CDC ME/CFS SEC Call

“Exercise Testing in the MCAM Study”
Dane B. Cook, PhD

May 13, 2021
3:00 PM ET
AGENDA

• Welcome—Christine Pearson
• CDC Program Overview—Dr. Beth Unger
• Guest Speaker—Dr. Dane B. Cook
• Questions and Answers

Federal Relay
Event ID: 4780203
For closed captioning, please visit

The findings and conclusions in these presentations are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.
Disclosure

Dr. Dane Cook received funding from CDC for the analysis of the MCAM study.
Exercise Testing in the MCAM Study

Dane B. Cook, PhD
University of Wisconsin-Madison
Rationale for Cardiopulmonary Exercise Testing (CPET)

Determine the Integrative response to physical effort
### CPET Measures & Indications

<table>
<thead>
<tr>
<th>DIRECT MEASURES</th>
<th>INDIRECT MEASURES</th>
<th>INDICATIONS/EVALUATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygen Consumption ((VO_2))</td>
<td>VE/(VO_2) &amp; VE/V(CO_2)</td>
<td>Exercise Tolerance</td>
</tr>
<tr>
<td>Carbon Dioxide Production (V(CO_2))</td>
<td>Oxygen Pulse ((VO_2/HR))</td>
<td>Heart and Lung Disease/Symptoms</td>
</tr>
<tr>
<td>Ventilation [VE: (Bf &amp; (T_v))]</td>
<td>(VO_2/WR)</td>
<td>Impairment/Disability</td>
</tr>
<tr>
<td>Heart Rate (HR)</td>
<td></td>
<td>Safety/Prescription for Rehabilitation</td>
</tr>
<tr>
<td>Work Rate (WR)</td>
<td></td>
<td></td>
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<tr>
<td>Oxygen Saturation</td>
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</tbody>
</table>
Exercise Testing in ME/CFS

• Valuable method and clinical tool:
  • Test cardiopulmonary system
  • Determine exercise tolerance
  • Guide exercise prescription
  • Challenge physiological systems
Phenomenon or Epi-phenomenon

• Critical for interpretation
• Recent meta-analysis found clinically meaningful differences in peak oxygen capacity
• We know little beyond threshold and peak responses

Franklin et al. 2019; Int J Sports Med
Chronotropic incompetence

- Cardiac responses to exercise have been the focus of several studies
- Meta-analysis showed large effect size differences between ME/CFS and controls at peak exercise
  - Effect size $d = 1.37$
  - Controls = 94% age-predicted
  - ME/CFS = 82.2% age-predicted

Purpose

1. Characterize
   • Exercise capacity of the MCAM cohort

2. Conduct
   • Comprehensive assessment of the cardiopulmonary, metabolic, and perceptual responses to exercise in ME/CFS

3. Determine
   • The role of aerobic fitness
Methods
Procedures

Participants

ME/CFS
(n=179; 65% Female)

Controls
(n=169; 68% Female)

Testing

20–24°C
40–60% relative humidity

No smoking 2 hrs
No caffeine or food 4 hrs
No exercise 24 hrs

12-lead ECG
Exercise Safety
Resting HR
Exercise Testing (Ramped Cycle Ergometry)

Sample Max Test

- Metabolic measurement
  - Oxygen consumption (VO2)
  - Carbon dioxide production (VCO2)
  - Ventilation (VE)
  - Heart rate (HR)
  - Work rate (Watts)
Metabolic Exercise Testing Analyses

- **Threshold Capacity**
  - VT
  - Peak VO₂

- **Efficiency**
  - VE/V̇CO₂
  - VE/VO₂
  - VO₂/HR

- **Work Rate**
  - Watts
  - ΔVO₂/ΔWR

- **Ventilation**
  - V̇ₜ and ḟᵣ
  - OUES
Data Processing (Independent & blind to clinical status)

Protocol check
- Systems Calibrated
- Obvious data artifacts

Peak Criteria check
- RER ≥ 1.1
- Reaching ≥ 85% age-predicted peak HR
- RPE ≥ 17

Calculation of Relative Exercise Intensities (0-100%)
- 20-sec intervlas (backward from peak VO2 timepoint)
- Linear model to determine the relative percent of peak VO2 for each variable
Results

Entire Sample and Fitness-Matched Subset
# Demographic Data

<table>
<thead>
<tr>
<th></th>
<th>Entire Sample</th>
<th>Fitness–Matched</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>ME/CFS (n=179)</td>
<td>Controls (n=169)</td>
</tr>
<tr>
<td>% Female</td>
<td>65</td>
<td>68</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>49.4 (13.2)</td>
<td>42.5 (14.0)</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.7 (0.1)</td>
<td>1.7 (0.09)</td>
</tr>
<tr>
<td>Weight (kgs)</td>
<td>78.5 (18.7)</td>
<td>73.0 (16.0)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.3 (6.9)</td>
<td>26.0 (5.1)</td>
</tr>
</tbody>
</table>
## Ventilatory and cardiac performance during exercise

<table>
<thead>
<tr>
<th>Ventilatory &amp; Cardiac Performance</th>
<th>Entire Sample</th>
<th>Fitness –Matched</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ME/CFS (n=179)</td>
<td>Controls (n=169)</td>
</tr>
<tr>
<td><strong>VE/VCO₂nadir</strong></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>27.8 (5.9)</td>
<td>25.3 (3.1)</td>
</tr>
<tr>
<td></td>
<td>(0.29 – 0.72)</td>
<td>(0.29 – 0.72)</td>
</tr>
<tr>
<td><strong>OUES</strong></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>1.87 (0.67)</td>
<td>2.16 (0.78)</td>
</tr>
<tr>
<td></td>
<td>(0.67)</td>
<td>(0.78)</td>
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<tr>
<td><strong>OUES&lt;sub&gt;BSA&lt;/sub&gt;</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.97 (0.30)</td>
<td>1.18 (0.39)</td>
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<tr>
<td></td>
<td>(0.30)</td>
<td>(0.39)</td>
</tr>
<tr>
<td><strong>% HRR&lt;sub&gt;adjusted&lt;/sub&gt;</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>83.5 (15.7)</td>
<td>89.8 (12.1)</td>
</tr>
<tr>
<td></td>
<td>(15.7)</td>
<td>(12.1)</td>
</tr>
<tr>
<td><strong>% Predicted Max HR</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>90.0 (9.8)</td>
<td>93.3 (7.8)</td>
</tr>
<tr>
<td></td>
<td>(9.8)</td>
<td>(7.8)</td>
</tr>
</tbody>
</table>
Dynamic Exercise Responses—Fitness

\[ \dot{V}O_2 \text{ (ml/kg/min)} \]

\[ \text{Percentage of peak} \]

\[ p < 0.05_{\text{adjusted}} \]

\[ \text{ME/CFS} \]

\[ \text{Control} \]

\[ \text{Watts} \]

\[ \text{Percentage of peak} \]

\[ p < 0.05_{\text{adjusted}} \]

\[ \text{ME/CFS} \]

\[ \text{Control} \]

\[ \dot{V}O_2 \text{ (ml/kg/min) (matched)} \]

\[ \text{Percentage of peak} \]

\[ \text{ME/CFS} \]

\[ \text{Control} \]

\[ \text{Watts (matched)} \]

\[ \text{Percentage of peak} \]

\[ \text{ME/CFS} \]

\[ \text{Control} \]
Dynamic Exercise Responses #1

**\( \dot{V}E \) (L/min)**
- ME/CFS
- Control

**fR (breaths/min)**
- ME/CFS
- Control

**VT (L/min)**
- ME/CFS
- Control

**\( \dot{V}E \) (L/min) (matched)**
- ME/CFS
- Control

**fR (breaths/min) (matched)**
- ME/CFS
- Control

**VT (L/min) (matched)**
- ME/CFS
- Control
Discussion
Summary & Conclusions

Entire Sample

- ↓ reduced oxygen uptake
- ↓ cardiac performance
- Inefficient pulmonary ventilation (↑ VE/VCO2 & VE/VO2)
- ↑ perception of effort

Fitness-Matched Sample

- Inefficient pulmonary ventilation:
  - ↑ VE/VCO2 & VE/VO2; ↓ breathing frequency & ↑ volume)
  - ↑ perception of effort
Summary & Conclusions #2

Gas Exchange

- VE/VCO₂ = poor perfusion
- VE/VO₂ = poor extraction from skeletal

Unique breathing pattern

- Improve alveolar ventilation (make-up for dead-space)
- Respiratory muscle fatigue and subsequent metaboreflex (vasoconstriction of exercising muscle) – aka Robin Hood for the lungs
Summary & Conclusions #3

Little evidence for overt chronotropic incompetence

• Fitness matching appears critical

Future Directions

• Relationships between cardiopulmonary inefficiencies
  • Symptoms
  • Cognition
  • Sleep
Take Home Message

We observed clinically relevant indications of a compromised cardiopulmonary response in ME/CFS

• Inefficient exercise ventilation even when accounting for fitness

ME/CFS is not a disease of low aerobic fitness

• False narrative
  • Damaging to ME/CFS community & research
  • Understanding how the cardiopulmonary system interacts with the disease is important
Acknowledgements

- Dane Cook, PhD
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- Pain and Fatigue Study Center, NY
- Center for Neuro-Immune Disorders, FL
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  - Open Medicine Clinic, CA
  - Sierra Internal Medicine Associates, NV
  - Fatigue Consultation Clinic, UT
  - Hunter-Hopkins Center, NC
  - Richard Podell Clinic, NJ
- CDC Chronic Viral Diseases Branch, ME/CFS Program
Questions and Answers

To ask a question within the Zoom webinar platform during the meeting, please:

• Click on the “Q&A” button.
• Type your question in the “Q&A” box.
• Submit your question.

If you have additional questions following the call, please email MECFSSEC@cdc.gov.
Extras
Dynamic Exercise Responses View Two

**Whole Sample**

**Fitness-Matched Sub-Sample**
Chronotropic Incompetence Part One

• HRR
  • ME/CFS—33% did not meet 80% criteria
  • Control—14%

• Peak HR
  • ME/CFS—21% did not meet 85% criteria
  • Controls—9%

• CTI
  • ME/CFS—ranged from 4-17% below slope of 0.8 for a given stage
  • Controls—1-13%
  • 100% for each group achieved a slope of > .8 at some point during exercise
Chronotropic Incompetence Part Two

- ≥ 85% of age-predicted maximal HR (APMHR)
- ≥ 80% of adjusted heart rate reserve (HRR/APMHR – HR_{rest})
- Chronotropic index (CTI – Wilkoff Model):
  - Based on estimated HR stages
  - measured HR_{stage} / estimated HR_{stage}
    - Ratios ≤ 0.80 are indicative of chronotropic incompetence

Brubaker and Kitzman, 2011-Chronotropic Incompetence Causes, Consequences, and Management.
Contemporary Reviews in Cardiovascular Medicine
Statistical Analyses

• Normality
  • Skewness, kurtosis, Q-Q plots, and the Shapiro-Wilk test
  • Data were normalized using a two-step approach as described by Templeton¹

• Levene’s Test
  • Equal variances between groups

• Hedge’s $d$ effect size with 95% confidence intervals²:
  • Subject characteristics, measures at the VT, OUES, and peak exercise

• Linear Mixed Effects models with repeated measures
  • VE, fR, $V_T$, VE/VO2, VE/VCO2, HR, $O_2$ pulse, CTI & RPE
  • $\alpha = 0.05$; Holm-Bonferroni Sequential Method

• Fitness-matched subset
  • $\pm 1$ ml/kg/min peak VO$_2$
  • $\pm 5$ years age

¹Templeton GF. A two-step approach for transforming continuous variables to normal: implications and recommendations for IS research. Communications of the Association for Information Systems. 2011;28(1):4.;
<table>
<thead>
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<td>27.3 (6.9)</td>
<td>26.0 (5.1)</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>67.9 (11.6)</td>
<td>62.2 (10.0)</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>121.8 (14.0)</td>
<td>121.5 (15.8)</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>79.6 (9.8)</td>
<td>76.7 (10.6)</td>
</tr>
<tr>
<td>Physical Function***</td>
<td>40.7 (5.3)</td>
<td>59.0 (6.5)</td>
</tr>
<tr>
<td>IPAQ Total (min/week)</td>
<td>46.1 (79.5)</td>
<td>106.7 (103.7)</td>
</tr>
<tr>
<td>IPAQ Recreation (min/week)</td>
<td>8.9 (23.9)</td>
<td>26.2 (30.8)</td>
</tr>
<tr>
<td>IPAQ Sitting Total (hrs/week)</td>
<td>60.1 (25.3)</td>
<td>54.9 (42.1)</td>
</tr>
<tr>
<td>Ventilatory Threshold</td>
<td>Entire Sample</td>
<td>Matching</td>
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<tr>
<td>-----------------------</td>
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</tr>
<tr>
<td>%peak VO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>52.9 (0.1)</td>
<td>51.2 (0.1)</td>
</tr>
<tr>
<td>VO&lt;sub&gt;2&lt;/sub&gt; (ml)</td>
<td>947.1 (396.7)</td>
<td>1089.3 (503.6)</td>
</tr>
<tr>
<td>VCO&lt;sub&gt;2&lt;/sub&gt; (ml)</td>
<td>52.8 (0.1)</td>
<td>51.3 (0.09)</td>
</tr>
<tr>
<td>RER</td>
<td>0.84 (0.07)</td>
<td>0.86 (0.08)</td>
</tr>
<tr>
<td>VE (L/min)</td>
<td>18.8 (7.1)</td>
<td>22.3 (9.5)</td>
</tr>
<tr>
<td>fR (breaths/min)</td>
<td>19.9 (5.2)</td>
<td>22.1 (4.8)</td>
</tr>
<tr>
<td>V&lt;sub&gt;T&lt;/sub&gt; (L/min)</td>
<td>1.02 (0.41)</td>
<td>1.03 (0.40)</td>
</tr>
<tr>
<td>VE/VO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>0.84 (0.07)</td>
<td>0.86 (0.08)</td>
</tr>
<tr>
<td>VE/VCO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>0.32 (0.13)</td>
<td>0.35 (0.15)</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>103.2 (17.6)</td>
<td>108.7 (19.8)</td>
</tr>
<tr>
<td>O&lt;sub&gt;2&lt;/sub&gt; pulse (VO&lt;sub&gt;2&lt;/sub&gt;/HR)</td>
<td>9.2 (3.5)</td>
<td>10.0 (4.1)</td>
</tr>
<tr>
<td>CTI</td>
<td>0.92 (0.13)</td>
<td>0.97 (0.15)</td>
</tr>
<tr>
<td>Watts</td>
<td>56.0 (27.7)</td>
<td>73.0 (35.2)</td>
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### Peak Responses

<table>
<thead>
<tr>
<th></th>
<th>Entire Sample</th>
<th>Fitness –Matched</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>ME/CFS (n=179)</td>
<td>Controls (n=169)</td>
</tr>
<tr>
<td>Peak VO₂ (ml/kg/min)</td>
<td>23.4 (8.6)</td>
<td>29.9 (10.9)</td>
</tr>
<tr>
<td>VO₂ (ml)</td>
<td>1817.3 (704.9)</td>
<td>2121.2 (761.8)</td>
</tr>
<tr>
<td>VCO₂ (ml)</td>
<td>2111.0 (766.2)</td>
<td>2423.9 (787.9)</td>
</tr>
<tr>
<td>RER</td>
<td>1.18 (0.1)</td>
<td>1.16 (0.08)</td>
</tr>
<tr>
<td>VE (L/min)</td>
<td>54.7 (21.3)</td>
<td>63.0 (21.2)</td>
</tr>
<tr>
<td>Fr (breaths/min)</td>
<td>34.7 (10.5)</td>
<td>38.9 (8.8)</td>
</tr>
<tr>
<td>V̇₆ (L/min)</td>
<td>1.79 (0.59)</td>
<td>1.74 (0.59)</td>
</tr>
<tr>
<td>VE/VO₂</td>
<td>38.5 (9.5)</td>
<td>34.0 (6.2)</td>
</tr>
<tr>
<td>VE/VCO₂</td>
<td>32.8 (7.4)</td>
<td>29.6 (4.7)</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>156.0 (20.2)</td>
<td>166.5 (17.6)</td>
</tr>
<tr>
<td>O₂ pulse (VO₂/HR)</td>
<td>11.6 (4.2)</td>
<td>12.8 (4.6)</td>
</tr>
<tr>
<td>CTI</td>
<td>0.93 (0.12)</td>
<td>0.96 (0.12)</td>
</tr>
<tr>
<td>Watts</td>
<td>138.6 (42.3)</td>
<td>163.3 (50.1)</td>
</tr>
<tr>
<td>RPE (6-20)</td>
<td>19.2 (1.0)</td>
<td>18.2 (2.0)</td>
</tr>
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