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Reply to Noel-Savina and collaborators: D_M and V_C impairment after COVID-19

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TO THE EDITOR: We read with great interest the article of Noel-Savina and collaborators, from Toulouse university hospital (France), about the outcomes of 72 patients with coronavirus disease 2019 (COVID-19) pneumonia, at 4 months after hospital discharge [1]. In their monocentric cohort, 76% of patients were admitted to intensive care unit. In such initially severe patients, thoracic high-resolution computed tomography at reassessment showed persistent interstitial opacities in 44% of them, and pulmonary function tests (PFTs) showed gas exchange impairment in 39% (as defined by a diffusing capacity of the lung for carbon monoxide (DLCO) < 70% of theoretical value and/or a drop in oxygen saturation ≥ 4% during the 6-minute walk test). These data are in line with a recently published, larger French multicentric cohort [2].

As part of several examinations aimed at determining the pathophysiology of gas exchange alterations, combined measurement of diffusing capacity of the lung for nitric monoxide (DLNO) was performed with DLCO. Indeed, this technique allows distinguishing between reductions of alveolar membrane diffusive conductance (D_M) and pulmonary capillary blood volume (V_C) [3–5]. Noel-Savina and collaborators reported a slight decrease in median V_C in their cohort, and a preserved median D_M [1]. This result drew our attention, because the opposite was found in two other monocentric series in which patients were reassessed after in-hospital treatment for COVID-19 pneumonia: one Italian study with 94 patients [6], and one Spanish work with 200 subjects [7]. In both of them, D_M was predominantly reduced. In our center (Avicenne university hospital, Bobigny, France), a functional evaluation comprising DLNO was systematically proposed after COVID-19: *a)* to patients having required hospitalization with oxygen therapy ≥ 3 $l.min^{-1}$ flow; or *b)* in case of persistent respiratory symptoms distant from the infection (*i.e.*, patients of various initial severity, some of them without pneumonia). In the first 132 of them, D_M was the most impaired functional variable (mean value: 48.7% ± 15.1). D_M was below the lower limit of normal (LLN) in 115 patients (87%), whereas V_C was below the LLN in only 38 of them (29%) [8]. Of note, the three aforementioned studies were performed with a MasterScreen™

apparatus (Vyaire Medical, Mettawa, IL, USA; formerly Jaeger-Viasys, CareFusion, Höchberg, Germany) [6–8].

Apart from the differences in populations, several technical factors may rather explain these discrepancies. Firstly, some assumptions are necessary to calculate the absolute values of D_M and V_C from DLCO and DLNO, according to the model of Guénard *et al*. with Roughton and Forster's equation: $1/DL = 1/D_M + 1/(\Theta.V_C)$ [3,9,10], where Θ is the reaction rate of CO or NO with the blood. Standardized consensual values of Θ_{CO}, Θ_{NO} and the constant ratio (α) between D_{MNO} and D_{MCO} have recently been published [11], but are inconstantly implemented in PFT softwares. Secondly, some disparities in DLNO absolute value can be observed between MasterScreen™ apparatus and HypAir apparatus (Medisoft, Dinant, Belgium) [12], that can subsequently introduce modifications in the calculation of absolute D_M and V_C. Lastly, several sets of equations for reference values are available. Two sets were obtained with MasterScreen™ apparatus [13,14], and two others with HypAir apparatus [15,16]. The three oldest sets [13,15,16] were subsequently combined in a unified set of equations [11]. Moreover, some PFT softwares propose old reference values for D_M and V_C by default, obtained with another technique not involving NO diffusion (but duplicate measurements of DLCO with high and low oxygen concentrations) [17]. These remarks highlight the need for greater standardization of the DLCO-DLNO technique, which we believe could help to unveil the pathophysiological mechanisms involved in gas exchange impairment after COVID-19, as well as in other respiratory diseases.

References:

[1] Noel-Savina E, Viatgé T, Faviez G, Lepage B, Mhanna L t, Pontier S, et al. Severe SARS-CoV-2 pneumonia: Clinical, functional and imaging outcomes at 4 months. Respir Med Res 2021;80:100822. https://doi.org/10.1016/j.resmer.2021.100822.

[2] Calcaianu G, Degoul S, Michau B, Payen T, Gschwend A, Fore M, et al. Mid-term pulmonary sequelae after hospitalisation for COVID-19: The French SISCOVID cohort. Respir Med Res 2022;82:100933. https://doi.org/10.1016/j.resmer.2022.100933.
[3] Guénard H, Varene N, Vaida P. Determination of lung capillary blood volume and membrane diffusing capacity in man by the measurements of NO and CO transfer. Respir Physiol 1987;70:113–20. https://doi.org/10.1016/s0034-5687(87)80036-1.
[4] Borland CDR, Higenbottam TW. A simultaneous single breath measurement of pulmonary diffusing capacity with nitric oxide and carbon monoxide. Eur Respir J 1989;2:56–63.
[5] Borland CDR, Hughes JMB. Lung Diffusing Capacities (DL) for Nitric Oxide (NO) and Carbon Monoxide (CO): The Evolving Story. Compr Physiol 2020;10:73–97. https://doi.org/10.1002/cphy.c190001.
[6] Barisione G, Brusasco V. Lung diffusing capacity for nitric oxide and carbon monoxide following mild-to-severe COVID-19. Physiol Rep 2021;9:e14748. https://doi.org/10.14814/phy2.14748.
[7] Núñez-Fernández M, Ramos-Hernández C, García-Río F, Torres-Durán M, Nodar-Germiñas A, Tilve-Gómez A, et al. Alterations in Respiratory Function Test Three Months after Hospitalisation for COVID-19 Pneumonia: Value of Determining Nitric Oxide Diffusion. J Clin Med 2021;10:2119. https://doi.org/10.3390/jcm10102119.
[8] Sesé L, Uzunhan Y, Khamis W, Nunes H, Bayou S, Bezza E, et al. Apport de la technique de double diffusion DLCO-DLNO dans l'évaluation des séquelles fonctionnelles respiratoires post-COVID. Rev Mal Respir 2022;14:138–9. https://doi.org/10.1016/j.rmra.2021.11.209.
[9] Roughton FJ, Forster RE. Relative importance of diffusion and chemical reaction rates in determining rate of exchange of gases in the human lung, with special reference to true diffusing capacity of pulmonary membrane and volume of blood in the lung capillaries. J Appl Physiol 1957;11:290–302. https://doi.org/10.1152/jappl.1957.11.2.290.
[10] Guénard HJ-P, Martinot J-B, Martin S, Maury B, Lalande S, Kays C. In vivo estimates of NO and CO conductance for haemoglobin and for lung transfer in humans. Respir Physiol Neurobiol 2016;228:1–8. https://doi.org/10.1016/j.resp.2016.03.003.
[11] Zavorsky GS, Hsia CCW, Hughes JMB, Borland CDR, Guénard H, van der Lee I, et al. Standardisation and application of the single-breath determination of nitric oxide uptake in the lung. Eur Respir J 2017;49:1600962. https://doi.org/10.1183/13993003.00962-2016.
[12] Radtke T, de Groot Q, Haile SR, Maggi M, Hsia CCW, Dressel H. Lung diffusing capacity for nitric oxide measured by two commercial devices: a randomised crossover comparison in healthy adults. ERJ Open Res 2021;7:00193–2021. https://doi.org/10.1183/23120541.00193-2021.
[13] van der Lee I, Zanen P, Stigter N, van den Bosch JM, Lammers J-WJ. Diffusing capacity for nitric oxide: reference values and dependence on alveolar volume. Respir Med 2007;101:1579–84. https://doi.org/10.1016/j.rmed.2006.12.001.
[14] Munkholm M, Marott JL, Bjerre-Kristensen L, Madsen F, Pedersen OF, Lange P, et al. Reference equations for pulmonary diffusing capacity of carbon monoxide and nitric oxide in adult Caucasians. Eur Respir J 2018;52:1500677. https://doi.org/10.1183/13993003.00677-2015.
[15] Zavorsky GS, Cao J, Murias JM. Reference values of pulmonary diffusing capacity for nitric oxide in an adult population. Nitric Oxide 2008;18:70–9. https://doi.org/10.1016/j.niox.2007.10.002.
[16] Aguilaniu B, Maitre J, Glénet S, Gegout-Petit A, Guénard H. European reference equations for CO and NO lung transfer. Eur Respir J 2008;31:1091–7. https://doi.org/10.1183/09031936.00063207.
[17] Cotes J. Reference values for adults of European descent. In: Lung Function - Assessment and Application in Medicine. 4th ed., Oxford: Blackwell Scientific publications; 1979, p. 365–87.