



The Cardiac Society of Australia and New Zealand

Guidelines for the Diagnosis and Management of Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT)

Development of these guidelines was co-ordinated by Dr. Andreas Pflaumer, Associate Professor Andrew Davis and members of the CSANZ Cardiovascular Genetic Diseases Council Writing Group. No authors have any relevant Conflict of Interest to disclose.

It was reviewed by the Quality Standards Committee and ratified at the CSANZ Board meeting held on Friday, 25th November 2016.

KEY POINTS:

- Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) is a highly lethal inherited arrhythmia, characterized 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 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.
- The addition of flecainide is helpful and increases the effectiveness of medical therapy.
- There is increasing evidence about efficacy of Left cervical sympathetic denervation (LCSD),
- Implantable cardioverter-defibrillators have a role and are part of current published guidelines but should only be prescribed after careful consideration of the additional diagnosis specific limitations in CPVT.

CLINICAL CHARACTERISTICS

Definition and prevalence

Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) is an inherited arrhythmia, characterized 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 [1]. The true prevalence is unknown with estimates of approximately 1:10000 although the prevalence may be currently underestimated. Polymorphic ventricular tachycardia is the result of uncontrolled calcium release from the sarcoplasmic reticulum [2].

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 [3]. 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 [3,4].

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 [5] 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 [4]
- Patients may develop polymorphic VT or VF without bidirectional ventricular tachycardia [5] .
- Supraventricular tachyarrhythmias including atrial fibrillation are also common [6].

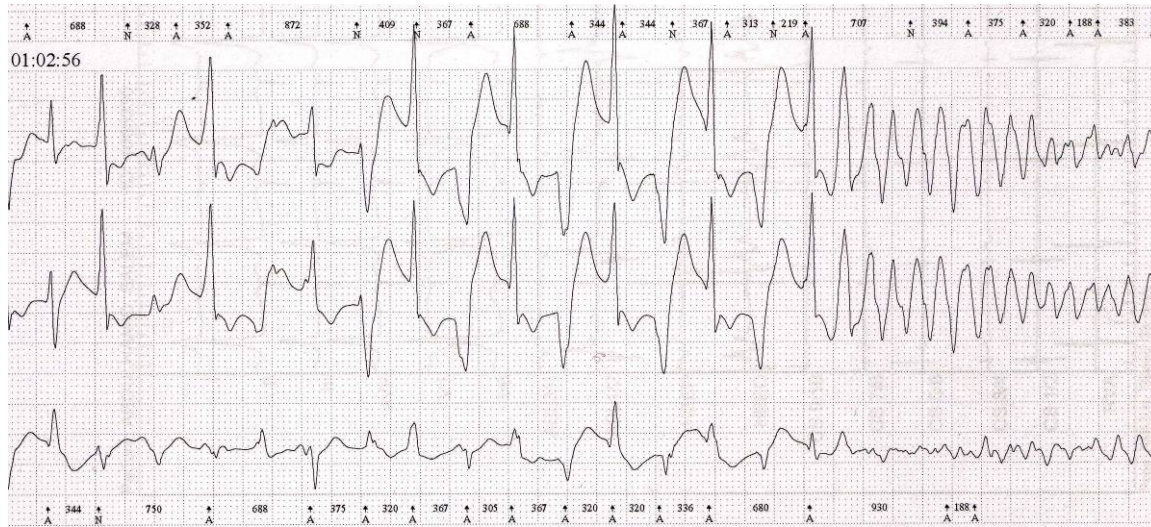


Figure 1: Bidirectional Ventricular Tachycardia degenerating to Ventricular Fibrillation in a patient who presented with a VF arrest

The clinical symptoms described might be found in other conditions:

- Exercise-related syncope is seen in LQT 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 characterized 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 the cardiac ryanodine receptor gene (*RYR2*), this is inherited in an autosomal dominant pattern. A less frequently 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 [7]. 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. Triadin (*TRDN*) mutations have been shown to cause autosomal recessive CPVT. Mutations in Ankyrin and *KCNJ2* might also cause a CPVT like picture though these patients do not have all the features of typical CPVT [8,9].

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 evaluating the first degree relatives [5]. The current yield of genetic testing in an index case with CPVT is in the range of 55%-70% only [6].

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. [6].

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 [6].

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 [3]. Invasive EP studies are not helpful [4]. 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 [7]. As supraventricular tachycardia (SVT) can trigger ventricular arrhythmia any SVT should be well treated. The HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes recommends the following lifestyle changes are made in all patients with a diagnosis of CPVT: a. Limit/avoid competitive sports; b. Limit/avoid strenuous exercise and c. Limit exposure to stressful environments [8].

Beta-Blockade:

Beta-Blockers are indicated for all patients diagnosed with CPVT [5,8]. 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 five years [4,9].

Flecainide:

There is strong evidence that flecainide is effective in treating CPVT[10] When flecainide is prescribed it should be given in addition to beta blockers [5]. Recent, limited data shows efficacy in up to 95% in children [7] and similar data in adults [11].

Left cervical sympathetic denervation (LSCD)

There is increasing evidence that LSCD can suppress breakthrough cardiac events in about 70% of patients with previous events [12]. Current published guidelines have not yet incorporated this data and although data is limited the authors feel that minimally invasive thoracoscopic LCS D 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 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 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 [13]. Secondly it has now been shown that shocks are not efficacious during polymorphic or bidirectional VT [14] and it is recommended that the ICD be programmed with long detection times [15].

According to the current available Guidelines, implantation of an ICD with use of beta-blockers are considered to be a class I indication for patients with CPVT who are survivors of cardiac arrest and have a good functional status. 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 [16]. 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 [17].

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Useful Websites for patients and family

www.cidg.org (Cardiac inherited disease group New Zealand)

www.stopSADS.org (US page – Link to Australian group)

REFERENCES

- [1] SY RW, Gollob MH, Klein GJ, Yee R, Skanes AC, Gula LJ, et al. Arrhythmia characterization and long-term outcomes in catecholaminergic polymorphic ventricular tachycardia. *Heart Rhythm Journal* 2011;8:864–71.
- [2] Liu N, Rizzi N, Boveri L, Priori SG. Ryanodine receptor and calsequestrin in arrhythmogenesis: what we have learnt from genetic diseases and transgenic mice. *J Mol Cell Cardiol* 2009;46:149–59.
- [3] Hayashi M, Denjoy I, Extramiana F, Maltret A, Buisson NR, Lupoglazoff J-M, et al. Incidence and risk factors of arrhythmic events in catecholaminergic polymorphic ventricular tachycardia. *Circulation* 2009;119:2426–34.
- [4] Priori SG, Napolitano C, Memmi M, Colombi B, Drago F, Gasparini M, et al. Clinical and molecular characterization of patients with catecholaminergic polymorphic ventricular tachycardia. *Circulation* 2002;106:69–74.
- [5] Authors/ Task Force Members, Priori SG, Blomstrom-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, et al. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC) Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). *Eur Heart J* 2015.

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- [6] Ackerman MJ, Priori SG, Willems S, Berul C, Brugada R, Calkins H, et al. HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies this document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA). *Heart Rhythm Journal* 2011;8:1308–39.
- [7] Roston TM, Vinocur JM, Maginot KR, Mohammed S, Salerno JC, Etheridge SP, et al. Catecholaminergic Polymorphic Ventricular Tachycardia in Children: An Analysis of Therapeutic Strategies and Outcomes from an International Multicenter Registry. *Circ Arrhythm Electrophysiol* 2015;8:633–42.
- [8] Priori SG, Wilde AA, Horie M, Cho Y, Behr ER, Berul C, et al. HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes: document endorsed by HRS, EHRA, and APHRS in May 2013 and by ACCF, AHA, PACES, and AEPC in June 2013. *Heart Rhythm* 2013;12: 1932-63.
- [9] Sumitomo N, Harada K, Nagashima M, Yasuda T, Nakamura Y, Aragaki Y, et al. Catecholaminergic polymorphic ventricular tachycardia: electrocardiographic characteristics and optimal therapeutic strategies to prevent sudden death. *Heart* 2003;89:66–70.
- [10] Bannister ML, Thomas NL, Sikkell MB, Mukherjee S, Maxwell C, MacLeod KT, et al. The mechanism of flecainide action in CPVT does not involve a direct effect on RyR2. *Circ Res* 2015;116:1324–35.
- [11] Khoury A, Marai I, Suleiman M, Blich M, Lorber A, Gepstein L, et al. Flecainide therapy suppresses exercise-induced ventricular arrhythmias in patients with CASQ2-associated catecholaminergic polymorphic ventricular tachycardia. *Heart Rhythm Journal* 2013;10:1671–5.
- [12] De Ferrari GM, Dusi V, Spazzolini C, Bos JM, Abrams DJ, Berul CI, et al. Clinical Management of Catecholaminergic Polymorphic Ventricular Tachycardia: The Role of Left Cardiac Sympathetic Denervation. *Circulation* 2015;131:2185–93.
- [13] Pizzale S, Gollob MH, Gow R, Birnie DH. Sudden death in a young man with catecholaminergic polymorphic ventricular tachycardia and paroxysmal atrial fibrillation. *J Cardiovasc Electrophysiol* 2008;19:1319–21.

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- [14] Miyake CY, Webster G, Czosek RJ, Kantoch MJ, Dubin AM, Avasarala K, et al. Efficacy of implantable cardioverter defibrillators in young patients with catecholaminergic polymorphic ventricular tachycardia: success depends on substrate. *Circ Arrhythm Electrophysiol* 2013;6:579–87.
- [15] Tan VH, Wilton SB, Kuriachan V, Sumner GL, Exner DV. Impact of programming strategies aimed at reducing nonessential implantable cardioverter defibrillator therapies on mortality: a systematic review and meta-analysis. *Circ Arrhythm Electrophysiol* 2014;7:164–70.
- [16] Zipes DP, Camm AJ, Borggrefe M, Buxton AE, Chaitman B, Fromer M, et al. ACC/AHA/ESC 2006 Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (writing committee to develop Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Circulation* 2006;114:e385–484.
- [17] Guidelines for Genetic Testing of Inherited Cardiac Disorders Ingles, Jodie et al. *Heart, Lung and Circulation* , Volume 20 , Issue 11 , 681 - 687