Long Covid – Cardiovascular and Autonomic Sequeale

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Disclosures

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Long Covid - Post-acute sequelae of COVID-19 (PASC)

Range of symptoms after COVID-19 infection

new, returning or ongoing symptoms

within 3 months of COVID-19 and duration> 2 months

Characteristic clusters of symptoms:

Fatigue

Brain fog

Dyspnea

Pain

Autonomic

1. Dixit et al. Post-Acute COVID-19 Syndrome and the cardiovascular system: What is known? Am Heart J Plus. 2021;5:100025. 2. Alabsi H. et al Retrospective Study of Neurologic Sequelae in Critically Ill vs Non-Critically Ill COVID-19 Patients. Poster presented at: Neurocritical Care Society Annual Meeting. 2021 Chicago 3. Assaf et al, 2020. What does COVID-19 recovery actually look like? Patient-led research collaborative. https://patientresearchcovid19.com/research /report-1/#Contributors. 4. Bishof, K., 2020. Post-COVID Syndrome Patient Experience & Needs Survey. COVID-19 Longhauler Advocacy Project. https://drive.google.com/file/d/18CrqtiKGDh yf6nVxcBsaCTMr1PNeuOMB/view. 5. Kedor et al 2021. Chronic COVID-19 Syndrome and Chronic Fatigue Syndrome (ME/CFS) Following the First Pandemic Wave in Germany – A First Analysis of a Prospective Observational Study. https://doi.org/10.1101/ 2021.02.06.21249256 medRxiv.

PASC – Surveys - Dysautonomia

Affect ~50% of survivors of SARS-CoV-2 infection. Neurologic symptoms vary across patients and can be disabling, irrespective of severity of initial COVID-19.

A survey of 640 PASC patients noted that the most common symptoms reported were symptoms of autonomic dysfunction.

Another survey of 1200 PASC patients performed by the COVID-19 Long-hauler Advocacy Project, noted **34%** of patient had a new diagnosis of autonomic dysfunction.

PASC patients noting significant change in their levels of energy had worse scores on the COMPASS-31, a validated questionnaire for autonomic dysfunction.

Dixit et al. Post-Acute COVID-19 Syndrome and the cardiovascular system: What is known? Am Heart J Plus. 2021;5:100025. Alabsi H. et al Retrospective Study of Neurologic Sequelae in Critically Ill vs Non-Critically Ill COVID-19 Patients. Poster at: Neurocritical Care Society Ann.Meet. 2021, Assaf et al, 2020. What does COVID-19 recovery actually look like? Patient-led research collaborative. https://patientresearchcovid19.com/research /report-1/#Contributors. Bishof, K., 2020. Post-COVID Syndrome Patient Experience & Needs Survey. COVID-19 Longhauler Advocacy Project. Kedor et al 2021. Chronic COVID-19 Syndrome and Chronic Fatigue Syndrome (ME/CFS) Following the First Pandemic Wave in Germany – A First Analysis of a Prospective Observational Study

Partners PASC Study

Aim: To characterize autonomic and related sings of PASC
Design: Retrospective
Inclusion criteria: +PASC criteria
Completion of comprehensive autonomic testing with skin biopsies.

Exclusion criteria included any disorder or medication that could affect the autonomic, pulmonary, cardiac or metabolic systems.

PASC criteria:
chronic (>4 weeks) fatigue (grade 3 or more on each of the Bristol Rheumatoid Arthritis Fatigue Numerical Rating Scales parts), and brain fog (grade 3 or more on an 11-point scale) which had developed within six weeks of the acute COVID-19 infection.

Novak et al, Annals of Neurology, 2021

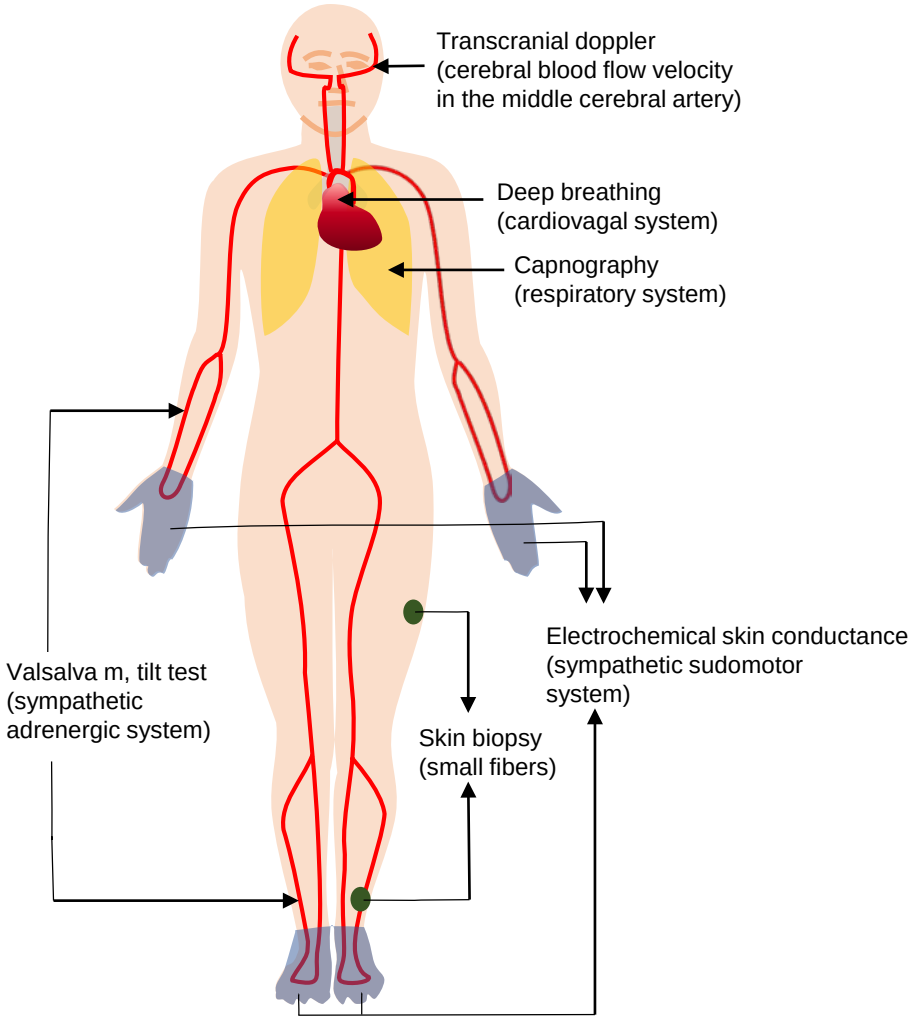
Brigham Protocol

Cerebrovascular

Respiratory

Autonomic

Small fibers



+ Low grade inflammation

(inflammatory/autoimmune markers-CRP,IL6, IL1B, TNA, …)

Novak et a. Annals of Allergy and Immunology, 2021, Annals of Neurology, 2021

Partners PASC Study

Inflammatory markers:

Neuronal antibodies (part of paraneoplastic panel):

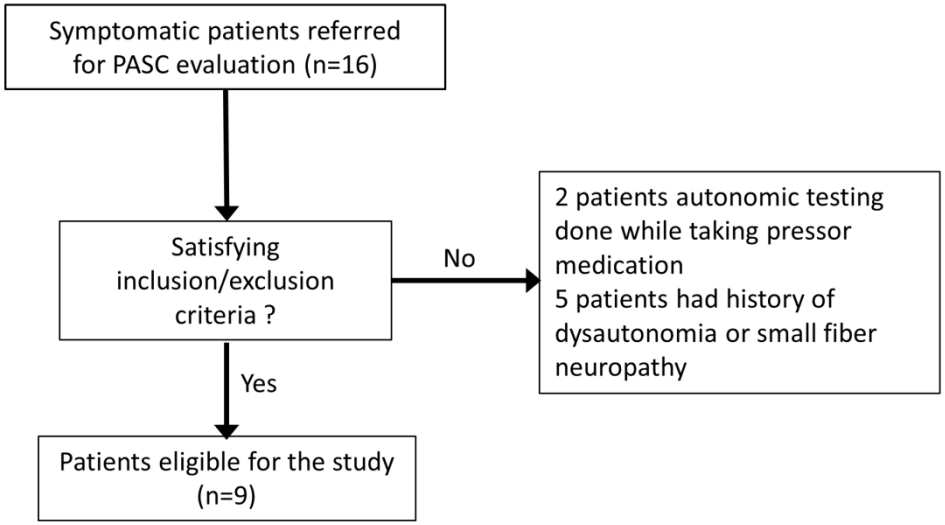
VGKC, CASPR2, LGI1,CAN,CAPQ, Ach,

Other antibodies: TSHDS, FGFR3 (Pestronk's lab, U. Washington)

Inflammatory proteins, cytokines: CRP, IL1B, IL6, IL10, Adiponectin, Leptin, TNA, Tryptase, growth hormone, myoglobin

Additional chemicals: plasma metanephrine, supine/standing norepinephrine

Partners PASC Study



Novak et al, Annals of Neurology, 2021

Partners PASC Study - Demographic

Enrolled 9 patients,
all white women,
average age of 35.8 (plus or minus 7.3 years).

All had mild COVID-19

- Probably delta variant
- Typical presentation was fever, cough, dyspnea, headache, loss of smell
- All treated as home observation,
- No one was vaccinated

PASC's were age- and sex-matched with 10 women who had postural tachycardia syndrome (POTS) and 15 healthy controls.

Novak et al, Annals of Neurology, 2021

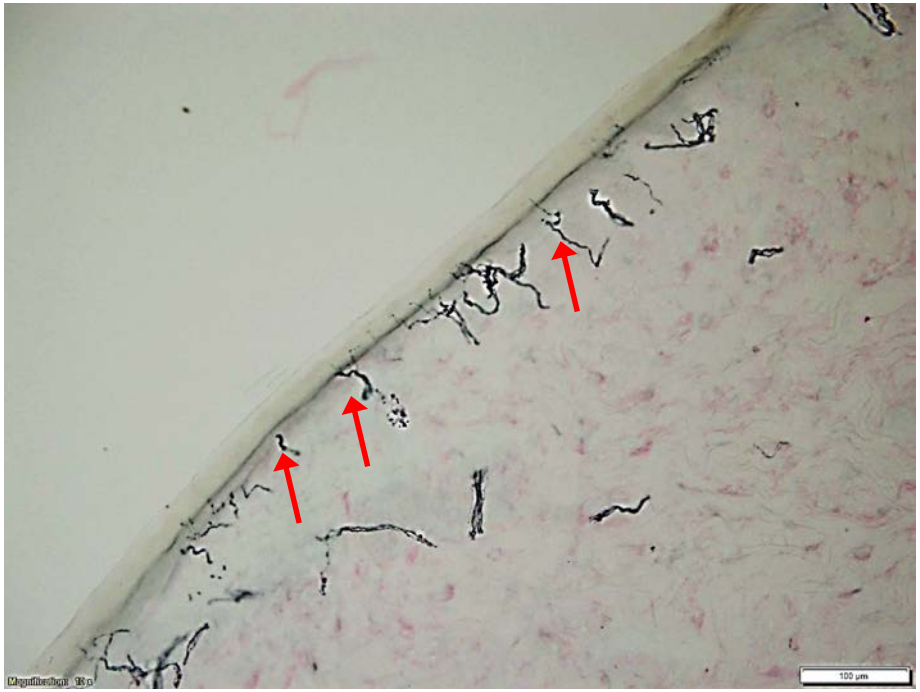
Partners PASC Study – Results

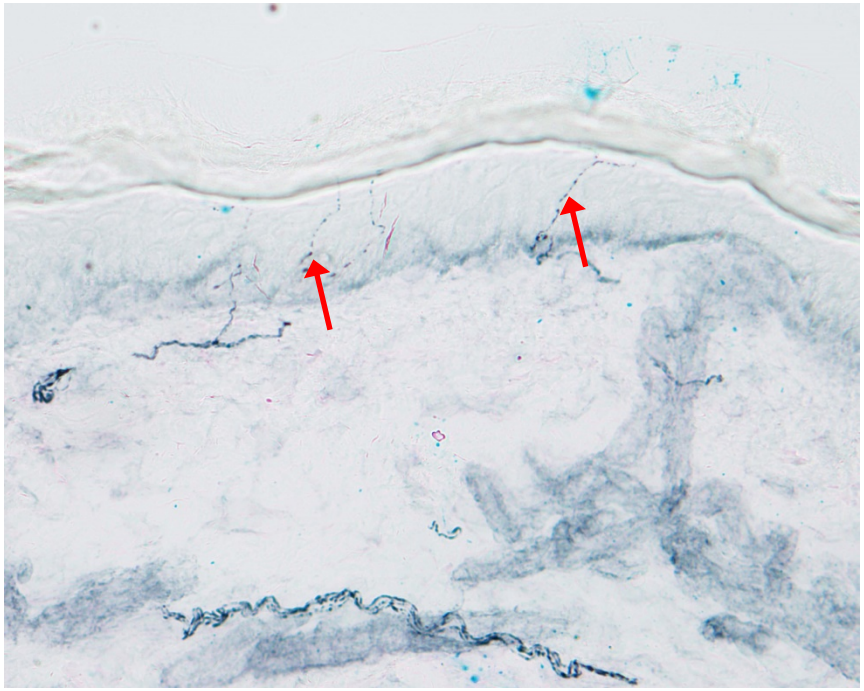
Small fiber neuropathy

PASC: 9 pts (89 %)

POTS: 6 pts (60%)

Controls: 0





Novak et al, Annals of Neurology, 2021

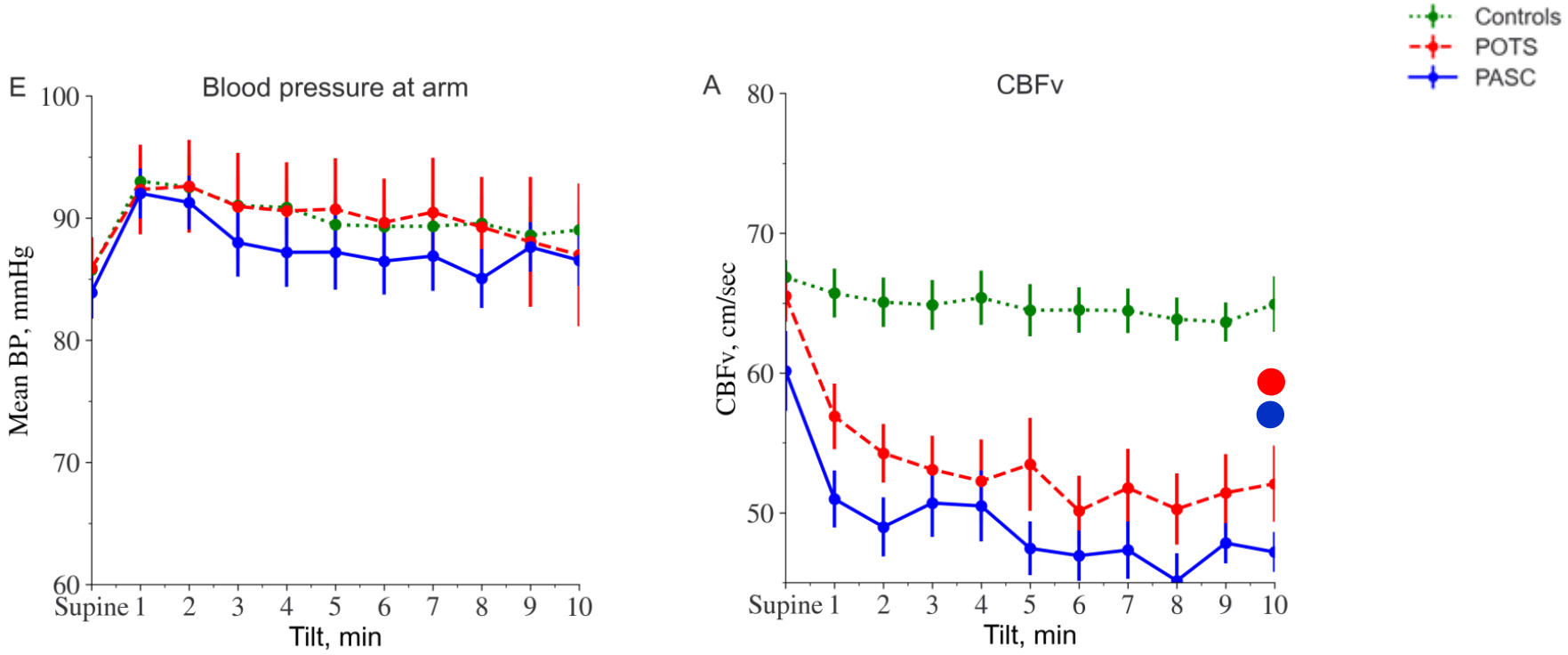
Partners PASC Study – Results

Cerebrovascular dysregulation

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)



Novak et al, Annals of Neurology, 2021

Partners PASC Study – Results

Dysautonomia

PASC: frequent (100%) – at least one domain, but mild to moderate

- Sudomotor dysfunction 67%
- Parasympathetic 40 %
- Sympathetic adrenergic 100 %

POTS: frequent (100%) – at least one domain, but mild to moderate

- Sudomotor dysfunction 67% percent
- Parasympathetic 27%
- Sympathetic adrenergic 67%

Controls: 0

Autonomic scores	**Controls**	**PASC**	**POTS**	**P (Controls-PASC-POTS)**	**P (PASC-POTS)**
N	11	15	15		
Sympathetic sudomotor (ESC), range 0-6	0.0 (0.0)	1.5 (1.3)	1.7 (1.8)	0.397	0.776
Sympathetic adrenergic (Valsalva maneuver), range 0-3	0.0 (0.0)	1.6 (0.6)	1.3 (1.0)	<0.001	0.246
Sympathetic adrenergic (Tilt), range 0-10	0.0 (0.0)	0.7 (2.2)	0.5 (1.2)	0.436	0.782
Autonomic failure, range 0-24	0.0 (0.0)	8.0 (5.1)	**12.9 (3.2)**	<0.001	0.005

Novak et al, Annals of Neurology, 2021

Autonomic Nervous System

- Small fibers – innervate all organs:

Autonomic “proper” (efferent or motor) small fibers

Sensory (afferent) small fibers

- Autonomic fibers

Motor, therefore we cannot feel them

Dysfunction is causing “dysautonomia”

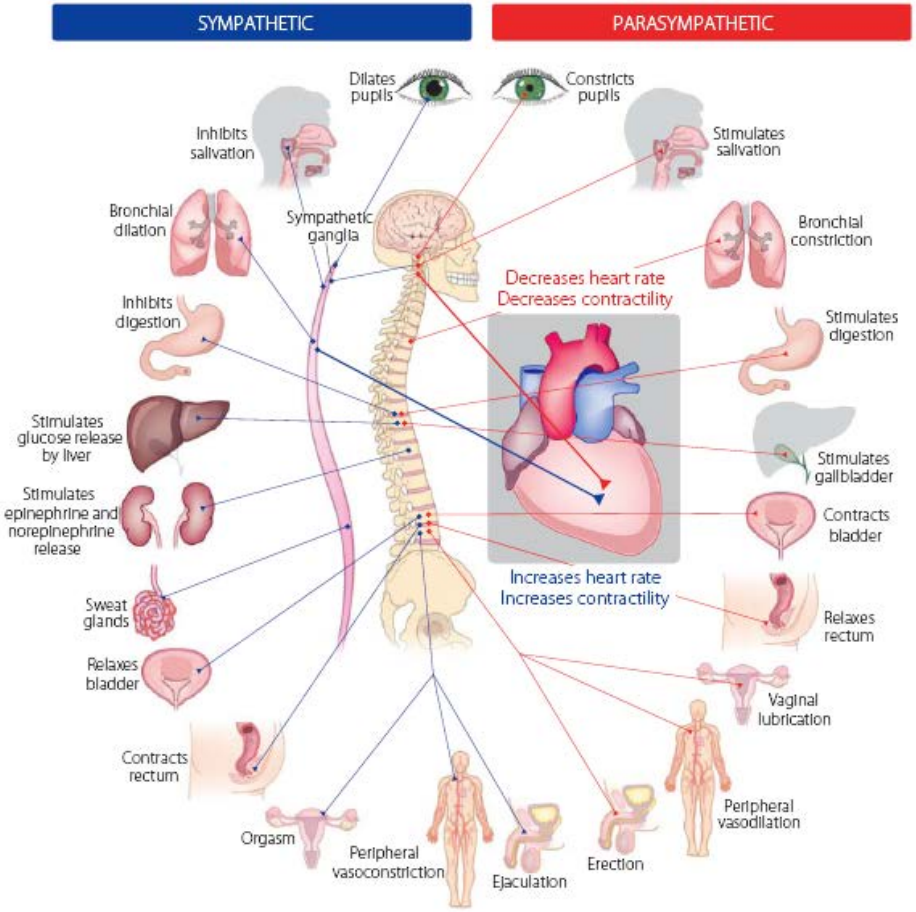
Autonomic dysfunctions manifests

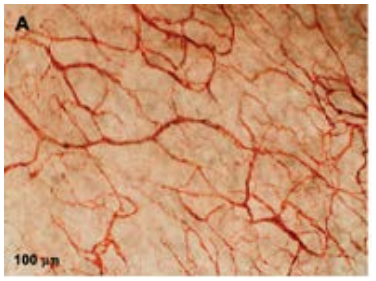
as end organ dysfunction

  - For example the enteric autonomic neuropathy may cause constipation

Dysfunction of sensory (afferent) fibers

-painful small fiber neuropathy





Vinik A, Erbas T, Casellini C. (2013). Diabetic cardiac autonomic neuropathy, inflammation and cardiovascular disease. *Journal of Diabetes* Investigation. 4 (1), 4-18; Novak et al, (2001). Autonomic impairment in painful neuropathy, Neurology, 56:861-868, Novak et al. (2009) J Cutan Pathol 36:296-301

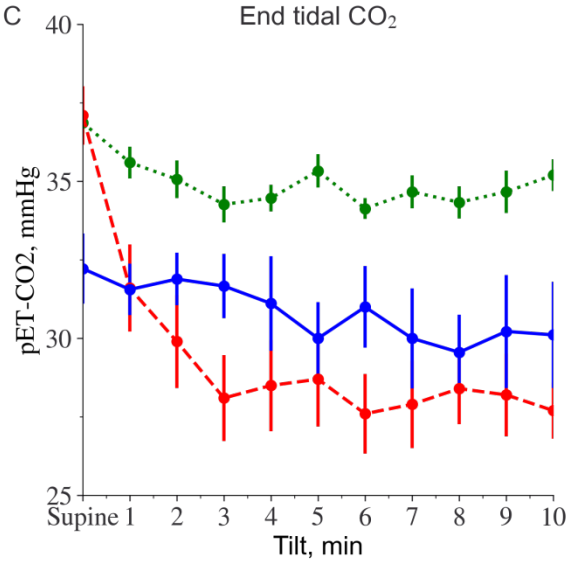
Partners PASC Study – Results

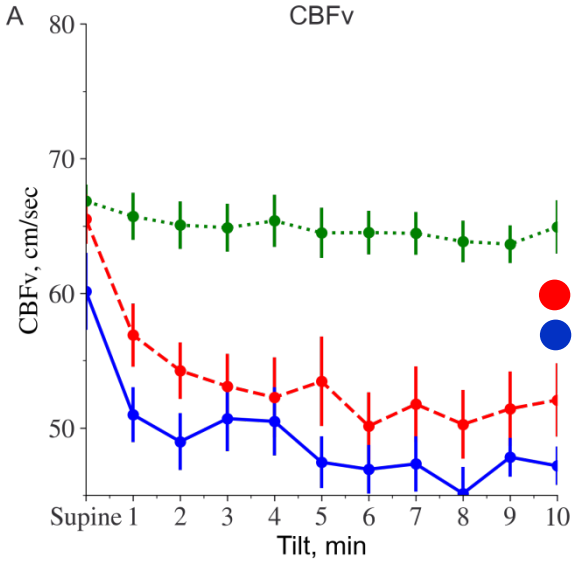
Respiratory dysregulation

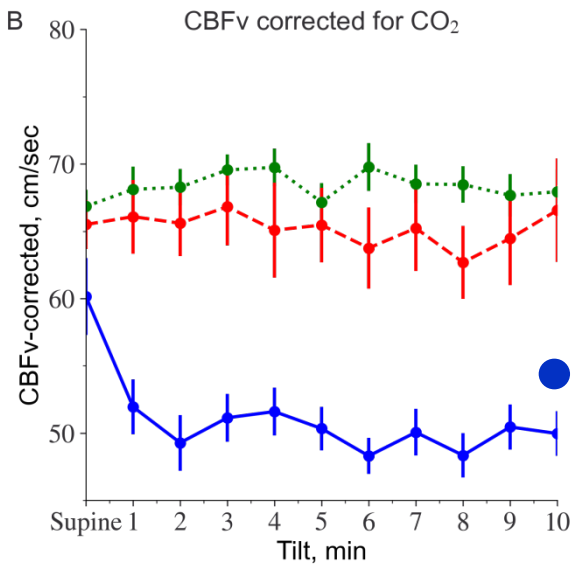
PASC: Supine and orthostatic hypocapnia (100%)

POTS: Orthostatic hypocapnia (75%)

Controls: No hypocapnia







Novak et al, Annals of Neurology, 2021

Partners PASC Study – Results

Inflammatory dysregulation
Elevated inflammatory markers:

PASC: 67% - heterogenous
POTS 70% -heterogenous

Consistent with low grade inflammation

Novak et al, Annals of Neurology, 2021

PASC - Conclusion

PASC is associated with multi system dysfunction affecting the following systems:
Cerebrovascular
Autonomic
Peripheral nervous – small fibers
Respiratory
Inflammatory

Our findings are most consistent with **low grade inflammation/autoimmunity, either** systemic or targeting vascular system.

Novak et al, Annals of Neurology, 2021

PASC –> Multi System Dysfunction

Clinical correlations of affected the systems:

Cerebrovascular -> cerebral orthostatic hypoperfusion due to persistent cerebral arteriolar vasoconstriction
may cause orthostatic intolerance, fatigue, brain fog,

Autonomic -> orthostatic intolerance
may participate to orthostatic intolerance, fatigue, dyspnea, temperature dysregulation, GI and urinary problems

Peripheral nervous system –> small fibers damage
may cause pain, sensory disturbances

Respiratory-> respiratory dysregulation with hypocapnia
may cause dyspnea, increased fatigue via alkalosis/tissue ischemia?

Inflammatory-> probably affecting the small vessels

Novak et al, Annals of Neurology, 2021

PASC – Multi System Dysfunction-Disability

Objective findings confirmed by several studies

Disability due:

Cerebral hypoperfusion-> fatigue, brain fog, cognitive problems

Hypocapnia/respiratory failure -> dyspnea, fatigue

Dysautonomia-> fatigue, exercise intolerance, dry mouth/eyes,
urinary and GI symptoms

Small fiber neuropathy -> chronic pain

Neuropsychological testing->deficit in attention, executive functions, memory, global cognition

PROM->fatigue, insomnia, anxiety, depression,

Mental and physical health can be severely impaired

Disability

severity of objective findings similar than in:

(all these conditions can be disabling)

Postural tachycardia syndrome (POTS)

ME/CFS

Small fiber neuropathy (SFN)

Novak et al, Annals of Neurology, 2021, van Campen et al, 2021, Abrams et al, 2021, Bungenberg 2022

Thank you