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Catecholaminergic Polymorphic Ventricular Tachycardia – Looking to the Future

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ABSTRACT

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a rare inheritable cardiac disorder, characterized by polymorphic ventricular tachycardia (PVT) or bidirectional ventricular tachycardia, triggered by adrenergic stress, and manifested most frequently as syncope or sudden cardiac death. The disease has a heterogeneous genetic basis, with mutations in the genes encoding the ryanodine and calsequestrin channels accounting for the majority of cases.

The diagnosis of CPVT is established in individuals with polymorphic ventricular premature beats, PVT or bidirectional ventricular tachycardia documented during exercise or adrenergic stress, who have a structurally normal heart and normal resting ECG. Genetic testing completes the diagnosis, but is limited by the fact that, to date, about one third of cases are genotype-unknown.

Treatment strategies have improved as the knowledge of the disease has evolved, and several therapeutic options are now available. They include pharmacologic measures (especially non-selective beta-blockers and flecainide), but also more complex interventions, such implantation of internal cardiac defibrillators and left cardiac sympathetic denervation.

There are many unknowns to CPVT, but one that is essential to clinical practice is risk stratification, which will aid in a more targeted treatment of these patients. This goal is to be achieved by creating large patient registries and bio-banks, and ultimately by incorporating both clinical and genetic data into a risk stratification score.

Keywords: cathecolaminergic polymorphic ventricular tachycardia, bidirectional tachycardia, sudden cardiac death, genetic mutations.

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INTRODUCTION

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a rare inherited disorder, characterized by polymorphic ventricular tachycardia (PVT) or bidirectional ventricular tachycardia, triggered by adrenergic stress. The disorder is responsible for numerous sudden cardiac deaths (SCD) in children and young adults (1), thus represents a matter of serious medical and social importance.

The prevalence of CPVT is considered to be 0.1:1000 (2), but this number is an estimate, as it is not derived from a systematic assessment of the population and the true frequency of the disease may be higher. CPVT is typically an underdiagnosed disease and its main diagnostic challenge lies in the fact that, unlike other inherited arrhythmia syndromes (long QT syndrome, Brugada syndrome, etc), it presents not only with a structurally normal heart, but also without resting ECG abnormalities (2).

Genetic background

Catecholaminergic polymorphic ventricular tachycardia is an inherited arrhythmogenic cardiac disorder, caused by mutations in the genes encoding channel-proteins involved in the balance of ionic currents, which are responsible for the excitation-contraction coupling in the cardiac myocytes (3).

There are two main genetic variants of the disease, which account for approximately 60-65% of all CPVT cases. The most frequent form of the disease (known as CPVT 1) is related to autosomal dominant mutations in the RyR2 gene (4), the "major CPVT gene", which encodes the cardiac ryanodine receptor (RYR2). The RYR2 is a large channel-protein, located in the sarcoplasmic reticulum (SR), with an important role in the cardiac myocytes' Ca^{2+} homeostasis. At present, there are over 160 CPVT1-causative mutations, the vast majority causing a gain of function of the RyR2 channels.

The second genetic variant of the disease (CPVT 2), accounting for less than 5% of cases, is related to an autosomal recessive mutation of the CASQ2 gene, encoding cardiac calsequestrin (5). Calsequestrin is a low-affinity high-capacity Ca^{2+} buffering protein, with an active role in the control of SR Ca^{2+} storage and release, being also an important regulator of the RYR2 channels (6) *via* its interaction with other proteins (triadin and junctin).

The above-mentioned gene mutations lead to ventricular arrhythmia through the alteration of the Ca^{2+} homeostasis (3). In normal conditions, the RYR2 opens briefly during the early plateau phase of the action potential, ensuring Ca^{2+} release from the SR, which initiates myocardial contraction in systole. The Ca^{2+} is then pumped back into the SR via the Ca^{2+}-ATPase, allowing the cardiac muscle to relax during diastole. Mutations in the RyR2 and CASQ2 genes lead to a leakage of Ca^{2+} from the SR in diastole, particularly under adrenergic stress (exercise, emotional stress), resulting in delayed after-depolarizations and consequent potential for ventricular arrhythmia.

Catecholaminergic polymorphic ventricular tachycardia has also been associated with mutations in other "minor genes", like KCNJ2 (sometimes called CPVT3 type), triadin (TRDN) (7), junctin (JCN), calmodulin (CALM1 and CALM2) (8) and NKYRIN-B. Because these mutations are identified in less than 5% of cases, the presence of other not yet identified loci is likely. Specifically, and in contrast to other cardiac channelopathies, the penetrance and expressivity of CPVT, particularly CPVT1, appears to be much higher, with an overall disease penetrance reported to be approximately 80% and a positive family history of SCD present in up to 60% of families demonstrating mutations in RYR2 (9).

There is an emerging need to further the knowledge on the genetics of CPVT, given that about one third of cases with a definite CPVT phenotype are without a genetic diagnosis. This will be achieved in the future with the aid of novel DNA sequencing techniques and the creation of bio-banks, allowing for the screening of a large number of genes.

It is important to note that there is a significant number of cases with de novo mutations, thus these patients will have no relevant family history.

Clinical presentation and diagnosis

Patients with CPVT usually present with stress-induced syncope or cardiac arrest, occurring in childhood or early adolescence. The initial presentation can be sudden cardiac death. There

are, however, cases with a less dramatic presentation, exhibiting palpitations and dizziness during exercise or emotional-stress (10). A significant number of patients have a misdiagnosis of seizures in their history, before being correctly diagnosed with CPVT.

According to the latest EHRA/HRS/APHRS expert consensus on ventricular arrhythmias (2), the clinical diagnosis of CPVT is established in individuals younger than 40 years, with polymorphic ventricular premature beats (VPB), PVT or bidirectional ventricular tachycardia documented during exercise or adrenergic stress, who have a structurally normal heart and normal resting ECG.

There is no consensus regarding the complexity of arrhythmia necessary for diagnosis or the protocol needed to trigger such an arrhythmia. However, reproducibility and a certain arrhythmia pattern appear to be characteristic of CPVT, which can be recognized during treadmill ECG testing. Typically, as sinus rhythm accelerates, VPBs appear, initially isolated, then organized into more complex arrhythmias (trigeminy, bigeminy), and further into non-sustained PVT runs or bidirectional ventricular tachycardia. The arrhythmia ceases if the adrenergic stimulus is stopped (in this case, the treadmill test) and is expected to degenerate into sustained PVT and even ventricular fibrillation, if the stimulus persists.

Other tests can be used in order to establish the diagnosis, especially in patients who are unable to exercise, such as drug challenge with epinephrine or isoproterenol, but the method appears to have low sensitivity (11). ECG monitoring is a useful tool in infants. Loop recorders aid in the diagnosis of CPVT in patients with emotional stress as a main trigger for arrhythmia (12). However, programmed electrical stimulation has no diagnostic value in CPVT (12).

Bidirectional ventricular tachycardia is specific for CPVT, but it must not be considered pathognomonic, as it is encountered in other circumstances (most frequently in digitalis toxicity, but can also develop in patients with Andersen Tawil syndrome).

By definition, patients with CPVT have a normal baseline ECG, but there are certain identifiable ECG features. Firstly, most patients exhibit sinus bradycardia during rest. The underlying mechanism is hypothesized to be related to the impaired Ca^{2+} handling by the mutated RYR2 channels in the sinoatrial node cells (13). Secondly, prominent U waves can be identified on the resting ECG, but their significance is not yet fully understood. Another characteristic of CPVT are the frequent supraventricular arrhythmias (atrial extrasystoles, atrial tachycardia, atrial fibrillation).

Patients with CPVT have a structurally normal heart, confirmed firstly by echocardiography, as it is the most available and most cost-effective method. In order to exclude structural heart disease, cardiac magnetic resonance, and in particular cases, coronary angiography (patients over the age of 40, with risk factors for atherosclerotic disease) can be performed.

Genetic testing confirms the diagnosis, if the patient has a known genetic variant. Additionally, genetic testing should be offered to the family members of a proband, in order to identify asymptomatic mutation carriers (2).

Management

The reported mortality of CPVT cases left untreated is 30-50% by the age of 20-30 years (14, 15), and the majority of patients (60-80%) will have an arrhythmic event by age 40 (10, 13). Given the high mortality rate, the initiation of a treatment strategy is crucial.

According to current guidelines (2), the first line therapy consists of changes in lifestyle, combined with the administration of beta-blockers.

All patients with a CPVT diagnosis should restrict physical activity and avoid stressful situations. The degree to which physical activity should be restricted is not clearly stated, but can be appreciated from the exercise stress test performed in the hospital setting, and is especially important for those with an exercise-induced form of CPVT.

The first preferred pharmacological regimen for CPVT is non-selective beta-blockers, without sympathomimetic activity, titrated to the maximum tolerated dose (12). Beta-blockers are indicated both for patients with a CPVT phenotype, as well as for the silent mutation carriers. Nadolol is the first choice in most countries (1-2 mg/kg *per* day), but propranolol can also be used (3-5 mg/kg *per* day), when nadolol is unavailable. It is essential that patients are fully compliant to treatment, as abrupt interruption can cause a re-

bound effect, with high probability of an arrhythmic event. Beta-blockers are reported to be effective in preventing further arrhythmic events in two thirds of patients. The remaining one third has persistent complex ventricular arrhythmias in either ECG monitoring or during exercise stress tests (16).

For this group of patients, flecainide (100-300 mg *per* day) has been shown to decrease the arrhythmia burden in a significant proportion in small studies and it is now considered the first choice addition, when the effect of beta-blockers is not complete (17). Flecainide directly inhibits RYR2, thus preventing the release of Ca^{2+} from the SR, in addition to its well-known role in blocking cardiac Na channels. The in vitro data are supported by clinical observations made by Watanabe *et al.* (18), who documented the complete suppression of ventricular arrhythmias in two patients with a diagnosis of CPVT, who were refractory to beta-blockers.

Verapamil has been reported to be beneficial in some case reports, but its long term effect is not known (19).

In addition to the pharmacologic treatment, there are several other therapeutic options. In patients who are refractory to maximal pharmacologic treatment, left cardiac sympathetic denervation (LCSD) can be performed, with significant reduction in arrhythmic events, as noted by De Ferrari *et al.* (20). However, the procedure is not widely available and is associated with complications such as pneumothorax and Horner syndrome (21, 22).

Finally, in patients who are refractory to maximal pharmacologic treatment and LCSD, when LCSD is not available or in patients with aborted cardiac arrest or recurrent syncope while on beta-blockers, guidelines indicate an implanted cardiac defibrillator (ICD) (12). It is very important to restrict the use of such a device to this high risk category of CPVT patients, as electric shocks may have a pro-arrhythmic effect, causing a vicious circle, ultimately leading to an electrical storm. Patients must be continued on pharmacologic therapy, and the device should be programmed with long delays before shock delivery and high cut-off rates, in order to avoid any unnecessary shocks. It is also important to note the high potential for post-implant complications in children, which is why such a decision should be made after careful assessment.

CONCLUSIONS

Catecholaminergic polymorphic ventricular tachycardia is a matter of great social importance, as it is responsible for a significant number of sudden cardiac deaths in the young population. Great progress has been made in identifying the underlying pathophysiologic mechanisms, and consequently, in the development of a targeted treatment. However, many aspects of the disease remain unknown.

Firstly, a third of the patients with a CPVT phenotype lack a genetic diagnosis, which is why further investigation of the underlying genetic mutations is necessary.

Secondly, there is an acute need for a risk stratification guideline, using both clinical and genetic factors, a task which will be accomplished in the future by creating large patient registries and bio-banks.

Furthermore, current diagnostic procedures are not standardized, which could lead to variability in diagnosis between centers. Also, there is no data certifying that diagnostic procedures should be similar for those with exercise induced symptoms and for patients symptomatic during emotional stress.

New treatment options are also needed, especially for those patients refractory to the medical therapy available at present. An interesting perspective for the future is gene-therapy, which entails a therapy targeted at correcting the genetic mutation responsible for the disease.

Also, some of the current treatment options, such as ICD therapy, might prove to be potentially harmful due to its proarrhythmic effects, whereas others might be more widely used in the future. ❑

Conflicts of interest: none declared.

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