

Catecholaminergic Polymorphic Ventricular Tachycardia un Update

Synonym(s): **Bidirectional tachycardia induced by catecholamine, CPVT, Double tachycardia induced by catecholamines, Malignant paroxysmal ventricular tachycardia Multifocal ventricular premature beats.**

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a rare channelopathy, or primary electrical disease clinically and genetically heterogeneous disease characterized by exercise, stress-induced or adrenergically mediated ventricular tachyarrhythmia, with recurrent syncope of uncertain etiology after physical and emotional stress or sudden cardiac death (SCD), usually in the pediatric or juvenile age group. Sudden infant death syndrome and juvenile sudden death exert a deep social impact, due to the young age of the victims and the unexpected occurrence of death (**Carturan 2007**).

Frequency: The prevalence of CPVT is estimated to be about 1 in 10,000 people. **Prevalence:** 1-5 / 10 000. Despite its rare occurrence, CPVT is an important cause of stress and emotion induced syncope and SCD in children (**Massin 2003**).

Familial occurrence has been noted in about 30% of cases.

Inheritance may be autosomal dominant (mutations of the cardiac Ryanodine receptor gene (RyR2) or recessive associated with homozygous mutations in the gene encoding the cardiac isoform of calsequestrin, CASQ2, calsequestrin gene CASQ2 mutations) usually with high penetrance (**Laitinen 2004**). ICD-10: I47.2 *OMIM*: [604772](#) [611938](#) [614021](#) [614916](#) [615441](#); Unified Medical Language System® (UMLS®): C1631597; Genetic and Rare Disease Information Center (*GARD*): [4421](#)

The causative genes have been mapped on chromosome 1, 7 and 14.

Due to its potential lethal outcome, exclusion or confirmation of CPVT in children with physical and emotional syncope is mandatory.

• The entity, together with Brugada syndrome (BrS), congenital long QT syndrome (LQTS), congenital short QT syndrome (SQTS) and familial atrial fibrillation (**Roberts 2003**) are members of a group called electrical heart diseases, purely electrical heart diseases (**Farwell 2007**), primary electrical heart diseases (**Makita 2007**), primary electrical disorders (**Schulze-Bahr 2000**), ion channel diseases, channelopathies or *sine material* sudden death disease, because apparent structurally intact or normal hearts are observed.

➤ Genetic analysis identifies two groups of patients:

1. Sporadic or nongenotyped: Patients with nongenotyped CPVT are predominantly women and become symptomatic later in life;
2. With mutation:
 - (2-A) Cardiac RyR: Autonomic Dominant (AD)
 - (2-B) Calsequestrin, CASQ2, Autonomic Recessive (AR) (**Eldar 2003**). CASQ2 mutations are more common than previously thought and produce a severe form of CPVT (**Postma 2002a**).

Catecholaminergic polymorphic ventricular tachycardia (CPVT) Genetic types

Mutations in four genes – RYR2, CASQ2, TRDN, and CALM1 – are known to cause CPVT or related phenotypes of adrenergically induced life-threatening arrhythmias. The presence of other as-yet unidentified loci is postulated.

Catecholamine- Dependent Polymorphic VT (CPVT) Catecholaminergic Polymorphic Ventricular Tachycardia

Arrhythmia	Chromosome	Gene	Protein	Inheritance pattern
CPVT1	1q42-43	RYR21	Cardiac RyR	AD
CPVT2	1p11.13.3; 1p13-21	CASQ2	Cardiac Calsequestrin	Autosomal recessive 1-2% of all cases
CPVT3	7p14-p22. (Bhuiyan 2007)	TRDN	?	AR malignant
CPVT4	14q32.11 (Nyegaard 2012)	CALM1		AD

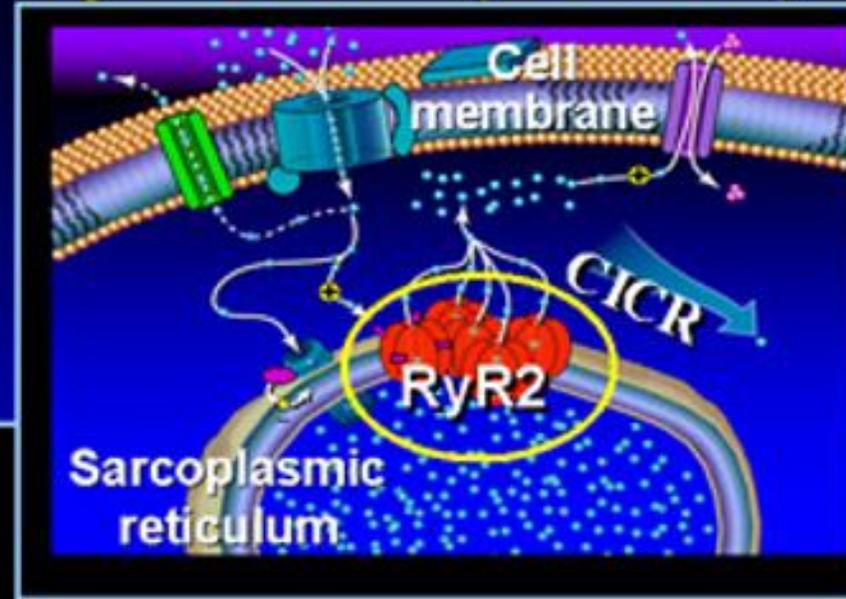
Mutations in either the *RYR2* or *CASQ2* gene disrupt the handling of calcium within myocytes. During exercise or emotional stress, impaired calcium regulation in the heart can lead to VT in people with CPVT.

Autosomal dominant inheritance means that one copy of the altered gene in each cell is sufficient to cause the disorder. In about half of cases, an affected person inherits an *RYR2* gene mutation from one affected parent. The remaining cases result from new mutations in the *RYR2* gene and occur in people with no history of the disorder in their family.

Autosomal recessive inheritance means that both copies of the gene in each cell have mutations. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition.

The genetic information proved to be important in the prediction of risk on lethal ventricular arrhythmias of affected individuals (**Wilde 2017 b**)

Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT)



Molecular



RyR2 (CPVT1, Ch 1q42.1-q43)

Mutations in *RyR2* cause 2/3 of CPVT

Intracellular calcium channels of the Sarcoplasmic Reticulum (SR)

I) Ca^{2+} release channel, Ryanodine receptor, hyperphosphorylated by protein kinase A (PKA) from the intracellular sarcoplasmic reticulum or CRC “Calcium Release Channel”.

II) Ca^{2+} -ATPase uptake pump or Ca^{2+} Mg^{2+} ATPase (Sarcoplasmic Ca^{2+} (ATPase) reticulum SERCA).

III) IP3 receptor, Inositol triphosphate or IP3: inositol 1,4,5-trisphosphate (IP3) receptor channel.

The SR is an intracellular structure that holds a key role in muscular contraction and relaxation by its capacity of fast release and uptake of myoplasm from the Ca^{2+} ion, by having only in the junctions with the T system of the plasmatic membrane, the so-called Ca^{2+} release channel, CRC (Calcium Release Channel) or Ryanodine receptor. This channel, intracytoplasmatically located in the SR membrane, is very close to the sarcolemmal channels $I_{\text{Ca-L}}$ type, and like this, is voltage and time-dependent. Each $I_{\text{Ca-L}}$ type channel controls a group between 4 and 10 ryanodine receptor channels.

Each channel is a large and complex protein of 30 S, formed by four polypeptidic subunits in firm association of $M_r \sim 560.000$ with quatrefoil or tetrameric morphology that contours a single hydrophilic, cation-selective pore, with conductance for divalent cations from 100 to 150 pS with 50 mM Ca^{2+} and for monovalent cations of ~ 750 pS with 250 mM K^+ that is found in the SR membrane and plays its role by releasing the cation of the SR lumen into the cytosol (efflux). It may be blocked by Ryanodine, a toxin derived from an alkaloid plant with nanomolar affinity, and for this reason it is known as ryanodine receptor.

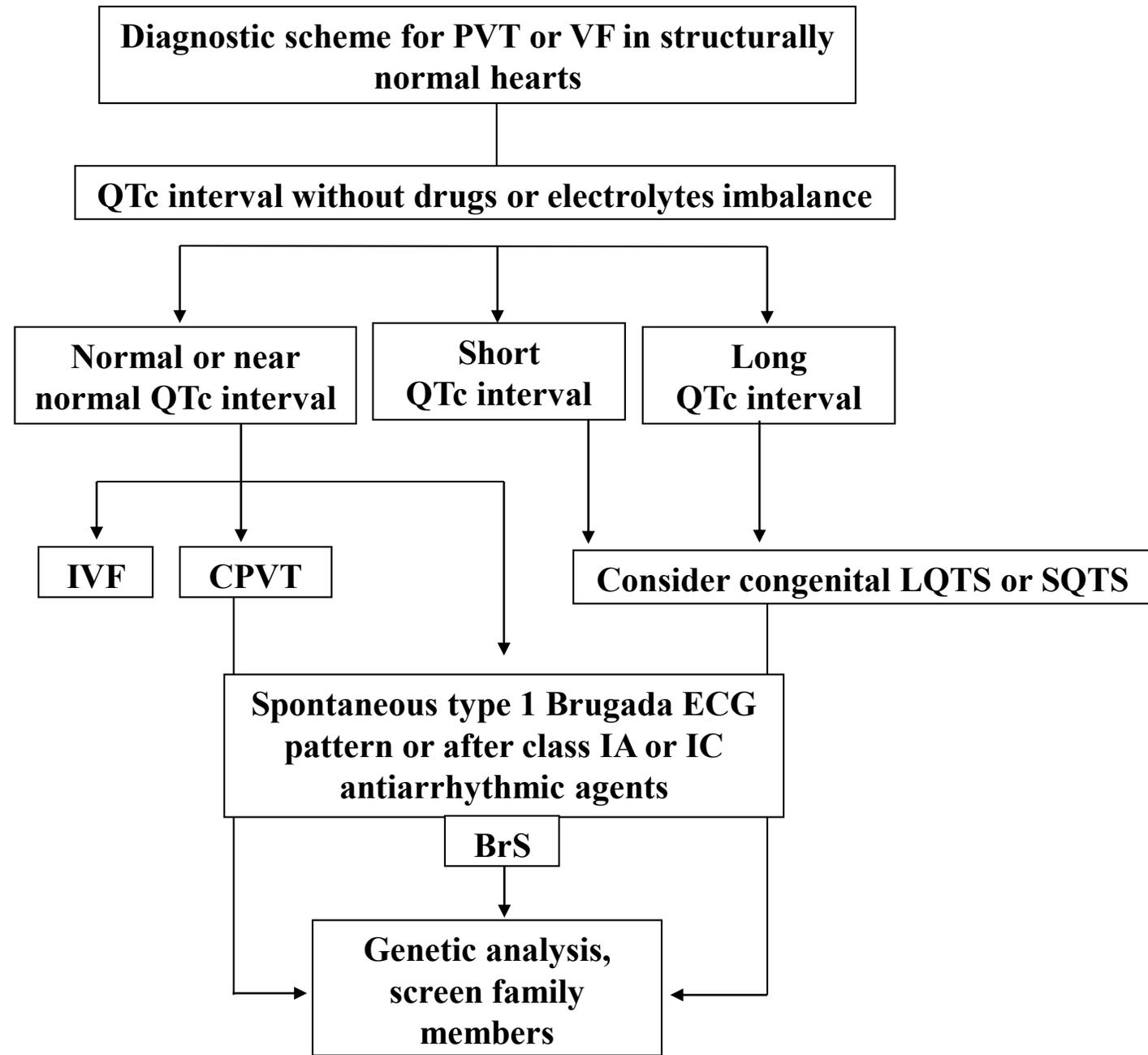
The substances that stimulate this channel improve contractility, and those that block, worsen it. It seems to be the most important channel in heart failure, since a dramatic increase has been observed in its phosphorylation (hyperphosphorylation) in patients with terminal heart failure, what would provide another basis for using β -blockers in this condition.

Ryanodine receptor (RyR) is the Ca^{2+} -induced Ca^{2+} release channel in cells. RyR1 and RyR2 are its isoforms expressed in the skeletal and cardiac muscles, respectively. Their missense mutations, which are clustered in three regions that correspond to each other, cause hereditary disorders such as malignant hyperthermia and central core disease in the skeletal muscle and CPVT, a form of arrhythmogenic right ventricular dysplasia (ARVD2), dilated cardiomyopathy, sinoatrial node and atrioventricular node dysfunction, atrial fibrillation, and atrial standstill in the cardiac muscle (**Bhuiyan 2007; Ogawa 2007**), usually with high penetrance.

The R176Q mutation in RyR2 predisposes the heart to catecholamine-induced oscillatory calcium-release events that trigger a calcium-dependent VT (**Kannankeril 2006**). Research points out that patients carriers of familial CPVT with dominant inheritance pattern present a missense mutation of the SR in the CRC channel in type 2 ryanodine receptor (RyR2) where three mutations were verified: (P2328S, Q4201R, V4653F). This entity of early clinical onset and mean mortality rate of 30% up to 30 years old, is characterized by bursts of bidirectional VT and/or PVT related to exercise (catecholamine-dependent), with no evidence of structural heart disease.

Catecholaminergic idiopathic ventricular fibrillation (IVF) is occasionally observed. Mice with the R176Q cardiac ryanodine receptor mutation exhibit catecholamine-induced ventricular tachycardia and cardiomyopathy.

Diagnostic scheme for PVT or VF in structurally normal hearts. Modified from Srivathsan (Srivathsan 2005).



Electrocardiographic features

- I. **Heart Rate (HR):** baseline bradycardia tendency off drugs is observed in all carriers (slow HR). CPVT patients often present bradycardia and SAN dysfunction
- II. **Rhythm:** Sinus rhythm is the rule. Abnormalities in sinoatrial node function, as well as atrioventricular nodal function, could produce atrial fibrillation, atrial flutter and atrial standstill (sick sinus syndrome).
- III. **QTc interval:** normal at resting ECG (**Postma 2005b**).
- IV. **U-wave alternans:** U-wave alternans was observed in the following clinical circumstances: After ventricular pacing at 160 bpm During the recovery phase after the exercise stress test Following a pause from sinus arrest and a change in T-wave was also noted. Precordial V₃-V₅ are the leads showing alternans more clearly (**Aizawa 2006**).

II. Arrhythmias

Supraventricular arrhythmias The atrium could be affected by the channelopathies, and arrhythmias in these chambers may cause syncope. Atrial fibrillation, atrial flutter, atrial standstill, and sick sinus syndrome are occasionally present (**Fazelifar 2007**).

Ventricular arrhythmias

The ECG features of this tachyarrhythmia are uniform. Characteristic is the sequence of junctional tachycardia, ventricular premature beats with quadrigeminy, trigeminy, and bigeminy; shorter or longer salvos of bidirectional tachycardia; and bursts of rapid, irregular, and polymorphic ventricular tachycardia; depending on the intensity of the adrenergic stimulation, the disappearance occurs in the reverse order.

- Ventricular arrhythmias elicited exclusively by exercise or adrenergic stress. Typically induced by isoproterenol infusion.
- Premature Ventricular Complex (PVCs): Calcium channel antagonist, verapamil, can suppress PVCs and nonsustained VT salvos in CPVT caused by RyR2 mutations. Modifying the abnormal calcium handling by calcium antagonists might have therapeutic value (**Swan 2005**). Calcium antagonists partially suppressed CPVT in autosomal dominant cases.
- Polymorphic ventricular tachycardia (PVT) occurs during physical exercise or emotional stress. Mean heart rate during CPVT was 192 beats/min. Most cases are non-sustained (72%), but 21% are sustained and 7% are associated with ventricular fibrillation.
- PVT and bidirectional in association are observed in 21% of cases in the pediatric group.

- There is 100% inducement of CPVT by exercise, 75% by catecholamine infusion, and none by programmed stimulation. No late potential is recorded. Onset is in the right ventricular outflow tract in more than 50% the cases (**Sumitomo 2003a**). The His-Purkinje system is an important source of focal arrhythmias in CPVT (**Cerrone 2007**).
- Bidirectional ventricular tachycardia is a more typical feature.

Electrophysiological mechanism in cases of CPVT: they are initiated by delayed afterdepolarizations and triggered activity (**Mohamed 2007**), with focus the origin of which is in the proximal region of the right bundle, triggering activity and alternating activation of the LV by the left anterior fascicle and posteroinferior left fascicle of the left branch. The events are caused by derangements of the control of intracellular calcium. A gain-of-function mutation of the cardiac ryanodine receptor RyR2 gene is the cause of familial or CPVT. In an animal model of mutant RyR2 that is characterized by reduced FKBP12.6 binding to the RyR2 on beta stimulation, the impaired coupled gating characteristic of these mutations was modeled by reducing cooperativity of the RyR2 activation. In current-clamp mode, the mutant RyR2 model exhibited increased diastolic RyR2 open probability that resulted in the formation of delayed afterdepolarizations (**Iyer 2007**). Calsequestrin is a high-capacity Ca^{2+} -binding protein expressed inside the SR, an intracellular Ca^{++} release and storage organelle in the muscle. Patients with a missense mutation of the calsequestrin 2 gene (CASQ2) are at risk for CPVT. This mutation (CASQ2(D307H)) results in decreased ability of CASQ2 to bind Ca^{2+} in the sarcoplasmic reticulum (SR). The CASQ2(D307H) mutation manifests its pro-arrhythmic consequences due to store-overload-induced Ca^{2+} release and delayed afterdepolarization formation due to excess free SR Ca^{2+} following rapid pacing and beta-adrenergic stimulation (**Faber 2007**).

Wang et al analyzed sinoatrial node (SAN) function in two CPVT families and in a novel knock-in (KI) mouse model carrying the RyR2R420Q mutation. Humans and KI mice presented slower resting heart rate. Accordingly, the rate of spontaneous intracellular Ca^{2+} ($[\text{Ca}^{2+}]_i$) transients was slower in KI mouse SAN preparations than in WT, without any significant alteration in the "funny" current (I_f). The L-type Ca^{2+} current was reduced in KI SAN cells in a $[\text{Ca}^{2+}]_i$ -dependent way, suggesting that bradycardia was due to disrupted crosstalk between the "voltage" and " Ca^{2+} " clock, and the mechanisms of pacemaking was induced by aberrant spontaneous RyR2- dependent Ca^{2+} release. This finding was consistent with a higher Ca^{2+} leak during diastolic periods produced by long-lasting Ca^{2+} sparks in KI SAN cells. These results uncover a mechanism for the CPVT-causing RyR2 N-terminal mutation R420Q, and they highlight the fact that enhancing the Ca^{2+} clock may slow the heart rhythm by disturbing the coupling between Ca^{2+} and voltage clocks. In other words, RyR2R420Q catecholaminergic polymorphic ventricular tachycardia mutation induces bradycardia by disturbing the coupled clock pacemaker mechanism. (**Wang 2017**)

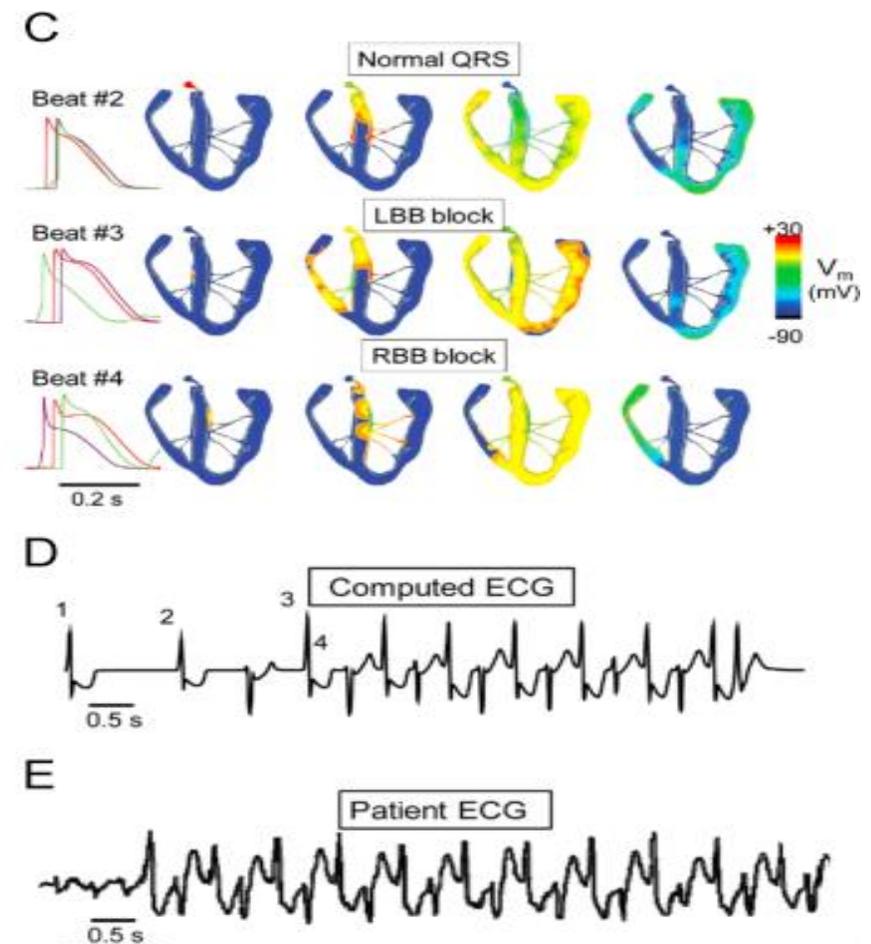
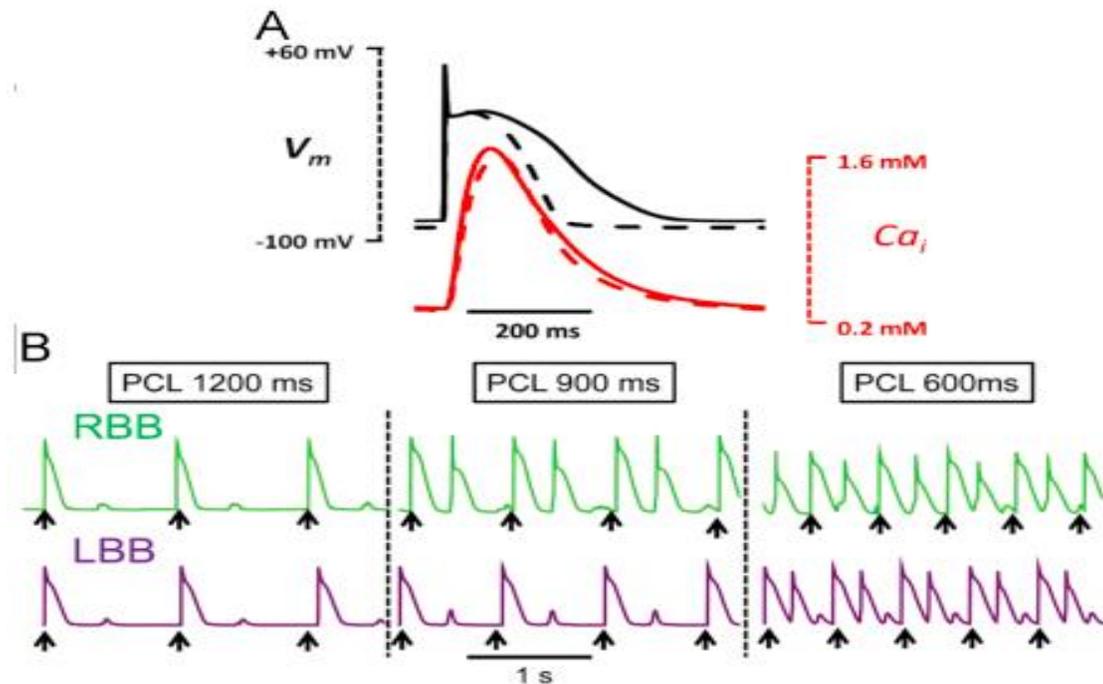
Concept: Bidirectional ventricular tachycardia is regular VT with pattern of CRBBB, alternating QRS axis, determining the presence of two morphologies of QRS, secondary to change in axis (SÂQRS) in the frontal plane, from beat to beat, with differences of approximately 180°. One beat presents SÂQRS between -60° and -90° and the following, approximately $+120^\circ$ to $+130^\circ$. The event may be both ventricular and supraventricular. The help of the His bundle electrogram is necessary to determine this.

Possible etiologies: low prevalence (rare). Acquired forms are mainly observed in elderly patients. The clinical setting may be:

- Digitalis toxicity or digitalis poisoning: it is the main clinical cause (**Kummer 2006**);
- Digoxin and amiodarone treatment for rapid atrial fibrillation (**Lien 2004**);
- Herbal aconite poisoning (**Smith 2005**). Aconitine and its related alkaloids are known cardiotoxins with no therapeutic role in modern western medicine. The rootstocks of Aconitum plants, which contain aconite alkaloids, have been common components of Chinese herbal recipes. All patients developed symptoms of aconite toxicity within 2 h of herb ingestion. Most developed tachyarrhythmias, including VT and VF. A strict surveillance of herbal substances with low safety margins is necessary.
- Severe myocardial disease (advanced cardiomyopathy)
- Cardiac metastasis (**Dorfman 2006**).
- Without structural heart diseases: CPVT and Andersen-Tawil Syndrome (ATS) mutations in KCNJ2, which encodes the α subunit of the potassium channel Kir2.1. The mutation is present in $\approx 60\%$ of cases.

The mechanism of bidirectional VT using computer simulation (Baher 2011**)**

Bidirectional VT(BVT) is the most characteristic feature of CPVT. In the His–Purkinje system, delayed after depolarizations (DAD) induced bigeminy may differ depending on whether they are induced by the right bundle branch(RBB) or the left bundle branch(LBB). The RBB caused a DAD induced bigeminy at a pacing rate of 900 ms, whereas the LBB induced a bigeminy at a pacing rate of 600 ms. In these situations, the sinus rate exceeded the threshold of the RBB-DAD induced bigeminy rate, and the beat after the sinus beat may have been induced from the RBB, resulting in a LBB block (LBBB) type PVC. The coupling interval of the normal sinus beat to the LBBB type PVC exceeded the threshold of the LBB-DAD induced bigeminy, and the next beat arose from LBB, resulting in a RBB block (RBBB) type PVC. When the coupling interval of the LBBB type PVC and RBBB type PVC exceeded the threshold of the RBB-DAD induced bigeminy, the next beat arose from the RBB followed by a beat from the LBB, one after the other . See next slide BVT mechanism explanation



A possible mechanism for bidirectional VT(BVT): ping-pong in the His–Purkinje system. (A) Comparison of simulated rabbit ventricular (dashed line) and Purkinje (solid line) APs and Ca_i transients during pacing at 600 ms. (B) Rate dependence of DADs and bigeminy in Purkinje cell AP models. For the green trace, the rate threshold for DAD-induced bigeminy was 67 bpm (pacing cycle length [PCL] 900 ms), such that pacing (black arrows) at both 900 and 600 ms induced bigeminy. For the purple trace, the bigeminy rate threshold was 100 bpm (PCL 600 ms), such that pacing at 600 ms, but not 900 ms, induced bigeminy. LBB: left bundle branch; RBB: right bundle branch. (C) Voltage snapshots depicting the activation sequence at BVT onset Beat #2 is the last paced beat, with normal activation. Beat #3 is the first beat of BVT, due to a DAD-triggered AP arising in the RBB, resulting in QRS with a LBBB pattern. Beat #4 is the second beat of BVT, due to a DAD-triggered AP arising in the LBB and results in a QRS with RBB block pattern. Traces on the right show the timing of APs recorded from the His bundle (red), RBB (green), and LBB (purple). (D) Computed ECG from the simulation in A, showing BVT. (E) ECG recorded in a patient during BVT.

The arrhythmogenic CASQ2 (D307H) mutation impairs SR Ca⁺⁺ storing and release functions and destabilizes the Ca⁺⁺-induced Ca²⁺ release mechanism by reducing the effective Ca⁺⁺ buffering inside the SR and/or by altering the responsiveness of the Ca⁺⁺ release channel complex to luminal Ca²⁺. These results establish at cellular level, the pathological link between CASQ2 mutations and the predisposition to adrenergically mediated arrhythmias observed in patients carrying the CASQ2 mutation (**Viatchenko-Karpinski 2004**).

CSQ2 not only determines the Ca²⁺ storage capacity of the SR but also positively controls the amount of Ca²⁺ released from this organelle during excitation-contraction coupling. CSQ2 controls Ca²⁺ release by prolonging the duration of Ca²⁺ fluxes through the SR Ca²⁺-release sites. In addition, the dynamics of functional restitution of Ca⁺⁺-release sites after Ca²⁺ discharge is prolonged when CSQ2 levels are elevated and accelerated in the presence of lowered CSQ2 protein levels. Furthermore, profound disturbances in rhythmic Ca²⁺ transients in myocytes undergoing periodic electrical stimulation are observed when CSQ2 levels are reduced. CSQ2 is a key determinant of the functional size and stability of SR Ca⁺⁺ stores in cardiac muscle. CSQ2 appears to exert its effects by influencing the local luminal Ca²⁺ concentration-dependent gating of the Ca²⁺-release channels and by acting as both a reservoir and a sink for Ca²⁺ in SR. The abnormal restitution of Ca⁺⁺-release channels in the presence of reduced CSQ2 levels provides a plausible explanation for VT associated with mutations of CSQ2 (**Terentyev 2003**).

Electrocardiographic characterization

- Regular VT
- Heart Rate between 140 bpm and 200 bpm
- CRBBB Pattern
- Sudden change of QRS morphology by change of SÂQRS, successively from beat to beat
- SÂQRS in the frontal plane with differences close to 180°: one beat presents ÂQRS between -60° and -90° (CRBBB + LAFB) and the following between +120° to +130° (CRBBB + LPFB).
- Occasionally alternating right and left bundle branch block morphology. The origin of the tachycardia is located near the His bundle bifurcation. This suggested a single focus at the interventricular septum with two exit sites, depolarizing the right and left ventricle in an alternate fashion (**Dorfman 2006**). Two sets of fairly constant and alternating VA intervals are recorded. This fact is consistent with two ventricular circuits used alternatively. It is postulated that the tachycardia is due to macroreentry involving the two fascicles of the left branch. Reentry may be a possible mechanism in some cases of bidirectional tachycardia.

Clue for electrocardiographic diagnosis of CPVT: association in ECG of sinus bradycardia + normal QTC interval + stress-related, bidirectional VT or PVT in the absence of apparent structural heart disease (Sumitomo 2003; Priori 2002; Liu 2007**)**



ECG12

Female, white, 20-year-old patient; recurrent syncope of uncertain etiology after physical and emotional stress; carrier of familial catecholaminergic cardiomyopathy. QRS complexes alternans are observed with alternating right and left bundle branch block morphology. The QRS axis shifts from -60° to $+120^{\circ}$.



ECG monitoring during a stress test (continuous strips). After an acceleration of the sinus rhythm, monomorphic ventricular premature beats appear with a bigeminy. Supraventricular tachycardia (atrial fibrillation and junctional tachycardia) with narrow QRS complexes are then recorded interfering with multiform ventricular premature beats and bidirectional ventricular tachycardia. At the end of the exercise, the arrhythmia disappears in the reverse order.

The diagnostic criteria of CPVT are as follows:(**Priori 2014 b**)

- I. CPVT is diagnosed in the presence of a structurally normal heart, normal ECG, and unexplained exercise or catecholamine-induced bidirectional VT, polymorphic ventricular premature beats or VT in individuals <40 years of age.
- II. CPVT is diagnosed in patients (index case or family member) who have a pathogenic mutation.
- III. CPVT is diagnosed in family members of a CPVT index case with a normal heart who manifests exercise-induced PVCs or bidirectional/polymorphic VT.
- IV. CPVT can be diagnosed in the presence of a structurally normal heart and coronary arteries, normal ECG, and unexplained exercise or catecholamine-induced bidirectional VT, polymorphic ventricular premature beats or VT in individuals >40 years of age.
- V. Priori S.G., Wilde A.A., Horie M. Executive summary: HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes. J Arrhythm. 2014;30:29–47.

Prognosis: The mortality rate in untreated individuals is 30-50% by age 40.

Postmortem genetic testing: Postmortem genetic testing of RyR2 should be considered as a part of the comprehensive medicolegal autopsy investigation of a sudden unexplained death case and that this potentially heritable and often elusive arrhythmia syndrome be scrutinized carefully in family members of those who experience sudden unexplained death (**Tester 2004**).

Treatment:

A) Drugs

- I. β - blockers** are effective pharmacological approach, unfortunately 30% of patients have recurrences with these drugs. β -blockers reduce arrhythmias, but in 30% of patients an implantable defibrillator(ICD) may be required (**Priori 2002**). ICD is necessary for prophylaxis of SCD because $\approx 30\%$ of patients still experience VTs (**Liu 2007**) that may arise in certain specific areas but the prognosis is poor. The onset of CPVT may be an indication for an ICD. The long acting β blocker, nadolol,(inexistent in Brazil) is preferred for prophylactic treatment of CPVT. Propranolol is also an effective medication; however, β -blockers cannot completely suppress the arrhythmic events in CPVT patients. Carvedilol is reported to inhibit the SOICR in an HEK 293 cell culture model. Among various β -blockers, only carvedilol inhibits *RyR2* activity.(**Zhou 2011**) Thus, carvedilol may be an effective β -blocker for CPVT, but its β blocking effect may be weak in comparison to the other β -blockers. Therefore, the efficacy of carvedilol needs to be further investigated.
- II. Verapamil** has also shown beneficial effects in some CPVT patients(**Rosso 2007; Swan 2005**). However, the long-term efficacy of verapamil is still controversial.
- III. Flecainide** reduced exercise-induced ventricular arrhythmias in patients with CPVT not controlled by conventional drug therapy.(**van der Werf 2011**). Watanabe discovered that flecainide directly inhibits RyR2 channels and prevent CPVT. (**Watanabe 2009a**), Among the Class I anti-arrhythmic medications, only flecainide and propafenone inhibit *RyR2* activity.(**Hwang2011**) However, recent report denies the direct suppression of *RyR2* by flecainide.(**Bannister 2015**) That may suggest another mechanism of flecainide, such as inhibition of NCX. Flecainide was effective in patients with genotype-negative CPVT, suggesting that spontaneous Ca(2+) release from ryanodine channels plays a role in arrhythmia susceptibility, similar to that in patients with genotype-positive CPVT.(**Watanabe 2013b**), Flecainide can completely prevent ventricular arrhythmia during exercise and partially prevent recurrent ICD shocks in high-risk patients with CPVT2.(**Khoury2013**) Flecainide can be added for primary prevention of a cardiac arrest when β -blockers alone cannot control the onset of arrhythmias during exercise stress test. (**Napolitano 2016**) In a randomized clinical trial of patients with CPVT, flecainide plus β -blocker significantly reduced ventricular ectopy during exercise compared with placebo plus β -blocker and β -blocker alone. (**Kannankeril 2017b**)

Flecainide suppresses cardiac tachyarrhythmias including paroxysmal AF, supraventricular tachycardia and arrhythmic long QT syndromes (LQTS), as well as the Ca^{2+} -mediated, CPVT. Anti-arrhythmic effects of flecainide that reduce triggering in CPVT models mediated by sarcoplasmic reticular Ca^{2+} release could arise from its primary actions on Na_v channels indirectly decreasing $[\text{Ca}^{2+}]_i$ through a reduced $[\text{Na}^+]_i$ and/or direct open-state RyR2- Ca^{2+} channel antagonism. The consequent $[\text{Ca}^{2+}]_i$ alterations could also modify AP propagation velocity and therefore arrhythmic substrate through its actions on $\text{Na}_v 1.5$ channel function. This is consistent with the paradoxical differences between flecainide actions upon Na^+ currents, AP conduction and arrhythmogenesis under circumstances of normal and increased RyR2 function. **(Salvage 2017)**

Left cardiac sympathetic denervation(LCSD) and bilateral thoracoscopic sympathectomy

LCSD is reported to be a useful therapeutic method for suppressing ventricular arrhythmias in CPVT patients. **(Wilde 2008; De Ferrari 2015)** In patients with uncontrollable VTs, **LCSD** is highly useful in controlling the events. The rate of complications involving Horner syndrome is very low if denervation is performed in the lower half of the T1 sympathetic ganglion through the T4 ganglion. **(De Ferrari 2015)** This approach is indicated in recurrent VTs for congenital LQTS and CPVT. There are studies suggesting an improvement in symptoms and survival for cardiac sympathetic denervation in a diverse range of underlying cardiac pathology. Some evidence supports that bilateral cardiac sympathetic denervation may be more effective at preventing recurrent VT compared to left sided alone. Despite recent studies demonstrating promising results, rigorous clinical trials demonstrating the effectiveness and safety of cardiac sympathetic denervation surgery are lacking. However, individuals with recurrent VT have a poor prognosis and a low quality of life, and surgical treatment may be justified in some individuals. Patients with recurrent VT, a multimodal approach should be used, including ICD, pharmacologic therapy, and catheter ablation. If VT persists after exhausting medical management, then **LCSD** may be considered. Future studies should focus on determining the impact of laterality on effectiveness and using novel imaging modalities to select patients most likely to benefit. **(Hong 2017)**

ICD

Implantation of an ICD should be considered in patients in the absence of controlled optimal therapy. **(van der Werf 2012)** However, implantation of an ICD in children still has a number of technical problems. Moreover, inappropriate or painful shocks may increase the risk of further ventricular arrhythmias, and electrical storms that may result in lethal events.

Catheter ablation

Pulmonary vein isolation is reported to be effective in some CPVT patients with atrial fibrillation. (Sumitomo 2010b; 2014 c) Purkinje cells are reported to be more arrhythmogenic than ventricular myocytes in a mutant knockout mouse model of CPVT. (Kang 2010) The onset of CPVT may be initiated from Purkinje cells. Successful catheter ablation has been reported at the site of Purkinje potentials or discrete prepotentials. (Kaneshiro 2012)

Experimental Viral delivered gene therapy

The recessive form CPVT 2 (CPVT2) is caused by mutations in cardiac calsequestrin (CASQ2), leading to protein deficiency. Kurtzwald-Josefson et al develop an experimental murine model viral-delivered gene therapy for CPVT2 and determine the relationship between CASQ2 expression and antiarrhythmic efficacy. The authors used a murine model of CPVT2 caused by the D307H human mutation (CASQ2^{D307H}) or CASQ2 knockout (CASQ2^{Δ/Δ}). Adeno-associated virus (AAV) particles containing the CASQ2 gene (AAV_{CASQ2}) were injected into the heart or intraperitoneally to 12-week-old mice. A telemetry device was implanted, and mice underwent provocation testing 7-8 weeks after gene therapy. CASQ2^{Δ/Δ} mice injected intracardiacally with AAV_{CASQ2} expressed 40% ± 25% of the normal CASQ2 protein level, which was increased compared to untreated CASQ2^{Δ/Δ} mice. Intraperitoneal therapy led to a significantly elevated expression of the CASQ2 protein, which was comparable in CASQ2^{D307H} and CASQ2^{Δ/Δ} mice. All control mice with CPVT2 had NS-VT and 8 of 13 had S-VT on provocation. Expressing ≥33% of the normal CASQ2 level was needed to protect from NS-VT as well as stress-induced PVCs. Lower levels of expression prevented S-VT in AAV_{CASQ2}-treated mice. The authors concluded that AAV_{CASQ2} displays a long-lasting capacity to attenuate and potentially cure CPVT2. Systemic delivery is feasible and convenient, reproducibly providing adequate levels of transgene expression. Antiarrhythmic efficacy depends on the CASQ2 level: ≥33% of the normal CASQ2 level is needed to prevent arrhythmia. However, even lower levels of protein protect from S-VT, thereby potentially reducing the risk of sudden death. (Kurtzwald-Josefson 2017)

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