Catecholaminergic Polymorphic Ventricular Tachycardia

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Sudden death because of cardiac arrhythmias in the young is a devastating event and remains underdiagnosed. The primary electric disorders responsible for polymorphic ventricular tachycardia (VT) or ventricular fibrillation are long-QT syndrome, Brugada syndrome, the short-coupled variant of torsades de pointes, short-QT syndrome, and catecholaminergic polymorphic VT (CPVT). CPVT is a rare arrhythmogenic disorder characterized by adrenergic-induced bidirectional and polymorphic VT. The prevalence of the disease is estimated to be 1:10 000 in Europe. The first case was reported in 1975,[1] followed by our first series of patients.[2,3] Key features include polymorphic VT reproducibly induced during exercise tests, isoproterenol infusion, or emotion and exercise. CPVT occurs in children and adolescents and causes syncope and sudden cardiac death at a young age, in the absence of structural heart disease. The resting ECG, including the QTc interval, is normal. The mortality of CPVT is extremely high, reaching 31% by the age of 30 years when untreated.[1,2] The estimated 4- and 8-year cardiac event rates were 33% and 58%, respectively, in our series of patients without β-blockers.[3] There is a clear correlation between the age of the first syncope and the severity of the disease, with a worse prognosis in the case of early occurrence. β-Blockers without sympathomimetic activity are clinically effective in reducing syncope.[3] However, arrhythmic event rate with β-blocker therapy remains significant, suggesting the need for alternate pharmacological and nonpharmacological therapies, which will be discussed.

With the advancements of molecular genetics and the identification of mutations in the genes encoding the cardiac ryanodine receptor and cardiac calsequestrin 2 in patients with CPVT, the central role of the intracellular calcium dysregulation in myocardial cells is progressively better understood through expression studies and murine models. Therapies targeting this dysregulation have been actually developed.

Genetic Background

Family history of syncope or sudden death in the initial reports was suggestive of a genetic origin.[3,4] This was established with the description of 2 large Finnish families with typical presentation of CPVT inherited on an autosomal dominant mode and the identification of the first locus on chromosome 1q42–43 in 1999.[5] Priori et al[6] and Laitinen et al[7] identified the first mutations in the cardiac ryanodine receptor gene (*RYR2*) in families suffering of this type of CPVT, now known as CPVT1. A recessive form in families belonging to a Bedouin tribe and mapped to chromosome 1p13–21 has been described by Lahat et al.[8] They identified a homozygous missense mutation in the cardiac calsequestrin gene (*CASQ2*) as the cause of this recessive form,[9] now known as CPVT2. We then described patients with homozygous nonsense *CASQ2* mutation, suggesting that complete absence of *CASQ2* in humans is not lethal and does not seem to induce any structural abnormality.[10] *RYR2* mutations are frequent, whereas *CASQ2* mutations are rare; altogether, mutations are only found in 50% to 60% of patients with CPVT, which suggests that other genes are involved. Recently, a new locus on chromosome 7p14–p22 was reported in an inbred Arab family, with an early-onset lethal form of recessive CPVT.[11]

Ryanodine Receptor

The cardiac ryanodine receptors (RyR2) are calcium (Ca^{2+}) release channels present in the sarcoplamic reticulum (SR), an intracellular vesicular network playing a major role in the regulation of Ca^{2+} homeostasis in the heart. The mechanism of their activation is called calcium-induced calcium release because it requires that Ca^{2+} provided by the activated L-type Ca^{2+} channel (Cav1.2). Calcium binds to RyR2 and triggers opening of a high-conductance channel, allowing rapid Ca^{2+} efflux from the SR. The consecutive high cytoplasmic Ca^{2+} induces myocardial contraction, then Ca^{2+} is reuptaken in the SR, where it is stored at high concentrations. This cycle is finely regulated, and its dysfunction is associated with cardiac diseases, such as CPVT, sudden death, and heart failure.[12]

RyR2 is a homotetramer; each monomer contains an enormous cytoplasmic domain that serves as a scaffold for regulatory subunits and enzymes that modulate the function of the channel[13] and a channel domain located at the carboxy terminus. Each monomer has at least 6 transmembrane segments forming the pore region of the channel.[14,15]

Many proteins are associated directly or indirectly with the N-terminal cytoplasmic domain of RyR2, including the 12.6-kDa FK506-binding protein (calstabin-2 or FKBP12.6),[16] protein kinase A,[17] calcium/calmodulin-dependent kinase II,[18] phosphodiesterase 4D3,[19] calmodulin,[20] protein phosphatases 1 and 2A,[17] and sorcin.[21] Calsequestrin, junctin, and triadin are linked to the C-terminus of RyR2.[22]

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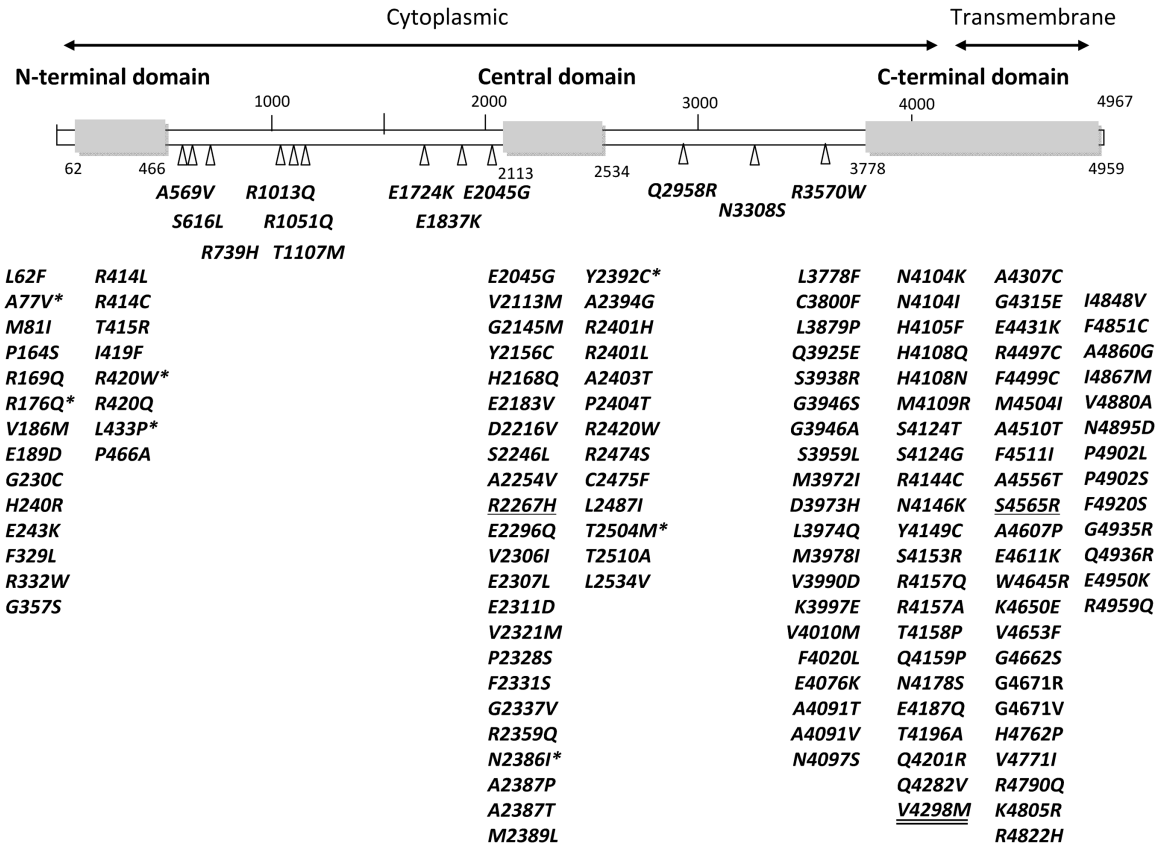

Figure 1. Schematic diagram of the RyR2 protein with the148 reported mutations. The most C-terminal amino acids (≈500) compose the transmembrane domain, whereas the major part is cytoplasmic. The mutations are largely clustered in 3 regions of the sequence (**gray boxes**): NH2 terminus, central domain, and C-terminal domain or channel region are denoted. Mutations initially described as *ARVD2* mutations, a phenotype that has not been confirmed by other teams, are denoted by an **asterisk**, mutations identified in children who died of small infant death syndrome are **underlined**, and the mutation reported in a long-QT family is **double underlined**. Some mutations occur in the 3 regions of divergence among the 3 ryanodine receptor (RyR) homologs: 1310–1423, 1815–1903 (E1837K), and 4208–4489 (Q4282V, V4298M, A4307C, G4315E, E4431K), which are proposed to underscore the functional differences between ryodine receptor isoforms.

RyR2 shares close to 70% with 2 other mammalian RyR isoforms[15]: RyR1 and RyR3. RyR1 is predominantly found in skeletal muscle, where it is activated directly by the L-type Ca^{2+} channel (Cav1.1) to release SR Ca^{2+} stores during skeletal muscle contraction. Mutations in the *RYR1* gene cause various muscle disorders, such as malignant hyperthermia or central core diseases.[23]

RYR2 Mutations

The 4967-amino acid RyR2 channel is encoded by one of the largest genes in the human genome, containing 105 exons. To date, >50 mutations have been reported, most of them for CVT1 and unexplained or exercise-induced sudden death (review in Refs 24–29). A few mutations have been identified in patients described as presenting with type 2 arrhythmogenic right ventricular cardiomyopathy,[30] sudden infant death syndrome,[31] or even associated with QT prolongation (Figure 1). Most of the *RYR2* mutations are missense mutations, occurring in 3 hotspot regions: the N-terminal region, the central region where the calstabin-2 binding domain is localized, and the C-terminal domain, including the channel region. These 3 regions are well conserved among the RyR gene family and are involved in the regulation of RyR channels. Similar mutation clustering is observed for *RYR1* disease–associated mutations.[23]

A recent screening of the 105 exons in a large cohort of patients with CPVT has confirmed these hot spots.[24] However, mutations are reported out of these hot spots, especially between domains I and II.[24,29,32] It is logical to first screen the most frequently mutated exons and then all the exons with known mutations, but new mutations may occur in other exons and thus necessitate performing a complete gene analysis. In addition, some large deletions have been reported,[24,26,33] and large genomic rearrangements may be much more frequent than thought because they are not explored with the techniques used in diagnostic laboratories. When a mutation is detected, siblings and parents have to be screened for the mutation, even if they are asymptomatic. For genetic counseling, it is important to note that de novo mutations are frequent (at least 20%–50% in sporadic cases). Furthermore, even if it is a rare event, germinal and somatic mosaicism may occur in an asymptomatic parent, as reported in 2 studies.[24,28] Somatic mosaicism is not investigated in most of the clinical diagnostic laboratories and requires additional tissues samples to analyze parental urinary cells, hair roots, or buccal epithelium DNA. Germinal mosaicism is only investigated when the same mutation is identified in 2 siblings and not identified in DNA from the parental blood. When a de novo mutation is detected, it is cautious and easier to screen the siblings for the sporadic proband mutation, even if they are asymptomatic.

High variability of the phenotypic expression among subjects of the same family or unrelated families was demonstrated and estimates of the penetrance range from 25% to 100%.[32,34–36] It is noteworthy that there are asymptomatic RyR2 mutation carriers with normal exercise stress tests. Some of them can further present with exercise-induced arrhythmia during a subsequent stress test,[32] but more importantly may die suddenly as the first manifestation of the disease.[34,35] No genotype-phenotype correlations have been established so far, even if there are mutations identified in large pedigrees supporting a lower penetrance.[32,34] In few patients, 2 mutations have been reported,[32,37]and the role of associated polymorphisms, either frequent, such as Q2958R, G1886S, and G1885E, or more rare, such as A1136V, is not known.[29] They may affect Ca^{2+} regulation, as suggested by in vitro studies, and increase the risk of sudden death in some patients.[38]

CASQ2

CASQ2 is the major intra-SR Ca^{2+}-binding protein and is localized at the junctional face membrane in the SR.[39] It is a highly acidic protein with numerous charged residues and binds Ca^{2+} ions with low affinity.[40] CASQ2 exists in the SR as a dynamic structure formed of monomers, dimmers, or multimers, depending of the Ca^{2+} concentration. Although the multimeric forms of CASQ2, formed at high Ca^{2+} levels in vitro, function as a Ca^{2+} buffer, the monomers seem to modulate SR Ca^{2+} release by influencing the open probability of the RyR2 channel, via interactions with triadin and junctin.[41] Triadin and junctin are structurally homologous proteins with a single transmembrane domain and a long highly positively charged C-terminal domain extending in the lumen of the SR and are involved in protein-protein interaction, especially with CASQ2. The SR luminal Ca^{2+}-dependent control of RyR2 activity by CASQ2 normally limits RyR2 open probability and contributes to RyR2 deactivation and to the development of a temporary refractory state that occurs after each Ca^{2+} release. Studies of cells or myocytes after overexpression of mutant proteins and various models of genetically modified mice deficient in CASQ2 or triadin have repeatedly shown that CASQ2 is an important regulator of SR Ca^{2+} release.[42] CPVT mutations reduce the extent and shorten the duration of Ca^{2+} signaling refractoriness and increase RyR2 open probability, thereby promoting SR Ca^{2+} release, and thus contribute to the genesis of the arrhythmias.[43,44] This implies that CASQ2 truncating mutations or missense mutations affecting either its polymerization or its interactions with RyR2, triadin, and possibly other proteins could deregulate the calcium release machinery and induce lethal arrhythmia under stress conditions.

CASQ2 Mutations

The 399-amino acid CASQ2 protein is encoded by a gene containing 11 exons. Twenty-one distinct *CASQ2* mutations have been reported, either homozygous or compound heterozygous mutations transmitted under a recessive mode of inheritance (Figure 2). Half of them are missense mutations localized in different exons.[9,45–50] The others lead to truncated proteins by various mechanisms, nonsense codon, small deletion, and abnormal splicing leading to premature stop codon.[10,35,46,51,52] Interestingly, a synonymous c.381C>T variation in exon 3, recently identified in a family with CPVT2, was shown to induce abnormal splicing and a premature stop codon using a splicing minigene assay.[52]

The phenotype is similar among the patients with 2 *CASQ2* mutations and the patients with an *RyR2* mutation. Most of the carriers of a single *CASQ2* mutation are healthy. Nevertheless, several clinical investigations suggested that a single *CASQ2* mutation could represent a potential susceptibility for ventricular arrhythmias in some subjects.[10,28,45] The origin of the variability among subjects of a same family is still unknown. Two nonsynonymous polymorphisms, Thr76Ala and Val76Met, have been described in CASQ2 in both white and Asian populations, but to our knowledge their possible mild functional effect has not been studied.[50,53] Variants in the multiple proteins of the calcium release complex may also contribute to this individual susceptibility.

Pathophysiological Background

CPVT1 and *CPVT2* mutations result in inappropriate calcium leakage from the SR,[6–9] leading to cytosolic calcium overload generating delayed afterdepolarizations, triggered activity, and ventricular arrhythmias, in particular under adrenergic conditions.[10–13]

RyR2 presents 3 sites of phosphorylation on serines S2808, S2814, and S2030. During stimulation with isoproterenol, S2808 is phosphorylated by protein kinase A and S2814 is phosphorylated by calmodulin-dependent kinase II.[54] Marx et al[17] have shown that, during adrenergic stimulation, protein kinase A increases the open probability of RyR2 by the phosphorylation of serine 2808 and the subsequent dissociation of calstabin-2. Whereas a general consensus exists that adrenergic stimulation increases spontaneous Ca^{2+} release and that this leak is amplified in the presence of *CPVT1* or *CPVT2* mutations, the role of RyR2 phosphorylation and calstabin dissociation remains controversial.[55–57]

There is increasing amount of data, provided by a mouse model of CPVT, showing a Purkinje origin of the ventricular premature beats.[58] In this setting, it has been shown that delayed afterdepolarizations caused by calcium overload are a more common occurrence in Purkinje cells than in ventricular myocytes, both at baseline and after β-adrenergic stimulation.[59] The Purkinje cells are probably critical contributors to arrhythmic triggers in animal models and humans with CPVT.[60]

Clinical Presentation

CVPT was first described in 1975 by Reid et al[1] and then in 1978 by Coumel et al,[2] who reported a series of children without cardiac disease presenting with reproducible, exercise-induced ventricular polymorphic arrhythmia. In 1995, our group studied a cohort of 21 patients with a 7-year follow-up and further refined the description of this entity in 2009 with a cohort of 101 patients.[3,35] CVPT is extremely uncommon before the age of 2 years. Some *RyR2* mutations have been identified postmortem in cases of sudden infant death syndrome.[31] However, because CPVT-related documented arrhythmias at this very young age has never been reported, these genetic findings may not be causal of this disease. The

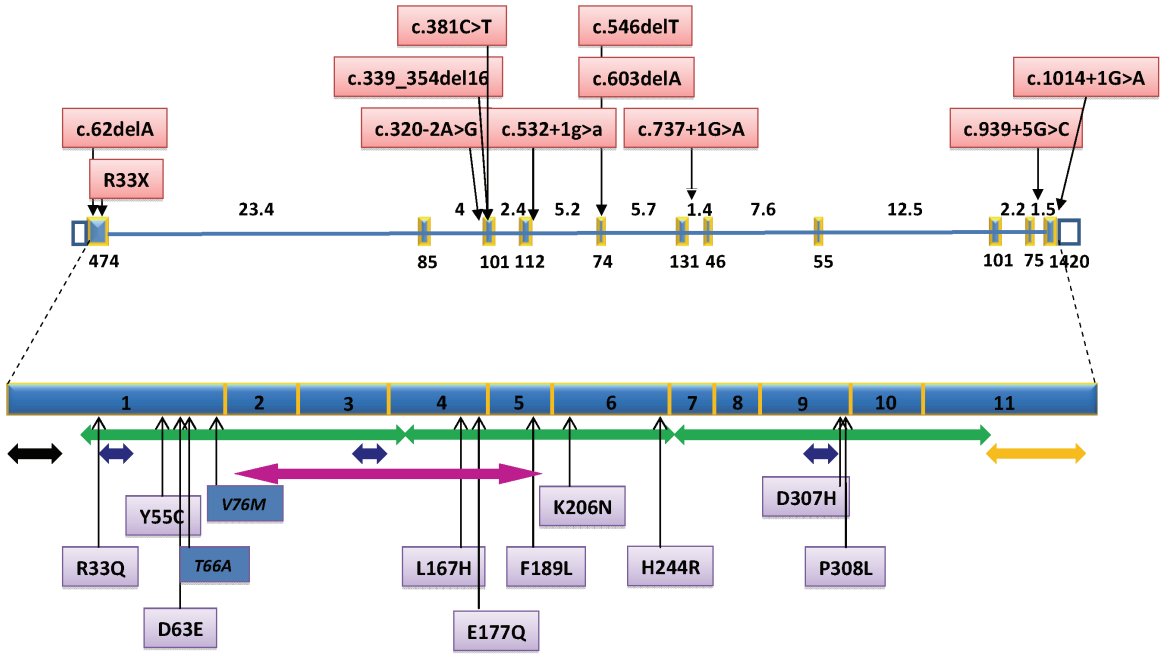

Figure 2. Schematic representation of the *CASQ2* gene, localization of the human mutations, and functional domains of the calsequestrin 2. **Upper part**: Genomic organization of *CASQ2* gene (68.77 Kb) with its 11 exons (**boxes**). The sizes are given in bp for exons and in Kb for introns. Nonsense (1), splicing (6) and deletions (4) mutations leading to putative nonfunctional truncated proteins are given. The loss of the acidic residues at the C-terminal domain, responsible for Ca^{2+} binding, induces inability to bind Ca^{2+}, disruption of the formation of head-to-tail dimmers, and polymerization of CASQ2. **Lower part**: The coding sequence is shown with the missense mutations in **purple** and 2 single nucleotide polymorphisms in **blue**. Some known functional sites of the corresponding protein are shown by **colored double arrows**. The overall structure of CASQ2 is composed of 3 identical thioredoxin-like domains (**green**). Every domain has a highly conserved hydrophobic core with acidic residues on the exterior, generating highly electronegative potential surfaces. The acidic C-terminal domain (356–399) includes another 28 negatively charged residues (**yellow**). In addition, the signal peptide (**black**), the junctional face membrane interaction domain (**pink**), the cardiac ankyrin repeat domain 1 protein (ANKRD1) binding sites, also known as CARP (**dark blue**), and the conserved sites among the various CASQ isoforms (**red**) are shown. Numerous residues are involved in front-to-front dimer interface, tetramer, and higher-order linear polymers with back-to-back interface, depending on the ionic environment. The residues are involved in the front-to-front (dimers) and back-to-back interfaces (tetramers and polymers). They are the most highly conserved residues in the entire sequence. *R33Q* and *D307H* mutations result in monomers that seem to be unable to form properly oriented dimers.

first episode of syncope usually occurs during the first or second decade of life. The symptoms are always triggered by exercise or emotional stress. Typically, the clinical presentation is syncope often associated with seizure induced by exercise or emotional stress. Often, epilepsy is diagnosed and children are inappropriately treated with long-term antiepileptic therapy. A mean delay in diagnosis of ≥2 years is usually reported in patients with syncope initially attributed to vasovagal or neurological causes. A family history of exercise-related syncope, seizure, or sudden death is reported in 30% of the patients. Family screening is mandatory because CPVT is an autosomal dominant disease. Asymptomatic carriers of a *RyR2* mutation are often detected during screening of the family members of an index patient.

Diagnosis

A history of exercise-induced or emotional stress–induced syncope with polymorphic ventricular arrhythmia in a child is highly suggestive of CVPT, although some patients with long-QT syndrome 1 can have a similar presentation. The resting ECG is normal, and the QT interval duration is normal but can be borderline in some cases. A lower than normal heart rate has been reported, particularly in boys with *RyR2* mutations.[3,35] The heart is structurally normal. The arrhythmia is reproducibly induced during an exercise test as well as during isoproterenol infusion. Holter monitoring or an exercise test can document CVPT by showing the ventricular arrhythmia progressively appearing after a heart rate threshold (around 120–130 beats per minute). Polymorphic VT is usually not inducible by programmed ventricular stimulation. Implantable loop recorders can be useful to record CVPT in children with adrenergically triggered, unexplained syncope. Molecular analysis has shown that there is a small group of patients with CPVT (mutation carriers) with an apparently normal phenotype, even after exercise tests.[35] It is worrying that some of these phenotypically normal patients with CVPT do experience syncope and sudden death, implying that an asymptomatic phenotype does not guarantee protection from polymorphic VT. Our recent report also demonstrated that cardiac and lethal (or near lethal) event rates were similar between 50 probands and 51 affected family members, suggesting that in the family of a proband with newly diagnosed CPVT identification of the affected relatives is mandatory.[35]

Electrocardiographic Key Features in CVPT

The resting ECG is usually normal, and there is progressive ventricular ectopy as heart rate increases during exercise or isoproterenol infusion. Frequency and complexity increase as heart rate increases, first monomorphic ventricular premature

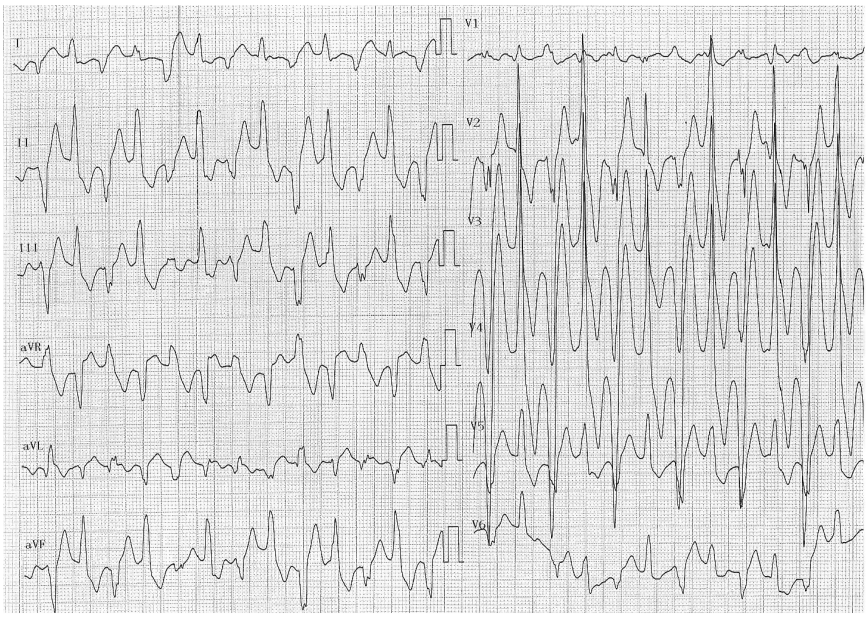

Figure 3. Twelve-lead ECG tracing during stress test shows the typical aspect of bidirectional ventricular tachycardia characterized by 180° alternating QRS axis on a beat-to-beat basis, with a right bundle branch block pattern suggesting a left ventricular origin.

beats (VPBs) followed by bidirectional VT (Figure 3). VPBs usually have a right bundle branch block pattern with alternating right and left axis deviation, suggesting a left ventricular origin. If the exercise is continued, salvos of polymorphic VT may appear and become more sustained and rapid, leading to syncope. Usually, the arrhythmia is self-terminating, but in some cases it can degenerate into ventricular fibrillation and sudden death (Figure 4). The arrhythmia disappears with the discontinuation of the exercise or after cessation of the isoproterenol infusion. The reverse heart rate–dependent sequence is usually observed during recovery. Some individuals expressing bidirectional VT during exercise may not have CPVT. Instead, clinical consideration of either Andersen-Tawil syndrome or long-QT syndrome and appropriate genetic testing may be warranted for individuals without an *RyR2* mutation but considered as patients with CPVT, particularly women. Careful inspection of the TU-wave morphology may assist in distinguishing between CPVT and Andersen-Tawil syndrome in a patient exhibiting exercise-induced bidirectional VT.[61] Atrial arrhythmias, including atrial fibrillation, are not uncommon during exercise tests and have been described in some adult patients.[25]

Current Management

β-Blockers

The first-line therapeutic option for patients with CPVT is β-blockers without sympathomimetic activity, in accordance with the arrhythmia's catecholaminergic mechanism, combined with exercise restriction. Nadolol, a long-acting drug, is preferred for prophylactic therapy and has been found to be effective clinically. In our experience, the dosage used to provide adequate prevention of CVPT and syncope is usually high (1.8 mg/kg). We reported in 2009 the long-term follow-up results of 101 patients with CPVT with an estimated 8-year cardiac event rate of 27%, even in those taking β-blockers.[35]

Numerous studies[3,13,14,16,24,25,27,29,35] have reported the heterogeneous proportion of near-fatal and fatal arrhythmic events in patients with CPVT. The apparent discrepancy in the efficacy of β-blocker treatment between the various studies probably reflects differences in genetic background in β-blocker dosages or a poor drug compliance. This discrepancy in β-blocker efficacy may also be because of the presence of polymorphisms influencing their metabolism. Larger groups of CPVT probands are needed to address the issue of β-blocker efficacy in CPVT.

Our study of 101 patients with CPVT showed that a younger age at the time of the diagnosis and the absence of β-blockers were independent predictors for cardiac events. A history of aborted cardiac arrest before diagnosis and absence of β-blockers were independent predictors of life-threatening events. It is worth noting that a history of syncope before diagnosis was not associated with higher cardiac or life-threatening event rates. In the subgroup of 81 patients receiving β-blockers, β-blockers other than nadolol, as well as a younger age at the diagnosis, were independent predictors for cardiac events.[35]

Meanwhile, the maximal well-tolerated dosages of β-blockers should be prescribed and Holter recordings and exercise tests should be repeated periodically to ensure that the degree of sinus tachycardia that precedes the onset of arrhythmias is never reached. Furthermore, once the diagnosis is established, it is crucial to make the patients aware of the necessity of faultless compliance with the β-blocker therapy, given the number of noncompliance-related sudden cardiac deaths. It is strongly suggested that genetically positive family members should receive β-blockers even after a negative exercise test.[35]

Asymptomatic VPBs usually persist on Holter recordings with an unmodified threshold of appearance. Complete suppression of asymptomatic VPBs seems not to be mandatory. We have identified that the presence of couplets or more successive VPBs during exercise testing was significantly associated with future arrhythmic events (sensitivity, 0.62; specificity, 0.67), suggesting to intensify the treatment in these cases.[35]

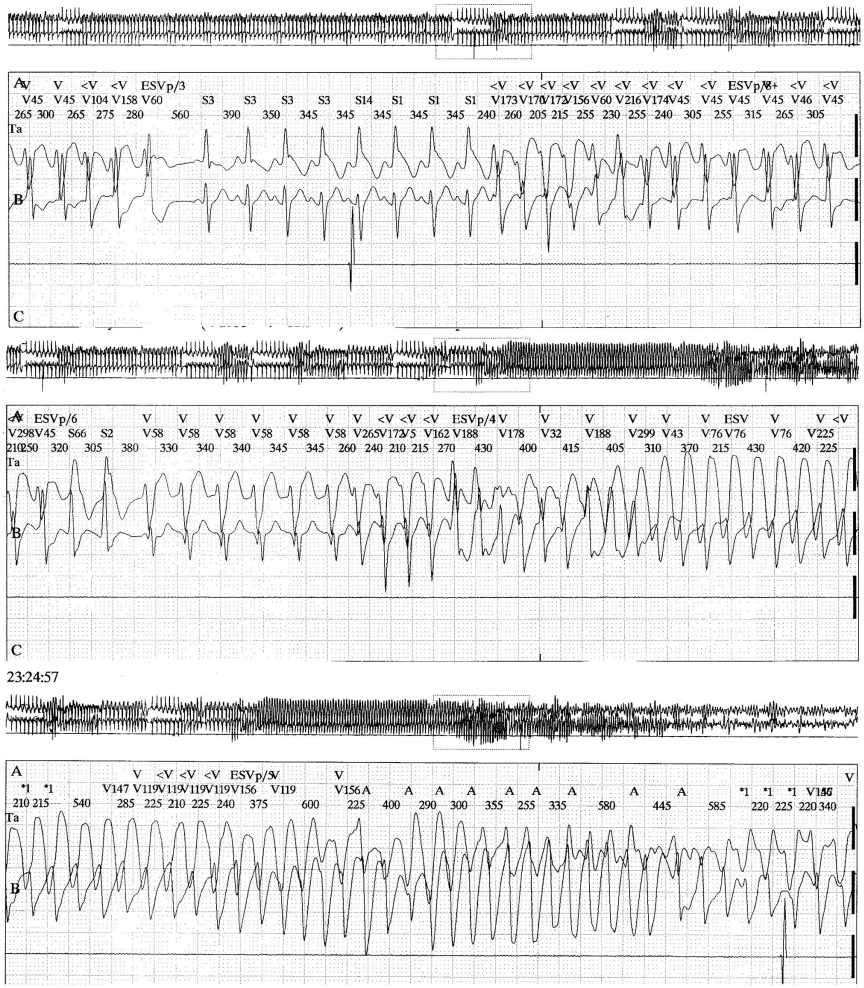

Figure 4. Holter tracings showing pleiomorphic and polymorphic ventricular tachycardia preceding the occurrence of ventricular fibrillation in a patient with catecholaminergic polymorphic ventricular tachycardia.

Implantable Cardioverter Defibrillator

An implantable cardioverter defibrillator (ICD) implantation is recommended in patients with CPVT and syncope or documented sustained VT, despite β-blocker therapy.[62] It should also be discussed with patients with a history of aborted cardiac arrest or in those with poor β-blocker tolerance or compliance.

Nevertheless, ICDs can potentially have proarrhythmic effects in patients with CPVT because stress caused by appropriate or inappropriate discharges could prove disastrous by evoking a self-induced vicious circle.[63,64]

However, a combination therapy involving both an ICD and an optimized dosage of β-blocker should safeguard against any such adverse effects and provide ultimate protection in nonresponsive patients. Flecainide and verapamil have been challenged in a small number of patients, with promising results. An ICD should be considered for patients who do not respond to a combination of β-blockers and flecainide or verapamil or for whom a left cardiac sympathetic denervation has been ruled out. Nonetheless, insertion of an ICD is a technical challenge in pediatric patients and problems, such as inappropriate shocks, and the need for a life-time protection requiring multiple reinterventions should be addressed when the decision is made.

Verapamil

Verapamil has been shown to be beneficial in some patients with CPVT by reducing the ventricular arrhythmia burden on top of β-blocker therapy during a short-term follow-up period.[65,66]

Flecainide

Flecainide has been proved to have RyR2 blocking properties and to significantly reduce the ventricular arrhythmia burden in 2 patients with highly symptomatic CPVT.[67,68] The efficacy of flecainide has been retrospectively confirmed in a multicenter study including 33 patients with CPVT.[67] The rationale to combine β-blockers to flecainide was the persistence of ventricular arrhythmias or symptoms while taking a β-blocker alone or combined with a calcium channel blocker. Twenty-two (76%) patients had either a partial (n=8) or complete (n=14) suppression of exercise-induced ventricular arrhythmias by flecainide. No patient experienced worsening of exercise-induced ventricular arrhythmias. During a median follow-up of 20 months (range, 12–40 months), no arrhythmic events occurred, except for 1 patient who experienced ICD shocks for polymorphic VT, which were associated with low flecainide levels. One patient already had been arrhythmia free for more than 25 years. However, the flecainide efficacy in the prevention of arrhythmic events remains to be demonstrated prospectively on a long-term basis.

Left Cardiac Sympathetic Denervation

Short series have been published reporting significant results of the left cardiac sympathetic denervation (LCSD) on cardiac events. The first publication reported the efficacy of LCSD in 3 young patients with CPVT, with a long follow-up in 2 (aged 20 and 10 years) in whom ventricular arrhythmias were not controlled by β-blocker therapy.[69] The following series reported results of LCSD in patients with resistant and symptomatic ventricular arrhythmias, despite optimal pharmacological therapy.[70–74] Although the short-term results seem encouraging, more data from a long-term follow-up are needed. LCSD is not available in many centers worldwide because it requires well-trained surgeons and dedicated techniques. Therefore, the place of LCSD in the therapeutic management of patients with CPVT resistant to optimal pharmacological therapy is actually unclear.

Management of Patients with CPVT: Next Steps

The class 1c antiarrhythmic agent propafenone was recently reported to have RyR2 blocking properties similar to flecainide.[70] It has been shown to prevent exercise-induced CPVT in *CASQ2*-mutated mice and to prevent ICD shocks in a 22-year-old patient with CPVT who had been refractory to maximal standard drug therapy and bilateral stellate ganglionectomy.[70] Propafenone might be a therapeutic option in resistant cases.

Other compounds, such as dantrolene[71] (acting by stabilizing the leaky RyR2 through the correction of the defective interdomain interaction) or JTV519,[72,74] an RyR2 channel inhibitor (acting as a ryanodine receptor modulator by improving the rebinding of calstabin-2 to hyperphosphorylated RyR2 channels), and KN93, an inhibitor of calcium/calmodulin-dependent protein kinase II,[73] are able to prevent exercise- and epinephrine-induced ventricular arrhythmias in CPVT mouse models. A prospective study with one of these compounds is actually ongoing in patients with CPVT. More data are needed to validate these potential new therapeutic options in patients with CPVT

Conclusions

Early diagnosis of CVPT is crucial considering the high risk of sudden death in untreated patients and the relative good response to β-blockers in the majority of cases combined with exercise restriction. Family screening by clinical evaluation and genetic testing is mandatory to identify undiagnosed patients and asymptomatic carriers who are at risk of cardiac events and should be treated. The place of the ICD is questionable considering the young age of the patients, its possible proarrhythmic effects, and the other pharmacological alternative therapies that have recently been proposed. However, long-term efficacy data are awaited. Some new compounds such as the RyR2 channel inhibitors are being prospectively studied. The therapeutic strategy in patients with CPVT will possibly been modified in the next years, thanks to the results of the ongoing studies.

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Disclosures

None.

References

1. Reid DS, Tynan M, Braidwood L, Fitzgerald GR. Bidirectional tachycardia in a child. A study using His bundle electrography. *Br Heart J*. 1975;37:339–344.
2. Coumel P, Fidelle J, Lucet V, Attuel P, Bouvrain Y. Catecholamine-induced severe ventriculae arrhythmias with Adams Stockes syndrome in children: report of four cases. *Br Heart J.* 1978;40:28–37.
3. Leenhardt A, Lucet V, Denjoy I, Grau F, Ngoc DD, Coumel P. Catecholaminergic polymorphic ventricular tachycardia in children. A 7-year follow-up of 21 patients. *Circulation*. 1995;91:1512–1519.
4. Strasberg B, Coelho A, Welch W, Swiryn S, Bauernfeind R, Rosen K. Doxepin induced torsade de pointes. *Pacing Clin Electrophysiol*. 1982;5:873–877.
5. Swan H, Piippo K, Viitasalo M, Heikkilä P, Paavonen T, Kainulainen K, Kere J, Keto P, Kontula K, Toivonen L. Arrhythmic disorder mapped to chromosome 1q42-q43 causes malignant polymorphic ventricular tachycardia in structurally normal hearts. *J Am Coll Cardiol*. 1999;34:2035–2042.
6. Priori SG, Napolitano C, Tiso N, Memmi M, Vignati G, Bloise R, Sorrentino V, Danieli GA. Mutations in the cardiac ryanodine receptor gene (hRyR2) underlie catecholaminergic polymorphic ventricular tachycardia. *Circulation*. 2001;103:196–200.
7. Laitinen PJ, Brown KM, Piippo K, Swan H, Devaney JM, Brahmbhatt B, Donarum EA, Marino M, Tiso N, Viitasalo M, Toivonen L, Stephan DA, Kontula K. Mutations of the cardiac ryanodine receptor (RyR2) gene in familial polymorphic ventricular tachycardia. *Circulation*. 2001;103:485–490.
8. Lahat H, Eldar M, Levy-Nissenbaum E, Bahan T, Friedman E, Khoury A, Lorber A, Kastner DL, Goldman B, Pras E. Autosomal recessive catecholamine- or exercise-induced polymorphic ventricular tachycardia: clinical features and assignment of the disease gene to chromosome 1p13-21. *Circulation*. 2001;103:2822–2827.
9. Lahat H, Pras E, Olender T, Avidan N, Ben-Asher E, Man O, Levy-Nissenbaum E, Khoury A, Lorber A, Goldman B, Lancet D, Eldar M. A missense mutation in a highly conserved region of CASQ2 is associated with autosomal recessive catecholamine-induced polymorphic ventricular tachycardia in Bedouin families from Israel. *Am J Hum Genet*. 2001;69:1378–1384.
10. Postma AV, Denjoy I, Hoorntje TM, Lupoglazoff JM, Da Costa A, Sebillon P, Mannens MM, Wilde AA, Guicheney P. Absence of calsequestrin 2 causes severe forms of catecholaminergic polymorphic ventricular tachycardia. *Circ Res*. 2002;91:e21–e26.
11. Bhuiyan ZA, Hamdan MA, Shamsi ET, Postma AV, Mannens MM, Wilde AA, Al-Gazali L. A novel early onset lethal form of catecholaminergic polymorphic ventricular tachycardia maps to chromosome 7p14-p22. *J Cardiovasc Electrophysiol*. 2007;18:1060–1066.
12. Kushnir A, Marks AR. The ryanodine receptor in cardiac physiology and disease. *Adv Pharmacol*. 2010;59:1–30.
13. Ter Keurs HE, Boyden PA. Calcium and arrhythmogenesis. *Physiol Rev*. 2007;87:457–506.
14. Du GG, Sandhu B, Khanna VK, Guo XH, MacLennan DH. Topology of the Ca2+ release channel of skeletal muscle sarcoplasmic reticulum (RyR1). *Proc Natl Acad Sci U S A*. 2002;99:16725–16730.
15. Ma J, Hayek SM, Bhat MB. Membrane topology and membrane retention of the ryanodine receptor calcium release channel. *Cell Biochem Biophys*. 2004;40:207–224.
16. Timerman AP, Jayaraman T, Wiederrecht G, Onoue H, Marks AR, Fleischer S. The ryanodine receptor from canine heart sarcoplasmic reticulum is associated with a novel FK-506 binding protein. *Biochem Biophys Res Commun*. 1994;198:701–706.
17. Marx SO, Reiken S, Hisamatsu Y, Jayaraman T, Burkhoff D, Rosemblit N, Marks AR. PKA phosphorylation dissociates FKBP12.6 from the calcium release channel (ryanodine receptor): defective regulation in failing hearts. *Cell*. 2000;101:365–376.
18. Wehrens XH, Lehnart SE, Reiken SR, Marks AR. Ca2+/calmodulin-dependent protein kinase II phosphorylation regulates the cardiac ryanodine receptor. *Circ Res*. 2004;94:e61–e70.
19. Lehnart SE, Wehrens XH, Reiken S, Warrier S, Belevych AE, Harvey RD, Richter W, Jin SL, Conti M, Marks AR. Phosphodiesterase 4D deficiency in the ryanodine-receptor complex promotes heart failure and arrhythmias. *Cell*. 2005;123:25–35.

20. Meissner G, Henderson JS. Rapid calcium release from cardiac sarcoplasmic reticulum vesicles is dependent on Ca2+ and is modulated by Mg2+, adenine nucleotide, and calmodulin. *J Biol Chem*. 1987;262:3065–3073.
21. Farrell EF, Antaramian A, Benkusky N, Zhu X, Rueda A, Gómez AM, Valdivia HH. Regulation of cardiac excitation-contraction coupling by sorcin, a novel modulator of ryanodine receptors. *Biol Res*. 2004;37:609–612.
22. Györke S, Terentyev D. Modulation of ryanodine receptor by luminal calcium and accessory proteins in health and cardiac disease. *Cardiovasc Res*. 2008;77:245–255.
23. Lanner JT, Georgiou DK, Joshi AD, Hamilton SL. Ryanodine receptors: structure, expression, molecular details, and function in calcium release. *Cold Spring Harb Perspect Biol*. 2010;2:a003996.
24. Medeiros-Domingo A, Bhuiyan ZA, Tester DJ, Hofman N, Bikker H, van Tintelen JP, Mannens MM, Wilde AA, Ackerman MJ. The RYR2-encoded ryanodine receptor/calcium release channel in patients diagnosed previously with either catecholaminergic polymorphic ventricular tachycardia or genotype negative, exercise-induced long QT syndrome: a comprehensive open reading frame mutational analysis. *J Am Coll Cardiol*. 2009;54:2065–2074.
25. Kazemian P, Gollob MH, Pantano A, Oudit GY. A novel mutation in the RYR2 gene leading to catecholaminergic polymorphic ventricular tachycardia and paroxysmal atrial fibrillation: dose-dependent arrhythmia-event suppression by ß-blocker therapy. *Can J Cardiol*. 2011;27:870. e7–870. e10.
26. Marjamaa A, Laitinen-Forsblom P, Wronska A, Toivonen L, Kontula K, Swan H. Ryanodine receptor (RyR2) mutations in sudden cardiac death: studies in extended pedigrees and phenotypic characterization in vitro. *Int J Cardiol*. 2011;147:246–252.
27. Meli AC, Refaat MM, Dura M, Reiken S, Wronska A, Wojciak J, Carroll J, Scheinman MM, Marks AR. A novel ryanodine receptor mutation linked to sudden death increases sensitivity to cytosolic calcium. *Circ Res*. 2011;109:281–290.
28. Roux-Buisson N, Egéa G, Denjoy I, Guicheney P, Lunardi J. Germline and somatic mosaicism for a mutation of the ryanodine receptor type 2 gene: implication for genetic counselling and patient caring. *Europace*. 2011;13:130–132.
29. Sy RW, Gollob MH, Klein GJ, Yee R, Skanes AC, Gula LJ, Leong-Sit P, Gow RM, Green MS, Birnie DH, Krahn AD. Arrhythmia characterization and long-term outcomes in catecholaminergic polymorphic ventricular tachycardia. *Heart Rhythm*. 2011;8:864–871.
30. Tiso N, Stephan DA, Nava A, Bagattin A, Devaney JM, Stanchi F, Larderet G, Brahmbhatt B, Brown K, Bauce B, Muriago M, Basso C, Thiene G, Danieli GA, Rampazzo A. Identification of mutations in the cardiac ryanodine receptor gene in families affected with arrhythmogenic right ventricular cardiomyopathy type 2 (ARVD2). *Hum Mol Genet*. 2001;10:189–194.
31. Tester DJ, Dura M, Carturan E, Reiken S, Wronska A, Marks AR, Ackerman MJ. A mechanism for sudden infant death syndrome (SIDS): stress-induced leak via ryanodine receptors. *Heart Rhythm*. 2007;4:733–739.
32. Postma AV, Denjoy I, Kamblock J, Alders M, Lupoglazoff JM, Vaksmann G, Dubosq-Bidot L, Sebillon P, Mannens MM, Guicheney P, Wilde AA. Catecholaminergic polymorphic ventricular tachycardia: RYR2 mutations, bradycardia, and follow up of the patients. *J Med Genet*. 2005;42:863–870.
33. Bhuiyan ZA, van den Berg MP, van Tintelen JP, Bink-Boelkens MT, Wiesfeld AC, Alders M, Postma AV, van Langen I, Mannens MM, Wilde AA. Expanding spectrum of human RYR2-related disease: new electrocardiographic, structural, and genetic features. *Circulation*. 2007;116:1569–1576.
34. Bauce B, Rampazzo A, Basso C, Bagattin A, Daliento L, Tiso N, Turrini P, Thiene G, Danieli GA, Nava A. Screening for ryanodine receptor type 2 mutations in families with effort-induced polymorphic ventricular arrhythmias and sudden death: early diagnosis of asymptomatic carriers. *J Am Coll Cardiol*. 2002;40:341–349.
35. Hayashi M, Denjoy I, Extramiana F, Maltret A, Buisson NR, Lupoglazoff JM, Klug D, Hayashi M, Takatsuki S, Villain E, Kamblock J, Messali A, Guicheney P, Lunardi J, Leenhardt A. Incidence and risk factors of arrhythmic events in catecholaminergic polymorphic ventricular tachycardia. *Circulation*. 2009;119:2426–2434.
36. Priori SG, Napolitano C, Memmi M, Colombi B, Drago F, Gasparini M, DeSimone L, Coltorti F, Bloise R, Keegan R, Cruz Filho FE, Vignati G, Benatar A, DeLogu A. Clinical and molecular characterization of patients with catecholaminergic polymorphic ventricular tachycardia. *Circulation*. 2002;106:69–74.
37. Aizawa Y, Mitsuma W, Ikrar T, Komura S, Hanawa H, Miyajima S, Miyoshi F, Kobayashi Y, Chinushi M, Kimura A, Hiraoka M, Aizawa Y. Human cardiac ryanodine receptor mutations in ion channel disorders in Japan. *Int J Cardiol*. 2007;116:263–265.
38. Koop A, Goldmann P, Chen SR, Thieleczek R, Varsányi M. ARVC-related mutations in divergent region 3 alter functional properties of the cardiac ryanodine receptor. *Biophys J*. 2008;94:4668–4677.
39. Franzini-Armstrong C, Protasi F, Tijskens P. The assembly of calcium release units in cardiac muscle. *Ann N Y Acad Sci*. 2005;1047:76–85.
40. Mitchell RD, Simmerman HK, Jones LR. Ca2+ binding effects on protein conformation and protein interactions of canine cardiac calsequestrin. *J Biol Chem*. 1988;263:1376–1381.
41. Györke I, Hester N, Jones LR, Györke S. The role of calsequestrin, triadin, and junctin in conferring cardiac ryanodine receptor responsiveness to luminal calcium. *Biophys J*. 2004;86:2121–2128.
42. Liu N, Rizzi N, Boveri L, Priori SG. Ryanodine receptor and calsequestrin in arrhythmogenesis: what we have learnt from genetic diseases and transgenic mice. *J Mol Cell Cardiol*. 2009;46:149–159.
43. Györke S, Stevens SC, Terentyev D. Cardiac calsequestrin: quest inside the SR. *J Physiol (Lond)*. 2009;587(Pt 13):3091–3094.
44. Katz G, Arad M, Eldar M. Catecholaminergic polymorphic ventricular tachycardia from bedside to bench and beyond. *Curr Probl Cardiol*. 2009;34:9–43.
45. de la Fuente S, Van Langen IM, Postma AV, Bikker H, Meijer A. A case of catecholaminergic polymorphic ventricular tachycardia caused by two calsequestrin 2 mutations. *Pacing Clin Electrophysiol*. 2008;31:916–919.
46. di Barletta MR, Viatchenko-Karpinski S, Nori A, Memmi M, Terentyev D, Turcato F, Valle G, Rizzi N, Napolitano C, Gyorke S, Volpe P, Priori SG. Clinical phenotype and functional characterization of CASQ2 mutations associated with catecholaminergic polymorphic ventricular tachycardia. *Circulation*. 2006;114:1012–1019.
47. Kirchhefer U, Wehrmeister D, Postma AV, Pohlentz G, Mormann M, Kucerova D, Müller FU, Schmitz W, Schulze-Bahr E, Wilde AA, Neumann J. The human CASQ2 mutation K206N is associated with hyperglycosylation and altered cellular calcium handling. *J Mol Cell Cardiol*. 2010;49:95–105.
48. Liu QQ, Oberti C, Zhang XQ, Ke T, Zhang T, Scheinman M, Hu DY, Wang QK. [A Novel mutation of F189L in CASQ2 in families with catecholaminergic polymorphic ventricular tachycardia]. *Zhonghua Yi Xue Yi Chuan Xue Za Zhi*. 2008;25:334–337.
49. Terentyev D, Nori A, Santoro M, Viatchenko-Karpinski S, Kubalova Z, Gyorke I, Terentyeva R, Vedamoorthyrao S, Blom NA, Valle G, Napolitano C, Williams SC, Volpe P, Priori SG, Gyorke S. Abnormal interactions of calsequestrin with the ryanodine receptor calcium release channel complex linked to exercise-induced sudden cardiac death. *Circ Res*. 2006;98:1151–1158.
50. Wong CH, Koo SH, She GQ, Chui P, Lee EJ. Genetic variability of RyR2 and CASQ2 genes in an Asian population. *Forensic Sci Int*. 2009;192:53–55.
51. Kim E, Youn B, Kemper L, Campbell C, Milting H, Varsanyi M, Kang C. Characterization of human cardiac calsequestrin and its deleterious mutants. *J Mol Biol*. 2007;373:1047–1057.
52. Roux-Buisson N, Rendu J, Denjoy I, Guicheney P, Goldenberg A, David N, Faivre L, Barthez O, Danieli GA, Marty I, Lunardi J, Faure J. Functional analysis reveals splicing mutations of the CASQ2 gene in patients with CPVT: implication for genetic counselling and clinical management. *Hum Mutat*. 2011;32:995–999.
53. Laitinen PJ, Swan H, Kontula K. Molecular genetics of exercise-induced polymorphic ventricular tachycardia: identification of three novel cardiac ryanodine receptor mutations and two common calsequestrin 2 amino-acid polymorphisms. *Eur J Hum Genet*. 2003;11:888–891.
54. Huke S, Bers DM. Ryanodine receptor phosphorylation at Serine 2030, 2808 and 2814 in rat cardiomyocytes. *Biochem Biophys Res Commun*. 2008;376:80–85.
55. Eschenhagen T. Is ryanodine receptor phosphorylation key to the fight or flight response and heart failure? *J Clin Invest*. 2010;120:4197–4203.
56. MacDonnell SM, García-Rivas G, Scherman JA, Kubo H, Chen X, Valdivia H, Houser SR. Adrenergic regulation of cardiac contractility does not involve phosphorylation of the cardiac ryanodine receptor at serine 2808. *Circ Res*. 2008;102:e65–e72.
57. Shan J, Kushnir A, Betzenhauser MJ, Reiken S, Li J, Lehnart SE, Lindegger N, Mongillo M, Mohler PJ, Marks AR. Phosphorylation of the ryanodine receptor mediates the cardiac fight or flight response in mice. *J Clin Invest*. 2010;120:4388–4398.
58. Cerrone M, Noujaim SF, Tolkacheva EG, Talkachou A, O'Connell R, Berenfeld O, Anumonwo J, Pandit SV, Vikstrom K, Napolitano C, Priori SG, Jalife J. Arrhythmogenic mechanisms in a mouse model of catecholaminergic polymorphic ventricular tachycardia. *Circ Res*. 2007;101:1039–1048.

59. Herron TJ, Milstein ML, Anumonwo J, Priori SG, Jalife J. Purkinje cell calcium dysregulation is the cellular mechanism that underlies catecholaminergic polymorphic ventricular tachycardia. *Heart Rhythm*. 2010;7:1122–1128.
60. Kang G, Giovannone SF, Liu N, Liu FY, Zhang J, Priori SG, Fishman GI. Purkinje cells from RyR2 mutant mice are highly arrhythmogenic but responsive to targeted therapy. *Circ Res*. 2010;107:512–519.
61. Tester DJ, Arya P, Will M, Haglund CM, Farley AL, Makielski JC, Ackerman MJ. Genotypic heterogeneity and phenotypic mimicry among unrelated patients referred for catecholaminergic polymorphic ventricular tachycardia genetic testing. *Heart Rhythm*. 2006;3:800–805.
62. Zipes DP, Camm AJ, Borggrefe M, Buxton AE, Chaitman B, Fromer M, Gregoratos G, Klein G, Moss AJ, Myerburg RJ, Priori SG, Quinones MA, Roden DM, Silka MJ, Tracy C. [Guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. Executive summary]. *Rev Esp Cardiol*. 2006;59:1328.
63. Mohamed U, Gollob MH, Gow RM, Krahn AD. Sudden cardiac death despite an implantable cardioverter-defibrillator in a young female with catecholaminergic ventricular tachycardia. *Heart Rhythm*. 2006;3:1486–1489.
64. Pizzale S, Gollob MH, Gow R, Birnie DH. Sudden death in a young man with catecholaminergic polymorphic ventricular tachycardia and paroxysmal atrial fibrillation. *J Cardiovasc Electrophysiol*. 2008;19:1319–1321.
65. Rosso R, Kalman JM, Rogowski O, Diamant S, Birger A, Biner S, Belhassen B, Viskin S. Calcium channel blockers and beta-blockers versus beta-blockers alone for preventing exercise-induced arrhythmias in catecholaminergic polymorphic ventricular tachycardia. *Heart Rhythm*. 2007;4:1149–1154.
66. Swan H, Laitinen P, Kontula K, Toivonen L. Calcium channel antagonism reduces exercise-induced ventricular arrhythmias in catecholaminergic polymorphic ventricular tachycardia patients with RyR2 mutations. *J Cardiovasc Electrophysiol*. 2005;16:162–166.
67. van der Werf C, Kannankeril PJ, Sacher F, Krahn AD, Viskin S, Leenhardt A, Shimizu W, Sumitomo N, Fish FA, Bhuiyan ZA, Willems AR, van der Veen MJ, Watanabe H, Laborderie J, Haïssaguerre M, Knollmann BC, Wilde AA. Flecainide therapy reduces exercise-induced ventricular arrhythmias in patients with catecholaminergic polymorphic ventricular tachycardia. *J Am Coll Cardiol*. 2011;57:2244–2254.
68. Watanabe H, Chopra N, Laver D, Hwang HS, Davies SS, Roach DE, Duff HJ, Roden DM, Wilde AA, Knollmann BC. Flecainide prevents catecholaminergic polymorphic ventricular tachycardia in mice and humans. *Nat Med*. 2009;15:380–383.
69. Wilde AA, Bhuiyan ZA, Crotti L, Facchini M, De Ferrari GM, Paul T, Ferrandi C, Koolbergen DR, Odero A, Schwartz PJ. Left cardiac sympathetic denervation for catecholaminergic polymorphic ventricular tachycardia. *N Engl J Med*. 2008;358:2024–2029.
70. Hwang HS, Hasdemir C, Laver D, Mehra D, Turhan K, Faggioni M, Yin H, Knollmann BC. Inhibition of cardiac Ca2+ release channels (RyR2) determines efficacy of class I antiarrhythmic drugs in catecholaminergic polymorphic ventricular tachycardia. *Circ Arrhythm Electrophysiol*. 2011;4:w128–w135.
71. Kobayashi S, Yano M, Uchinoumi H, Suetomi T, Susa T, Ono M, Xu X, Tateishi H, Oda T, Okuda S, Doi M, Yamamoto T, Matsuzaki M. Dantrolene, a therapeutic agent for malignant hyperthermia, inhibits catecholaminergic polymorphic ventricular tachycardia in a RyR2(R2474S/+) knock-in mouse model. *Circ J*. 2010;74:2579–2584.
72. Lehnart SE, Wehrens XH, Laitinen PJ, Reiken SR, Deng SX, Cheng Z, Landry DW, Kontula K, Swan H, Marks AR. Sudden death in familial polymorphic ventricular tachycardia associated with calcium release channel (ryanodine receptor) leak. *Circulation*. 2004;109:3208–3214.
73. Liu N, Ruan Y, Denegri M, Bachetti T, Li Y, Colombi B, Napolitano C, Coetzee WA, Priori SG. Calmodulin kinase II inhibition prevents arrhythmias in RyR2(R4496C+/-) mice with catecholaminergic polymorphic ventricular tachycardia. *J Mol Cell Cardiol*. 2011;50:214–222.
74. Wehrens XH, Lehnart SE, Reiken SR, Deng SX, Vest JA, Cervantes D, Coromilas J, Landry DW, Marks AR. Protection from cardiac arrhythmia through ryanodine receptor-stabilizing protein calstabin2. *Science*. 2004;304:292–296.

KEY WORDS: catecholaminergic polymorphic ventricular tachycardia ■ sudden death ■ electrocardiography ■ calcium channel ■ genetics

ADDENDUM

In the Genetic Background

Triadine is as a new gene involved in an autosomal recessive form of catecholaminergic polymorphic ventricular tachycardia. Three new mutations in the triadin gene (*TRDN*), a protein that links RyR2 and CASQ2, were found in a cohort of 97 patients with catecholaminergic polymorphic ventricular tachycardia, which cosegregated with the disease on a recessive mode of transmission in 2 families. Two *TRDN* mutations, a 4-bp deletion and a nonsense mutation, resulted in premature stop codons; the third mutation was a p.T59R missense mutation. The mutations identified led to the absence of the protein.[1]

In the Management of Catecholaminergic Polymorphic Ventricular Tachycardia Patients: Next Steps

A carvedilol analog was recently shown to prevent stress-induced ventricular tachyarrhythmias in *RyR2* mutant mice.[2] It was more effective when combined with a selective β-blocker metoprolol or bisoprolol. No human data have yet been published with such a drug association.

Catheter Ablation

Catheter ablation of the bidirectional ventricular premature beats that trigger ventricular fibrillation may become an adjunctive therapy in patients with refractory catecholaminergic polymorphic ventricular tachycardia.[3] The published experience is actually very limited.

References

1. Roux-Buisson N, Cacheux M, Fourest-Lieuvin A, Fauconnier J, Brocard J, Denjoy I, Durand P, Guicheney P, Kyndt F, Leenhardt A, Le Marec H, Lucet V, Mabo P, Probst V, Monnier N, Ray PF, Santoni E, Trémeaux P, Lacampagne A, Fauré J, Lunardi J, Marty I. Absence of triadin, a protein of the calcium release complex, is responsible for cardiac arrhythmia with sudden death in human. *Hum Mol Genet*. 2012;21:2759–2767.
2. Zhou Q, Xiao J, Jiang D, Wang R, Vembaiyan K, Wang A, Smith CD, Xie C, Chen W, Zhang J, Tian X, Jones PP, Zhong X, Guo A, Chen H, Zhang L, Zhu W, Yang D, Li X, Chen J, Gillis AM, Duff HJ, Cheng H, Feldman AM, Song LS, Fill M, Back TG, Chen SR. Carvedilol and its new analogs suppress arrhythmogenic store overload-induced Ca2+ release. *Nat Med*. 2011;17:1003–1009.
3. Kaneshiro T, Naruse Y, Nogami A, Tada H, Yoshida K, Sekiguchi Y, Murakoshi N, Kato Y, Horigome H, Kawamura M, Horie M, Aonuma K. Successful catheter ablation of bidirectional ventricular premature contractions triggering ventricular fibrillation in catecholaminergic polymorphic ventricular tachycardia with RyR2 mutation. *Circ Arrhythm Electrophysiol*. 2012;5:e14–e17.

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2. Zhou Q, Xiao J, Jiang D, Wang R, Vembaiyan K, Wang A, Smith C.D, Xie C, Chen W, Zhang J, Tian X, Jones P.J, Zhong X, Guo A, Chen H, Zhang L, Zhu W, Yang D, Li X, Chen J, Gillis A.M, Duff H.J, Cheng H, Feldman A.M, Song L.S, Fill M, Back T.G, Wayne Chen S.R. Carvedilol and its new analogs suppress arrhythmogenic store overload-induced Ca2+ release. *Nat Med*. 2012;17:1003-1009.

3. Kaneshiro T, Naruse Y, Nogami A, Tada H, Yoshida A, Sekiguchi Y, Murakoshi N, Kato Y, Horigome H, Kawamura M, Horie M, Aonuma K. Successful catheter ablation of bidirectional ventricular premature contractions triggering ventricular fibrillation in

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