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Review

Current topics in catecholaminergic polymorphic ventricular tachycardia

Naokata Sumitomo, MD, PhD*

Department of Pediatric Cardiology, Saitama Medical University International Medical Center, 1397-1 Yamane, Hidaka-City, Saitama 350-1298, Japan

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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.

Contents

1. Introduction

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is induced by emotional stress or exercise in patients without

* Tel.: +81 429 84 4111x8625; fax: +81 429 84 4121.
E-mail address: sumitomo@saitama-med.ac.jp

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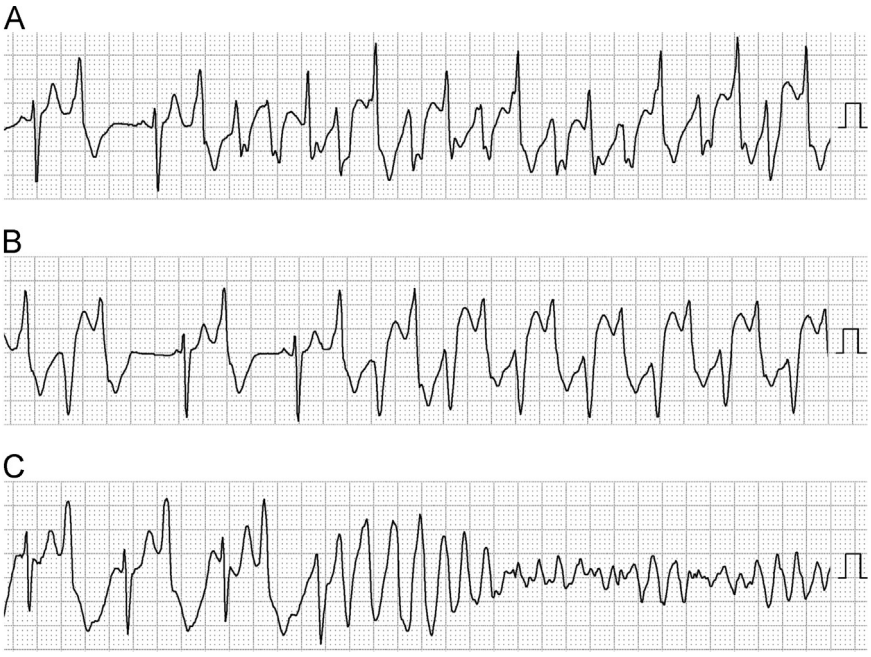

Fig. 1. Typical features of ventricular tachycardia in a patient with CPVT. (A) Polymorphic ventricular tachycardia. (B) Bidirectional ventricular tachycardia. (C) Rapid polymorphic ventricular tachycardia deteriorating into ventricular fibrillation. These electrocardiograms were recorded by Holter monitoring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

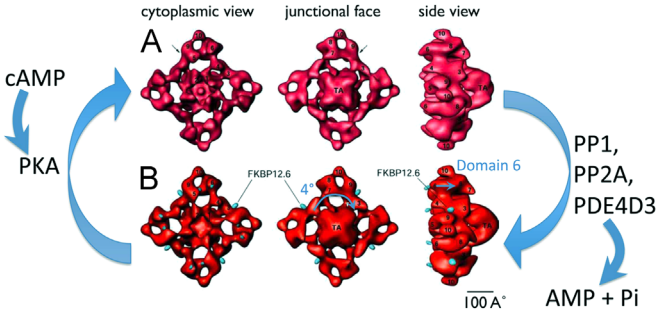

Fig. 2. Surface representations of *RyR2* 3D reconstructions with and without bound FKBP12.6. [7]. (A) High activity state of *RyR2*. A 3D map of *RyR2*, obtained by in vitro assembly of purified *RyR2* incubated with FKBP12.6 alone. (B) Low activity state of *RyR2*. A 3D map of *RyR2*, obtained by incubating *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.

organic heart disease and may be polymorphic or bidirectional (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].

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