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REVIEW

Clinical Challenges in Catecholaminergic Polymorphic Ventricular Tachycardia

Jacopo F. Imberti, BS [a], Katherine Underwood, BS [a], Andrea Mazzanti, MD [a], Silvia G. Priori, MD, PhD [a,b*]

[a]Molecular Cardiology, IRCCS Salvatore Maugeri Foundation, Pavia, Italy
[b]Department of Molecular Medicine, University of Pavia, Pavia, Italy

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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

*Corresponding author at: Molecular Cardiology - IRCCS Salvatore Maugeri Foundation, University of Pavia, Via Maugeri, 10 - 27100 Pavia, Italy.
Tel.: +390382592040; fax: +390382592059, Email: silvia.priori@fsm.it

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

interesting examples of arrhythmic conditions that phenocopy each other.

Despite this genetic heterogeneity, about one third of CPVT cases still remain classified as genotype-unknown today. As it has been seen with other channelopathies, it is expected that more related genes will be identified with the widespread use of new technologies for DNA sequencing, such as next generation sequencing, which will allow for the screening of a large number of genes, and even the entire genome when required, at reduced prices and turnaround times. This will also increase the importance of creating and maintaining bio-banks to store DNA samples for patients with a clinical diagnosis of CPVT, even when their initial genetic screening for known candidate genes yields negative results.

According to the current guidelines for the appropriate use of genetic testing [8], patients with a clinical suspicion of CPVT should be screened on *RyR2* and *CASQ2*. The latter is also analysed in non-consanguineous families as the result of the documentation of cases with double heterozygosity [21] and due to the fact that an autosomal dominant form due to *CASQ2* mutations may not be excluded [22]. If the initial genotyping tests are negative, screening of additional putative genes may be considered [8].

When a likely pathogenic mutation is identified in a patient with CPVT, family members should also be offered genetic screening. In this way, it is possible to identify other carriers of the same variant and offer them further investigations and/or therapies.

Challenges concerning genetics in CPVT:

- *Almost one third of CPVT cases remain genotype-unknown;*
- *In addition to the classical forms of CPVT, there are also life-threatening diseases that may be phenocopies, such as Long QT Syndrome type 4 and 7.*

Potential solutions:

- *Next generation sequencing, massive DNA screening and well-maintained biobanks of patient samples will help to identify new genes for these cases that are currently genotype-unknown.*

Clinical Manifestations and Diagnosis

Patients with CPVT typically present to medical attention with either stress-induced syncope or cardiac arrest, both of which will have occurred most frequently during childhood or early adolescence [5,6]. When left untreated, the clinical course of CPVT is severe: approximately 30% of affected individuals will experience symptoms before the age of 10 years and the majority (60% to 80%) of patients will have one or more symptomatic arrhythmia episodes before age 40 [5,6,23,24].

According to current guidelines [3], the clinical diagnosis of CPVT is based on the documentation of polymorphic ventricular arrhythmias that are induced by adrenergic stimuli, such as exercise or emotions, in patients without any other structural or electrical cardiac abnormality [3]. Since the exact number and complexity of arrhythmias sufficient for diagnosis has not been agreed upon yet, there still exists a certain degree of variability between individual centres in their diagnostic abilities. Even in the early reports published by Coumel et al. [5], it has been observed that arrhythmias in CPVT often appear in a uniform and reproducible pattern that facilitates the recognition of affected patients. Sinus rhythm accelerates with exercise and is progressively overcome by a junctional automatic focus. Beyond a heart-rate of 120-130 beats per minute, ventricular premature beats (VPB) appear that are at first isolated and monomorphic and then increase with heart-rate to quadrigeminy, trigeminy, and bigeminy. Subsequently, the VPBs become polymorphic, and, finally they form bursts of non-sustained polymorphic ventricular tachycardia (VT). If the activity is stopped, the arrhythmia disappears in the reverse order without clinical symptoms. However, when the activity is continued, the arrhythmia persists and becomes more rapid, eventually assuming the appearance of polymorphic, fibrillation-like, very fast VT that leads to syncope (Figure 1).

The hallmark sign of CPVT, highly specific but not present in all patients, is a peculiar form of polymorphic VT characterised by a 180° beat-to-beat rotation of the ectopic QRS complexes that is therefore termed ''bidirectional''. This arrhythmia was initially described in patients with digitalis intoxication: the drug inhibits the Na^+/K^+ ATPase pump and leads to an increased concentration of intracellular sodium ions that, in turn, results in intracellular calcium overload and the triggering of arrhythmogenic delayed after-depolarisations [25,26]. Experimental data suggest that bidirectional VT originates from the alternating activation of the Purkinje fibres of the two ventricles [27]. Using a mouse model of CPVT that precisely recapitulates the human disorder ($RyR2^{R4496C/+}$), Cerrone et al. found that the Purkinje cells of affected animals generated arrhythmias at lower levels of adrenergic stimulation than wild type mice [28], and Herron et al. demonstrated that Purkinje cells show significantly more calcium leakage than ventricular myocytes isolated from the same heart [29].

Despite the often unremarkable baseline ECGs found in CPVT patients, some features may help the clinician to identify affected individuals. First, most CPVT patients show a significant sinus bradycardia in resting condition. This may be another consequence of the diastolic calcium leakage from the ryanodine receptor, facilitated by either *RyR2* or *CASQ2* mutations. An experimental study in $RyR2^{R4496C/+}$ mice [30] showed that the intracellular calcium overload in mutant sino-atrial cells induces a slowing of the mechanism that controls the spontaneous depolarisation of the so-called

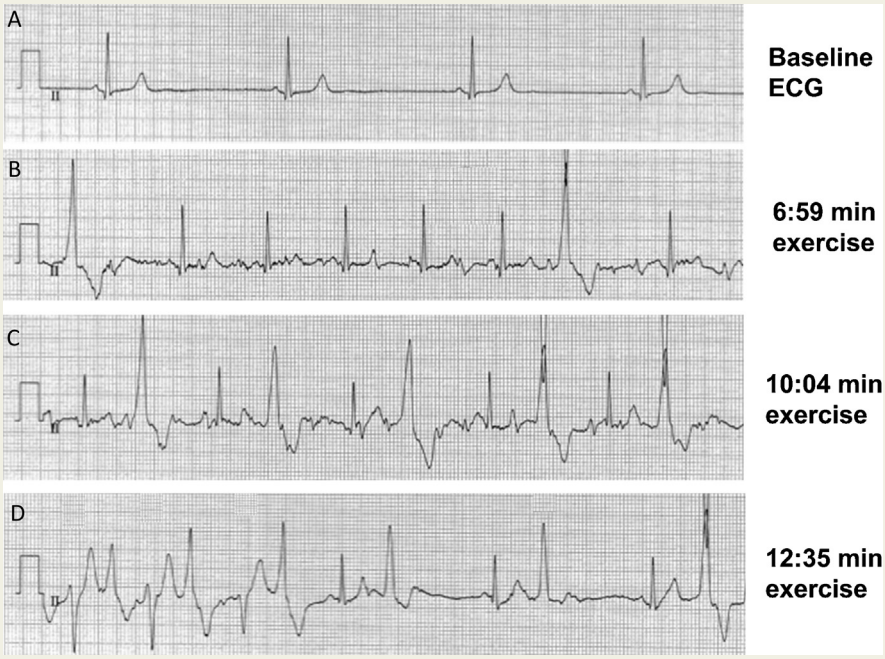

Figure 1 Electrocardiographic manifestations of CPVT.
Different phases of an exercise stress test in a 27-year-old CPVT patient carrier of a *RyR2* mutation. Panel A shows the baseline ECG characterised by sinus bradycardia (heart rate, HR, 33 bpm), normal atrio-ventricular and intraventricular conduction and normal QT interval (QTc 372ms). At 6:59 min of exercise and a HR of 71 bpm, isolated ventricular premature beats (VPB) appear (panel B), which become bigeminal at 10:04 min and a HR of 86 bpm (panel C). VPBs have a LBBB morphology with inferior axis (not shown), and a long coupling interval (ms), consistent with delayed after-depolarisation-induced triggered activity. Panel D shows a run of bidirectional VT arisen at the peak of the exercise and characterised by a 180° beat-to-beat rotation of the QRS complexes.

''calcium clock'' of the heart, which determines the intrinsic beating frequency of the sinus node [30].

Second, the ECGs of CPVT patients are often characterised by prominent U waves, which are dynamic in their appearance and whose genesis and significance are not yet fully understood [31]. Finally, supraventricular arrhythmias, including isolated atrial ectopic beats, non-sustained supraventricular tachycardias and bursts of atrial fibrillation, are common in CPVT [5].

Due to the dynamic nature of CPVT-related arrhythmias, exercise stress testing is the most helpful tool for the study of patients with any clinical suspicion, since it can also help monitor the response to therapy in reproducible conditions. These tests should be complemented by 24-hours Holter recordings, which are especially valuable in infants and younger children. In the subset of patients for whom emotions represent a more powerful arrhythmic trigger than exercise, implantable loop recorders play an important diagnostic role: they help to monitor heart rhythm for a long period of time in physiological conditions [3]. For patients who are unable to exercise, epinephrine infusions can aid in the diagnosis of CPVT, although there are conflicting results concerning the sensitivity of this method [32]. On the contrary, programmed electrical stimulation has no diagnostic or prognostic value in CPVT, since neither bidirectional nor polymorphic VT depends on re-entrant circuits [3].

Genetic testing is used for diagnosis confirmation and should be offered to families of genotype-positive index cases in order to identify asymptomatic carriers of a pathogenic mutation [8] who are considered affected according to current guidelines [3] and should be treated even in the absence of a positive exercise stress test [3,33].

Challenges concerning the clinical manifestations and diagnosis of CPVT:

- *It is difficult to establish a timely diagnosis due to normal baseline ECGs, a structurally normal heart, and commonly misattributed syncopal episodes;*
- *There is a lack of consensus on the number and complexity of arrhythmias necessary to make a diagnosis, especially in patients who do not show bidirectional VT.*

Potential solutions:

- *A more thorough clinical history can increase clinical suspicion;*
- *12 leads Holter monitoring and 12 leads exercise stress testing can help establish the diagnosis;*
- *Genetic testing can confirm the diagnosis.*

Management

The therapeutic approach to CPVT includes changes in lifestyle, pharmacological measures, left ventricular denervation and the use of implantable defibrillators. However, none of these options is fully effective and all have associated side effects; therefore therapy should strive towards synergistic combinations.

According to current guidelines [3], all patients with CPVT should restrict physical activity and reduce exposure to stressful situations. The limits for allowed physical activity can be set on the basis of exercise stress testing done in the hospital setting, and heart-rate monitoring devices can be helpful in keeping the heart-rate within a safe range during physical activity.

As a consequence of the adrenergic nature of arrhythmias in CPVT, the most effective pharmacological therapy is non-selective beta blockers, titrated at the maximum tolerated dose in the absence of contraindications (e.g. asthma). Nadolol (1-2 mg/kg per day) is considered the most clinically effective choice [34,35]; in countries where nadolol is not available, propranolol (3-5 mg/kg per day) can be used.

Holter recordings and exercise tests should be repeated periodically throughout beta blocker therapy, to ensure that heart-rate is controlled during exercise. Asymptomatic VPBs may persist, but this does not usually seem to portend a negative prognosis.

Since cardiac arrest may occur also in silent carriers of a pathogenic mutation, these patients need to receive beta blockers even when they do not exhibit arrhythmias during exercise stress testing. In the case series published by Hayashi et al. in 2012, two of 16 (13%) mutation carriers with negative exercise stress test had a cardiac arrest during follow-up, in the absence of therapy [36].

It is important to highlight to patients the need to be compliant with therapy [3]. According to clinical experience, many patients who have had arrhythmic events while on therapy might have been non-compliant and the abrupt interruption of beta blockade may cause a rebound effect of catecholamines on the heart [5].

Remarkably, even with appropriate use of beta blockers up to one third of CPVT patients may experience recurrent arrhythmic events or show persistence of complex arrhythmias at exercise stress test [34].

Why beta blockers are not fully effective remains unclear, but there may be some degree of a mutation-specific therapy response. Priori et al. reported that patients affected by the highly malignant R4497C mutation have an extremely lethal form of the disease, with five of seven (72%) carriers experiencing recurrent VT or ventricular fibrillation (VF) during beta blocker therapy [6]. The same finding was confirmed by Cerrone et al. who demonstrated a lack of efficacy for propranolol in preventing arrhythmias in mice carrying the correspondent genetic variant [27].

Kurtzwald-Josefson et al. provided another possible explanation when they demonstrated that the alpha-adrenergic pathway contributes to the pathogenesis of catecholamine-induced arrhythmias in a murine model of CPVT and demonstrated that alpha-blockade may efficaciously control arrhythmias in the animal model [37], but data in humans are still missing.

Patients with arrhythmias refractory to beta blockers should receive flecainide (a Class IC antiarrhythmic) at the dosage of 100-300 mg/day (1.5-4.5 mg/kg/day) as additional therapy [3]. This indication is based on the observation made in 2009 by Watanabe et al., who reported that two CPVT patients refractory to conventional therapy had a complete suppression of adrenergic-induced arrhythmias with the use of flecainide [38]. The result was further confirmed by van der Werf et al., who noticed an acute suppression of exercise-induced ventricular arrhythmias in 76% of CPVT patients with persistent arrhythmias despite beta blocker therapy [39]. Although preliminary reports seem encouraging, randomised clinical trials proving data for the long-term efficacy of flecainide are still ongoing (https://clinicaltrials.gov/ct2/show/NCT01117454). There is *in vitro* evidence that flecainide exerts its anti-arrhythmic effects through a dual mode of action. In addition to blocking the cardiac sodium channels (NaV1.5) and thus suppressing triggered activity, flecainide also directly inhibits RYR2, to prevent the spontaneous release of calcium from the SR [38].

Although current practice often prescribes flecainide in combination with beta blockers, Padfield et al. [40] recently proposed the use of flecainide as a stand-alone therapy in CPVT patients who are intolerant to beta blockers. However, there is limited clinical evidence supporting this theory and it should therefore be applied cautiously [41].

Patients who experience recurrent symptoms and/or implantable cardioverter defibrillator (ICD) shocks despite optimal medical therapy may benefit from the surgical/endoscopic resection of a portion of the sympathetic chain [3]. Moss et al. first applied this procedure of left cardiac sympathetic denervation (LCSD) in a patient with Long QT Syndrome [42]. Over the years several reports [43,44] have suggested the possible role for LCSD in patients with CPVT, and this has been recently confirmed by De Ferrari et al. who observed a statistically significant reduction of arrhythmic events after LCSD in a cohort of 38 symptomatic CPVT patients over a follow-up period of 43 months [45]. The complexity of this surgical procedure and the potential complications (e.g., Horner's syndrome or pneumothorax) [46] require a specialised surgical centre, therefore limiting the broad use of this technique, which has obtained a Class IIb recommendation in current guidelines for the prevention of SCD (it may be considered, but efficacy is less well-established by evidence) [3].

Finally, in patients who are at particularly high risk of cardiac arrest an ICD may be required. Candidates are patients who have survived a cardiac arrest or those who have experienced syncope or sustained VT despite optimal medical therapy and LCSD [3]. Implantable cardioverter defibrillators may have harmful pro-arrhythmic effects in some patients, since painful shocks can increase catecholamine release and trigger further arrhythmias, leading to a malignant cycle of ICD

shocks that may even culminate in death. To reduce the risk of inappropriate shocks, it is important to always concurrently administer beta blockers. Moreover, ICDs should be programmed carefully, with long delays before shock delivery and high cut-off rates for heart rate recognition.

Challenges concerning the management of CPVT:

- *Up to one-third of patients experience recurrent symptoms despite beta blocker therapy;*
- *The therapy must be taken once a day all life long, therefore the compliance sometimes is poor;*
- *Non-medical therapies* (e.g. *ICD and LCSD) have several side effects*.

Potential solutions:

- *New therapies need to be developed that aim to correct the genetic defect* (i.e. *gene therapy)*.

Perspectives for the Future

One of the most appealing perspectives for the future treatment of CPVT is gene-therapy. This approach aims at curing and reverting the genetically determined phenotype of the disease by restoring the normal function of the gene. Our group, using a knock-in murine CASQ2$^{R33Q/R33Q}$ model of the autosomal recessive form of CPVT, has demonstrated that gene transfer using a viral vector carrying the wild-type calsequestrin gene is able to induce its functional long-term expression, preventing and reverting the manifestation of the disease [47,48]. Thus, encouraging results from animal models are beginning to emerge highlighting the future potential for clinical applications.

Conclusions

In spite of many advances in the understanding and treatment of CPVT, several aspects of the disease still remain unclear.

Recognition and diagnosis of affected individuals, identification of risk factors for SCD and treatment of ventricular arrhythmias resistant to beta blockers remain challenges to overcome in the future. The creation of patient registries will help to gather large numbers of patients in order to better characterise the natural history and risk profile of CPVT.

New tools for treatment, in addition to traditional drugs, will include therapies targeted at correcting the genetic defects responsible for the disease.

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