



The
**Ehlers
Danlos**
Society

2020
**VIRTUAL
SUMMER
CONFERENCE**

Orthostatic Intolerance in EDS: the Basics

Peter C. Rowe, MD

Professor of Pediatrics

Sunshine Natural Wellbeing Foundation Professor

Director, Chronic Fatigue Clinic

Johns Hopkins University School of Medicine, Baltimore, MD



Presenter Disclosure Information

Peter C. Rowe, MD

- No relationships to disclose
- Off-label uses of several drugs will be discussed, where possible supplemented by short-term physiologic studies

Orthostatic intolerance in EDS

Earlier webinars:

- EDS Society

Orthostatic intolerance in EDS, 19 December 2018

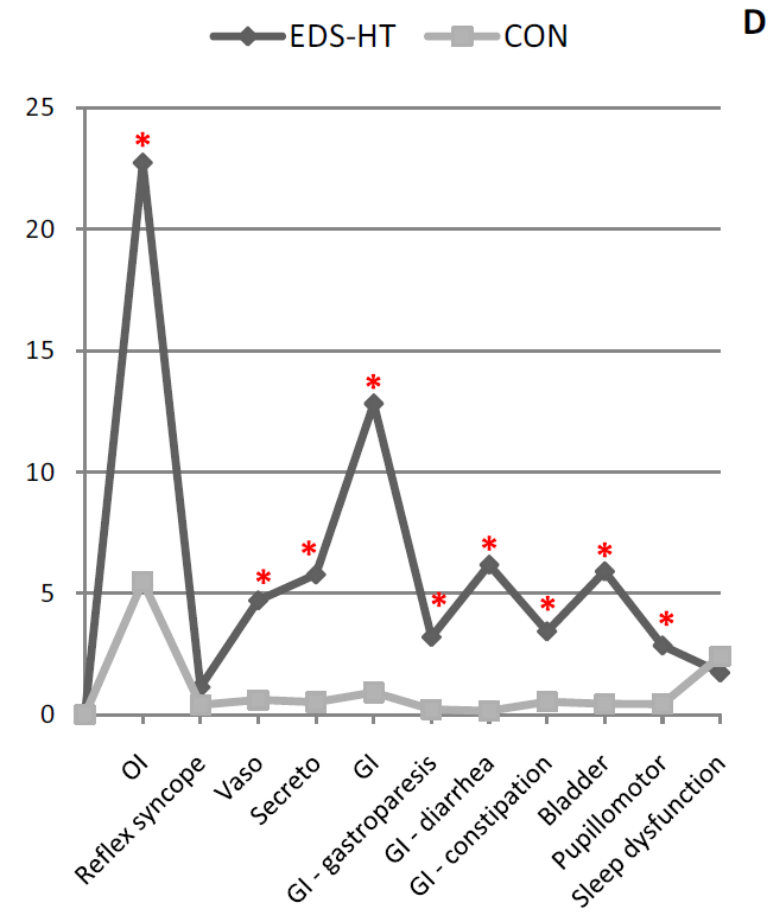
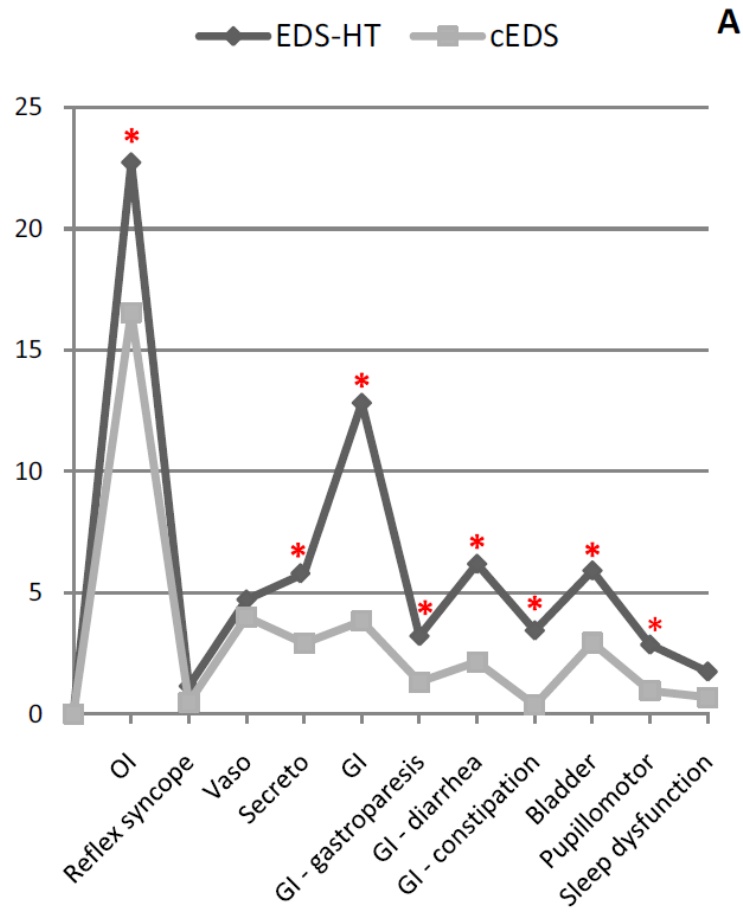
https://www.youtube.com/watch?v=7lA3Vcbz_w8

- EDS ECHO 06/24/2019, 11/13/2019, 02/27/2020
- Connecting the Dots between EDS and POTS

<https://www.youtube.com/watch?v=srUJRRihvsE>

Autonomic symptoms in EDS and controls

De Wandele I, et al. Seminars Arth Rheum 2014

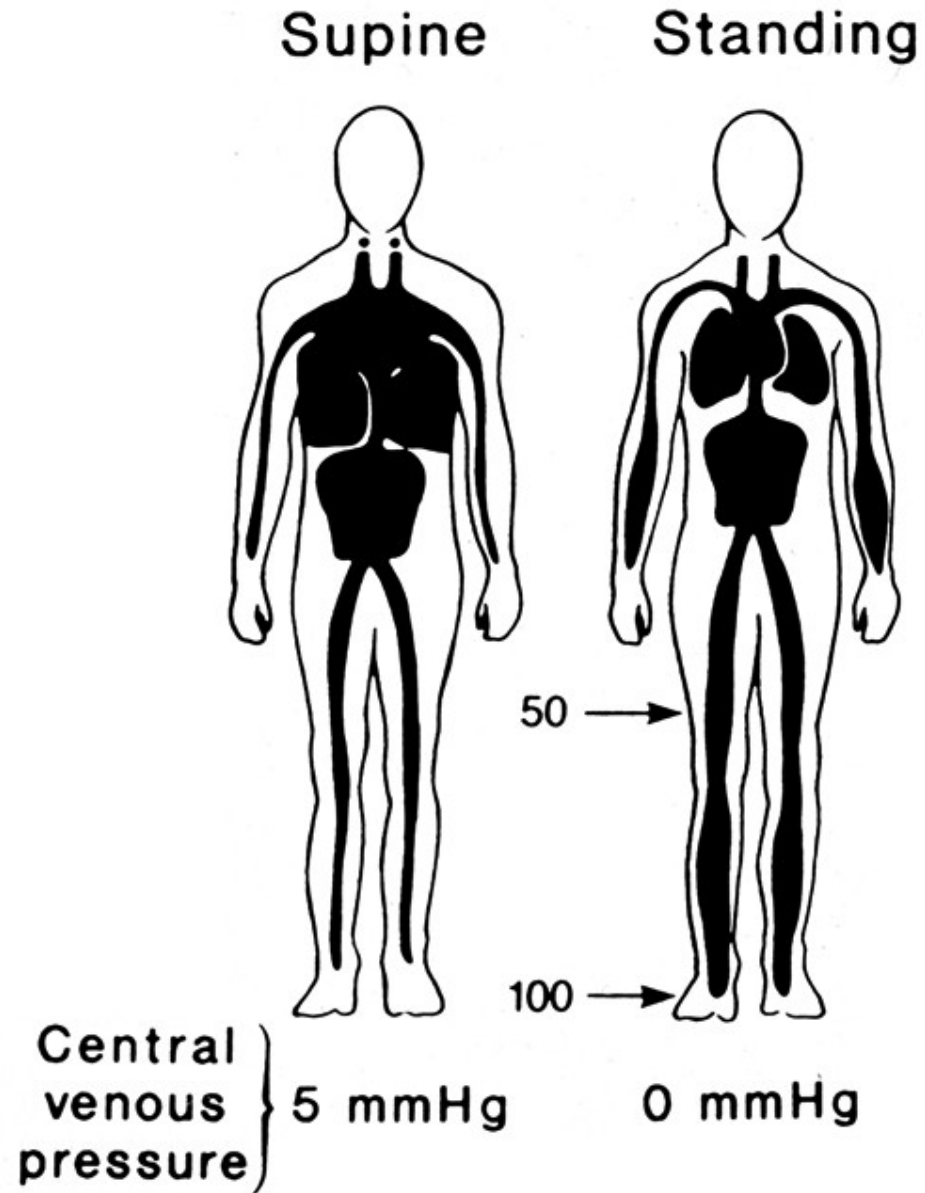


Orthostatic Intolerance

“Orthostatic” means “upright.”

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

Modified from: Low PA, Sandroni P, Joyner M, Shen WK.
Postural tachycardia syndrome (POTS).
J Cardiovasc Electrophysiol 2009;20:352-8.



500-750 mL of blood pools in the lower half of the body on standing.

The normal response is a 10-20 beat increase in heart rate and better blood vessel constriction to return blood to the heart and brain.

Low PA

Symptoms of Orthostatic Intolerance

Lightheadedness

Syncope

Diminished concentration

Headache

Blurred vision

Fatigue

Exercise intolerance

Dyspnea

Chest Discomfort

Palpitations

Tremulousness

Anxiety

Diaphoresis

Nausea

Due to reduced cerebral blood flow

Lightheadedness

Syncope

Diminished concentration

Headache

Blurred vision

Fatigue

Exercise intolerance

Dyspnea

Chest Discomfort

Palpitations

Tremulousness

Anxiety

Diaphoresis

Nausea

Due to higher levels of catecholamines (adrenaline and noradrenaline or epinephrine and norepinephrine)

Lightheadedness

Syncope

Diminished concentration

Headache

Blurred vision

Fatigue

Exercise intolerance

Dyspnea

Chest Discomfort

Palpitations

Tremulousness

Anxiety

Diaphoresis

Nausea

Historical questions with high yield in OI

- Have you ever fainted?
- Do you feel lightheaded or unwell when you stand for more than 5 minutes?
- How do you feel in the following settings:
 - Waiting in line, shopping?
 - Standing at a reception, in chorus, at a service?
 - After taking a hot shower, bath, or sauna?
 - In a warm environment (in a hot room, on a hot day)?
- Do you study in a reclining position, with knees to chest, or feet under you?
- Do you fidget and move around when standing?

Diagnostic testing

- Orthostatic vital signs—HR and BP measured supine, sitting, and standing—often measured over < 2 minutes: insufficient to identify most forms of chronic orthostatic intolerance. Prolonged testing of ≥ 10 minutes usually needed.
- Standing test (usually 10 min after a variable time supine):
 - Passive Stand Test
 - Active Stand Test

Passive Standing Test

Supine: 5 min with BP and HR every minute

Standing: 10-15 min with feet positioned 6 inches apart, 6 inches from a wall, leaning slightly backwards against the wall.

HR & BP measured each minute

Symptoms recorded every 1-2 minutes

Hyatt KH, Jacobson LB, Schneider VS. Comparison of 70° tilt, LBNP, and passive standing as measures of orthostatic tolerance. Aviat Space Environ Med 1975;46:801-8.

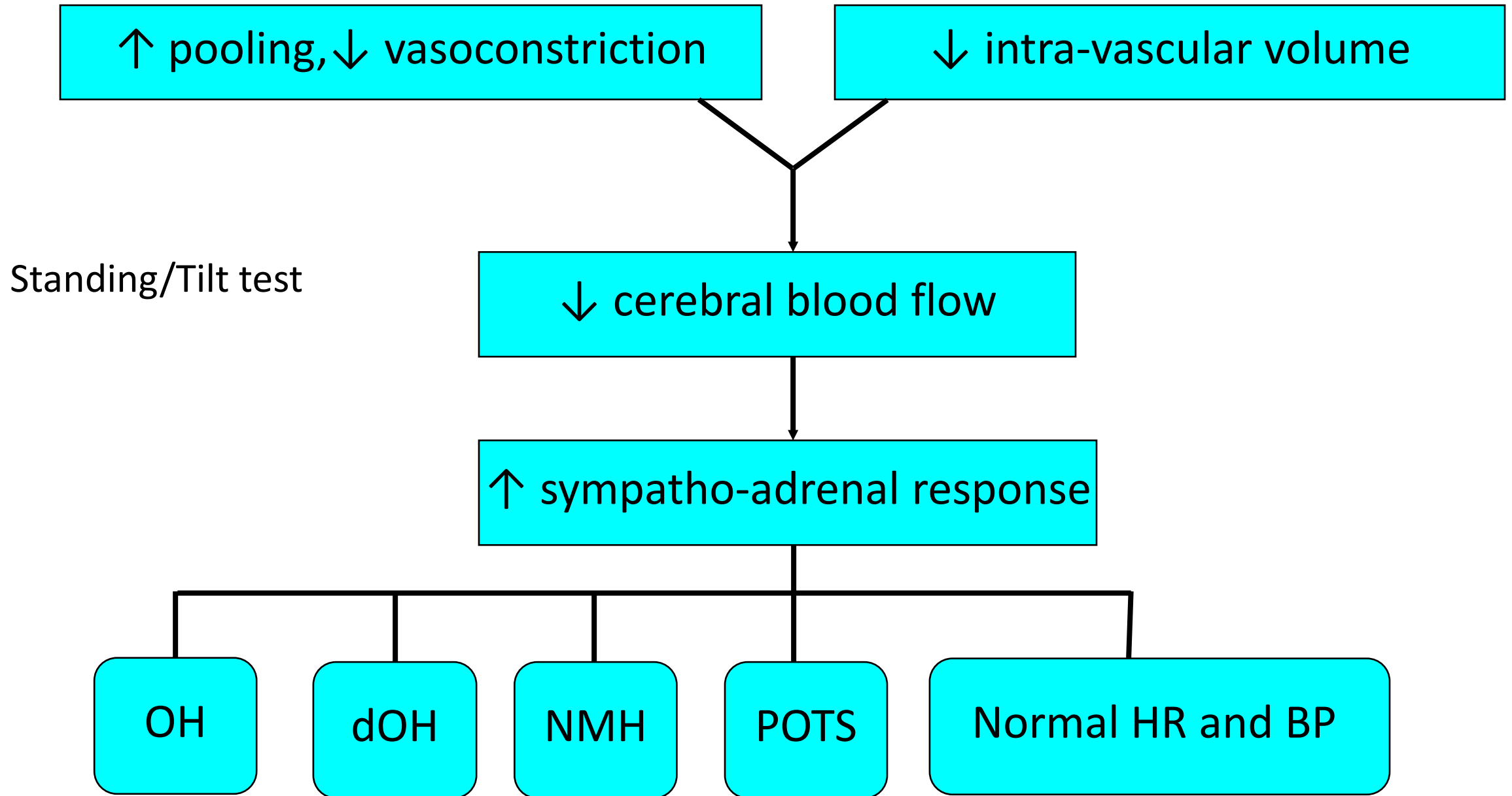
Head-up tilt table testing

Supine: Obtain baseline HR and BP values

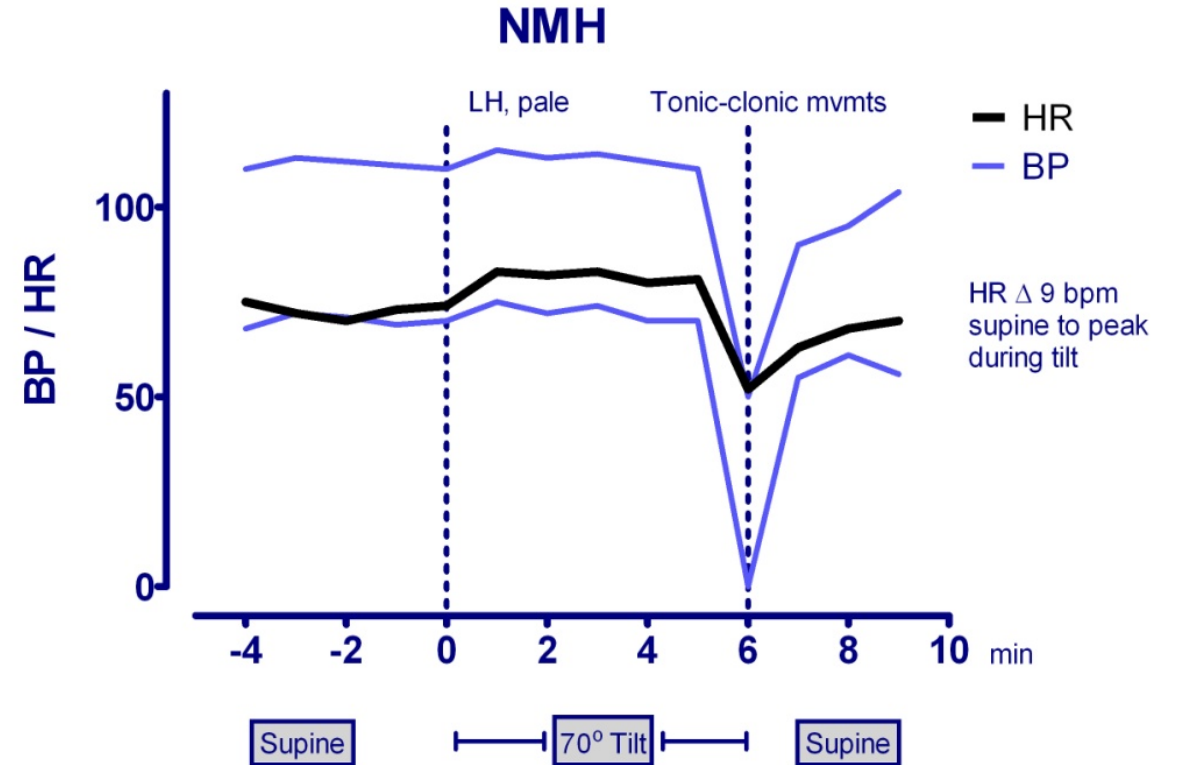
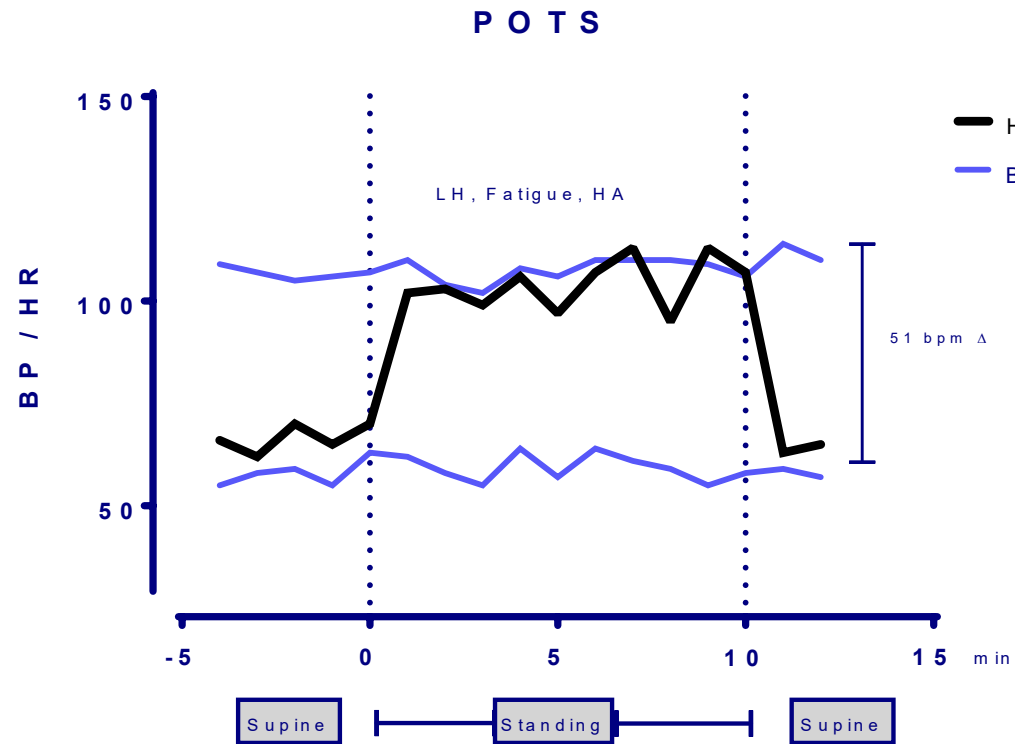
Stage 1: head-up tilt to 70° for ~ 45 min

Stage 2 (optional): return to supine for 10 minutes, then head-up tilt for 15 minutes with isoproterenol (1-2 mcg/kg/min).

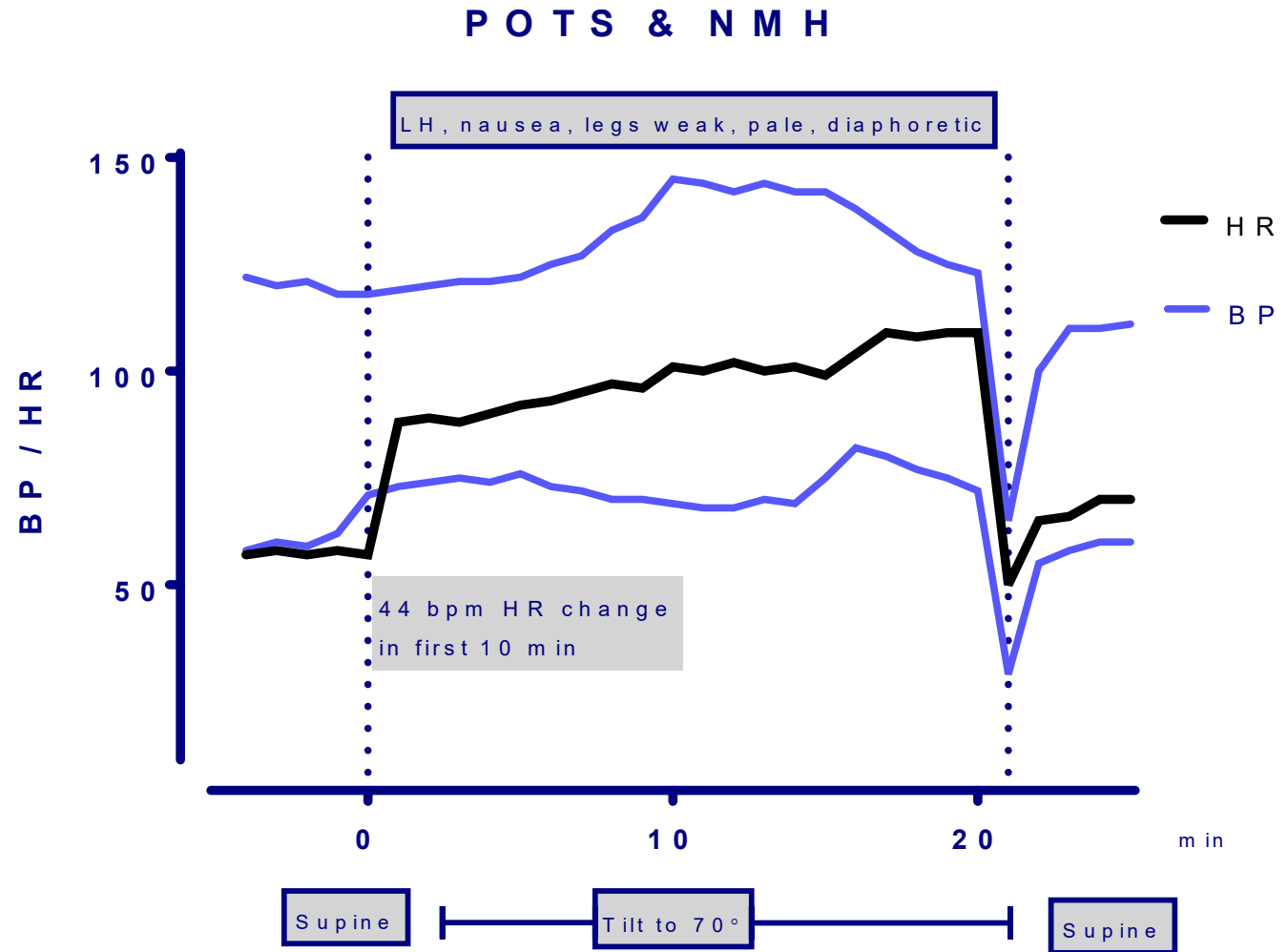




Common forms of orthostatic intolerance




POTS and NMH can occur together



Acrocyanosis is common in OI



Passive standing tests for the office diagnosis of postural tachycardia syndrome: New methodological considerations

Maria Roma, Colleen L. Marden and Peter C. Rowe 

Division of General Pediatrics and Adolescent Medicine, Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, MD, USA

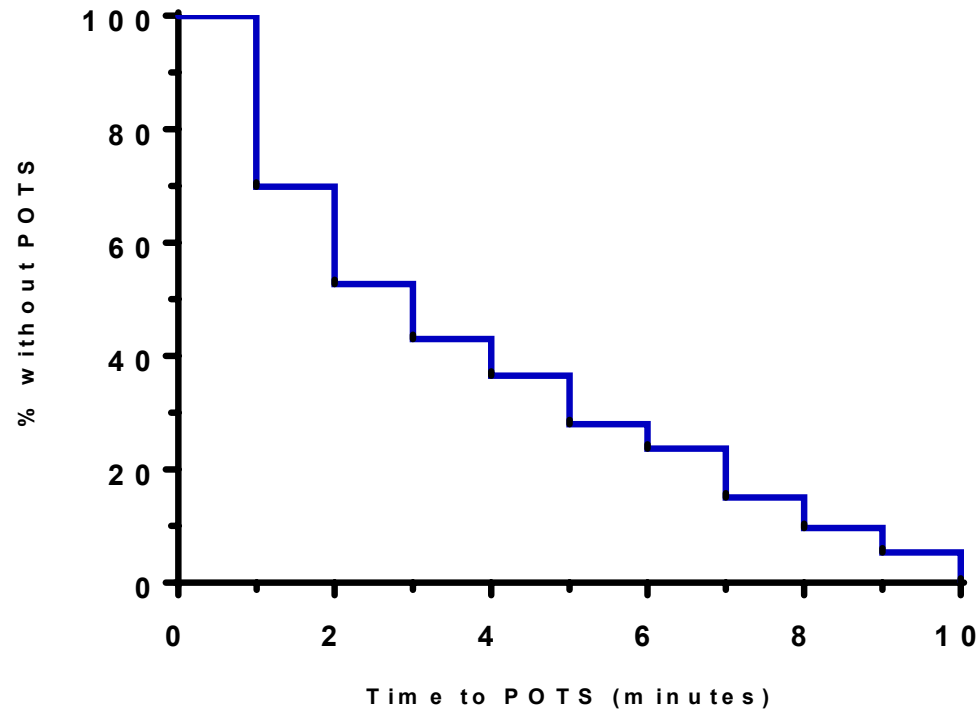


Table 3. Proportion of POTS diagnoses that would be missed at each minute of an abbreviated standing test (full sample, $N = 93$).

Minutes upright	POTS diagnoses missed at each minute
%	(95% CI)
1	70 (60–78)
2	53 (43–63)
3	43 (33–53)
4	37 (27–47)
5	27 (19–37)
6	24 (16–33)
7	15 (9–24)
8	10 (5–17)
9	5 (2–12)
10	0

Similar findings in ME/CFS adults

Low Sensitivity of Abbreviated Tilt Table Testing for Diagnosing Postural Tachycardia Syndrome in Adults With ME/CFS

C. (Linda) M. C. van Campen¹, Peter C. Rowe^{2*} and Frans C. Visser¹

What does it mean if you have lots of symptoms with standing, but the formal tests of heart rate and blood pressure are normal during a passive standing test or a head-up tilt table test?

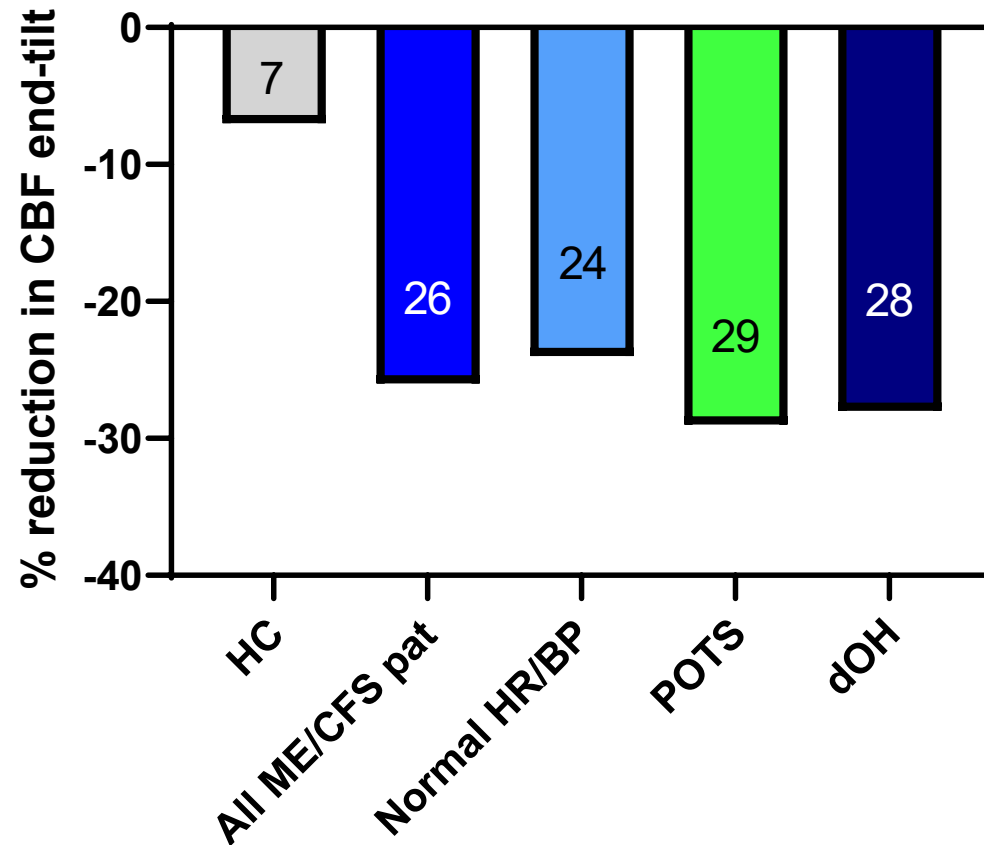
Does this mean nothing is wrong?

What does it mean if you have lots of symptoms with standing, but the formal tests of heart rate and blood pressure are normal during a passive standing test or a head-up tilt table test?

Does this mean nothing is wrong?

NO!

Changes in CBF during 30 minutes of HUT compared to supine values in 44 HC and 429 ME/CFS

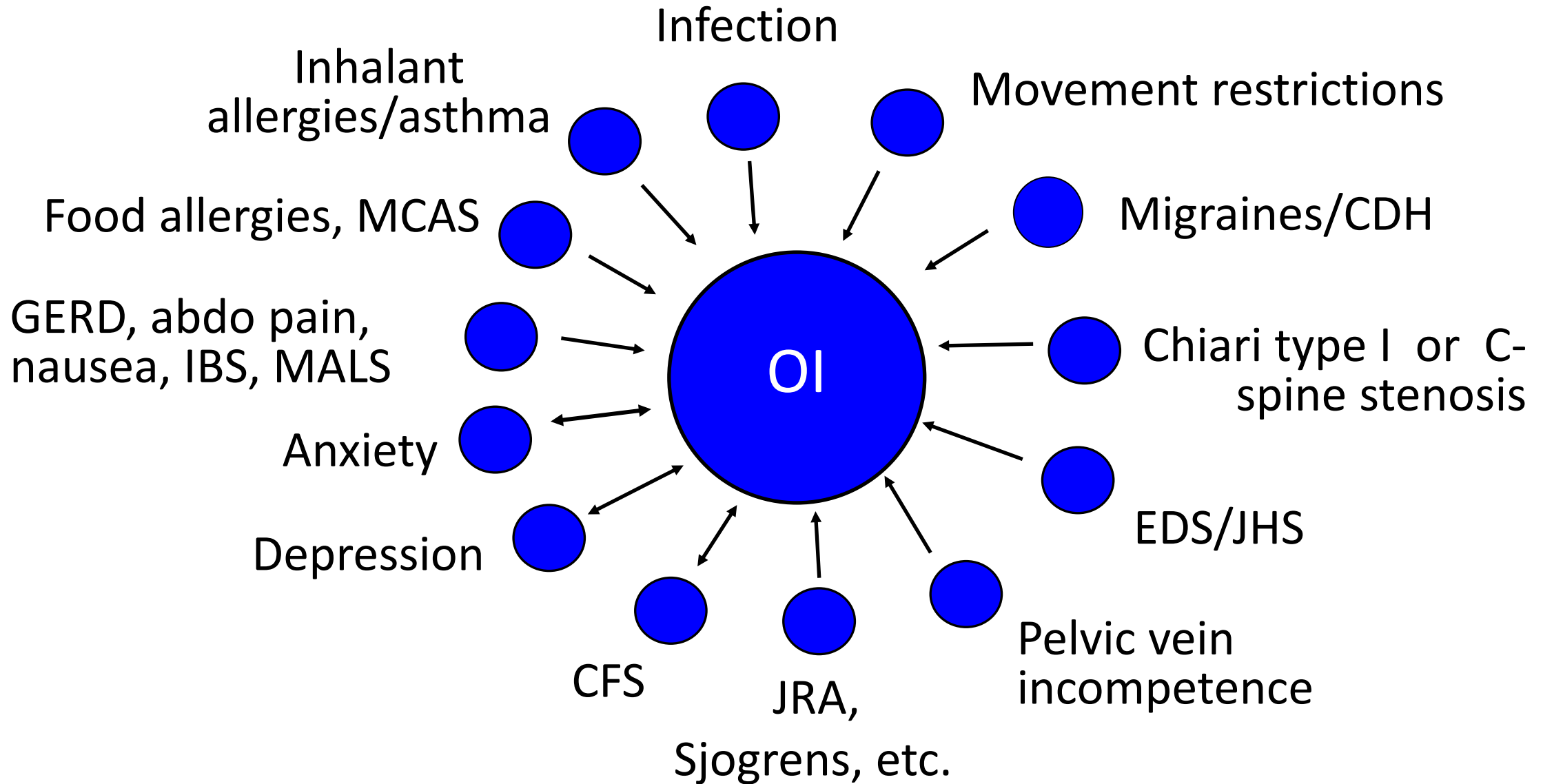


For all ME/CFS groups vs HC, $P < 0.001$.
(No differences in CBF supine pre-tilt)

van Campen CMC, Vergheut FWA, Rowe PC, Visser FC,
Clinical Neurophysiology Practice 2020;5

Treatment of Orthostatic Intolerance

- Step 1: Non pharmacologic measures
- Step 2: Treat contributory conditions
- Step 3: Medications
 - Monotherapy
 - Rational polytherapy



Pharmacologic Therapy

Vasoconstrictors

Midodrine, dextedrine,
methylphenidate, SSRIs, SNRIs;
L-DOPS (Droxidopa)

Volume expanders

Sodium (PO & occasionally IV),
fludrocortisone, clonidine, OCPs,
desmopressin

↓ HR
↓ Catecholamine
release/effect

β-blockers, disopyramide, SSRIs,
ACE inhibitor, ivabradine,
pyridostigmine bromide

Management of orthostatic intolerance

- requires careful attention by the patient and the practitioner to the factors that provoke symptoms
- requires a willingness to try several medications before a good fit is achieved
- requires a realization that meds often can treat symptoms but do not necessarily cure OI
- management of OI is one part of a comprehensive program of care

Resources



Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome Diagnosis and Management in Young People: A Primer

Peter C. Rowe¹, Rosemary A. Underhill^{2}, Kenneth J. Friedman³, Alan Gurwitt⁴,
Marvin S. Medow⁵, Malcolm S. Schwartz⁶, Nigel Speight⁷, Julian M. Stewart⁸,
Rosamund Vallings⁹ and Katherine S. Rowe¹⁰*

Open Access, so available to all free of charge

OI in EDS references

- Barron, D.F., et al., 2002. Joint hypermobility is more common in children with chronic fatigue syndrome than in healthy controls. *J Pediatr.* 141, 421-5.
- De Wandele, I., et al., 2014a. Autonomic symptom burden in the hypermobility type of Ehlers-Danlos syndrome: A comparative study with two other EDS types, fibromyalgia, and healthy controls. *Semin Arthritis Rheum.* 44, 353-61.
- De Wandele, I., et al., 2014b. Dysautonomia and its underlying mechanisms in the hypermobility type of Ehlers-Danlos syndrome. *Semin Arthritis Rheum.* 44, 93-100.
- De Wandele, I., et al., 2016. Orthostatic intolerance and fatigue in the hypermobility type of Ehlers-Danlos syndrome. *Rheumatology (Oxford).* 55, 1412-20.
- Gazit, Y., et al., 2003. Dysautonomia in the Joint Hypermobility Syndrome. *Am J Med.* 115, 33-40.
- Hakim, A., et al., 2017. Cardiovascular autonomic dysfunction in Ehlers–Danlos syndrome—hypermobile type. *Am J Med Genet Part C (Seminars in Medical Genetics).* 175C, 168-74.
- Roma M, et al. Postural tachycardia syndrome and other forms of orthostatic intolerance in Ehlers-Danlos syndrome. *Autonomic Neuroscience: Basic and Clinical* 2018; 215: 89-96.
- Rowe, P.C., et al., 1999. Orthostatic intolerance and chronic fatigue syndrome associated with Ehlers-Danlos syndrome. *J Pediatr.* 135, 494-9.

- ME/CFS - Solve ME/CFS Initiative
<http://solvecfs.org/>
- ME/CFS - International Association for CFS/ME
www.iacfsme.org
- OI - Search “Dr. Peter Rowe” on YouTube for webinar on “Managing Orthostatic Intolerance”
- OI - Dysautonomia International is a non-profit
www.dysautonomiainternational.org
- EDS - Ehlers-Danlos Society
<http://ehlers-danlos.com/>

THANK YOU

- Grants from NIAID, DoD, CFIDS Association of America/SMCI
- Sunshine Natural Wellbeing Foundation (endowed Chair)
- Research Coordinator Colleen Marden
- Summer students (John Fan, Alli Johns, Marissa Flaherty, Jocelyn Ray, Samantha Jasion, Erica Cranston, Megan Lauver, Maria Roma)
- Many families and patients:
 - Special thanks to the following: Berger, Biegel, Boies, Bowen, Caldwell, Cornell, Dweck, Ellen, Fox-Penner, Kelly, Kiely, Lauver, McFerron, Newbrand, Scheidlinger, Smith, and Vogel families.