2015 Webinar Series | Thursday, July 16, 2015 | 1:00 PM Eastern

Inducing Post-Exertional Malaise: A Look at the Research Evidence

Peter Rowe, MD
Professor of Pediatrics, Johns Hopkins Children’s Center

www.SolveCFS.org
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Inducing Post-Exertional Malaise: A Look at the Research Evidence

Peter Rowe, MD
Professor of Pediatrics, Johns Hopkins Children’s Center

www.SolveCFS.org
Inducing post-exertional malaise in ME/CFS: a look at the research evidence

July 16, 2015

Peter C. Rowe, MD
From the Pediatric CFS Clinic
Johns Hopkins Children’s Center
Baltimore, MD
Post-exertional malaise

• PEM is an exacerbation of some or all of an individual’s ME/CFS symptoms
• Usually occurs soon after a specific form of exertion, but can begin 5-7 days afterwards
• It occurs after levels of physical or cognitive exertion that were normally tolerated before disease onset
• It leads to a reduction in functional ability

IOM 2015
43 year old with ME/CFS

Fatigue is constant, worse with even modest exertion, such as carrying the grocery bags or walking around the block. On a good day, if she tends to do more, she gets worse symptoms for the next 2-3 days. After watching her son’s baseball game, she had to recline for much of the next 2 days. She has to limit the number of errands she performs each day, often to just 1 trip out of the house, and can’t do the same activity 2 days in a row without getting worse fatigue and much more difficulty concentrating. She is more exhausted when standing in line or sitting for long periods. She is able to read, but more complex texts wear her out.
Why is it important to understand PEM at a research level?
Research triggers for PEM

- Best recognized and studied
  - Physical exertion
- Less well characterized
  - Cognitive exertion
  - Orthostatic stress
- Recently described
  - Biomechanical strain
Research triggers for PEM

• Best recognized and studied
  – Physical exertion
• Less well characterized
  – Cognitive exertion
  – Orthostatic stress
• Recently described
  – Biomechanical strain
Postexertional Malaise in Women with Chronic Fatigue Syndrome

J. Mark VanNess, Ph.D., Staci R. Stevens, M.A., Lucinda Bateman, M.D., Travis L. Stiles, B.S., and Christopher R. Snell, Ph.D.
Study design

• 25 females with CFS (Fukuda definition)
• 23 sedentary controls
• Maximal cardiopulmonary exercise test (duration 5-15 minutes)
• Daily written responses to questions about how they felt and duration of symptoms
<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Speed (mph)</th>
<th>Grade (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>2–4</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>4–6</td>
<td>2</td>
<td>6</td>
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<tr>
<td>6–8</td>
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<td>9</td>
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<td>8–10</td>
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<td>12</td>
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<tr>
<td>10–12</td>
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<td>15</td>
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<tr>
<td>12–14</td>
<td>2</td>
<td>18</td>
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<tr>
<td>14–16</td>
<td>2</td>
<td>21</td>
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<tr>
<td>16–18</td>
<td>3</td>
<td>21</td>
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<tr>
<td>18–20</td>
<td>4</td>
<td>21</td>
</tr>
<tr>
<td>20–22</td>
<td>5</td>
<td>21</td>
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</table>

## Rates of full recovery

<table>
<thead>
<tr>
<th></th>
<th>By 24 hours</th>
<th>By 48 hours</th>
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<tbody>
<tr>
<td>CFS</td>
<td>0%</td>
<td>4%</td>
</tr>
<tr>
<td>Healthy controls</td>
<td>87%</td>
<td>100%</td>
</tr>
</tbody>
</table>

60% of CFS patients reported that it took ≥ 5 days to fully recover
## Fatigue

<table>
<thead>
<tr>
<th></th>
<th>Immediately after test</th>
<th>At 24 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFS</td>
<td>76%</td>
<td>68%</td>
</tr>
<tr>
<td>Healthy controls</td>
<td>48%</td>
<td>4%</td>
</tr>
</tbody>
</table>

Dizziness/lightheadedness

<table>
<thead>
<tr>
<th></th>
<th>Immediately after test</th>
<th>At 24 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFS</td>
<td>68%</td>
<td>24%</td>
</tr>
<tr>
<td>Healthy controls</td>
<td>22%</td>
<td>0%</td>
</tr>
</tbody>
</table>

# Cognitive dysfunction

<table>
<thead>
<tr>
<th></th>
<th>Immediately after test</th>
<th>At day 7</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CFS</strong></td>
<td>28%</td>
<td>48%</td>
</tr>
<tr>
<td><strong>Healthy controls</strong></td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

# Pain

<table>
<thead>
<tr>
<th></th>
<th>Immediately after test</th>
<th>At 48 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CFS</strong></td>
<td>28%</td>
<td>56%</td>
</tr>
<tr>
<td>Healthy controls</td>
<td>26%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Moderate Exercise Increases Expression for Sensory, Adrenergic, and Immune Genes in Chronic Fatigue Syndrome Patients But Not in Normal Subjects

Alan R. Light,* † Andrea T. White, † Ronald W. Hughen,* and Kathleen C. Light*
Study design

- 19 with CFS (Fukuda definition); 15 F
- 16 controls; 11 F
- 25 minutes of arm leg cycle ergometer exercise, maintaining heart rate at 70% of age-predicted maximal HR
- Symptom reports and gene expression markers from WBCs at baseline and up to 48 hours for metabolite detection, adrenergic function, and immune function
Light AR, et al.
J Pain 2009

* indicates significant difference from baseline within groups, P<.05
Influence of Exhaustive Treadmill Exercise on Cognitive Functioning in Chronic Fatigue Syndrome

John J. LaManca, PhD, Sue Ann Sisto, PhD, John DeLuca, PhD, Susan K. Johnson, PhD, Gudrun Lange, PhD, Jacqueline Pareja, BS, Sean Cook, BS, Benjamin H. Natelson, MD, Newark, New Jersey

Am J Med 1998;105 (3A);59S-65S
Study design

• 19 with CFS (Fukuda definition)
• 20 controls; 11 F
• Cognitive tests before, immediately after, and 24-hours post treadmill exercise to exhaustion
• Treadmill started at 2.5 mph on level. After 3 min raised to 3.5 mph. Then incline raised every 3 minutes until subjects could go no further
• Test duration: 15.7 (1.3) vs. 19.8 (1.1); P=.037
Stroop test

• Word test:  
  Black  Red  Blue  Green

• Color test:  
  XXX  XXX  XXX  XXX

• Color/Word test:  
  Black  Red  Blue  Green
Stroop word, color, and color/word tests before, immediately after, and 24 hrs after exercise testing

How does the 2-day repeated CPET paradigm inform the discussion about inducing PEM?
Measurements of workload at peak exercise (A) and at the ventilatory threshold (B) in individuals with CFS and control subjects obtained during cardiopulmonary exercise test #1 (blue bars) and cardiopulmonary exercise test #2 (gold bars).

Changes in physiological and work variables from Test 1 to Test 2 at maximal intensity. Inset: Non-significant test differences for maximal respiratory exchange ratio showed that subjects achieved consistently high RER (>1.1) for Test 1 and Test 2, with maximum efforts on both tests (P = .157). **P < 0.01 and *P < 0.05.
• Testing on day 2 measures the changes in exercise capacity following the first test, and confirms that exercise can lead to an objective, measurable decrease in performance in some with ME/CFS that correlates with patient reports.

• We would expect the CPET on day 2 to lead to worse PEM over the next week, but thus far these changes have not been recorded.
Research triggers for PEM

• Best recognized and studied
  – Physical exertion
• Less well characterized
  – Cognitive exertion
  – Orthostatic stress
• Recently described
  – Biomechanical strain
"My back is fine. My mind went out."
Cognitive Functioning in People With Chronic Fatigue Syndrome: A Comparison Between Subjective and Objective Measures

Susan J. Cockshell and Jane L. Mathias
The University of Adelaide

Neuropsychology
2014, Vol. 28, No. 3, 394–405
Study design

- 50 with CFS (Fukuda definition); 39F, 11M
- 50 healthy controls; 40F, 10M
- Tests of verbal memory, visual memory, attention, conducted over 3 hours
- Mental fatigue assessed after completion and 24 hours after testing
- Time to recovery recorded
Mean recovery time: HC 7 hrs. vs. CFS 46 hrs., P<.01
The delayed fatigue effect in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS)

Megan A. Arroll*, Elizabeth A. Attree, John M. O’Leary and Christine P. Dancey

Fatigue: Biomedicine, Health, and Behavior 2014;2:57-63

Uncontrolled study of 32 with ME/CFS evaluated with 6 tests from the computerized Cambridge Neuropsychological Test Automated Battery, over 90 minutes

Table 1. Means, standard deviations, and t-values for fatigue, anxiety, and depression scores pre- and post-cognitive testing.

<table>
<thead>
<tr>
<th></th>
<th>Pre-test</th>
<th></th>
<th>Post-test</th>
<th></th>
<th>t value</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>General fatigue</td>
<td>11.34</td>
<td>1.78</td>
<td>13.56</td>
<td>3.49</td>
<td>-3.93</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Physical fatigue</td>
<td>13.16</td>
<td>1.72</td>
<td>14.50</td>
<td>3.09</td>
<td>-2.38</td>
<td>0.02</td>
</tr>
<tr>
<td>Mental fatigue</td>
<td>11.21</td>
<td>1.77</td>
<td>12.38</td>
<td>2.35</td>
<td>-2.63</td>
<td>0.01</td>
</tr>
<tr>
<td>Reduced activity</td>
<td>13.38</td>
<td>1.66</td>
<td>13.59</td>
<td>2.95</td>
<td>-0.34</td>
<td>0.74</td>
</tr>
<tr>
<td>Reduced motivation</td>
<td>11.84</td>
<td>2.37</td>
<td>11.34</td>
<td>3.34</td>
<td>0.98</td>
<td>0.33</td>
</tr>
<tr>
<td>Anxiety</td>
<td>8.09</td>
<td>4.78</td>
<td>8.03</td>
<td>5.26</td>
<td>0.12</td>
<td>0.91</td>
</tr>
<tr>
<td>Depression</td>
<td>8.06</td>
<td>3.66</td>
<td>9.72</td>
<td>4.95</td>
<td>-2.62</td>
<td>0.01</td>
</tr>
</tbody>
</table>
Have we established at a research level that cognitive exertion can trigger PEM?
Research triggers for PEM

• Best recognized and studied
  – Physical exertion
• Less well characterized
  – Cognitive exertion
  – Orthostatic stress
• Recently described
  – Biomechanical strain
Orthostatic Intolerance

The term “orthostatic intolerance” refers to a group of clinical conditions in which symptoms worsen with quiet upright posture and are ameliorated (although not necessarily abolished) by recumbency.

In 1932, Sir Thomas Lewis described a young soldier who had been unable to play strenuous games as a schoolchild due to “breathlessness and the early onset of exhaustion.” He was investigated because he had fainted on guard duty when attempting to salute an office of high rank of whom he became aware abruptly.

He developed syncope and relative bradycardia developed during a venipuncture, with a heart rate 50–60 beats/min and a systolic blood pressure of 50 mmHg.

“He was tremulous and tired for 36 hours subsequently” providing an early instance of prolonged fatigue following a single episode of vasovagal (or neurally mediated) hypotension.

Lewis T. BMJ 1932;1:873
Is neurally mediated hypotension an unrecognised cause of chronic fatigue?

Peter C Rowe, Issam Bou-Holaigah, Jean S Kan, Hugh Calkins


The Relationship Between Neurally Mediated Hypotension and the Chronic Fatigue Syndrome

Issam Bou-Holaigah, MD; Peter C. Rowe, MD; Jean Kan, MD; Hugh Calkins, MD

JAMA 1995;274:961-7
Characteristics of CFS patients

- 23 with CFS (18 F)
- Mean age $34 \pm 12$ yrs (range 14-49)
- Median duration of CFS:
  - 5 yrs (range 11 mo - 36 yrs)
- 74% unable to attend school or work
- Family history of CFS in 5

Features compatible with orthostatic intolerance in 23 patients with CFS (%)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lightheadedness</td>
<td>96</td>
</tr>
<tr>
<td>Diaphoresis</td>
<td>83</td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>78</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>78</td>
</tr>
<tr>
<td>Syncope</td>
<td>43</td>
</tr>
</tbody>
</table>
Conditions exacerbating fatigue (%)

- Physical exertion: 100
- Hot shower: 78
- Prolonged standing: 78
- Warm environment: 74
- Lightheaded episode: 43

Symptoms during the first 45 minutes of head-up tilt to 70°

<table>
<thead>
<tr>
<th></th>
<th>CFS</th>
<th>CONT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worse fatigue</td>
<td>23</td>
<td>n/a</td>
</tr>
<tr>
<td>Lightheadedness</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>Warmth</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>Diaphoresis</td>
<td>4</td>
<td>0</td>
</tr>
</tbody>
</table>

OI and PEM

• Patients often reported a “crash” following HUTT, akin to exacerbations following exercise tests
To Doc Rout UMBRO

THANKS!

No more time trials!
To Doc Rout.

Thanks!

No more 1018 Eb.
OI and PEM

- Many tilt testing labs (ours included) responded by administering saline infusions following a tilt, which appeared to prevent the post-tilt relapse in symptoms
- Saline infusion post-tilt incorporated into Florinef trial design
OI and PEM

• Thus far, no formal studies have been conducted to confirm the observation that tilt testing can trigger prolonged symptomatic flares.

• As a result, OI is not a proven trigger for PEM, although this is a testable hypothesis.
Tilt test

Randomization

IV Saline on completion

Placebo

Symptoms/biomarkers over the next week

Trial design to test whether orthostatic stress is a PEM trigger
OI and PEM

• Upright posture is a well recognized method of inducing an acute increase in CFS symptoms

• Given this, OI needs to be accounted for in research settings as a confounder, especially in studies of cognitive challenge and PEM
Increasing orthostatic stress impairs neurocognitive functioning in chronic fatigue syndrome with postural tachycardia syndrome

Anthony J. OCON*, Zachary R. MESSER†, Marvin S. MEDOW*†
and Julian M. STEWART*†‡

*Department of Physiology, New York Medical College, Valhalla, NY, U.S.A., †Department of Pediatrics, New York Medical College, Valhalla, NY, U.S.A., and ‡Department of Medicine, New York Medical College, Valhalla, NY, U.S.A.
Study design

- 16 with CFS (Fukuda definition) and POTS
- 20 healthy controls
- Age range 16-29 yrs
- N-back testing performed at 0°, 15°, 30°, 45°, 60°, and 75° for 10 minutes at each angle
N-back testing

• Tests working memory, concentration, attention, information processing
  – 0-back: subject responds if the character on screen is the one they were told to expect
  – 1-back: subject responds when the current character is the same as displayed “1” back
  – 2-back: same character as was displayed 2 characters back
Research triggers for PEM

• Best recognized and studied
  – Physical exertion
• Less well characterized
  – Cognitive exertion
  – Emotional stress
  – Trauma
  – Orthostatic stress
• Recently described
  – Biomechanical strain
Clinical observation

CFS patients often report:

• PEM-like worsening of symptoms for 1-2 days after their initial physical therapy assessment (an examination of range of motion but without active exercise)
Symptom changes with SLR over 12 minutes in an adolescent with CFS

Severity

Degrees of SLR
Symptom changes with SLR over 12 minutes in an adolescent with CFS

Severity

Degrees of SLR

Fatigue
LH
Cog Fog
Vis Blur
Impaired Range of Motion of Limbs and Spine in Chronic Fatigue Syndrome

Peter C. Rowe, MD1, Colleen L. Marden1, Marissa A. K. Flaherty, MD1, Samantha E. Jasion1, Erica M. Cranston1, Allison S. Johns1, John Fan, MD1, Kevin R. Fontaine, PhD2, and Richard L. Violand, PT3

(J Pediatr 2014;165:360-6).

1Department of Pediatrics, JHUSOM, Baltimore, MD;
2Department of Health Behavior, University of Alabama School of Public Health, Birmingham, AL;
3Violand and McNerney, PA, Ellicott City, MD.
Results: symptom provocation

More CFS subjects had abnormal symptomatic responses to at least 1 ROM test:

40% vs. 4%, (P < .001)

More CFS subjects reported increased fatigue after the ROM exam:

44% vs. 0%, (P < .001)

Symptoms increased markedly (n=2), moderately (n=6), minimally (n=13)
Neuromuscular Strain in CFS
R. Violand, K. Fontaine, P. Rowe

Funding: CFIDS Association of America

Study Design

Screening & Enrollment → Baseline testing → Controls randomized to

- Neuromuscular Strain (N = 10)
- Sham Test (N = 10)

CFS randomized to

- Neuromuscular Strain (N = 30)
- Sham Test (N = 30)
#145 CFS Strain

<table>
<thead>
<tr>
<th>Time</th>
<th>Symptom Severity Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre</td>
<td>1</td>
</tr>
<tr>
<td>5 min</td>
<td>3</td>
</tr>
<tr>
<td>10 min</td>
<td>5</td>
</tr>
<tr>
<td>15 min</td>
<td>7</td>
</tr>
<tr>
<td>Post</td>
<td>9</td>
</tr>
<tr>
<td>24 hr</td>
<td>10</td>
</tr>
</tbody>
</table>

- Tired
- Ache
- Lightheaded
- Concentration
- Headache
Comments about prolonged symptoms after 15 minutes of SLR

Today is the first day I'm feeling better from the study but I'm still not feeling great. I was in a lot of pain all weekend. My whole body hurt, I was exhausted but couldn't sleep. I wasn't capable of holding a coherent conversation or making decisions all weekend. Friday I was emotionally unstable and cried a lot, also nauseated and couldn't eat. I'm still having more brain fog than usual.
Conclusions

• There are multiple testing paradigms for triggering PEM, some of which involve combining physiological stressors

• At present, the occurrence of PEM is best documented after physical activity

• Further study is needed on other physiological stressors to help understand the mechanisms by which ME/CFS symptoms are aggravated
ACKNOWLEDGEMENTS

- Grants from CFIDS Association of America (now Solve ME/CFS Initiative), NIAID, DoD
- Sunshine Natural Wellbeing Foundation (endowed Chair)
- Volunteer RA Colleen Marden
- Summer students (John Fan, Alli Johns, Marissa Flaherty, Jocelyn Ray, Samantha Jasion, Erica Cranston)
- Many families and patients:
  - Special thanks to the following:
    Boies, Caldwell, Cornell, Kelly, Kiely, McFerron, Newbrand, Smith, Steffensmeier families
    Megan Lauver, Hannah Vogel
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Our Mission
Make ME/CFS understood, diagnosable and treatable.

Our Strategy
Stimulate participatory research aimed at the early detection, objective diagnosis and effective treatment of ME/CFS through expanded public, private and commercial investment.