Upright Activity and Exercise Intolerance: Critical Concepts in the Evaluation of Chronic Fatigue

Lucinda Bateman MD
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Disclosures for Lucinda Bateman MD

- Clinician, Medical Director and Principle Investigator employed by the Bateman Horne Center (BHC), a 501(c)3 nonprofit clinic, research and educational organization.

- BHC contracts with organizations to conduct clinical research, including:
  - pharmaceutical companies Cortene, Teva, Tonix and Lundbeck
  - NIH ME/CFS Collaborative Center grants

- BHC accepts donations and seeks other grant support for all operations of the organization.

- Lucinda Bateman MD has no personal relevant financial relationships to disclose
Objectives

1) Determine the presence or absence of Post-Exertional Malaise (PEM) and utilize the information to develop appropriate physical rehabilitation advice for a patient with chronic fatigue.

2) Assess impairment of function using a combination of readily available standardized questionnaires (HADS, FIQ-R, OHQ/OIQ) and reported HUA (Hours of Upright Activity) as defined in the lecture.

3) Perform bedside orthostatic testing to determine the presence, nature and most appropriate management of orthostatic intolerance.
Case Presentation: 30 year old woman

**Childhood:**
- Under weight infant. Breastfed.
- Active childhood.

**As a teenager:**
- Dysmenorrhea/heavy menses
- reflux and constipation
- migraines
- anxiety → Rx paroxetine
- “mono” with normal recovery

**During college**
- Social anxiety → rx citalopram
- Dx hypothyroid
- Migraines
- “mono again”

**Left college after first year**
Case Presentation: 30 year old woman

Age 20-26:
- Running, half marathon.
- Worked retail

Age 26:
- MVA→ whiplash, low back strain, concussion with sx; no workup

Age 26-28:
- Biking, Yoga, Weights, Pilates

Age 28:
- Weaned off citalopram and PPIs
- Stayed active.
- More GERD→ “restrictive diet
- Anxiety increased
- Moved to UT with boyfriend

Age 29:
- Summer trip to Europe (2017)
Case Presentation: 30 year old woman

Dec 2017:
- **Flu-like illness:** cough, sinus → abx. Flared again in 2 weeks. Lasted 6 weeks. Never fully recovered.
- Boyfriend left. Restarted citalopram. Moved in with Mom.

Jan 2018:
- **Flu-like illness:** chills, fever, later a sinus infection → abx.
- GERD worse.
- Rx nystatin for “yeast.”
- **Crashed.**

Feb 2018:
- “Everything in slow motion”

Mar 2018:
- **Medical leave from work.**

Providers:
- GI, endocrine, OB/gyn, MH APRN, needs PCP.
Case Presentation: 30 year old woman

- **Chronic fatigue**, “barely able to walk from bed to couch,” persistent after rest. Low energy for activity. After activity she crashes and sx worsen for days/weeks. Weakness of arms/legs. Dizzy and “bumping into walls”

- **Widespread pain** complaints: burning, achy, morning stiffness, muscle pain, joint (knees), atypical CP (ECG & Echo OK), tension headaches and migraines. Numbness and tingling in hands and feet. Sweating, cold and heat intolerance, sound and light sensitivity.

- **Depression, anxiety, suicidal thoughts**.
2015 ME/CFS clinical diagnostic criteria

*LBMD opinion 😊
The **Institute of Medicine** (IOM)*
published evidence-based **clinical diagnostic criteria** for **ME/CFS**

The 2014 project was published in a report on Feb 10, 2015


*The IOM is now the **National Academy of Medicine***
The purpose of the 2015 IOM/NAM Report is to increase clinical diagnosis and improve care.

- The new diagnostic criteria are focused on the **common core symptoms** of ME/CFS (as currently defined) that distinguish it from other disorders.
- Easier for clinicians to recognize and accurately diagnose patients in a timely manner.
The **CORE criteria** (required for diagnosis)

1) *Impaired function in association with exhaustion/fatigue/low stamina
2) *PEM: post exertional malaise (illness relapse after physical or cognitive activity)
3) *Unrefreshing sleep (disordered sleep not explained by another disorder)
4) A. *Cognitive impairment and/or
   B. Orthostatic intolerance

*Must be moderate-severe, present >50% of the time

Other common features of illness, not considered “core” or required for diagnosis
---Pain of all types
---Immune impairment (allergy, inflammation, sensitivities)
---Infection symptoms, onset with infection, relapse after an infection

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*Editors: Committee on the Diagnostic Criteria for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome; Board on the Health of Select Populations; Institute of Medicine. **Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness.** Washington (DC): National Academies Press (US); 2015 Feb*
Diagnose **ME/CFS** definitively after 6 months of supportive care and diagnostic investigations.

- No "exclusionary criteria" are detailed but it is assumed that…
- A **differential diagnosis**, **appropriate workup and treatment** of symptoms, including referral to specialists, is expected of health care providers.
- All other identifiable illnesses should be diagnosed and treated, including supportive care, observation, reduction of risk factors.
- **ME/CFS** can be a "working diagnosis" in the meantime.
Can medical providers Assess Impaired Function and PEM?

- Mental health screen (we use HADS* plus interview)
- Ideally SF-36 (RAND-36) but complex scoring
- Fibromyalgia Impact Questionnaire (FIQ-R)
- HUA (Hours of Upright Activity)
- Good Day/Bad Day form
- Take a good history about the consequences of physical, cognitive, emotional and upright activity (PEM)
- Orthostatic testing---in clinic: 10 min NASA Lean Test
- Consider CPET
- Assess cognitive impairment if indicated

Why SF-36? (or RAND-36 free to clinicians)


SF-36 Scores in ME/CFS and Our Case

RAND 36 Sub-scale Scores [SF-36]

Physical Function: 0
Role Physical: 0
Bodily Pain: 20
General Health: 25
Vitality/energy/fatigue: 0
Social functioning: 0
Role Emotional: 0
Mental Health: 16

Score Key: 100/100 possible in each sub-scale. A lower score indicates more severe impairment.
Why Fibromyalgia Impact Questionnaire (FIQ-R)? Pain Symptoms and the Impact of Pain on Function

http://fiqr.info/FIQR%20FORM.pdf

- Functional domain---9 questions
- Overall domain---2 questions
- Symptom severity---9 questions

There is a version called the Sickness Impact Questionnaire/SIQ
Interpretation of FIQ score

5 min Fibromyalgia Impact Questionnaire

A study of 2228 patients evaluating FM using FIQ suggests the following quartile scores:

- 0 to 42 = mildly affected
- 43 to 59 = moderately affected
- 60 to 74 = severely affected.
- 75 to 100 = extremely affected

The average FIQ-R score in FM studies is 58.2 (± 21.6), with a median value of 58-60.

Our Case FIQ-R Score

FIQ-R (Fibromyalgia Impact Questionnaire-Revised): 86

Score Key (impact of pain on function):
- 0-42 Mild
- 43-59 Moderate
- 60-74 Severe
- 75-100 Extreme

Our Case had no FM Tender Points on physical examination.
My best tool to estimate impaired function: HUA

HUA: Hours of “Upright” Activity:
The #hours spent with feet-on-floor in 24 hours (sitting, standing, walking)

Must ask the question clearly to be sure time spent sitting is considered in the total.

Thanks and credit to David Bell MD
Typical HUA*
HUA in 24 hours

- Normal healthy folks: HUA 14-17
- Chronic illness/FM: HUA 10-12
- ME/CFS: HUA 0-7

*based only on BHC clinical data and my own experience

HUA=Hours of Upright Activity
Good/Bad Day HUA Questionnaire*

◇ Average number of GOOD/BAD days per MONTH:

◇ Average hours of UPRIGHT activity (HUA) on a GOOD/BAD day:
  ◇ sitting, standing, walking --- activities with FEET ON FLOOR

◇ Average hours of non-upright activity on a GOOD/BAD day:
  ◇ lying in bed, reclining, elevating feet, sitting cross legged

(Hours of upright activity + Hours of non-upright activity = 24 hours)

◇ Give examples of activities/tasks you CAN do on a good/bad day:

◇ Give examples of activities/tasks you CAN NOT do on a good/bad day:

*Designed for use at BHC by Lucinda Bateman MD
Good Day: Our Case Study

Average number of GOOD days per MONTH: “5-10 days”

Average hours of UPRIGHT activity (HUA) on a GOOD day (sitting, standing, walking --- activities with FEET ON FLOOR): “1-2 hours”

Average hours of non-upright activity on a GOOD day (reclining, elevating feet, laying in bed): “23-24 hours”

Give specific examples of activities/tasks you CAN do on a good day: “Drive, go on a short walk, stretch, run an errand with help”

Give specific examples of activities/tasks you CAN NOT do even on a good day: “Clean, make my own meals, go to work”
Bad Day: Case Study

Average number of bad days per MONTH: “20-25 days”

Average hours of UPRIGHT activity (HUA) on a BAD day (sitting, standing, walking --- activities with FEET ON FLOOR): “30 min- maybe”

Average hours of non-upright activity on a BAD day (reclining, elevating feet, laying in bed): “All day”

Give specific examples of activities/tasks you CAN still do on a BAD day: “Sit up, read, watch tv, eat..”

Give specific examples of activities/tasks you CAN NOT do when it's a BAD day: “Walk, have conversations”
What is Post Exertional Malaise (PEM)?

PEM is a prolonged exacerbation of a patient’s baseline symptoms after physical/ cognitive/orthostatic exertion or stress. It may be delayed relative to the trigger(s).

Patient Descriptions of PEM

- “crash,” “relapse,” “collapse”
- mentally tired after the slightest effort
- physically drained or sick after mild activity
- the more demanding, prolonged or repeated the activity, the more severe and prolonged the payback

Gene Expression Captures a Glimpse of PEM:
the Sensory, Adrenergic, Inflammatory Response
after an Exercise Stressor
The research team used **exercise as a stressor** to study post-exertional gene expression in patients with CFS, CFS/FM and FM-only. **Patients exercised on an Airdyne bike at 70% of age-predicted max heart rate for 25 minutes** (moderate sustained activity approximating daily needs).

Blood was drawn:
- **Before** exercise
- **After** exercise at 30 min, 8 hours, 24 and 48 hours

Gene expression changes were analyzed.


<table>
<thead>
<tr>
<th>mRNA Fold Increases (±SEM)</th>
<th>Baseline</th>
<th>30 min</th>
<th>8 h</th>
<th>24 h</th>
<th>48 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>All controls (n=15)</td>
<td></td>
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<td></td>
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<tr>
<td>All CFS patients (n=19)</td>
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<tr>
<td>Multiple sclerosis patients with fatigue (n=9)</td>
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</tbody>
</table>
Gene expression tracks the severity of CFS
CFS+FMS patients grouped by clinical severity

Survey on PEM

- 150 subjects dx with CFS by Fukuda criteria completed a survey about PEM symptoms: different triggers, onset and duration of PEM.
- 90% experienced PEM after physical and cognitive exertion or emotional distress.
- Onset and duration of PEM varied. 84% experience PEM for 24 hours or more.
- Symptoms of PEM: Fatigue was the most commonly exacerbated symptom but cognitive difficulties, sleep disturbances, headaches, muscle pain, and flu-like feelings were cited by over 30%. At least one inflammatory/immune-related symptom was reported by 60%. Subjects also cited gastrointestinal, orthostatic, mood-related, neurologic and other symptoms.

Does it help to keep energy expenditure close to available energy? (pacing)

114 ME/CFS subjects were randomly assigned to four interventions in which they were provided 13 biweekly sessions with a trained nurse therapist. We collected baseline, post-treatment, and six- and twelve-month follow-up data. Jason, Benton, et al. divided this entire sample of patients with ME/CFS into two groups:

✧ those who were able to keep expended energy close to available energy
✧ those who were not successful at this task

Those who were able to stay within their energy envelopes had significant improvements in physical functioning and fatigue severity.

PACING: Staying “inside energy envelope” versus “outside energy envelope” improves prognosis

Physical Function Scores

Fatigue Severity Scores

Clinical significance of PEM

Exceeding cellular energy capacity results in “illness payback” symptoms.

PEM is physiologic and multisystem.

The key to ME/CFS management is to understand these physical and cognitive limitations and learn to preventively “pace” all activity in order to avoid inducing severe or prolonged PEM.

The total of all activity---physical, cognitive, emotional---must not dramatically exceed the patient’s energy capacity to create the opportunity for improvement.

This must be considered in all rehabilitation efforts.
FCE: Functional Capacity Evaluations

Can be a misleading measure of disability in patients with ME/CFS
Because they don’t evaluate PEM: the consequences of activity
What is Orthostatic Intolerance (OI)?

Orthostatic intolerance is the development of symptoms while standing upright that are relieved or partially relieved by reclining.
Orthostatic Intolerance (OI)

Orthostatic Intolerance/Autonomic Dysfunction/POTS symptoms

1) Cerebral under-perfusion symptoms and signs
   - lightheadedness, fainting, impaired cognition, disorientation, headaches, visual changes, unusual neurologic symptoms, exhaustion

2) Peripheral cardiovascular symptoms and signs
   - Sympathetic nervous system activation---palpitations, nausea, abdominal and chest discomfort, facial pallor, cold hands and feet, anxiousness, shortness of breath, sweating, tremor...

Worsened by heat, dehydration, prolonged standing, deconditioning and weakness, and feels worse immediately after exercise
OI may be caused/worsened by:

- **HEART**: Heart arrhythmias, heart valve failure, myocardial infarction, cardiomyopathies
- **LUNG**: Pulmonary embolus, primary pulmonary hypertension
- **DRUG SIDE EFFECTS**: diuretics, tricyclic antidepressants, blood pressure drugs, drugs for prostate disease (doxazosin, tamsulosin), Yaz birth control (drospirenone/ethinyl estradiol)...
- **CENTRAL NERVOUS SYSTEM**: Brain stem and mid-brain lesions (may underlie ME/CFS), Parkinson’s, Multiple Sclerosis, Parkinsons...
- **PERIPHERAL NERVOUS SYSTEM**: diabetic neuropathy, spinal cord injury, craniocervical instability (CCI), small fiber neuropathy...
Causes of chronic OI are numerous: small fiber neuropathy, post-viral autoantibodies to adrenergic and muscarinic receptors, midbrain or brainstem inflammation, hypermobility syndromes...

### Symptoms of OI

<table>
<thead>
<tr>
<th>Acute OI—more obvious</th>
<th>Chronic OI---more subtle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fainting, lightheadedness</td>
<td>Nausea or low appetite</td>
</tr>
<tr>
<td>Altered vision (blurred, double vision, tunnel vision)</td>
<td>Chest and abdominal complaints</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Neurocognitive deficits, brain fog</td>
</tr>
<tr>
<td>Fatigue and weakness</td>
<td>Heat intolerance</td>
</tr>
<tr>
<td>Headache</td>
<td>Sleep problems</td>
</tr>
<tr>
<td>Heart palpitations, heart pounding/racing</td>
<td>Headaches</td>
</tr>
<tr>
<td>Shortness of breath, hyperventilation</td>
<td>Varied dizziness, disequilibrium, vertigo</td>
</tr>
<tr>
<td>Tremor</td>
<td>Tremor</td>
</tr>
</tbody>
</table>
Why assess and treat OI?

Orthostatic intolerance is:
- Measurable (heart rate, blood pressure, S&S)
- Treatable or at least manageable.

May lead to insight about the underlying disease process(es)

Remember: OI can exist in someone who has low, normal or high blood pressure in the seated position at rest.
Defined Syndromes of Chronic Orthostatic Intolerance/OI

- **Orthostatic hypotension**: a BP reduction of at least 20 mm Hg systolic or 10 mm Hg diastolic within the first 3 min of upright posture

- **Postural Orthostatic Tachycardia Syndrome (PoTS)**: the reproduction of orthostatic symptoms together with a +30 bpm increase in HR, from supine to 10 min upright, or an increase in HR of ≥120. Age 12-19 heart rate increase must be +40 bpm

- **Neurally Mediated Hypotension/Syncope (NMH/S)**: synonymous with vasovagal syncope, neurocardiogenic syncope

HR and BP may not tell the whole story

- 150 ME/CFS patients and 37 HC underwent Tilt Table testing. Stroke Volume Index (SVI) and Cardiac Index (CI) were measured by suprasternal aortic Doppler imaging in the supine position, prior to the tilt, and twice during the tilt.

- A normal heart rate and blood pressure response was observed during the tilt in both ME/CFS and HC.

- Stroke volumes and cardiac output were related to the severity of the disease in ME/CFS.

- Decreases in SVI and CI during the tilt were significantly larger in ME/CFS compared to HC.

- The decrease in SVI and CI were similar and not significantly different between the mild, moderate, and severe ME groups.
“Easy” Clinical Assessment of Chronic Orthostatic Intolerance
• The Orthostatic Hypotension Questionnaire (OHQ) was developed with two components: the 6-item symptoms assessment scale and a 4-item daily activity scale to assess the burden of symptoms.

• The OHQ was validated in 137 Neurogenic Orthostatic Hypotension (NOH) subjects in a phase IV, double blind, randomized, cross over, placebo-controlled trial of the alpha agonist midodrine;

• Clinical Validity: The floor and ceiling effects were minimal. OHQ scores were highly correlated with other patient reported outcome measures, indicating excellent convergent validity. Test-retest reliability was good.
Hours of Upright Activity (HUA): #hours in 24 hours with feet on the floor.

Upright = sitting with feet on the floor, standing, walking -- versus -- Lying down (includes sleeping), reclining or sitting with feet elevated or tucked.

Orthostatic Intolerance Symptom Assessment (OISA)  
Score: 0=None and 10=Severe

- Dizziness, lightheadedness, feeling faint, or feeling like blackout
- Problems with vision (blurring, seeing spots, tunnel vision, etc.)
- Weakness
- Fatigue
- Trouble concentrating
- Head/neck discomfort

Orthostatic Intolerance Daily Activity Scale (OIDAS)  
0=No Interference; 10=Complete Interference

- Standing a short time
- Standing a long time
- Walking a short time
- Walking a long time


Jihyun Lee MSPH, BSN, Pelle Wall BS, medical student
The OIQ and HUA were tested on 25 ME/CFS Female Subjects and 25 matched HC (Age, Gender, Race) via Online form. All subjects reported HUA and completed two questionnaires (OISA, OIDAS). Rating scores were recorded on the REDCap online database.

HUA was sub-categorized as 1-2 hours, 3-4 hours, 5-7 hours and >8 hours in 24 hours. OIDAS was used to assess interference of daily activity due to OI and the OISA was used to assess OI symptoms.

Comparisons between ME/CFS and healthy controls (HC) were evaluated.
Hours of Upright Activity (HUA) correlate with OISA (symptom) scores

<table>
<thead>
<tr>
<th>OISA Orthostatic Intolerance Symptom Assessment</th>
<th>Healthy Control</th>
<th>ME/CFS Group (n=26)</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean of 0-10 scores in 6 domains</td>
<td>N=25</td>
<td>N=7</td>
<td>N=11</td>
<td>N=5</td>
<td>N=2</td>
<td></td>
</tr>
<tr>
<td>Dizziness, lightheadedness, feeling faint, or feeling like you might blackout</td>
<td>1.16</td>
<td>5.57</td>
<td>5.09</td>
<td>6.4</td>
<td>9</td>
<td>&gt;0.001</td>
</tr>
<tr>
<td>Problems with vision (blurring, seeing spots, tunnel vision)</td>
<td>1.04</td>
<td>2.29</td>
<td>3.73</td>
<td>5.8</td>
<td>5</td>
<td>&gt;0.001</td>
</tr>
<tr>
<td>Weakness</td>
<td>1.12</td>
<td>6.57</td>
<td>4.09</td>
<td>7.2</td>
<td>9</td>
<td>&gt;0.001</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1.12</td>
<td>7.29</td>
<td>6.09</td>
<td>8</td>
<td>9.5</td>
<td>&gt;0.001</td>
</tr>
<tr>
<td>Trouble concentrating</td>
<td>1.04</td>
<td>5.29</td>
<td>5.9</td>
<td>7.6</td>
<td>8.5</td>
<td>&gt;0.001</td>
</tr>
<tr>
<td>Head/neck discomfort</td>
<td>1.24</td>
<td>6.29</td>
<td>3.72</td>
<td>5.4</td>
<td>7.5</td>
<td>&gt;0.001</td>
</tr>
</tbody>
</table>
Hours of Upright Activity (HUA) correlate with OIDAS (activity interference) scores

<table>
<thead>
<tr>
<th>Activity</th>
<th>Healthy Group (n=25)</th>
<th>ME/CFS Group (n=26)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Healthy Control</td>
<td>Mild</td>
<td>Mild-Moderate</td>
</tr>
<tr>
<td>OIDAS Mean 0-10 scores</td>
<td>mean</td>
<td>HUA: 8+</td>
<td>HUA: 5-7</td>
</tr>
<tr>
<td>Orthostatic Intolerance Daily Activity Scale</td>
<td>N=25</td>
<td>N=7</td>
<td>N=11</td>
</tr>
<tr>
<td>Standing a short time</td>
<td>1</td>
<td>4.1</td>
<td>4.18</td>
</tr>
<tr>
<td>Standing a long time</td>
<td>1.72</td>
<td>7.85</td>
<td>7.91</td>
</tr>
<tr>
<td>Walking a short time</td>
<td>1</td>
<td>4.28</td>
<td>4.36</td>
</tr>
<tr>
<td>Walking a long time</td>
<td>1.36</td>
<td>8.14</td>
<td>8.09</td>
</tr>
</tbody>
</table>
Orthostatic intolerance testing

Head Up Tilt Table Testing
The Gold Standard

10 min stand/lean testing
The 10 min NASA Lean Test
10 minute “NASA” Lean test—the standing portion after resting supine measurements.
32 year old woman with fatigue, severe migraines, fibromyalgia, depression, dizziness unresponsive to traditional therapies.

**Supine** (10-15 min in quiet room):

- Supine BP: 116/60 Pulse: 85  **PULSE PRESSURE: 56**

**Standing straight with shoulder blades against the wall and feet 6" from the wall**

- Standing 0 minute BP: 104/80 Pulse: 85
- Standing 2 minute BP: 96/70 Pulse: 116
- Standing 4 minute BP: 98/78 Pulse: 120 Arms "almost feel like they are tingling"
- Standing 6 minute BP: 91/73 Pulse: 125 Lightheaded and dizzy (as if she is spinning)
- Standing 8 minute BP: 96/74 Pulse: 122 Increased lightheadedness, nausea
- Standing 10 minute BP: 93/80 Pulse: 120 Increased "electrical buzz"  **PULSE PRESSURE: 13**

**Summary:**

-27 mmHg drop in SBP meets criteria for systolic orthostatic hypotension (> 20 mmHg decrease)
+41 bpm increase in Heart Rate meets criteria for POTS (>30 bpm increase for adults)

Postural Orthostatic Tachycardia Syndrome
Our Case: 30 year old woman

**OI Questionnaires**

**OIQ:** 76/100

- OHSA 47/100 (symptoms)
- OHDAS 29/100 (activity)

**10 min Lean Test**

Seated VS: HR 110 BP 116/84

10 min NASA Lean:

- HR 75→118 (+43 bpm= POTS)
- SBP 106--? 100?.
- PP 30→16 or less
Our Case: 10 min NASA Lean test

Supine measurements: Patient has been resting supine for 15 minutes.
◇ 1 min BP: 102/76 PP: 26 HR (bpm): 75 SpO2: 99%
◇ 2 min BP: 106/76 PP: 30 HR (bpm): 75 SpO2: 99%

Standing measurements: Standing straight, shoulder blades against the wall, feet 6” from the wall
◇ 2 min BP: 102/? PP: ? HR (bpm): 110
◇ 6 min BP: 110/94 PP: 16 HR (bpm): 103 Diastolic blood pressure dropped out.
◇ 8 min BP: 100/92 PP: 8 HR (bpm): 119 Quiet BP, moderate purple hue of toes.
◇ 10 min BP: ? PP: 0 HR (bpm): 118 SpO2: 99%

SUMMARY: HR 75→118 (+43 bpm). SBP 106→100?. PP 30→16 or less
Cardiopulmonary Exercise Testing (CPET)

Most patients with ME/CFS are unable to replicate the test parameters when tested 2 days in a row.

This can be helpful for documenting disability, but can exacerbate ME/CFS…
Peak Oxygen Consumption (VO2) in ME/CFS compared to Healthy Controls tested twice in 24 hours

This decrement of exercise capacity has been replicated
Test 1 = dark grey bars    Test 2 = light grey bars

Cognitive impairment

Neurocognitive manifestations (IOM Report Chap 4, pp 96-107)

◊ Impairments in cognitive function are frequently reported
◊ Cognitive impairment can be measured. The strongest evidence demonstrates *slowed information processing*. There are some data to support *deficits in working memory* and *reduced attention*.
◊ Neuroinflammation has been documented*

Observation is objective

Signs of cognitive impairment:
- Difficulty remembering instructions from previous visit
- Completely forgot to do something suggested in the previous visit
- Delayed verbal responses, worsening as fatigue progresses
- Easily confused by long complex explanations or instructions
- Looks to companion for help answering questions or remembering details
- Trouble remembering medications and pill strength
- Dull eyes
- Brings notes to visit to remember items of discussion
- Attempts to take notes during visit but may have trouble
Cognitive efficiency worsens after orthostatic stress (Pre- Post)

Clinical significance (cognition):

- Cognitive slowing, cognitive fatigability and cognitive PEM may be the most limiting aspects of ME/CFS illness, and a primary reason people with ME/CFS are unable to sustain employment or succeed in school.
Objectives

1) Determine the presence or absence of Post-Exertional Malaise (PEM) and utilize the information to develop appropriate physical rehabilitation advice for a patient with chronic fatigue.

2) Assess impairment of function using a combination of readily available standardized questionnaires (HADS, FIQ-R, OHQ/OIQ) and reported HUA (Hours of Upright Activity) as defined in the lecture.

3) Perform bedside orthostatic testing to determine the presence, nature and most appropriate management of orthostatic intolerance.
Supplemental Slides
Cognitive Testing (DANA Brain Vital app) SRT PRT GNG

DANA Brain Vital

This is a test of response speed, so respond as fast as possible.
Tap this symbol quickly when it appears.

One of these numbers will appear. Tap the appropriate button as quickly as possible.

Tap the symbol above to start

Tap a button below to start.

2 OR 3  4 OR 5

BLAST

*DANA Brain Vital Set: SRT, PRT, GNG*
Percentage of ME/CFS patients and healthy controls reporting neurocognitive manifestations of at least **moderate severity** that occurred **at least half of the time** during the past 6 months.

<table>
<thead>
<tr>
<th></th>
<th>ME/CFS</th>
<th>Healthy Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Problems remembering</td>
<td>80%</td>
<td>7%</td>
</tr>
<tr>
<td>Difficulty expressing thoughts</td>
<td>73%</td>
<td>2%</td>
</tr>
<tr>
<td>Difficulty paying attention</td>
<td>69%</td>
<td>7%</td>
</tr>
<tr>
<td>Slowness of thought</td>
<td>66%</td>
<td>2%</td>
</tr>
<tr>
<td>Absentmindedness</td>
<td>68%</td>
<td>5%</td>
</tr>
<tr>
<td>Difficulty understanding</td>
<td>55%</td>
<td>2%</td>
</tr>
</tbody>
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IOM report 2015
Potential contributors to “brain fog” and cognitive slowing

- **Medications** for sleep, pain, anxiety, migraine
- **Chronic sleep disturbances**
- **Secondary mental health** conditions---depression, anxiety
- **Orthostatic intolerance** and other causes of reduced cerebral blood flow and perfusion. “Perfusion” is the circulation or delivery of blood to every cell, bringing oxygen, glucose, nutrients, everything needed for cell function…
- Cognitive fatigue and fatigability
- **Low cellular energy production**. Capacity for “function” is reduced.
- PEM—the consequences of exceeding cellular energy capacity
- **Neuroinflammation**
Neural Consequences of PEM in ME/CFS.

15 female ME/CFS and 15 female HC. 30 min sub max exercise (70% peak HR) cycle ergometer. fMRI during a fatiguing cognitive task. PASAT: paced auditory serial addition task

Acute exercise exacerbated symptoms, impaired cognitive performance and affected brain function in ME/CFS patients.
Total errors on PASAT testing

Total errors represent both incorrect responses and missed responses (i.e. errors of omission). There was a significant Group by Time Interaction (F = 8.4, p = 0.007).
Interventions for OI:

Recognize and **avoid** the common triggers

- Heat, getting overheated
- Dehydration
- Prolonged standing in place
- Prolonged sitting with feet on floor
- Prolonged bedrest *(confuses the ANS)*
- Muscle atrophy and weakness
  - Abdomen/core, upper and lower legs
- Medications that cause/worsen OI
Interventions for OI:

External compression or internal constriction of blood vessels
- Compression socks, pants, sleeves, abdominal binder
- Midodrine, a peripheral alpha-1 receptor agonist (stimulates the receptor) FDA approved for orthostatic hypotension

Increase volume in the vasculature (blood vessels)
- Consume extra water/fluids to expand blood volume
- Increased salt intake helps retain water in the circulation and tissues
- fludrocortisone 0.1 mg once or twice daily FDA approved for orthostatic hypotension
- Rapid water ingestion (16 oz) helps reduce OI within 20 minutes (chugging)
- IV normal saline. Can be very helpful as “rescue” and support, especially when ill, dehydrated, or having medical procedures such as colonoscopy
Interventions for OI:

Control the rapid heart rate response if indicated and helpful.

- Low dose beta blockers: Propranolol 10 mg bid to tid (off label use—FDA approved for supraventricular tachycardia, migraine, tremor)

Augment parasympathetic nervous system

- Pyridostigmine (off label use—FDA approved for myasthenia gravis, but recommended in the literature for POTS) Raises acetylcholine, the neurotransmitter at the neuromuscular junction and much of the parasympathetic nervous system.

Strengthen and use the muscular “pumps” for better venous return.

Muscular pumps = leg and abdominal muscles

Orthostatic Intolerance/OI
Suggested ICD-10 coding?

◊ Orthostatic Hypotension (OH)  ICD-10 I95.1

◊ Conditions with no ICD-10 codes:
  ▪ Postural Orthostatic Tachycardia Syndrome (PoTS)
  ▪ Neurally Mediated Hypotension (NMH)
  ▪ Neurogenic Orthostatic Hypotension/Syncope (NOH)

◊ Misc. dysautonomias:
  ▪ Other disorders of the autonomic nervous system  G90.8
  ▪ Disorder of the autonomic nervous system  G90.9