Caution in interpretation of abnormal carbon monoxide diffusion capacity in COVID-19 patients

To the Editor:

We read with much interest the recent findings published in the *European Respiratory Journal* of reduced gas transfer in patients following coronavirus disease 2019 (COVID-19). Mo *et al.* [1] investigated conventional pulmonary function in survivors of mild, moderate and severe COVID-19 approximately 20–30 days after onset of symptoms. While patients had relatively normal spirometry, diffusing capacity of the lung for carbon monoxide (D_{LCO}) was reduced in 50% and D_{LCO}/alveolar volume (V_A) (or K_{CO}, to avoid misinterpretation) reduced in 25%. These findings are welcome as they provide significant insight into the long-term lung function impairment associated with COVID-19.

In response, Nusair [2] contributed the interpretation that "low D_{LCO} is caused mainly by reduced alveolar volume, and not residual interstitial abnormalities or pulmonary vascular abnormalities caused by COVID-19", *i.e.* normal capillary–alveolar units. However, we believe that this interpretation does not consider the complex relationship between V_A, D_{LCO} and K_{CO}, and may prematurely rule out the presence of abnormal gas exchange. To demonstrate our point, figure 1 illustrates the expected effect of a reduction in V_A on D_{LCO} and K_{CO} due to either suboptimal alveolar expansion or loss of alveolar units (with normal expansion in communicating alveoli) [3]. Firstly, it is evident that in the "severe pneumonia" patients in the study by Mo *et al.* [1], the impairment in D_{LCO} [1] (represented by the star) is considerably greater than expected if a reduction in V_A was the sole abnormality, regardless of the mechanism for the reduced V_A. Secondly, a reduction in V_A due to either aforementioned mechanism would be is associated with an *increase* in K_{CO}, which is opposite to the *reduced* K_{CO} in many of the discharged patients with severe COVID-19 [3]. This reduction in K_{CO} suggests that loss of alveolar units is not sufficient to cause the observed impairment in D_{LCO}.

Thus, while the D_{LCO} findings of Mo *et al.* [1] are partially explained by reduced V_A, the reduction in K_{CO} measured at that reduced V_A also implicates abnormal gas exchange. Whether this is due to disruption of

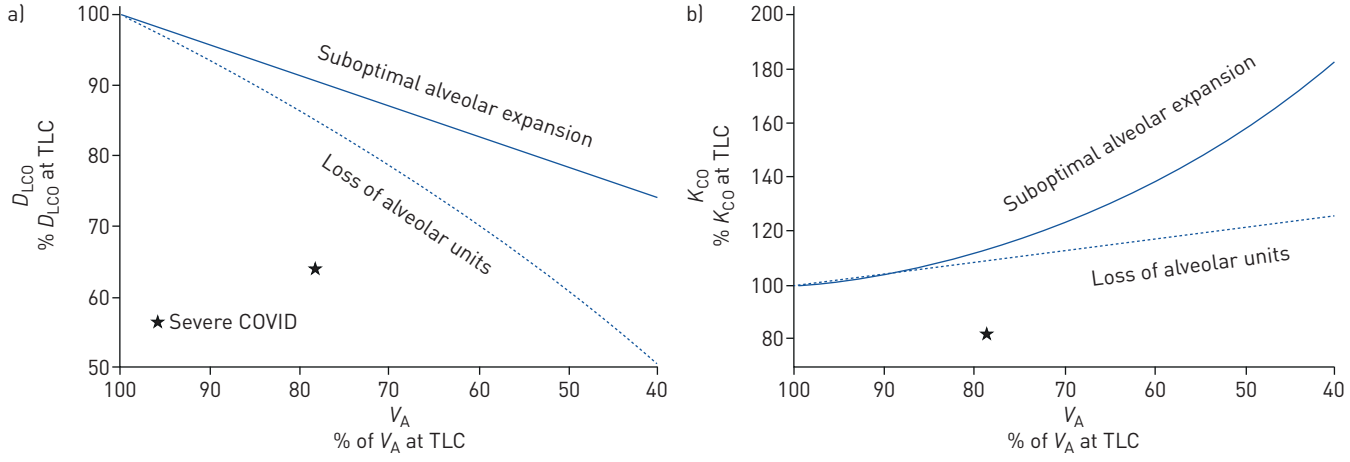

FIGURE 1 The relationship between alveolar volume (V_A) and, a) diffusing capacity of the lung for carbon monoxide (D_{LCO}) and b) rate constant for carbon monoxide uptake (K_{CO}), are plotted as a percentage of the value at total lung capacity (TLC). The relationships are shown for two situations that result in reduced V_A: suboptimal alveolar expansion (D_{LCO} and K_{CO} measured at volumes below maximum TLC, solid line); and loss of alveolar units (*e.g.* theoretical removal of lobules or lobes with remaining lung expanded to its normal TLC, dashed line). The star represents the group mean data of the "severe pneumonia" from Mo *et al.* [1]. Mean V_A was calculated as mean percent predicted D_{LCO}/mean percent predicted K_{CO}. The relationship between V_A, D_{LCO} and K_{CO} was calculated using the equations as described in [3]; for suboptimal alveolar expansion, $K_{CO} = 0.43 + (0.57/V_A)$; for loss of alveolar lung units, change in $K_{CO} = 0.4x + 2.1$, where x is the proportion of volume diverted to the remaining lung; for both scenarios, $D_{LCO} = V_A \times K_{CO}$.

the alveolar–capillary barrier or abnormal pulmonary blood volume cannot be determined based on their data. Lung fibrosis associated with acute respiratory distress syndrome in COVID-19 patients [4] would likely damage alveolar–capillary units, leading to loss of alveolar units and impaired gas exchange. The result would be a reduction in both V_A and K_{CO} (for the reduced V_A). There is increasing suggestion of altered pulmonary haemodynamics in COVID-19 patients [5], including vascular pruning and reduced pulmonary blood volume measured *via* high resolution computed tomography [6]. Use of more specific measures of the alveolar–capillary membrane, such as combined D_{LCO} and diffusing capacity of the lung for nitric oxide measurements or advanced imaging techniques, are likely required to determine whether interstitial abnormalities or pulmonary vascular abnormalities contribute to reduced D_{LCO} in patients who have recovered from COVID-19.

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Reduced K_{CO} in discharged patients with COVID-19 suggests persistent abnormalities in gas exchange. Further research is required to understand why. https://bit.ly/2Hb00gq

Cite this article as: Chapman DG, Badal T, King GG, *et al*. Caution in interpretation of abnormal carbon monoxide diffusion capacity in COVID-19 patients. *Eur Respir J* 2021; 57: 2003263 [https://doi.org/10.1183/13993003.03263-2020].

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Received: 25 Aug 2020 | Accepted: 14 Oct 2020

Conflict of interest: D.G. Chapman has nothing to disclose. T. Badal has nothing to disclose. G.G. King reports personal fees, non-financial support and other from AstraZeneca, Boehringer Ingelheim, GSK, Menarini, MundiPharma and Novartis (consultancy fees for talks, chairmanship, advisory boards and conference sponsorship), unrestricted research grants from NHMRC, Boehringer Ingelheim, CycloPharma, GlaxoSmithKline, Menarini, MundiPharma, philanthropic individuals and societies, and non-financial support from Restech (research collaboration and in-kind support), outside the submitted work. C. Thamrin has nothing to disclose.

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