Catecholaminergic polymorphic ventricular tachycardia: Update

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COI disclosure

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The author has no financial conflicts of interest to disclose concerning the presentation.
Diagnosis of catecholaminergic polymorphic ventricular tachycardia

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

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class⁹</th>
<th>Level¹⁰</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>
</tr>
</tbody>
</table>

CPVT = catecholaminergic polymorphic VT; ECG = electrocardiogram; VT = ventricular tachycardia.

⁹Class of recommendation.

¹⁰Level of evidence.
Typical features of ventricular tachycardia in a patient with CPVT

A

B

C

Sumitomo N. J Arrhythm 2016;32:344-351
Kaplan-Mayer survival curve

Cumulated survival rate

0 0.2 0.4 0.6 0.8 1

Years from first diagnosis

0 5 10 15 20

Age distribution and sex difference at the onset of CPVT

Female: 59 Pts (63%)
Male: 34 Pts (37%)

Incidence of gene anomaly

- ND, 47, 53%
- RyR2, 38, 43%
- RyR2(-), CASQ2, 2, 2%

Familial CPVT

- Familial, 4, 5%
- Sporadic, 81, 95%
The genetics underlying idiopathic ventricular fibrillation: A special role for catecholaminergic polymorphic ventricular tachycardia?

Main genetic findings in the Finnish and Italian IVF patients

76 Finnish and Italian patients mean age 31.2 years at VF event
Pathogenic and likely pathogenic variants (9%)

VUS 17, 22%
VDFE 6, 8%
ND; Not detected

VUS; Variants of unknown significance
VDFE; Variants with demonstrated functional effects

## CPVT subtypes

<table>
<thead>
<tr>
<th></th>
<th>CPVT1</th>
<th>CPVT2</th>
<th>CPVT3</th>
<th>CPVT4</th>
<th>CPVT5</th>
<th>CPVT related diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence (%)</td>
<td>50 - 60</td>
<td>1</td>
<td>&lt;&lt;1</td>
<td>&lt;&lt;1</td>
<td>&lt;&lt;1</td>
<td>&lt;&lt;1 &lt;&lt;1</td>
</tr>
<tr>
<td>inheritance</td>
<td>AD</td>
<td>AR</td>
<td>AR</td>
<td>AD</td>
<td>sporadic</td>
<td>AD           AD</td>
</tr>
<tr>
<td>Onset of symptoms (yrs)</td>
<td>10</td>
<td>7</td>
<td>22, 18, 4</td>
<td>4</td>
<td>2, 26</td>
<td>14, 9, 17             ?</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>1:1</td>
<td>1:1</td>
<td>1:1</td>
<td>1:1</td>
<td>M=3</td>
<td>F&gt;M?                   ?</td>
</tr>
<tr>
<td>Chromosome locus</td>
<td>1q43</td>
<td>1p13.1</td>
<td>4p13.1</td>
<td>14q32.11</td>
<td>6q22.31</td>
<td>17q24.3     4q25-26</td>
</tr>
<tr>
<td>Gene</td>
<td><em>RyR2</em></td>
<td><em>CASQ2</em></td>
<td><em>TECRL</em></td>
<td><em>CALM1</em></td>
<td><em>TRD</em></td>
<td><em>KCNJ2</em>     <em>ANK2</em></td>
</tr>
<tr>
<td>Protein</td>
<td>Ryanodine receptor</td>
<td>Carsequestrin 2</td>
<td>trans-2,3-enoyl-CoA reductase like protein</td>
<td>CaM</td>
<td>Triadin</td>
<td>Kᵢ₂.₁α</td>
</tr>
<tr>
<td>Sudden death (%)</td>
<td>≈10</td>
<td>≈42</td>
<td>≈57</td>
<td>≈18</td>
<td>≈25</td>
<td>?                     ?</td>
</tr>
</tbody>
</table>

Modified from Guidelines for Diagnosis and Management of Inherited Arrhythmias (JCS 2017); [http://www.j-circ.or.jp/guideline/pdf/JCS2017_aonuma_h.pdf](http://www.j-circ.or.jp/guideline/pdf/JCS2017_aonuma_h.pdf)
Circadian Variation of Ventricular Arrhythmias in Catecholaminergic Polymorphic Ventricular Tachycardia

A

Mean hourly activity cpm (95% CI)

300 400 500 600 700 800

7-8 9-10 11-12 13-14 15-16 17-18 19-20 21-22

Hour of the day

B

Holter

ICD/ILR

# Ventricular Events

12am 6am 12pm 6pm 11pm

0 10 20 30 40 50

Distribution of Events During Waking Hours

80 patients (53% male, age <21 years at diagnosis), 61% with an ICD, experienced 423 VT events during a median follow-up time of 6 years (2 to 10 years). When compared to morning hours, VT was more likely to occur in the afternoon (odds ratio [OR]: 2.54; 95% confidence interval [CI]: 1.69 to 3.83) or evening hours (OR: 2.91; 95% CI: 1.82 to 4.67).

Bradycardia is a Specific Phenotype of Catecholaminergic Polymorphic Ventricular Tachycardia Induced by RYR2 Mutations

Definition of Bradycardia in This Study

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Heart rate (bpm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>&lt;100</td>
</tr>
<tr>
<td>1–3</td>
<td>&lt;95</td>
</tr>
<tr>
<td>4–5</td>
<td>&lt;75</td>
</tr>
<tr>
<td>6–8</td>
<td>&lt;65</td>
</tr>
<tr>
<td>≥ 9</td>
<td>&lt;60</td>
</tr>
</tbody>
</table>

Distribution of the bradycardia

<table>
<thead>
<tr>
<th></th>
<th>Bradycardia</th>
<th>Normal heart rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPVT (n=44)</td>
<td>19</td>
<td>25</td>
</tr>
<tr>
<td>LQT (n=9)</td>
<td>8</td>
<td>1</td>
</tr>
</tbody>
</table>

P = 0.024

Association of Atrial Arrhythmia and Sinus Node Dysfunction in Patients With Catecholaminergic Polymorphic Ventricular Tachycardia

Result of electrophysiological study

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Onset</th>
<th>AH</th>
<th>HV</th>
<th>RA-ERP</th>
<th>AVN-ERP</th>
<th>W rate</th>
<th>SNRT</th>
<th>CSNRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>13</td>
<td>F</td>
<td>syncope</td>
<td>70</td>
<td>40</td>
<td>230</td>
<td>310</td>
<td>190</td>
<td>1430</td>
<td>695</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>F</td>
<td></td>
<td>76</td>
<td>26</td>
<td>230</td>
<td>250</td>
<td>160</td>
<td>1617</td>
<td>785</td>
</tr>
<tr>
<td>2</td>
<td>11</td>
<td>F</td>
<td>syncope</td>
<td>96</td>
<td>55</td>
<td>270</td>
<td>315</td>
<td>180</td>
<td>1316</td>
<td>407</td>
</tr>
<tr>
<td>3</td>
<td>15</td>
<td>F</td>
<td>syncope</td>
<td>70</td>
<td>40</td>
<td>210</td>
<td>410</td>
<td>180</td>
<td>1930</td>
<td>930</td>
</tr>
<tr>
<td>4</td>
<td>37</td>
<td>F</td>
<td>syncope</td>
<td>95</td>
<td>35</td>
<td>290</td>
<td>320</td>
<td>140</td>
<td>1305</td>
<td>440</td>
</tr>
<tr>
<td>5</td>
<td>9</td>
<td>F</td>
<td>familial</td>
<td>60</td>
<td>35</td>
<td>285</td>
<td>300</td>
<td>170</td>
<td>890</td>
<td>190</td>
</tr>
<tr>
<td>6</td>
<td>11</td>
<td>F</td>
<td>familial</td>
<td>60</td>
<td>35</td>
<td>275</td>
<td>285</td>
<td>200</td>
<td>760</td>
<td>155</td>
</tr>
<tr>
<td>7</td>
<td>13</td>
<td>M</td>
<td>syncope</td>
<td>62</td>
<td>44</td>
<td>210</td>
<td>264</td>
<td>200</td>
<td>1248</td>
<td>552</td>
</tr>
<tr>
<td>8</td>
<td>15</td>
<td>F</td>
<td>syncope</td>
<td>85</td>
<td>38</td>
<td>210</td>
<td>530</td>
<td>100</td>
<td>2002</td>
<td>889</td>
</tr>
</tbody>
</table>

Effects of Individualized Exercise Training in Patients With Catecholaminergic Polymorphic Ventricular Tachycardia Type 1

Individual and mean threshold HR for VA measured for ET and SED patients

ET; 12-week high-intensity ergometer bicycle ET program with 60 min exercise sessions 3 times per week.
SED; sedentary control

Comparison of the development in threshold HR for VA during the study period in ET and SED patients
*p <0.05
The threshold HR for VA increased in ET compared with SED patients (+ 11 vs - 12 beats/min, p < 0.05).

In conclusion, patients with CPVT1 benefitted from individualized ET with improved aerobic capacity and increased threshold HR for VA compared with SED patients.

Although sports participation is a risk taking behavior in undiagnosed and untreated CPVT, the risk may be acceptable for a well-treated and well-informed athlete following the diagnosis of CPVT.
Exercise training prevents ventricular tachycardia in CPVT1 due to reduced CaMKII-dependent arrhythmogenic Ca$^{2+}$ release

Ryr2-R2474S mice (RyR-RS) performed a 2 week interval treadmill exercise training protocol. Each exercise session comprised five 8 min intervals at 80–90% of the running speed at maximal oxygen uptake (VO2max) and 2 min active rest periods at 60%. VO2max increased by 10±2% in exercise trained RyR-RS (ET), while no changes were found in sedentary controls (SED). RyR-RS ET showed fewer episodes of ventricular tachycardia compared with RyR-RS SED. Detraining reverses VO2max, VT episodes, and Ca$^{2+}$ waves in RyR-RS.

Nadolol decreases the incidence and severity of ventricular arrhythmias during exercise stress testing compared with β1-selective β-blockers in patients with catecholaminergic polymorphic ventricular tachycardia.

34 patients with CPVT (mean age 34 ± 19 years)
30 (88%) RyR2 variant positive.
3 bicycle exercise stress tests
(1) before β-blocker
(2) 46 weeks after β1-selective β-blockers (metoprolol, or bisoprolol)
(3) 46 weeks after nadolol

The incidence and severity of ventricular arrhythmias decreased during treatment with nadolol compared with during treatment with β1-selective β-blockers. β1-Selective β-blockers did not change the occurrence or severity of arrhythmias compared with no medication.

Clinical Management of Catecholaminergic Polymorphic Ventricular Tachycardia
The Role of Left Cardiac Sympathetic Denervation

Kaplan–Meier curve of cumulative survival to a first major cardiac event before and after left cardiac sympathetic denervation in symptomatic patients with catecholaminergic polymorphic ventricular tachycardia

before LCSD

after LCSD

Gaetano M. De Ferrari et al. Circulation. 2015;131:2185-2193

63 patients with CPVT
## Summary of CPVT patients who received an ICD in the 10 studies with detailed outcomes

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Recruitment period (y)</th>
<th>Inclusion criteria</th>
<th>Total number of patients</th>
<th>Patients with ICD, n (%)</th>
<th>Primary prevention, n (%)</th>
<th>≥1 Appropriate shock, n (%)</th>
<th>≥1 Inappropriate shock, n (%)</th>
<th>Electrical storm, n (%)</th>
<th>Other complications, n (%)</th>
<th>OAT, n (%)</th>
<th>Death despite ICD, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hayashi et al</td>
<td>Retro</td>
<td>NR</td>
<td>Clinical and/or genetic CPVT</td>
<td>101*</td>
<td>16 (16)</td>
<td>12 (75)</td>
<td>4 (25)</td>
<td>6 (38)</td>
<td>NR</td>
<td>2 (13)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>van der Werf et al</td>
<td>Retro</td>
<td>2009–2010</td>
<td>Clinical and genetic CPVT and received flecainide</td>
<td>33</td>
<td>12 (36)</td>
<td>11 (92)</td>
<td>1 (8)</td>
<td>1 (8)</td>
<td>1 (8)</td>
<td>NR</td>
<td>10 (83)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Sy et al</td>
<td>Retro</td>
<td>NR</td>
<td>Clinical and/or genetic CPVT</td>
<td>27</td>
<td>15 (56)</td>
<td>6 (40)</td>
<td>3 (20)</td>
<td>6 (40)</td>
<td>1 (1)</td>
<td>NR</td>
<td>4 (27)</td>
<td>2 (13)</td>
</tr>
<tr>
<td>Roses-Noguer et al</td>
<td>Retro</td>
<td>NR</td>
<td>Clinical and/or genetic CPVT with ICD</td>
<td>13</td>
<td>13 (100)</td>
<td>6 (46)</td>
<td>8 (62)</td>
<td>5 (38)</td>
<td>NR</td>
<td>12 (92)</td>
<td>7 (54)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Miyake et al</td>
<td>Retro</td>
<td>1999–2001</td>
<td>Clinical and/or genetic CPVT with ICD and symptom onset&lt;21 y</td>
<td>24</td>
<td>24 (100)</td>
<td>8 (33)</td>
<td>10 (42)</td>
<td>11 (46)</td>
<td>4 (17)</td>
<td>8 (33)</td>
<td>0 (0)†</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Kozlovski et al</td>
<td>Retro</td>
<td>NR</td>
<td>Clinical and/or genetic CPVT</td>
<td>35</td>
<td>27 (77)</td>
<td>10 (37)</td>
<td>11 (41)</td>
<td>4 (15)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Roston et al</td>
<td>Retro</td>
<td>2012–2014</td>
<td>Clinical and genetic CPVT and symptom onset &lt;19 y</td>
<td>226†</td>
<td>118 (54)</td>
<td>51 (43)</td>
<td>55 (47)</td>
<td>21 (17)</td>
<td>21 (18)</td>
<td>28 (23)</td>
<td>NR</td>
<td>3 (2)</td>
</tr>
<tr>
<td>De Ferrari et al</td>
<td>Retro</td>
<td>1988–2014</td>
<td>Clinical and/or genetic CPVT</td>
<td>63 §</td>
<td>37 (60)</td>
<td>23 (62)</td>
<td>23 (62)</td>
<td>7 (19)</td>
<td>12 (32)</td>
<td>17 (46)</td>
<td>NR</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Wanguemert et al</td>
<td>Retro</td>
<td>1994–2015</td>
<td>Carriers of the RYR2 p.G357S mutation</td>
<td>182</td>
<td>40 (22)</td>
<td>24 (60)</td>
<td>3 (10)</td>
<td>1 (3)</td>
<td>NR</td>
<td>NR</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Broendberg et al</td>
<td>Retro</td>
<td>Up to June 2016</td>
<td>RYR2 genotype-positive CPVT</td>
<td>51</td>
<td>28 (55)</td>
<td>7 (14)</td>
<td>8 (16)</td>
<td>4 (8)</td>
<td>NR</td>
<td>9 (18)</td>
<td>NR</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td></td>
<td><strong>750</strong></td>
<td><strong>330 (44)</strong></td>
<td><strong>158 (48)</strong></td>
<td><strong>126 (38)</strong></td>
<td><strong>66 (20)</strong></td>
<td><strong>39 (19)</strong></td>
<td><strong>76 (32)</strong></td>
<td><strong>21 (20)</strong></td>
<td><strong>6 (2)</strong></td>
</tr>
</tbody>
</table>

CPVT = catecholaminergic polymorphic ventricular tachycardia; ICD = implantable cardioverter-defibrillator; NR = not reported to extrapolate data on patients with implantable cardioverter-defibrillator; OAT = optimal antiarrhythmic therapy.

*Two subjects excluded who were in another cohort (analysis undertaken in 99 patients).
† Before ICD.
§ Eight subjects excluded who were in another cohort (analysis undertaken in 218 patients).
§ One subject excluded who was in another cohort (analysis undertaken in 62 patients).

Conclusion

• The onset of CPVT is around 10 years old.
• The incidence of RyR2 or CASQ2 genetic anomaly is as high as 95% in our cohort.
• Family history of the proband of CPVT is not as high as we expected.
• Ventricular event was more likely to occur in the afternoon or evening hours.
• Exercise training may reduce the possibility of cardiac event.
• Nadolol is the most effective β blocker.
• ICD is effective in some patients but association with optimal medical treatment is mandatory.
β blockers

Effective pharmacological approach. Unfortunately, ≈30% of patients have recurrences, and an ICD may be required. The long acting β-blocker, nadolol is preferred for prophylactic treatment of CPVT. Propranolol is also an effective medication. Carvedilol is reported to inhibit the SOICR in an HEK 293 cell culture model. Additionally, among various β-blockers, only carvedilol inhibits RyR2 activity (Zhou et al., 2011).

Verapamil

Beneficial effects in some CPVT patients (Rosso et al., 2007). The long-term efficacy of verapamil is controversial.

Flecainide

Very effective medication to decrease incidence and severity of VA. It is recommended with the use of β-blocker.
VATS-LCSD indications

1. When β-blockers are contraindicated or not tolerated: history of asthma; moderate to severe chronic obstructive pulmonary disease, i.e., with forced expiratory volume reduction <50% of the predicted value; patients on chronic bronchodilator treatment; and chronic airflow limitation with evidence of ≥20% reversibility in airway obstruction in response to inhaled salbutamol.

2. Syncope recurrence despite maximum-dose β-blockade + flecainide;

3. ICD shocks recurrence or electrical storms;

4. High risk of SCD despite being asymptomatic on β-blocker therapy(Schwartz, 2014).

Implantation of an ICD should be considered in patients in the absence of controlled optimal therapy. However, implantation of an ICD in children still has several technical problems. Moreover, inappropriate or painful shocks may increase the risk of further VTs, and electrical storms that may result in lethal events. The effectiveness of ICD shock therapy in CPVT depends on the mechanism of the rhythm treated. Shocks delivered to initiating triggered arrhythmias nearly always fail, whereas those for subsequent VF are usually effective.
Exercise training with maximal optimal therapy may be beneficial in well informed patients with CPVT. However, further investigation may be needed.
Side effects of VATS-LCSD

1. Dryness on left side (59%)
2. Harlequin-type (unilateral) facial flush (55%)
3. Contralateral hyperhidrosis (39%)
4. Differential hand temperatures (11%)
5. Permanent (9%) or transient ptosis (11%)
6. Thermoregulation difficulties (9%)
7. Left arm paresthesia (7%)
8. Sympathetic flight/fright response loss

Modeling of Catecholaminergic Polymorphic Ventricular Tachycardia With Patient-Specific Human-Induced Pluripotent Stem Cells

Circumstances immediately preceding life-threatening cardiac event(s) in the 122 patients reporting syncope and 86 with cardiac arrest.
Modeling of Catecholaminergic Polymorphic Ventricular Tachycardia With Patient-Specific Human-Induced Pluripotent Stem Cells

Forskolin; a direct activator of adenylate cyclase

Pharmacological Interventions

In about 40% of patients with CPVT, disease-specific mutations are not identified.

Eligibility for practicing sports activity in patients with catecholaminergic polymorphic ventricular tachycardia (CPVT).

- Mutations in RyR2 and mutations in the cardiac calsequestrin gene CASQ2
- Genetic testing
- Asymptomatic gene carriers should also follow these recommendations
- Lifestyle modification avoiding competitive sports, strenuous exercise, and stressful environments (physical and emotional).
  - Sport avoided:
    - Competitive and even moderate leisure-time sports are formally contraindicated
    - Sudden bursts of exercise should be strictly avoided
- A long-acting beta-blocker therapy is first choice
- If exercise testing under therapy shows no recurrence of tachyarrhythmias,
  - Sport allowed: low-to moderate leisure-time sports can be performed,
  - Immediate re-evaluation if symptoms recur