



Abnormal carbon monoxide diffusion capacity in COVID-19 patients at time of hospital discharge

To the Editor:

I have read with great interest the article by Mo *et al.* [1] entitled “Abnormal pulmonary function in COVID-19 patients at time of hospital discharge” recently published in the *European Respiratory Journal*. In this study, the authors describe pulmonary function tests in patients who suffered from coronavirus disease 2019 (COVID-19), which were performed on discharge from hospital. Patients were classified into three groups of severity. In the patients who suffered more severely, measured carbon monoxide diffusion capacity (D_{LCO}) was lower. However, when looking at D_{LCO}/V_A , which represents the transfer factor of carbon monoxide, the picture is different. Patients who had severe pneumonia had an average D_{LCO}/V_A of 82% of predicted while patients in groups classified as having mild disease or pneumonia had average values above 90%. Notably, all these averages have relatively high standard deviation values (e.g. 13.9% in severe pneumonia), meaning that some patients in the post-severe pneumonia group had a $D_{LCO}/V_A >90\%$ of predicted.

The authors present timely and important data as questions are now being raised concerning the long-term effects of COVID-19 [2]. However, I disagree with the authors concerning their interpretation of both the diffusion data and also what their findings mean clinically. In presenting their results the authors use the phrase “ D_{LCO} corrected for alveolar volume (D_{LCO}/V_A)” which is not a correct expression and the notion of “ D_{LCO} corrected for alveolar volume” is not acceptable these days [3]. The authors explain further that “ D_{LCO}/V_A was still within the normal range, which might indicate that D_{LCO} decrease was more than the D_{LCO}/V_A in recovered subjects”, which is actually restating a finding without drawing a conclusion.

It is important to give emphasis here that by using carbon monoxide, D_{LCO} represents the gas diffusion capacity across the alveolar-capillary barrier and is in fact a mathematical product of the rate constant representing alveolar carbon monoxide uptake efficiency (D_{LCO}/V_A) multiplied by alveolar volume (V_A) [3]. Thus, when D_{LCO}/V_A is normal or near normal, D_{LCO} may still be low because of reduced alveolar volume, which means that complete acini with alveoli and blood vessels surrounding them are affected [3, 4]. In the remaining functionally available alveolar volume, the actual carbon monoxide uptake is normal as the diffusion through the alveolar-capillary barrier is not impaired and the blood volume within the pulmonary capillary bed is not reduced. Interstitial abnormalities or pulmonary vascular abnormalities are associated with reduced D_{LCO}/V_A which accompanies reduced D_{LCO} [4].

In the discussion of their findings, the authors cite previous studies describing follow-up of severe acute respiratory syndrome (SARS) patients having impaired D_{LCO} as the most common abnormality, with affected proportion of patients ranging from 15.5% to 43.6%. It would be important to describe how impaired D_{LCO} was defined in those studies, citing values as % of predicted and comparing that with the findings of the present study.

The conclusion which can be obtained from this study is that low D_{LCO} is caused mainly by reduced alveolar volume, and not residual interstitial abnormalities or pulmonary vascular abnormalities caused by COVID-19. The latter is important, since the proposed pathogenic mechanism describes an initial abnormality induced by COVID-19 similar to the effect of SARS and consists of a microvascular injury with some interstitial thickening with clear lungs on imaging and physical examination accompanied by profound hypoxaemia [5, 6], followed by development of alveolar abnormalities with consequent gradual

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On recovery from COVID-19 it is important to draw attention to the CO diffusion test and the actual meaning of the findings when considering the values of D_{LCO} and D_{LCO}/V_A put together
<https://bit.ly/36k2O2Q>

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loss of the alveolar spaces [6]. The filling of the alveoli with exudate at a later stage causes the loss of lung volume and reduced pulmonary compliance [7]. The finding of decreased alveolar volume on discharge may be explained by transient changes in mechanical properties of the chest wall and respiratory muscles after critical illness and may well address the concerns about a possible long lasting pulmonary parenchymal dysfunction post-COVID-19 [2].

In conclusion, the authors presented very useful data, but it is important to draw attention to the up-to-date manner in which we look at the carbon monoxide diffusion test and the actual meaning of the findings when considering the results of D_{LCO} and D_{LCO}/V_A together.

Samir Nusair ^{1,2}

¹Rokach Center for the Prevention of Lung Diseases, Clalit Health Services, Jerusalem Region, Affiliated to The Faculty of Medicine, Hebrew University and Hadassah, Jerusalem, Israel. ²Institute of Pulmonary Medicine, Hadassah-Hebrew University Medical Center, Jerusalem, Israel.

Correspondence: Samir Nusair, Institute of Pulmonary Medicine, Hadassah-Hebrew University Medical Center, PO Box 12000, Jerusalem 91120, Israel. E-mail: samjack@actcom.co.il

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Impaired pulmonary function in discharged patients with COVID-19: more work ahead

From the authors:

We are grateful for the opportunity to respond to the letter by S. Nusair, whom we thank for his interest and thoughtful remarks about our study on the abnormal pulmonary function in coronavirus disease 2019 (COVID-19) patients [1].



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Impairment of diffusion capacity is the most common abnormality in discharged patients with COVID-19. Both decreased alveolar volume and K_{CO} contribute to the pathogenesis of impaired diffusion capacity. More follow-up work is needed. <https://bit.ly/2YL2eaK>

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Diffusing capacity of the lung for carbon monoxide (D_{LCO}) reflects the capacity of carbon monoxide transfer from the environment to the pulmonary capillary blood, which is the most clinically useful routine methodology to evaluate the function of the lung to exchange gas. K_{CO} is the rate constant for carbon monoxide uptake from alveolar gas, which is influenced mostly by the thickness and area of the alveolar capillary membrane, the volume of blood in capillaries supplying ventilated alveoli, and the concentration and properties of haemoglobin in the alveolar capillary blood. D_{LCO} is mainly determined by K_{CO} and the alveolar volume (V_A). Mathematically, K_{CO} can be calculated as D_{LCO}/V_A under body temperature, ambient pressure, saturated with water vapour conditions [2].

We agree with S. Nusair that it should be noted that D_{LCO}/V_A is not a simple ratio and in fact the relationship between lung volume and carbon monoxide uptake is linear and certainly less than 1:1 [3]. Recent studies have tended to use K_{CO} instead of D_{LCO}/V_A , as it may be inferred from the use of the term D_{LCO}/V_A that D_{LCO} can be normalised for V_A . The 2017 European Respiratory Society/American Thoracic Society standards for single-breath carbon monoxide uptake in the lung recommends that the term of K_{CO} is preferred to D_{LCO}/V_A [2]. However, in practice, many pulmonary function test reports from different manufacturers still present with D_{LCO}/V_A and not K_{CO} . Besides, in order for an easier and direct comparison with some previous studies on pulmonary function in patients with severe acute respiratory syndrome (SARS) [4, 5], D_{LCO}/V_A was kept in our report. It is important to understand the interpretation of K_{CO} and D_{LCO}/V_A , but the term of K_{CO} is recommended for more popular use in future.

Decreased K_{CO} occurs in alveolar-capillary damage, microvascular pathology or anaemia. Causes of low V_A include reduced alveolar expansion, alveolar damage or loss, or inspired gases maldistributed with airflow obstruction. When K_{CO} turns normal, in the presence of a low D_{LCO} it is associated with low V_A . Because only the functional alveolar units had been sampled, a biased picture toward more preserved areas of the lungs is thereby provided [3]. Crucially, the same D_{LCO} may occur with various combinations of K_{CO} and V_A , each suggesting different pathologies. It is difficult to interpret which is the predominant role because both decreased alveolar volume and K_{CO} contribute to the pathogenesis of impaired diffusion capacity. D_{LCO} gives an overall assessment of gas exchange for the lung, while the alveolar-capillary membrane diffusing capacity for carbon monoxide (D_{MCO}) only depends on molecular diffusion of the membranes. However, D_{MCO} can be calculated using different equations but is not yet standardised, and as such is not a commonly used gas diffusing parameter [6].

In our study, 51 patients with COVID-19 had impaired D_{LCO} , including 29 patients who showed both impaired D_{LCO} and K_{CO} . The number of patients with both impaired D_{LCO} and K_{CO} (29/51) was 24% larger than the number of patients with impaired K_{CO} alone (22/51). Moreover, the percentage of patients with decreased total lung capacity was less than the percentage of patients with decreased K_{CO} . Furthermore, vascular injury and thrombosis have been demonstrated to be important contributing factors in the pathogenesis of COVID-19. SARS coronavirus 2 infects the endothelial cells via angiotensin-converting enzyme 2. The recruitment of immune cells to the endothelial cells facilitates the induction of endotheliitis in several organs, which contributes to systemic impaired microcirculatory function [7]. Acute pulmonary embolism has been reported during the clinical course [8]. *Post mortem* studies have reported vascular injury and thrombi in multiple organs [7, 9]. ACKERMANN *et al.* [10] compared the lung pathology of COVID-19 with H1N1. The result showed that patient with COVID-19 presented distinctive vascular features, consisting of severe endothelial injury associated with the disruption of intercellular junctions, cell swelling and a loss of contact with the basal membrane. From the above, it is probable that the effect of membrane lesion plays an important role on the impaired diffusion capacity in patients with COVID-19.

Our study showed that, similar to D_{LCO} , D_{LCO}/V_A (representing the transfer factor of carbon monoxide) also showed an association with the disease severity: as the patients progressed to a more severe condition, the mean value of D_{LCO}/V_A compared to predicted values was lower. Since the standard deviation values suggest that individual differences have effects on lung function, we also provided the distribution of the D_{LCO}/V_A of predicted in patients with different severities. 42% of the subjects with severe pneumonia had a D_{LCO}/V_A of less than 80% of predicted, compared to only 27% in the patients with pneumonia and 13% in patients with mild illness, respectively.

In previous follow-up studies of SARS, impaired D_{LCO} was defined as when D_{LCO} was <80% of the predicted value, irrespective of K_{CO} or the alveolar volume. In follow-up studies of rehabilitating SARS patients ranging from 0.5 to 2 years, the impaired D_{LCO} was the most common abnormality, accounting for 15.5% to 43.6% [11–13]. The mean D_{LCO} ranged from 77.7% to 93.8% pred in the studies above, with the longest follow up of 2 years. Our study showed a mean D_{LCO} of 78.2% pred at time of discharge but follow-up data is not available yet. It is unclear how the impaired diffusion capacity changes in survivors of COVID-19, as well as how the changes may be reflected on chest computed tomography (CT). In one study, where surviving SARS

patients were seen 6 months after admission, 43(75.4%) of patients showed radiological abnormalities, including 62.8% who had abnormal D_{LCO} [11]. Thus, the lung function impairment findings are consistent with the CT images of SARS survivors showing persistent ground glass opacity, reticular opacities and traction bronchiectasis suggesting the fibrosis [14]. Likewise, in discharged patients with COVID-19, WANG *et al.* [15] reported that 94% (66/70) of patients who were discharged from hospital at the end of the study still had mild to substantial residual lung abnormalities on their last CT scans.

Our study was a pilot study which first described the impaired pulmonary function in patients with COVID-19 at time of discharge. Impairment of diffusion capacity is the most common abnormality followed by restrictive ventilatory defects. However, more follow-up work is needed to assess the longitudinal variation of these deficits.

Ruchong Chen¹, Yi Gao¹, Mu Chen², Wenhua Jian¹, Chunliang Lei², Jinping Zheng¹ and Shiyue Li¹

¹State Key Laboratory of Respiratory Disease, National Clinical Research Center for Respiratory Disease, Guangzhou Institute of Respiratory Health, First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China. ²Dept of Respiratory Medicine, Guangzhou Eighth People's Hospital, Guangzhou, China.

Correspondence: Shiyue Li, State Key Laboratory of Respiratory Disease, National Clinical Research Center for Respiratory Disease, Guangzhou Institute of Respiratory Health, First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China. E-mail: lishiyue@188.com

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