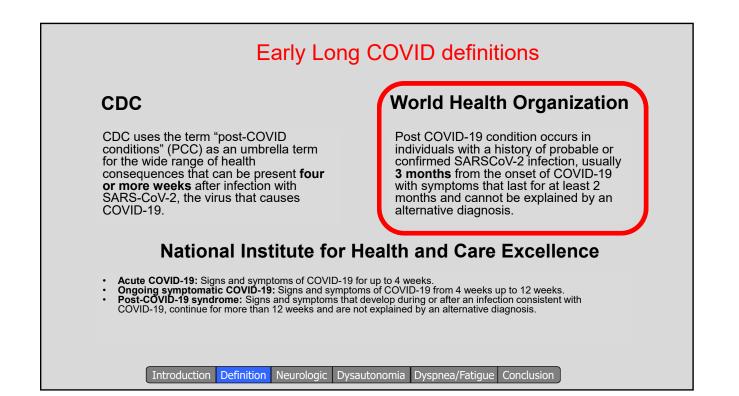
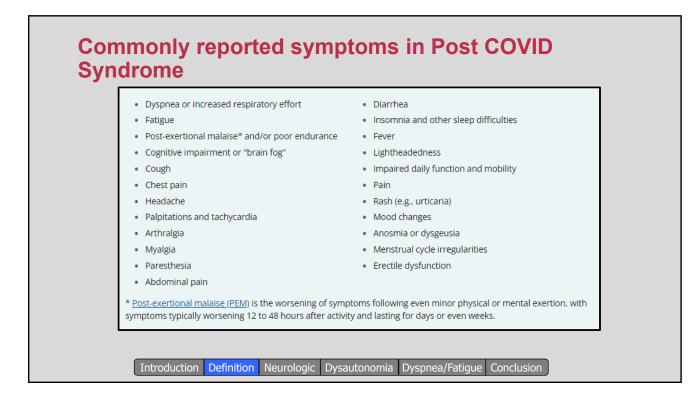


### **Objectives**

- Understand working criteria for the diagnosis of Post Acute Sequelae of COVID-19 (PASC) or Long COVID
- Understand therapies commonly used to manage Long COVID symptoms
- Understand the impact of Long COVID on patients' quality of life and functional status





# Development of a Definition of Post Acute Sequelae of COVID19 (RECOVER Initiative)

Symptom	Log odds ratio	Score
Smell/taste	0.776	8
Postexertional malaise	0.674	7
Chronic cough	0.438	4
Brain fog <sup>b</sup>	0.325	3
Thirst	0.255	3
Palpitations	0.238	2
Chest pain <sup>b</sup>	0.233	2
Fatigue <sup>b</sup>	0.148	1
Sexual desire or capacity	0.126	1
Dizzines	0.121	1
Gastrointestinal	0.085	1
Abnormal movements	0.072	1
Hair loss	0.049	0

- 9764 adult participants at 33 sites.
- 8646 had SARS-CoV-2 infection; there were 1118 non-infected controls.
- Self-reported symptoms assessed by a standardized questionnaire.
- A rule for identifying PASC was derived by statistical analysis.
- 12 symptoms were identified with scores from 1-8
- Using a cutoff of 12, 23% of infected and 3.7% of uninfected participants were identified with PASC

Thaweethai T, Jolley SE, Karlson EW, et al. Development of a Definition of Postacute Sequelae of SARS-CoV-2 Infection. *JAMA*. 2023;329(22):1934-1946.

Symptom patterns (What Long COVID looks like to a clinician)		
		,
- 1	'Brain fog"	
	Chronic fatigue	
- 1	Fibromyalgia-like symptoms (muscle	
	aching, fatigue, poor sleep)	
	Dyspnea on exertion, +/- cough	
	Palpitations, chest pain	
	Dysautonomia – POTS, dizziness,	
	nyperhidrosis, post-exertional malaise	
•	Loss of smell and taste	
	Miscellaneous symptoms – GI, skin, sexual	
Introduction Definition Neurologic Dysautonomia Dyspnea/Fatigue Conclusion		

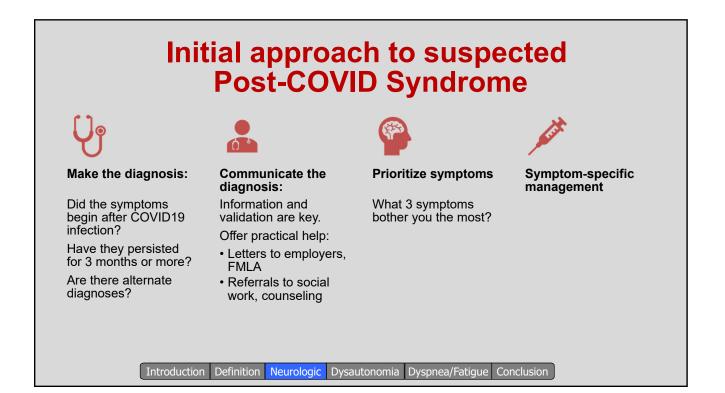
### Common Neuropsychological Symptoms in Long COVID

Cognitive ("brain fog")	Trouble concentrating, forgetfulness, word-finding difficulty, semantic dysfluency, cognitive fatigability
Fatigue	Task-related, continuous, intermittent, diurnal, post- exertional malaise (PEM)
Paresthesia	Myalgia (generalized, localized, migratory), tingling, numbness
Dysautonomia	Heart rate, respiration, dysphonia, dysphagia, post- prandial fullness, diarrhea, sexual dysfunction, "hot flashes"
Headache	Chronic daily headache, migraine
Mood symptoms	Anxiety, depression – primary versus reactive (adjustment disorder)
Sleep disturbance	Trouble falling asleep, frequent or early awakening
Disturbances of smell and taste	Absence, reduction, distortion
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### Case study: Long COVID and brain fog

- 33-year-old woman. Overweight (BMI 29). Otherwise healthy. On no meds. Not vaccinated for COVID19.
- Customer service manager for IT firm, loves her job. Married, husband is selfemployed (contractor), children ages 5 and 8.
- COVID-19 January 12, 2023. Moderate URI symptoms and fatigue. Off work for one week.
- Upon returning to work, notices difficulty completing simple tasks and recalling words, information and workflows; constant fatigue, worsening through the day; daily headaches; myalgias; anxiety; insomnia.
- February: normal TSH, CBC, ESR, autoimmune panel. Referred to Neuro.
- Neurology (March): Non-focal exam. Normal brain MRI. Dx: chronic daily headache. Recommends stress reduction.

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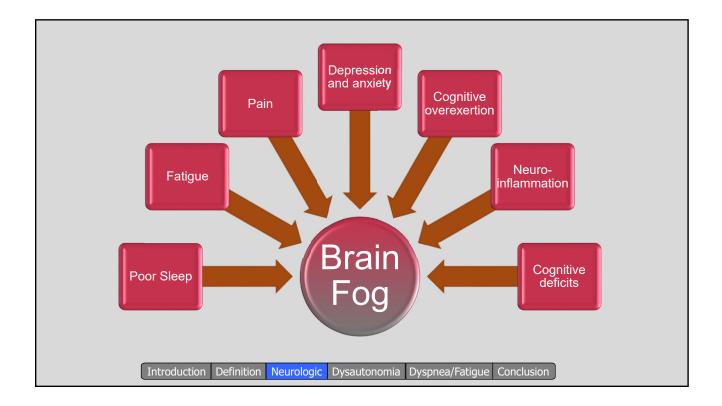
### **Communication: sometimes better than pills**

### Diagnosis

- · Validation is therapeutic for many patients
- Diagnosis allows patients to communicate with others (workplace, family, friends)
- Diagnosis permits chronic disease education and selfmanagement

### **Prognosis**

- Not bad for patients with duration < 12 months.
- · Reason for optimism for recently infected.
- Allows planning for possible short-term or long-term disability, and necessary accommodations.



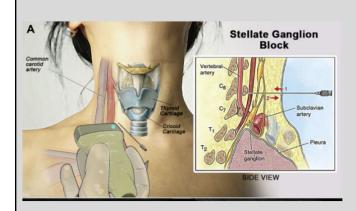
Limited energy: you can use it to work, or you can use it to heal.	Ideally: one month off from work to for rest and rehabilitation. After that, stepwise return.	Modify based on what's feasible (sick time, company policies, financial stresses).
Owning your condition and asking for help. You have a serious illness and it's going to take time to recover.	Very successful approach in many patients.	Not for everyone (i.e. already disabled, retired, unable to take time off)

### **Treating Long COVID Neurologic Symptoms**

- Neurocognitive fatigue ("brain fog")
  - · Cognitive rest
  - Work accommodations
  - Cognitive rehabilitation
  - Pharmacotherapy: amantadine, modafinil, donepezil, low dose naltrexone
- Fibromyalgia-like symptoms
  - Symptom-titrated physical therapy
  - Pharmacotherapy: gabapentinoids, tricyclic antidepressants (TCA)
- Headache
  - Cognitive Behavior Therapy / mindfulness training
  - Amitriptyline (TCA)
  - CGRP inhibitors

- Adjustment disorder
  - · Education, reassurance
  - Cognitive Behavioral Therapy
- Depression and anxiety
  - SSRIs
  - Bupropion when fatigue is prominent
- Poor sleep
  - Cognitive Behavioral Therapy
  - Melatonin
  - Amitriptyline (TCA) / other agents
- Anosmia (and maybe brain fog...)
  - Stellate ganglion block

### Stellate ganglion block for Long COVID symptoms (case series, n=41)

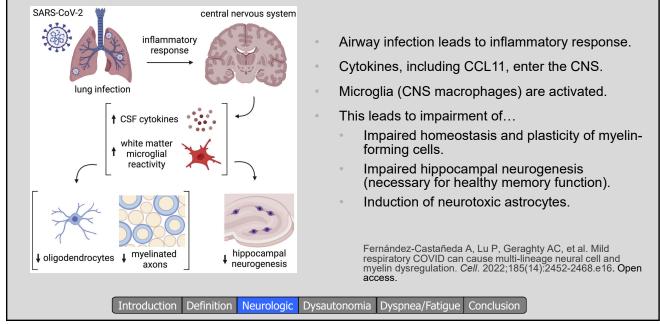


Symptom	# subjects	% improved
Fatigue	35	77
Brain fog	33	79
Mood	21	76
Taste/smell	18	56
Dyspnea	17	88
Insomnia	14	71
Tachycardia	9	78

Waldron NH, Fudim M, Mathew JP, Piccini JP. Neuromodulation for the Treatment of Heart Rhythm Disorders. JACC Basic Transl Sci. 2019;4(4):546-562. Open access.

Pearson L, et al. Stellate Ganglion Block Relieves Long COVID-19 Symptoms in 86% of Patients: A Retrospective Cohort Study. Cureus. 2023;15(9):e45161.

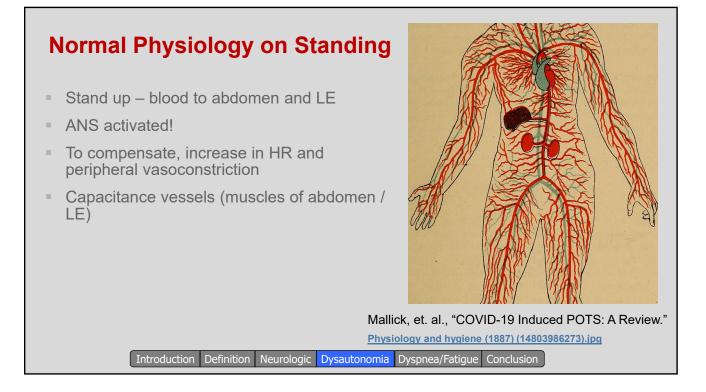




### Takeaway points – management of neurologic symptoms

- Diagnosis, validation and patient education are important.
- · Cognitive rehabilitation is a first-line treatment.
- Pacing has been shown effective for fatigue and brain fog in at least one controlled trial.
- The prognosis for eventual recovery is reasonably good, especially in patients with onset of Long COVID < 1 year</li>
- Repurposed medicines in clinical use:
  - Guanfacine/ NAC
  - Amantadine
  - Modafinil and Armodafinil
  - Low dose naltrexone
  - SSRIs
- Procedures: stellate ganglion block





### POTS (Postural Orthostatic Tachycardia Syndrome)

- Suspect in patient w/ palpitations, light-headedness, chest pain, SOB, esp. when standing
- Other manifestations can include fatigue,
  GI symptoms, difficulty with temperature regulation / cognition

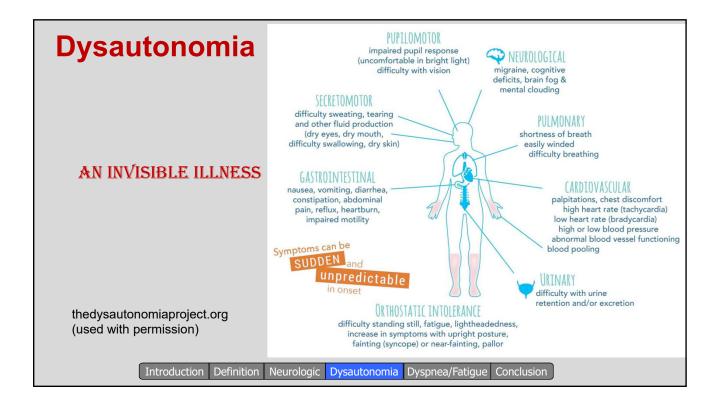
Mallick, et. al., "COVID-19 Induced POTS: A Review." Acrocyanosis in POTS patient.jpg

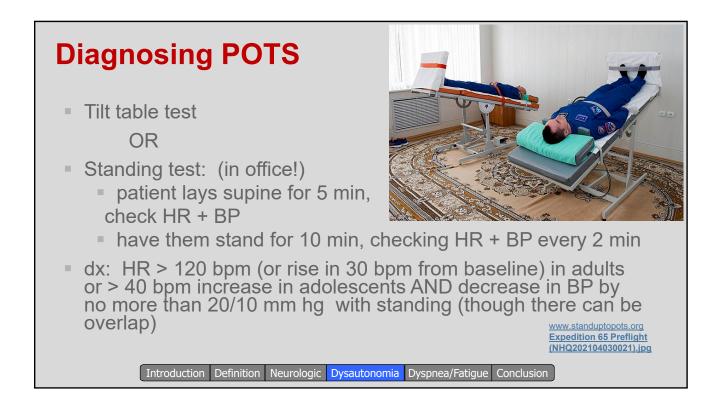


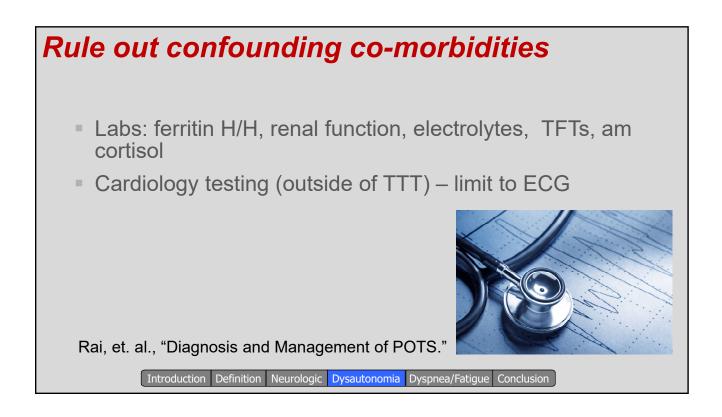
### **Potential causes of POTS**

- Autoimmunity
- Neuropathy, esp. small fiber neuropathy
- Hypovolemia and deconditioning
- Neuroendocrine dysfunction
- Specific for post-COVID subset of POTS direct toxic effects of SARS CoV2 virus on CNS and ANS

Mallick, et. al., "COVID-19 Induced POTS: A Review." Coronavirus. SARS-CoV-2.png





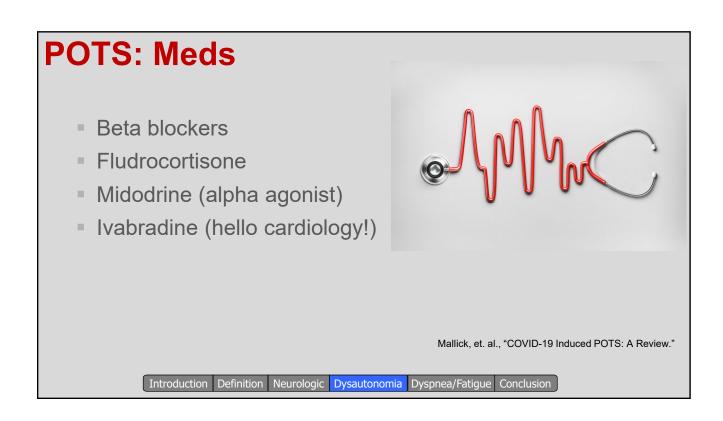


# Management of POTS

- Lifestyle modification = cornerstone of therapy
- Medications only after maximizing lifestyle modification
- Fluids: 3 L / day
- Salts: 10-12 grams per day, can be difficult to ingest, consider salt tabs
- Compression garments: Knee, thigh, waist
- Small frequent meals
- Supine / recumbent exercise (balance with postexertional malaise)
- Counter pressure movements



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Mallick, et. al., "COVID-19 Induced POTS: A Review."
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## Also Runs With: Post Exertional Malaise (PEM)

- First identified in ME-CFS (myalgic encephalomyelitis / chronic fatigue syndrome)
- Can be triggered by variety of stimuli, including physical, cognitive, emotional, social or mental exertions
- The fatigue / malaise can occur immediately or 24-72 hours after event
- Management includes pacing, staying within one's energy envelop, radical resting



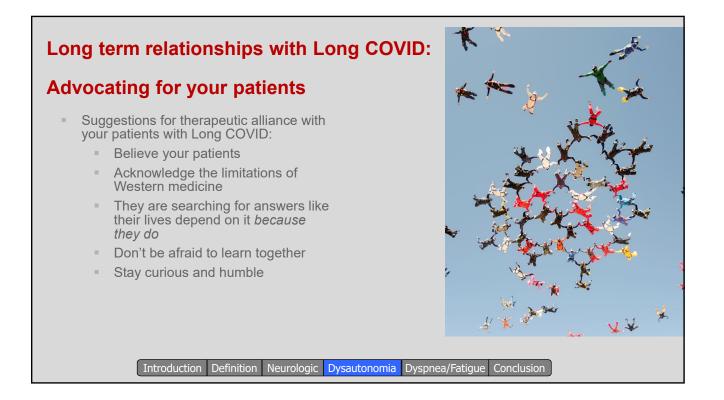
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### Good to Know: Patient-Led Research Collaborative

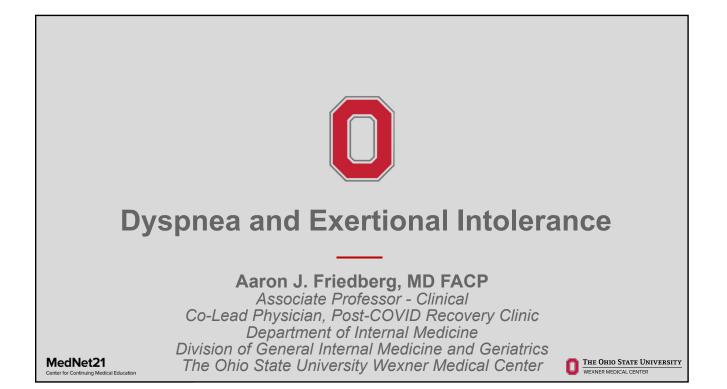
- Group of patients with Long COVID, ME-CFS and POTS who are also researchers and *led first research* on Long COVID in spring 2020
- Mission:
  - Principles of disability justice
  - Participatory research methods
  - Knowledge that those who experience an illness are best able to identify research questions and solutions

https://patientresearchcovid19.com/





# Mallick, et. al., "COVID 19 Induced Postural Orthostatic Tachycardia Syndrome: A Review." <u>Curreus</u> 2023 Mar; 15(3): e36955. https://www.curreus.com/articles/142335-covid-19-induced-postural-orthostatic-tachycardia-syndrome-pots-a-review#!/ Accessed November 12, 2023. https://patientresearchcovid19.com/ Rai et. al., "Diagnosing and managing postural orthostatic tachycardia syndrome." <u>CMAJ</u>. 2022 Mar 14;194(10):E378-E385. doi: 10.1503/cmaj.211373. PMID: 35288409; PMCID: PMC8920526. Accessed November 12, 2023. www.standuptopots.org www.thedysautonomiaproject.org



### Case: Dyspnea and Exertional Intolerance

- Late 30's white male first responder married with young children with attention deficit disorder on stimulants and well-controlled ulcerative colitis on mesalamine
- Diagnosed with COVID Late 2021
- Mild initial infection
- Returned to work 10 days after diagnosis

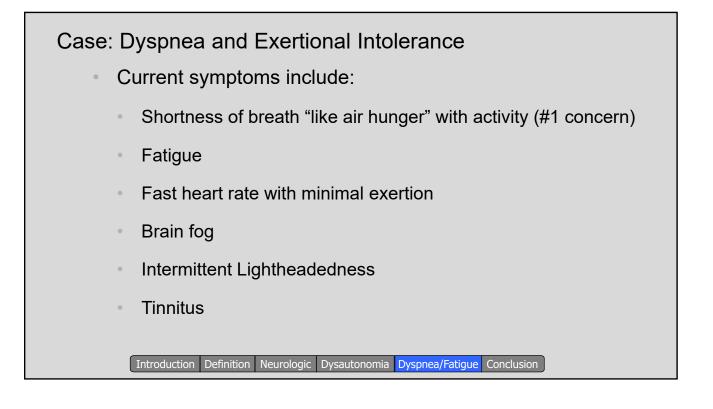
### Case: Dyspnea and Exertional Intolerance

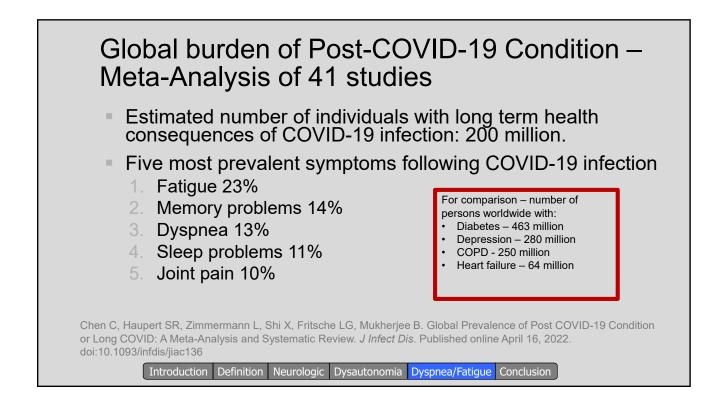
- On first day back, with physical exertion developed severe fatigue, shortness of breath, and "crushing" substernal chest pain
- Seen in the ED, had normal ECG, BNP, and troponin, and CT PE only showed "subtle ground glass opacities in the bilateral lower lobes"
- Given short steroid taper for diagnoses of pleurisy and COVID-19
- Also subsequently had normal echo, normal PFT's, mild fibrosis at inferior RV attachment site but otherwise normal cardiac MRI

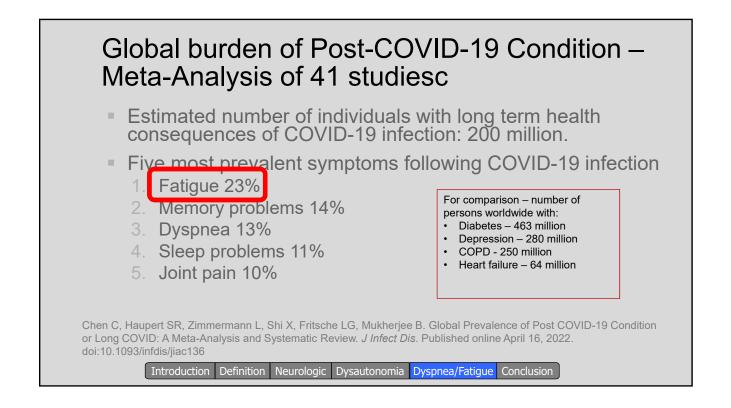
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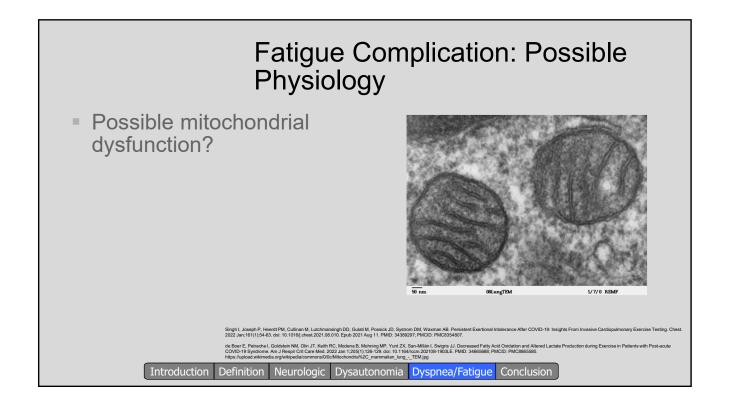
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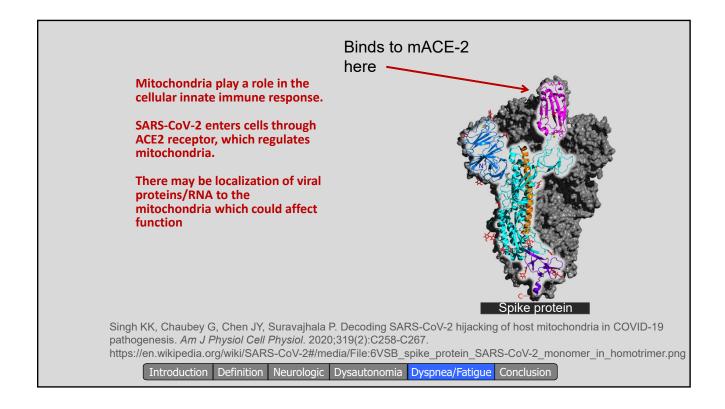
- Took 1 month off work-felt great!
- On return, had same symptoms of shortness of breath, severe fatigue, chest discomfort, and also tachycardia with exertion
- Heart rate in 130's with minimal exertion on ECG's
- Back at work but struggling, ultimately switched to light duty but still unable to perform usual work by mid-2022
- Previously very active-crossfit, lifting, frequent half-marathon runner, now hard to get around the block

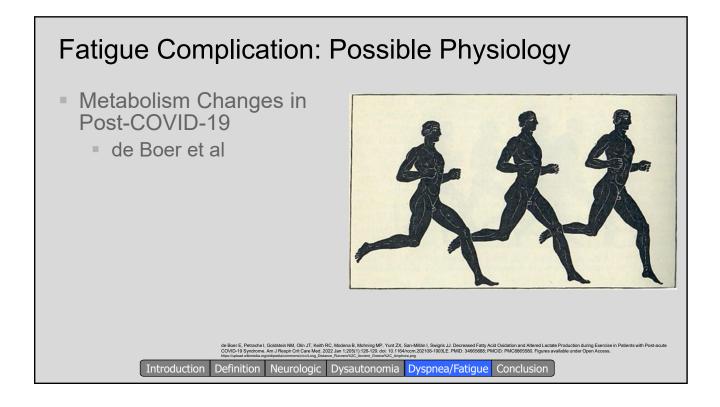


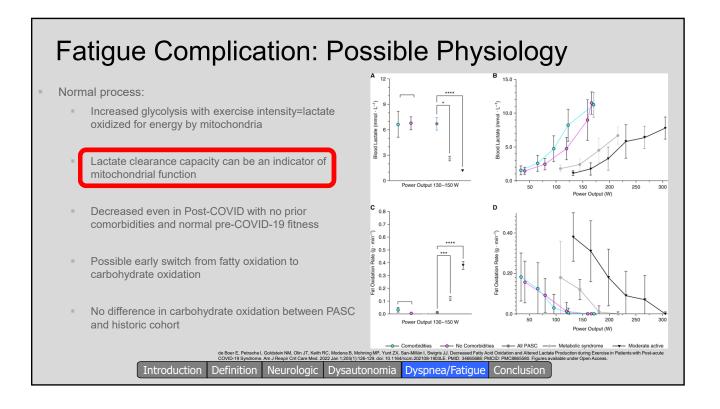


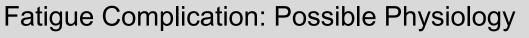










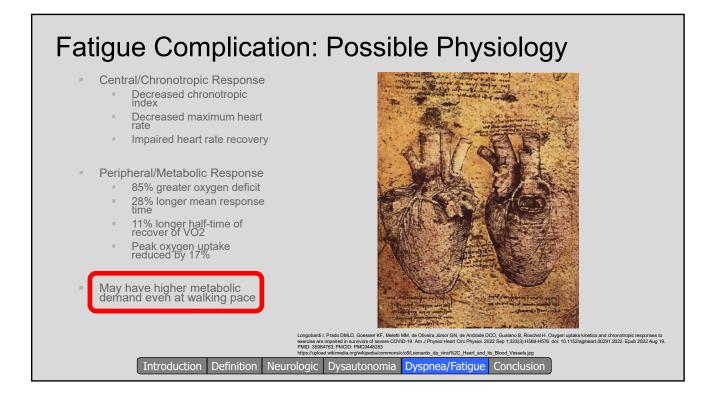


Impaired oxygen uptake and chronotropic responses in severe COVID-19

-Longobardi et al



Longobardi, I, Prado DMLD, Goessier KF, Meletti MM, de Oliveira Júnior GN, de Andrade DCO, Gualano B, Roschel H. Oxyganu plake kinetica and chronotropic responses to exercise are impaired in survivors of severe COVID-19. Am J Physiol. Hardt Circ Physiol. 2022 Sept 1:32(3):H569:H576. doi: 10.1152/ajpheart.00291.2022. Epub 2022 Aug 19 PMID: 35984783; PMCD: PMCGH48283 https://loglaw.dwimedia.com/bikedialcommons/ol/BLeonardo, da, vind%2C, Heart, and, its, Blood Vessels.jpg



### Fatigue Complication: Possible Physiology

Persistent Exercise Intolerance Even in non-severe COVID -Singh et al



Singh I, Joseph P, Heerdt PM, Cullinan M, Lutchmansingh DD, Gulati M, Possick JD, Systrom DM, Waxman AB. Persi 2022 Jan;161(1):54-63. doi: 10.1016/j.chest.2021.08.010. Epub 2021 Aug 11. PMID: 34389297; PMCID: PMC8354807 https://doi.org/10.1016/j.chest.2021.04061 Fibit Bibt Low Vento II.op Portate I of Addib Fibit

### Fatigue Complication: Possible Physiology

- Reduced peak aerobic capacity
- Impaired systemic oxygen extraction
  - Based on Fick principle, without mechanical problem, if peak VO2 is reduced, either or both decreased cardiac output/cardiac index response or impaired systemic extraction
  - Cardiac output 115% predicted on average
  - Oxygen delivery preserved
- Abnormal slope of ventilatory efficiency
- Increased hyperventilatory response to exercise



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  - Cardiac output 115% predicted on average
  - Oxygen delivery preserved
- Abnormal slope of ventilatory efficiency
- Increased hyperventilatory response to exercise

Improvement with exercise was due to both EO2 and CI, but at 75% of peak and at peak VO2, further increases in post-COVID were limited by EO2 and not cardiac index



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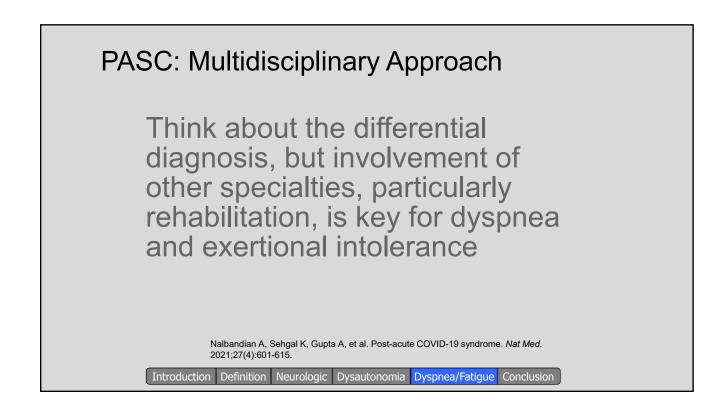
### Pulmonary Complications: Use of imaging & PFTs?

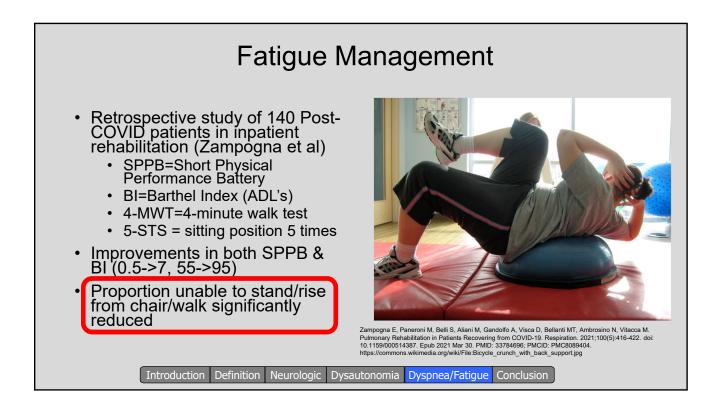


Moreno-Pérez O, Merino E, Leon-Ramirez J-M, et al. Post-acute COVID-19 syndrome. Incidence and risk factors: A Mediteranean cohort study. J Infect. 2021;82(3):378-383. https://commons.wikimedia.org/wiki/File:Nor mal\_posteroanterior\_(PA)\_chest\_radiograp h\_(X-ray).jpg

### Usually not that useful

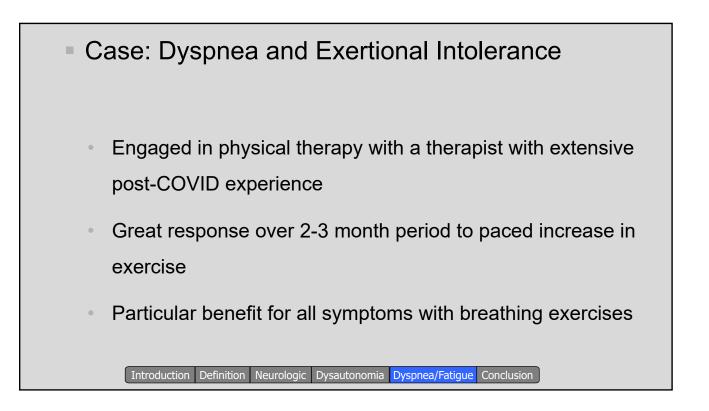
- Spirometry & Imaging: 269 patients, no prior lung diseases Mediterranean Cohort Study Moreno-Pérez et al
- Abnormal PFT's: 9.3%, mainly obstructive & mild
- Imaging changes: 18.9%
  - 52.9% free of respiratory symptoms
- Patients with cough or dyspnea
  - Abnormal imaging: 20.7%
  - Abnormal PFTs: 14.3%
- Only higher imaging score in acute infection was associated with persistence of abnormal imaging
  - both for whole group and severe pneumonia





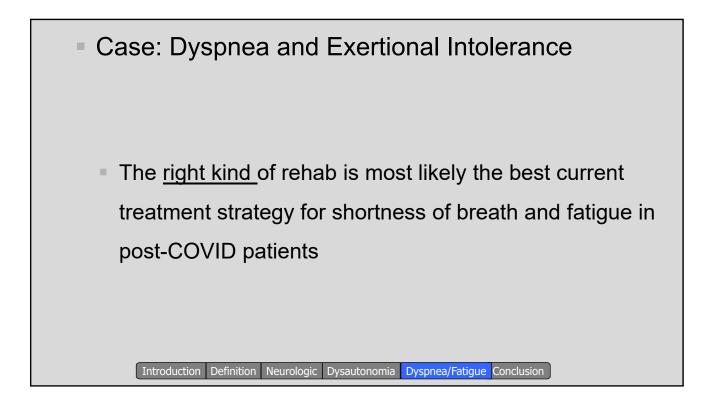
### Fatigue/Dyspnea Management

- We collaborate with Physical Therapists who have gained significant experience managing patients with PASC
- Typical program will be an initial assessment both subjective (PROMIS-29 in our clinic) and strength, mobility, and stamina testing
- Engage in "symptom-titrated physical activity"
- Focus on energy conservation- "3 P's"
  - Pacing
  - Planning
  - Prioritizing
- Watch for post-exertional symptom exacerbation
- Frequency first, then duration, then intensity
- Stasis breathing-diaphragmatic breathing program



### Case: Dyspnea and Exertional Intolerance

- Diagnosed with POTS with positive tilt table test, uses beta blocker intermittently to good effect
- Ultimately with rehabilitation was much more comfortable in daily activities within 2-3 months, between 60-80% of normal, chest pain significantly improved
- Some delays with relapsing remitting pattern of symptoms but ultimately able to return to part-time duty mid- 2023



### Conclusion

- Post-COVID (PASC) is a common condition in our patients
- Many different body systems can be affected
- Behavioral interventions and medical therapies can help
- Being familiar with PASC symptoms and management strategies can make a tremendous difference in the quality of our patients' lives