Exercise-Induced Desaturations and Functional Limitation in Post-COVID-19 Lung Disease: Cause or Correlate?

Throughout the current pandemic, much has been written on the relationship between hypoxemia and the presence of respiratory symptoms in acute COVID-19 lung disease. Now that we are faced with a large population of patients suffering from the sequelae of acute COVID-19 infection whom we hope to assist with rehabilitation, we must again revisit the relationship between hypoxemia (in this case, exertional desaturations) and symptom burden. The vast majority of patients who recover from COVID-19 continue to endure prolonged symptoms even months after hospital discharge, especially dyspnea and fatigue,[1,2] and more than half continue to have functional limitations impacting daily activities of living.[3] The most common lingering abnormality on pulmonary function testing even after clinical recovery is a reduced diffusing capacity,[4,5] which can persist in up to a third of patients after one year and which correlates with persistent imaging findings such as residual ground-glass opacities that do not appear to fully resolve.[6]

From these findings, we know that exertional symptoms, some of which correlate with physiologic abnormalities, persist for months after acute COVID-19 illness, though they will likely slowly improve over time. What remains less well characterized is the degree to which exertional dyspnea correlates with gas exchange abnormalities, including exertional desaturations. It is in this context that Vitacca et al[7] present their findings of exercise-induced desaturation in survivors of COVID-19. These survivors had been quite ill, with 95% requiring supplemental oxygenation and 35% requiring intubation during their acute illness, which is a known risk factor for prolonged symptoms after recovery.[5] At an average of 46 d after onset of illness, 40 of the 150 survivors (26.6%) were found to be normoxemic at rest but noted to have exercise-induced desaturations (despite only 5 of the 40 having been prescribed supplemental oxygen with exertion on hospital discharge); this proportion is higher than that described in another post–COVID-19 cohort, which comprised subjects with less severe acute disease and longer follow-up.[8] On pulmonary function testing, these patients overall demonstrated mild restriction and moderate diffusion limitation, but with significant limitations in both daily functioning attributed to dyspnea (mean modified Medical Research Council score of 2.5) and symptoms of exertional dyspnea (mean end-exercise Borg dyspnea score of 3.5), as well as mild limitations in their 6-min walk distance (350 m on average, 68% predicted), which is in keeping with other studies of this patient population.

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The authors use as comparator groups 2 cohorts of subjects with chronic lung disease: interstitial lung disease (ILD) and COPD. The pattern of predominantly low D_{LCO} with preserved mechanics noted in the post–COVID-19 group is commonly seen in less severe ILD, and indeed the comparison group of ILD subjects had a relatively low ILD-GAP index with 76% $<$ 5 points, suggesting more mild disease. However, physiologic similarities between ILD and post–COVID-19 could have been presumed given what we already know about the fibrotic disease seen after ARDS from other coronavirus infections[9]; and longer follow-up of post–COVID-19 lung disease suggests that many will continue to improve both symptomatically and physiologically,[6] suggesting that this relationship will dissolve over time.

What is perhaps more problematic, however, is the implication that exertional desaturations are the major cause of dyspnea and exercise limitation in COVID-19, ILD, or COPD. Dyspnea is a complex symptom that arises from a multitude of stimuli (eg, pulmonary and vascular receptors as well as chemoreceptors) and interactions between desired and achieved tidal volume and ventilation: that is, neuromechanical or efferent-reafferent dissociation. Furthermore, dyspnea is associated with a range of qualitatively distinct sensations that may lead to a number of affective and behavioral responses.[10] Given this complexity, it is no wonder that the underlying physiology of exercise limitation varies dramatically between ILD and COPD and is not well studied in COVID-19 lung disease.

In ILD, exertional dyspnea, as well as overall prognosis, correlates with the presence and severity of exertional desaturations occurring from ventilation-perfusion mismatching

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and diffusion limitation[11] but is typically not alleviated significantly with supplemental oxygen. Therefore, reduced compliance of the lungs and stimulation of pulmonary receptors by the inflammatory and/or fibrotic process likely play a greater role. In contrast, exercise limitation in COPD is more closely albeit imperfectly linked to ventilatory mechanics (eg, FEV_1), with dynamic hyperinflation and deconditioned skeletal muscles leading to a greatly disadvantaged work of breathing and reduced efficiency.[12] In both conditions, however, the downstream effects of these ventilatory constraints on inspiratory neural drive are closely correlated to the sensation of dyspnea.[13] It would have been interesting to compare post–COVID-19 patients to patients with ILD individually matched by degree of restriction and diffusion limitation in order to maximize the ability to detect differences in either the severity of exertional desaturations or functional limitations in post–COVID-19 patients. An additional comparator group of interest would include patients with chronic pulmonary vascular disease, a disease process that has been implicated as a possible cause of persistent diffusion limitation after COVID-19.[14]

The current study's results lead to additional questions that deserve attention. First, despite obvious gas exchange abnormalities with exercise, how much of the exercise limitation in post–COVID-19 patients can be traced to the respiratory system? The authors note that the severity of exertional hypoxemia was correlated with the severity of dyspnea and inversely correlated with walk distance. However, an abundance of factors can lead to exertional limitations in post–COVID-19 subjects, most importantly peripheral deconditioning but also cardiac limitations and, intriguingly, abnormal central ventilatory control leading to exercise hyperventilation.[15,16] As would be expected given the myriad of other causative factors, end-exercise oxygen saturation is an extremely weak predictor of the severity of exertional symptoms after COVID-19 infection.[17] Qualitative assessments of dyspnea could have shed additional light on the specific etiology of functional limitation[18] as, of course, would cardiopulmonary exercise testing.

Second, how does the presence of exercise-induced desaturations affect our management of these patients? The included subjects were required only to have exercise-induced desaturation, not hypoxemia (often defined as $<= 88\%$); but with a mean saturation nadir of 86.2%, many would have qualified for supplemental oxygen with exercise. It would have been informative to know whether oxygen supplementation significantly altered the degree of exertional dyspnea or the walk distance, or even whether this effect could be reproduced with use of additional flow of room air delivered by nasal cannula, given that inspiratory flows that seem inadequate to the patient are strong drivers of dyspnea,[19] most likely mediated by upper-airway receptors. Additionally, the presence of significant desaturation during exercise, regardless of the qualification for supplemental oxygen, suggests underlying persistent architectural lung abnormalities or pulmonary vascular disease and the absence of a significant ventilatory reserve; these patients should be evaluated for the presence of residual organizing pneumonia (which may benefit from prolonged corticosteroid treatment[20]) or more aggressive pulmonary rehabilitation.

In summary, Vitacca et al describe a well-characterized cohort of post-COVID lung disease subjects with exertional hypoxemia and dyspnea, a clinical pattern that is now becoming all too common and similar in many respects to patients with other causes of ILD. To what degree exertional hypoxemia contributes significantly to dyspnea and exercise limitation is still unclear. Regardless, these findings warrant attention to screening such patients for exertional hypoxemia, both as a treatable characteristic in and of itself as well as a marker for poor prognosis and additional therapy.

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