of cardiac events or incomplete protection from exercise-induced arrhythmias. Furthermore, we showed that approximately half of the "resistant" patients who received an implantable cardioverter-defibrillator (ICD) and were maintained on high doses of beta-blockers had appropriate device intervention after 20 months of follow-up.[6] Data from larger series are needed to determine the reasons for such contradicting results.

Notwithstanding, exercise stress test and Holter monitoring are extremely important in titrating the initial beta-blocker dosage (in our center, nadolol is started at 1.5–2 mg/kg/day). These tests should be performed on a regular basis during follow-up in order to achieve optimal control of arrhythmias.

Additional forms of pharmacologic treatment of catecholaminergic polymorphic VT have been proposed, but failures using sodium channel blockers[5,10] and amiodarone[5] have been reported. Other authors have reported partial effectiveness with use of verapamil in a single patient,[10] but this finding has not been confirmed by others (SG Priori, personal communication). Thus, no drugs can be considered definitely effective in providing additional protection in combination with beta-blockers. Although indicated for all patients resuscitated from cardiac arrest, ICD placement also should be considered for those with recurrence of syncope/sustained VT while undergoing therapy with beta-blockers.[24] Beta-blockers also are indicated for all silent carriers of an *RyR2* mutation.[24]

Conclusion and future perspectives

The medical community has actively worked to gather a large amount of information on the clinical presentation and diagnosis of catecholaminergic polymorphic VT. Analyses of the natural history and clinical presentation depict a severe disorder that has a straightforward diagnosis in the majority of patients because of the typical pattern of arrhythmias during exercise stress test. However, possibly because of the low level of awareness of the clinical features among physicians diagnosis of the disease may be delayed, placing patients at increased risk for life-threatening arrhythmias.

With the exception of beta-blockers, no pharmacologic therapy of proven effectiveness is available. Thus, patients with catecholaminergic polymorphic VT who still present with arrhythmias despite chronic therapy with maximally tolerated doses of beta-blocker are candidates for ICD placement. Experimental studies and animal models[4,25] will be crucial to designing novel therapies in the future.

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