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Review

Current topics in catecholaminergic polymorphic ventricular tachycardia

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ABSTRACT

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is induced by emotions or exercise in patients without organic heart disease and may be polymorphic or bidirectional in nature. The prognosis of CPVT is not good, and therefore prevention of sudden death is of utmost importance. Genetic variants of CPVT include *RyR2*, *CASQ2*, *CALM2*, *TRD*, and possibly *KCNJ2* and *ANK2* gene mutations. Hypotheses that suggest the causes of CPVT include weakened binding of FKBP12.6 and *RyR2*, a store overload-induced Ca^{2+} release (SOICR), unzipping of intramolecular domain interactions in *RyR2*, and molecular and functional abnormalities caused by mutations in the *CASQ2* gene. The incidence of an *RyR2* anomaly in CPVTs is about 35–79%, whereas anomalies in the *CASQ2* gene account for 3–5% CPVTs. The ping-pong theory, suggesting that reciprocating delayed after depolarization induces bigeminy of the right and left bundle branches, may explain the pathogenesis of bidirectional ventricular tachycardia. Flecainide, carvedilol, left sympathetic nerve denervation, and catheter ablation of the PVC may serve as new therapeutic strategies for CPVT while gene-therapy may be applied to some types of CPVT in the future. Although, not all sudden cardiac deaths in CPVT patients are currently preventable, new medical and interventional therapies may improve CPVT prognosis.

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1. Introduction

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is induced by emotional stress or exercise in patients without organic heart disease and may be polymorphic or bidirectional

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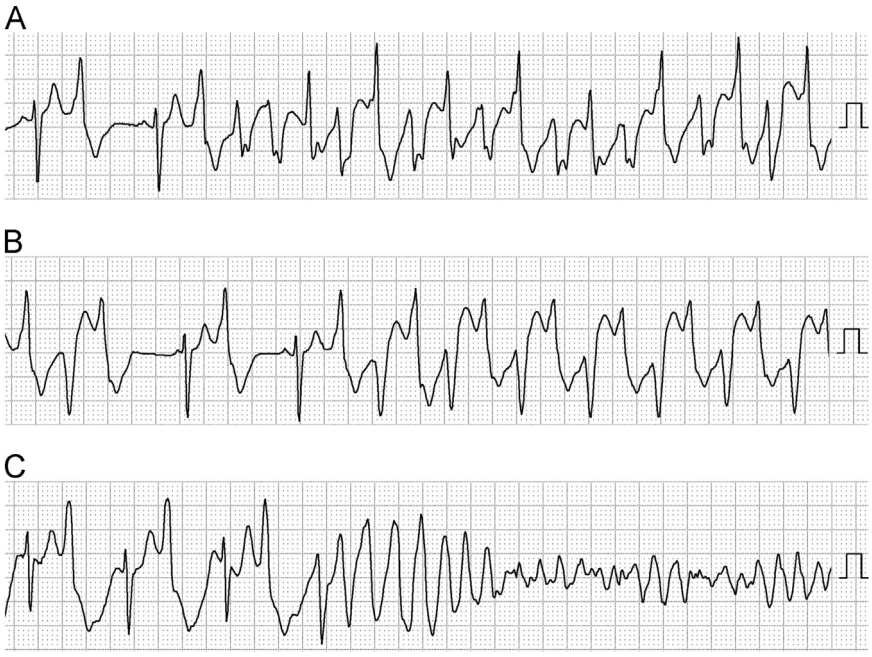

Fig. 1. Typical features of ventricular tachycardia in a patient with CPVT. (A) Polymorphic ventricular tachycardia. (B) Bidirectional ventricular tachycardia. (C) Rapid polymorphic ventricular tachycardia deteriorating into ventricular fibrillation. These electrocardiograms were recorded by Holter monitoring in the CM3 lead in the same patient.

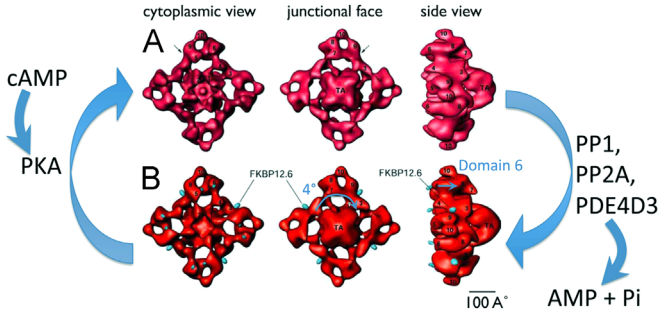

Fig. 2. Surface representations of *RyR2* 3D reconstructions with and without bound FKBP12.6. [7]. (A) High activity state of *RyR2*. A 3D map of *RyR2*, obtained by in vitro assembly of purified *RyR2* incubated with FKBP12.6 alone. (B) Low activity state of *RyR2*. A 3D map of *RyR2*, obtained by incubating *RyR2* with FKBP12.6 and an excess of FK506. FKBP12.6 is denoted by the blue dots. The major difference in these structures is observed in domain 6, which extends in the vertical direction (shown by the blue arrow), and the transmembrane assembly is rotated about 4° (shown by the blue arrow in the lower center panel). FKBP12.6: calstabin2, protein kinase A: PKA, phosphatase 1: PP1, phosphatase 2A: PP2A, phosphodiesterase 4D3: PDE 4D3, TA: transmembrane assembly.

(Fig. 1) [1–3]. This ventricular arrhythmia sometimes degenerates into rapid polymorphic ventricular tachycardia and ventricular fibrillation (Fig. 1) and may lead to syncope or sudden death. The incidence of CPVT is reported to be as high as 1:10,000, but its real prevalence is unclear.

2. Clinical manifestations and prognosis

The first clinical manifestations of CPVT are syncope or aborted sudden cardiac death during exercise or emotional stress and appear during the first or second decade of life [1–3]. CPVT differs from seizures, in that almost all syncopal events are associated with physical activity or emotional stress and do not occur during a resting state.

The prognosis of CPVT is very poor. About 40% patients die within 10 years of diagnosis [3]. Although prognosis in recent times could be better than previous reports, sudden death and severe brain damage are still reported in CPVT patients.

3. Diagnosis of CPVT

CPVT patients usually have a normal resting ECG, or just a lower heart rate than is normal for their age [3]. During exercise in these patients, monomorphic premature ventricular contractions (PVCs) increase, then polymorphic, or bidirectional PVC bigeminy appear, followed by bidirectional or polymorphic VT. Exercise induced supraventricular arrhythmias (atrial fibrillation, premature atrial contraction, and atrial tachycardia) are also common in the patients with CPVT [4]. The diagnostic criteria of CPVT are as follows [5]:

1. 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.
2. CPVT is diagnosed in patients (index case or family member) who have a pathogenic mutation.
3. CPVT is diagnosed in family members of a CPVT index case with a normal heart who manifests exercise-induced PVCs or bidirectional/polymorphic VT.
4. 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.

4. Mechanism of CPVT

The major pathogenic mechanism of CPVT is thought to involve the malfunction of *RyR2*. *RyR2* is a large tetrameric protein expressed on the sarcoplasmic reticulum (SR) membrane. *RyR2* is anchored to calsequestrin (CASQ2) by satellite proteins such as calmodulin (*CaM*), FKBP12.6, (calstabin2), protein kinase A (PKA), phosphatase 1 (PP1), and phosphatase 2A (PP2A) bound to the cytoplasmic region and junction, and triadin (TRD) bound to the luminal side [6].

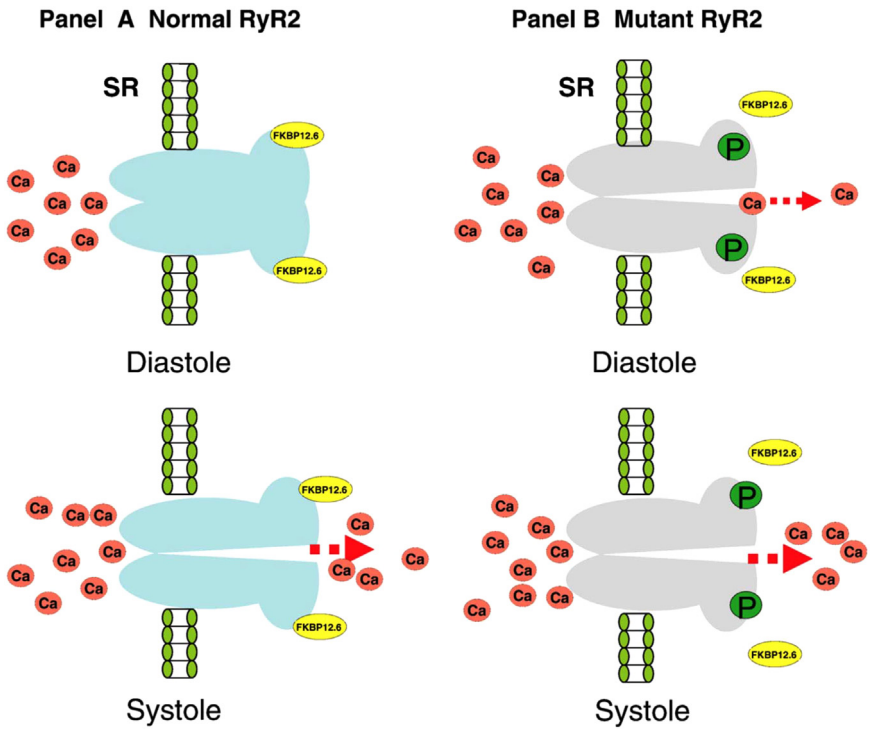

Fig. 3. FKBP12.6 dissociation from mutant *RyR2* in the pathogenesis of CPVT [8]. FKBP12.6 acts as a stabilizer that preserves the closed *RyR2* channel during diastole. Weakened binding affinity with FKBP12.6 may lead to a Ca^{2+} leak during diastole.

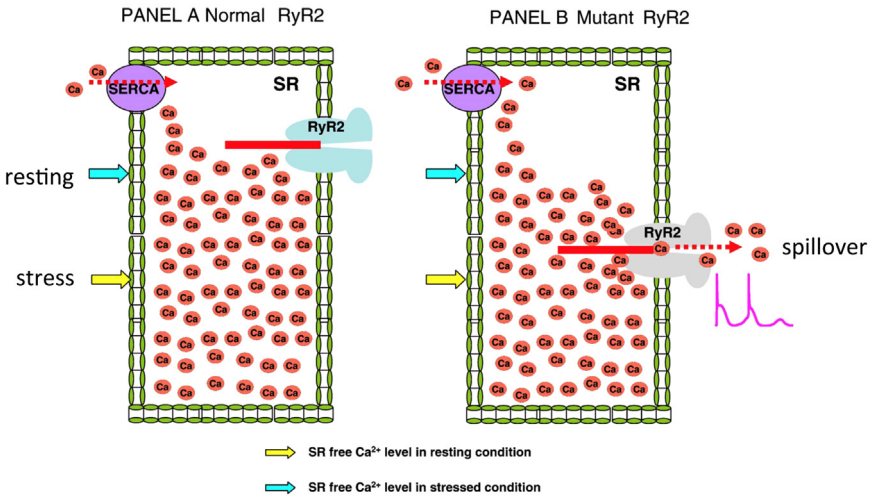

Fig. 4. The store overload-induced Ca^{2+} release (SOICR) hypothesis [8]. With normal *RyR2*, the resting and stress levels of free calcium are below the SOICR threshold (panel A). If the SOICR threshold falls below the level of free SR calcium as with mutant *RyR2*, a leak of Ca^{2+} will occur and generate a delayed after-depolarization.

A three-dimensional reconstruction of *RyR2* bound to FKBP12.6 is shown in Fig. 2B. When *RyR2* is bound to FKBP12.6, it forms a stable structure with closed pores, the domain 6 of *RyR2* was found to protrude into the luminal side, when observed from the junctional face after the transmembrane assembly (TA) was rotated counterclockwise by about 4° [7]. When unbound to FKBP12.6, *RyR2* assumes an open state (Fig. 2A) [7].

Several pathogenic hypotheses have been reported regarding the causes of CPVT [8]. The first theory suggests the dissociation of FKBP12.6 from *RyR2*. The normal *RyR2* channel is stabilized by FKBP12.6 and closes during diastole. With mutant *RyR2*, the binding affinity with FKBP12.6 is weakened, and phosphorylation of *RyR2* by protein kinase A (PKA) results in dissociation of FKBP12.6 from *RyR2*, resulting in open channels which may leak Ca^{2+} during diastole (Fig. 3).

The second hypothesis is a store overload-induced Ca^{2+} release (SOICR) theory [8]. With normal *RyR2*, the resting and stress levels of free Ca^{2+} are below the SOICR level. However, with mutant *RyR2*, the SOICR threshold drops below the level of free Ca^{2+} in the SR. This may cause a spillover of Ca^{2+} from the SR (Fig. 4).

The third hypothesis considers defective intramolecular domain interaction [8]. *RyR2* is stabilized by a tight zipping of the intramolecular structure. If a mutation interferes with this zipping structure, the intramolecular domain interaction is weakened, causing an unzipping of the interdomain structure and leads leaking of Ca^{2+} from the SR (Fig. 5).

The fourth hypothesis suggests that the molecular and functional abnormalities are related to mutations in the *CASQ2* gene [8]. *CASQ2* is a Ca^{2+} storage protein inside the SR. The functional storage capacity of *CASQ2* or its reduced levels, may lead to increased levels of free Ca^{2+} inside the SR, leading to a Ca^{2+} leak during diastole (Fig. 6). It is also known that *CASQ2* stabilizes binding of *RyR2* with *TRD* and the junction.

This Ca^{2+} overload activates the forward mode of the Na^{+}/Ca^{+} exchanger (NCX), increases the transient inward current (Iti), and induces ventricular arrhythmias due to delayed after depolarizations (DADs).

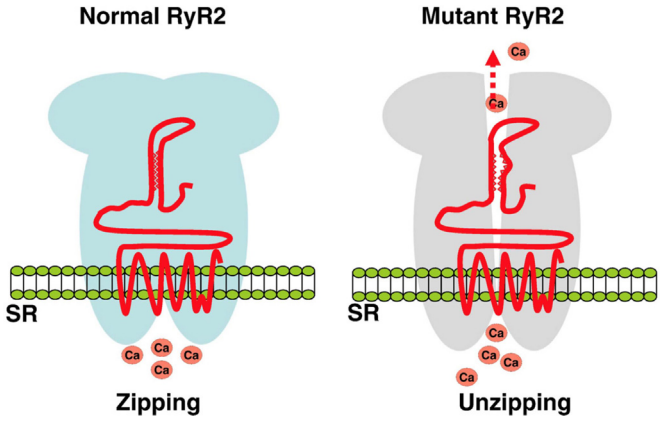

Fig. 5. Defective intramolecular domain interactions in *RyR2* mutations [8]. The N terminal domain and the central domain of *RyR2* interact with a tight "zipping" that serves to stabilize the channel (left panel). A mutation in either domain weakens this interaction (unzipping), which results in leaking of Ca^{2+} from *RyR2* (right panel).

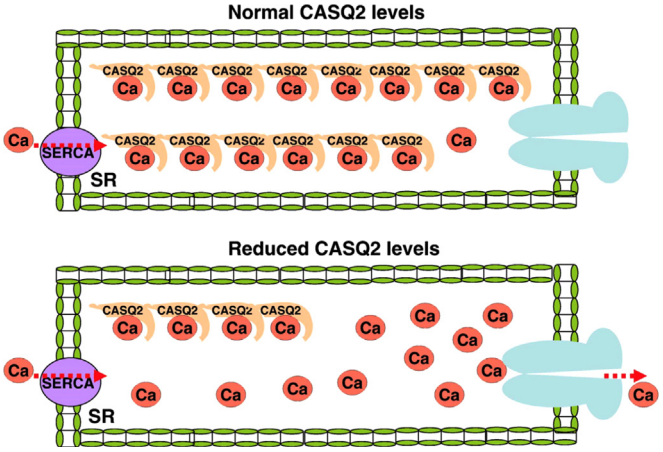

Fig. 6. Molecular and functional abnormalities related to mutations in the CASQ2 gene [8]. Storage of Ca^{2+} in the SR largely depends on the level and function of CASQ2 (upper panel). Decreased levels or function of CASQ2 results in increase in the free SR Ca^{2+} that may result in a Ca^{2+} leak from *RyR2* during diastole (lower panel).

5. Subtypes of CPVT

Several subtypes of CPVT have been reported (Table 1). The most common type of CPVT is caused by an anomaly in the *RyR2* gene (CPVT1) [9,10]. This accounts for more than 50% of CPVT cases. In our CPVT cohort, about 79% of the CPVT cases were related to an anomaly in the *RyR2* gene. The inheritance of CPVT1 is autonomic dominant, and sudden death was observed in about 10% of these patients. There were no sex differences noted in this CPVT.

The second most common type of CPVT is caused by a *CASQ2* gene anomaly (CPVT2) [11,12]. The inheritance of CPVT2 is autosomal recessive, and the rate of sudden death is higher than that observed in CPVT1. However, autosomal dominant mutations of *CASQ2* are also reported [13–15].

CPVT3 was reported in a family with showing a 7p22-p14 chromosome anomaly, but the gene responsible has not been identified yet [16]. Recently, calmodulin (*CALM*) [17] and triadin (*TRD*) [18] anomalies have been found to responsible for CPVT4 and CPVT5, respectively.

CALM is a protein that involves the calcium dependent I_{Ca} inactivation of the L-type Ca channel. Further, *CALM* also stabilizes the *RyR2* channel. Thus, a mutation in *CALM* may easily cause Ca^{2+} overload. *TRD* is a protein that connects *CASQ* to *RyR2*, and stabilizes the *RyR2* channel. A mutation in *TRD* may also result in a diastolic leak of Ca^{2+} and Ca^{2+} overload in the myocytes.

KCNJ2 encodes the cardiac inward rectifier K channel. A mutation in *KCNJ2* causes the Andersen–Tawil syndrome (LQT7), and is also reported in patients with exercise induced bi-directional VT [19]. Whether or not this type of mutation should be included as a subtype of CPVT is a matter of controversy. Mutations in the *ANK2* gene are well known as a cause of LQT4. Recently, a patient with an *ANK2* mutation was reported to have bi-directional VT [20]. This may be another disease related to CPVT.

A type of adult CPVT has also been reported [21,22]. In this disease, the patients are predominantly female, with CPVT onset at the age of around 40 years, and no sudden death is reported. We believe that this may not be a specific type of CPVT, but rather a mild form of the disease.

In the Japanese CPVT registry, 78 patients (M:F=26:52, age=11.2 ± 8.2 years) were enrolled. In this registry, only 6% of the cases were familial cases whereas 94% of the cases were sporadic

Table 1
Subtypes of CPVT.

Subtypes	**Juvenile type**							**Adult type**
	CPVT1	**CPVT2**	**CPVT3**	**CPVT4**	**CPVT5**	**CPVT related diseases**		
						ATS	LQT4	
Incidence (%)	50–60	1	$\ll 1$	$\ll 1$	$\ll 1$	$\ll 1$	$\ll 1$	≈ 30
Inheritance	AD	AR	AR	AD	Sporadic	AD	AD	Sporadic
Onset of symptoms	10 years	7 years	10 years	4 years	2, 26 years	14, 9, 17 years	?	$>$ 20 years (40 years)
Sex	M:F=1:1	M:F=1:1	M:F=1:1	M:F=1:1	M=3	F > M?	?	F $\gg$ M
Chromosome locus	1q43	1p13.1	7p22–p14	14q32.11	6q22.31	17q24.3	4q25-26	
Gene	*RyR2*	*CASQ2*	?	*CALM1*	*TRD*	*KCNJ2*	*ANK2*	*RyR2* $\approx$ 30%
Protein				CaM		$K_{ir}2.1\alpha$	Ankyrin-B	
Sudden death (%)	≈ 10	≈ 42	≈ 75	≈ 18	≈ 25	?	?	0

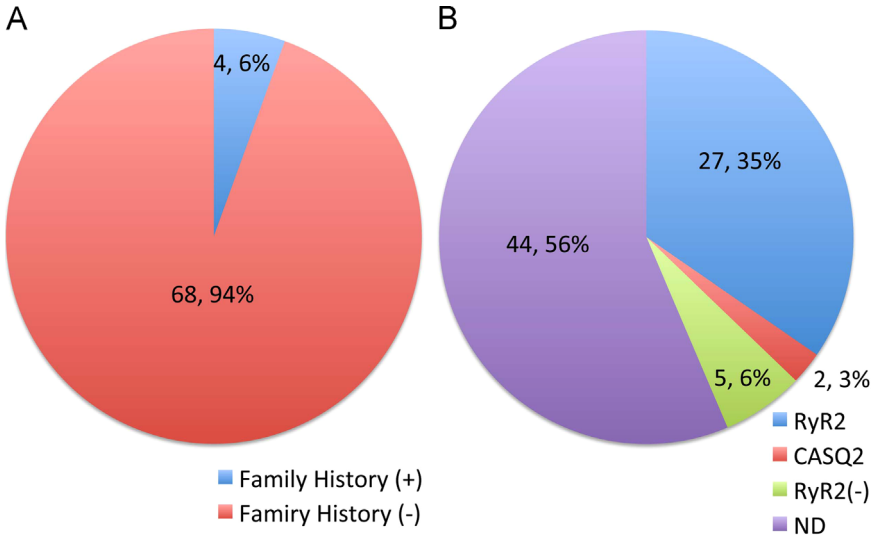

Fig. 7. Family history and gene anomalies in the Japanese registry. (A) Family history in the registry. (B) Gene mutations ND; gene testing was not performed.

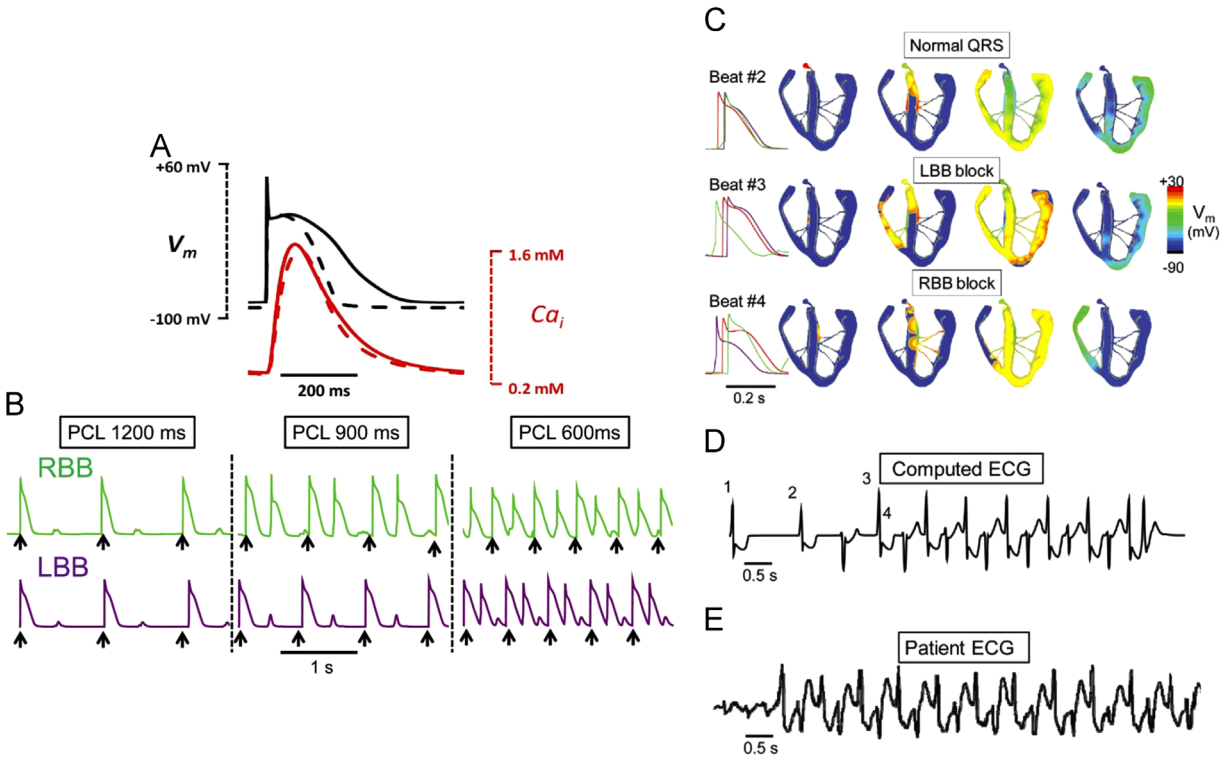

Fig. 8. A possible mechanism for bidirectional ventricular tachycardia: ping-pong in the His–Purkinje system [27]. (A) Comparison of simulated rabbit ventricular (dashed line) and Purkinje (solid line) action potentials (APs) and Cai transients during pacing at 600 ms. (B) Rate dependence of delayed after depolarizations (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 action potential (AP) arising in the right bundle branch (RBB), resulting in QRS with a left bundle branch (LBB) block 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.

(Fig. 7A). In this cohort, 56% of the patients had not undergone genetic testing. However, of the 46% patients who underwent genetic testing, 79% of the patients had an *RyR2* gene anomaly, 6% had a *CASQ2* gene anomaly, and in 15% of the patients the specific causative gene anomaly was unknown (Fig. 7B). The estimated *RyR2* genotype percentage is reported to range from 35% [23] up to 65% [24,25], and the *CASQ2* genotyped patients are estimated to account for approximately 3–5% [25].

The proportions of familial cases reported in other studies were 21.3% [26] and 30% [21]. The lower percentage of familial cases observed in our cohort may be because half of the registered cases are over 15 years old, at which time only information of familial

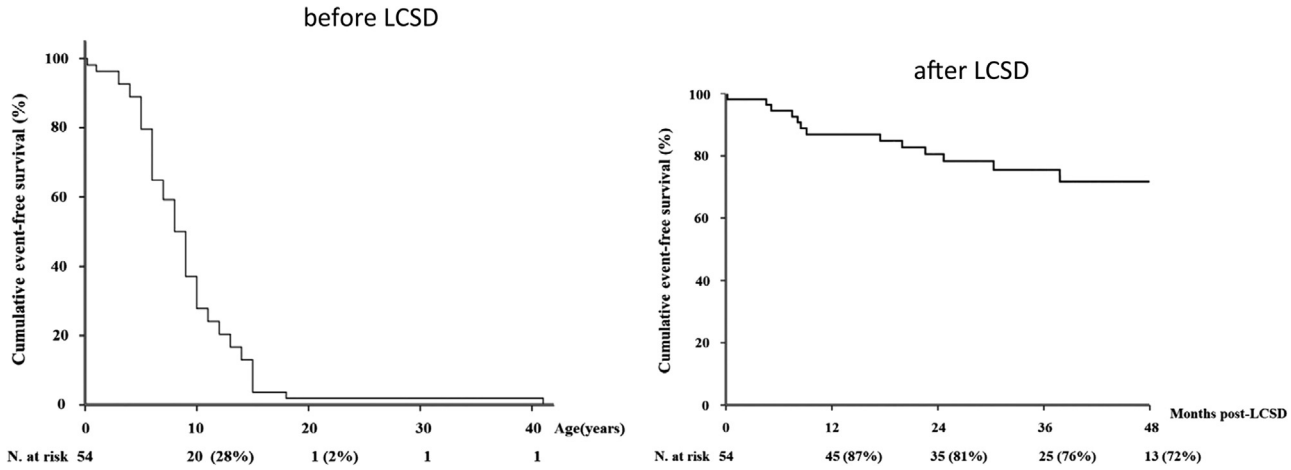

Fig. 9. Kaplan–Meier curve of cumulative survival to a first major cardiac event before and after left cardiac sympathetic denervation (LCSD) in symptomatic patients with CPVT [38]. In 63 patients with CPVT, the cumulated event free survival significantly improved after LCSD.

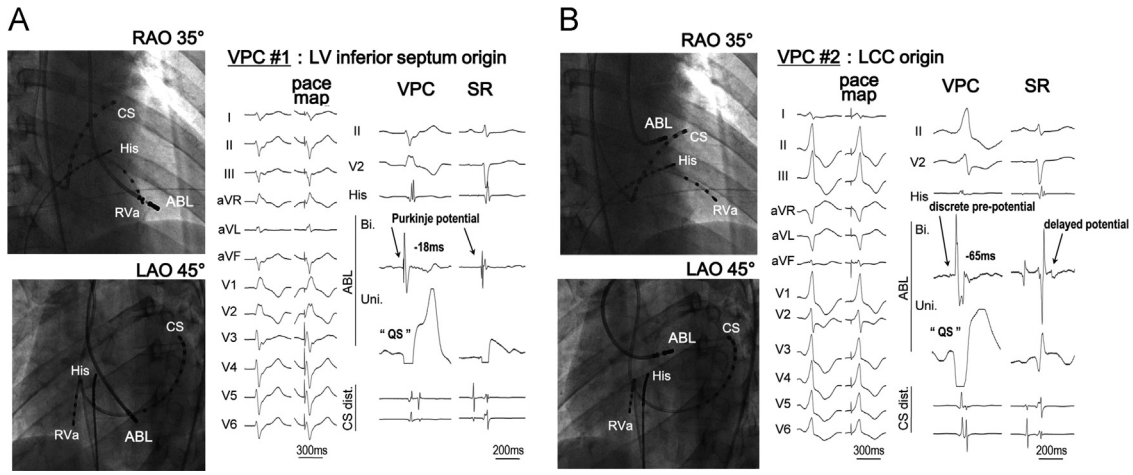

Fig. 10. Pace mapping of PVC in a patient with CPVT [43]. (A) A perfect pace map of the second beat of the CPVT was obtained on the left ventricular septum. Purkinje potential at that point was recorded during the PVC and sinus rhythm. (B) A perfect pace map of the first beat of a PVC was obtained at the left coronary cusp. A discrete pre-potential was recorded during the PVC, and a delayed potential was recorded during sinus rhythm.

history was taken without exercise or genetic testing. This may result in an apparently lower percentage of familial cases. Kawamura et al. have reported that *RyR2* positive CPVT cases are more likely to have clinically diagnosed CPVT-affected family members with bidirectional VT, and sinus bradycardia [26].

6. The mechanism of bidirectional VT

Bidirectional VT is the most characteristic feature of CPVT. In the His–Purkinje system, DAD induced bigeminy may differ depending on whether they are induced by the right bundle branch or the left bundle branch. The right bundle branch (RBB) caused a DAD induced bigeminy at a pacing rate of 900 ms (Fig. 8B), whereas the left bundle branch (LBB) induced a bigeminy at a pacing rate of 600 ms (Fig. 8B) [27]. 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 RBBDAD induced bigeminy, the next beat arose from the RBB followed by a beat from the LBB, one after the other (Fig. 8C) [27]. This computer simulation suggests a mechanism for the bidirectional VT.

7. Therapy for the CPVT

7.1. β Blockers

The long acting β blocker, nadolol, 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 [28].

Carvedilol is reported to inhibit the SOICR in an HEK 293 cell culture model. Among various β blockers, only carvedilol inhibits *RyR2* activity [29]. 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.

7.2. Verapamil

Verapamil has also shown beneficial effects in some CPVT patients [30,31]. However, the long-term efficacy of verapamil is still controversial.

7.3. Flecainide

Flecainide is an effective medication for CPVT [32–34]. Flecainide treatment shows improvement of ventricular arrhythmias in 74% of the genotype positive CPVT cases [32], and in 92% of the genotype negative CPVT cases [34]. Flecainide is thought to function by direct suppression of the *RyR2* receptor. Among the Class I anti-arrhythmic medications, only flecainide and propafenone inhibit *RyR2* activity [35]. However, recent report denies the direct suppression of *RyR2* by flecainide [36]. That may suggest another mechanism of flecainide, such as inhibition of NCX.

7.4. Left cardiac sympathetic denervation

Left cardiac sympathetic denervation is reported to be a useful therapeutic method for suppressing ventricular arrhythmias in CPVT patients [37,38]. In patients with uncontrollable ventricular arrhythmias, left cardiac sympathetic denervation is highly useful in controlling ventricular tachyarrhythmias (Fig. 9). 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 [38].

7.5. ICD

Implantation of an ICD should be considered in patients in the absence of controlled optimal therapy [39]. However, implantation of an ICD in children still has a number of technical problems [40]. Moreover, inappropriate or painful shocks may increase the risk of further ventricular arrhythmias, and electrical storms that may result in lethal events.

7.6. Catheter ablation

Pulmonary vein isolation is reported to be effective in some CPVT patients with atrial fibrillation [41]. Purkinje cells are reported to be more arrhythmogenic than ventricular myocytes in a mutant knockout mouse model of CPVT [42]. 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 (Fig. 10) [43].

7.7. Gene therapy

The homozygous R33Q knock-in mouse has a dysfunctional *CASQ2*, which may cause CPVT. In this mouse model, isoproterenol induced DADs, which were markedly reduced after 12 months following infection with an adenoviral vector (serotype 9), that carried the normal *CASQ2* gene [44]. This report suggested the possible use of gene therapy for some types of CPVT in the future.

Conflict of interest

All authors declare no conflict of interest related to this study.

Acknowledgment

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