Cardiopulmonary exercise testing might be helpful for interpretation of impaired pulmonary function in recovered COVID-19 patients

Reply to D.G. Chapman and co-workers:

We are grateful to have the opportunity for an in-depth discussion with Nusair [1] and D.G. Chapman and co-workers. We sincerely appreciate their insightful comments on our study about the impaired pulmonary function in coronavirus disease 2019 (COVID-19) patients [2, 3], which helps to interpret the parameters of abnormal lung diffusion capacity more accurately.

According to the algorithm pointed out by D.G. Chapman and co-workers, the mean alveolar volume (V_A) for total, mild, pneumonia and severe pneumonia patients with COVID-19 in our study were 84.9%, 85.3%, 86.4% and 78.5%, respectively [2]. Recently, another retrospective study by Frija-Masson *et al.* [4] showed more than half of patients with COVID-19 pneumonia presented abnormal lung function 30 days after symptom onset. Similarly, a rough value of V_A for total, none/mild, moderate, severe patients with COVID-19 were 85.1%, 87.9%, 80.2%, 78.9%, respectively. If we plotted these data into the curve of $D_{LCO}/D_{LCO,TLC}$ and $K_{CO}/K_{CO,TLC}$ plotted against volume loss $V_A/V_{A,TLC}$ presented by Hughes *et al.* [5], we can see a greater impairment in diffusion capacity of the lung for carbon monoxide (D_{LCO}) and a normal but not increased carbon monoxide transfer coefficient (K_{CO}) especially in severe cases, which is not in parallel with the expected result if a reduction in V_A is the sole factor that results in lung diffusion abnormality. Both studies supported the view that loss of alveolar units is not sufficient to cause the observed impairment in D_{LCO}.

D_{LCO} depends on both V_A and K_{CO}. The same D_{LCO} may occur with various combinations of K_{CO} and V_A, each suggesting different pathologies. Currently, limited data on pathology showed that diffuse alveolar damage (DAD) was the predominant lung pathology, with various levels of progression and severity and residual interstitial abnormalities [6]. Additionally, pulmonary microangiopathy, fibrin clotting within small capillaries around alveoli, small vessel thrombosis and thickening of alveolar capillaries were also found in different *post mortem* studies [7, 8]. From this perspective, it suggested that not only reduced V_A, but also residual interstitial abnormalities and pulmonary vascular abnormalities, contributed to the abnormal diffuse function in patients with COVID-19. We agree with D.G. Chapman and co-workers' point that "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}." Moreover, a combination of dynamic chest computed tomography scans help to assess the status of patients with COVID-19 having abnormal lung function.

In clinical practice, some rehabilitated patients with COVID-19 have presented various levels of exertional dyspnoea. Besides the impairment of static pulmonary function tests, a decreasing capability or utilisation of oxygen uptake should be noted. Therefore, we performed the dynamic functional evaluation through cardiopulmonary exercise test (CPET) in 10 rehabilitated patients with COVID-19 (*i.e.* three moderate cases, two severe cases, five critically ill cases) 1-month post-discharge in our centre between January and March 2020.

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Besides the impaired lung diffusion capacity, impairment of exercise endurance in recovered patients with COVID-19 should also be considered https://bit.ly/3qrzPDY

Cite this article as: Gao Y, Chen R, Geng Q, *et al.* Cardiopulmonary exercise testing might be helpful for interpretation of impaired pulmonary function in recovered COVID-19 patients. *Eur Respir J* 2021; 57: 2004265 [https://doi.org/10.1183/13993003.04265-2020].

TABLE 1 Clinical characteristics, pulmonary function tests (PFTs) and cardiopulmonary exercise testing (CPET) at 1-month post-discharge follow-up

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10	Mean±SD
Illness severity	Moderate	Moderate	Moderate	Severe	Severe	Critical	Critical	Critical	Critical	Critical	
Gender	Male	Female	Female	Male	Female	Male	Male	Male	Male	Male	
Age	50	25	56	26	83	65	58	41	50	53	50.7±17.3
BMI	19.83	20.43	20.63	26.58	23.13	21.63	23.42	28.18	25.43	24.27	23.4±2.8
PFTs											
FEV_1 % pred	111	98	106	102	138	115	99	87	92	93	104.1±14.7
FVC % pred	107	93	111	106	138	106	90	87	85	95	101.8±15.7
FEV_1/FVC	85.5	92.6	80.6	81.3	79.1	85	87.7	83.8	87.3	78.8	84.2±4.4
$FEF_{25\%-75\%}$ % pred	101	111	75	87	90	109	127	81	116	69	96.6±19.1
D_{LCO} % pred	86	93	88	95	61	85	69	80	78	84	81.9±10.5
K_{CO} % pred	74	103	92	89	70	90	81	88	86	84	85.7±9.3
CPET											
Peak V'_{O_2} % pred	73	76	74	61	77	66	44	73	58	60	66.2±10.5
V'_{O_2}@AT % pred	55.9	53.5		37.8		52.2	43.5	50	42.8	44.7	47.6±6.3
Breath reserve	66.6	65.3	65.5	46.9	70.9	66.4	58.3	65.3	53.9	59.9	61.9±7.2
V'_{O_2}/HR % pred	74	94	107	64	106	65	54	76	66	74	78±18.3
V'_E/V'_{CO_2}@AT	25.4	26.5		27.7		30.4	34.6	28.7	31.3	32.1	29.6±3.1

FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; $FEF_{25\%-75\%}$: mean forced expiratory flow between 25% and 75% of FVC; D_{LCO}: carbon monoxide diffusion capacity; K_{CO}: carbon monoxide transfer coefficient; V'_{O_2}: oxygen uptake; V'_{O_2}@AT: oxygen uptake at anaerobic threshold; V'_{O_2}/HR: oxygen pulse; V'_E/V'_{CO_2}@AT: ventilatory equivalents for carbon dioxide at anaerobic threshold.

Our results showed that spirometry was within the normal range in all cases and abnormal D_{LCO} (<80% pred) was only found in three cases. However, of note, all cases had reduction in peak oxygen uptake and seven cases displayed decreasing oxygen pulse relative to predicted values. On the contrary, eight cases displayed normal ventilatory equivalents for carbon dioxide at anaerobic threshold (table 1). This indicated that pulmonary dysfunction and gas transfer inefficiency was not the sole reason for exercise limitation in patients with COVID-19; extrapulmonary factors, especially cardiac dysfunction after long-term bed rest during hospitalisation, should be considered.

To date, no data regarding CPET in patients with COVID-19 has been reported. A previous study on severe acute respiratory syndrome (SARS) by Ong *et al.* [9] showed, despite the fact that half of the recovered patients with SARS had pulmonary function defects, the impairment was mild in majority of cases. Many patients had decreased exercise capacity that cannot be accounted for by impairment of pulmonary function, which was consistent with our preliminary results. Thus, it is necessary to further evaluate the impairment of exercise endurance in patients with COVID-19.

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Received: 19 Nov 2020 | Accepted: 24 Nov 2020

Conflict of interest: None declared.

References

1 Nusair S. Abnormal carbon monoxide diffusion capacity in COVID-19 patients at time of hospital discharge. *Eur Respir J* 2020; 56: 2001832.
2 Mo X, Jian W, Su Z, *et al.* Abnormal pulmonary function in COVID-19 patients at time of hospital discharge. *Eur Respir J* 2020; 55: 2001217.
3 Chen R, Gao Y, Chen M, *et al.* Impaired pulmonary function in discharged patients with COVID-19: more work ahead. *Eur Respir J* 2020; 56: 2002194.
4 Frija-Masson J, Debray M-P, Gilbert M, *et al.* Functional characteristics of patients with SARS-CoV-2 pneumonia at 30 days post-infection. *Eur Respir J* 2020; 56: 2001754.
5 Hughes JMB, Pride NB. Examination of the carbon monoxide diffusing capacity (DLCO) in relation to its KCO and VA components. *Am J Respir Crit Care Med* 2012; 186: 132–139.
6 Ackermann M, Verleden SE, Kuehnel M, *et al.* Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. *N Engl J Med* 2020; 383: 120–128.
7 Carsana L, Sonzogni A, Nasr A, *et al.* Pulmonary post-mortem findings in a series of COVID-19 cases from northern Italy: a two-centre descriptive study. *Lancet Infect Dis* 2020; 20: 1135–1140.
8 Fox SE, Akmatbekov A, Harbert JL, *et al.* Pulmonary and cardiac pathology in African American patients with COVID-19: an autopsy series from New Orleans. *Lancet Respir Med* 2020; 8: 681–686.
9 Ong K-C, Ng AW-K, Lee LS-U, *et al.* Pulmonary function and exercise capacity in survivors of severe acute respiratory syndrome. *Eur Respir J* 2004; 24: 436–442.