Post-COVID Definition and Neurologic/Psychiatric Complications

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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

Early Long COVID definitions

CDC

CDC uses the term “post-COVID conditions” (PCC) as an umbrella term for the wide range of health consequences that can be present **four or more weeks** after infection with SARS-CoV-2, the virus that causes COVID-19.

World Health Organization

Post COVID-19 condition occurs in individuals with a history of probable or confirmed SARSCoV-2 infection, usually **3 months** from the onset of COVID-19 with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis.

National Institute for Health and Care Excellence

- **Acute COVID-19:** Signs and symptoms of COVID-19 for up to 4 weeks.
- **Ongoing symptomatic COVID-19:** Signs and symptoms of COVID-19 from 4 weeks up to 12 weeks.
- **Post-COVID-19 syndrome:** Signs and symptoms that develop during or after an infection consistent with COVID-19, continue for more than 12 weeks and are not explained by an alternative diagnosis.

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Commonly reported symptoms in Post COVID Syndrome

- Dyspnea or increased respiratory effort
- Fatigue
- Post-exertional malaise* and/or poor endurance
- Cognitive impairment or "brain fog"
- Cough
- Chest pain
- Headache
- Palpitations and tachycardia
- Arthralgia
- Myalgia
- Paresthesia
- Abdominal pain
- Diarrhea
- Insomnia and other sleep difficulties
- Fever
- Lightheadedness
- Impaired daily function and mobility
- Pain
- Rash (e.g., urticaria)
- Mood changes
- Anosmia or dysgeusia
- Menstrual cycle irregularities
- Erectile dysfunction

* Post-exertional malaise (PEM) is the worsening of symptoms following even minor physical or mental exertion, with symptoms typically worsening 12 to 48 hours after activity and lasting for days or even weeks.

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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[b]	0.325	3
Thirst	0.255	3
Palpitations	0.238	2
Chest pain[b]	0.233	2
Fatigue[b]	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.

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Symptom patterns (What Long COVID looks like to a clinician)

- "Brain fog"
- Chronic fatigue
- Fibromyalgia-like symptoms (muscle aching, fatigue, poor sleep)
- Dyspnea on exertion, +/- cough
- Palpitations, chest pain
- Dysautonomia – POTS, dizziness, hyperhidrosis, post-exertional malaise
- Loss of smell and taste
- Miscellaneous symptoms – GI, skin, sexual

Pathological sequelae of long-haul COVID | Nature Immunology

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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

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 self-employed (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.

Now she's in your office…

- Symptoms the same – brain fog, fatigue, headaches, myalgias. Struggling to maintain job and family roles.
- Productivity and quality of work have declined sharply. Using up her sick time. Supervisor concerned.
- "By the time I get home, I feel dead." No energy for family. Sleeping 10 hours but awakening exhausted. Rests all weekend and feels a little better by Monday.
- Husband wonders if she has early Alzheimer's. Sister telling her there's nothing wrong with her and she needs to snap out of it.

What are your next steps?

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Initial approach to suspected Post-COVID Syndrome

Make the diagnosis:

Did the symptoms begin after COVID19 infection?

Have they persisted for 3 months or more?

Are there alternate diagnoses?

Communicate the diagnosis:

Information and validation are key.

Offer practical help:

- Letters to employers, FMLA
- Referrals to social work, counseling

Prioritize symptoms

What 3 symptoms bother you the most?

Symptom-specific management

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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 self-management

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.

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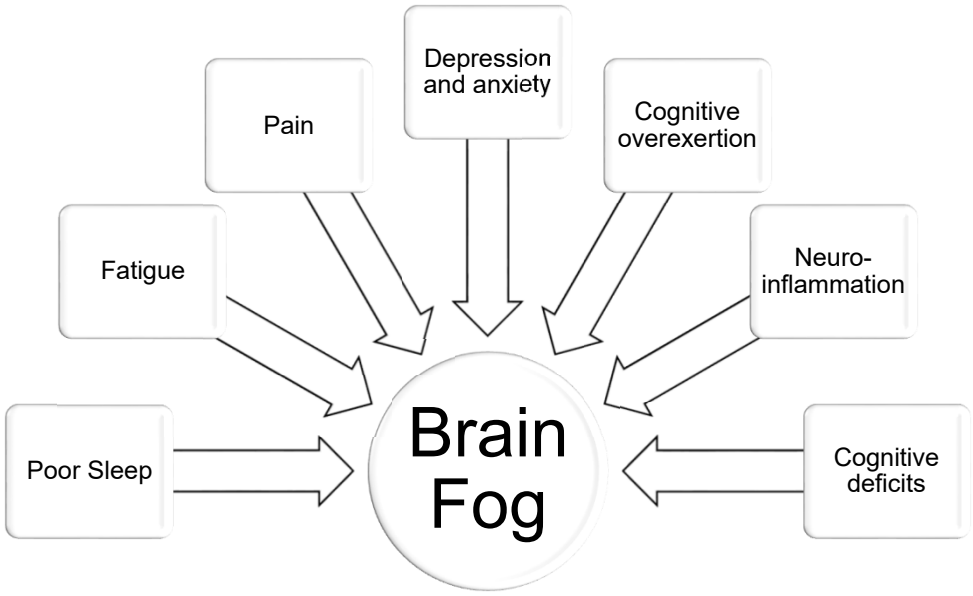

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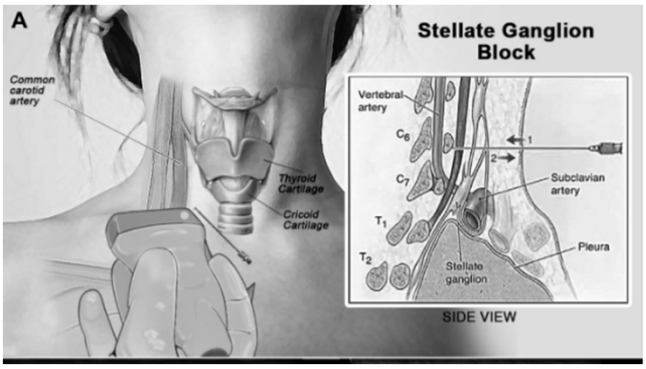
First line: rest and pacing

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.

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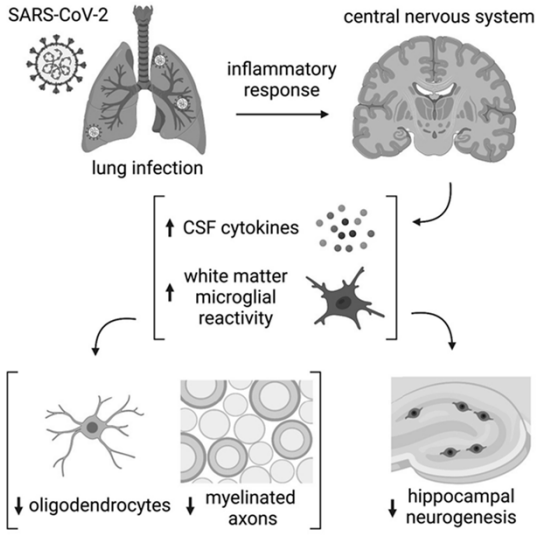
Brain fog: neuroinflammatory hypothesis



- Airway infection leads to inflammatory response.
- Cytokines, including CCL11, enter the CNS.
- Microglia (CNS macrophages) are activated.
- This leads to impairment of…
  - Impaired homeostasis and plasticity of myelin-forming cells.
  - Impaired hippocampal neurogenesis (necessary for healthy memory function).
  - Induction of neurotoxic astrocytes.

Fernández-Castañeda A, Lu P, Geraghty AC, et al. Mild respiratory COVID can cause multi-lineage neural cell and myelin dysregulation. *Cell*. 2022;185(14):2452-2468.e16. Open access.

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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
- Repurposed medicines in clinical use:
  - Guanfacine/ NAC
  - Amantadine
  - Modafinil and Armodafinil
  - Low dose naltrexone
  - SSRIs
- Procedures: stellate ganglion block

Post-COVID, POTS, and Patient Advocacy

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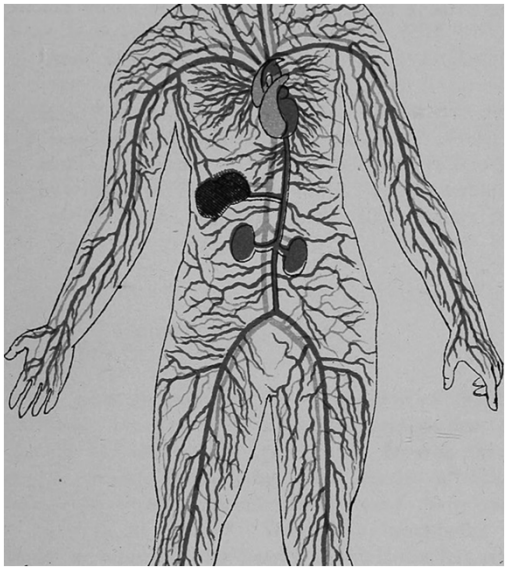
Normal Physiology on Standing

- Stand up – blood to abdomen and LE
- ANS activated!
- To compensate, increase in HR and peripheral vasoconstriction
- Capacitance vessels (muscles of abdomen / LE)



Mallick, et. al., "COVID-19 Induced POTS: A Review."

Physiology and hygiene (1887) (14803986273).jpg

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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

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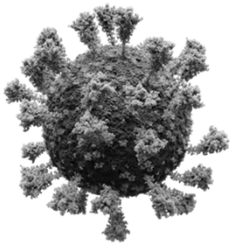
Potential causes of POTS



- 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

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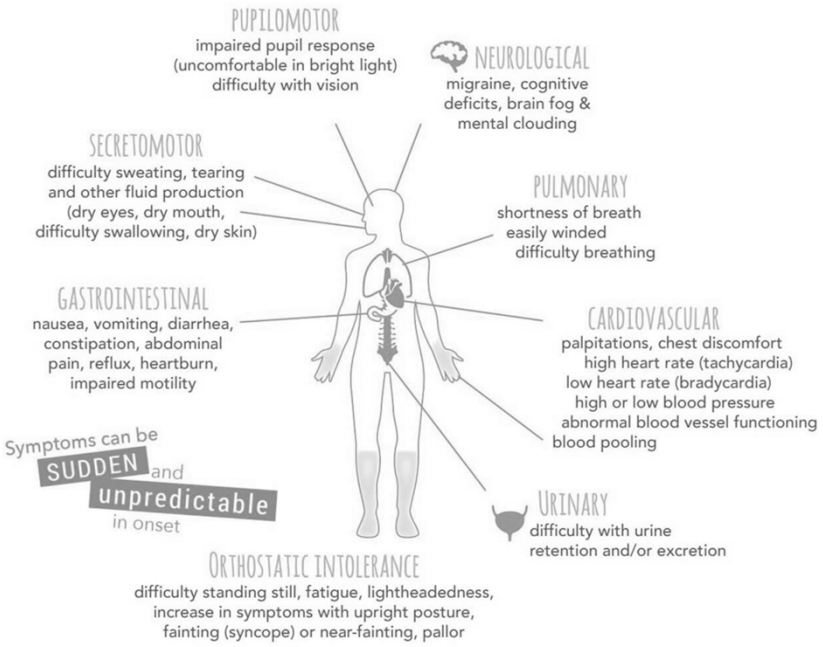
Dysautonomia

AN INVISIBLE ILLNESS



thedysautonomiaproject.org
(used with permission)

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Diagnosing POTS

- Tilt table test

  OR

- Standing test: (in office!)
  - patient lays supine for 5 min, check HR + BP
  - have them stand for 10 min, checking HR + BP every 2 min
- dx: HR > 120 bpm (or rise in 30 bpm from baseline) in adults or > 40 bpm increase in adolescents AND decrease in BP by no more than 20/10 mm hg with standing (though there can be overlap)

www.standuptopots.org
Expedition 65 Preflight (NHQ202104030021).jpg

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Rule out confounding co-morbidities

- Labs: ferritin H/H, renal function, electrolytes, TFTs, am cortisol
- Cardiology testing (outside of TTT) – limit to ECG

Rai, et. al., "Diagnosis and Management of POTS."

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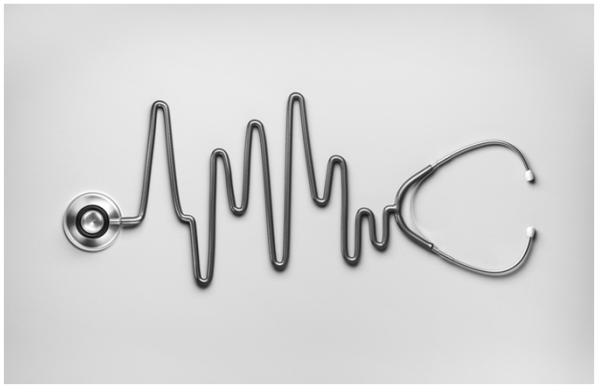
Management of POTS

- 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 post-exertional malaise)
- Counter pressure movements

Mallick, et. al., "COVID-19 Induced POTS: A Review."

POTS: Meds

- Beta blockers
- Fludrocortisone
- Midodrine (alpha agonist)
- Ivabradine (hello cardiology!)



Mallick, et. al., "COVID-19 Induced POTS: A Review."

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/

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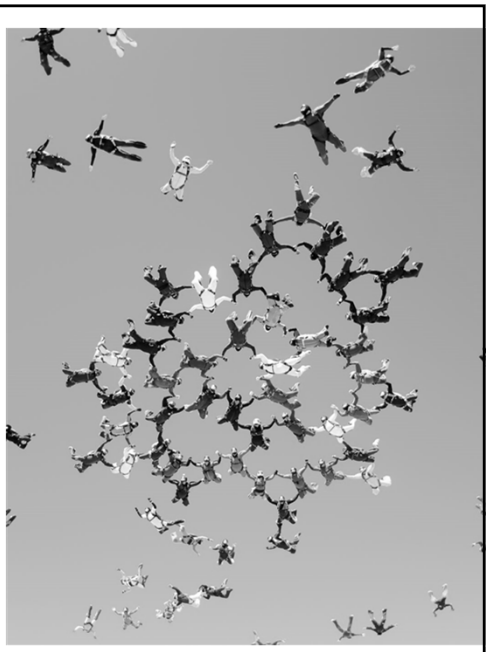
Long term relationships with Long COVID:

Advocating for your patients

- Suggestions for therapeutic alliance with your patients with Long COVID:
  - Believe your patients
  - Acknowledge the limitations of Western medicine
  - They are searching for answers like their lives depend on it *because they do*
  - Don't be afraid to learn together
  - Stay curious and humble



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References

- Mallick, et. al., "COVID 19 Induced Postural Orthostatic Tachycardia Syndrome: A Review." Cureus. 2023 Mar; 15(3): e36955. https://www.cureus.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." CMAJ. 2022 Mar 14;194(10):E378-E385. doi: 10.1503/cmaj.211373. PMID: 35288409; PMCID: PMC8920526. Accessed November 12, 2023.
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Dyspnea and Exertional Intolerance

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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

Case: Dyspnea and Exertional Intolerance

- 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

Case: Dyspnea and Exertional Intolerance

- Current symptoms include:
  - Shortness of breath “like air hunger” with activity (#1 concern)
  - Fatigue
  - Fast heart rate with minimal exertion
  - Brain fog
  - Intermittent Lightheadedness
  - Tinnitus

Global burden of Post-COVID-19 Condition – Meta-Analysis of 41 studies

- Estimated number of individuals with long term health consequences of COVID-19 infection: 200 million.
- Five most prevalent symptoms following COVID-19 infection
  1. Fatigue 23%
  2. Memory problems 14%
  3. Dyspnea 13%
  4. Sleep problems 11%
  5. Joint pain 10%

For comparison – number of persons worldwide with:
- Diabetes – 463 million
- Depression – 280 million
- COPD - 250 million
- Heart failure – 64 million

Chen C, Haupert SR, Zimmermann L, Shi X, Fritsche LG, Mukherjee B. Global Prevalence of Post COVID-19 Condition or Long COVID: A Meta-Analysis and Systematic Review. *J Infect Dis*. Published online April 16, 2022. doi:10.1093/infdis/jiac136

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Fatigue Complication: Possible Physiology

- Possible mitochondrial dysfunction?

Singh I, Joseph P, Heerdt PM, Cullinan M, Lutchmansingh DD, Gulati M, Possick JD, Systrom DM, Waxman AB. Persistent Exertional Intolerance After COVID-19: Insights From Invasive Cardiopulmonary Exercise Testing. Chest. 2022 Jan;161(1):54-63. doi: 10.1016/j.chest.2021.08.010. Epub 2021 Aug 11. PMID: 34389297; PMCID: PMC8354807.

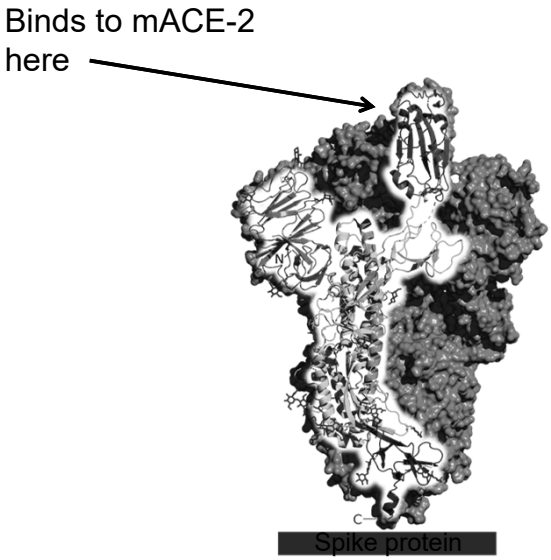
de Boer E, Petrache I, Goldstein NM, Olin JT, Keith RC, Modena B, Mohning MP, Yunt ZX, San-Millán I, Swigris JJ. Decreased Fatty Acid Oxidation and Altered Lactate Production during Exercise in Patients with Post-acute COVID-19 Syndrome. Am J Respir Crit Care Med. 2022 Jan 1;205(1):126-129. doi: 10.1164/rccm.202108-1903LE. PMID: 34655688; PMCID: PMC8865580.

https://upload.wikimedia.org/wikipedia/commons/0/0c/Mitochondria%2C_mammalian_lung_-_TEM.jpg

Mitochondria play a role in the cellular innate immune response.

SARS-CoV-2 enters cells through ACE2 receptor, which regulates mitochondria.

There may be localization of viral proteins/RNA to the mitochondria which could affect function



Singh KK, Chaubey G, Chen JY, Suravajhala P. Decoding SARS-CoV-2 hijacking of host mitochondria in COVID-19 pathogenesis. *Am J Physiol Cell Physiol*. 2020;319(2):C258-C267.
https://en.wikipedia.org/wiki/SARS-CoV-2#/media/File:6VSB_spike_protein_SARS-CoV-2_monomer_in_homotrimer.png

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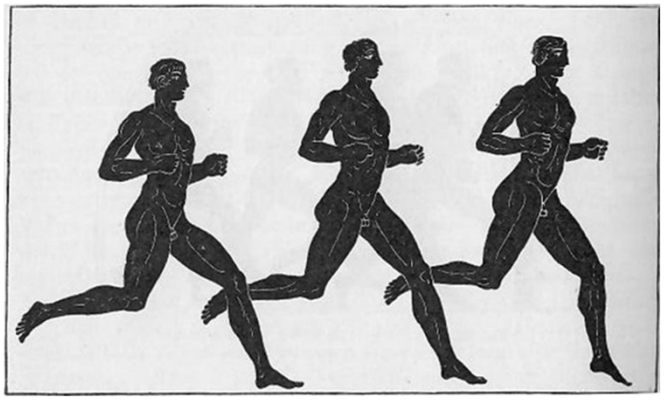
Fatigue Complication: Possible Physiology

- Metabolism Changes in Post-COVID-19
  - de Boer et al



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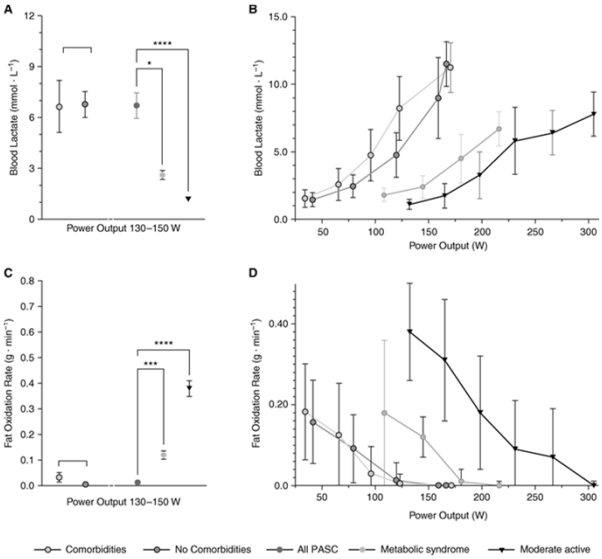
Fatigue Complication: Possible Physiology

- Normal process:
  - Increased glycolysis with exercise intensity=lactate oxidized for energy by mitochondria
  - Lactate clearance capacity can be an indicator of mitochondrial function
  - Decreased even in Post-COVID with no prior comorbidities and normal pre-COVID-19 fitness
  - Possible early switch from fatty oxidation to carbohydrate oxidation
  - No difference in carbohydrate oxidation between PASC and historic cohort



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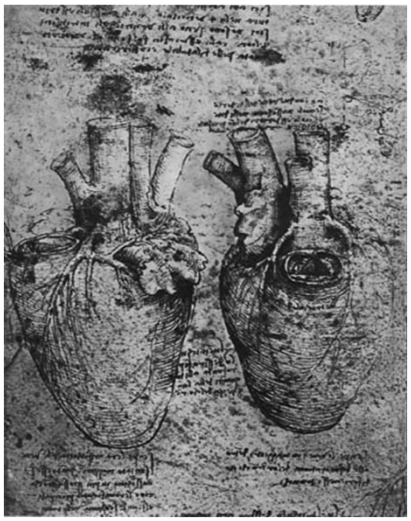
Fatigue Complication: Possible Physiology

Impaired oxygen uptake and chronotropic responses in severe COVID-19

-Longobardi et al

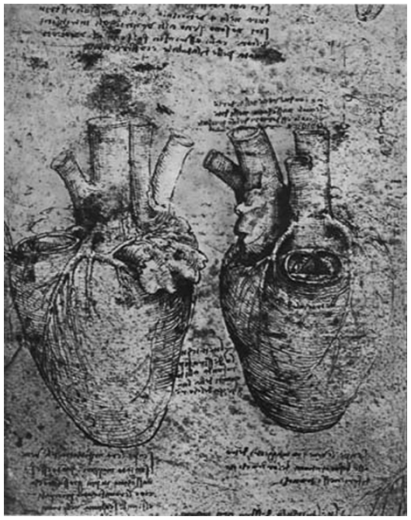


Longobardi I, Prado DMLD, Goessler KF, Meletti MM, de Oliveira Júnior GN, de Andrade DCO, Gualano B, Roschel H. Oxygen uptake kinetics and chronotropic responses to exercise are impaired in survivors of severe COVID-19. Am J Physiol Heart Circ Physiol. 2022 Sep 1;323(3):H569-H576. doi: 10.1152/ajpheart.00291.2022. Epub 2022 Aug 19. PMID: 35984763; PMCID: PMC9448283

https://upload.wikimedia.org/wikipedia/commons/c/c8/Leonardo_da_vinci%2C_Heart_and_its_Blood_Vessels.jpg

Fatigue Complication: Possible Physiology

- Central/Chronotropic Response
  - Decreased chronotropic index
  - Decreased maximum heart rate
  - Impaired heart rate recovery
- Peripheral/Metabolic Response
  - 85% greater oxygen deficit
  - 28% longer mean response time
  - 11% longer half-time of recover of VO2
  - Peak oxygen uptake reduced by 17%
- May have higher metabolic demand even at walking pace



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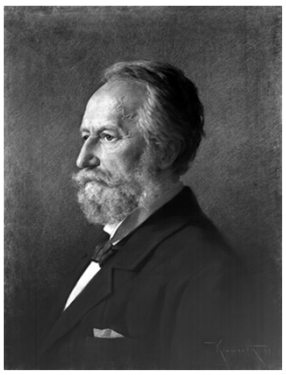
Fatigue Complication: Possible Physiology

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



4) Hr. Fick hält einen Vortrag über die Messung des Blutquantums, das in jeder Systole durch die Herzventrikel ausgeworfen wird, eine Grösse, deren Kenntniss ohne Zweifel von grösster Wichtigkeit ist. Gleichwohl sind darüber die abweichendsten Ansichten aufgestellt. Während Th. Young die in Rede stehende Grösse auf etwa 45ccm anschlägt, corrigirt in den neueren Lehrbüchern der Physiologie meist sehr viel höhere Angaben, welche, gestützt auf die Schätzungen von Volkmann und Vierordt, sich bis auf 180ccm belaufen. Bei dieser Sachlage ist es seltsam, dass man noch nicht auf folgenden naheliegenden Weg gekommen ist, auf dem diese wichtige Grösse wenigstens an Thieren direkter Bestimmung zugänglich ist. Man bestimme, wie viel Sauerstoff ein Thier während einer gewissen Zeit aus der Luft aufnimmt und wie viel Kohlensäure es abgibt. Man nehme ferner dem Thiere während der Versuchszeit eine Probe arteriellen und eine Probe venösen Blutes. In beiden ist der Sauerstoffgehalt und der Kohlensäuregehalt zu ermitteln. Die Differenz des Sauerstoffgehaltes ergibt, wie viel Sauerstoff jedes Cubikcentimeter Blut beim Durchgang durch die Lungen aufnimmt, und da man weiss, wie viel Sauerstoff im Ganzen während einer bestimmten Zeit aufgenommen wurde, so kann man berechnen, wie viel Cubikcentimeter Blut während dieser Zeit die Lungen passirten, oder wenn man durch die Anzahl der Herzschläge in dieser Zeit dividirt, wie viel Cubikcentimeter Blut mit jeder Systole des Herzens ausgeworfen wurden. Die entsprechende Rechnung mit den Kohlensäuremengen gibt eine Bestimmung desselben Werthes, welche die erstere controllirt.

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Singh I, Joseph P, Heerdt PM, Cullinan M, Lutchmansingh DD, Gulati M, Possick JD, Systrom DM, Waxman AB. Persistent Exertional Intolerance After COVID-19: Insights From Invasive Cardiopulmonary Exercise Testing. Chest. 2022 Jan;161(1):54-63. doi: 10.1016/j.chest.2021.08.010. Epub 2021 Aug 11. PMID: 34389297; PMCID: PMC8354807.
https://upload.wikimedia.org/wikipedia/commons/b/b3/Adolf_Fick_Bild_korr_kleiner1.jpg Portrait of Adolph Fick.
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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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Fatigue Complication: Possible Physiology

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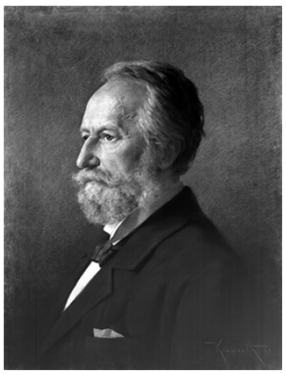
  - Cardiac output 115% predicted on average
  - Oxygen delivery preserved
- Abnormal slope of ventilatory efficiency
- Increased hyperventilatory response to exercise
- Improvement with exercise was due to both EO2 and CI, but at 75% of peak and at peak VO2, further increases in post-COVID were limited by EO2 and not cardiac index



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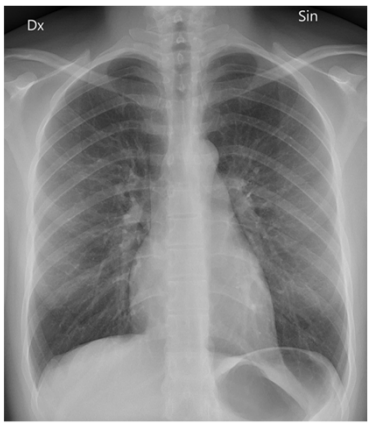
Pulmonary Complications: Use of imaging & PFTs?



Moreno-Pérez O, Merino E, Leon-Ramirez J-M, et al. Post-acute COVID-19 syndrome. Incidence and risk factors: A Mediterranean cohort study. *J Infect*. 2021;82(3):378-383. https://commons.wikimedia.org/wiki/File:Normal_posteroanterior_(PA)_chest_radiograph_(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

PASC: Multidisciplinary Approach

Think about the differential diagnosis, but involvement of other specialties, particularly rehabilitation, is key for dyspnea and exertional intolerance

Nalbandian A, Sehgal K, Gupta A, et al. Post-acute COVID-19 syndrome. *Nat Med*. 2021;27(4):601-615.

Fatigue Management

- Retrospective study of 140 Post-COVID patients in inpatient rehabilitation (Zampogna et al)
  - SPPB=Short Physical Performance Battery
  - BI=Barthel Index (ADL's)
  - 4-MWT=4-minute walk test
  - 5-STS = sitting position 5 times
- Improvements in both SPPB & BI (0.5->7, 55->95)
- Proportion unable to stand/rise from chair/walk significantly reduced

Zampogna E, Paneroni M, Belli S, Aliani M, Gandolfo A, Visca D, Bellanti MT, Ambrosino N, Vitacca M. Pulmonary Rehabilitation in Patients Recovering from COVID-19. Respiration. 2021;100(5):416-422. doi: 10.1159/000514387. Epub 2021 Mar 30. PMID: 33784696; PMCID: PMC8089404.
https://commons.wikimedia.org/wiki/File:Bicycle_crunch_with_back_support.jpg

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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

Introduction | Definition | Neurologic | Dysautonomia | Dyspnea/Fatigue | Conclusion

Case: Dyspnea and Exertional Intolerance

- Engaged in physical therapy with a therapist with extensive post-COVID experience
- Great response over 2-3 month period to paced increase in exercise
- Particular benefit for all symptoms with breathing exercises

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

- Case: Dyspnea and Exertional Intolerance

  - The right kind of rehab is most likely the best current treatment strategy for shortness of breath and fatigue in post-COVID patients

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