

September 23, 2022



CTS INSPIRATIONS

CTS NEWS

President's Message

Dear CTS friends:

It's hard to believe that fall season is here and winter is around the corner. Our annual northern California CME conference is planned for **January 13-15, 2023** at the Portola Hotel and Spa in Monterey. Please save the date on your calendar. I would like to highlight our conference program co-chairs, Dr. Gaurav Singh from Veteran Affairs Medical Center at Stanford, and Dr. Nick Kolaitis from UCSF, who are working closely with the planning committee to put together an amazing agenda.

CTS membership is a great way to stay up to date on advances in pulmonary, critical care, and sleep medicine as well as connect and collaborate with colleagues. I encourage you to renew your memberships or join as new members, in particular trainees and junior faculty! Please visit our updated website for membership information and also learn about institutional memberships.

Last but not least, please keep an eye out for announcements regarding our Friday educational webinars, with an opportunity for live questions and answers with an expert faculty.

Warmly,

A handwritten signature in black ink that reads "Michelle Cao".

Michelle Cao, DO
Stanford University



Cardiopulmonary Exercise Testing and Persistent Breathlessness in Post-Acute COVID Syndrome

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The COVID-19 pandemic has resulted in a large population of patients with multisystem symptoms of varying degree. As much as 10-20% of those infected with SARS-CoV-2 have at least one persistent symptom up to a year after their initial infection, though a recent article in *Nature*, which followed largely non-hospitalized patients for one year after their initial infection, estimated as high as 85% of patients will report continued symptoms after one year (1). The same article identified dyspnea as one of the more common persistent symptoms, occurring in 44% of patients, and had essentially no change in occurrence over the one-year period. While there are likely many different explanations and etiologies for dyspnea in any given patient, many patients have relatively normal objective findings from pulmonary function testing, CT scans, and resting echocardiography and suffered from relatively mild infectious courses. As such, cardiopulmonary exercise testing (CPET) has been a widely used investigational modality for persistent dyspnea and has an expanding collection of published studies in the Post-acute COVID Syndrome (PACS) population.

There have been several case series using CPET to examine the underlying limitation of PACS patients. Two early series from 2020 in previously hospitalized patients showed that 3 months post-discharge, 38-90% of patients had a reduced peak VO_2 and elevated post-exercise lactic acid most consistent with a muscular or peripheral circulatory limitation to exercise (2,3). This was felt to be most likely due to deconditioning and anemia. Continuing into 2021, several more case series showed similar findings. Rinaldo et al. showed 41/75 patients with moderate to severe disease had reduced peak VO_2 at 3 months post-discharge, again felt to be a muscular limitation (4). Baratto et al. matched 18 hospitalized COVID patients with healthy controls and performed CPET, PFT, exercise ECHO, and exercise ABGs (5). Reduction in peak VO_2 , O_2 pulse, VO_2/work slope, and respiratory exchange ratio (RER) were noted. There was also a notable elevation in VE/VCO_2 without a ventilatory limitation. Peak exercise ECHO demonstrated higher cardiac output in the post-COVID cohort, which was felt to be likely due to anemia or myopathic changes with the cardiac output elevation indicating a response to presumed reduction in the arteriovenous oxygen difference. Given the lack of adverse myocardial response to exercise, the VE/VCO_2 elevation was felt to be due to altered chemoreceptor sensitivity resulting in appropriate exercise hyperventilation.

The findings of Baratto were later confirmed by invasive CPET testing by Singh et al.; however, their cohort consisted of patients with only mild disease (6). These patients underwent CPET with pulmonary artery catheterization with central ABG and lactic acid monitoring. Cardiac output was preserved, and impaired systemic oxygen extraction was observed with an elevated mixed venous oxygen saturation at peak exercise (Fig 1). Compared to a matched control cohort, the peak VO_2 was again reduced, and there was elevation in VE/VCO_2 without increase in dead space indicating inappropriate hyperventilator response to exercise. These findings were interpreted as being similar to prior CPET data in chronic fatigue syndrome/myalgic encephalitis, which has shown impairment of the arteriovenous difference on invasive testing. This is also a similar pattern that is observed in heart failure patients who also develop a skeletal muscle myopathy that contributes to their exercise impairment and exercise hyperventilation.

Though there is not much data around possible myopathic changes in post-COVID patients, a small study by Hejbøl et al. identified a 75% incidence of myopathic electromyography changes (7). Corresponding muscle biopsies highlighted mitochondrial changes and T-lymphocyte inflammatory changes in 62% and capillary changes involving increased basal lamina thickness in 75% of patients. It is yet to be seen if this may be a significant contributor to post-COVID symptoms.

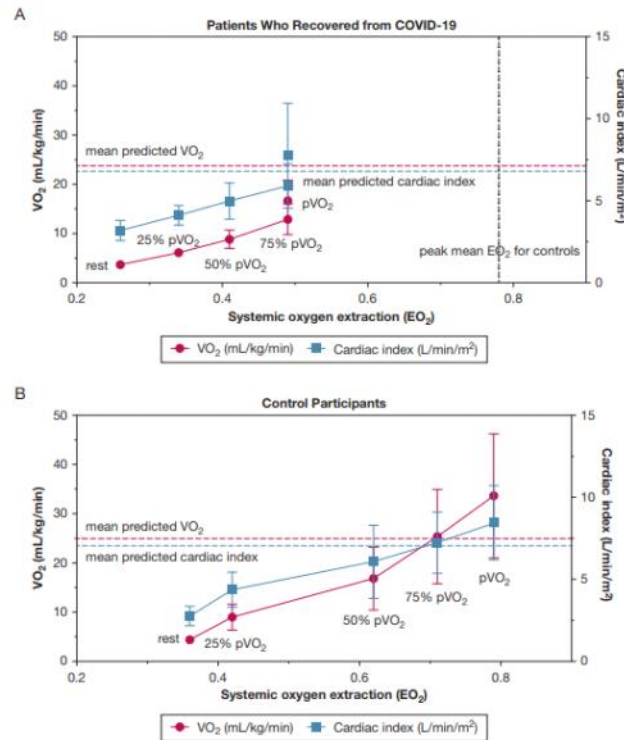


Fig 1: Impaired peripheral oxygen extraction, Singh et al

In addition to these findings several CPET series have demonstrated a significant presence of dysfunctional breathing patterns. Barrato et al., Gruenewaldt et al., and Mancini et al. have shown an elevation in VE/VCO_2 , indicating inappropriate exercise hyperventilation (5,8,9). In addition, these series have shown significant deviations from other expected ventilatory responses to exercise without the present of a reduction in breathing reserve, which would indicate a primary ventilatory limitation to exercise. Typically, tidal volume increases faster relative to respiratory rate in exercise up until anaerobic threshold. At this point, respiratory rate increases substantially faster, but patients will still recruit tidal volume. Post-COVID patients in these studies show significant aberrations in this pattern with erratic increases and decreases in both respiratory rate and exercise throughout exercise (Fig 2.).

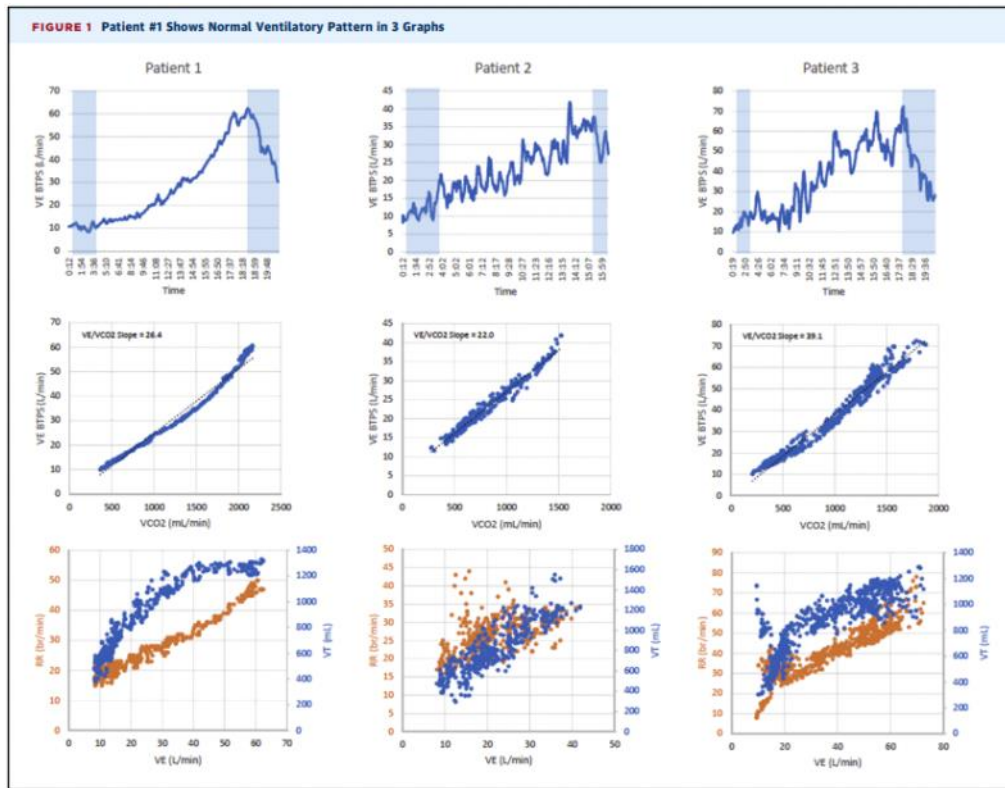


Fig 2: Dysfunctional breathing pattern in post-COVID patients, Mancini et al

In contrast to the studies above, a recent cardiac magnetic resonance augmented-CPET showed a preserved arteriovenous difference and reduced cardiac output in symptomatic post-COVID patients compared to fully recovered post-COVID patients and healthy controls (10). However, this was not due to a decrement in ejection fraction, impairment in right or left ventricular contractility, or diastolic dysfunction, but rather, inadequate preload. This was postulated to be autonomic changes resulting in poor venous compliance, which has also been shown in chronic fatigue syndrome patients. A similar finding was reported in two patients in the Mancini et al. study using pulmonary artery catheters.

As the discussed studies have shown, there are certainly pathological changes that occur in post-COVID patients, though the ultimate etiology or unifying diagnosis has not been fully established. There are significant overlaps with CFS/ME and dysautonomia, and many of the demonstrated findings can contribute to many of the multisystem complaints that these patients experience. However, as a recent poster discussion at ATS demonstrates, reported symptoms do not consistently equate to adverse findings on CPET. This abstract looked at 38 patients 6 months after COVID infection and showed normal exercise capacity in 65.8% despite similar rates of fatigue, exertional dyspnea, and chest discomfort compared to those with a reduction in peak VO₂. It is not unreasonable to expect a substantial amount of patients to improve with time based on a Lancet study using longitudinal cardiac MRI, CPET, and PFTs, which demonstrated serial improvement at 2-3 months and 6 months in multiple CPET parameters including peak VO₂, VO₂ at AT, VE/VCO₂, and O₂ pulse.

CPET is a valuable tool to help identify underlying objective functional limitations in PACS. The available CPET data broadly points away from a central cardiopulmonary etiology to reported symptoms, though this may not be a universal expectation. CPET can be particularly useful at

ruling out more dangerous etiologies (i.e. myocardial ischemia, pulmonary hypertension, etc). Many of these patients can improve with graded exercise programs, which has been demonstrated in several studies utilizing pulmonary rehabilitation (13,14). Evaluation for underlying dysautonomia and CFS/ME symptomology is paramount to guide patients towards appropriate specialty support.

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SOUTHWEST JOURNAL OF PULMONARY, CRITICAL CARE AND SLEEP ANNOUNCEMENT

The next Arizona Thoracic Society speaker will be Prof. Peter Barnes from London on November 2. The title of his lecture will be “Accelerated aging as a driving mechanism of COPD”. Because of the time difference, he will be giving a “live” Zoom lecture at 12 noon PDT. This will be followed with a taped performance at 6 PM PDT that evening. A Zoom link will be posted on the Southwest Journal home page (<https://www.swjpc.com>) at a later date and there is no need to register.

A list of our most recent offerings follow on the next page.

Southwest Journal of Pulmonary, Critical Care and Sleep Volume 25 Issues 1 & 2

Volume 25, Issues 1 & 2							
Title (Click on title to open the manuscript)	Journal Section	First Author	Year	Vol	Issue	Pages	Date Posted
Point-of-Care Ultrasound and Right Ventricular Strain: Utility in the Diagnosis of Pulmonary Embolism	Critical Care	Ibrahim R	2022	25	2	34-36	8/27/22
Point of Care Ultrasound Utility in the Setting of Chest Pain: A Case of Takotsubo Cardiomyopathy	Critical Care	Ibrahim R	2022	25	2	30-33	8/11/22
A Case of Brugada Phenocopy in Adrenal Insufficiency-Related Pericarditis	Critical Care	Kim A	2022	25	2	25-29	8/6/22
Medical Image of the Month: An Unexpected Cause of Chronic Cough	Imaging	Khair Y	2022	25	2	23-24	8/2/22
August 2022 Imaging Case of the Month: It's All About Location	Imaging	Gotway MB	2022	25	2	15-22	8/1/22
Effect Of Exogenous Melatonin on the Incidence of Delirium and Its Association with Severity of Illness in Postoperative Surgical ICU Patients	Critical Care	Gupta K	2022	25	1	7-14	7/25/22
July 2022 Medical Image of the Month: Pulmonary Nodule in the Setting of Pyoderma Gangrenosum (PG)	Imaging	Goswami U	2022	25	1	4-6	7/2/22
July 2022 Sleep Case of the Month: A Sleepy Scout	Sleep	Fukui CS	2022	25	1	1-3	7/1/22

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