The Cardiac Society of Australia and New Zealand

Guidelines for the diagnosis and management of Catecholaminergic Polymorphic Ventricular Tachycardia

Development of these guidelines was co-ordinated by Dr Andreas Pflaumer, Dr Andrew Davis and members of the Cardiovascular Genetic Diseases Council Writing Group.

The guidelines were reviewed by the Continuing Education and Recertification Committee and ratified at the CSANZ Board meeting held on Wednesday, 10th August 2011.

1. Clinical Characteristics

1.1 Definition and prevalence

Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) is an inherited arrhythmia syndrome, characterized by polymorphic ventricular tachycardia induced by adrenergic stress. Structural heart disease is usually absent and the baseline ECG is usually normal however bradycardia and 'borderline' QT interval have been reported. Exact prevalence is unknown with estimates of approximately 1:10000.

1.2 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 are exercised induced palpitations or dizziness. The mean age of presentation is around 6-10 years, although CPVT is a proven cause of sudden infant death and presentation as late as 40 years has been reported. Limited data from small studies show that about 35% of affected individuals become symptomatic before the age of 10 and 75% before the age of 20 years.

1.3 Clinical diagnosis

In patients presenting with sudden cardiac arrest in the absence of structural cardiac disease CPVT should always be considered in the differential diagnosis. Clinical diagnosis is made based on family history, exercise- or emotional stress-induced symptoms and – most important - **response to exercise** or catecholamine infusion. In children, who are not able to perform exercise testing, Holter ECG and event recorders might be of additional help to detect the typical ECG findings during exercise or emotional stress.

- Classically at a certain heart rate threshold above 100-120 beats per minute, isolated premature ventricular contractions develop first, 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 subsequent development of bidirectional ventricular tachycardia (see Figure 1)
- The above typical sequence is not always seen.[1]
- Patients may develop polymorphic VT or VF without the QRS vector alternans.[2]
- Exercise induced supraventricular tachyarrhythmias including atrial fibrillation in this patient group are common [3].

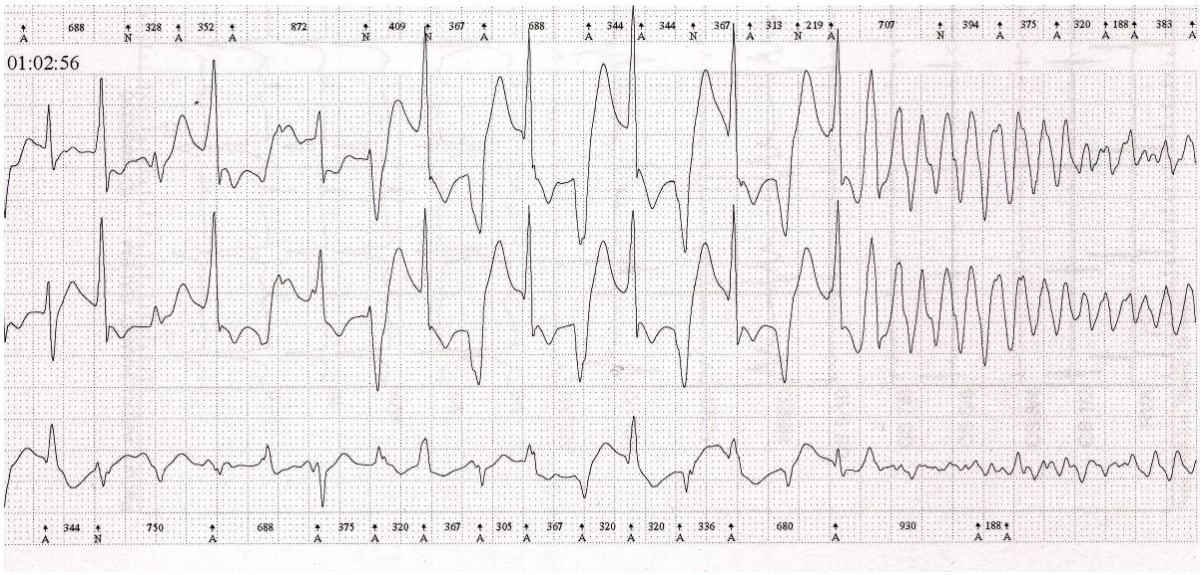


Figure 1: Bidirectional Ventricular Tachycardia degenerating to Ventricular Fibrillation

The clinical symptoms described might be found in other conditions:

- Exercise-related syncope is also found in LQT syndrome. LQT syndrome can be present in patients with normal QT interval.
- Andersen-Tawil syndrome (ATS) is an inherited arrhythmogenic disorder caused by mutations in the KCNJ2 gene and characterized by QT prolongation and distinctive facial features. Patients with this condition may also develop bidirectional VT
- Coronary abnormalities, ARVD and hypertrophic cardiomyopathy might present with similar symptoms. The underlying structural heart disease can be subtle, therefore adequate imaging should be included in the workup.

2. 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.[4] The presence of other not yet identified loci is postulated. Currently molecular genetic testing identifies heterozygous *RYR2* mutations in about half of probands and homozygous *CASQ2* mutations in about 2%. Recently a report has been published, showing that even heterozygous CASQ2 mutations might cause the clinical picture of CPVT

Genetic testing is not yet commercially available and confined to research studies in NZ and Australia.

3. Management

3.1 Affected individuals

Assessment of risk:
Up to now there are insufficient data for satisfactory risk stratification. 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 CPVT diagnosis is a predictor of future cardiac events.[6] Invasive EP studies are not helpful.[1] 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 CPVT is not mentioned in the "Recommendations for Physical Activity and Recreational Sports Participation for Young Patients With Genetic Cardiovascular Diseases" published by the AHA in 2004[5], the recommendations for patients with CPVT could be extrapolated from the LQTS guidelines, due to the similarity of the triggers in LQTS and CPVT.

Beta Blockade:
Beta Blockers are indicated for all patients who are clinically diagnosed with CPVT on the basis of the presence of spontaneous or documented stressed-induced ventricular arrhythmias (currently a class I indication).[7]

Beta Blockade should be initiated and then 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 provoke lethal arrhythmias. There are few data regarding efficacy of different beta blockers.[6]

Calcium Channel Blockers:
Two studies showed some advantage of combining beta blocking agents with calcium channel blocker (verapamil)[8,9], although this could not yet be demonstrated in a long-term study.

Flecainide:
There is strong evidence that flecainide is helpful in treating CPVT by inhibiting cardiac ryanodine receptor-mediated Ca^{2+} release.[10] This is appealing, as the underlying molecular defect is directly targeted. Further studies are currently underway to examine this approach. When flecainide is prescribed it should be done in addition to beta blockers.

Cardioverter-defibrillators (ICD):
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.[7] 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.

An ICD might be of consideration in selected high risk patients having a strong family history of sudden death. It must always be remembered that children have a higher risk of ICD complications than adults.

ICD treatment without concomitant use of beta blockers is dangerous because of the risk of electrical storm induced by the adrenergic surge related to a shock.[11, 12]

Left cervical sympathectomy:
Selective left cervical sympathectomy, which can now be done thoracoscopically, may be considered for:
1. Patients in whom beta blockers are contra-indicated or not adhered to
2. An AICD cannot be placed or is not wanted.
3. Recurrent VT in those with an AICD despite maximal medical treatment [13-15].

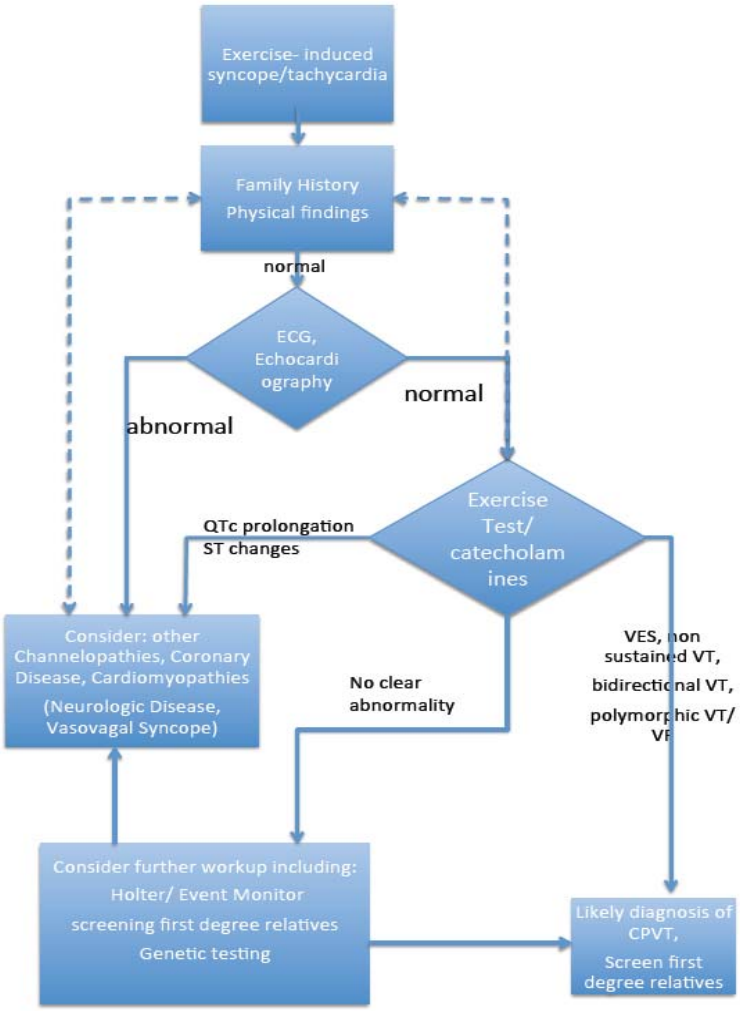
3.2 Asymptomatic family members

All first degree relatives should be evaluated with ECG, Holter monitoring and exercise stress testing. Echocardiography might be useful in cases where CPVT is not yet proven in the family or overlap with other conditions might be suspected.

Genetic analysis might identify silent carriers of CPVT – related mutations. The mean penetrance of RYR2 mutations is over 80%. Recent studies suggest that it is indicated to treat even completely symptom free carriers with beta blockers.[6] As a consequence cascade genetic testing should be considered in conjunction with genetic counselling.[16]

4. Further Information

4.1 Flowchart



Useful Websites for patients and family

www.cidg.org (Cardiac Inherited Disease Group New Zealand)
www.sads.org/sads-australia

4.2. References

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