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LETTER TO THE EDITOR

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Worsening of gas exchange parameters at high FiO_2 in COVID-19: misleading or informative?

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ABSTRACT

Background: In COVID-19, higher than expected level of intrapulmonary shunt has been described, in association with a discrepancy between the initial relatively preserved lung mechanics and the hypoxia severity. This study aim was to measure the shunt fraction and variations of PaO_2/FiO_2 ratio and oxygen alveolar-arterial gradient (A-a O_2) at different FiO_2.

Methods: Shunt was measured by a non-invasive system during spontaneous breathing in 12 patients hospitalized at COVID-19 Semi-Intensive Care Unit of Papa Giovanni XXIII Hospital, Bergamo, Italy, between October 22 and November 23, 2020.

Results: Nine patients were men, mean age (±SD) 62±15 years, mean BMI 27.5±4.8 Kg/m^2. Systemic hypertension, diabetes type 2 and previous myocardial infarction were referred in 33%, 17%, and 7%, respectively. Mean PaO_2/FiO_2 ratio was 234±66 and 11 patients presented a bilateral chest X-ray involvement. Mean shunt was 21±6%. Mainly in patients with a more severe respiratory failure, we found a progressive decrease of PaO_2/FiO_2 ratio with higher FiO_2. Considering (A-a O_2), we found a uniform tendency to increase with FiO_2 increasing. Even in this case, the more severe were the patients, the higher was the slope, suggesting FiO_2 insensitiveness due to a shunt effect, as strengthened by our measurements.

Conclusion: Relying on a single evaluation of PaO_2/FiO_2 ratio, especially at high FiO_2, could be misleading in COVID-19. We propose a two steps evaluation, the first at low SpO_2 value (*e.g.*, 92-94%) and the second one at high FiO_2 (*i.e.*, >0.7), allowing to characterize both the amendable (ventilation/perfusion mismatch), and the fixed (shunt) contribution quote of respiratory impairment, respectively.

Key words: COVID-19; ARDS; shunt; pneumonia; SARS-CoV-2.

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Availability of data and materials: The data used to support the findings of this study are available from the corresponding author upon reasonable request.

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Consent for publication: Not applicable.

Dear Editor,

The main manifestation of Coronavirus Disease 2019 (COVID-19) is an interstitial pneumonia, which can lead to respiratory failure. Respiratory impairment can be severe, possibly meeting Acute Respiratory Distress Syndrome (ARDS) criteria [1]. However, respiratory features of these patients differ somehow from those of typical ARDS. Actually, some Authors have described a discrepancy between the initial relatively well-preserved lung mechanics, and the severity of hypoxemia, with a higher than expected level of pulmonary shunt [2]. Furthermore, COVID-19 endothelial dysfunction seems to cause a microscopic thrombosis of blood vessels, including pulmonary capillaries [3-6], and failure of the hypoxic pulmonary vasoconstriction has also been described as a further mechanism contributing to ventilation-perfusion (V/Q) mismatch [7]. Considering these peculiar emerging features, assessment, and management of COVID-19 respiratory failure represent a clinical challenge.

Irrespectively to the underlying mechanisms, the severity of respiratory failure can be expressed as PaO_2/FiO_2 ratio. Once PaO_2, and $PaCO_2$ are available, and FiO_2 is known, also O_2 alveolar-arterial gradient (A-a O_2), can be calculated from the alveolar gas equation [8]. However, despite being simple and readily available, these parameters are quite coarse, and limited in describing the mechanism of respiratory failure [9]. Especially PaO_2/FiO_2 ratio, and its variations at different FiO_2, depend on ventilation, perfusion, O_2 arterio-venous difference, haemoglobin concentration, and shunt, with the latter of remarkable importance [9-11]. Therefore, the PaO_2/FiO_2 ratio, and FiO_2 relation are not linear. Thus, the interpretation of these parameters is not that simple, requiring a good understanding of cardiopulmonary physiology. Eventually, the huge number of patients to treat, leads to a profound structural, and logistical reorganization of hospitals [12,13], with the resulting involvement of medical doctors who do not have specific skills in the treatment of respiratory failure.

The aims of this exploratory study were to measure the shunt fraction in COVID-19 patients, and evaluate variations of standard severity parameters of respiratory failure (*i.e.*, PaO_2/FiO_2 ratio, and (A-a) O_2) at different FiO_2.

We investigated twelve patients hospitalized at the COVID-19 Semi-intensive Respiratory Care Unit of Papa Giovanni XXIII Hospital in Bergamo, Italy, between 22nd October and 23rd November 2020. Out of them, 9 were men (75%), mean age ±SD was 62±15 years, mean Body Mass Index (BMI) was 27.5±4.8 Kg/m^2. Medical history included systemic hypertension in four patients (33%), diabetes in two patients (17%), and previous ischemic myocardial infarction in one patient. Respiratory failure was characterized by a mean PaO_2/FiO_2 ratio of 234 ± 66, and 11 patients out of 12 presented with a bilateral chest X-ray involvement.

We measured the level of shunt by a non-invasive system (BEACON Caresystem, Mermaid Care A/S, Denmark). The instrument combines a gas analyser with a pulse oximeter, and a software, enabling accurate estimation of pulmonary gas exchange parameters from a procedure where FiO_2 is varied in 4-6 steps over 15-20 min, obtaining an SpO_2 in the range of 90-100%. The patient is connected to the instrument with an appropriately sized oronasal facemask equipped with a pneumotachograph, and a side stream sampling for measurement of O_2 and CO_2. During measurements, the patient remains spontaneously breathing through a T-tube connected to the facemask in a sitting position. The T-tube provides high flow mixture of gases (*i.e.*, O_2 and room air) at variable FiO_2, preventing room air inhalation and subsequent FiO_2 perturbance. For each patient an arterial blood sample was taken at different FiO_2, only once the instrument provided stability of expired gases, allowing to accurately measure PaO_2, $SatO_2$, and $PaCO_2$. In accordance with this technique, we found a mean level of shunt of 21±6 % (range 8-28%).

In Figure 1 are reported the relationships between PaO_2/FiO_2 ratio, (A-a O_2), and FiO_2. The shape of the relationship between PaO_2/FiO_2 ratio and FiO_2 shows huge interpatient variability; how-

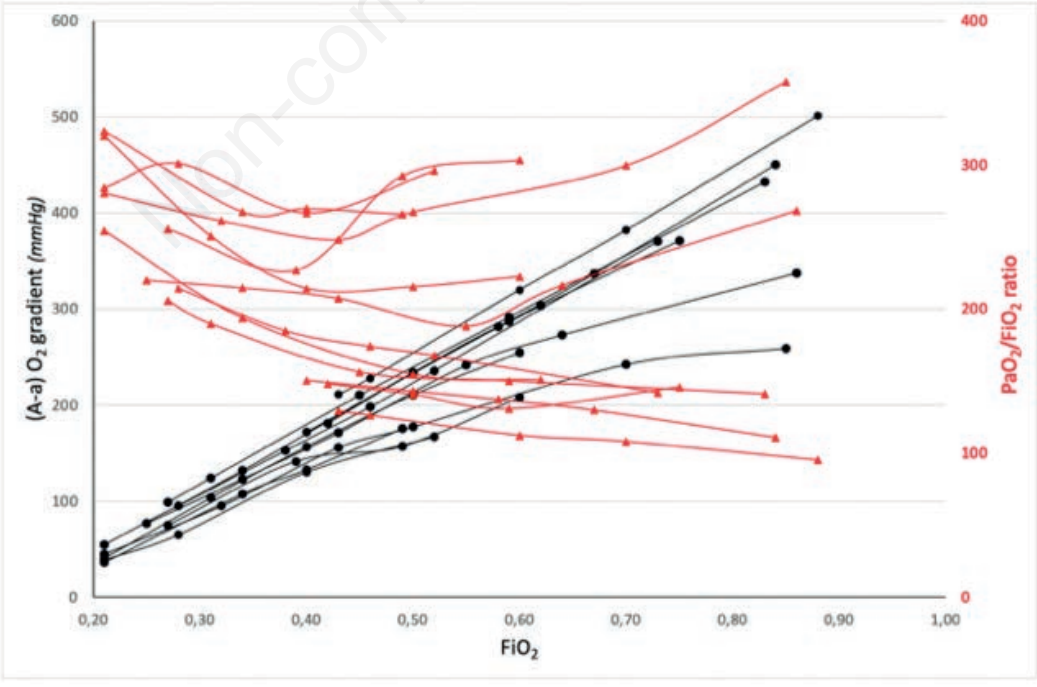

Figure 1. Relationship between (A-a) O_2 gradient, PaO_2/FiO_2 ratio and FiO_2. Black lines, oxygen alveolar-arterial gradient, (A-a) O_2 gradient, at different FiO_2; red lines, PaO_2/FiO_2 ratio at different FiO_2.

ever, mainly in patients with a more severe respiratory failure, we found a progressive decrease of PaO_2/FiO_2 ratio with higher FiO_2. Considering (A-a O_2), we found a uniform tendency with FiO_2 increasing. The steepness of the lines reflects the gas exchange impairment, with a profound dissociation between the calculated alveolar oxygen partial pressure (PAO_2), and the measured arterial oxygen partial pressure (PaO_2). Even in this case, the more severe were the patients, the higher was the slope. These findings are not specific for intrapulmonary shunt, but are compatible with it, and are strengthened by our measurements.

Considering Figure 2, where SpO_2 *vs* FiO_2 are represented, two main considerations can be made. Firstly, when evaluating patients at a fixed SpO_2 in the lower range of normality (*i.e.*, SpO_2 94%), their need of O_2 supplementation is highly variable, ranging between 0.22 and 0.67. This oxygen demand at normal-low SpO_2 reflects the magnitude of respiratory impairment, which consists both of a V/Q mismatch, and shunt. Increasing FiO_2 to high values (*i.e.*, FiO_2 >0.70), the V/Q mismatch contribution becomes gradually negligible, and the behaviour of the curve is mainly shunt-driven. When shunt is significant, and this the case in COVID-19, the increase of FiO_2 leads to a dramatic worsening of all the parameters of gas exchange (Figure 1).

In COVID-19 pneumonia severity indices worsen at high FiO_2, but how can we interpret this phenomenon to obtain information and not to be misled? Wherever possible and feasible, we suggest a non-invasive shunt evaluation. However, taking into account the reduced availability of this method, we suggest a two-point assessment regarding patients' oxygen requirements. The physiologic rationale is the same, *i.e.,* to evaluate the differences in terms of gas exchanges at variable FiO_2. The first evaluation should be at a low SpO_2 value (*e.g.*, 92-94%), providing the actual O_2 requirement to partially compensate both V/Q mismatch, and shunt. The second evaluation, performed at high FiO_2 (*i.e.*, >0.7), gives us information about the magnitude of shunt. The comparison between the two evaluations is the real informative part of the process, allowing to characterize both the amendable (V/Q mismatch contribution), and the fixed (shunt contribution) quote of respiratory impairment. However, considering the pathophysiological design of the study, whether baseline shunt fraction or its changes during hospitalization could have a prognostic role in COVID-19 pneumonia warrants further investigations. From a practical point of view, having clear the patient's respiratory situation, would allow stratifying COVID-19 patients on the basis of their real oxygen requirement, avoiding artifactually low PaO_2/FiO_2 ratio due to shunt and FiO_2 insensitiveness.

In conclusion, not taking into account the FiO_2 insensitiveness in case of shunt, and/or relying on a single evaluation for PaO_2/FiO_2 ratio, especially if carried out at high FiO_2, could lead to an inaccurate judgement of patients' severity, and eventually to an inappropriate intensification of the setting of care.

Abbreviations

(A-a O_2):	alveolar-arterial oxygen gradient;
ARDS:	acute respiratory distress syndrome;
COVID-19:	coronavirus disease 2019;
PAO_2:	Alveolar partial pressure of oxygen;
$PaCO_2$:	Partial arterial pressure of carbon dioxide;
PaO_2/FiO_2 ratio:	partial arterial pressure of oxygen and fraction of inspired oxygen ratio;
$SatO_2$:	arterial hemoglobin saturation of oxygen;
SpO_2:	peripheral capillary hemoglobin saturation of oxygen;
V/Q:	ventilation and perfusion ratio.

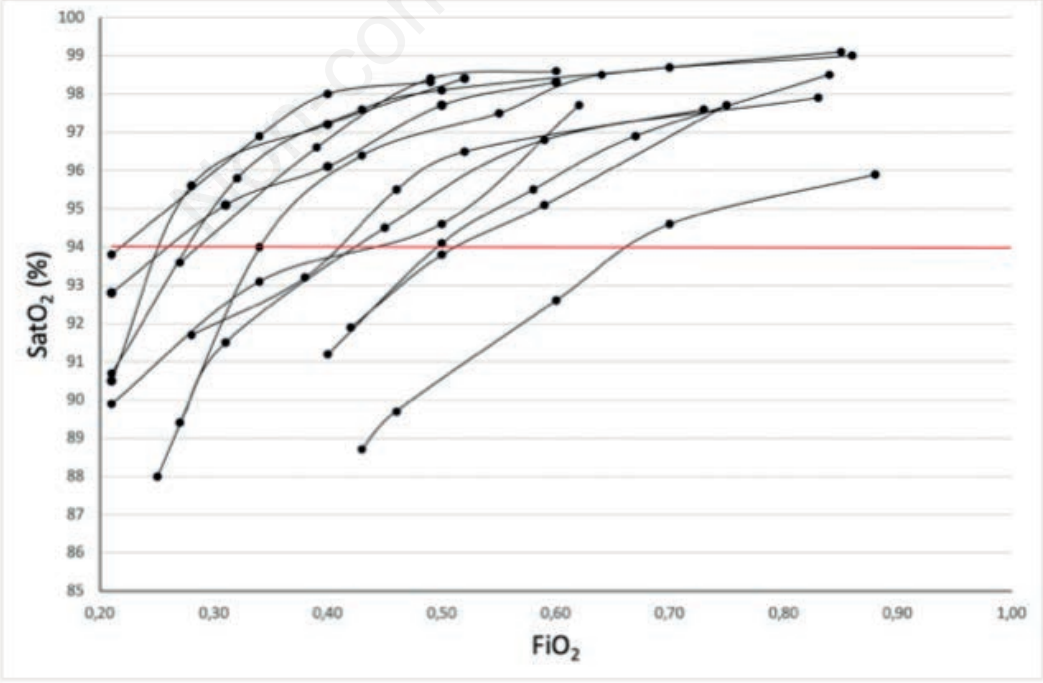

Figure 2. Relationship between $SatO_2$, and FiO_2. The vertical axis represents $SatO_2$, as measured by an arterial blood gas analysis (ABG) when expired gases stability was reached. Red line corresponds to $SatO_2$ of 94%.

References

1. Ferguson ND, Fan E, Camporota L, Antonelli M, Anzueto A, Beale R, et al. The Berlin definition of ARDS: An expanded rationale, justification, and supplementary material. Intensive Care Med 2012;38:1573-82.
2. Gattinoni L, Coppola S, Cressoni M, Busana M, Rossi S, Chiumello D. COVID-19 does not lead to a "typical" acute respiratory distress syndrome. Am J Respir Crit Care Med 2020;201:1299-300.
3. Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F, et al. Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19. N Engl J Med 2020;383:120-8.
4. Schaller T, Hirschbühl K, Burkhardt K, Braun G, Trepel M, Märkl B, et al. Postmortem Examination of Patients with COVID-19. JAMA 2020;323:2518-20.
5. Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, et al. Endothelial cell infection and endotheliitis in COVID-19. Lancet 2020;395:1417-8.
6. Lowenstein CJ, Solomon SD. Severe COVID-19 Is a microvascular disease. Circulation 2020;142:1609-11.
7. Lang M, Som A, Mendoza DP, Flores EJ, Reid N, Carey D, et al. Hypoxaemia related to COVID-19: vascular and perfusion abnormalities on dual-energy CT. Lancet Infect Dis 2020;20:1365-6.
8. Sharma S, Hashmi MF, Burns B. Alveolar Gas Equation. StatPearls; Treasure Island: 2020. Available from: https://www.ncbi.nlm.nih.gov/books/NBK482268
9. Feiner JR, Weiskopf RB. Evaluating pulmonary function: An assessment of Pao2/Fio2. Crit Care Med 2017;45:e40-8.
10. Aboab J, Louis B, Jonson B, Brochard L. Relation between PaO2/FIO2 ratio and FIO2: A mathematical description. Intensive Care Med 2006;32:1494-7.
11. Broccard A. Making sense of the pressure of arterial oxygen to fractional inspired oxygen concentration ratio in patients with acute respiratory distress syndrome. OA Crit Care 2013;1:9.
12. Buoro S, Di Marco F, Rizzi M, Fabretti F, Lorini FL, Cesa S, et al. Papa Giovanni XXIII Bergamo Hospital at the time of the COVID-19 outbreak: Letter from the warfront… Int J Lab Hematol 2020;42:8-10.
13. Novelli L, Raimondi F, Ghirardi A, Pellegrini D, Capodanno D, Sotgiu G, et al. At the peak of Covid-19 age and disease severity but not comorbidities are predictors of mortality. Covid-19 burden in Bergamo, Italy. Panminerva Med 2021;63:51-61.