Tachycardie ventriculaire catécholergique

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Tachycardies ventriculaires catécholergiques

- CPVT is a rare (1:10,000) and one of the most malignant inherited arrhythmogenic disorders
- It is characterized by adrenergic-induced premature ventricular complexes (PVCs), polymorphic or bidirectional VT or sudden death, usually associated with vigorous physical exercise or mental stress.
- Beta-blockers are the standard therapy in CPVT, although evidence of treatment failure has grown recently.

Tachycardies ventriculaires catécholergiques

- Children: 2 y. < age < 15 y., experiencing syncope during typical circumstances: emotion, stress, exercice, noyade (1)
- Neurologic symptoms: seizures
- History of familial sudden cardiac death/syncope, same circumstances
- Normal basal EKG (QTc), bradycardia
- No morphologic cardiac abnormality

From 236 patients, 25% had atypical triggers

Tachycardies ventriculaires catécholergiques

- ESV polymorphes à l’effort :
  - ESV isolées,
  - Bigéminisme
  - Salves polymorphes
  - TV bidirectionnelles et TV polymorphes

- Reproductibilité :
  - Effort (Holter/ ECGE) si FC > 110 bpm
  - Sous isoprotéronol
  - Non inductibilité EEP

### Executive Summary

HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes.

### 2015 ESC Guidelines

For the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death.

### 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.

### Diagnosis of catecholaminergic polymorphic ventricular tachycardia

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class^a</th>
<th>Level^b</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPVT is diagnosed in the presence of a structurally normal heart, normal ECG and exercise- or emotion-induced bidirectional or polymorphic VT.</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>CPVT is diagnosed in patients who are carriers of a pathogenic mutation(s) in the genes RyR2 or CASQ2.</td>
<td>I</td>
<td>C</td>
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*Europace. 2015;17:1601-87.*
Approximately 50% to 60% of CPVT = heritable or sporadic mutations in the RYR2-encoded cardiac ryanodine receptor/calcium release channel

- a critical regulator of intracellular calcium
- RYR2 is one of the largest genes in the human genome, 105 translated exons, encodes for a protein containing 4,967 amino acids

Rare autosomal recessive subtypes = mutations in CASQ2-encoded calsequestrin 2 (CPVT2) or TRDN encoding the junctional protein triadin (CPVT4).

- Mutations in CALM1 encoding calmodulin were discovered recently in 1 family with autosomal dominant CPVT-like phenotype (CPVT5)
- Mutations in the KCNJ2-encoded Kir2.1 can express a clinical phenotype that mimics autosomal dominant CPVT
Tachycardies ventriculaires catécholergiques

Incidence and Risk Factors of Arrhythmic Events in Catecholaminergic Polymorphic Ventricular Tachycardia

No. at risk
Cardiac event 101 84 67 49 32 23 12 7 6 3 1
Fatal or near-fatal event 101 88 69 56 39 30 14 8 6 3 1

Tachycardies ventriculaires catécholergiques

Incidence and Risk Factors of Arrhythmic Events in Catecholaminergic Polymorphic Ventricular Tachycardia

- After diagnosis: mean F.up 7.9 ± 4.9 years
- After 8 years:
  - Cardiac events: 27%
  - Fatal or near fatal events: 11%

- Index case vs. Family:
  - No difference

- Asymptomatic + mutation vs. Others:
  - No difference

Tachycardies ventriculaires catécholergiques
Modification du style de vie

'NO SPORT''

Sir Winston Churchill

NO STRESS
Tachycardies ventriculaires catécholergiques
Modification du style de vie

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

Class I
1. The following lifestyle changes are recommended in all patients with a diagnosis of CPVT:
   a. Limit/avoid competitive sports
   b. Limit/avoid strenuous exercise
   c. Limit exposure to stressful environments.

2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death

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<td>C</td>
<td>This panel of experts</td>
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Incidence and Risk Factors of Arrhythmic Events in Catecholaminergic Polymorphic Ventricular Tachycardia

![Graphs showing event-free survival over time with and without BBL.]

Estimation 8 ans: 27% vs. 58%
Estimation 8 ans: 11% vs. 25%

Efficacy of Nadolol in CPVT patients

Arrhythmias were less frequent and less severe during nadolol treatment than both before the initiation of β-blocker treatment and during β1-selective β-blocker treatment. I.S. Leren et al. Heart Rhythm 2016; 13:433-40.
Effect of flecainide derivatives on sarcoplasmic reticulum calcium release suggests a lack of direct action on the cardiac ryanodine receptor.
Clinical Management of Catecholaminergic Polymorphic Ventricular Tachycardia

The Role of Left Cardiac Sympathetic Denervation

![Diagram showing patient numbers before and after LCSD]

- MCE pre-LCSD
  - ≥15: 16
  - 5-14: 6
  - 1-4: 16
  - 0: 16

- MCE post-LCSD
  - ≥15: 2
  - 5-14: 4
  - 1-4: 7
  - 0: 41

![Graph showing cumulative event-free survival]

Cumulative event-free survival (%)

- N. at risk: 54
  - 12: 45 (87%)
  - 24: 35 (81%)
  - 36: 25 (76%)
  - 48: 13 (72%)

![Bar chart showing patients with recurrences post-LCSD]

- Incomplete LCSD (n=5)
- Complete LCSD (n=33)
Single Delivery of an Adeno-Associated Viral Construct to Transfer the CASQ2 Gene to Knock-In Mice Affected by Catecholaminergic Polymorphic Ventricular Tachycardia Is Able to Cure the Disease From Birth to Advanced Age

Marco Denegri, PhD*; Rossana Bongianino, MSc*; Francesco Lodola, PhD*; Simona Boncompagni, PhD; Verónica C. De Giusti, MD, PhD; José E. Avelino-Cruz, PhD; Nian Liu, MD; Simone Persampieri, MS; Antonio Curcio, MD, PhD; Francesca Esposito, MD; Laura Pietrangelo, MSc; Isabelle Marty, PhD; Laura Villani, MD; Alejandro Moyaho, PhD; Paola Baiardi, PhD; Alberto Auricchio, MD; Feliciano Protasi, PhD;

A 12 months

WT + ISO

R33Q + ISO

R33Q-INF + ISO

0 mV

20 mV

1 sec

B

Incidence of DADs (%)

*** ***

WT R33Q R33Q-INF

all groups

C

Incidence of TA (%)

*** ***

WT R33Q R33Q-INF

all groups

Circulation 2014;129:2673-81
Implantable cardioverter-defibrillator harm in young patients with inherited arrhythmia syndromes: A systematic review and meta-analysis of inappropriate shocks and complications.

- Systematic review and meta-analysis of inherited arrhythmia syndromes (ARVC/D, BS, CPVT, HCM, lamin DCM, LQTS, SQTS)
- 63 studies comprising 4916 patients
- Inappropriate shocks in 20% of patients (crude annual rate of 4.7% per year)
  - CPVT 36%, \( p=0.04 \) (+++ SVT)
- 22% ICD-related complications (4.4% per year)
  - CPVT 85% - mean FU 54±43 months
- 0.5% ICD-related mortality (0.08% per year)

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

Silvia G. Priori, (HRS Chairperson)1, Arthur A. Wilde, (EHRA Chairperson)2, Minoru Horie, (APHRS Chairperson)3, Yongkeun Cho, (APHRS Chairperson)4, Elijah R. Behr5, Charles Berul6, Nico Blom7, Josep Brugada8, Chern-En Chiang9, Heikki Huikuri10, Prince Kannankeril11, Andrew Krahn12, Antoine Leenhardt13, Arthur Moss14, Peter J. Schwartz15, Wataru Shimizu16, Gordon Tomaselli17, Cynthia Tracy18

Verapamil

Verapamil has been shown to be beneficial in some CPVT patients by reducing the ventricular arrhythmia burden on top of beta-blocker therapy during a short-term follow-up period,63,64 though its long-term effect remains controversial.

Catheter ablation

Catheter ablation of the bidirectional VPBs that trigger VF may become an adjunctive therapy in patients with refractory CPVT. However, the published experience is very limited and is therefore not discussed in the recommendation.74

Evaluation of family members

Family screening (siblings and parents) by clinical evaluation and genetic testing (when a mutation has been detected) is mandatory to identify undiagnosed patients and asymptomatic carriers who are at risk of arrhythmic events and should be treated. It is suggested that genetically positive family members should receive beta-blockers even after a negative exercise test.60,75
Calcium channel blocker

L-type calcium channel

β blocker

Adrenergic β-receptor

Plasma membrane

cAMP-dependent activation

Calcium leak

Calcium release channel (ryanodine receptor)

RYR2

PKA phosphorylation

flecainide dantrolene

CASQ2

SR

CPVT patients

- Restrictions for vigorous exercise and competitive sports

First Step

- β-blocker in the highest tolerable dose

Second Step

- Flecainide
- Verapamil

Third Step

- Left cardiac sympathetic denervation
- Implantable cardioverter defibrillators
Tachycardies ventriculaires catécholergiques

- Actually no good markers of prognosis.
- >90% of severe events between 13 and 26 y. of age in our cohort
- Younger age at diagnosis (HR: 0.31 per decade; 95% CI: 0.14–0.69; P = 0.004).
- The presence of couplets or more successive VPBs during exercise testing are significantly associated with future arrhythmic events (sensitivity 0.62; specificity 0.67).
- Treatment with beta-blockers other than nadolol [HR: 3.12; 95% CI: 1.16–8.38; P=0.02] is associated with future arrhythmic events.

Tachycardies ventriculaires catécholergiques

• Maladie rare, mais grave
• Y penser, c’est en faire le diagnostic
  – Syncope effort++++
  – Convulsion effort
  – Mort subite effort – piscine
• Importance du bilan familial
• Bêtabloquant (nadolol +++ 1,8 mg/kg). Observance ++, ± flecaïnide ± stellectomie ± DAI
• Centres de référence