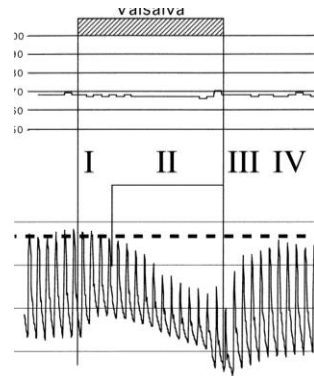
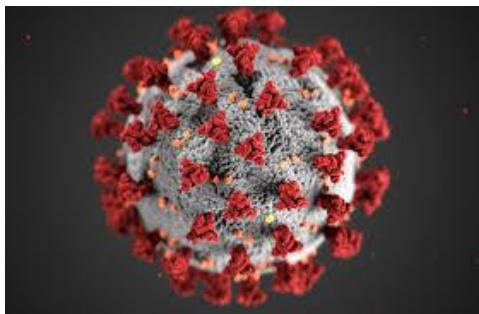




# Common Underlying Mechanisms of Chronic Illness: Lessons from postural tachycardia syndrome (POTS), myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), and Long-COVID/PASC

Mitchell Miglis, MD  
Associate Professor of Neurology  
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Stanford University



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| Consultant                 | 2 <sup>nd</sup> MD, Infinite MD, Guidepoint LLC, MED-IQ |
| Speakers' Bureaus          |                                                         |
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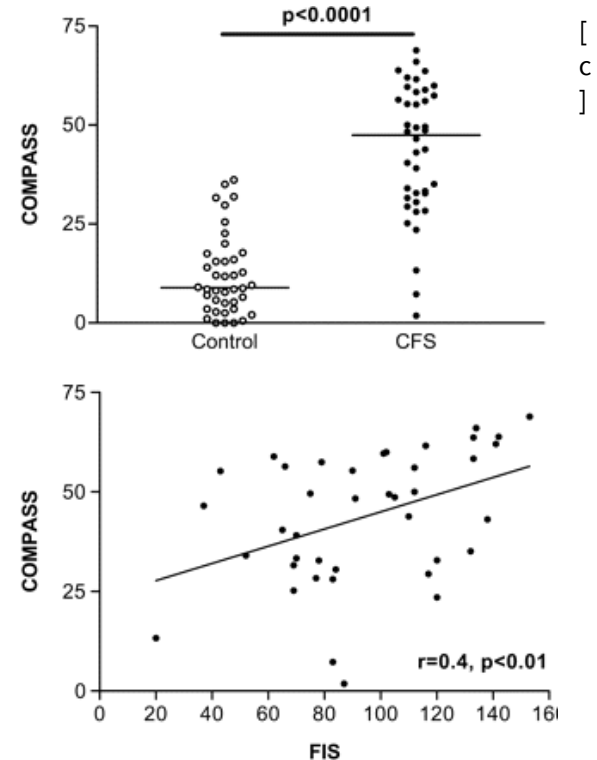
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- 1.
  - 2.
  - 3.

## Long COVID symptoms that overlap w/those commonly seen in patients with autonomic disorders including POTS

- **Fatigue-** most patients' chief complaint; many describe more fatigue than sleepiness, insomnia common
- **Cognitive-** "brain fog"
- **Gastrointestinal-** nausea, bloating, early satiety, constipation, diarrhea, motility disorders
- **Urinary-** Increased frequency, urgency, incontinence
- **Pain-** many pt's dx with fibromyalgia, small fiber neuropathy, more common in those with joint hypermobility/Ehlers-Danlos syndrome
- **Migraine-** extremely common
- **Psychiatric-** anxiety, "hyperarousal," panic attacks
- **Sleep-** insomnia, hypersomnia
- **Allergic-** Skin flushing, hives, dermatographia, food and drug allergies (mast cell)

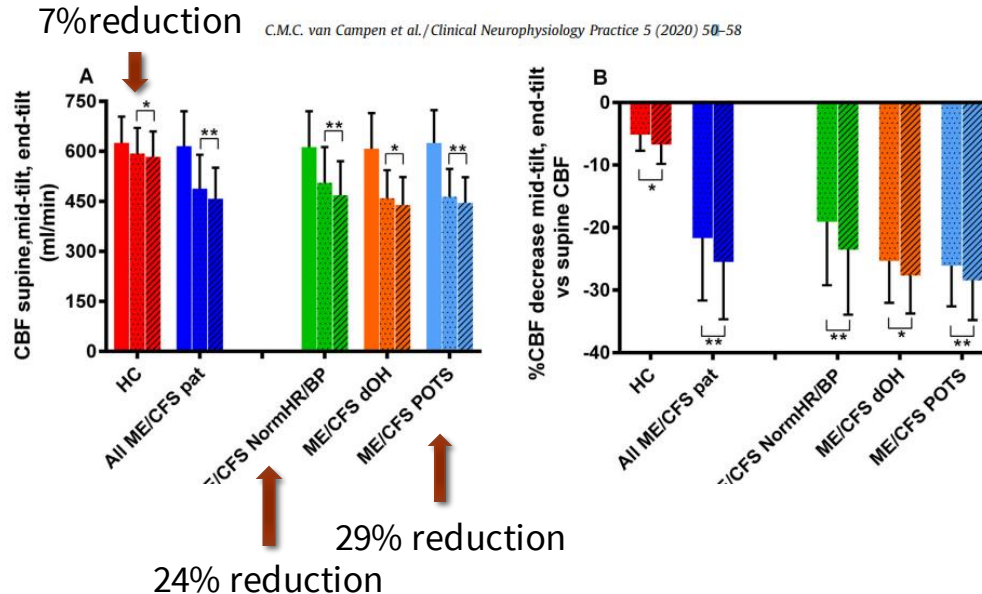
# ANS Dysfunction in ME/CFS

- Symptoms of ANS Dysfunction are common in ME/CFS
- OI is most common
  - › > 50% of patients<sup>[1]</sup>
- Most studies have assessed ANS function with tilt table testing, active stand and/or heart rate variability (HRV) analyses
- POTS is most commonly diagnosed ANS disorder in ME/CFS
  - › ~20-50%<sup>[1,2]</sup>



# Orthostatic cerebral blood flow and CO2 data in ME/CFS

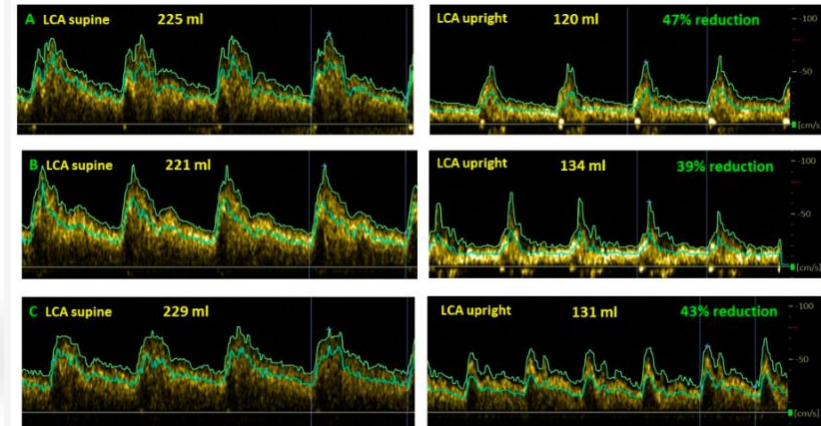
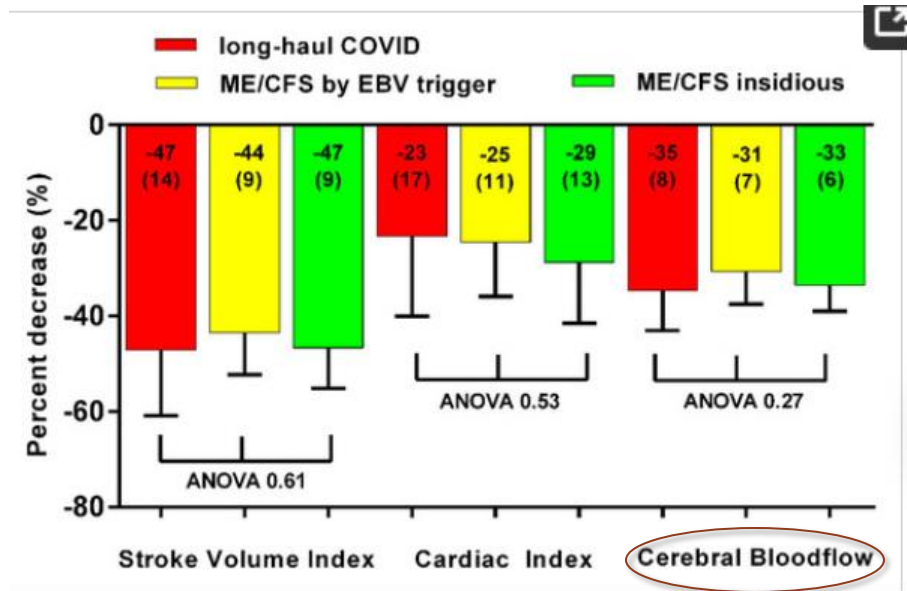
- Studies have demonstrated orthostatic reduction in CBF<sup>1</sup> as well as baseline and orthostatic hypocapnia<sup>2</sup> in ME/CFS



- 28% ME/CFS pts (n=429) met criteria for POTS, 58% normal hemodynamic response on tilt
- Even in patients with OI only, not meeting criteria for POTS or OH

# Orthostatic cerebral blood flow and CO2 data in PASC

- CBF reduction similar to ME/CFS not due to SARS-CoV-2

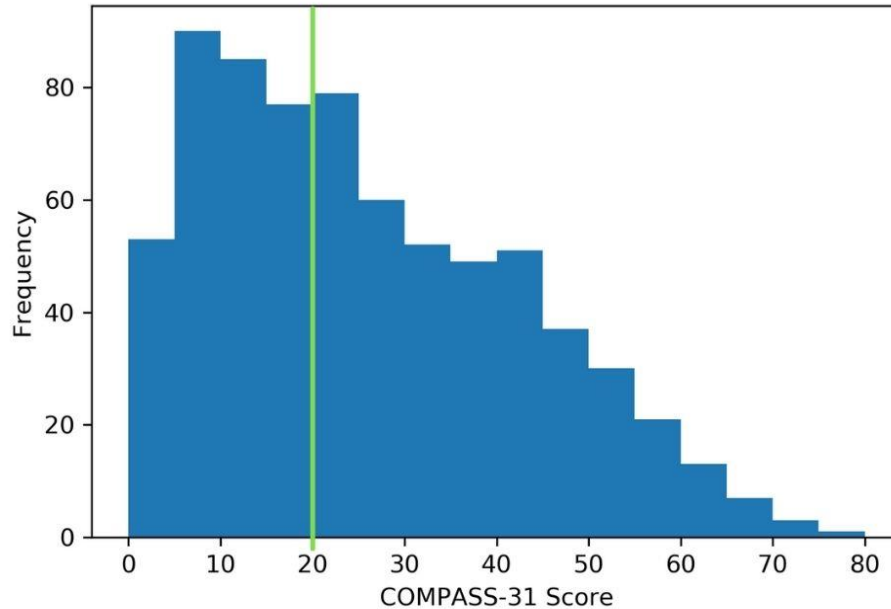


# Published Case Series of post-COVID Dysautonomia

- >100 cases published, >70%F
- POTS most common primary dx
- Mild to moderate initial symptoms
- Prominent cognitive impairment (brain fog), headaches, fatigue, orthostatic intolerance, sx of hyperadrenergic state and mast cell activation
- Pain syndrome may be present, suggestive of small fiber neuropathy
- Many patients have a history of very mild pre-existing or self-limiting autonomic symptoms, suggesting individual susceptibility



# Symptoms of Autonomic Dysfunction are Common in PASC



n= 2,314 PASC  
265 hospitalized  
2049 non-hospitalized

**67 %** of participants had a median COMPASS-31 score of 20 or above, suggestive of moderate to severe autonomic dysfunction.

5.9 → 17.8M US population

No difference in total COMPASS-31 scores between hospitalized and non-hospitalized participants ( $p=0.06$ ), suggesting that total autonomic symptom burden in PASC is independent of the severity of the acute SARS-CoV-2 infection.

# Effect of pre-existing conditions on COMPASS-31 scores

**Table 2.** Medical History of Survey Respondents Prior to COVID-19

| Variable                                  | Test Confirmed<br>(N=1249, %) | Test Unconfirmed (N=1065, %) |
|-------------------------------------------|-------------------------------|------------------------------|
| Anxiety                                   | 412 (33%)                     | 252 (23.7%)                  |
| Depression                                | 299 (23.9%)                   | 225 (21.1%)                  |
| Former smoker/vaper                       | 255 (20.4%)                   | 250 (23.5%)                  |
| Vitamin D deficiency                      | 258 (20.7%)                   | 201 (18.9%)                  |
| Asthma                                    | 256 (20.5%)                   | 203 (19.1%)                  |
| Food or environmental allergies           | 195 (15.6%)                   | 196 (18.4%)                  |
| Obesity                                   | 254 (20.3%)                   | 118 (11.1%)                  |
| High blood pressure                       | 212 (17%)                     | 109 (10.2%)                  |
| Autoimmune disease                        | 136 (10.9%)                   | 128 (12%)                    |
| Insomnia                                  | 103 (8.2%)                    | 91 (8.5%)                    |
| Anemia                                    | 112 (9%)                      | 79 (7.4%)                    |
| Current smoker/vaper                      | 68 (5.4%)                     | 73 (6.9%)                    |
| Obstructive sleep apnea                   | 86 (6.9%)                     | 54 (5.1%)                    |
| Neuropathy                                | 50 (4%)                       | 59 (5.5%)                    |
| Ehlers-Danlos syndrome                    | 34 (2.72%)                    | 67 (6.3%)                    |
| Diabetes                                  | 52 (4.2%)                     | 29 (2.7%)                    |
| Cancer                                    | 37 (3%)                       | 24 (2.3%)                    |
| Former chewing tobacco user               | 10 (0.8%)                     | 7 (0.7%)                     |
| Current chewing tobacco user              | 6 (0.5%)                      | 4 (0.4%)                     |
| Any form of dysautonomia                  | 64 (5.1%)                     | 88 (8.3%)                    |
| Postural orthostatic tachycardia syndrome | 51 (4.1%)                     | 73 (6.8%)                    |
| Vasovagal or neurocardiogenic syncope     | 15 (1.2%)                     | 25 (2.3%)                    |
| Orthostatic intolerance                   | 9 (0.7%)                      | 17 (1.6%)                    |
| Orthostatic hypotension                   | 7 (0.6%)                      | 17 (1.6%)                    |
| Inappropriate sinus tachycardia           | 9 (0.7%)                      | 13 (1.2%)                    |
| Autonomic neuropathy                      | 5 (0.4%)                      | 11 (1%)                      |
| Autonomic failure                         | 2 (0.2%)                      | 4 (0.4%)                     |
| Autoimmune autonomic ganglionopathy       | 2 (0.2%)                      | 0                            |
| Other types of dysautonomia               | 3 (0.2%)                      | 6 (0.6%)                     |

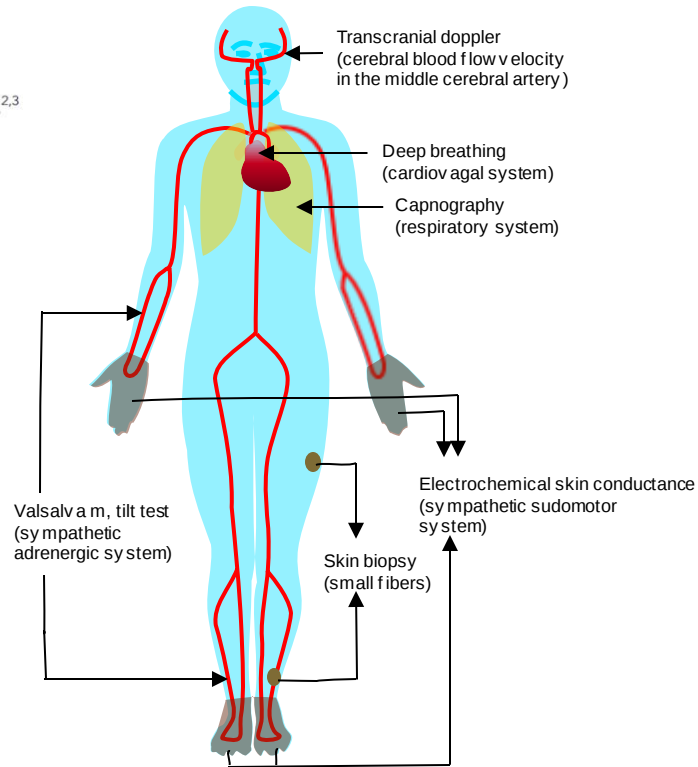
Pre-existing conditions associated with significantly higher total COMPASS-31 scores:

- Asthma
- Obesity (test-unconfirmed group only)
- Vitamin D deficiency
- Autoimmune disease
- Food or environmental allergies
- Anxiety
- Depression
- Smoking/vaping

# Multisystem Involvement in Post-Acute Sequelae of Coronavirus Disease 19

Peter Novak, MD, PhD<sup>1,2</sup> Shibani S. Mukerji, MD, PhD<sup>2,3</sup> Haitham S. Alabsi, DO<sup>2,3</sup>  
David Systrom, MD<sup>2,4</sup> Sadie P. Marciano, PA-C,<sup>1</sup> Donna Felsenstein, MD<sup>2,5</sup>  
William J. Mullally, MD,<sup>1,2†</sup> and David M. Pilgrim, MD<sup>1,2†</sup>

1. PASC (9)
2. Non-COVID POTS (10)
3. Controls (15)



# Brigham PASC Study – Results

**100% of PASC patients had at abnormalities in at least one autonomic domain on autonomic reflex testing (mild to moderate)**

**Sudomotor dysfunction 67%**

**Parasympathetic 40 %**

**Sympathetic adrenergic 100 %**

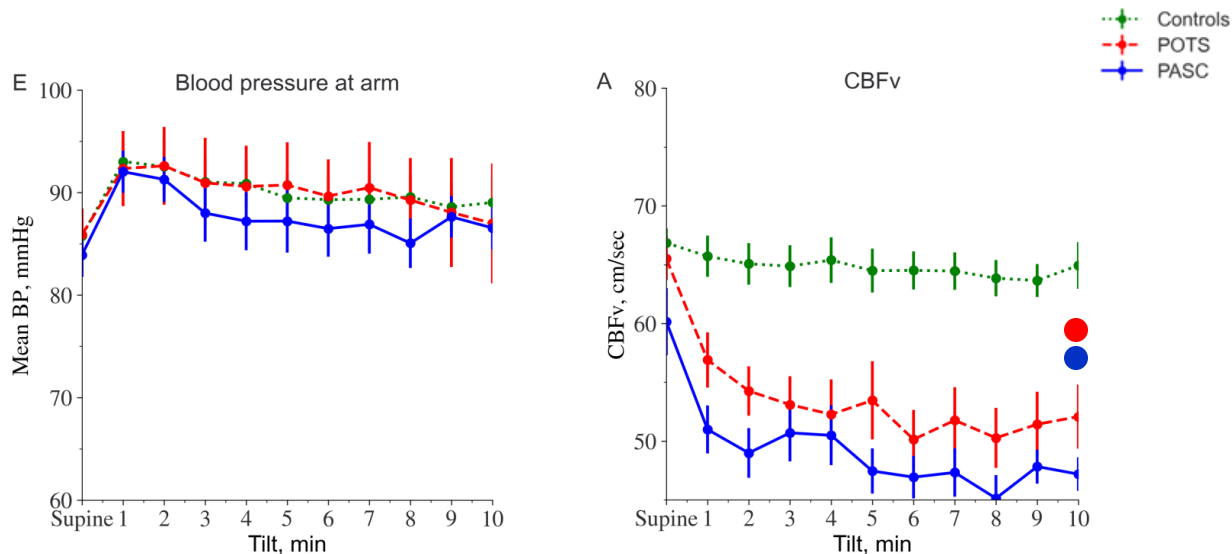
# Brigham PASC Study – Results

## Cerebrovascular dysregulation

PASC: 100% Orthostatic cerebral blood flow velocity (CBFv)  
declined ( $-20.0 \pm 13.4\%$ )

POTS: ( $-20.3 \pm 15.1\%$ )

Controls ( $-3.0 \pm 7.5\%$ ,  $p = 0.001$ )



# Brigham PASC Study – Results

**PASC: 100% Orthostatic cerebral blood flow velocity (CBFv) declined (-20.0 ± 13.4%)**

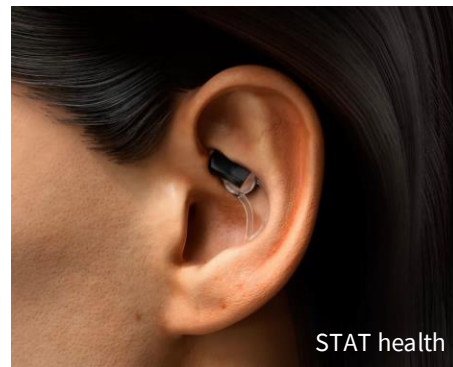
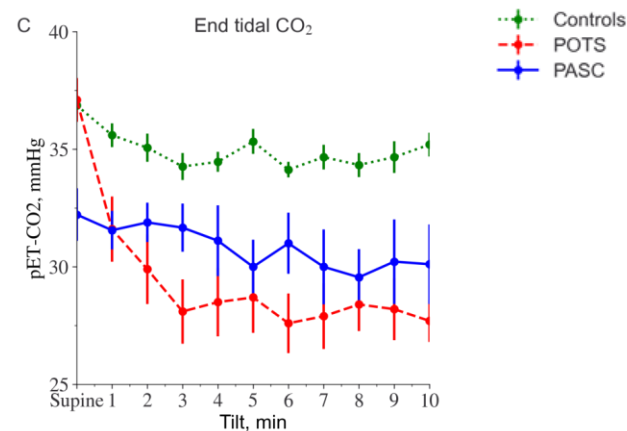
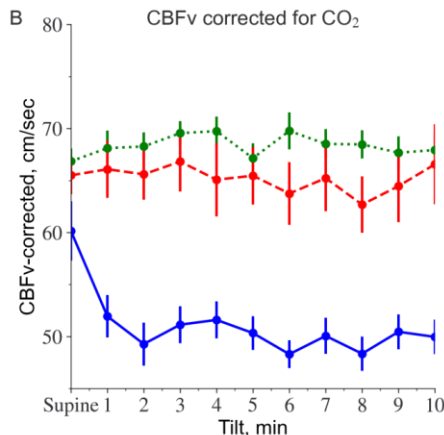
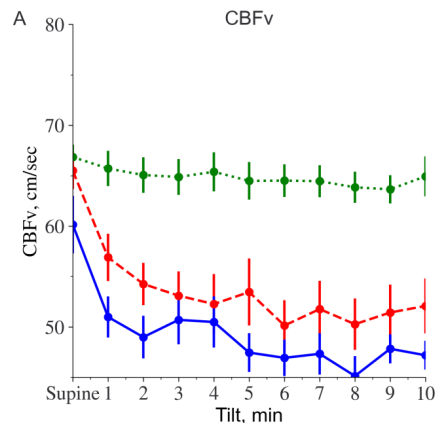
**POTS: (-20.3 ± 15.1%)**

**Controls (-3.0 ± 7.5%,  $p = 0.001$ )**

**PASC: Supine and orthostatic hypocapnia (100%)**

**POTS: Orthostatic hypocapnia (75%)**

**Controls: No hypocapnia**



STAT health

# Stanford Protocol

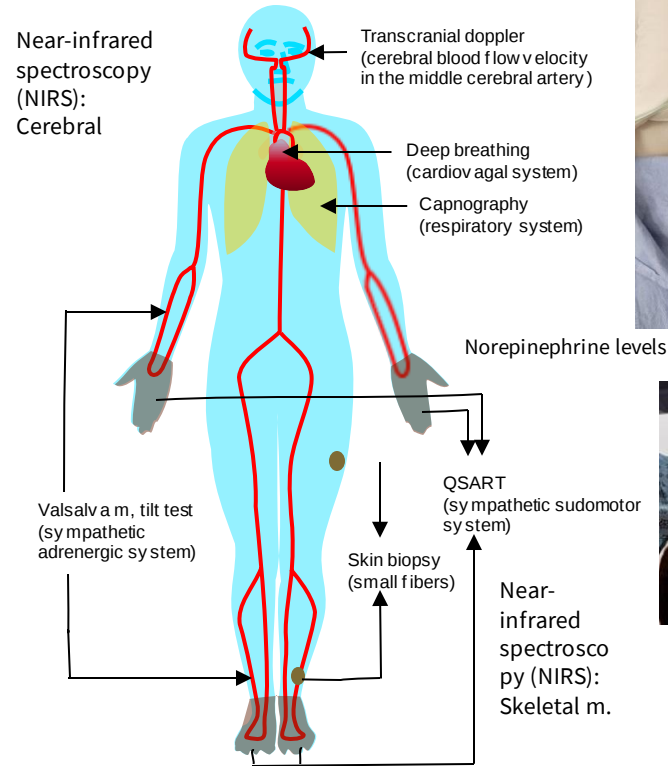
Cerebrovascular

Respiratory

Autonomic

Small fibers

+Cytokine and other inflammatory markers, novel GPCR AAb assay



# Stanford Preliminary Data

- PC-POTS (n=18) and controls (n=8) of similar age and gender (33 yrs vs 31 yrs; 70 vs 60% female).
- On HUTT, PC-POTS exhibited greater orthostatic HR changes, (47 bpm vs 16 bpm,  $p < 0.05$ ) and higher SBPs (149 vs 129 mmHg,  $p < 0.05$ ).
- CBFv abnormal in 75% of PC-POTS and in no controls.

In addition to POTS, our patients have:

- Sudomotor dysfunction 56% percent
  - Parasympathetic 27%
  - Controls: no dysautonomia
- 
- No significant difference in ETCO<sub>2</sub>, pO<sub>2</sub>, NIRS, or NE values between groups.

# Skin Biopsy Results

Brigham:

Small fiber neuropathy

**PASC: 9 pts (89 %)**

**POTS: 6 pts (60%)**

**Controls: 0**

Stanford:

PC-POTS (n=18)

**SFN: 43%**

**P-syn: 36% (!)**

Controls: (n=8)

**SFN: 13%**

**P-syn: 0%**

CLINICAL/SCIENTIFIC NOTE

OPEN ACCESS

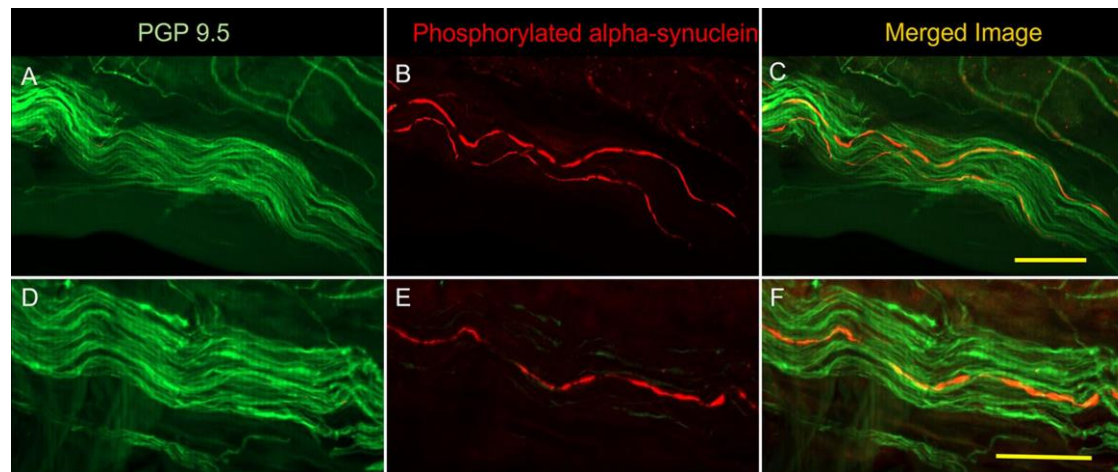
## Peripheral Neuropathy Evaluations of Patients With Prolonged Long COVID

Anne Louise Oaklander, MD, PhD, Alexander J. Mills, BS, Mary Kelley, DO, Lisa S. Toran, MD, Bryan Smith, MD, Marinos C. Dalakas, MD,\* and Avindra Nath, MD\*

*Neurol Neuroimmunol Neuroinflamm* 2022;9:e1146. doi:10.1212/NXI.0000000000001146

Correspondence

Dr. Oaklander  
aloaklander@mgh.harvard.edu



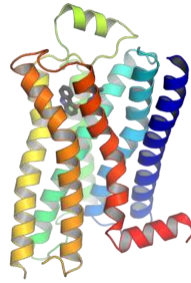
## Potential mechanisms of post-COVID conditions, including PC-dysautonomia and PC-ME/CFS

- Endothelial damage
- Viral Persistence
- Immune dysregulation
- Microclotting
- Baroreflex impairment
- Deconditioning (contributing factor)
- Gender Physiology (contributing factor)

# Immune dysregulation

- Many autoimmune diseases/manifestations during acute COVID-19 infection- ARDS, AIHA, ITP, SLE, aPLs, GBS, Kawasaki-like disease (MIS-C) in children
- Inflammatory markers are often elevated
- Several autoantibodies have been identified, though unclear if causative
- GPCR AAbs have been identified, though unclear if causative
- Vagal nerve damage

# Autoantibodies



Functional autoantibodies against G-protein coupled receptors in patients with persistent Long-COVID-19 symptoms

Gerd Wallukat<sup>a,b,\*</sup>, Bettina Hohberger<sup>c</sup>, Katrin Wenzel<sup>b</sup>, Julia Fürst<sup>d</sup>, Sarah Schulze-Rothe<sup>b</sup>, Anne Wallukat<sup>b</sup>, Anne-Sophie Hönicke<sup>b</sup>, Johannes Müller<sup>b</sup>



- **Zhou et al (2020)**- 21 patients critically ill with COVID-19 were investigated for the presence of autoantibodies. 20% had anti-52 kDa SSA/Ro antibodies, 25% had anti-60 kDa SSA/Ro antibodies and 50% had + ANA
- **Wang et al (2021)**- found an “expansive autoantibody landscape” in 172 COVID-19 pts, high prevalence of AAbs directed against cytokines, chemokines, complement components and cell-surface proteins including autoantibodies targeting vascular cells, CNS tissues, GI tract, skin and connective tissue
- **Lyons-Weiler (2020)**- 29 SARS-CoV-2 proteins have homological immunogenic sequences to human peptides involved in adaptive immune response, the largest number being those of the SARS-CoV-2 spike protein
- **Wallukat et al (2021)**- G-protein coupled receptor autoantibodies (GPCR-AAbs) in 31 patients with COVID-19, 29 of whom were diagnosed with PACS. Included those targeting the  $\beta_2$ ,  $\alpha_1$ , angiotensin II, muscarinic M2-receptor, ETA-receptors (all which previously reported in POTS patients)

# Viral Persistence



Preprints are preliminary reports that have not undergone peer review.  
They should not be considered conclusive, used to inform clinical practice,  
or referenced by the media as validated information.

## SARS-CoV-2 infection and persistence throughout the human body and brain

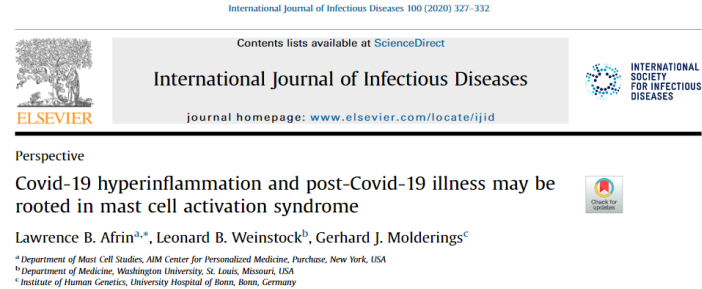
- SARS-CoV-2 RNA detected in at least one tissue in over half of 27 post-mortem cases beyond day 14, and evidence of prolonged viral replication in extra pulmonary tissues as late as day 99.
- Spike RNA detected in most heart and brain tissue
- Suggests viremia leading to body-wide dissemination, including across the blood-brain barrier, and viral replication early in COVID-19, even in asymptomatic or mild cases

### Clinical Advances

- 12.7% of patients may shed SARS-CoV-2 RNA in the feces 4 months after diagnosis and 3.8% at 7 months.  
GI symptoms correlated with fecal shedding.

Gastrointestinal symptoms and fecal shedding of SARS-CoV-2 RNA suggest prolonged gastrointestinal infection

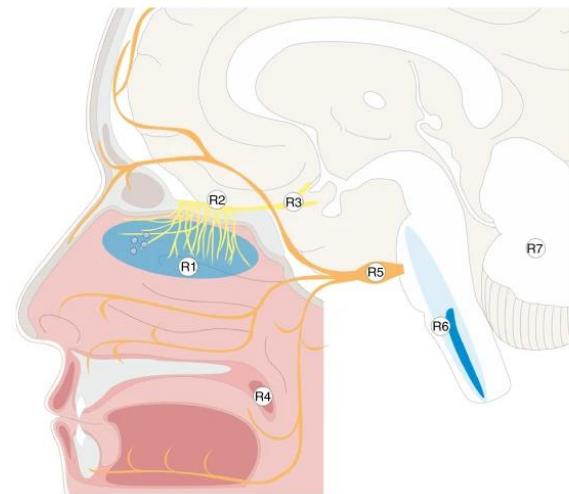
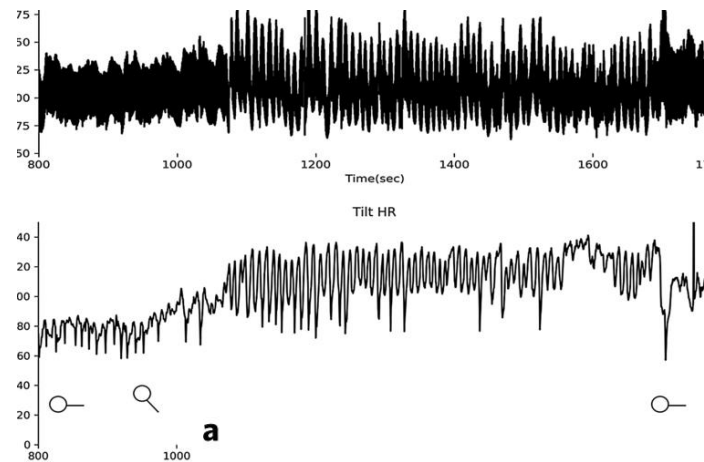
# Mast Cell Activation



- Mast cells express ACE-2 receptors
- May be involved in cytokine storm seen in ARDS in severe COVID-19
- H1/2 blockers and mast cell stabilizers may have role in treatment
- GPCR AAbs can stimulate early maturation of mast cells

## Baroreflex Impairment

- **Canetta et al (2020)**- syncope reported in 25/41 (9%) of patients on presentation, though other repots (Rass et al., 2021) report prevalence of ~1%.
- **Rass et al (2021)**- orthostatic hypotension reported in 1% of 137 hospitalized patients
- Hyperadrenergic state reported in several new-onset POTS cases, ACE2 receptors present in NTS of medulla



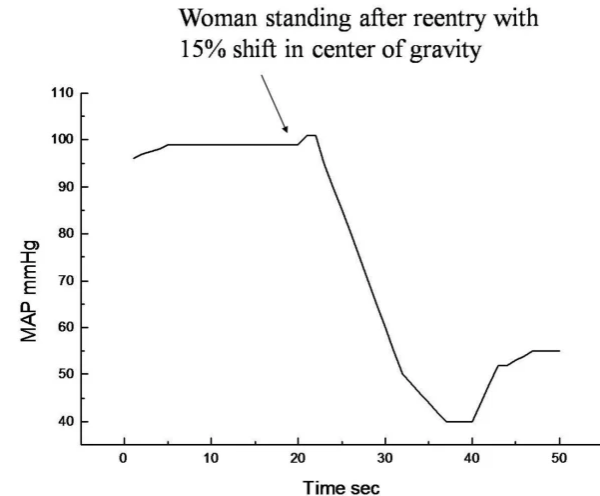
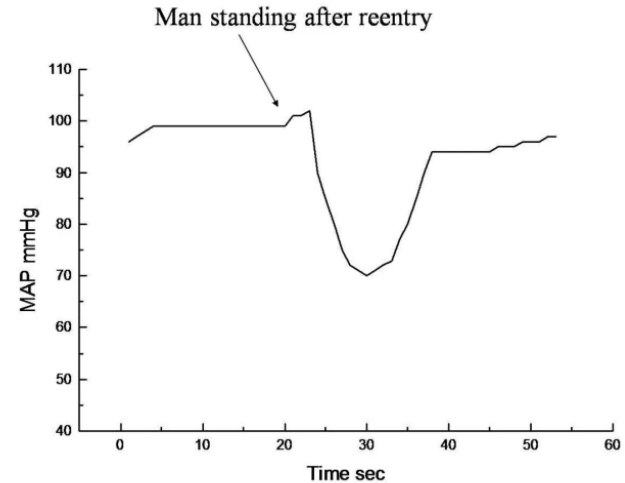
**b**  
log<sub>10</sub> SARS-CoV-2 RNA copies per

## Deconditioning

- Reduced physical activity common, leading to deconditioning
- As in POTS, deconditioning is likely part of pathogenesis though does not explain entirety of illness
- Low SV, CO and cardiac mass have been reported in POTS (Parsaik et al. 2012)
- Does not explain myriad of systemic symptoms
- Exercise may lead to **improvement but not resolution** of symptoms in some, and certain physiological parameters such as blood volume
- Some patients may experience post-exertional malaise (PEM), in which case exercise should be recommended with caution

# Gender Physiology

- Early data supports the observation that PACS affects female>males
- (POTS >80% females)
- Women have 1/3 less skeletal muscle mass (less muscle pump) and have smaller hearts
- More prone to pelvic venous pooling
- All of which may be significantly exacerbated if deconditioning is introduced
- Women more prone to autoimmune disease, with an approximately 4:1 ratio compared to men
- Sex hormones may also play a role (most female PASC patients note worse symptoms during menstrual cycle)



## Treatment: Additional thoughts

- Rule out cardiopulmonary and thromboembolic disease
- Symptomatic treatment depending on presentation with non-pharmacologic volume expansion and compression garments if disorder of OI is diagnosed
- Graduated exercise program if possible, mindful of PEM
- Symptomatic pharmacological treatment depending on presentation
- Consider immunomodulatory therapies if other signs of autoimmune disease present
- Anti-inflammatory medications? LDN, low dose aripiprazole (experience drawn from ME/CFS literature)
- Neuromodulators/vagal nerve stimulation? TMS?
- Antivirals? (ex. paxlovid)- trials ongoing

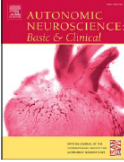
# Future Directions



Contents lists available at [ScienceDirect](https://www.sciencedirect.com)

Autonomic Neuroscience: Basic and Clinical

journal homepage: [www.elsevier.com/locate/autneu](https://www.elsevier.com/locate/autneu)



Review

Preparing for the long-haul: Autonomic complications of COVID-19

Nicholas W. Larsen<sup>a</sup>, Lauren E. Stiles<sup>b</sup>, Mitchell G. Miglis<sup>a,\*</sup>

<sup>a</sup> Department of Neurology and Neurological Sciences, Stanford University, Palo Alto, CA, USA

<sup>b</sup> Department of Neurology, Stony Brook University Renaissance School of Medicine, Stony Brook, NY, USA



- Define diagnostic criteria, define the name. ICD-10 U09.9, Working group on consensus definition of Long-COVID/PASC
- Establish patient registries with open access to de-identified data
- Longitudinal studies assessing symptoms and objective markers of ANS and cognitive function (RECOVER)
- Greater understanding of immunological markers that may suggest increased susceptibility
- Treatment trials!

# Thank you!

