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POSITION STATEMENT

An Update on the Diagnosis and Management of Catecholaminergic Polymorphic Ventricular Tachycardia☆

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Key Points

- Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) is a highly lethal inherited arrhythmia, characterised by polymorphic ventricular tachycardia induced by adrenergic stress.
- Causes of CPVT include autosomal dominant mutations the cardiac ryanodine receptor gene (*RYR2*) and less commonly autosomal mutations in the cardiac calsequestrin gene (*CASQ2)* and other gene defects.
- The heart is structurally normal and the baseline electrocardiograph (ECG) has no pathognomonic features although bradycardia may be present. Patients with CPVT often present with exercise or emotion induced syncope, the first presentation may also be sudden cardiac death.
- In addition to avoidance of triggers, treatment with beta blockers is the mainstay of therapy. Nadolol might be superior to other beta blocking agents.
- The addition of flecainide improves the effectiveness of medical therapy.
- There is increasing evidence regarding the efficacy of left cervical sympathetic denervation (LCSD).
- Implantable cardioverter defibrillators have a role and are part of current published guidelines. However, since DC shock can sustain or trigger a VT storm, they should only be prescribed after careful consideration of the additional diagnosis specific limitations in CPVT.

Introduction

This update follows the previously published ''Guidelines for the Diagnosis and Management of CPVT" [1]. The key points of difference are

- Genetic testing has become more significant
- Asymptomatic carriers of CPVT should be treated
- Recent studies show treatment efficacy of flecainide and left cervical sympathetic denervation (LSCD)
- The implantation of a cardioverter/defibrillator needs special considerations

Clinical Characteristics

Definition and Prevalence

Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) is an inherited arrhythmia, characterised by polymorphic ventricular tachycardia induced by adrenergic stress. Structural heart disease is absent and the baseline ECG is usually normal, however, sinus bradycardia, prominent u-waves and 'borderline' QT interval have been reported [2]. The true prevalence is unknown with estimates of approximately 1:10,000 although the prevalence may be currently underestimated. Polymorphic ventricular tachycardia is the result of uncontrolled calcium release from the sarcoplasmic reticulum [3].

☆Development of this expert opinion was co-ordinated by Associate Professor Andreas Pflaumer, Associate Professor Andrew Davis and members of the CSANZ Cardiovascular Genetic Diseases Council Writing Group.

☆☆The authors wrote the previous guidelines for the CSANZ Council [1] and were approved to write this update at the 2015 annual general meeting of the CSANZ Genetic Council.

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Clinical Presentation

Patients with CPVT often present with exercise or emotion induced syncope. Unfortunately, the first presentation can also be sudden cardiac death. Minor symptoms may include exercise induced palpitations, ventricular ectopy or dizziness. The mean age of presentation is between 6 and 10 years, although CPVT is a proven cause of sudden infant death and presentation as late as 40 years has been reported.

Patients presenting later in life are more likely to be female and less likely to have a mutation in RYR2 [4]. Studies show that about 30% of affected individuals become symptomatic before the age of 10 and 60% before the age of 20 years, only 20% of patients stay event free until the age of 50 years [4,5].

Clinical Diagnosis

CPVT should always be considered in the differential diagnosis of sudden cardiac arrest in the absence of structural cardiac disease, even when the event is not exercise related. Clinical diagnosis is made based on family history, exercise or emotional stress-induced symptoms and most importantly, exercise stress testing [6] or catecholamine infusion. In children, who are not able to perform exercise testing, Holter ECG and event recorders might be of additional help to make the diagnosis. It is the authors' experience that a tailored exercise test with sprinting rather than a Bruce protocol may be more likely to demonstrate diagnostic features of CPVT.

- Classically (but not uniformly) at a threshold heart rate above 100–120 beats per minute, isolated premature ventricular contractions become manifest followed by short runs of non-sustained VT.
- With continued exercise, VT duration often prolongs, and the VT may become sustained.
- A classical feature is the development of bidirectional ventricular tachycardia (Figure 1). Bidirectional ventricular tachycardia may be present but not visible in every ECG lead.
- The typical sequence noted above occurs in only about 30–40% of patients [5].
- Patients may develop polymorphic ventricular tachycardia (VT) or ventricular fibrillation (VF) without bidirectional ventricular tachycardia [6].
- Supraventricular tachyarrhythmias including atrial fibrillation are also common [7].

The clinical symptoms described might be found in other conditions:

- Exercise-related syncope is seen in Long QT syndrome (LQTS). LQTS can be present in patients with a normal QT interval.
- Andersen-Tawil syndrome (ATS-LQT7) is an inherited disorder caused by mutations in the KCNJ2 gene and characterised by QT prolongation and dysmorphic features and periodic paralysis. Patients with this condition commonly have prominent U waves and may also develop bidirectional VT.
- Congenital coronary abnormalities, arrhythmogenic right ventricular cardiomyopathy and hypertrophic cardiomyopathy might present with similar symptoms. Underlying structural heart disease can sometimes be subtle and appropriate imaging should be included in the workup.

Molecular Genetics

CPVT can be caused by mutations in the cardiac ryanodine receptor gene (*RYR2*), this is inherited in an autosomal

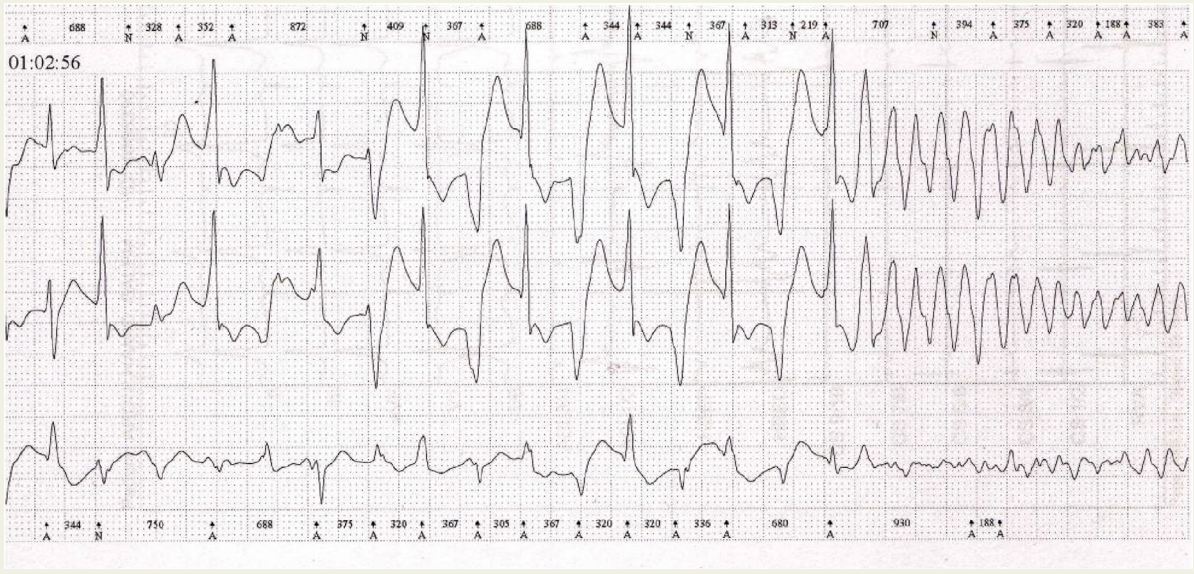

Figure 1 Bidirectional Ventricular Tachycardia degenerating to Ventricular Fibrillation in a patient who presented with a VF arrest.

dominant pattern. A less frequent cause is autosomal recessive inheritance caused by mutations in the cardiac calsequestrin gene *(CASQ2)*.

Both genes are involved in the release of calcium ions from the sarcoplasmic reticulum, for excitation–contraction coupling [8]. The presence of other, not yet identified, loci is postulated. Currently molecular genetic testing identifies heterozygous *RYR2* mutations in about 60% of probands and homozygous *CASQ2* mutations in about 4%.

Mutations in calmodulin (CALM1) have recently been shown to cause autosomal dominant CPVT but may also cause LQTS. Trans-2,3-enoyl-CoA reductase-like (TECRL) and Triadin (TRDN) mutations have been shown to cause autosomal recessive CPVT [9]. Mutations in Ankyrin and KCNJ2 might also cause a CPVT-like picture though these patients do not have all the features of typical CPVT.

Although routine genetic testing in Australia is not yet covered by Medicare, it can be performed in tertiary referral centres in Australia and New Zealand often as part of a multi gene panel using ''next generation'' sequencing. Comprehensive genetic testing is recommended for patients in whom a cardiologist has established a high clinical index of suspicion for CPVT, especially to help evaluate the first degree relatives [6]. The current yield of genetic testing in an index case with CPVT is in the range of 55–70% only [10].

Management

Asymptomatic Family Members

All first-degree relatives should be thoroughly evaluated with ECG, Holter monitoring and exercise stress testing. Echocardiography might be useful in cases where CPVT is not yet proven, seeking cardiomyopathic conditions. Cascade genetic testing is recommended if a definitive mutation is identified in a proband. [10].

The mean penetrance of RYR2 mutations is over 80%. Although probands are at higher risk of sudden death and syncope, studies suggest that treatment with beta blockers is indicated even in completely asymptomatic carriers [10].

Affected Individuals

Assessment of Risk

Patients who have had an episode of VF and those who have sustained or haemodynamically unstable VT while receiving beta blockers are considered at highest risk. Younger age at diagnosis is a predictor of future cardiac events [4]. Invasive EP studies are not helpful [5]. Genetic analysis does not yet contribute to risk stratification in clinically diagnosed patients.

Removal of Triggers

Either physical or emotional exertion can trigger ventricular tachycardia, although cardiac events have been recorded during normal activity and sleep [11]. As supraventricular tachycardia (SVT) can trigger ventricular arrhythmia any SVT should be well treated. The Heart Rhythm Society/European Heart Rhythm Association/Asia Pacific Heart Rhythm Society (HRS/EHRA/APHRS) expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes recommends guidance regarding athletic activity be made after a comprehensive evaluation by a heart rhythm specialist with appropriate experience in this field. The individual and family must be well informed and have an action plan in place which may include a personal or family advisory defibrillator. Symptomatic, genotype positive athletes may consider participating in sports once adequate control is achieved for a minimum of 3 months. If it is not possible with therapy to eliminate exercise induced ventricular contractions in bigeminy, couplets or VT then participation in competitive sports, (particularly swimming) is not recommended [12].

Beta Blockade

Beta blockers are indicated for all patients diagnosed with CPVT [6,12]. Compliance with medication is a critical issue, especially in the adolescent age group.

Beta blockade should be titrated up to an effective level. High doses are usually required. Therapy may be guided by exercise testing and Holter monitoring to ensure that an appropriate dose has been achieved. Missing doses can allow occurrence of lethal arrhythmias. Although beta blockers are effective in many, events despite medication are seen in 25–30% of patients with a follow-up of 5 years [5,13]. Nadolol has been recommended by a consensus document of the HRS as the preferred beta blocker, supported by a study of Hayashi [4] and Leren [14]. Nadolol in Australia is currently only available through the Special Access Scheme, Category C.

Flecainide

There is strong evidence that flecainide is effective in treating CPVT [15] When flecainide is prescribed it should be given in addition to beta blockers [6]. Recent, limited data shows efficacy in up to 95% in children [11] and similar data in adults [16]. Additional evidence for flecainide comes from a randomised trial showing that the addition of flecainide significantly reduced ventricular ectopy during exercise compared with placebo plus β-blocker and β-blocker alone [17].

Left Cervical Sympathetic Denervation (LSCD)

There is increasing evidence that LSCD can suppress breakthrough cardiac events in about 70% of patients with previous events [18]. Current published guidelines have not yet incorporated this data and although data is limited the authors feel that minimally invasive thoracoscopic LSCD is likely to be increasingly used in various situations including:

1. Patients in whom beta blockers are contra-indicated or not adhered to
2. Before an automated implantable cardioverter defibrillator (AICD) is placed, cannot be placed, or is not wanted.
3. Breakthrough episodes in those with an AICD despite optimal medical treatment with beta blockers and flecainide.

Cardioverter Defibrillators (ICD)

There are special considerations with respect to the use of ICDs in CPVT. Firstly, a shock in and of itself may cause an adrenergic surge causing further VT/VF and even potentially lethal electrical storm and deaths have been reported [19]. Secondly, it has now been shown that shocks are not efficacious during polymorphic or bidirectional VT [20] and it is recommended that the ICD be programmed with long detection times [21].

According to the currently available Guidelines, implantation of an ICD with use of beta blockers is considered to be a Class I indication for patients with CPVT who are survivors of cardiac arrest and have a good functional status [22]. Patients with CPVT who experience syncope or sustained VT while receiving beta blockers are considered to have a Class IIa indication for an ICD implantation [12]. One could argue that all patients with CPVT requiring an ICD should have LCSD to decrease the chance of storm, at least in centres where this is readily available thoracoscopically with minimal complication. In addition, we speculate that increasing use of combined therapy with beta blocker, flecainide and LCSD may appropriately decrease the prescription of ICDs in children but more data is needed to confirm this as an appropriate approach.

Psychological Care

Of paramount importance is the fact that a diagnosis of CPVT is a giant burden for children and adolescents as well as their families. Appropriate psychological support should be strongly considered early [23].

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