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Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT): A Review

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Abstract: *Catecholaminergic polymorphic ventricular tachycardia (CPVT) is an inheritable arrhythmogenic cardiac disease, which represent by exercise or emotional stress induced ventricular arrhythmias in the nonappearanceof structural heart disease. CPVT is linked to disorder in calcium handling and the changes in Genes coding for ryanodine receptors are generally considered as responsible for the disorder. Fifty percent of cases have been reported mutations in the ryanodine receptor 2 (RyR2) gene, which regulates release of calcium from the sarcoplasmic reticulum. β-blocker treatment is a suggestive recommendation in CPVT individuals, which reduce the influence of catecholamines by blockade of β-receptor–induced intracellular signaling, which leads to destabilization of RyR2. In this review, we carried out the etiology, mechanism, diagnosis and treatment of CPVT.*

Keywords*:Bidirectional Ventricular Tachycardia (BDVT), Catecholaminergic polymorphic ventricular tachycardia (CPVT), Polymorphic ventriculat tachycardia (PMVT), RyR2 gene, Sudden Death*

I. Introduction

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is an inheritable arrhythmogenic cardiac disease, which represent by exercise or emotional stress induced ventricular arrhythmias in the absence of structural heart disease [1]. CPVT was first noted in a case report in 1975 [2]. In 1978, Philippe Coumel reported catecholamine-induced syncopal ventricular tachycardia (VT) in four children[3]. CPVT is a paramount cause of sudden cardiac arrest (SCA) in adolescent individuals with an estimated prevalence of 1:10,00 [4]. If left untreated, cardiac event rates have been reported as high as 80% before the age of 40 years. [5]. In the course of physical activity or emotional stress, patients experience palpitations or syncope due to ventricular arrhythmias, but SCA may also be the first manifestation of the disease [6, 7]. The ultimate knowing clinical tool to detect CPVT exercise stress testing reveals periodic premature ventricular contractions [6, 8] arrhythmias of increasing severity as workload increases, and sooner or later bidirectional or polymorphic ventricular tachycardia (VT), which might degenerate to ventricular fibrillation [8, 9].

CPVT is a cardiomyopathy related arrhythmia, which linked to disorder in calcium handling [10]. Conventionally, typical bidirectional ventricular tachycardia is induced by physical activity [11]. The changes in Genes coding for ryanodine receptors are generally considered as responsible for the disorder [12]. Fifty percent of cases have been reported mutations in the ryanodine receptor 2 (RyR2) gene, which encodes for the cardiac ryanodine receptor, which regulate release of calcium from the sarcoplasmic reticulum. In the presence of catecholamine stimulation mutations can lead to calcium leakage causing after-depolarizations, which can generate bidirectional or polymorphic ventricular tachycardia [13].

The ryanodine receptor 2 (RyR2) is a probable pathogenic variant, which causes CPVT in about 60% of cases [14]. Catecholaminergic stimulation of the β-receptor provokes calcium release from an unstable RyR2 channel, which causes malignant ventricular arrhythmias [7]. In patients with CPVT, β-blocker treatment is a suggestive recommendation, which reduce the influence of catecholamines by blockade of β-receptor–induced intracellular signaling, which leads to destabilization of RyR2. β-Blockers are suggested to provide arrhythmia protection by reducing the influence of catecholaminesby blocking the β-receptor–induced intracellular signaling, which leads to destabilization of RyR2. Though, limited data subsist on how antiarrhythmic effects differ in specific β-blockers, which varies in lipid solubility, half-life, selectivity and bioavailability[15].

II. Mechanism of CPVT

In CPVT, calcium releases from the sarcoplasmic reticulum by the mutation of the ryanodine receptor [16]. Cardiac calsequestrin mutations can also confer to abnormal cellular calcium regulation [16]. Delayed after depolarization mediates abnormal calcium handling which can lead to arrhythmias [17]. CPVT can be caused by mutations in the cardiac ryanodine receptor gene (*RYR2*), this is inherited in an autosomal dominant pattern. Mutations in Cardiac calsequestrin gene *CASQ2* causes autosomal recessive inheritance. In excitation–contraction coupling, *RYR2* and *CASQ2* genes are ramified in the release of calcium ions from the sarcoplasmic reticulum [18]. Currently published literatures show, molecular genetic testing identifies heterozygous *RYR2* mutations in about half of probands and homozygous *CASQ2* mutations in about 2% and even heterozygous CASQ2 mutations also causes CPVT. Sympathetic stimulation either by exercise or by epinephrine infusion leads to Arrhythmia. Polymorphic Ventricular Tachycardia, ventricular ectopy, and bidirectional Ventricular Tachycardia may occur with increasing heart rate. Syncope leads to continuation of provocative testing. After provocative testing, Intravenous β-blocker therapy can be used to suppress ventricular arrhythmias in CPVT [13].

III. Clinical management

The first clinical expression of CPVT is syncope, which triggered by emotional or physical stress and the mean age of onset of manifestation is between 7 to 9 years. In CPVT patients, the cardiac imaging exploration is normal and the resting electrocardiogram (ECG) is often undistinguished, without atrioventricular and intraventricular conduction defects, QT prolongation and lack of Brugada-like ST-segment pattern. CPVT diagnosis is confirmed by an exercise stress or Holter test to evidence ventricular arrhythmias otherwise it is missed [19]. Recent studies show, probands percentage with a family history of syncope, seizures, or sudden death is approximately 30%. A detailed examination may helpful to establishing the proper diagnosis because sudden death might be the first manifestation of CPVT [16]. If cardiopulmonary resuscitation is not easily available sudden death can occur because of degeneration of ventricular tachycardia into ventricular fibrillation[20].

It has been suggested that there are may be 2 types of CPVT exist “juvenile” and “adult”. A recent study suggests, the juvenile type CPVT that has a greater risk of sudden cardiac death is associated with RyR2 mutation present with the first two decades of life and has no difference in gender. Adult type of CPVT is associated with RyR2 mutation, present in females at around 40 years and has less risk of sudden cardiac death [13, 21].

In CPVT, sinus bradycardia noted which is associated with RyR2 mutation and atrial tachycardia has also noted in later diagnosed CPVT patients [22, 23].Takotsubo cardiomyopathy has been reported in CPVT [24]. A case report from Japan showed a relation between left ventricular noncompaction (LVNC) and RyR2 exon 3 deletion, which suggest that espial of this deletion with LVNC in patients may help in prognostication for CPVT patients [25].

IV. Diagnosis

CPVT Diagnosis is established on family history, emotional stress or exercise induced symptoms; moreover exercise or catecholamine infusion response. It might be of supplementary work to identify the typical ECG patterns in exercise or emotional stress in children who are not able to achieve Holter ECG and exercise examination. Prolongation of QT interval does not occur in patients with CPVT. At rest, CPVT patients do not show ECG abnormalities. Patients with CPVT are sometimes present with Sinus bradycardia and supraventricular arrhythmias such as unspecified supraventricular tachycardia (SVT), sick sinus syndrome, and atrial ectopic tachycardia [22, 23, 26].

Recorders such as Holter monitor recording, implanted loop and loop recorder monitoring are useful to monitor stress test. These recorders can also be accessible to further describe associated sine node dysfunction or SVT. They can be diagnostic for patients in whom ventricular tachycardia may be analogous to emotions or stress and not exercise induced[27]

CVPT diagnosis most often bases on the presentation of venricular tachycardia with exercise testing; moreover a negative stress test does not rule out CPVT. The ventricular tachycardia becomes more articulate when the sinus rate increases with the account of 110-130 beats per minute in exercise. It often starts as premature ventricular complex, continue to ventricular couplets and triplets and downgrade into a ventricular tachycardia. VA is typically characterized as bidirectional ventricular tachycardia (BDVT) with beat-to beat alteration in the QRX complex; moreover they could just loom to be polymorphic ventricular tachycardia (PMVT) [27, 28]. Published data have reported that inceptive beat of ventricular tachycardia comes periodically from the right or left outflow tract region [11].

Intravenous epinephrine infusion has been used to aid in CPVT diagnosis due to the catecholamine dependent nature of CPVT. A published literature on 27 patients with CPVT reports that exercise testing aggravated ventricular tachycardia in 63% and epinephrine in 82% of the patients [13]. It has been

recommended that epinephrine may be a different choice to exercise testing; moreover a recent published literature from Finland reported a specificity 98% and sensitivity of 28% in comparison to exercise stress testing [29].

V. Differential Diagnosis

CPVT should always be investigated in the differential diagnosis in sudden cardiac arrest patients caused by the nonappearance of structural cardiac disease. Long –QT syndrome (LQTS), Andersen–Tawil syndrome (ATS) and AC are the main differential diagnosis of CPVT. Syncopal events are induced by torsades de points instead of a bi-directional ventricular tachycardia in LQTS. ECG can show a regularQTc pattern in LQTS, which can be challenging to determine CPVT. Though, exercise stress examination is distinct as it shows QTc prolongation in LQTS, but does not cause VA. The Andersen–Tawil syndrome is induced by a mutation in the KCNJ2 gene. During exercise testing, affected ATS patients can present with bidirectional ventricular tachycardiya or identical ventricular ectopy. AC is also caused by exercise induced arrhythmias and structural deformity. Echocardiography and MRI both tools can classify AC features in affected individuals genotype [30].

VI. Treatment

A number of treatment options are reachable for CPVT management. Generally, β-blockers have using as a drug of choice but new therapeutic options have also reported.

6.1 □-blockers

β-blockers are marked for all individuals who are diagnosed with CPVT[31]. Beta Blockade should be admitted; moreover high doses are usually mandatory. Exercise examination and Holter monitoring may be a tool with a therapy to confirm that a relevant drug dose has been achieved. Missing doses of β-blockers can enrage lethal arrhythmias. There are scanty data regarding efficacy of different β-blockers [5].

6.2 Calcium channel blockers

Calcium channel blockers (CCBs) can block the influx of Ca^{2+} into the sarcoplasmic reticulum via the L-type Ca^{2+} channel. Verapamil, which is a Calcium channel blocker, has been used in addition to beta-blockade in a small case series of patients [32, 33]. Recent published literatures in mice with CASQ2 mutation have recommended that verapamil is the most adequate drug of choice in ventricular arrhythmias caused by epinephrine infusion or exercise and this affect has been reported in a cohort study of CASQ2 mutation-positive individuals which suggests a specific role for verapamil in CPVT [34].

6.3 Sodium channel blockers

Clinical and experimental data show that by inhibiting cardiac ryanodine receptor, Flecainide is helpful in treating CPVT [35, 36]. Flecainide (100-300 mg/day) can be given along with β-blockers to patients who have repetitiveness of syncope during exercise[17, 36].

6.4 Implantable cardiac defibrillator

Implantations of an ICD with use of β-blockers have a good practical status, which is considered to be a class I indication for CPVT patients who experience cardiac arrest, recurrent syncope or polymorphic/bidirectional VT. CPVT individuals who present sustained VT although receiving β-blockers are considered to have a class IIa indication for implantation of ICD [31]. Without the use of β-blockers, ICD treatment is dangerous due to the risk of electrical storm cause by adrenergic surge related to a shock [37].

VII. Conclusion

The past and recent published clinical and experimental literatures have provided interesting new exploration of the etiology, genetic mutation and mechanism of CPVT. Research discoveries have been strongly suggested from the bench to the bedside, and constructed a base of this disease and navigate our approach to its diagnosis and treatment. Furthermore studies of CPVT will yield a finer understanding of the adequacy and drawback of established diagnostic passage and therapies as well as build novel blueprint of diagnosis and treatment.

Conflicts of interest

There are no conflicts of interest.

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