Ventricular arrhythmia in Pediatric Cardiomyopathy

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Nonischemic Cardiomyopathies

2006, AHA.

- HCM
- ARVC/D
- LVNC
- Glycogen storage
  - PRKAG2
  - Danon
- Conduction defects
- Mitochondrial myopathies

- LQTS
- Brugada syndrome
- SQTS
- CVPT
- Asian SUNDS

- DCM
- Restrictive (non-hypertrophied and non-dilated)

- Inflammatory (myocarditis)
- Stress-provoked ("tako-tsubo")
- Peripartum
- Tachycardia-induced
- Infants of insulin-dependent diabetic mothers

- Infiltrative
- Storage
- Toxicity
- Endomyocardial
- Inflammatory (granulomatous)
- Endocrine
- Cardiofacial
- Neuromuscular / neurological
- Nutritional deficiencies
- Autoimmune / collagen
- Electrolyte imbalance
- Consequence of cancer therapy
Pediatric Cardiomyopathies

(incidence: 1.5/100,000)

Circ Res. 2017;121:855-873

- Dilated CM
- Hypertrophic CM
- Restrictive CM
- Noncompaction CM
- Arrhythmogenic RV Cardiomyopathy

JACC, 2015
Dilated CM in Pediatric Pts

- Annual incidence 0.57/100,000
- Dominant mutations in the genes encoding the sarcomere
- Inflammation, either postinfectious or autoimmune, toxin

- **Arrhythmias**
  - *Especially increased with LMNA gene* mutations
    - Highly associated with conduction system Ds (SND, atrial arrhythmias, AV heart block, and ventricular tachyarrhythmias)

- Sustained monomorphic VT is an uncommon.
- Infrequently induced at EP study.

*Circ Res. 2017;121:855-873
Am Heart Assoc. 2016;5:e003450*
Sudden death or major ventricular arrhythmias in DCM

*J Am Heart Assoc.* 2016;5:e003450

47 pediatric pts (15 ± 3 yrs) vs. 141 adult pts (47 ± 13 yrs)

Effect of age on SD/MVA

$P < 0.0001$

Linear effect $p = 0.02$
The Arrhythmic Burden in Pediatric DCM

![Table showing incidence of events in adult and pediatric populations](image)

**ICD Implantation in Pediatric DCM**

1. pts with unexplained syncope and at least moderate LV dysfunction (IIa, or with LVEF <35% and NYHA class II–III (IIb, C).
2. adolescent pts with a familial cardiomyopathy associated with SD or for younger pts, considering the risk–benefit ratio and technical issues
Risk for Ventricular arrhythmias or SCD in Adult DCMP

Myocardial fibrosis assessment by LGE in adult pt → VA occurrence

But, Not established in Pediatric pts
Hypertrophic CM in Pediatric Pts

- Annual incidence 0.47/100,000
- Dominant mutations in the genes encoding the sarcomere
- Presentation: In infancy, inborn errors of metabolism and malformation syndromes

Arrhythmias
- Impaired energy use and resultant energy deficiency contributes to diastolic impairment
  → Progressive LA enlargement → atrial arrhythmias
- Cellular hypertrophy, interstitial fibrosis, and myofiber disarray
  → increase the risk of (arrhythmic) sudden cardiac death

*Circ Res.* 2017;121:855-873
Childhood HCM in the UK (1980-2017)

European Heart J, 2019 40, 986–993

687 pts with HCM aged 16 years or younger (Median age, 5.2 years)

Arrhythmic events: 58 pts (8.4%)
- 20 SCD, 11 resuscitated cardiac arrest, 8 sustained VT, 19 ICD shock
The survival rates of children of HCM

1085 children with HCM (1990 to 2006)

687 pediatric pts with HCM

*Children with worse prognosis
: Diagnosed < 1 year of age, pts with inborn errors of metabolism or with mixed phenotypes.

Inborn errors of metabolism

P<0.0001.

Lancet. 2013; 382(9908): 1889–97

European Heart J, 2019 40, 986–93
### Table: HCM with inborn error of metabolism or malformation syndrome and SCD

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Age at presentation</th>
<th>Symptoms at presentation</th>
<th>Phenotype</th>
<th>History of arrhythmias</th>
<th>Interventions</th>
<th>SCD or equivalent event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1: Danon’s disease</td>
<td>13 years</td>
<td>Unexplained syncope</td>
<td>Concentric LVMWT 30 mm LVOT 10 mmHg</td>
<td>Nil</td>
<td>ICD implanted aged 14 years</td>
<td>Sustained VT aged 16 years</td>
</tr>
<tr>
<td>Patient 2: Glycogen storage disease</td>
<td>3 months</td>
<td>NYHA 1</td>
<td>Concentric LVMWT 9 mm LVOT 6 mmHg</td>
<td>Nil</td>
<td>Reveal device implanted aged 14 (unexplained syncope aged 13)</td>
<td>SCD—reveal device documented VT + fine VF aged 14</td>
</tr>
<tr>
<td>Patient 3: Noonan’s</td>
<td>13 years</td>
<td>NYHA 2</td>
<td>ASH LWT 18 mm LVOT 58 mmHg</td>
<td>NSVT aged 16 years</td>
<td>Nil</td>
<td>SCD aged 18 years</td>
</tr>
<tr>
<td>Patient 4: Noonan’s</td>
<td>11 years</td>
<td>NYHA 1</td>
<td>Concentric LVMWT 18 mm LVOT 23 mmHg</td>
<td>NSVT aged 15 years</td>
<td>Primary prevention ICD implanted aged 16 years</td>
<td>Appropriate ICD therapy aged 16 years</td>
</tr>
<tr>
<td>Patient 5: Noonan’s</td>
<td>9 days</td>
<td>NYHA 2</td>
<td>BVH LVMWT 14 mm LVOT 32 mmHg</td>
<td>Nil</td>
<td>Myectomy aged 5 years</td>
<td>SCD aged 8 years</td>
</tr>
<tr>
<td>Patient 6: Other RASopathy</td>
<td>2 years</td>
<td>NYHA 1</td>
<td>ASH LVMWT 18 mm LVOT 16 mmHg</td>
<td>NSVT aged 9 years</td>
<td>Nil</td>
<td>Aborted cardiac arrest aged 10 years</td>
</tr>
<tr>
<td>Patient 7: Noonan’s</td>
<td>3 months</td>
<td>NYHA 3</td>
<td>BVH LVMWT 12 mm LVOT 73 mmHg RVOTO</td>
<td>Nil</td>
<td>Nil</td>
<td>Sustained VT aged 14 months</td>
</tr>
</tbody>
</table>
Arrhythmia Risk Stratification in Pediatric HCM

CMR imaging derived perfusion and viability (delayed gadolinium enhancement) is associated with severity of hypertrophy and risk of ventricular arrhythmia → SCD in childhood HCM
CMR T₁ mapping imaging:

- diffuse fibrosis in HCM

*Predictor of NSVT and aborted SCD in adult HCM. Circ Cardiovasc Imaging 2015;8.
Apical LV aneurysms portends a higher risk for arrhythmic sudden death in adult HCM. J Am Coll Cardiol 2017;69:761–73.

1,940 Adult HCM pts, 93 (4.8%) pts with LV apical aneurysm, mean age, 56 ± 13 yrs.
QRS Fragmentation and QTc Duration Relate to Malignant Ventricular Tachyarrhythmias and SCD

*J Cardiovasc Electrophysiol, 2015; 26:547-555*

<table>
<thead>
<tr>
<th></th>
<th>Overall (n = 195)</th>
<th>No VTA/SCD (n = 169)</th>
<th>VTA/SCD (n = 26)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>QRS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration, ms</td>
<td>97 ± 12</td>
<td>97 ± 12</td>
<td>99 ± 13</td>
<td>0.30</td>
</tr>
<tr>
<td>Fragmentation, n (%) ≥ 3 territories</td>
<td>15 (8)</td>
<td>10 (6)</td>
<td>5 (19)</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>QTc</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration, ms</td>
<td>427 ± 28</td>
<td>425 ± 25</td>
<td>440 ± 34</td>
<td>0.01</td>
</tr>
<tr>
<td>≥460 ms, n (%)</td>
<td>26 (13)</td>
<td>18 (11)</td>
<td>8 (31)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

195 Adult HCM pts (mean age 52 ± 13 yrs)

- QTc 487 ms resuscitation for VF after 2.4 years
- QRS fragmentation in 3 territories, QTc 527 ms ATP for sustained VT after 1.1 years
Cumulative survival free of ventricular tachyarrhythmia or sudden cardiac death

A

\[
\begin{array}{cccccc}
\text{Freedom from ventricular tachyarrhythmia or sudden cardiac death} & & & & & \\
\text{Follow up (years)} & 0 & 2 & 4 & 6 & 8 & 10 \\
\text{QTc < 460 ms} & 1.0 & 0.8 & 0.6 & 0.4 & 0.2 & 0.0 \\
\text{QTc \geq 460 ms} & 0.8 & 0.6 & 0.4 & 0.2 & 0.0 & 0.0 \\
\end{array}
\]

Log rank p 0.009

B

\[
\begin{array}{cccccc}
\text{Freedom from ventricular tachyarrhythmia or sudden cardiac death} & & & & & \\
\text{Follow up (years)} & 0 & 2 & 4 & 6 & 8 & 10 \\
\text{fQRS < 3 territories} & 1.0 & 0.8 & 0.6 & 0.4 & 0.2 & 0.0 \\
\text{fQRS \geq 3 territories} & 0.8 & 0.6 & 0.4 & 0.2 & 0.0 & 0.0 \\
\end{array}
\]

Log rank p 0.004

Patients at risk

<table>
<thead>
<tr>
<th>QTc &lt; 460 ms</th>
<th>169</th>
<th>133</th>
<th>95</th>
<th>74</th>
<th>48</th>
<th>36</th>
</tr>
</thead>
<tbody>
<tr>
<td>QTc \geq 460 ms</td>
<td>26</td>
<td>20</td>
<td>16</td>
<td>12</td>
<td>10</td>
<td>5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>fQRS &lt; 3 territories</th>
<th>180</th>
<th>140</th>
<th>101</th>
<th>81</th>
<th>57</th>
<th>40</th>
</tr>
</thead>
<tbody>
<tr>
<td>fQRS \geq 3 territories</td>
<td>15</td>
<td>13</td>
<td>10</td>
<td>5</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
Restrictive CM in Pediatric pts

- Diastolic dysfunction from abnormalities affecting the contractile apparatus
- Altered calcium homeostasis
- 1/3 pts with RCM - mixed phenotype with HCM

Arrhythmias

- Enlarged atria → increase the risk of clot formation, stroke and atrial arrhythmias
- Sudden death risk <28 %
  (ventricular arrhythmias, ischemic changes, pulmonary HT)
- 5 –years survival from the Dx of RCM : 68 %
Noncompaction CM in Pediatric Pts

- Premature arrest of myocardial development during embryogenesis
- 40% of pts: infants, family Hx of CM: 25%
- Mixed phenotype: HCM/DCM (28%), HCM (27%), DCM (19%)

Arrhythmias

- 1/3 of pts: tachyarrhythmias
  - VT (17%), AT (6%), reentrant SVT (8%)
- Survival: 18%-25% died or heart TPL
high spatial QRS-T angles are at increased risk for VT in Pediatric Noncompaction

39 pts with NCCM, 8 pts developed VA (20.5%).

<table>
<thead>
<tr>
<th></th>
<th>VA (8)</th>
<th>no VA (30)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>1.0 (0.8-3.0)</td>
<td>0.5 (0.2-12.0)</td>
<td>0.335</td>
</tr>
<tr>
<td>Male sex</td>
<td>6 (35.5%)</td>
<td>12 (35.5%)</td>
<td>0.076</td>
</tr>
<tr>
<td>Follow-up (months)</td>
<td>3.0 (1.0-24.0)</td>
<td>24.0 (14.0-36.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Familial recurrence</td>
<td>4 (50.0%)</td>
<td>14 (45.2%)</td>
<td>1.000</td>
</tr>
<tr>
<td>TTN</td>
<td>0 (0.0%)</td>
<td>3 (10.0%)</td>
<td>0.083</td>
</tr>
<tr>
<td>MYH7</td>
<td>3 (33.3%)</td>
<td>3 (10.0%)</td>
<td>0.187</td>
</tr>
<tr>
<td>LVEDV indexed (ml/m^2)</td>
<td>207.5 (201.3-209.9)</td>
<td>187.4 (156.0-195.2)</td>
<td>0.031</td>
</tr>
<tr>
<td>Late enhancement presence</td>
<td>0 (0.0%)</td>
<td>3 (9.7%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>22.5 (17.0-28.0)</td>
<td>25.0 (15.9-35.8)</td>
<td>0.171</td>
</tr>
<tr>
<td>Fractional Shortening (%)</td>
<td>10.0 (9.5-12.0)</td>
<td>12.0 (11.9-18.0)</td>
<td>0.057</td>
</tr>
<tr>
<td>Lateral T-wave inversions</td>
<td>8 (100.0%)</td>
<td>25 (80.6%)</td>
<td>0.313</td>
</tr>
<tr>
<td>Inferior T-wave inversions</td>
<td>5 (62.5%)</td>
<td>18 (58.1%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Third degree heart block</td>
<td>0 (0.0%)</td>
<td>1 (3.3%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>139 (115-144)</td>
<td>155 (144-165)</td>
<td>0.001</td>
</tr>
<tr>
<td>QRSd (ms)</td>
<td>68 (64-132)</td>
<td>76 (70-78)</td>
<td>0.413</td>
</tr>
<tr>
<td>QTc (ms)</td>
<td>477 (460-499)</td>
<td>434 (430-477)</td>
<td>0.057</td>
</tr>
<tr>
<td>Spatial peaks QRS-T angle (degrees)</td>
<td>147 (138-163)</td>
<td>113 (107-143)</td>
<td>0.015</td>
</tr>
<tr>
<td>QRS vector magnitude (milli-volts)</td>
<td>2.89 (1.36-3.00)</td>
<td>1.73 (1.22-2.51)</td>
<td>0.392</td>
</tr>
</tbody>
</table>

Spatial peaks QRS-T angle
ECG predictors of VA in NCCM

Ann Noninvasive Electrocardiol. 2019;24:e12588

cutoff of $147^\circ$, $p = 0.039$
Arrhythmogenic RV CM in Pediatric Pts

✓ Progressive fibrofatty replacement of the RV myocardium
✓ Inherited CM with an autosomal dominant pattern
✓ Gene encoding desmosomal protein

Arrhythmias

- RV or biventricular dysfunction and ventricular arrhythmias
- 20% or more SCD in young pts
Definite ARVC Dx: 2 major or 1 major + 2 minor or 4 minor from different categories.
Diagnosing ARVC in Children and Adolescents

**J Am Coll Cardiol 2015;65:987–95**

(142 pts, 2005-2009)

- Structural, functional, and electrical alterations in the RV may be minimal in pediatric pts.
- **CMR findings** are powerful Dx modality for ARVC in children and adolescents.
- **CMR parameters** including RV EDVi and WMAs, are important contributors to diagnosing ARVC.
# Management of VT in CM

## Pharmacotherapies of VAs

**Amiodarone** - reduces the occurrence of VAs without the increase in the mortality in pt with HF.

In pts with an ICD implantation, **Amiodarone + beta-blockers** significantly reduces ICD shocks.

**Sotalol** - less effective in CM pts

## ICDs

(i) CM with experience an aborted SCD, unexplained syncope, or hemodynamically unstable VT/VF,
(ii) primary prevention for DCM pts With NYHA functional classes II-III and a decreased LVEF of ≤35% in spite of ≥3 months of pharmacological Tx,
(iii) HCM pts with a high risk of SCD,
(iv) ARVC pts with well-tolerated sustained VTs, after balancing the risk of ICD therapy

## Catheter ablation

limited reports for pediatric CMs

*Antiarrhythmic agents may be effective as an adjunctive therapy for the Tx of VAs in CM pts.*
CRT-D implantation in DCM with VT


12-year-old boy
DCMP (LVEF 22%),
Hx of VT
LBBB, QRS 200ms
Endocardial and epicardial substrates in adult pt with DCM


Endo, Bipolar voltage mapping

Epi, Bipolar voltage mapping

Late potential

Epi, Unipolar voltage mapping

Endo, Unipolar voltage mapping
Summary (I)

- In pediatric CM, the identification of predictors of VA and SCD are essential.

- A specific gene mutation is important with the occurrence of VA in pediatric DCM.

- LGE of CMR finding is associated with the risk of VA in pediatric HCM and powerful diagnostic tool in pediatric ARVC.

- Pharmacologic and non pharmacologic Tx of VA are somewhat limited in pediatric CM.
Thank you for your attention!