Lung pathophysiology in patients with long COVID-19: one size definitely does not fit all

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Shareable abstract (@ERSpublications)
Despite reduced resting lung volumes and D_{LCO}, patients with long COVID and dyspnoea have similar physiological response to exercise to healthy subjects. D_{LCO} impairment can marginally explain heterogeneity of complex syndromes such as long COVID. https://bit.ly/40j4aX6

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Independent of disease severity or the need for hospitalisation, patients that experience coronavirus disease 2019 (COVID-19) are at high risk of having one or more sequelae or new symptoms within 3 months after the acute infection, a condition internationally recognised as "long COVID" (l-COVID) [1]. Depending on reports, the prevalence of patients that present with at least one residual symptom once recovered from the acute event varies from 43% to 62% [2], leading to a significant economic burden with estimated direct and indirect costs reaching $3.7 trillion in the USA [3]. According to a recent meta-analysis that included 194 studies conducted on patients with l-COVID, fatigue and breathlessness are two of the leading symptoms reported, independent of the severity of disease [2]. So far, the origin of dyspnoea and poor exercise performance in l-COVID patients has been investigated in numerous physiological and clinical studies; contrasting findings were obtained mostly because of the heterogeneity of patients, small sample size, variety of applied procedures and methodology [4–13]. Persistence of dyspnoea in patients that experienced COVID-19 pneumonia or milder forms appears to be unrelated to the degree of disease severity or the residual impairment in lung function, which often corresponds to a mild/moderate reduction in lung diffusion capacity for carbon monoxide (D_{LCO}) and, although to a minor extent, of total lung capacity (TLC) [5, 9, 11–13].

In this context, we read with interest the study by Barisione and Brusasco [14], who investigated the behaviour of both D_{LCO} and lung diffusion capacity for nitric oxide (D_{LNO}) at rest and after a short course of treadmill exercise in outpatients with dyspnoea (modified Medical Research Council (mMRC) score ⩾1–2) and l-COVID and in healthy subjects. At rest, l-COVID patients had small though significant reduction of TLC, alveolar volume (V_A), D_{LNO} and D_{LCO}, but normal forced vital capacity and forced expiratory volume in 1 s. Furthermore, the D_{LNO}/D_{LCO} ratio was not significantly different from controls. After walking on the treadmill, both patients and controls experienced a significant increase in D_{LNO}, D_{LNO}/D_{LCO} and V_A, with no increase in D_{LCO} or significant changes in D_{LNO}/V_A or D_{LCO}/V_A. However, the relative changes caused by exercise in all variables were similar in l-COVID patients and healthy subjects. Nevertheless, the results were considered suggestive of reduced operational volumes at rest to be the major determinant of dyspnoea in l-COVID patients, the lowered V_A in these patients reflecting the heterogeneity of residual lung damage after SARS-CoV-2 infection.

Loss of lung units secondary to parenchymal damage with persistent lung consolidations has been demonstrated especially in patients with severe pneumonia in association with reduced D_{LCO} [15, 16]. Recently, Schlemmer *et al.* [17] have reported that during a follow-up of 12 months, >50% of COVID-19 patients still experienced dyspnoea on exertion independent of the severity of the initial disease, and in >40% of the study sample, D_{LCO} showed a mild to severe impairment apparently not secondary to a

diffusion defect. A functional loss of V_A during tidal breathing and during forced expiration was also observed by Scaramuzzo *et al.* [10] while measuring the regional distribution of ventilation by means of electrical impedance tomography in patients with dyspnoea (mMRC ⩾1) 12 months after SARS-CoV-2 infection. In this case, D_{LCO}, D_{LCO}/V_A and lung volumes were not different as compared with patients without dyspnoea [10]. Persistent dyspnoea has been found to be associated to dysfunctional small airways 3 months after discharge, independently of the severity of disease and parenchymal/radiological sequelae [18]. However, this is in contrast with the findings of Rinaldo *et al.* [13] and Beaudry *et al.* [5], who did not find any association between dyspnoea and cardiopulmonary impairment or lung function parameters in COVID-19 patients 3–6 months post-infection. Indeed, Li *et al.* [19] demonstrated the presence of two different latent phenotypes using a volume-independent contrastive learning model with inspiratory and expiratory chest computed tomography (CT) images in 140 post-COVID-19 patients, one with normal volumes and D_{LCO} but CT signs of air trapping and one with reduced volumes and D_{LCO} but only an interstitial fibrotic like pattern.

The lack of a post-exercise rise in D_{LCO} and the relationship of this observation with a supposedly blunted capillary volume (V_c) recruitment is in contrast with previous findings, obtained in COVID-19 survivors 3 months post-hospital discharge during a cardiopulmonary exercise test coupled with echocardiographic assessment [20]. Rinaldo *et al.* [20] studied 16 patients with mild to moderate D_{LCO} impairment, the majority of whom still presented with chest CT abnormalities, without finding any exercise limitation in terms of ventilatory or cardiovascular reserve, with no evidence of impairment of pulmonary haemodynamics or right cardiac function, indicating a prompt recovery of cardiopulmonary performance even in subjects with persistent reduction of D_{LCO}. Inhomogeneous involvement of V_c or membrane diffusion could possibly be due to different radiological involvement and pulmonary sequelae [15]; an evaluation of the extent of V_c recruitment was, however, absent in the study by Barisione and Brusasco [14], as D_{LCO} measurement at different fractions of inspired oxygen were not performed.

The work by Barisione and Brusasco [14] raises several questions about the possible pathophysiological explanations that might justify persistent dyspnoea in l-COVID patients. Unfortunately, the authors did not correlate their physiological findings with the extent of dyspnoea at rest and during/after exercise or with gas exchange parameters [14]. One limitation, also raised by the authors, is that the matching of patients with controls was not sufficiently accurate to allow for an appropriate conclusion [14]. Furthermore, all the studies mentioned indicate that in post-COVID-19 patients, the connection between dyspnoea and lung function variables, diffusion capacity included, is either absent or unproven. The observations by Barisione and Brusasco [14] point to the conclusion that all their l-COVID patients suffered from dyspnoea but only half of them presented altered D_{LCO} and D_{LNO}, and that the six patients recovering from milder forms of the disease, despite having significant dyspnoea, had normal lung function parameters.

Once more, the attempts to investigate the cause of dyspnoea in patients experiencing l-COVID lead to observations that seem difficult to fit to a specific group/phenotype or to explain without invoking a holistic approach to this complex disease.

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