# Orthostatic Intolerance
# Part 1: Assessment

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University of Utah Health Project ECHO

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# Bateman Horne Center (BHC)

BHC is a 501(c)3 non-profit organization with a mission to improve lives through direct **clinical care,** facilitation of **research,** and dissemination of **educational** resources.

This specifically/exclusively includes the lives of people with:

- **myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS)**
- fibromyalgia (FM)
- post-viral syndromes and
- related comorbid conditions (small fiber neuropathy, mast cell activation syndrome, hypermobile EDS, postural orthostatic tachycardia syndrome/POTS)

# Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)

- A chronic, debilitating, multisystem illness characterized by **central and peripheral nervous system impairment, immune dysfunction, and impaired cellular metabolism**.

- ME/CFS is thought to be a post-viral or post-infectious syndrome in most, but not all, cases.



Advances in Understanding the Pathophysiology of Chronic Fatigue Syndrome. Komaroff AL. JAMA. 2019 Aug 13;322(6):499-500. doi: 10.1001/jama.2019.8312. PMID: 31276153

# 2015 IOM Criteria for Diagnosis of ME/CFS (Myalgic Encephalomyelitis/Chronic Fatigue Syndrome)

Diagnosis requires that the patient have the following three symptoms

1. A substantial reduction or impairment in the ability to engage in pre-illness levels of occupational, educational, social, or personal activities, that persists for more than 6 months and is accompanied by fatigue, which is often profound, is of new or definite onset (not lifelong), is not the result of ongoing excessive exertion, and is not substantially alleviated by rest, and
2. Post-exertional malaise,* and
3. Unrefreshing sleep*

At least one of the two following manifestations is also required:

1. Cognitive impairment* or
2. Orthostatic intolerance

* Frequency and severity of symptoms should be assessed. The diagnosis of ME/CFS (SEID)[a] should be questioned if patients do not have these symptoms at least half of the time with moderate, substantial, or severe intensity

[a] The recommendation for the term systemic exertion intolerance disease (SEID) was not adopted.

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- There is no single sensitive and specific biomarker for the diagnosis of ME/CFS.
- These are the core clinical criteria to rule in a diagnosis of ME/CFS, though MANY additional comorbid symptoms and conditions can be present.
- Post-Exertional Malaise (PEM) is widely considered pathognomonic for ME/CFS.

# The PEM experience in Long COVID and ME/CFS

| | LONG COVID N (%) | ME/CFS N (%) | P-VALUE |
|---|---|---|---|
| **Trigger** | | | |
| Low physical exertion | 14 (18%) | 33 (22%) | .49 |
| Medium physical exertion | 67 (84%) | 108 (72%) | .31 |
| High physical exertion | 58 (73%) | 48 (32%) | <.001 |
| Low cognitive exertion | 8 (10%) | 14 (9%) | .86 |
| Medium cognitive exertion | 36 (45%) | 62 (41%) | .66 |
| High cognitive exertion | 55 (69%) | 26 (17%) | <.001 |
| Stress | 62 (78%) | 17 (11%) | <.001 |
| Food or chemical sensitivities | 23 (29%) | 2 (1%) | <.001 |
| Temperature extremes | 37 (46%) | 7 (5%) | <.001 |
| Insufficient sleep | 62 (78%) | 7 (5%) | <.001 |
| Illness | 32 (40%) | 1 (1%) | <.001 |
| **Experience** | | | |
| Fatigue | 77 (96%) | 130 (86%) | .44 |
| Sleepy | 64 (80%) | 24 (16%) | <.001 |
| Muscle and joint pain | 56 (70%) | 91 (60%) | .38 |
| Infection and immune reaction | 31 (39%) | 56 (37%) | .84 |
| Respiratory | 47 (59%) | 29 (19%) | <.001 |
| Neurologic | 57 (72%) | 103 (68%) | .79 |
| Depressed and anxious | 39 (49%) | 20 (13%) | |
| Gastrointestinal symptoms | 27 (34%) | 50 (33%) | .94 |
| Orthostatic intolerance | 51 (64%) | 88 (58%) | .61 |
| Changes in body temperature | 42 (53%) | 30 (20%) | |
| Excessive thirst | 24 (30%) | 5 (3%) | <.001 |
| Excessive urination | 11 (14%) | 3 (2%) | <.001 |
| **Recovery** | | | |
| Rest | 72 (90%) | 139 (92%) | .88 |
| Sleep | 59 (74%) | 50 (33%) | <.001 |
| Limit stimulation | 46 (58%) | 18 (12%) | <.001 |
| Hydrate | 60 (75%) | 55 (36%) | <.001 |
| Modify diet | 36 (45%) | 43 (29%) | .04 |
| Take vitamins and supplements | 45 (56%) | 13 (9%) | <.001 |
| Take medication | 23 (29%) | 15 (10%) | <.001 |
| Relieve pain | 31 (39%) | 27 (18%) | .003 |
| Practice coping | 43 (54%) | 18 (12%) | <.001 |
| Light activity | 21 (26%) | 6 (4%) | <.001 |
| **Prevention** | | | |
| Physical awareness | 48 (60%) | 119 (79%) | .11 |
| Pacing | 43 (54%) | 57 (38%) | .08 |
| Avoidance | 56 (70%) | 25 (17%) | <.001 |
| Lifestyle | 40 (50%) | 18 (12%) | <.001 |
| Environment | 23 (29%) | 11 (7%) | <.001 |
| Coping | 36 (29%) | 6 (9%) | <.001 |
| Treatment | 38 (31%) | 9 (14%) | <.001 |
| Nothing | 28 (22%) | 3 (4%) | <.001 |

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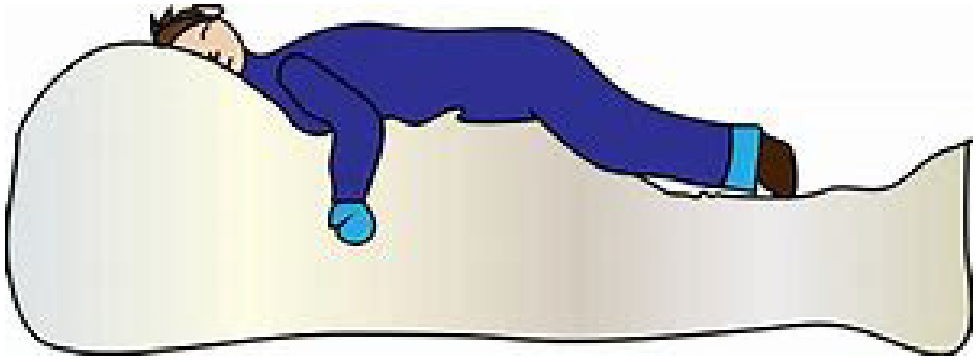
*Long COVID and ME/CFS manuscript submitted for publication*

Hartle M, Bateman L, Vernon, SD. (3.2021): Dissecting the nature of post-exertional malaise, Fatigue: Biomedicine, Health & Behavior, DOI: 10.1080/21641846.2021.1905415

# What is Orthostatic Intolerance (OI)?

Orthostatic intolerance is the development of symptoms in **upright posture** that are relieved or partially relieved by **reclining** or **laying down.**



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# Orthostatic Intolerance

- When transitioning from laying down to sitting or standing, gravity exerts a force that decreases overall blood flow in the brain.

- Healthy people are able to adapt to the force of gravity and maintain blood flow to the brain through activation of the "autonomic nervous system," which detects the change in position and sends a multitude of signals that help blood vessels constrict and maintain a similar amount of blood flow to the brain when upright.

- In "dysautonomia," these initial adaptive features of the autonomic nervous system are inadequate to maintain enough blood flow to the brain to function optimally.

- **Remember: OI can occur in someone who has low, normal or high blood pressure in the seated position at rest.**

# Orthostatic Intolerance Symptoms

Upright positioning can worsen a multitude of symptoms, including (but not limited to) lightheadedness and dizziness, heart palpitations, brain fog, muscle pain or aching, cognitive attention or focus, gastrointestinal function, headaches, shortness of breath.

**Orthostatic Intolerance/Autonomic Nervous System Dysfunction Symptoms:**

**Cerebral Under-Perfusion:** lightheadedness, fainting, impaired cognition, disorientation, headaches, visual changes, unusual neurologic symptoms, neck and shoulder pain, exhaustion

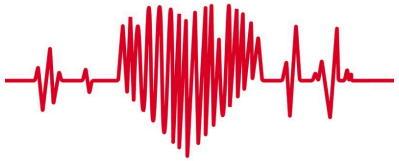
**Peripheral Cardiovascular Perturbations:** **sympathetic nervous system activation**---palpitations, nausea, abdominal and chest discomfort, facial pallor, cold hands and feet, anxiousness, shortness of breath, sweating, tremor…

The majority of these symptoms are thought to be directly or indirectly related to maladaptive blood flow responses to upright positioning as a result of inadequate functioning of the "autonomic nervous system."

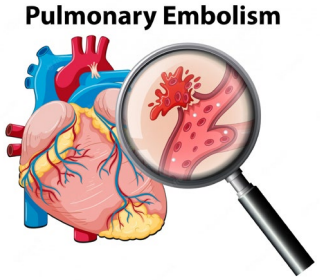


Beyond Myalgic Encephalomyelitis: Redefining an Illness. Institute of Medicine. Washington (DC): National Academies Press (US); 2015 Feb 10. ISBN-13: 978-0-309-31689-7ISBN-10: 0-309-31689-8

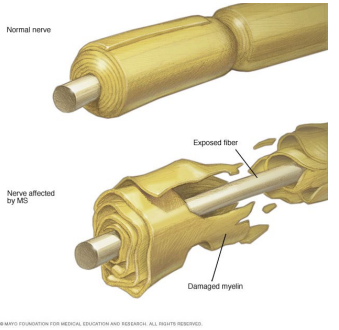
# OI may be caused/worsened by many factors



- **HEART DISEASE:** Heart arrhythmias, heart valve failure, MI, cardiomyopathies
- **LUNG DISEASE:** 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, Multiple Sclerosis, Parkinsons, craniocervical instability (CCI)…
- **PERIPHERAL NERVOUS SYSTEM**: Diabetic neuropathy, spinal cord injury, small fiber neuropathy, autonomic neuropathy…




- **ENVIRONMENTAL/BEHAVIORAL:** Heat, dehydration, prolonged sitting or standing, deconditioning, exercise (during or immediately after)

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# Definitions of OI Syndromes

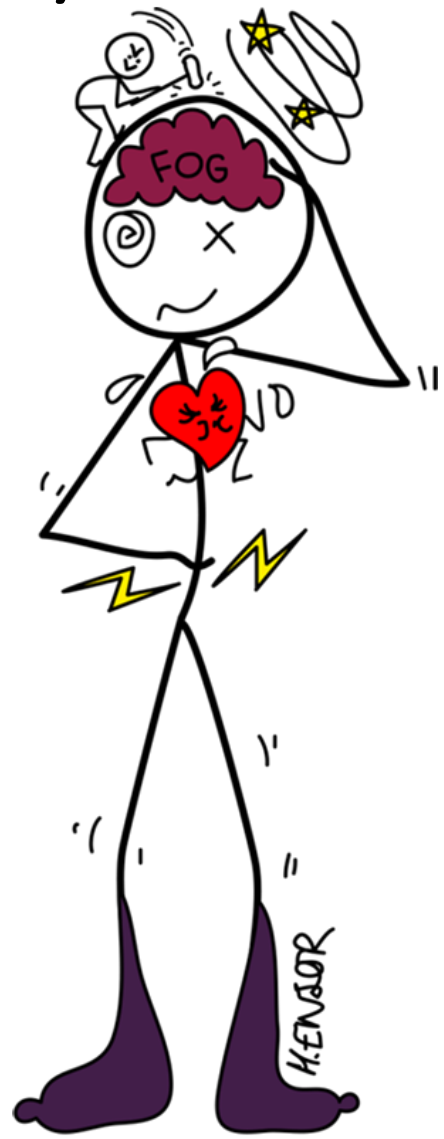
- **Orthostatic Hypotension:** BP reduction of at least 20 mm Hg systolic and/or 10 mm Hg diastolic within the first 3 min of upright posture
- **Postural Orthostatic Tachycardia Syndrome (POTS):** the reproduction of orthostatic symptoms together with a +**30 bpm** increase in HR, from supine to 10 min upright, or a standing HR of ≥120
  - Age 12-19 heart rate increase must be +**40 bpm**
- **Neurally Mediated Hypotension/Syncope:** synonymous with vasovagal syncope, neurocardiogenic syncope. Sudden syncope during quiet upright posture.
- **Orthostatic Hypertension:** sustained increase in SBP ≥ 20 mm Hg and/or DBP of ≥10 mm Hg within first 3 minutes of upright posture



Freeman R et al., Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome. Clin Auton Res. 2011 Apr;21(2):69-72. https://doi.org/10.1161/HYPERTENSIONAHA.120.14340 Hypertension. 2020;75:1151–1158

# Postural Orthostatic Tachycardia Syndrome (POTS)

- Often referred to as a “disease” or “syndrome,” but is better defined as an easily measured ADAPTIVE RESPONSE to upright positioning when the initial functions of the autonomic nervous system fail to maintain adequate blood flow to the brain and other organs.
- In POTS specifically, the adaptive response is to increase the heart rate rapidly with upright positioning so as to maintain “cardiac output” from the heart, to attempt to get more blood flow back to where it needs to be to function adequately when upright.
- Thus, the increase in heart rate, while it can often make people feel worse, is not the actual pathological process itself but rather a response to an underlying pathology with the autonomic nervous system.
- Another adaptive response to upright positioning known as a “narrowing of the pulse pressure,” (SBP - DBP) appears to be a vascular response to help maintain as much blood flow to the brain as possible may also be present in dysautonomia and orthostatic intolerance.



# **Reduced Cerebral Blood Flow** is a core manifestation of Orthostatic Intolerance in ME/CFS

- **Cerebral blood flow is reduced in ME/CFS during head-up tilt testing even in the absence of hypotension or tachycardia: A quantitative, controlled study using Doppler echography.** van Campen CLMC, et al. Clin Neurophysiol Pract. 2020 Feb 8;5:50-58. doi: 10.1016/j.cnp.2020.01.003. PMID: 32140630

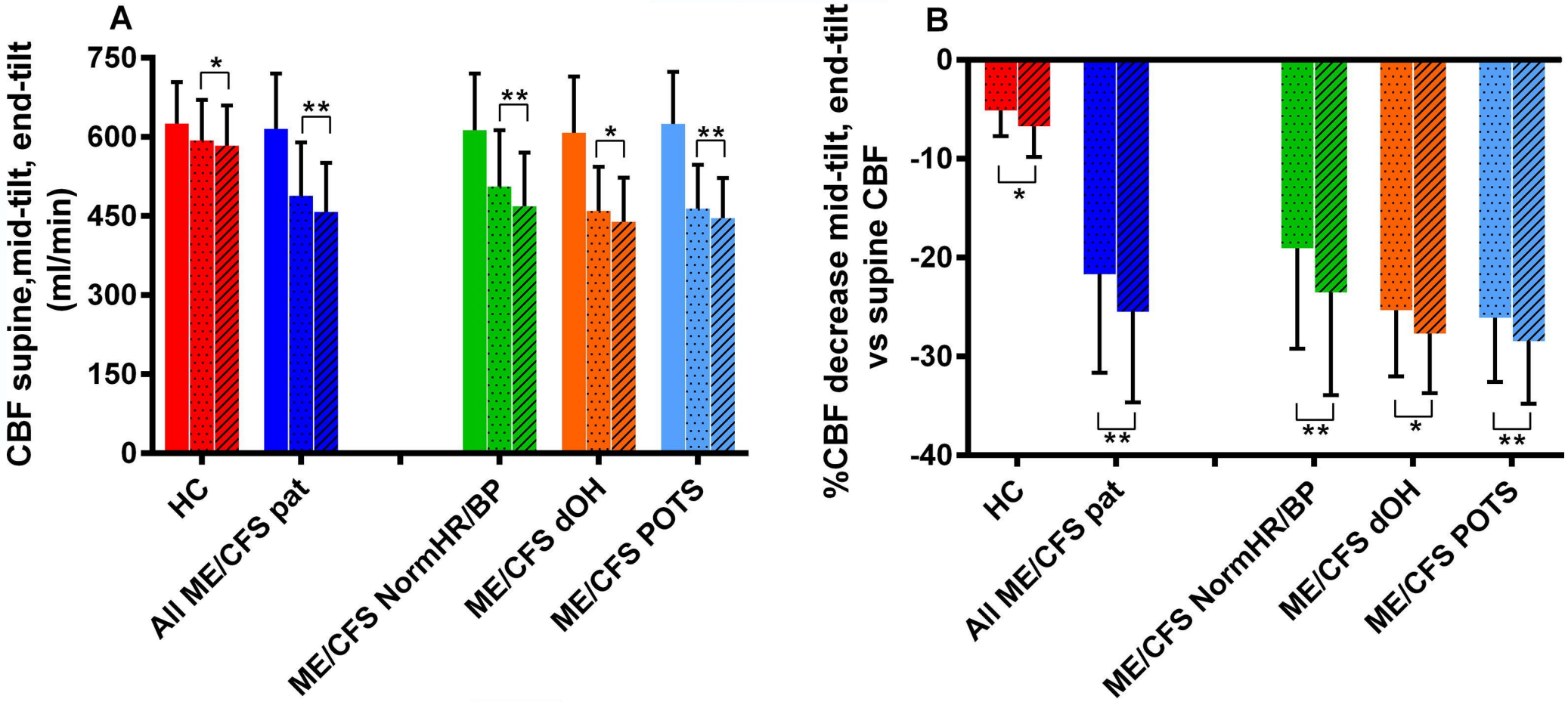
- **Cerebral Blood Flow Is Reduced in Severe Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Patients During Mild Orthostatic Stress Testing: An Exploratory Study at 20 Degrees of Head-Up Tilt Testing.** van Campen CLMC, et al. Healthcare (Basel). 2020 Jun 13;8(2):169. doi: 10.3390/healthcare8020169. PMID: 32545797

- **Deconditioning does not explain orthostatic intolerance in ME/CFS (myalgic encephalomyelitis/chronic fatigue syndrome).** van Campen CLMC, et al. J Transl Med. 2021 May 4;19(1):193. doi: 10.1186/s12967-021-02819-0. PMID: 33947430

- **Cerebral blood flow remains reduced after tilt testing in myalgic encephalomyelitis/chronic fatigue syndrome patients.** van Campen CLMC, Rowe PC, Visser FC. Clin Neurophysiol Pract. 2021 Sep 23;6:245-255. doi: 10.1016/j.cnp.2021.09.001. PMID: 34667909

# Orthostatic Intolerance: Reduced CBF

- Left Column: Supine
- Dotted Column: Mid-tilt
- Hatched Column: End-tilt




Cerebral Blood Flow (CBF)

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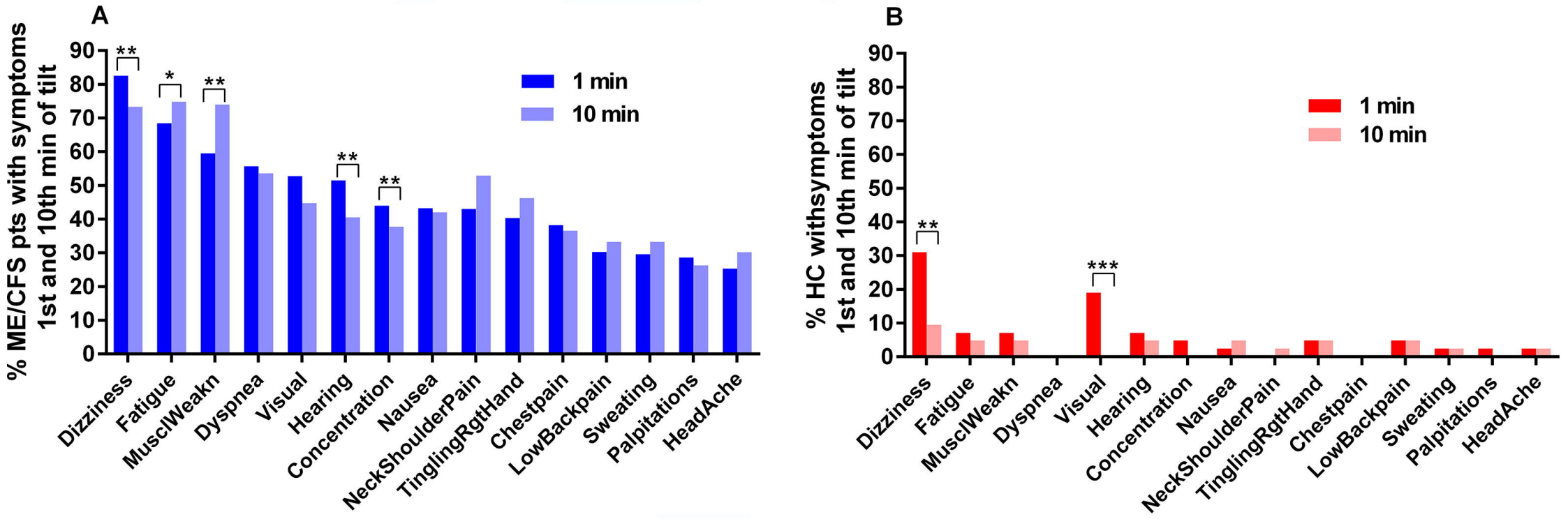
Van Campen, C. (Linda), et al. "Cerebral Blood Flow Is Reduced in ME/CFS during Head-up Tilt Testing Even in the Absence of Hypotension or Tachycardia: A Quantitative, Controlled Study Using Doppler Echography." *Clinical Neurophysiology Practice*, vol. 5, 2020, pp. 50–58., https://doi.org/10.1016/j.cnp.2020.01.003.

# Orthostatic Intolerance: Reduced CBF

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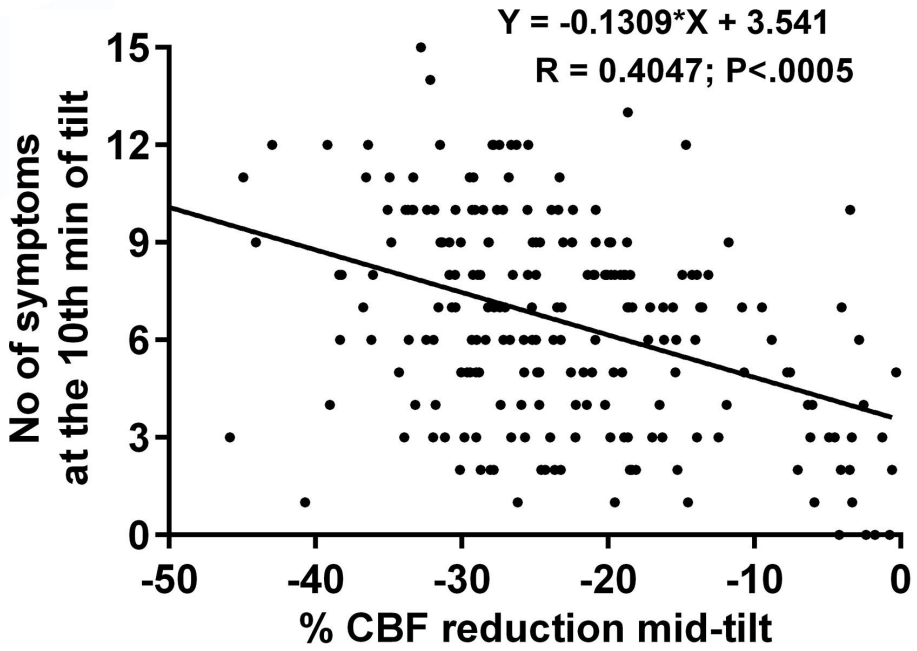
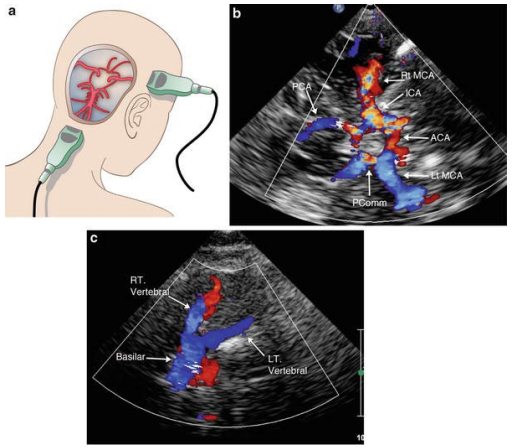
# Orthostatic Intolerance: Reduced CBF

- **Results:** End-tilt CBF reduction was 7% in HC versus 26% in the overall ME/CFS group, 24% in patients with a normal HR/BP response, 28% in those with dOH, and 29% in POTS patients (all P < .0005)
- Clinically significant reduction in cerebral blood flow during heads-up tilt (HUT) in those with ME/CFS compared to controls
- Degree of reduction in cerebral blood flow is strongly correlated with the provocation of orthostatic intolerance symptoms during HUT
- Doppler imaging of the internal carotid and vertebral arteries may some day be an additional tool for orthostatic intolerance assessment.
  - Especially beneficial for those with reported OI symptoms but **without** heart rate and blood pressure changes on provocative testing (HUT, 10-minute NASA Lean Test)

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# Assessment of OI:

- Hours of Upright Activity (HUA)
- Orthostatic Questionnaire
- 10-Minute NASA Lean Testing

# A simple tool to estimate impaired function due to OI: Ask about HUA

**HUA: Hours of "Upright" Activity**:

The # of hours spent with **feet-on-floor** in 24 hours (i.e. 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*

## Hours of Upright Activity in 24 hours

- Normal healthy folks → HUA 14-17
- Chronic Illness (MS, RA, CHF, COPD, FM) → ~~HUA~~ 10-12
- ME/CFS & PASC → HUA 0- 7

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*Based on clinical experience at the Bateman Horne Center

# 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.

**Orthostatic Hypotension Symptom Assessment (OHSA)** 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 Hypotension Daily Activity Scale (OHDAS)** 0=No Interference; 10=Complete Interference

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

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Kaufmann H, et al. The Orthostatic Hypotension Questionnaire (OHQ): validation of a novel symptom assessment scale. Clin Auton Res. 2012 Apr;22(2):79-90. doi: 10.1007/s10286-011-0146-2. Epub 2011 Nov 2.

25 ME/CFS female subjects and 25 matched HC (age, gender, race) enrolled in a research protocol reported their average HUA and filled out the OHQ.

OHQ scores and reported HUA were found to correlate well with each other, and with illness severity.



Clinically accessible tools for documenting the impact of orthostatic intolerance on symptoms and function in ME/CFS.
Jihyun Lee, Pelle Wall, Chris Kimler, Lucinda Bateman, Suzanne D Vernon. Work. 2020;66(2):257-263.
doi: 10.3233/WOR-203169. PMID: 32568144

# Hours of Upright Activity (HUA) correlate with OHSA (symptom) scores

| | Healthy Group (n=25) | ME/CFS Group (n=26) | | | | |
|---|---|---|---|---|---|---|
| | Healthy Control | Mild | Mild-Moderate | Moderate-severe | Severe | P-value |
| OHSA Orthostatic Hypotension Symptom Assessment ---Mean of 0-10 scores in 6 domains--- | Mean | HUA:8+ | HUA:5-7 | HUA:3-4 | HUA:1-2 | |
| | N=25 | N=7 | N=11 | N=5 | N=2 | |
| Dizziness, lightheadedness, feeling faint, or feeling like you might blackout | 1.16 | **5.57** | **5.09** | **6.4** | **9** | >0.001 |
| Problems with vision (blurring, seeing spots, tunnel vision) | 1.04 | **2.29** | **3.73** | **5.8** | **5** | >0.001 |
| Weakness | 1.12 | **6.57** | **4.09** | **7.2** | **9** | >0.001 |
| Fatigue | 1.12 | **7.29** | **6.09** | **8** | **9.5** | >0.001 |
| Trouble concentrating | 1.04 | **5.29** | **5.9** | **7.6** | **8.5** | >0.001 |
| Head/neck discomfort | 1.24 | **6.29** | **3.72** | **5.4** | **7.5** | >0.001 |

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# Hours of Upright Activity (HUA) correlate with OHDAS (activity interference)

| | Healthy Group (n=25) | ME/CFS Group (n=26) | | | | |
|---|---|---|---|---|---|---|
| | Healthy Control | Mild | Mild-Moderate | Moderate-severe | Severe | P-value |
| OHDAS Mean 0-10 scores<br>Orthostatic Hypotension Daily Activity Scale | mean | HUA: 8+ | HUA:5-7 | HUA:3-4 | HUA:1-2 | |
| | N=25 | N=7 | N=11 | N=5 | N=2 | |
| Standing a short time | 1 | 4.1 | 4.18 | 4.4 | **5** | >0.001 |
| Standing a long time | 1.72 | **7.85** | **7.91** | **8.6** | **10** | >0.001 |
| Walking a short time | 1 | 4.28 | 4.36 | 4.2 | 4.5 | >0.001 |
| Walking a long time | 1.36 | **8.14** | **8.09** | **9.8** | **9** | >0.001 |

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Clinically accessible tools for documenting the impact of orthostatic intolerance on symptoms and function in ME/CFS.
Jihyun Lee, Pelle Wall, Chris Kimler, Lucinda Bateman, Suzanne D Vernon. Work. 2020;66(2):257-263.
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# Orthostatic Intolerance Testing

**Head Up Tilt Table Testing (HUT)**

The Gold Standard

**10 min stand/lean testing**

The 10-Minute NASA Lean Test

# Evaluate for Orthostatic Intolerance: 10-Minute NASA Lean Test

HR and BP after 10-15 minutes of quiet supine rest

HR and BP every 1-2 minutes for 10 minutes while standing/leaning in upright posture

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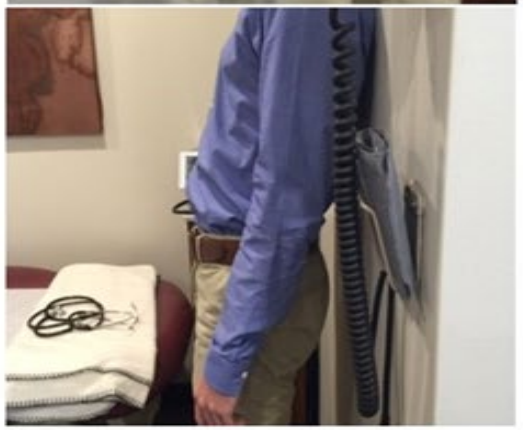
# What is the 10-Minute NASA Lean Test? (a standardized passive lean test)

**10 minutes NASA Lean Test**

**Orthostatic Vital Signs/The NASA 10-minute Lean Test**

| | Blood Pressure (BP) | | Pulse | Comments |
|---|---|---|---|---|
| | Systolic | Diastolic | | |
| Supine 1 minute | | | | |
| Supine 2 minute | | | | |
| | | | | |
| Standing 0 minute | | | | |
| Standing 1 minute | | | | |
| Standing 2 minute | | | | |
| Standing 3 minute | | | | |
| Standing 4 minute | | | | |
| Standing 5 minute | | | | |
| Standing 6 minute | | | | |
| Standing 7 minute | | | | |
| Standing 8 minute | | | | |
| Standing 9 minute | | | | |
| Standing 10 minute | | | | |



Hyatt, K. H., Jacobson, L. B., & Schneider, V. S. (1975). Comparison of 70 degrees tilt, LBNP, and passive standing as measures of orthostatic tolerance. Aviation, Space, and Environmental Medicine, 46(6), 801-808.

# 32-year-old woman with severe fatigue, migraines, fibromyalgia, and dizziness unresponsive to traditional therapies. (Undiagnosed ME/CFS)

| Position & Timing | Blood Pressure | Heart Rate | Comments and observations |
|---|---|---|---|
| **Patient rested supine in a quite/low stimulation room for 10-15 minutes** | | | |
| Supine | 116/60<br>**Pulse pressure: 56** | **85 bpm** | |
| **Standing straight with shoulder blades against the wall and feet 6" from the wall** | | | |
| Standing, minute 0 | 104/80 | 85 bpm | |
| Standing, minute 2 | 96/70 | 116 bpm | |
| Standing, minute 4 | 98/78 | 120 bpm | Arms “almost feel like they are tingling” |
| Standing, minute 6 | 91/73 | **125 bpm** | Lightheaded and dizzy (as if she is spinning) |
| Standing, minute 8 | 96/74 | 122 bpm | Increased lightheadedness, nausea |
| Standing, minute 10 | 93/80<br>**Pulse pressure: 13** | 120 bpm | Increased “electrical buzz” |

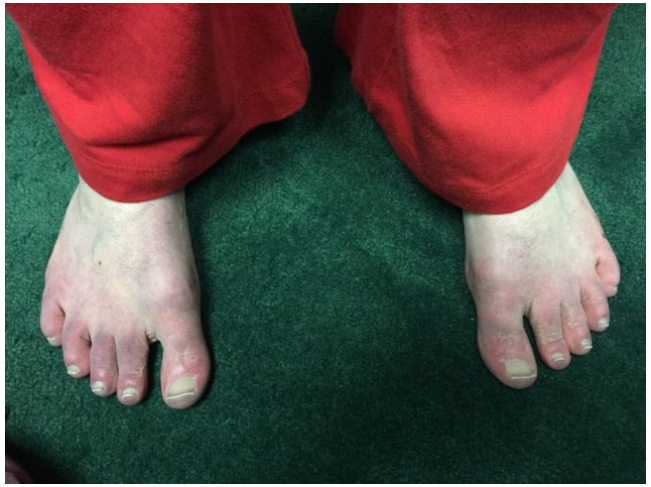
**Summary:**

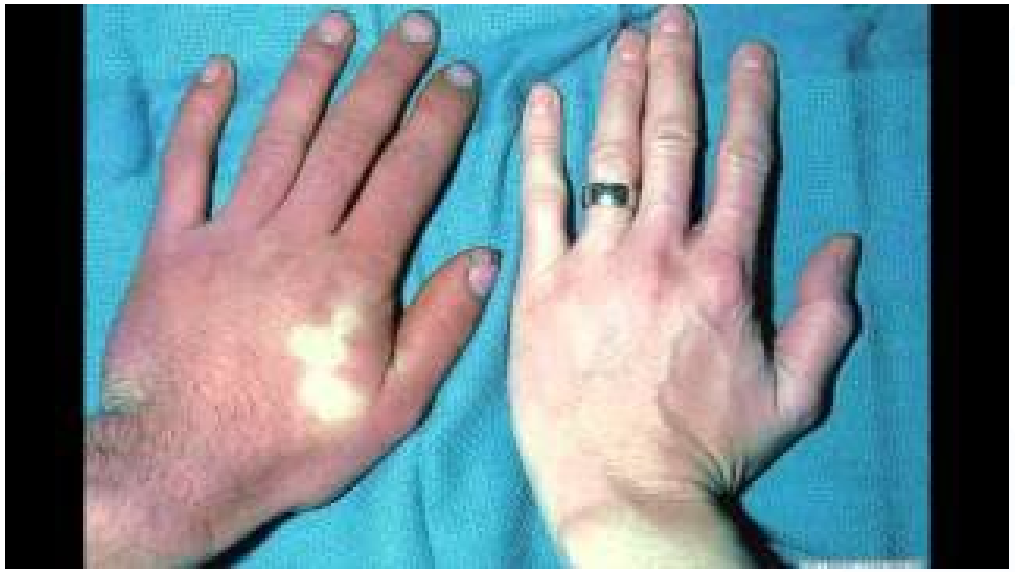
**-27** mmHg drop in SBP meets criteria **for systolic orthostatic hypotension** (> 20 mmHg decrease)

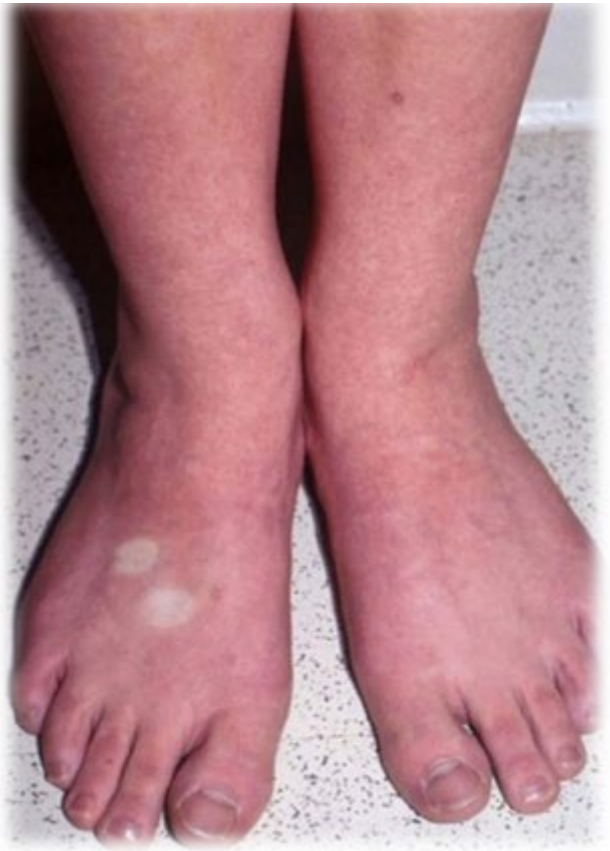
**+41** bpm increase in Heart Rate meets criteria for **POTS**

**Postural Orthostatic Tachycardia Syndrome** (>30 bpm increase for adults, >40 for youth)

# Acrocyanosis During NASA Lean Testing

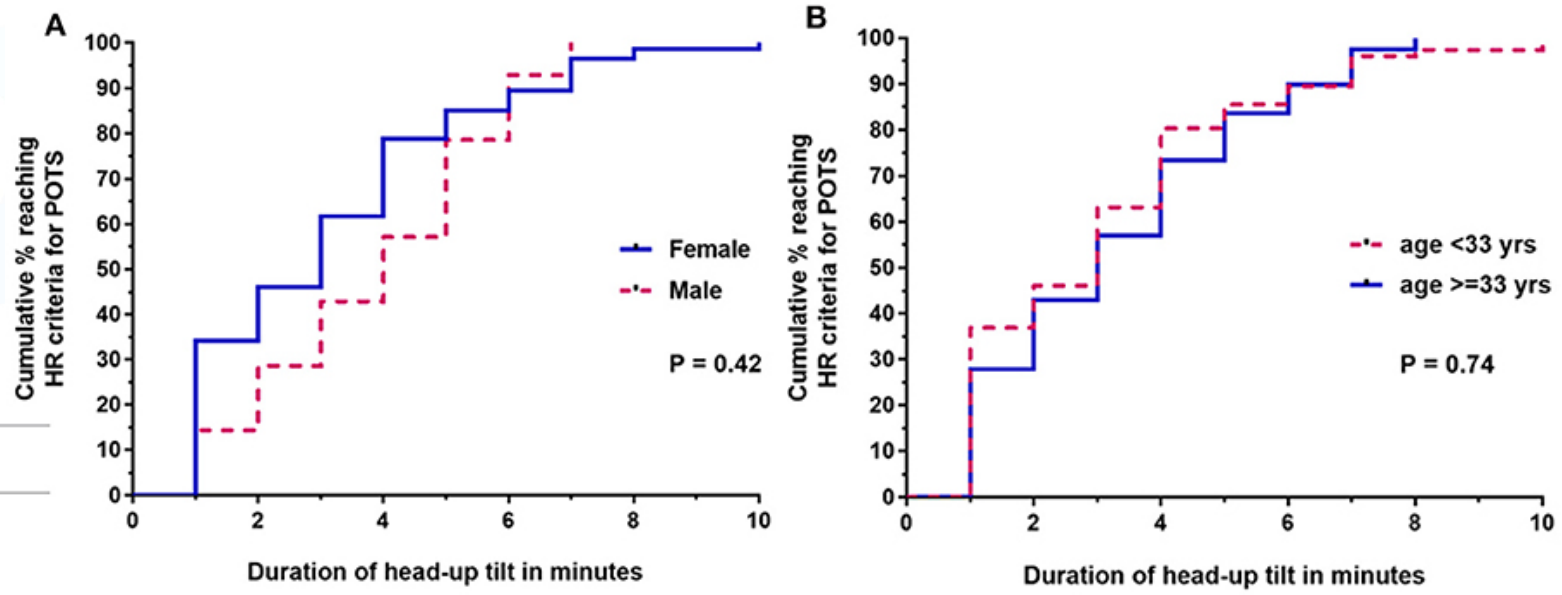






# Orthostatic Intolerance Testing

| Minutes upright | POTS diagnoses missed at each minute | |
|---|---|---|
| | % | (95% CI) |
| 1 | 68 | (60–75) |
| 2 | 55 | (48–63) |
| 3 | 40 | (33–48) |
| 4 | 23 | (17–30) |
| 5 | 15 | (11–22) |
| 6 | 10 | (6–16) |
| 7 | 3 | (1–7) |
| 8 | 2 | (0–4) |
| 9 | 2 | (0–4) |
| 10 | 0 | |




- Sensitivity for detecting POTS increases over ten minutes during the NASA Lean Test
- NASA Lean appears to be **more sensitive** for detecting OI/POTS than the "gold-standard tilt-table testing"

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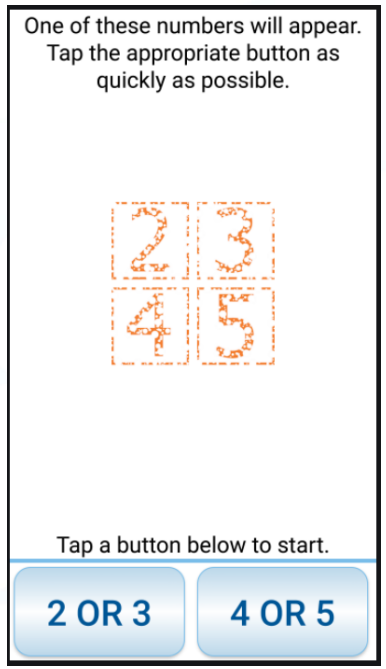
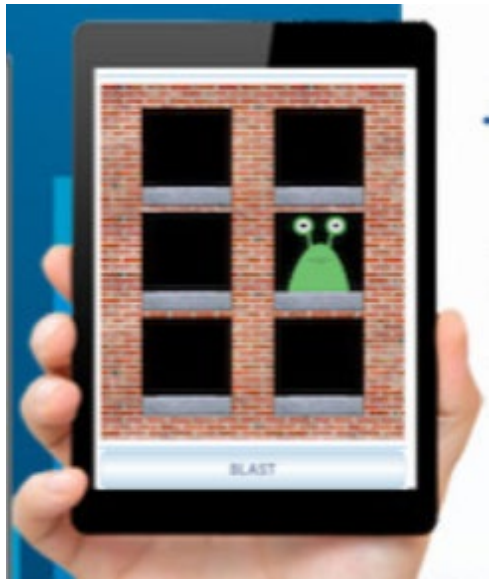
Van Campen, C. (Linda), et al. "Low Sensitivity of Abbreviated Tilt Table Testing for Diagnosing Postural Tachycardia Syndrome in Adults with ME/CFS." *Frontiers in Pediatrics*, vol. 6, 2018, https://doi.org/10.3389/fped.2018.00349.

# DANA Brain Vital: 5 min



**Simple Reaction Time (SRT)**
A speed-of-processing task with just one stimulus that requires patient to respond as quickly as possible (measured in milliseconds) by touching the target when it appears.

**Procedural Reaction Time (PRT)** **Go-No-Go (GNG)**
Both are tests of choice reaction time where there are multiple stimuli, and each requires a different response. These tests assess the patient's ability to maintain attention and vigilance for the target stimulus and the ability to inhibit responses to nontarget stimuli.

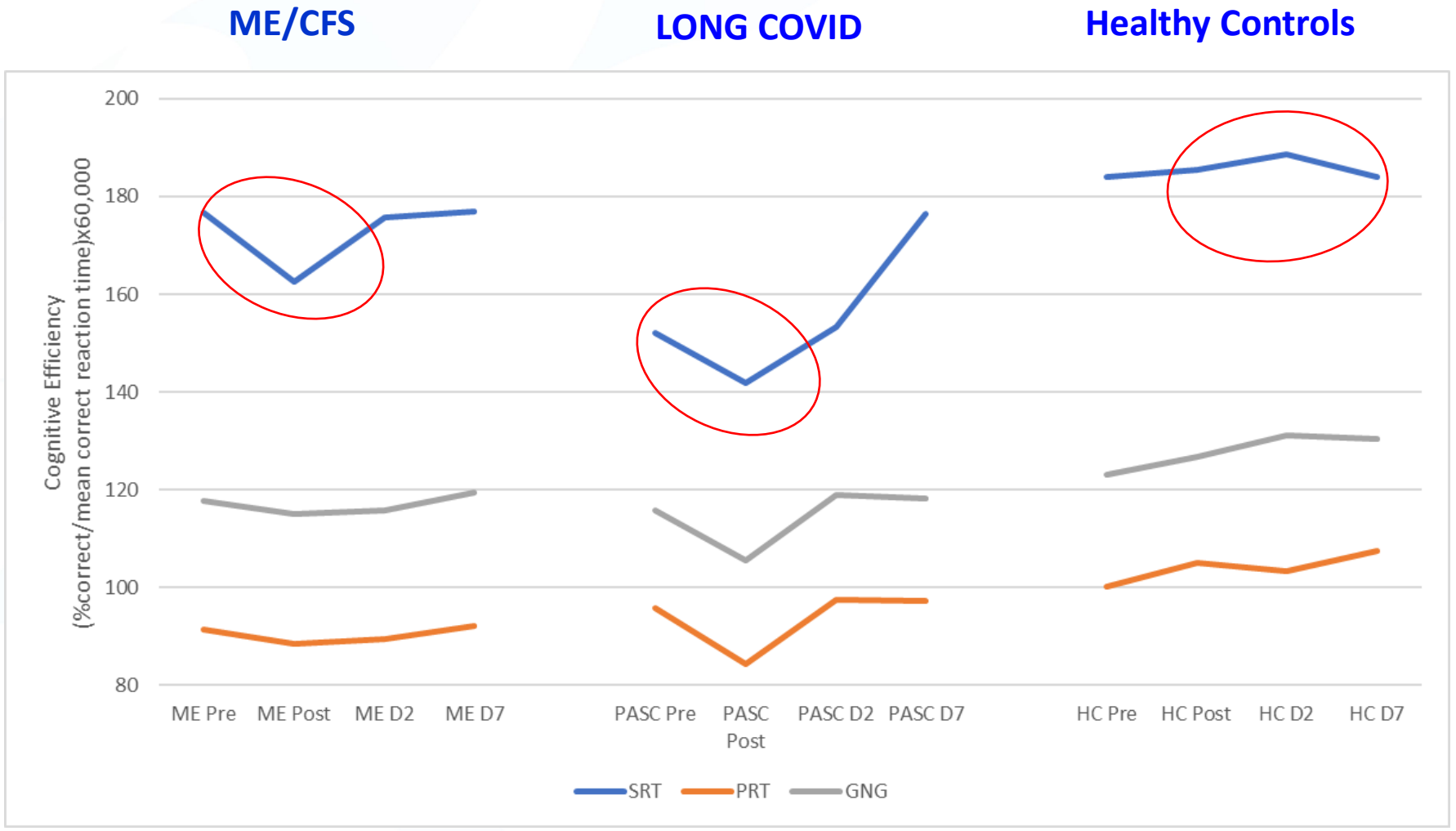
**Slowed reaction time is one of the most sensitive measures of impaired cognitive functioning.**

# Cognitive Results Before & After 10-Minute NASA Lean Test

**SRT: Simple Reaction Time**

**Long COVID**
**N= 26**

*Unpublished data from BHC study

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# Other resources

**OI/POTS:** http://dysautonomiainternational.org/

**BHC YouTube site education videos:** https://www.youtube.com/user/OFFERUtah

**BHC website → provider resources:** https://batemanhornecenter.org/

**ME/CFS:** https://www.mayoclinicproceedings.org/article/S0025-6196(21)00513-9/fulltext