Catecholaminergic polymorphic ventricular tachycardia in 2012

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Abstract

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a rare, potentially lethal inherited arrhythmia syndrome characterized by stress or emotion-induced ventricular arrhythmias. CPVT was first described in 1960, while the genetic basis underlying this syndrome was discovered in 2001. The past decade has seen substantial advances in understanding the pathophysiology of CPVT. In addition, significant advances have been made in elucidating clinical characteristics of CPVT patients and new treatment options have become available. Here, we review current literature on CPVT to present state-of-the-art knowledge on the subject of the genetic basis, pathophysiology, clinical presentation, diagnosis, treatment and prognosis.

Introduction

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a malignant inherited arrhythmia syndrome. The main pathologic feature is adrenergic-induced bidirectional or polymorphic ventricular tachycardia (VT) in the absence of organic heart disease and apparent 12-lead ECG abnormalities.¹ CPVT is a relatively new entity.

The first report on patients with the clinical characteristics of CPVT was described by Berg in 1960.² CPVT was definitely acknowledged as a primary arrhythmia syndrome in 1995 after a patient series described by Leenhardt *et al.*¹ The genetic basis underlying CPVT was discovered ten years ago.³⁻⁵ In recent years, significant progress has been made in understanding the genetic basis, pathophysiology and phenotype of CPVT and how to apply this knowledge in the clinical management of patients and families with CPVT. This review aims to provide an update on current state-of-the-art knowledge regarding CPVT.

Genetic basis

Whereas a genetic component in CPVT was recognized since its first description, Swan *et al.* set the first step in identifying the genetic basis of CPVT.⁶ They described two unrelated families including multiple individuals with the typical CPVT phenotype. Genetic linkage analysis assigned the disease locus on a region on the long (q) arm of chromosome 1. However, no mutations or polymorphisms were identified by sequencing putative candidate genes.

In 2001 this group⁴ and Priori *et al.*³ demonstrated that mutations in the gene encoding the human cardiac ryanodine receptor (RyR2) underlie CPVT. Priori *et al.* identified RyR2 missense mutations in four out of 12 probands with a strong CPVT phenotype (S2246L, R2474S, N4104K, and R4497C).³ Three mutations were *de novo*, whereas the fourth mutation cosegregated with the phenotype in four relatives of the proband. Laitinen *et al.* identified a RyR2 missense mutation in three large families that fully cosegregated with the phenotype as well (P2328S, Q4201R, and V4653F).⁴

RyR2 is a 105-exon-containing gene residing on chromosome 1 (1q42-q43). The majority of mutations in RyR2 are missense mutations. Mutations tend to be clustered in three hotspots: the N-terminal domain (aminoacids 77-466), the central domain (aminoacids 2246-2534), and the channel region (aminoacids 3778-4959) (Figure 1).⁷ This phenomenon is the reason why using a tiered strategy in RyR2 sequencing, starting with those exons known to host most unique mutations, is currently the most reasonable approach.⁷ This will probably change in the near future, when high-throughput sequencing instruments will become available and provide whole-gene sequencing in a single step.

Whereas almost all RyR2 mutations seem to result in a classic CPVT phenotype, some exceptions exist. In 2007 our group reported a more complex phenotype caused by a large genomic deletion that involved RyR2 exon-3.⁸ Sixteen carriers from two separate families showed decreased left ventricular function leading to dilated cardiomyopathy, progressive atrioventricular block, sinoatrial node dysfunction, atrial fibrillation, and atrial standstill. In addition, several families with RyR2 missense mutations and discrete right ventricular abnormalities have been identified.^{9,10}

A rare, recessively inherited CPVT phenotype was first described by Lahat *et al.* in 2001.¹¹ This report included 9 children who died suddenly and 13 surviving children with a CPVT phenotype, from seven related Bedouin families. In a subsequent report in 2001, this group reported mutations in cardiac calsequestrin (CASQ2) to underlie this autosomal recessive form of CPVT (D307H).⁵

To date, the prevalence mutations in RyR2

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and CASQ2 are identified in approximately 60% and 5% of CPVT patients, respectively (see *Genetic testing*).

In 2007, a third, highly malignant autosomal recessive CPVT phenotype was mapped to a 25-Mb interval on chromosome 7p14-p22 in a study including four children from a highly inbred family.¹² All children showed the classic CPVT phenotype, and eventually three children died suddenly while playing. To date, the causal gene has not been identified.

Finally, Andersen-Tawil syndrome (LQTS type 7), which is caused by mutations in the gene encoding KCNJ2, may resemble the CPVT phenotype (see *Differential diagnosis*).

Pathophysiology

Ventricular arrhythmias in CPVT are caused by alterations in a critical element of cardiac excitation-contraction coupling: calcium-induced calcium release (CICR).^{13,14} CICR is initiated by calcium influx through the L-type calcium channels in the sarcolemma (Figure 2). This triggers calcium release from the sarcoplasmic reticulum (SR), the main intracellu-

lar calcium storage, through opening of RyR2. The released calcium binds to troponin C and eventually results in muscle contraction. This process ends when SR calcium release is terminated, leading to relaxation. The released calcium is mainly recycled back to the SR by the SR calcium-ATPase (SERCA) pump, or extruded from the cell by the sodium/calcium exchanger (NCX).

CPVT-related variants in RyR2 or CASQ2 cause spontaneous RyR2 openings, leading to spontaneous calcium release from the SR.^{15,16} The subsequent increase in cytosolic calcium activates the electrogenic NCX, which causes a transient inward current. This current eventually produces delayed afterdepolarizations (DAD), which may trigger an action potential and lead to triggered arrhythmias. This process is enhanced especially under conditions of β -adrenergic stimulation.^{17,18} It has been proposed that this mechanism underlying CPVT principally originates in the His-Purkinje system.^{19,20}

Mutations in RyR2 alter the channel regulation mechanism, particularly its sensitivity to calcium activation. A recent study provided data supporting the hypothesis that mutations in RyR2 destabilize the channel by mediation of defective interdomain interaction.²¹ The coupled conformational changes lead to erroneous activation of the channel and spontaneous calcium release.

CASQ2 mutations probably cause CPVT by several independent mechanisms.²² First, CASQ2 is the main calcium buffering protein of the SR, and mutated CASQ2 can result in a loss of Ca buffering. Second, loss of CASQ2 may lead to a reduced direct inhibitory effect on RyR2. Lastly, CASQ2 mutations may lead to remodeling of SR structure and proteins, particularly a reduction of the CASQ2-binding proteins triadin and junctin.

Genotype-phenotype correlation

To date, only data on genotype-phenotype comparing RyR2 mutation-related and non-RyR2 mutation related CPVT patients (in whom CASQ2 and KCNJ2 were not tested) are available.^{23,24} Priori *et al.* observed RyR2 mutation-carrying index patients were more often male and became symptomatic at younger age.²³ Sy *et al.* observed a higher proportion of symptomatic patients among RyR2 mutation-carrying index patients, but the number of patients was low.²⁴ CPVT patients carrying mutations in CASQ2 are thought to have a worse phenotype, with expression at younger age, compared to CPVT patients with RyR2 or no mutations.^{11,25}

While different RyR2 mutated transgenic and knock-in mouse models show similar phenotypes,^{26,27} genotype-phenotype correlations based on RyR2 mutation location have not been studied in humans.

Clinical characteristics

Clinical presentation

The classic CPVT patient is a young child presenting with syncope triggered by exercise and/or emotion, usually accompanied by a family history of sudden cardiac death (SCD) at young age.¹ Eventually, aborted cardiac arrest (ACA) or SCD under similar circumstances may occur. Patients may be misdiagnosed with

epilepsy, because syncope can be accompanied by convulsive movements.^{28,29}

In recent years it has been observed that probands presenting at older age are not uncommon. Recently, a distinction between juvenile-onset CPVT and late-onset CPVT has been proposed by Sy *et al.*²⁴ This group classified these two groups using a cut-off age of 21 years. The yield of genetic testing was significantly higher in the juvenile-onset group, whereas probands in the late-onset group were more likely to be female and were less likely to have affected family members. This could implicate that the pathophysiological substrate between these two subtypes is different. However, in RyR2 mutation-carrying relatives onset of symptoms may occur at older age, and that does not make it two different types of diseases.

Figure 1. RyR2 structure and mutation clustering. Yield indicates the proportion of RyR2 mutations identified per domain (indicated by the aminoacid number estimated for each domain). AA, amino acid. Adapted from Medeiros-Domingo *et al.*⁷ and Priori *et al.*¹³

Figure 2. Calcium homeostasis in a ventricular cardiomyocyte. Adapted from Knollmann *et al.*,¹⁴ with permission.

Most CPVT cases are related to familial RyR2 mutations, and cascade screening of the CPVT-causing mutation in the proband may lead to the identification of more mutation-carrying relatives. Thus, it is conceivable that among all CPVT patients known to date, mutation-carrying relatives are predominant. However, data on disease penetrance and expression in mutation-carrying relatives are scarce. In one study on 30 RyR2 mutation-carrying relatives, eight (27%) reported CPVT-related symptoms.³⁰ During exercise testing 23 relatives (77%) showed signs of disease penetrance.

Electrocardiographic characteristics

CPVT patients show a tendency towards having sinus bradycardia (Figure 3A).³¹ In a patient series including RyR2 mutation-carrying CPVT patients from our group, resting heart rate of 12 probands was 20 beats per minute lower as compared to matched controls.³² In addition, symptomatic mutation-carrying relatives had a lower resting heart rate than asymptomatic family members. Sinus bradycardia was more pronounced in males. Two possible explanations were postulated: an impaired calcium ion handling by mutated RYR2 channels in sino-atrial node cells, or vagally-mediated effect through a feedback mechanism that lowers the likelihood of reaching the detrimental threshold at which ventricular arrhythmia starts. The exact underlying mechanism of sinus bradycardia in CPVT has not been clarified. In some patients' resting ECGs prominent U-waves have been observed.^{33,34}

Ventricular arrhythmias tend to initiate at an individually fixed and reproducible threshold, usually between 110 and 135 beats per minute.³⁰ Typically ventricular arrhythmias evolve from single isolated ventricular premature beats (VPB) to bigeminy, couplets and non-sustained polymorphic or bidirectional VT (Figure 3B-D). However, complexity of ventricular arrhythmias may be limited in some patients (see *Genetic testing*). Polymorphic VT occurs in approximately 60% of patients, while the proportion of patients with bidirectional VT is much lower.^{24,31} In more than half of the cases the initiating VPB originates from the right ventricular outflow tract.^{24,31}

Diagnosis

Clinical diagnosis

The clinical diagnosis of CPVT is made when ventricular arrhythmias, in particular bidirectional or polymorphic VT, are recorded under conditions of increased β -adrenergic drive, and echocardiography and 12-lead ECG show no apparent abnormalities and thereby

reasonably rule out structural heart disease. Exercise testing may be considered as the gold standard diagnostic test in CPVT. In patients with or suspected for long QT syndrome (in particular type 1) exercise testing may also trigger ventricular arrhythmias, but ventricular ectopy beyond isolated VPBs is much more common (87.5%) in CPVT patients as compared with long QT syndrome patients (7%).³⁵ The presence of bigeminy has a specificity of 96% and a sensitivity of 81% for CPVT.³⁵

Holter monitoring may be used as an alternative test, for instance in children that are too young to undergo exercise testing, or when a patient's symptoms are more emotion- than exercise-related. Finally, catecholamine infusion may be used to unmask CPVT.^{24,31} Sumitomo *et al.* observed ventricular arrhythmias induced by exercise testing in all 27 patients, while 12/16 (75%) had ventricular arrhythmia during catecholamine infusion, and 16/23 (69%) during Holter monitoring.³¹ However, Sy *et al.* reported that catecholamine infusion provoked ventricular arrhythmia in three patients who did not show any ventricular arrhythmias on either Holter recordings or exercise testing.²⁴ Thus, exercise testing is the first choice diagnostic test, but the diagnostic approach may be tailored to individual patients.

Genetic testing

In the recent HRS/EHRA Expert Consensus Statement on the State of Genetic Testing for the Channelopathies and Cardiomyopathies, genetic testing in CPVT is recommended for *any patient in whom a cardiologist has established a clinical index of suspicion for CPVT*

based on examination of the patient's clinical history, family history, and expressed electrocardiographic phenotype during provocative stress testing with cycle, treadmill, or catecholamine infusion.³⁶ Genetic testing should start with sequencing a limited number of exons in RyR2 (see *Genetic basis*). In case of a negative result this can be followed by analyzing the remaining RyR2 exons in a stepwise fashion,⁷ and CASQ2. RyR2 mutations are detected in approximately 60% of cases. However, the exact yield is related to the patient's phenotype (see below). The prevalence of CASQ2 mutations is estimated to be approximately 5%.

Importantly, genetic testing should not be limited to patients meeting the full spectrum of typical marked clinical diagnostic criteria (*i.e.*, the presence of exercise-induced bidirectional or polymorphic VT), because it has been well established that in some patients CPVT may express with less severe ventricular arrhythmias. However, the presence of exercise-induced bidirectional or polymorphic VT is associated with increased odds of identifying a pathogenic mutation: in patients with documented exercise- or emotion-induced bidirectional or polymorphic VT in the absence of structural cardiac disease, RyR2 mutations are detected in 50-70%.^{7,37} This drops to 38% in patients with a history of exertion-induced syncope who show ventricular ectopy, but not bidirectional or polymorphic VT, during exercise testing.⁷ One study including a small number of probands suggested that the odds of identifying a RyR2 mutation is higher in younger probands.²⁴

The yield of RyR2 genetic testing is 5-31% in

Figure 3. Examples of resting and exercise electrocardiogram (ECG) in a catecholaminergic polymorphic ventricular tachycardia (CPVT) patient. A) Resting ECG showing sinus bradycardia. The U-wave in lead V2 and V3 is of moderate amplitude. B-D) Exercise testing showing increasing complexity of ventricular arrhythmias. Panel B shows ventricular premature beats in bigeminy, panel C shows polymorphic couplets, and panel D polymorphic non-sustained ventricular tachycardia of four beats.

patients with exercise- or emotion- induced syncope without documented ventricular arrhythmias during exercise testing.^{7,37} Moreover, RyR2 mutations are identified in 15% of individuals with a normal ECG who are relatives of young SCD or ACA victims when these events were exercise or emotional stress-related.³⁷ However, in the absence of (possible) electrocardiographic signs of CPVT genetic testing is not recommended.³⁶

RyR2 mutations are also believed to play a role in sudden infant death syndrome (SIDS; unexplained death of an infant under one year of age after extensive postmortem examination). In one study including 134 unrelated SIDS victims two novel RyR2 mutations were detected in two cases.³⁸

Finally, the HRS/EHRA Expert Consensus Statement recommends genetic testing for family members and appropriate relatives following the identification of the CPVT-causative mutation in an index case (so-called cascade screening).³⁶ As CPVT can manifest at a very young age and RyR2 mutations have been associated with SIDS, cascade screening is recommended at birth.³⁶

Differential diagnosis

In patient presenting with exercise or emotional stress-induced syncope or ACA, LQTS, in particular type 1, is an alternative diagnosis. When the resting 12-lead ECG is inconclusive, exercise testing can help to discriminate between LQTS and CPVT, as previously discussed (see *Clinical diagnosis*).

Another differential diagnosis of exercise-induced bidirectional VT includes Andersen-Tawil syndrome (LQTS type 7). This condition is usually associated with extracardiac manifestations, *i.e.* periodic paralysis and facial dysmorphisms, and is caused by loss of function mutations in the gene encoding *KCNJ2* gene.³⁹

Other alternatives may include (initially concealed) structural heart disease, in particular mitral valve prolapse, arrhythmogenic right ventricular dysplasia/cardiomyopathy, hypertrophic cardiomyopathy and myocardial ischemia.

Clinical management

Considering the adrenergically mediated nature of the arrhythmias in CPVT, β -blockers at the maximum tolerable dose are considered the mainstay of treatment. Nadolol is probably most effective.⁴⁰ However, β -blockers do not completely suppress ventricular arrhythmias in most patients. In addition, it has been well established that a subset of patients are not well protected against arrhythmic events by β -blockers. In the largest cohort described to date (including 101 patients, of whom 50 were probands) an 8-year arrhythmic event rate of 27% was observed in patients on β -blockers.⁴⁰

Recently, we systematically reviewed all studies on efficacy of β -blockers.⁴¹ Among the 403 patients included, 88% were on β -blockers. We observed 8-year overall, near-fatal, and fatal event rates of 37.2%, 15.3%, and 6.4%, respectively (Figure 4). Importantly, some events occurring on β -blockers may be explained by non-compliance rather than true β -blocker therapy failure. In one study, patients on β -blockers showed an earlier onset of ventricular arrhythmias during exercise testing (on the same workload) as compared to baseline,³⁰

which would not be a preferable effect. In 2002 Priori *et al.* observed similar β -blocker efficacy in RyR2-mutation related and non-RyR2-mutation related CPVT, but event rates in this study were extremely high²³ and not in line with subsequent observations.⁴¹

Two studies reported promising results on the use of the L-type calcium channel blocker verapamil.^{42,43} However, on the long term verapamil does not prevent arrhythmic events in all patients.⁴⁴ Verapamil may be most effective in patients carrying CASQ2 mutations. In one

Figure 4. All (A), near-fatal (B) and fatal (C) arrhythmic event curves in catecholaminergic polymorphic ventricular tachycardia (CPVT) patients on β -blockers therapy. The red line and its corresponding area indicate the proportion of patients with arrhythmic events and its corresponding 95% confidence interval based on a random-effects meta-analysis model. The green data points represent the arrhythmic event rates of the individual studies. The area of each data point is proportional to its number of patients and statistical weight. Adapted from van der Werf *et al.*,⁴¹ with permission.

study, verapamil was the most effective antiarrhythmic drug in reducing ventricular arrhythmia in CASQ2 mutation carrying mice and humans.⁴⁵

Recently, it was discovered that flecainide prevented ventricular arrhythmias in a CASQ2 knock-out mouse model, presumably by directly targeting the underlying defect in CPVT.⁴⁶ Subsequently, we evaluated the efficacy and safety of this flecainide on top of conventional drug therapy in 33 mutation-carrying CPVT patients with continuous symptoms or ventricular arrhythmias.⁴⁷ In 22 patients (76%) ventricular arrhythmia were partly or completely suppressed ($P < 0.001$). During a median follow-up of 20 months (range: 12-40) one patient received appropriate ICD shocks, but this event was associated with very low flecainide levels. The other patients remained free of arrhythmic events.

According to current guidelines, ICD implantation is indicated in patients with CPVT who are survivors of cardiac arrest or patients with syncope and/or documented sustained VT despite β -blocker therapy.⁴⁸ However, in recent year several examples have shown that ICDs may be proarrhythmic in CPVT, as ICDs may trigger ventricular storms by inappropriate or appropriate shocks.^{28,49,50} Indeed, CPVT patients may be at increased risk of inappropriate shocks due to CPVT-related supraventricular arrhythmias.^{51,52}

In 2008, the first three CPVT patients with successful prevention of adrenergically-mediated arrhythmias with left cardiac sympathetic denervation (LCSD) were described, some with long-term follow-up.⁵³ After this, more successful experiences with LCSD in CPVT have been published.⁵⁴⁻⁵⁶ Given the excellent results, some authors argue that LCSD should be performed before considering ICD implantation.⁵⁷

Future treatment options may include propafenone,⁵⁸ dantrolene,⁵⁹ and further development of the newly developed compounds S107,⁶⁰ K201 (JTV519),⁶¹ and KN93.⁶²

Effectiveness of therapy should be monitored regularly using exercise testing and/or holter monitoring. In addition, discouraging participation in competitive sports and emphasizing therapy compliance may be critical to prevent arrhythmic events. CPVT patients should also be advised not to go swimming alone.⁶³

To date, data on risk stratification in CPVT patients are scarce. In particular, predictors for a very low risk for arrhythmias (which would make active treatment unnecessary) have not been identified, as silent mutation carriers are also at risk of arrhythmic events.^{30,40} Thus, based on current knowledge all phenotypically and/or genotypically affected CPVT patients should receive treatment. The only exception may apply for older RyR2-mutation carrying individuals (over approximately 60 years of

age) who are identified by cascade screening and have been asymptomatic lifelong.

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