Making the case for clinical exercise testing in CFS/ME research and treatment

Christopher R. Snell, PhD
Staci Stevens, MA
Mark Van Ness, PhD
Brian Moore, PhD

University of the Pacific
Stockton, California
The Disease with the Dragon Tattoo

The Stigma of CFS/ME

With apologies to Stieg Larsson
Why won’t you talk to doctors?

Because they don’t listen to what I say

*Lisbeth Salander, The Girl Who Kicked the Hornet’s Nest*
Asking the Right Questions

- **Immune**
  - Sleep disturbance
  - Flu-like

- **Fatigue**
  - Tiredness
  - Difficulty concentrating

- **Pain**
  - Muscle
  - Joint
  - Migrating pain
  - Stiffness

- **Neuroendocrine**
  - Sensory changes
  - Orthostasis
  - Dizziness

EXERCISE RECOVERY QUESTIONS
(Post-Exertional Pathophysiology in CFS)

July 01 - Fem 21

Date of Exercise Test: 9/24 - 9/25

How did you feel following the first exercise test?

a little sore and tired

Describe how you felt the day after the first exercise test.

felt a little tired but otherwise

that felt fine

How did you feel following the second exercise test?

didn't go home and did housework actually felt a little energetic

Describe how you felt the day after the second exercise test.

Tired

How long did it take you to recover from the exercise test? Circle the appropriate time... (in days)

less than 0 1 2 3 4 5 6 7 still not recovered

Comments:

Describe symptoms, if any, experienced after the exercise tests.

No

EXERCISE RECOVERY QUESTIONS
(Post-Exertional Pathophysiology in CFS)

Study ID: DEM 28

Date of Exercise Test: 11/5, 11/6, 11/7

1. How did you feel following the first exercise test?

weak, shaky, nausea, some dizziness, tired

1 needed to rest - and wanted to either lie down or sit. slight headache - legs tired, brain short of breath - "fog".

2. Describe how you felt the day after the first exercise test.

Tired - hard to get up in the morning. Legs felt tired, low energy. Brain "fog", arms & legs felt "heavy". Some sadness in legs/muscles.

3. How did you feel following the second exercise test?

short of breath, very shaky, legs very tired, weak, some nausea, weak, fog. In the afternoon and evening I got a bad headache. Some nausea. Hip joint pain, tired / sleepy. Too tight to eat dinner.

4. Describe how you felt the day after the second exercise test.

Tired. I was very tired. Strong headache, strong nausea, exhausted, weak, brain "fog". My joints felt stiff and hurt. Lower back stiffness. My body feels shakier harder to get up because of very low energy, some dizziness

5. How long did it take you to recover from the exercise test? Circle the appropriate time... (in days)

less than 1 2 3 4 5 6 7 still not recovered

Comments: I had nausea and headaches daily for almost a week after the tests.

6. Describe symptoms, if any, experienced after the exercise tests.

see comments / details in items 1-5 above.
Van Ness et al 2010 – *Journal of Women’s Health*
The remaining 15% of control subjects recovered within 48 hours

Only one subject with CFS recovered within 48 hours!

Van Ness et al 2010 – *Journal of Women’s Health*
What Does “Exercise Intolerance” Mean?

- Diminished functional capacity
- Reduced physical working capacity
- Post-Exertional Malaise
- Exacerbation of symptoms (“flare-up”)
- Post-Exertional Neuroimmune Exhaustion
  - Immune and neurological symptoms
Overtraining Syndrome

Sustained reductions in performance often accompanied by other biochemical, physiological and psychological changes
Overtraining Indicators

• Physical
  – Constant Fatigue
  – Reduced Performance
  – Muscle Soreness
  – Swollen Lymph Glands
  – Infection
  – Decreased Exercise Heart Rate

• Behavioral
  – Lethargy
  – Changes in Sleep Pattern
  – Poor Concentration
  – Irritability
  – Clumsiness
  – Sluggishness
Fact or Fiction?

Graded exercise is an effective treatment for people with CFS/ME.
Summary of Research Findings on Graded Exercise in CFS

- Beneficial effect on physiological functioning and health perceptions
- Mixed effects on self-reported activity level
- Less adherence to treatment
- But do people with CFS really improve?
Well Intentioned Exercise that Doesn’t Improve Function

<table>
<thead>
<tr>
<th></th>
<th>May 2009</th>
<th>June 2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{VO}_2 )</td>
<td>21ml/kg/min</td>
<td>17.6 = 16% drop</td>
</tr>
<tr>
<td>( \text{VO}_2\text{AT} )</td>
<td>10 ml/kg/min</td>
<td>8.4 = 16% drop</td>
</tr>
</tbody>
</table>

- Walking program: Aerobic capacity and anaerobic threshold did not improve.
Assessing Function

Vs.
Value of Exercise Testing

- Organs and organ systems have built-in reserve capacity
- Disease states reduce this capacity
- In the absence of stress, reduction in functional capacity isn’t always seen
- Exercise is an effective way to induce stress
Stressing the System

![Image of a person lying in a swimming pool]

![Bar chart showing cardiac output (L/Min) at Rest, Max CO in Health, and Max CO in Disease with an arrow labeled jogging]
What is goal of exercise testing?

• Assess function of the cardio-respiratory system

• Determine functional capacity
  – Focus on aerobic capacity
Energy Production

Two Main Energy Liberation Systems:

**Aerobic Metabolism**
- oxygen dependent
- very efficient
- time intensive
- predominates at lower workloads
- CO₂ is byproduct

**Anaerobic metabolism**
- No oxygen needed
- Contributes more at higher workloads
- 2 ATP per glucose vs. 30-36
- Lactic acid is byproduct

Exercise Intensity
Why the fuss over Lactic Acid?

Lactic Acid → Lactate + H^+

Altered muscle and blood pH!
- Pain
- Reduced muscle function
- Altered enzyme activity
- Cessation or reduction in activity
Quantifying Aerobic Capacity

<table>
<thead>
<tr>
<th>VO2 MAX</th>
<th>Anaerobic Threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum amount of oxygen system can deliver and combust (L/min). AKA maximal oxygen consumption.</td>
<td>The level of exercise oxygen consumption above which aerobic energy production is supplemented by anaerobic mechanisms.</td>
</tr>
</tbody>
</table>

Both VO₂Max and Anaerobic Threshold (AT) can be determined:

1) **Directly** measured during a graded exercise test
   - Gas exchange techniques
   - Measurement of blood lactate levels

2) **Indirectly** estimated by recording HR response or onset of fatigue during a graded exercise test and apply regression equations developed from study populations
Modes of Testing Aerobic Capacity with a Graded Exercise Test

- Field tests
  - Cooper 12-minute test
  - Rockport One-Mile Fitness Walking Test
  - 6 minute walk test

- Step tests

- Treadmill tests

- Cycle ergometer tests
Field Tests
Field Tests

• Advantages
  – Easy to administer
  – Ability to test many individuals at once
  – Require minimal equipment

• Disadvantages
  – Unmonitored BP and HR
  – Aerobic capacity is estimated.
  – May result in inadvertent max testing in some populations
  – Motivation and pacing plays a big role in results
Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial

6-min walking test n=110 (69%)
Baseline distance (m) 312
52-week distance (m) 379*

1.94-2.35 mph
2 Mets = 7ml/min/kg O₂
Weber/NYHA Severely Disabled

1.94 mph vs 2.35 mph
Treadmill  Cycle Ergometer  Step Test
Indirect Estimation of Aerobic Capacity

Employ regression equations derived from experimental data to estimate $V_{O_2}\text{max}$ and anaerobic threshold from performance on field tests, step tests, treadmill or ergometer.
Limitations of Indirect Assessment

- May not apply to special populations/disease states
- Biased by tested population
- Biologic variability of heart rate response to exercise
- Dangers of using regression models outside tested values
- Assumptions must be made
  - Steady state of HR achieved during exercise
  - Linear relationship between measured variable and VO₂
  - Response for given age group is uniform
  - Mechanical efficiency is same for every individual
  - Individual is not on medications that effect measured variable
May not apply in Disease

• “Mild exercise led to rapid fatigue, with hyperventilation and disproportionate tachycardia.”

• “In conclusion, the association of an abnormal stress response with nonmetabolic factors, including backscatter and blunted peak heart rate…”
Biologic Variability of Heart Rate

• “SRBD is associated with reduced physical working capacity and a modified hemodynamic response to exercise.”

• Variables affecting heart rate response
  – Medications
  – Ambient temperature
  – Environmental noise
  – Body temperature
  – Elevation
  – Time of day
  – Illness
Biased by Tested Population

• “These findings demonstrate that a novel treadmill-based PRET can yield predictions of VO2max that are acceptably reliable and valid amongst young, healthy, and active adults.”

• “These results indicate that a four minute aerobic dance test provides a valid and reliable sub-maximal protocol for estimating VO2max and providing an index of aerobic fitness in apparently healthy 18 to 40 yr old females.”
Regression Modeling Limitations

• Linear relationship may break down outside of a specified range
Direct Assessment of Aerobic Capacity

- Maximum Oxygen Consumption (VO₂max)
- Anaerobic Threshold (AT)
Principles of Gas Exchange

- Aerobic metabolism burns O₂ and produces CO₂
- By measuring the difference between inspired and expired gases, it can be determined how much O₂ is consumed and how much CO₂ is produced
Maximal Oxygen Uptake

- VO$_2$ max is strongly correlated with endurance performance capability
- Dependent on cardiovascular limitations; ability of heart, lungs, and circulatory system to deliver O$_2$ to working muscle
Anaerobic Threshold

- Exercise intensity above which aerobic metabolism is significantly supplemented by anaerobic energy production.

- Can be identified through measuring gas exchange.
Measuring AT with Gas Exchange

- Respiratory Exchange Ratio RER (R)

\[
\frac{CO_2 \text{ Produced}}{O_2 \text{ Consumed}}
\]

Average R value with modern diet, \( R = 8.0 \)
With increasing exercise intensity R value exceeds 1?
Why?
Measuring AT with Gas Exchange

![Graph showing VCO₂ vs. VO₂](image-url)
Accuracy of Direct vs Indirect Measurements of Aerobic Capacity

- Indirect estimates of VO$_2$max can routinely vary by $\pm 25\%$
- Ventilatory threshold is highly correlated to blood lactate threshold and aerobic performance.
- Measuring gas exchange allows you to accurately and reliably determine effort
Respiratory Exchange Ratio (VCO₂:VO₂)

“This physiological response to exercise is consistent in apparently healthy subjects and all patient populations, which makes peak RER the most accurate and reliable gauge of subject effort. A peak RER of 1.10 is generally considered an indication of excellent subject effort.”

Summary

• Determining aerobic capacity is crucial when assessing level of function and constructing an exercise protocol.
• Oxygen uptake and anaerobic threshold are two parameters that are closely correlated to aerobic performance.
• Direct measurements of aerobic capacity are much more accurate, especially in special populations and disease states.
## Moderate to Severe Impairment in CFS/ME

<table>
<thead>
<tr>
<th>Severity of Impairment</th>
<th>Peak VO$_2$ (ml/kg/min)</th>
<th># of patients</th>
<th>Group VO$_2$ (ml/kg/min)</th>
<th>Predicted VO$_2$ (ml/kg/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None to Mild</td>
<td>&gt;25</td>
<td>33</td>
<td>29.5 ± 0.9</td>
<td>38.6 ± 1.2</td>
</tr>
<tr>
<td>Mild to Mod</td>
<td>20-25</td>
<td>72</td>
<td>22.1 ± 0.2</td>
<td>35.3 ± 0.8</td>
</tr>
<tr>
<td><strong>Mod to Severe</strong></td>
<td>15-20</td>
<td><strong>77</strong></td>
<td>17.2 ± 0.2</td>
<td>34.2 ± 0.6</td>
</tr>
<tr>
<td>Severe</td>
<td>&lt;15</td>
<td><strong>21</strong></td>
<td>12.1 ± 0.5</td>
<td>33.0 ± 0.6</td>
</tr>
</tbody>
</table>
Reduced Functional Capacity

- Riley et al., 1990
- Demitrack et al., 1998
- DeBecker et al., 2000
- VanNess et al., 2003
- Vermulen et al., 2010
- Jones et al., 2011

*Difficult to separate “CFS effects” from detraining*
Exercise Test-Retest Paradigm

- Waxing and waning of symptoms
- Fluctuations in fatigue levels

*“Induced”* Post-Exertional Effect
Reduced Ability to Utilize Oxygen in the Post-Exertional State

Metabolic Dysfunction

Repeated Exercise Tests

• Demonstrates the effect of post-exertional malaise
• Quantifies the magnitude of the post-exertional effect (Fatigue Effect)
• Informs the mechanisms of the response
• Reproducibility?
The Abnormal Stress Test: Objective Evidence of CFS Disability

Decline in VO$_2$peak/AT values:

1. Atypical recovery response
   Abnormal stress test
   Post-exertional malaise

2. Distinguishes CFS from other illnesses

Pacific Study: CFS 24.5% decrease.

Prior: Other illnesses 7.28% variability.

Ciccolella et al, 2007

Clinical Exercise Testing (Weisman & Zeballos), p.28
TEST-RETEST

ATVO2 (ml/kg/min); ATWL (Watts)

ME/CFS ATVO2
CONTROL ATVO2
ME/CFS ATWL
CONTROL ATWL

T1 T2
Failure to Reproduce?

- Inflammatory cytokine elevation (Klimas et al., 2007)
- Neuroendocrine dysfunction
- Cardiovascular abnormalities
- Mitochondrial abnormalities (Whister et al., 2006, Wong et al., 1992)
Exercise Intolerance - Summary

- CFS/ME patients have reduced physical working capacity
- Aerobic energy generation is impaired in CFS
- Activity exacerbates symptoms
Conclusions

• Cardiopulmonary exercise testing can provide objective measures of fatigue in CFS/ME (functional endpoint for clinical trials; disability assessment)

• A single exercise test may be insufficient to distinguish between CFS/ME and sedentary controls

• As a quantifiable stressor, CPET has the capacity to reveal abnormalities across multiple systems

• Availability of the RER, a measure exclusive to analysis of expired gases, provides the most accurate and reliable gauge of subject effort
Energy Systems in CFS
Oxygen Debt: Rest is Key

- **Oxygen debt**: the difference between oxygen required for activity/exercise and oxygen supplied and used

- **Oxygen deficit** = fatigue

- *For CFS ADLs Create Debt*

- *Payback Debt with Rest*
Credit Card Analogy

- Athlete: 5% interest rate
- Sedentary: 10% interest
- CFS: 50% interest
Activity Biofeedback

- Maintain heart rate below anaerobic threshold
- Calculate or measure heart at anaerobic threshold
- Perceived exertion scale
- Maintain a log
### Rating of Perceived Exertion

<table>
<thead>
<tr>
<th>Number</th>
<th>Description</th>
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<tbody>
<tr>
<td>6</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Very, very light</td>
</tr>
<tr>
<td>8</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Very light</td>
</tr>
<tr>
<td>10</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Fairly light</td>
</tr>
<tr>
<td>12</td>
<td></td>
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</tbody>
</table>
# Sample Activity Log

<table>
<thead>
<tr>
<th>Time</th>
<th>Activity</th>
<th>HR</th>
<th>RPE</th>
<th>Body Position</th>
<th>Under AT</th>
</tr>
</thead>
<tbody>
<tr>
<td>8:00am</td>
<td>Meal</td>
<td>90</td>
<td>10</td>
<td>Sit</td>
<td>Yes</td>
</tr>
<tr>
<td>8:30</td>
<td>Dishes</td>
<td>120</td>
<td>15</td>
<td>Stand</td>
<td>No</td>
</tr>
<tr>
<td>9:00</td>
<td>Shower</td>
<td>140</td>
<td>15</td>
<td>Stand</td>
<td>No</td>
</tr>
<tr>
<td>10:00</td>
<td>Rest</td>
<td>85</td>
<td>10</td>
<td>Lie</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Ask the Right Questions

1. What **activities** do you do you?
2. How do you feel immediately…the next day?
3. Do you experience post-activity/PT relapse?
4. Is PT changing ADLs?
Types of Energy/Stressors

- Physical
- Cognitive/Mental
- Social
- Emotional
- Spiritual
Dual Focus for Therapy

- Adaptation by both patient and therapist
  - Increase capacity through activity modification education
  - Balance rehab with quality of life for patient
  - Train the short term energy system
Energy Conservation
Education

Be Smart: Think Differently
Energy Conservation Therapy

• Pacing
  – Rest breaks

• Body Position
  – Sit vs. stand

• Joint Protection
  – Assistive devices

• Activity Planning
  – Balance light and heavy tasks
Energy Saving Tips

- Learn to say “no”…or “yes”
- Prioritize
- Simplify clothing and makeup choices
- Shower seated
- Use an answering machine
- Take it with you
- Make the bed while you’re in it
- Cook ahead
- Use a disabled parking placard
- Pack groceries smart

Stevens & Potratz 2002 – The CFIDS Chronicle
Analeptic Exercise

• Functional movement that will not exacerbate symptoms

• Goal is to improve range of motion and functional strength
Core Concepts

- Appropriate exercise is movement from which the patient recovers
- Exercise needs to be restorative physically and mentally
- Fit program to function
- Payback: Diaphragmatic breathing
- Make room for the program in place of another daily activity
Therapeutic Exercise Progression

• Stage 1: Education and Breathing
• Stage 2: Stretching with Anaerobic Conditioning
• Stage 3: Dose Controlled Interval Training
• Stage 4: Maintenance
Summary

• Understand activity limitations

• Develop an individualized plan
  – Identify activity coping style
  – Stay out of debt/energy conservation
  – Anaerobic therapy
How To Tell It’s Working…

- Empowerment
- Improved Quality of Life
- Sense of Control
- Off the Roller Coaster/Couch
Case Study

- CFS, orthostatic intolerance, 17 year old female.
- ATHR = 110, 38% of predicted VO2 max
- Symptom ranking: fatigue, feel cold, insomnia
- CPX Recovery Response:
  - Immediate: “extremely tired, achiness in muscles and joints”
  - Next day: “extreme fatigue, neck, back, muscle and joint pain”
  - Recovery Time: 1 week unable to participate in any activity
Activity Biofeedback and Breathing

• Activity coping style: avoider
• Plan
  – Stop walking
  – Use HR monitor for ADLs
  – Use breathing for recovery/relaxation
  – Plan enjoyable activity: mini golf, concert
Results

• Activity monitoring: HR exceeds AT when going upstairs and showering.
• Adaptation: Rest halfway up the stairs and breathe. “Breathing relaxes me and the HR monitor goes down 15-20 beats when I do it.”
• Sit down while showering
• “I can do more without feeling as tired. I was able to go miniature golfing and was tired the next day but was able to do it.”
Exercise Program

• Supine resistance bands and stretching (4 bands)
• Ball exercises with weights
• Interval Training
Concert Tips

1. Body Position: recline and rest while driving to concert.
2. Wear support hose or diabetic socks
3. Keep well hydrated
4. Use disabled parking placard to minimize walking
5. Take spray bottle with water to keep cool outside
6. Bring healthy snacks to eat during the event
7. Plan to rest after the concert
Concert Results

- “The concert was great! I followed all of the suggestions and they really helped me. The day after the concert I was tired but on Monday I only felt achy. By Monday night I was back to my pre-concert energy level. Thank you!”