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REVIEW

Clinical Challenges in Catecholaminergic Polymorphic Ventricular Tachycardia

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Catecholaminergic polymorphic ventricular tachycardia (CPVT) is an inheritable cardiac disorder associated with exercise- and stress-induced sudden death in young individuals.
Although important steps forward have been made in the comprehension and treatment of this disease, several aspects remain unclear. Firstly, from an epidemiological standpoint the actual prevalence of CPVT is still unknown and possibly underestimated. In addition, the diagnostic process remains very challenging and can be supported by genetic analysis in only about half of the cases. Finally, up to one third of CPVT patients continue to present complex arrhythmias despite beta blocker treatment; the role of newer therapeutic options, such as flecainide and left cardiac sympathetic denervation, needs to be further elucidated. All these points constitute challenges for the cardiologist in the management of CPVT patients and fuel research into new diagnostic, prognostic and therapeutic approaches.

Keywords Catecholaminergic polymorphic ventricular tachycardia • Sudden cardiac death • Bidirectional ventricular tachycardia • RyR2 • CASQ2 • Flecainide

Introduction

Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) is a lethal disease characterised by syncope and cardiac arrest occurring during exercise or emotional stress [1]. Although it is rare, this condition is clinically relevant due to the fact that it is responsible for many sudden deaths in children and young adults with morphologically normal hearts [2].

Catecholaminergic polymorphic ventricular tachycardia belongs to a group of inheritable disorders referred to as ''channelopathies'', caused by mutations in genes coding for channel-proteins that regulate cardiac electrical function [3]. In the absence of evident heart abnormalities, CPVT and the other channelopathies alter the balance of ionic currents that generate the cardiac action potential and control the excitation-contraction coupling in the cardiomyocytes, favouring the onset of life-threatening arrhythmias.

In the present document we will review the principal characteristics of CPVT (epidemiology, genetic background, clinical manifestations, diagnosis and management of patients), highlighting those aspects that still need to be improved upon and that constitute clinical challenges for the cardiologist.

Epidemiology

Catecholaminergic polymorphic ventricular tachycardia is considered a rare disorder, with a commonly quoted

Abbreviations: bpm, beats per minute; CASQ2, Calsequestrin 2; CPVT, Catecholaminergic Polymorphic Ventricular Tachycardia; ECG, Electrocardiogram; HR, Heart Rate; ICD, Implantable Cardioverter Defibrillator; LBBB, Left Bundle Branch Block; LCSD, Left Cardiac Sympathetic Denervation; RyR2, Ryanodine Receptor 2; SCD, Sudden Cardiac Death; SR, Sarcoplasmic Reticulum; VPB, Ventricular Premature Beat; VT, Ventricular Tachycardia

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incidence of 1 in 10,000 [4], but its actual frequency in the general population is unknown. Additionally, a variety of factors suggest that this incidence may be an underestimate.

First, resting electrocardiograms (ECG), which are the mainstay for the diagnosis of other channelopathies (such as the Long QT Syndrome or Brugada Syndrome), are often unremarkable in CPVT [5]. Additionally, exercise-induced syncope, a common presenting symptom for CPVT [6], can be falsely attributed to non-cardiac conditions unless there is enough clinical suspicion and specific tests are performed. To support this statement, Roston et al. found in a study on 226 CPVT patients that the diagnosis was established almost two years after the first symptomatic event [7], thus leaving patients untreated and exposed to arrhythmic risk. Finally, in patients whose first manifestation is sudden death, the diagnosis may be missed during autopsy because CPVT does not induce those structural alterations in cardiac muscle that can normally be detected by macroscopic and/or microscopic methods. In these cases only molecular analysis may help unveil the diagnosis [8], as reported in a recent paper by Jiménez-Jáimez et al., who found that 14% (5/35) of sudden deaths in patients with negative autopsies were associated with CPVT-related mutations [9]. On the basis of these and similar evidences, the European Society of Cardiology has recently released a guideline document for the prevention of Sudden Cardiac Death (SCD) that recommends performing an autopsy in all cases of unexplained sudden death. Importantly, post-mortem examination of the heart should be performed by experts in cardiac pathology and should include the collection and preservation of tissue to allow for DNA analysis when the death is deemed to be related to inherited conditions, such as CPVT [3].

Challenges to calculating the true prevalence of CPVT:

- *It is difficult to recognise CPVT patients, due to normal resting ECGs, unless there is an increased degree of clinical suspicion;*
- *Sudden Cardiac Death can be the first presentation of CPVT and often is not investigated further.*

Potential solutions:

- *Encourage family and sport doctors to further investigate patients with symptoms suggestive of CPVT, such as syncope occurring during exercise;*
- *Implement molecular autopsies in the standard post-mortem examination of cases of unexplained sudden death.*

Genetic Background

The familial nature of CPVT has been recognised since the first reports of the disease [5] and was confirmed in the early 2000s with the identification of two main genetic variants that explain the majority of genotype-positive cases. The most frequent form of CPVT (about 60% of cases) [10] is related to autosomal dominant mutations in the *RyR2* gene, which encodes for the cardiac ryanodine receptor [6]. RYR2 is a large channel-protein consisting of four identical subunits that is located in the sarcoplasmic reticulum (SR) membrane and involved in electromechanical coupling, the process that links the electrical activation of the heart to its mechanical contraction [11]. The second variant of CPVT (less than 5% of cases) [10] is related to autosomal recessive mutations in the *CASQ2* gene encoding for cardiac calsequestrin [12], a calcium-buffering protein situated within the SR that also has inhibitory effects on RYR2 activity [13].

Both the autosomal dominant and the autosomal recessive variants lead to arrhythmias via a shared mechanism that alters the calcium homeostasis in cardiomyocytes [11]. In physiological conditions, RYR2 opens briefly during the early plateau phase of the action potential and mediates a massive release of calcium from the SR that initiates the contraction of the cardiomyocyte (i.e. the systolic phase of the cardiac cycle) [14]. After systole is completed, calcium ions are actively pumped back into the SR by the SR Ca-ATPase (SERCA2a) to allow for the relaxation of cardiac muscle (i.e. the diastolic phase), thereby completing this ''calcium cycle'' [11]. Mutations in both *RyR2* and *CASQ2* cause spontaneous leakage of calcium ions from the SR in diastole, particularly during intense adrenergic activation, such as strenuous physical activity or emotions. The resultant calcium overload induces the development of delayed after-depolarisations that can trigger supraventricular and ventricular extrasystoles, which have the potential to degenerate into sustained hyperkinetic arrhythmias [15].

Although *RyR2* and *CASQ2* are evidently major substrates for the disease, they do not account for all cases of CPVT and therefore other genes involved in the cardiac calcium release complex have also been investigated as potential candidates. Roux-Buisson et al. screened 97 probands and found three related variants in the Triadin gene *TRDN*, encoding a protein that links RYR2 and CASQ2 in the SR [16]. In 2015, Rooyrk et al. also found two mutations in *TRDN*, providing further support for the role this protein may play in the disease [17]. Moreover, by performing a genome-wide linkage analysis in a large Swedish family with severe dominantly inherited CPVT-like arrhythmias, Nyegaard et al. identified *CALM1* as a new candidate gene for CPVT [18]. *CALM1* encodes calmodulin, which is a ubiquitous calcium-binding protein that stabilises RYR2 and reduces the probability of its opening during diastole [18].

Finally, mutations in *Ank2* [19] and *KCNJ2* [20] genes may be found in a minority of patients (<1%) who exhibit both adrenergically-induced ventricular arrhythmias and QT interval prolongation. Due to this overlap of phenotypes, both genes have been linked to variants of Long QT Syndrome (type 4 and type 7, respectively), and they offer