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, followed by our first series of patients. 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. The estimated 4- and 8-year cardiac event rates were 33% and 58%, respectively, in our series of patients without β-blockers. 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. 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. 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. Priori et al 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. They identified a homozygous missense mutation in the cardiac calsequestrin gene (CASQ2) as the cause of this recessive form, 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. 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.

**RYR2 and CASQ2 Mutations**

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 and a channel domain located at the carboxy terminus. Each monomer has at least 6 transmembrane segments forming the pore region of the channel.

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), protein kinase A, calcium/calmodulin-dependent kinase II, phosphodiesterase 4D3, calmodulin, protein phosphatases 1 and 2A, and sorcin. Calsequestrin, junctin, and triadin are linked to the C-terminus of RYR2.

**Ryanodine Receptor**

The cardiac ryanodine receptors (RyR2) are calcium (Ca2+) release channels present in the sarcoplasmic reticulum (SR), an intracellular vesicular network playing a major role in the regulation of Ca2+ homeostasis in the heart. The mechanism of their activation is called calcium-induced calcium release because it requires that Ca2+ provided by the activated L-type Ca2+ channel (Cav1.2). Calcium binds to RyR2 and triggers opening of a high-conductance channel, allowing rapid Ca2+ efflux from the SR. The consecutive high cytoplasmic Ca2+ induces myocardial contraction, then Ca2+ 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.

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**CASQ2**

The cardiac calsequestrin gene (CASQ2) encodes an intracellular calcium-binding protein stored in the SR, where it is stored at high concentrations. Its dysfunction is associated with cardiac diseases, such as CPVT, sudden death, and heart failure.

**Catecholaminergic Polymorphic Ventricular Tachycardia**

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RyR2 shares close to 70% with 2 other mammalian RyR isoforms; 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 domain 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 **RYRI** disease–associated mutations.21

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.

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**Figure 1.** Schematic diagram of the RyR2 protein with the 148 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): NH\(_2\) 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 sudden 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 ryanodine receptor isoforms.
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%. 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, but more importantly may die suddenly as the first manifestation of the disease. No genotype-phenotype correlations have been established so far, even if there are mutations identified in large pedigrees supporting a lower penetrance. In few patients, 2 mutations have been reported and the role of associated polymorphisms, either frequent, such as Q2958R, G1886S, and G1885E, or more rare, such as A1136V, is not known. They may affect Ca2+ regulation, as suggested by in vitro studies, and increase the risk of sudden death in some patients.

**CASQ2**

CASQ2 is the major intra-SR Ca2+-binding protein and is localized at the junctional face membrane in the SR. It is a highly acidic protein with numerous charged residues and binds Ca2+ ions with low affinity. CASQ2 exists in the SR as a dynamic structure formed of monomers, dimmers, or multimers, depending of the Ca2+ concentration. Although the multimeric forms of CASQ2, formed at high Ca2+ levels in vitro, function as a Ca2+ buffer, the monomers seem to modulate SR Ca2+ release by influencing the open probability of the RyR2 channel, via interactions with triadin and junctin. 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 Ca2+-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 Ca2+ release. Studies of cells or myocytes after overexpression of mutant proteins and various models of genetically modified 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. The others lead to truncated proteins by various mechanisms, nonsense codon, small deletion, and abnormal splicing leading to premature stop codon.

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.

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. 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. 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, leading to cytosolic calcium overload generating delayed afterdepolarizations, triggered activity, and ventricular arrhythmias, in particular under adrenergic conditions.

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. Marx et al 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 Ca2+ 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.

There is increasing amount of data, provided by a mouse model of CPVT, showing a Purkinje origin of the ventricular premature beats. 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. The Purkinje cells are probably critical contributors to arrhythmic triggers in animal models and humans with CPVT.

**Clinical Presentation**

CVPT was first described in 1975 by Reid et al and then in 1978 by Coumel et al, 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. CVPT is extremely uncommon before the age of 2 years. Some RyR2 mutations have been identified postmortem in cases of sudden infant death syndrome. 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
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 $\geq 2$ years is usually reported in patients with syncope initially attributed to vaso-vagal 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 $\text{RyR2}$ 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 $\text{RyR2}$ mutations. 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. 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.

**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
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 \( \text{RyR2} \) mutation but considered as patients with CPVT, particularly women. 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 studies1,13,14,16,24,25,27,29,35 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
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. 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.

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. It has been proved to have RyR2 blocking properties and to significantly reduce the ventricular arrhythmia burden in 2 patients with highly symptomatic CPVT. The efficacy of flecainide has been retrospectively confirmed in a multicenter study including 33 patients with CPVT. 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.

Figure 4. Holter tracings showing pleomorphic ventricular tachycardia preceding the occurrence of ventricular fibrillation in a patient with catecholaminergic polymorphic ventricular tachycardia.
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 flecaïnide.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 inter-domain 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,75 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 be modified in the next years, thanks to the results of the ongoing studies.

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Disclosures

None.

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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. 


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


Catecholaminergic Polymorphic Ventricular Tachycardia
Antoine Leenhardt, Isabelle Denjoy and Pascale Guicheney

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