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REVIEW

50 Years of Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) – Time to Explore the Dark Side of the Moon

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Despite significant progress in understanding catecholaminergic polymorphic ventricular tachycardia (CPVT), there are still multiple uncertainties and gaps in our knowledge. Like the dark side of the moon, we cannot see them directly. Unfortunately, clinicians must make diagnostic and therapeutic decisions without solid evidence. Instead of summarising the current state of science and reiterating the guidelines, we review difficulties in understanding the disease mechanism, diagnosis and therapy. Highlighting these truths helps to avoid misconceptions, think clearly about our patients and direct future research efforts. It has become clear that CPVT encompasses more than just uniformly expressed ryanodine receptor mutations leading to bidirectional ventricular tachycardia, rather it is a disease caused by different genetic mutations, overlapping with other entities and possibly affecting not only the heart. Treatment in addition to beta blockers is often necessary: flecainide and left cardiac sympathetic denervation are therapies that come before consideration of defibrillator implantation and new treatment options are on the horizon.

Keywords Catecholaminergic polymorphic ventricular tachycardia • Defibrillators, implantable • Channelopathies • Death, Sudden Cardiac

Introduction

It is now over 50 years since Coumel et al. published their observation of four children with catecholamine-induced ventricular tachycardia and syncope [1]. We do not present a new update or set of guidelines, as those have been recently published in this Journal [2]. Rather, we will look at the multifaceted dilemmas clinicians are confronted with: understanding the underlying basis of catecholaminergic polymorphic ventricular tachycardia (CPVT); making the diagnosis in a timely fashion with high precision and accuracy; and managing this sneaky and potentially deadly disease with the least impact on quality of life. We review recent developments—and highlight underexplored areas. Like the dark side of the moon, we cannot see them directly, they are less studied and difficult to reach. When dealing with rare diseases, especially those that are severe, clinicians are frequently forced to make important decisions despite a lack of knowledge. It is essential to be aware of the unknown so we can avoid misconception and steer our research efforts productively.

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Difficulties in Understanding the Disease Mechanism

The most important step towards effectively treating a disease is to understand the mechanism, as exemplified by the germ theory, which allowed understanding and treatment of epidemic diseases. Genetic investigators have demonstrated that most families with CPVT have mutations in genes regulating the level and/or function of proteins responsible for the balance of intracellular myocyte calcium. In addition to autosomal dominant mutations in the ryanodine receptor (RYR2), mutations in calsequestrin-2 (CasQ2), Kir2.1-inward-rectifier potassium channel (KCNJ2), calmodulin (CALM1) and triadin (TRDN) have been identified in families with the clinical picture of CPVT. De novo malignant mutations are relatively frequent in CPVT, though this has not been systematically studied.

Most models to explain the disease focus on RyR2 mutations, as they account for more than half of diagnosed cases and multiple mutations have been identified. The mouse models of RyR2 mutations suggested that delayed afterdepolarisations (DADs) are triggered in all myocytes when exposed to known stressors, such as caffeine and adrenaline [3], or even spontaneously [4]. Recent data using transgenic mice put the focus more on Purkinje cell calcium dysregulation as the underlying cellular mechanism causing CPVT [5], but there are no clinical data to support this.

This potential shift in mechanism understanding has triggered hope that CPVT might be amendable to ablation. The two published small clinical studies focussing on finding the origin of ventricular ectopy in CPVT [6,7], however, show the majority originating in the right ventricular outflow tract (RVOT). Although the average QRS width of the triggering ectopic beat seems to be compatible with a Purkinje fibre (PF) origin and single reports of successful PF ablation have been published [8], the current understanding is that PFs are relatively sparse or absent in the RVOT [9]. Current data has a significant diversity of findings. As most of the experimental data is derived from mouse or rabbit models, determining the role of PFs in human CPVT will be important to build a reliable model [10].

Another unanswered question is the possible overlap of CPVT with other cardiomyopathies (CMP) including arrhythmogenic (right and left) ventricular CMP (ACM) [11], and non-compaction CMP [12]. While these overlaps are rather rare, overlap with channelopathies are more frequent.

CPVT has been perceived as a single organ disease though recent larger studies of affected families showed an increased incidence of neurodevelopmental problems [13], especially intellectual disability (8% vs 1–3% in a general population). Interestingly this subgroup had a more malignant cardiac phenotype involving supraventricular tachycardia in 50% and a high rate of ventricular arrhythmic events despite adequate medical therapy. On the subcellular level, RyR2 dysfunction seemed to be more severe in variants associated with neurodevelopmental problems [13]. CPVT and intellectual disability may share common underlying pathophysiological mechanisms involving caffeine hyper-responsive, RYR2-mediated, intracellular calcium handling in the heart and the brain. A potential confounder is, of course, brain damage secondary to cardiac syncopal events.

Another clue to a wider impact of the RYR2 receptor has been found in the mouse model [14] and recently in a family [15]: Mutations apparently triggering spontaneous generalised seizures in the absence of cardiac arrhythmias suggest that cardiac symptoms in CPVT might be only a part of the story and not all observed seizures in CPVT might be cardiac in origin. The possibility of two diseases being present, however, is not excluded. If this association proves true, it will further complicate the diagnosis and treatment of this disease. A multidisciplinary approach and closer collaboration with neurologists might help answering some of these questions in the future.

Difficulties in Diagnosis

Many inherited arrhythmia syndromes have a signature phenotypic electrocardiogram (ECG) feature present at rest including long QT syndrome (LQTS) and Brugada Syndrome. Although bradycardia may be a feature of CPVT, the ECG in CPVT has no signature feature to point into the direction of a lethal disease. Relative bradycardia is frequently noted in RYR2 variants with a clinical CPVT picture [16]. Among carriers of a pathogenic RYR2 mutation identified through cascade screening, sinus bradycardia was present in 5–20% of individuals [17]. Bradycardia is also a feature of fitness. Therefore, CPVT will escape basic ECG screening efforts and symptoms might be dismissed as neurally mediated syncope or non-cardiac causes. Retrospective data shows that diagnosis for CPVT is frequently delayed over a year after onset of symptoms [18].

Detailed history taking, awareness and knowledge of the symptoms of CPVT are essential to ensure consideration of this disease in the differential diagnosis of syncope. While exercise-induced syncope is a clear warning sign, larger studies show that syncope or death in CPVT can be induced by all catecholaminergic stress even during routine daily activity, rest or in sleep in up to 25% [19]. Reproduction of this stress though might be difficult, and single Holter ECGs and exercise tests can be inconclusive, especially if too little stress has been present during the test. In the authors' experience, rapid increase in heart rate with the patient pushed hard in a modified "sprint" exercise test is more likely to trigger ectopy and ventricular tachycardia (VT). A sprint test is tailored to the patient's capabilities and performed by initially gently increasing the gradient and when the patient appears comfortable in their stride rapidly increasing the speed until the patient's maximum capacity is reached. The test is individualised and depending on the patient's capacity the gradient may also be further increased. If there is a high degree of suspicion, repeated tests are recommended.

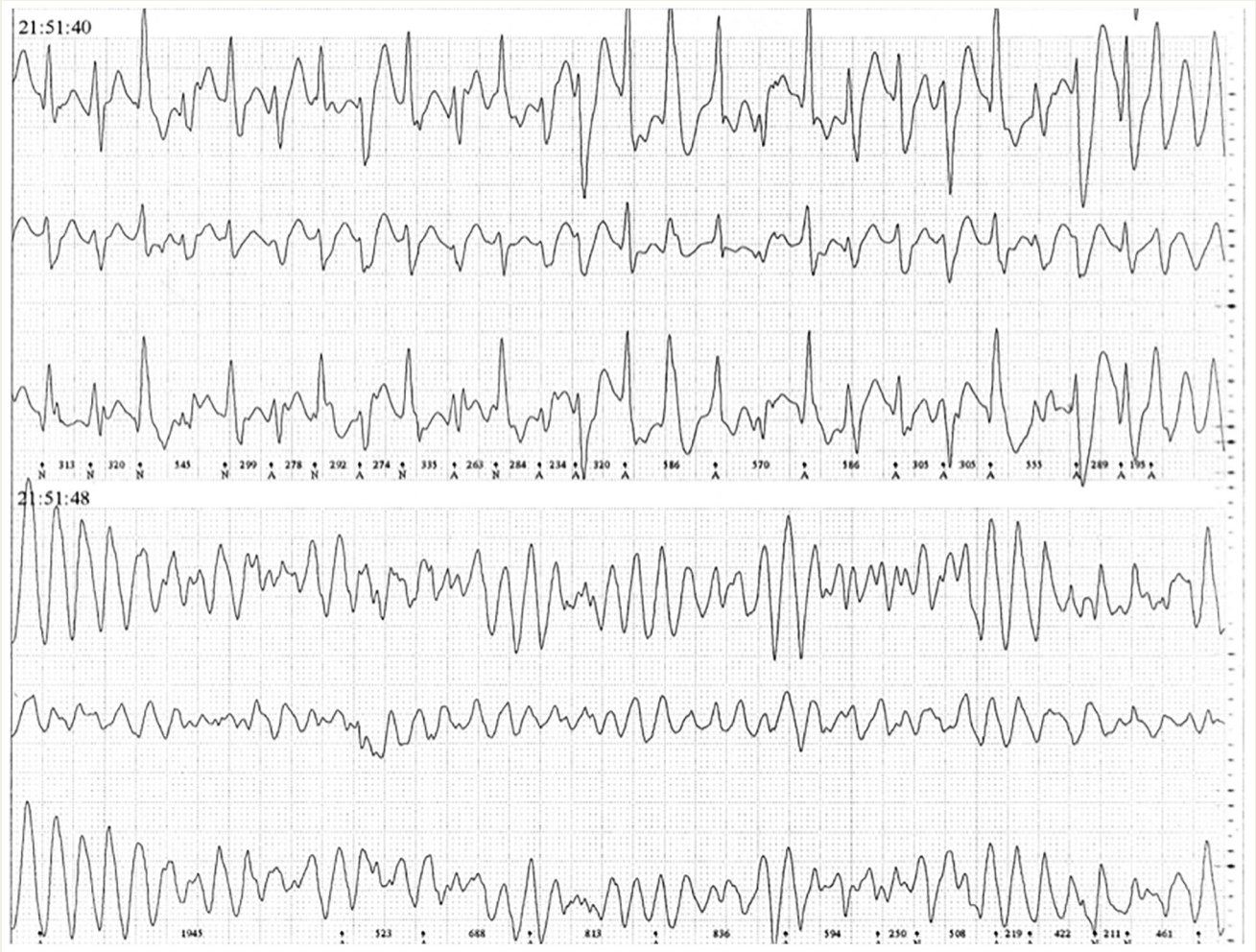

Figure 1 Bidirectional ventricular tachycardia (VT) degenerating to ventricular fibrillation.

Typical bidirectional VT which might degenerate to VF (Figure 1, Figure 2a) is highly specific for CPVT, however is only rarely triggered; more frequently, mono- and polymorphic (bidirectional) ectopy can be seen, starting at a relatively low rate heart rate (100–110/min, Figure 3) and disappearing in recovery. Triggering an atrial tachycardia, especially a multifocal atrial tachycardia (MAT) (Figure 4) with exercise should also raise suspicion for a potential underlying CPVT [20,21].

Although used widely in adults [22,23], the lack of increase in heart rate with adrenaline infusion in children might explain the failure of this test to induce ventricular ectopic activity in patients with CPVT, while other monitoring later revealed arrhythmic activity or even VT (A.M. Davis, RCH, personal communication, 2017).

While repeated Holter ECG and implantable loop recorders can facilitate the diagnosis of CPVT, they bear the risk of a cardiac event during the monitor period leading to an unwitnessed cardiac arrest with a tragic outcome. Although there is good experience in the diagnosis of CPVT, objective and systematic data from larger studies on clinical diagnosis are lacking. Current guidelines [24] only define specific findings leading to the diagnosis of CPVT, though not a reliable diagnostic pathway with high sensitivity and specificity.

CPVT might not always be limited to catecholamine-induced abnormal ventricular activity. Moreover bradycardia [16], atrial arrhythmias including multifocal atrial tachycardia [20,21], neurodevelopmental or structural cardiac abnormalities might be part of the spectrum of the disease and do not exclude its diagnosis.

Another challenge confronting the clinicians is diseases that mimic or overlap with CPVT. Andersen-Tawil Syndrome (ATS) is a channelopathy caused by autosomal dominant mutations mostly in the KCNJ2 gene, characterised also by bidirectional VT (Figure 2b). The typical periodic paralysis and dysmorphic features may be subtle or are not always manifest. Approximately 30% of the disease-causing *KCNJ2* variant carriers show only cardiac phenotypes [25], therefore, in these cases, differential diagnosis might be difficult [26]. A major difference compared to RyR2-related CPVT is the presence of abundant ventricular ectopy

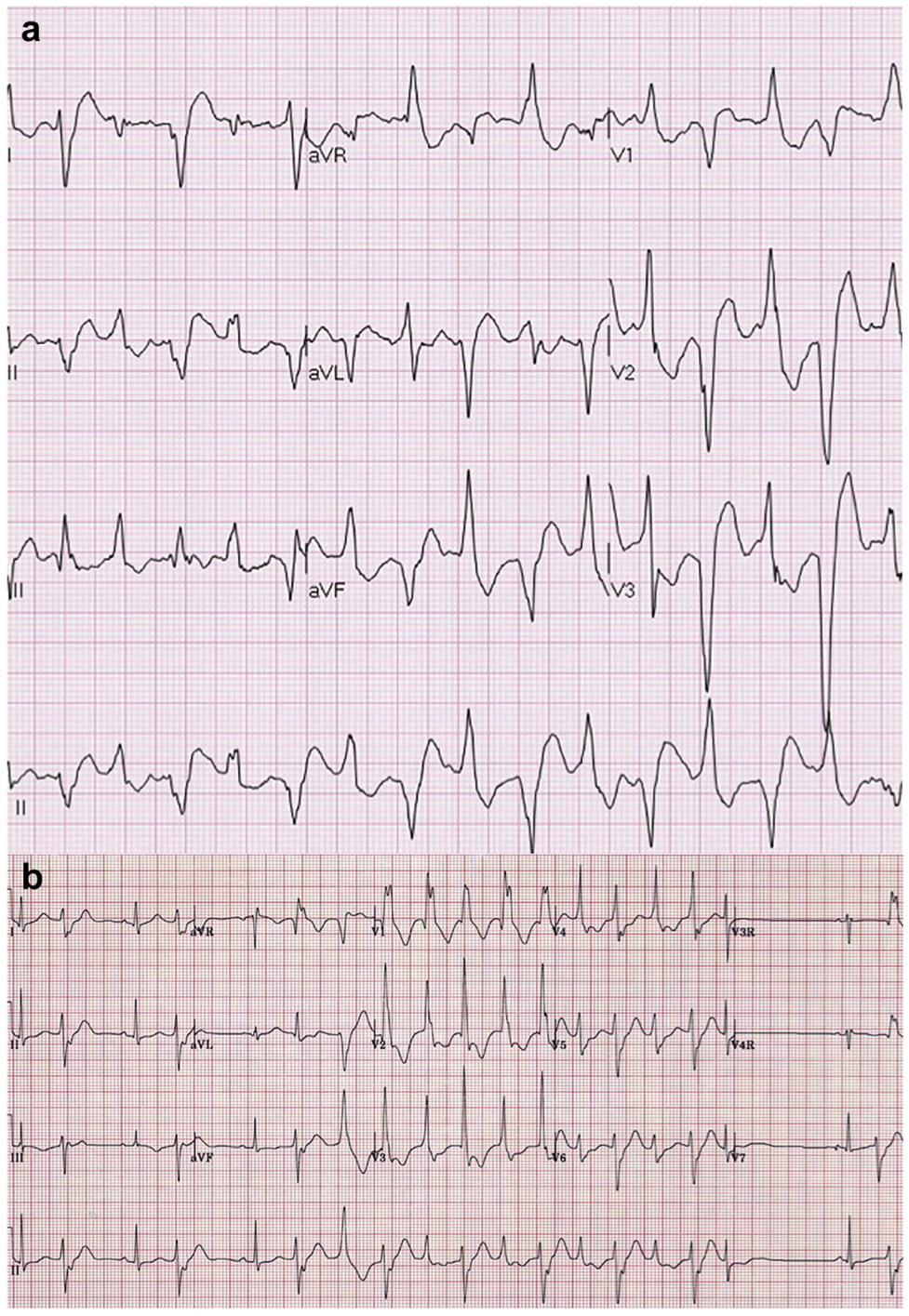

Figure 2 Bidirectional VT in CPVT (a) and in Andersen-Tawil Syndrome (b).
Abbreviations: VT, ventricular tachycardia; CPVT, catecholaminergic polymorphic ventricular tachycardia.

throughout the day in ATS whereas in CPVT this is usually absent. A similar disease, i.e. abundant ectopy throughout the day, which does increase during exercise, has been identified in families with SCN5A variants [27,28].

Well known for SCN5A mutations, there are now multiple examples of different phenotypes caused by different mutations in the same gene. Mutations in calmodulin cause adrenergic-induced life-threatening arrhythmias [29]. Most patients present with either a severe LQT-phenotype (50%, QTc well over 500 ms) or a CPVT phenotype (30%, early onset, high penetrance, U waves). A small number present with features of both CPVT and LQTS or a predominant neurological phenotype, making treatment even more difficult [30]. Similarly, loss of function in ankyrin-B (ANK2) can cause phenotypes ranging from bradycardia, conduction block, LQTS, atrial fibrillation as well as CPVT [31].

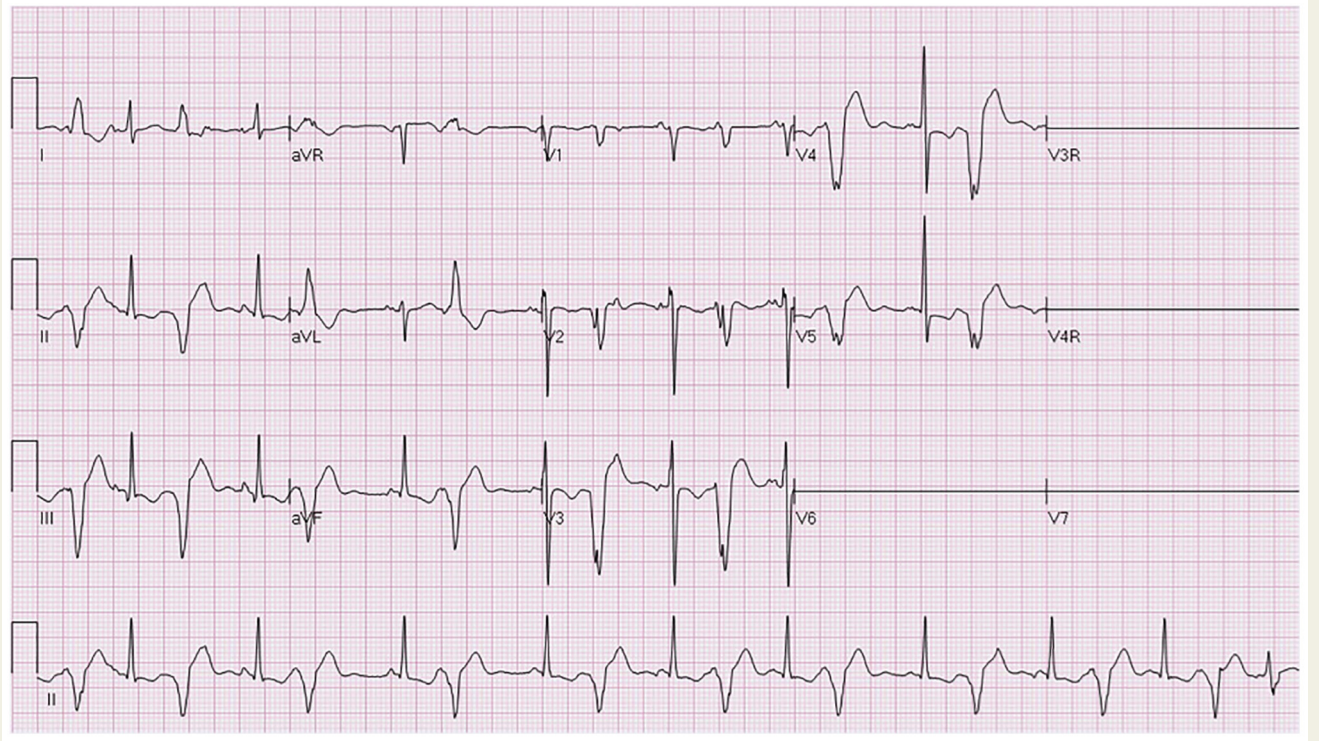

Figure 3 Uniform PVCs in CPVT as bigeminy.
Abbreviations: PVCs, premature ventricular contractions; CPVT, catecholaminergic polymorphic ventricular tachycardia.

Mutations in the TECRL gene which encodes the trans-2,3-enoyl-CoA reductase-like protein have recently been described with clinical features of both LQTS and CPVT [32]. Tester et al. recently reported plakophilin-2 (PKP2) mutations in previously genotype negative, clinically diagnosed CPVT patients [33]. This, however, likely represents a very early stage of ACM with CPVT like symptoms.

According to the 2013 guidelines [24], CPVT is diagnosed in patients (proband) who fulfill specific clinical criteria. In families where a pathogenic mutation has been identified, family members with this mutation are also diagnosed with CPVT. 'Mutation calling' is, as in other inherited disease entities, a challenge in CPVT. The background rate of innocent rare variants is in the order of 3% in the Caucasian race and maybe even higher in African Americans. Functional evidence to support causality is only present in a minority of variants. In order to overcome the >3% background rate of rare RyR2 variants, Kapplinger et al. have specified specific genetic variables that can be of use to discriminate pathogenic from non-pathogenic variants [34]. Based on the observations that the likelihood to identify a causal variant is related to specificity of the phenotype, a subsequent study introduced the phenotypic details into the interpretation of RyR2 variants. This phenotype-guided approach markedly decreased the percentage of variants of unknown significance and increased the yield of finding a pathogenic or non-pathogenic (i.e. [likely]-benign) variant [35].

Despite the increasing number of identified genes causing CPVT, the likelihood of a negative gene test in patients with clinical CPVT is still about 30%.

Difficulties in Therapy

Due to the high risk of lethal cardiac events, treatment of all patients and gene positive relatives with beta blockers has been recommended. This is also reflected in the guidelines as a Class I recommendation for symptomatic patients and as a Class IIa recommendation for patients without clinical manifestations [24].

While these recommendations are clear, other treatment strategies are less well defined or subject to change due to newer findings. Different to LQTS, where QTc duration, gender, age, previous syncope and genetic subtype define the patient's future risk for cardiac events, there are limited well-defined prognostic factors in CPVT. Some important details are emerging in recent research. CPVT caused by homozygous CasQ2 mutations appears to be especially malignant and RyR2 mutations accompanied by neurodevelopmental problems seem to have a high-risk profile [13,19]. On the other hand, a family history of sudden death seems not to be a reliable predictor [19].

While beta blocker therapy is the mainstay, the choice of beta blockers is less clear, though there is some evidence that nadolol is superior to other beta blockers [36,37]. Unfortunately, the availability of nadolol is limited in many countries

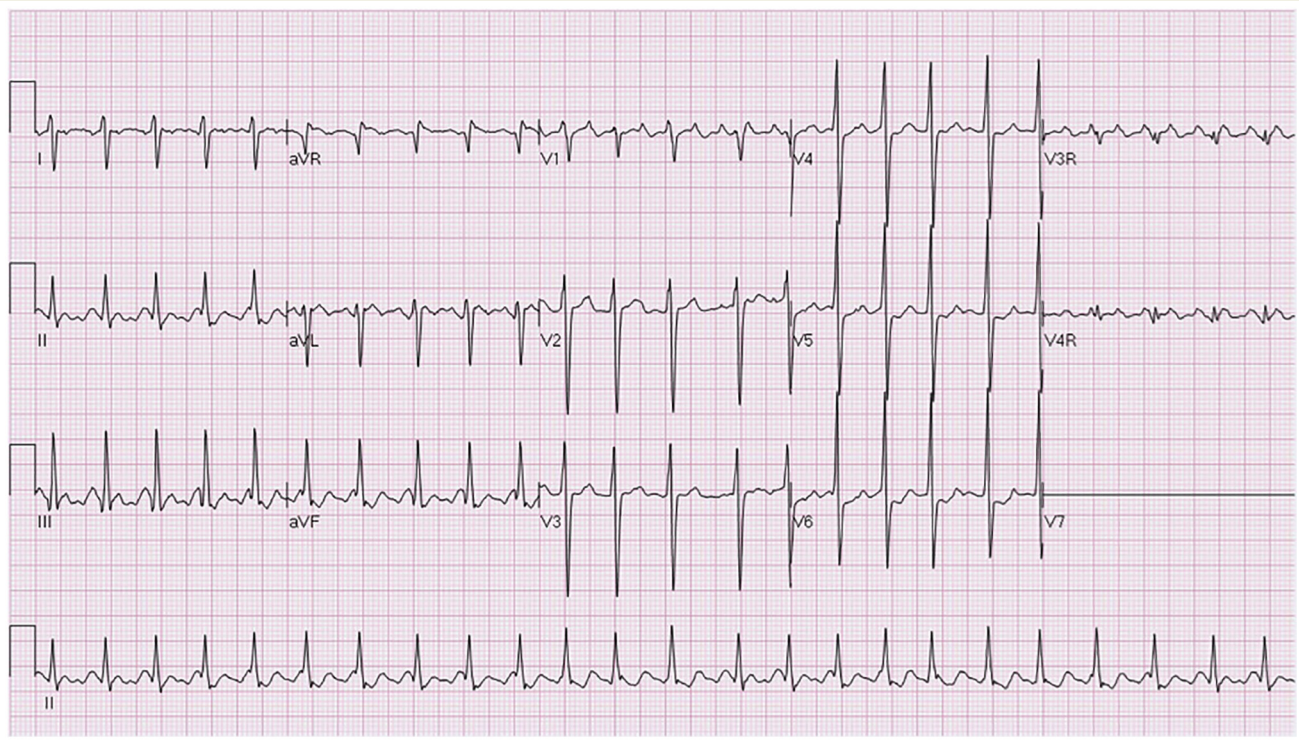

Figure 4 Multifocal atrial tachycardia in CPVT (with variable AV conduction), P wave morphology changes very subtle, multiple foci around the pulmonary veins confirmed in invasive EP study.
Abbreviations: CPVT, catecholaminergic polymorphic ventricular tachycardia; AV, atrioventrciular.

including Australia and there is no commercial interest in many countries to bring the drug to market [37].

Miyake et al. showed an increase of cardiac events in the evening hours [38]. Non-adherence to the prescribed medication was found in 60% of the events. This shows that, as expected, medication adherence is an important factor. The type of medication used by these patients is not reported, so it remains unclear which medication and what schedule will have the highest adherence rate. Absence of beta blocker therapy was also shown by Hayashi et al. to be associated with worse outcome [39].

The addition of the sodium channel blocker flecainide to beta blockers has been shown to be superior to a placebo in a single-blinded study [40] and retrospective studies [18,41]. Only very few flecainide-resistant cases have been reported [42], we think that flecainide should be part of the standard therapy for symptomatic patients but current guidelines do not reflect the recent studies yet and of course this does make medication adherence more problematic.

It has been shown that arrhythmia initiation is depending on both heart rate and sympathetic stimulation [43]. This could be one potential reason that combination therapy is the clue to improve therapy significantly. Other antiarrhythmic agents like ivabradine (a hyperpolarisation-activated cyclic nucleotide-gated [HCN] channel blocker) have been tried occasionally [44], though the inherent underlying sinus-bradycardia in many patients might hinder its utilisation.

Implantable cardioverter defibrillators (ICDs) have been overutilised in most channelopathies under the false promise of living without medication and carefree. The fear of litigation in the medical community might be another significant driver.

However, high rates of inappropriate shocks, problems with leads, and failure to convert bidirectional VT [45] and triggering of electrical storms (sometimes with fatal consequences) have, in recent years, changed the threshold for ICD prescription significantly [46–48].

Presentation of a patient with sudden cardiac arrest before the initial diagnosis of CPVT needs no longer be considered an indication for ICD implantation [46]. The current guidelines [24] state that an ICD is recommended in CPVT patients only after cardiac arrest, recurrent syncope or catecholamine-induced bidirectional VT despite optimal medical management and/or left cardiac sympathetic denervation (LCSD). Given the increasing evidence of the effectivity of LCSD [49,50] we would recommend that an ICD should not be implanted without a previous LCSD, and ICD therapy should be very judiciously considered.

Whilst established for some cases of Brugada syndrome, invasive electrophysiology (EP) studies and ablation of triggering beats are based on the concept of local changes and not all myocytes being equally affected. This remains unproven for CPVT. There have been some case reports of primary successful ablation [51], though the follow-up is short, effectiveness is not very high and so far ablation might

be an option for adjunctive therapy in severe cases with symptoms despite maximal medical therapy.

Atrial arrhythmias including MAT remain another unsolved problem in patients with CPVT. In longer term follow-up, the incidence is up to 20% [52]. Atrial arrhythmias are often recurrent and can cause significant ongoing palpitations, inappropriate shocks, development of atrial fibrillation and cardiomyopathy. Flecainide seems to reduce the incidence or control of atrial arrhythmias in some, though not all patients [20]. Ablation has been described by some to be possible and others not successful [53]. The lack of data here does not allow a conclusion, nonetheless raises the suspicion that the effect of RyR2 mutations is not limited to Purkinje cells.

While the avoidance of adrenaline and related drugs is non-controversial and should be followed even in resuscitation scenarios [54], lifestyle modifications have a higher degree of uncertainty in the therapy of CPVT. The previously cited guidelines from 2013 include in their Class I recommendations: limiting/avoiding competitive sports, strenuous exercise and limiting exposure to stressful environments for all patients, regardless of being a proband or asymptomatic affected relative. These scenarios include a significant part of everyday life and a strict adherence to this would limit the quality of life in many patients significantly, leaving a dilemma for the treating physician.

A recent study of sports participation in CPVT concluded that the "risk may be acceptable for a well-treated and well-informed athlete following the diagnosis of CPVT" although 14% of athletes experienced further events [55]. Given the current difficulties in risk stratification and the still looming risk of break-through events in treated patients, we still recommend a careful individualised approach to exercise prescription in CPVT patients including a shared decision-making process [56] with the patient and the parents. This involves a thorough understanding of risks and chances on both sides, ongoing close follow-up, excellent adherence to therapy and ongoing adaptation to events or new findings. Therapy should be guided by regular exercise tests, Holter-ECG or implantable loop recorders.

Collaborative efforts have demonstrated the cure of CPVT in mice from birth to advanced age with the single delivery of an adeno-associated viral construct, enabling transfer of CASQ2 [57]. Intensive work continues in this exciting field but we are yet unable to predict when this will be available as a routine therapy for human patients [58,59].

Conclusion

Although knowledge regarding CPVT has grown considerably in recent years, significant gaps in the knowledge of disease mechanism, diagnosis and treatment remain.

The establishment of international registries will help to monitor outcomes and define risk factors in the future. These are steps in the right direction. In addition, clever, prospective multicentre studies are needed for further progress regarding specific questions. Government and institutional support to give patients access to medications like nadolol is needed as well as further engagement with companies in developing drugs for rare diseases.

We hope that in the near future, new techniques like gene editing with CRISPR-associated protein-9 nuclease (Cas 9) will help us understand the mechanism of this disease [60], and optogenetics (which combines the use of light-sensitive proteins with genetic targeting strategies) will help us characterise CPVT mutations and enable drug testing [61]. In the meantime, we will have to be aware that there is the dark side of the moon and be aware of the gaps in knowledge. Choosing our diagnostic and therapeutic tools judiciously on an individualised basis and aiming for both safety and a good quality of life will help to achieve the best outcome possible for this patient group.

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