Exercise Response in Children and Adolescents Late After Kawasaki Disease According to Early Coronary Status

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Conflicts of Interest

- Data are from a Pharmaceutical sponsored multicenter study
- Independent analysis
- No conflict of interest
- No financial relationship
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Introduction

• KD classified under the **vasculitis** nomenclature

• Severity of cardiovascular sequelae associated with the severity of coronary artery (CA) lesions.

• **Endothelial dysfunction**; **Impaired myocardial flow reserve**; abnormal **SN** and **AV node function**; **QT interval dispersion**; **Autonomic dysfunction**; **ventricular dilation**; **Histologic myocardial alterations**.

• KD causes **inflammatory myocarditis** in all patients
Exercise testing in KD

• Most patients → no obvious clinical functional limitations with exercise after the convalescent stage:
  – A similar exercise capacity between KD and healthy children of the same age (Rhodes 1996; Gravel 2012)
  – A similar exercise capacity with or without CA aneurysms or perfusion defects (Paridon 1995; Gravel 2012)

• Recent studies:
  – Exercise-induced perfusion defects (Kashyap 2011; Zanon 2008)
  – Exercise-induced ECG abnormalities (Gravel 2012)

Even in subjects without CA lesions
Research Questions

Does exercise challenge highlight chronotropic or barotropic alterations following KD?
Is it associated with CA aneurysm status?

Besides exercise “duration” and “ischemic” changes, valuable information can be obtained from stress tests:

• Blood pressure response
• Chronotropic response
• Heart-rate recovery
Objectives

- Cardiolite-301, a multicenter study conducted in 2006-2008: «A Study to Evaluate the Use and Safety of Cardiolite™ in Pediatric Patients with Kawasaki Disease»

- Post-hoc analysis describing response to exercise challenge late after KD to determine response according to coronary artery status at onset:
  1. Exercise capacity late during childhood after KD
  2. Heart-rate and blood-pressure response during exercise and during recovery
  3. Evaluate if the severity of CA disease upon onset affects these parameters
Methods

- **Inclusions:**
  - Treadmill test
  - >6 years old
  - >1 year after the acute phase

- **Exclusion:**
  - Stationary cycle ergometer testing
  - Medication affecting exercise response
  - History of CA intervention
  - Uncertain presence/absence of aneurysm

**Final study population (450 C-301 → 250 pts):**
- KD without CA aneurysm: n=117
- KD with CA aneurysm(s): n=133
Analysis

- **Exercise challenge measurements:**
  - Endurance time
  - Heart Rate, systolic BP and diastolic BP
  - At the following time points: *Rest*, 3-minute stages, peak exercise, and recovery (1min, 3min, 5min and 10min)

- **Myocardial perfusion defects**
  - Assessed by Tc-99m Sestamibi SPECT imaging
  - Core-lab analysis by 3 independent readers
Analysis

- Raw data were compared between groups
  &

- Normalized to Z-scores calculated for gender and age, using available reference values:
  - Chatrath et al. 2002 «Physical Fitness of Urban American Children»
  - Ahmad et al. 2001 «Responses of Non-Obese White Children to Treadmill Exercise»
Results: Basic characteristics

<table>
<thead>
<tr>
<th></th>
<th>No CAAN</th>
<th>With CAAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>10.7±2.7</td>
<td>11.0±2.7</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>143.6±16.4</td>
<td>145.5±17.3</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>41.7±16.7</td>
<td>42.3±16.8</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>19.6±4.7</td>
<td>19.3±4.1</td>
</tr>
<tr>
<td>Asian/Caucasian/other (%)*</td>
<td>47/40/13</td>
<td>65/27/8</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>63/47</td>
<td>71/29</td>
</tr>
<tr>
<td>Time since diagnosis (yrs)</td>
<td>6.8±3.1</td>
<td>7.5±3.6</td>
</tr>
<tr>
<td>Reported cardiac symptoms (%)</td>
<td>17%</td>
<td>14%</td>
</tr>
</tbody>
</table>

* p < 0.05
## Results: CAAN vs no CAAN

<table>
<thead>
<tr>
<th></th>
<th>No CAAN</th>
<th>With CAAN</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Endurance time (min)</strong></td>
<td>11.3±2.6</td>
<td>11.0±2.6</td>
<td>0.343</td>
</tr>
<tr>
<td><strong>Peak heart rate (% for age)</strong></td>
<td>86.7±5.0</td>
<td>87.4±6.2</td>
<td>0.291</td>
</tr>
</tbody>
</table>

### HR response & recovery

<table>
<thead>
<tr>
<th>Time</th>
<th>No CAAN</th>
<th>With CAAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T-max</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R-1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R-5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### BP response

**Exercise challenge (min)**

- T0
- T3
- T6
- T9
- T-max
- R-1
- R-5

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*ExerciseResponseinChildrenandAdolescentsLateAfterKDKDS-2015*
BP response: CAAN vs no CAAN

BP response
All subjects

BP (mmHg)

Exercise challenge (min.)

No CAAN
With CAAN
Myocardial perfusion

<table>
<thead>
<tr>
<th></th>
<th>No CAAN</th>
<th>With CAAN</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fixed defects</td>
<td>12.8%</td>
<td>11.3%</td>
<td>0.708</td>
</tr>
<tr>
<td>Stress-induced defects</td>
<td>22.2%</td>
<td>16.5%</td>
<td>0.255</td>
</tr>
</tbody>
</table>

Subjects were redistributed based on perfusion scan, irrespective of CA status.

Subsequent analysis

ExerciseResponseinChildrenandAdolescents
LateAfterKDIKDS-2015
Abnormal perfusion imaging identified:
- lower HR
- lower diastolic BP

during recovery
Patients with normal MIBI

<table>
<thead>
<tr>
<th></th>
<th>No CAAN</th>
<th>With CAAN</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Endurance</strong></td>
<td>11.47±2.7</td>
<td>11.1±2.6</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Peak HR (%-age)</strong></td>
<td>86.6±5.2</td>
<td>87.6±6.2</td>
<td>NS</td>
</tr>
</tbody>
</table>

![Graph showing BP response](image1)

![Graph showing HR response](image2)

ExerciseResponseinChildrenandAdolescents
LateAfterKDIKDS-2015
Normalized heart-rate response

Comparable at all stages between CAAN+ and CAAN-

P-values
NS: not significant
*: p<.01
**: p<.001
Normalized Systolic BP response

Comparable at all stages between CAAN+ and CAAN-

- NS: not significant
- *: p<.01
- **: p<.001

P-values

ExerciseResponseinChildrenandAdolescentsLateAfterKDKDS-2015
Normalized Diastolic BP response

Comparable at all stages between CAAN+ and CAAN-

P-values
NS: not significant
*: p<.01
**: p<.001
Conclusion

- **Exercise capacity is preserved:**
  - Irrespective of CAAN status
  - Irrespective of myocardial perfusion status

- **Chronotropic response:**
  - HR acceleration is NOT affected by CAAN or perfusion status
  - Faster HR recovery in subjects with abnormal perfusion

- **Blood pressure response**
  - Is NOT affected by the CAAN status
  - Diastolic BP is lower at recovery in subjects with abnormal perfusion

- **Normalized** HR and BP response sub-normal vs. published pediatric series of healthy children
Questions ?
Lessons and future directions

• Assess autonomic system behavior post KD

• Assess response to exercise based on NT-proBNP profiling at onset.
Introduction

• KD classified under the vasculitis nomenclature

• Severity of cardiovascular sequelae associated with the severity of coronary artery (CA) lesions:
  - aneurysms → the most severe complications
  - stenosis → Incremental prevalence during youth
  - Primary myocardial infarction: first year after onset
  - Secondary myocardial infarction: pre-adolescence and up

• KD causes inflammatory myocarditis in all patients
## BP response: all normal MIBI scan

<table>
<thead>
<tr>
<th>SBP/DBP (mmHg)</th>
<th>No CAAN (n=111)</th>
<th>With CAAN (n=91)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>107±13/65±12</td>
<td>112±12/67±9</td>
<td>0.005/NS</td>
</tr>
<tr>
<td>3 min</td>
<td>117±23/63±8</td>
<td>123±19/66±10</td>
<td>NS/0.045</td>
</tr>
<tr>
<td>6 min</td>
<td>124±22/64±10</td>
<td>129±24/66±12</td>
<td>NS / NS</td>
</tr>
<tr>
<td>9 min</td>
<td>132±25/63±8</td>
<td>133±28/66±10</td>
<td>NS / NS</td>
</tr>
<tr>
<td>Peak</td>
<td>136±26/69±16</td>
<td>143±29/70±17</td>
<td>NS / NS</td>
</tr>
<tr>
<td>Rec.1min</td>
<td>135±29/67±16</td>
<td>134±27/68±15</td>
<td>NS / NS</td>
</tr>
<tr>
<td>Rec.5min</td>
<td>120±23/65±12</td>
<td>121±19/66±10</td>
<td>NS / NS</td>
</tr>
</tbody>
</table>