Πολύμορφη κατεχολαμινεργική κοιλιακή ταχυκαρδία: Θα πρέπει όλοι οι ασθενείς να λαμβάνουν θεραπεία;

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Catecholaminergic polymorphic ventricular tachycardia (CPVT)

- **channelopathy**, without apparent structural heart disease

- heterogeneous disease characterized by
  - normal resting ECG, and
  - ventricular events triggered by
  - exercise, acute emotion, stress-induced or adrenergically mediated
  - premature ventricular contractions (PVCs),
  - polymorphic ventricular tachycardia (PVT), and/or bidirectional VT (BVT), with recurrent character and
  - CPVT1 is frequently associated with sinus bradycardia (20%) and supraventricular tachycardia (16-26%). Even multifocal atrial tachycardia is not rare

- In approximately **25%** of symptomatic patients, cardiac events are precipitated by only normal wakeful rest and **normal daily activities** challenging the paradigm that CPVT arrhythmias are isolated to times of adrenergic stress
- usually when the heart rate (HR) gets >120 bpm
- Mean HR during CPVT is 192 bpm.
- Most cases are NSVTs (≈70%), but ≈20% are SVTs and 7% are associated with VF
- PVT and BVT in association are observed in ≈20% of cases in the pediatric group
Age and Prevalence

- **Prevalence**: It is estimated ≈1–5,000/10,000 people
- **Familial occurrence**: ≈30% of cases
- From *early childhood to early adulthood*, with an average between 2 and 21 years
- Approximately 30% of affected individuals will experience symptoms *before the age of 10 years* and
  - the majority (60% to 80%) of patients will have one or more symptomatic arrhythmia episodes *before age 40*
- In the CPVT-1 and CPVT-3 subtypes, the onset of symptoms occurs at ≈10 years;
  - CPVT-2 at ≈7 years
  - CPVT-4 at ≈4 years
  - CPVT-5 at ≈2.26 years
- in the *nongenotyped variant*, CPVT becomes symptomatic later in life.
The high de novo rate may be explained by the high lethality rate during childhood and adolescence.
Ryanodine  RyR2
Calsequestrin 2 CASQ2
Triadin
Calmodulin
• 1. Presence of a structurally normal heart, normal ECG, and unexplained exercise or catecholamine-induced BVT, polymorphic PVCs or VT in individuals <40 years of age

• 2. Patients (proband or family member) who have a pathogenic mutation

• 3. Family members of a CPVT index case with a normal heart who manifests exercise-induced PVCs or BVT/PVT

• 4. Presence of a structurally normal heart and coronary arteries, normal ECG, and unexplained exercise or catecholamine-induced BVT, polymorphic PVCs or VT in individuals >40 years of age.
Prognosis

• Data from the recent PACES CPVT Registry suggest that

• **Sudden death** is reported in up to *30% as an initial presentation* and in approximately *half of patients by 20–30 years* of age

• three of every four children present with **life-threatening symptoms**

• Even after initiation of **medical treatment**, high-risk ventricular arrhythmias were induced during exercise stress test in most RyR2-positive CPVT

• **diagnostic delay** of >1 year occurs in 38% of these cases
Algorithms for risk stratification in CPVT

- **Probands** are at higher risk of life-threatening arrhythmias and treatment failure events than their affected relatives.

- **CPVT1** may also confer a higher risk of life threatening events compared with genetically elusive disease.

- The PACES CPVT Registry has also suggested an association between life-threatening events and **mutations in specific regions of RyR2** (C-terminal region of RyR2)
• The difficulty in predicting phenotype on the basis of genotype alone is likely influenced by a variety of factors, including
  – incomplete familial penetrance
  – unidentified genetic modifiers, and
  – a limited knowledge of pathogenicity for many novel mutations

• Its rarity and heterogeneity make it difficult to assemble populations large enough to reach meaningful conclusions

• The International CPVT Registry based out of Amsterdam has been enrolling since 2013.

• Paediatric partner registry, based in Vancouver, BC, includes children with CPVT and their first-degree relatives.

• Combined, these registries have enrolled over 400 subjects to date. (2017)
A greatest challenge is the **poor predictive value of exercise testing**.

In one large family of >1000 relatives, the initial exercise test was *normal in 72% of mutation-positive patients*.

Life-threatening events, including *sudden death*, have also been known to occur *despite normal exercise testing*.

In 2012, Hayashi et al reported exercise testing as having *low sensitivity (62%) and specificity (67%) for predicting future arrhythmic events* in 67 asymptomatic relatives of proband cases.

Indirect data from studies on medications and interventions suggest that risk stratification based on arrhythmic burden on exercise testing is a helpful tool.

**Out of necessity**, the exercise test is used to *aid clinical decision making*, and the expert consensus guidelines recommend *therapeutic escalation* on the basis of exercise-provoked arrhythmias.
Life style measurements

- advising against participation in **competitive sports** and
- emphasizing the great importance of **drug compliance** are essential.
- In addition, CPVT patients should be informed that the use of sympathomimetic agents is contraindicated.
therapy

• (step 1) should be a **β-blocker** in the highest tolerable dose, preferably nadolol.
  - Even with appropriate use of beta-blockers up to one third of CPVT patients may experience recurrent arrhythmic events or show persistence of complex arrhythmias at exercise stress test

• (step 2) addition of **flecainide** is preferred and more effective when β-blocker therapy fails

• (step 3) In patients resistant to combination therapy with β-blocker and flecainide, either LCSD should be performed or an ICD should be implanted

• Left cardiac sympathetic denervation may be preferred when an expert surgeon is available to perform this procedure

• Every next step and/or change in drug type or dose should probably be carefully monitored by exercise testing, and, if necessary and possible, Holter monitoring or ICD interrogation.
Oral antiarrhythmic drug therapy in CPVT

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
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<tbody>
<tr>
<td>Nadolol</td>
<td>40-320 mg/day</td>
</tr>
<tr>
<td>Propranolol</td>
<td>2-4 mg/kg/day (subdivided into 3-4 doses per day)</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>1.4 ±0.7 mg/kg/day</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>0.14 ±0.01 mg/kg/day</td>
</tr>
<tr>
<td>Flecaainide</td>
<td>100-300 mg/day</td>
</tr>
<tr>
<td>Propafenone</td>
<td>300-900 mg/day</td>
</tr>
<tr>
<td>Verapamil</td>
<td>240-480 mg/day (subdivided into 3-4 doses per day)</td>
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</tbody>
</table>

NB: Exercise test should be performed to adjust the antiarrhythmic drugs dosage in order to prevent ventricular tachycardia appearance as well.
**ICD**

- **Candidates** are patients who have survived a cardiac arrest or those who have experienced syncope or sustained VT despite optimal medical therapy and LCSD.

- CPVT subjects with ICD have to continue BB and eventually also Flecainide, in order to avoid ICD shocks.

- **ICD lacking in interrupting polymorphic or bi-directional VT** has often been described in literature, whilst the shocks are more effective in case of ventricular fibrillation.

- In a recent meta-analysis, it has been demonstrated that **inappropriate shocks** are significantly more common in CPVT than in other hereditary arrhythmic syndromes (36% vs 20%), most of all during supraventricular arrhythmias episodes.

- Lastly, 85% of those with CPVT and ICD suffer from related to device (minor and major) **complications**.
Proposed treatment strategy

• there is a lack of data to identify CPVT patients with such a low risk of arrhythmic events that would make treatment unnecessary.

• Thus, all phenotypically and/or genotypically diagnosed CPVT patients should receive appropriate therapy.

• Since cardiac arrest may occur also in silent carriers of a pathogenic mutation, these patients need to receive beta-blockers even when they do not exhibit arrhythmias during exercise stress testing. (Hayashi et al. 2012, 13% mutation carriers with negative exercise stress test had a cardiac arrest during follow-up, in the absence of therapy)

• although in clinical practice exceptions are (and probably can safely be) made in asymptomatic patients over ~60 years of age who are newly diagnosed by cascade screening
ΕΥΧΑΡΙΣΤΩ
• More than three-quarters will be symptomatic by the fifth decade of life
• Familiarity for repeated syncopes and SCD is present in 30% of individuals with CPVT with age being less than 40

• mortality rate in untreated individuals is 30%-50% by age 40

• Even after initiation of medical treatment, high-risk ventricular arrhythmias were induced during exercise stress test in most RyR2-positive CPVT
• strict exercise restriction
• Implantable cardioverter defibrillator (ICD) is necessary for prophylaxis of SCD because ≈30% of patients still experience VTs that may arise in certain specific areas but the prognosis is poor
Genetic types

CPVT has been mapped on chromosomes 1, 7, 14, 4, and 17.

Genetic analysis identifies two main groups and related entities:
1. With mutation or juvenile
2. Sporadic or nongenotyped:
   These are predominantly women and become symptomatic later in life.
   Incidence: ≈30%; M/F ratio: F>M;
   Inheritance: sporadic or gene-negative CPVT;
   Onset of symptoms: >20 years.
3. CPVT-related entities
• PVCs with quadrigeminy, trigeminy, and bigeminy
• shorter or longer salvoes of BVT and
• bursts of rapid, irregular PVT
• VTs elicited exclusively by exercise or adrenergic stress.
• Mean HR during CPVT is 192 bpm.
• Most cases are NSVTs (∼70%), but ∼20% are SVTs and 7% are associated with VF
• PVT and BVT in association are observed in ∼20% of cases in the pediatric group
• 100% inducement of CPVT by exercise, 75% by catecholamine infusion, and none by programmed ventricular stimulation
Expert Consensus Recommendations on CPVT Diagnosis

1. CPVT is diagnosed in the presence of a structurally normal heart, normal ECG, and unexplained exercise or catecholamine-induced bidirectional VT or polymorphic ventricular premature beats (VPBs) or VT in an individual younger than 40 years.

2. CPVT is diagnosed in patients (index case or family member) who have a pathogenic mutation.

3. CPVT is diagnosed in family members of a CPVT index case with a normal heart who manifest exercise-induced premature ventricular contractions or bidirectional/ polymorphic VT.

4. CPVT can be diagnosed in the presence of a structurally normal heart and coronary arteries, normal ECG, and unexplained exercise or catecholamine-induced bidirectional VT or polymorphic VPBs or VT in an individual older than 40 years.
• A Focus on Pharmacological Management of Catecholaminergic Polymorphic Ventricular Tachycardia.
• Claudio B1, Alice M2, Daniel S2
Classic polymorphic ventricular tachycardia
• A high index of suspicion is essential in evaluating patients with exertional or emotionally induced syncope or sudden cardiac arrest, as this is a hallmark of disease, and treatment is usually life-saving.

• In addition, children may also suffer cardiac events at rest or events triggered by normal daily activities, and it is important to bear in mind that non-exertional triggers do not preclude a diagnosis of CPVT.
Cascade screening of 15 Dutch families revealed de novo RyR2 variants in nearly half of the family probands. This high de novo rate may be explained by the high lethality rate during childhood and adolescence.
### Expert Consensus Recommendations on CPVT Therapeutic Interventions

<table>
<thead>
<tr>
<th>Class</th>
<th>Statement</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>The following lifestyle changes are recommended in all patients with a diagnosis of CPVT:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>a. Limit/avoid competitive sports</td>
<td></td>
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<tr>
<td></td>
<td>b. Limit/avoid strenuous exercise</td>
<td></td>
</tr>
<tr>
<td></td>
<td>c. Limit exposure to stressful environments.</td>
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<tr>
<td></td>
<td>2. Beta-blockers are recommended in all symptomatic patients with a diagnosis of CPVT.</td>
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<td></td>
<td>3. ICD implantation is recommended in patients with a diagnosis of CPVT who experience cardiac arrest, recurrent syncope or polymorphic/bidirectional VT despite optimal medical management, and/or LCSD.</td>
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</tr>
</tbody>
</table>

**Executive summary:** HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes

Silvia G. Priori, Arthur A. Wilde, Minoru Horie, Yongkeun Cho, Elijah R. Behr, Charles Berul, Nico Blom, Josep Brugada, Chern-En Chiang, Heikki Huikuri, ... Show more

*EP Europace*, Volume 15, Issue 10, 1 October 2013, Pages 1389–1406,
<table>
<thead>
<tr>
<th>Class</th>
<th>4. Flecaïnide can be a useful addition to beta-blockers in patients with a diagnosis of CPVT who experience recurrent syncope or polymorphic/bidirectional VT while on beta-blockers.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5. Beta-blockers can be useful in carriers of a pathogenic CPVT mutation without clinical manifestations of CPVT (concealed mutation-positive patients).</td>
</tr>
<tr>
<td>Class</td>
<td>6. LCSD may be considered in patients with a diagnosis of CPVT who experience recurrent syncope or polymorphic/bidirectional VT/several appropriate ICD shocks while on beta-blockers and in patients who are intolerant or with contraindication to beta-blockers.</td>
</tr>
<tr>
<td>III</td>
<td>7. ICD as a stand-alone therapy is not indicated in an asymptomatic patient with a diagnosis of CPVT.</td>
</tr>
<tr>
<td></td>
<td>8. Programmed electrical stimulation is not indicated in CPVT patients.</td>
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• Painful shocks by ICD can increase the sympathetic tone and trigger further arrhythmias, leading to a malignant cycle of ICD shocks and even death. Because of this, the ICD should be programmed with long delays before shock delivery and high cutoff rates.
Challenges concerning genetics in CPVT:
- Almost one third of CPVT cases remain genotype-unknown;
- In addition to the classical forms of CPVT, there are also life-threatening diseases that may be phenocopies, such as Long QT Syndrome type 4 and 7.

Potential solutions:
- Next generation sequencing, massive DNA screening and well-maintained biobanks of patient samples will help to identify new genes for these cases that are currently genotype-unknown.
Approximately 30% of affected individuals will experience symptoms before the age of 10 years and the majority (60% to 80%) of patients will have one or more symptomatic arrhythmia episodes before age 40.
• In genetically elusive families, it is important to monitor potentially at-risk relatives with serial exercise testing to avoid missing the diagnosis.

• The PACES CPVT Registry has also suggested an association between life-threatening events and mutations in specific regions of RyR2

• higher incidence of non-sustained ventricular tachycardia in patients with mutations that localised to the C-terminal region of RyR2

• Further complicating factors in risk stratification are variants of unknown significance and incomplete penetrance in families

• Collectively, these data support the existence of genotypic and arrhythmic predictors of cardiac events, however, larger studies of unselected populations are needed before these prognosticators can be used to inform therapeutic decisions.
• observed in the pediatric, adolescent, or juvenile adult age group.
• Rarely, it is the underlying cause of sudden infant death syndrome (SIDS) and juvenile SCD,
• exerting a deep social impact, due to the young age of the victims and the unexpected occurrence of them.
Inheritance

• may be autosomal dominant (AD) (mutations of the cardiac Ryanodine receptor gene (RyR2))

• or recessive associated with mutations in the gene encoding the cardiac isoform of calsequestrin, with high penetrance.
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Beta blockers (BB) are prescribed in secondary prevention (Class I recommendation) [11], as well as in primary in individuals with a genetic mutation among those responsible for CPVT, since the first disease manifestation may be SCD (Class IIa recommendation)