Post-COVID Syndrome and POTS

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COVID Pandemic

• Started in Wuhan, China in December 2019

• As of 9/22/2021, more than 4.71 million deaths have confirmed, making it one of the deadliest pandemic history

• Infection fatality ratio (mortality when infected) is estimated to be 0.24% to 1.49%.

• So, the rest 98% of them are happy?

Nature. 590 (7844): 140–145
About 13.7% will continue to have Sx > 12 weeks after COVID-19 infection
Long COVID symptoms are disabling

Figure 1: Most people with self-reported long COVID experienced some limitation to their day-to-day activities as a result.

Number of people with self-reported long COVID according to activity limitation, UK: four-week period ending 6 March 2021.

- Any duration
- Duration 12+ weeks

No activity limitation

Activities limited a little

Activities limited a lot
Pain that lingers
A subset of COVID-19 patients experiences ongoing symptoms and complications such as organ damage, and researchers are proposing reasons for some of them (bottom). Scientists are trying to identify such symptoms, how common they are, how long they last, who’s at risk, and how to treat and prevent them.

1 Brain fog
Difficulty thinking can occur after acute COVID-19 infection. The virus may damage brain cells, and inflammation in the brain or body may also cause neurologic complications. Other viral infections can also lead to brain fog.

2 Shortness of breath
Doctors are eyeing lung and heart complications including scarring. Patients who become critically ill with COVID-19 seem more likely to have lingering shortness of breath, but those with mild cases are also at risk.

3 Heart arrhythmia
The virus can harm the heart, and doctors are concerned about long-term damage. How the heart heals after COVID-19 could help determine whether a patient develops an irregular heartbeat.

4 Hypertension
Some patients have high blood pressure after an acute infection, even when cases were relatively mild and people were previously healthy, possibly because the virus targets blood vessels and heart cells.
Post-acute Sequelae SARS-CoV-2 infection (PASC)

- Long haulers
- Long haul COVID
- Long COVID syndrome
- Post-COVID syndrome

- Definition at this point: *any* symptoms lasting > 8 weeks after recovery of initial COVID infection
Collection of many different things

- Post-ICU syndrome?
- Cardiomyositis?
- Pulmonary Fibrosis?
- Pulmonary Embolism?
- POTS

...or is this a completely new disease?

PASC
Why is POTS suspected?

- Increasing numbers of case reports/series of dysautonomia among long haulers
- Symptoms are very characteristic for POTS
- POTS is known to be post-viral in nature (~40-50%)
- However, many providers are not familiar with POTS
POTS (Postural Orthostatic Tachycardia Syndrome)

- Coined by Dr. Philp Low at Mayo in 1993

- Diagnosed with combination of clinical exam and a tilt table test:
  - > 30bpm increase (40bpm for pediatrics) within 10 min or HR reaches >120bpm within 10 min, typically accompanied by reproduction of Sxs

- NOT a cardiac condition – cardiac function should be normal

- Suggesting failure in neural control of circulation
Vasomotor Denervation

- Most vessels are innervated by post-ganglionic sympathetic nerve fibers
- It “pumps” the blood to the tissues (muscle, brain, etc.)
- Sympathetic denervation can lead to inadequate blood supply

Fail to Supply Blood Circulation?

Pump Failure?

Muscle
- Muscle cramp/pain after exercise (lactic acid?)

Brain
- Migraine
- Brain fog
- Reduced concentration

Heart
- Orthostatic intolerance
- Chronic fatigue
- Exercise intolerance
Central Sympathetic Activation (Compensation)

**Fight or Flight Symptoms**
- Anxiety
- Palpitation
- Orthostatic Tachycardia
- Sleep disturbance
- Nausea +/- vomiting
- Hyperhidrosis

**Brain**
- Migraine
- Brain fog
- Reduced concentration

**Sympathetic Compensation**

**Muscle**
- Muscle cramp/pain after exercise (lactic acid?)

**Heart**
- Orthostatic intolerance
- Chronic fatigue
- Exercise intolerance
Vasomotor Sympathetic Dysfunction

Brain fog
Exercise intolerance
Orthostatic intolerance
Chronic Fatigue
Delayed onset muscle soreness
Exertional dyspnea
Headache
Venous pooling

Sympathetic Over-compensation

Palpitation
Heat intolerance
Coat hanger pain
Anxiety
Insomnia
Chronic nausea
Abdominal pain
Lack of appetite

Dysfunction

Diaphoresis
Chest pain

POTS Symptom Cluster
Hypothesis

COVID19 Antibody \[\rightarrow\] Auto-antibody \[\rightarrow\] Autonomic nerve cell

**POTS**
(Inflammation to sympathetic vasomotor fibers)
Principles of Treatment

• There is no disease-modifying treatment

• The goal is to *restore function*

• Pump failure -> aggressive volume expansion

• Sympathetic overcompensation -> sympatholytics or psychological interventions
Treating Pump Failure Symptoms
– Volume Expansion

- Oral hydration (typically ~ 4 liters of water and 4-5g of sodium per day)
- IV hydration – temporary
- +/- medications, such as midodrine and/or florinef
- Physical exercise
Overall Strategy for Volume Expansion

- Physical therapist
- Occupational therapist
- Nutritionist
- Psychologist

Exercise
Lifestyle modification
Medications
Increased water and sodium

Cardiologist
Gastroenterologist
Neurologist
Endocrinologist
Rheumatologist
How Exercise Works (Theoretically)

- Basically, using skeletal muscles in the lower limbs as a “pump”

- Normal cardiac output = 4-8L (~1-2gallons)/min

- During cardiovascular exercise = 20-25L (~4-6 gallons)/min, up to 35L/min in trained athletes

- But it’s difficult!
HR response to exercise in POTS

Point of no return!

Training stopped
Immune treatments?

• Likely beneficial on selective cases

• Urgent need to identify biomarkers

• IVIG is known to improve symptoms of POTS
Future (& Ongoing) Plans

- Establishing post-COVID POTS cohort
- Passive transfer experiment
- Clinical trials with immune drugs