Study investigates why some long COVID patients continue to have difficulty exercising while others recover

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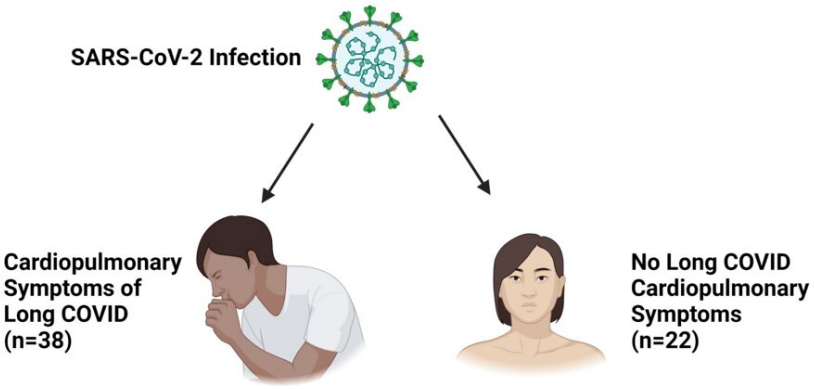
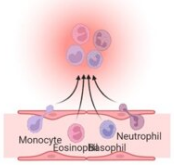


Cardiopulmonary Exercise Testing at Median 18 Months

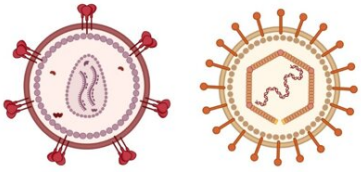
< 85% Predicted:	**18/37 (49%)**	**3/19 (16%)**
Peak VO_2 (ml/kg/min):	**22.7 ± 8.1**	**29.6 ± 7.0**

Adjusted odds ratio: **2.8 per -5ml/kg/min (1.4 to 5.4; p=0.004)**
Adjusted difference: **-5.2 ml/kg/min (-8.3 to -2.1; p=0.001)**

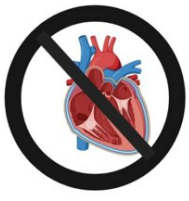
Most common abnormal exercise pattern: **chronotropic incompetence (inability to increase heart rate during exercise),** *not ventilatory, cardiac, or deconditioning*



Exercise capacity correlated with earlier inflammatory biomarkers



EBV reactivation and HIV were associated with chronotropic incompetence



No evidence of myocarditis or arrhythmias

Graphical Abstract. Credit: *The Journal of Infectious Diseases* (2023). DOI: 10.1093/infdis/jiad131

While some patients recover from the effects of SARS-CoV-2 infection, others have experienced the aftereffects of COVID-19 long after the initial infection. One of these long COVID symptoms is reduced exercise capacity. But questions remain about the mechanisms underlying why some COVID patients continue to experience diminished exercise capacity while others recover without this condition.

In a study recently published in the *Journal of Infectious Diseases*, a team of researchers from UC San Francisco found that lower than expected exercise capacity was common among people with long COVID and chronotropic incompetence (inadequate heart rate increase during exercise) was the most common reason.

They also found reduced exercise capacity to be correlated with early post-COVID elevations of inflammatory biomarkers. In addition, they found that reactivation of Epstein-Barr virus (EBV) may be related to reduced heart rate while exercising.

First author Matthew Durstenfeld, MD, MAS, designed the cardiovascular sub-study as part of the Long-Term Impact of Infection with Novel Coronavirus (LIINC) study which was led by Michael Peluso, MD, MHS, UCSF assistant professor of Medicine. LIINC was designed to evaluate physical and mental health following COVID-19 infection by including individuals representing the full spectrum of acute illness and post-acute recovery.

The study started in November 2020 using echocardiograms to evaluate cardiac conditions underlying post-COVID symptoms.

When the initial echocardiogram-based study did not reveal cardiac mechanisms of symptoms, the team amended the study protocol to conduct a second visit with the study participants one year later for advanced testing including cardiopulmonary exercise testing (CPET), cardiac magnetic resonance imaging (CMR), and ambulatory heart rhythm monitoring. Participants in the sub-study also had blood samples collected and processed for serum and plasma at their echocardiogram visit.

Sixty participants with a median age of 53 were studied at about a year and a half following COVID infection. On CPET, 49% with symptoms had reduced exercise capacity compared to 16% without symptoms. Adjusted peak VO_2 (the volume of oxygen the body consumes during exercise) was 16.9% percent lower than predicted among those with symptoms. Chronotropic incompetence was a common finding, and inflammatory biomarkers and antibody levels in the first few months after COVID-19 were negatively correlated with peak VO_2 more than one year later.

"The findings suggest that chronotropic incompetence—failure to achieve 80% of expected maximum heart rate while exercising - contributes to exercise limitations in long COVID," said Durstenfeld, a cardiologist and UCSF assistant professor of Medicine. "We also found evidence of EBV reactivation in all individuals with chronotropic incompetence, however, we found no evidence of myocarditis, cardiac dysfunction, or clinically significant arrhythmias."

The authors note the clinical diagnostic challenge that patients with symptoms present when there are no objective findings of cardiac dysfunction on multimodality cardiopulmonary testing. They suggest

translational and proof-of-concept clinical research to characterize distinct phenotypes and mechanisms of post-acute COVID symptoms is urgently needed to identify potential therapies.

Until additional therapies are available, the authors believe individuals living with reduced exercise capacity may benefit from exercise training to improve their symptoms. Patient advocates have raised important concerns about the safety of exercise in those with overlapping myalgic encephalitis/chronic fatigue syndrome.

"Although exercise is unlikely to cure long COVID, preliminary data suggest that exercise training is the only intervention demonstrated to improve exercise capacity, symptoms and quality of life," said Durstenfeld. "Given patient concerns that exercise may worsen symptoms for some people, we need to rigorously study the role of exercise in long COVID."

More information: Matthew S Durstenfeld et al, Reduced exercise capacity, chronotropic incompetence, and early systemic inflammation in cardiopulmonary phenotype Long COVID, *The Journal of Infectious Diseases* (2023). DOI: 10.1093/infdis/jiad131

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