Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Commentary

Standardised PaO_2/FiO_2 ratio in COVID-19: Added value or risky assumptions?

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The coronavirus disease 2019 (COVID-19) causes acute respiratory failure (ARF) altering the pulmonary microvasculature with simultaneous vasoconstriction and thrombosis in ventilated areas, hyperperfusion [1] and neo-angiogenesis in gasless regions [2]. The progressive derangement of the lung vasculature and parenchyma worsens the shunt fraction and deadspace, and consequently hypoxaemia and hypercapnia.

Traditionally, PaO_2 normalised for FiO_2 (PaO_2/FiO_2 ratio) reflects the severity of the oxygenation defect and given its simplicity, it is the *de-facto* standard for the classification of ARDS severity as it correlates with mortality predictions [3]. However, PaO_2/FiO_2 ratio presents several limitations: it is not linearly related to the set FiO_2 (i.e., the same patient may have different PaO_2/FiO_2 at different FiO_2) [4]; it is influenced by cardiac output and by the mean airway pressure [5]. A key additional limitation is that PaO_2/FiO_2 does not reflect the compensatory mechanisms induced by hypoxia, such as the minute ventilation resulting from increased respiratory effort. The respiratory effort when excessive may be responsible for the Patient Self-Inflicted Lung Injury (P-SILI) exacerbating the respiratory failure [6,7]. Moreover, a significant proportion of patients with COVID-19 have high respiratory drive and effort without reporting dyspnoea or air hunger (the so-called "silent hypoxaemia") [8]. The only sign of increased minute ventilation is hypocapnia and – in a later stage – increase in respiratory rate. Therefore, it seems meaningful that, to thoroughly evaluate the derangements of gas exchange, also the arterial carbon dioxide tension ($PaCO_2$) should be considered. Therefore, attempting to adjust PaO_2/FiO_2 for $PaCO_2$ may potentially help discriminating patients at higher risk of death or intubation.

Prediletto et al. [9] studied 349 patients with ARF due to COVID-19 admitted to the respiratory ward. The authors suggest that standardising PaO_2/FiO_2 for $PaCO_2$ ($_{ST}PaO_2/FiO_2$) may better predict the risk of in-hospital mortality compared to the traditional PaO_2/FiO_2. Although $_{ST}PaO_2/FiO_2$ performed relatively better than PaO_2/FiO_2 in predicting in-hospital mortality - given the statistical difference in area under the ROC curve - the difference in performance was clinically trivial (0.71 vs 0.69); and it is unclear whether a similar analysis on mortality using cut-off values in PaO_2/FiO_2 would have resulted in similarly significant differences in outcome. The slight superiority of $_{ST}PaO_2/FiO_2$ can be explained by the fact that 88.5% of patients had $PaCO_2 < 40$ mmHg – in other words, the vast majority of patients were able to increase their minute ventilation enough to induce hypocapnia. Also, their high work of breathing or deadspace was not appreciated, as most of these patients were on standard oxygen, and only 11% received non-invasive support.

On a more conceptual level, the formula used to standardise PaO_2/FiO_2 for $PaCO_2$ ($_{ST}PaO_2/FiO_2$) represents the relationship between the tension of the two gases and it is used to predict the PaO_2 given a measured $PaCO_2$ [10]. The limitations of the study may be better understood when considering the factors in the formula implemented by Prediletto et al. to "standardise the PaO_2/FiO_2 ratio" (Eq. (1)).

$$stPaO_2 = PaO_2 + (1.66 \times PaCO_2 - 66.4) \quad (1)$$

The difference between the *standardised* and the actual $PaO_2$is a sort of "PaO_2 deficit" when accounting for hypocapnia, and it is equal to zero when $PaCO_2$ is 40 mmHg (as the factors within parenthesis in Eq. (1) are equal to zero) and it is *less* than zero when $PaCO_2$ is < 40 mmHg. Indeed, this formula is based on a series of assumptions: (1) that the arterial $PaCO_2$ is equal to the alveolar PCO_2 ($PACO_2$); (2) that alveolar PO_2 is calculated through the alveolar gas equation (Eq. (2)) using a respiratory quotient (RQ) equal to 0.6 (given that 1.66 is equal to 1/RQ when RQ=0.6; 3) the term 66.4 is simply obtained multiplying a *standard* $PaCO_2$ of 40 mmHg by 1.66.

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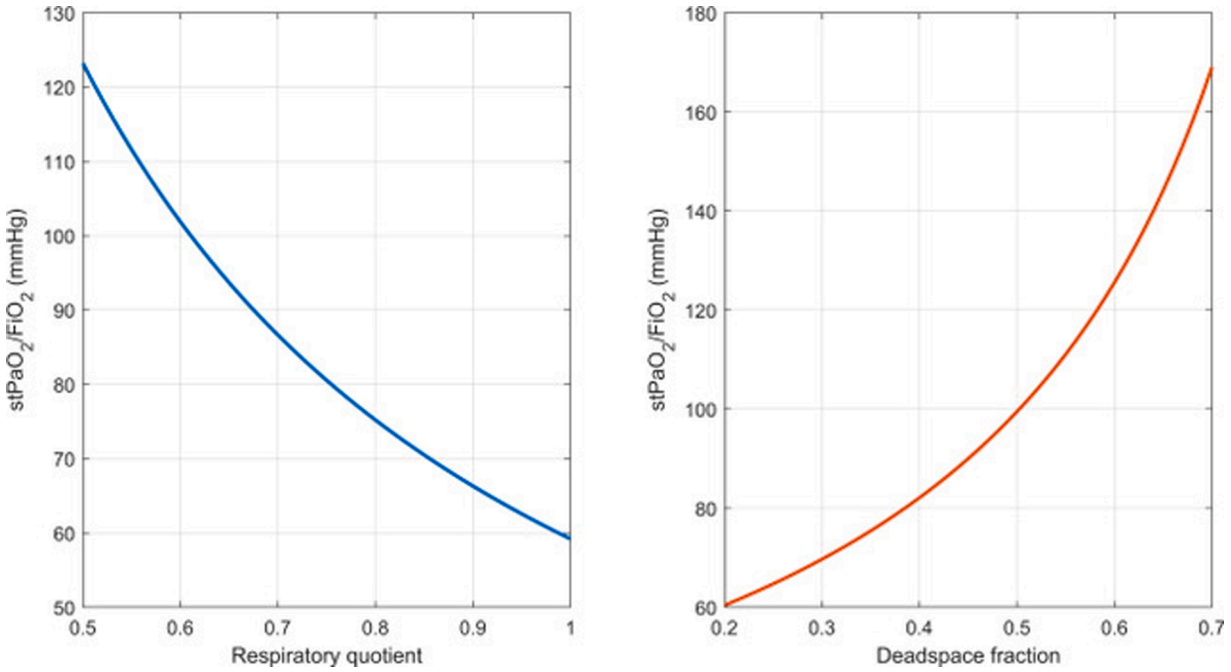

Fig. 1. Effects of varying respiratory quotient or arterial tension of carbon dioxife on standardised PaO_2/FiO_2 ratio. Panel A: $_{ST}PaO_2/FiO_2$ at varying respiratory quotient (RQ) while maintaining constant the measured PaO_2 and $PaCO_2$ (in this case equal to the mean values recorded in the original study, i.e., PaO_2 = 64 mmHg, $PaCO_2$ = 32 mmHg). Panel B: $_{ST}PaO_2/FiO_2$ at varying deadspace fraction while maintaining constant the measured PaO_2 (64 mmHg), VCO_2 (assumed to be 200 ml/min) and minute ventilation (respiratory rate equal to the mean values recorded in the study, i.e., 22 bpm and tidal volume assumed to be 500 ml).

$$PAO_2 = P_{Barometric} \times FIO_2 - \frac{PaCO_2}{RQ} \quad (2)$$

As it is clear from these two equations and the underlying assumptions, this "oxygen deficit" is significantly affected by the changes in RQ. In Fig. 1A, we show how modifications in RQ will affect the calculated $_{ST}PaO_2/FiO_2$ (assuming a constant PaO_2 and FiO_2). Therefore, a calculation of RQ is crucial in this computation. Moreover, this PaO_2-$PaCO_2$ relationship may be helpful – as the authors suggest - early in the disease process before respiratory failure and hypoxaemia are fully manifest, or if hypercapnia is due to hypoventilation. However, with worsening in severity of lung pathology – suggested by an increase of deadspace [11] - this methodology may become misleading. In these cases, the $PaCO_2$--$PaCO_2$ slope may shift along the PaO_2 axis or change due to increasing ventilation/perfusion inequalities [10].

The validity of the method may therefore be meaningful in the specific phase of the disease studied by the authors and the $_{ST}PaO_2/FiO_2$ should be interpreted with caution when tracking over time patients with worsening dead space or shunt fractions (transitioning from hypocapnia to hypercapnia despite constant or even increased minute ventilation). Indeed, in Fig. 1B we show what happens to the $_{ST}PaO_2/FiO_2$ when deadspace increases with constant CO_2 production (VCO_2) and minute ventilation: $_{ST}PaO_2/FiO_2$ *paradoxically* improves, while the lung condition deteriorates. This is even more relevant in COVID-19, given the high incidence of pulmonary perfusion abnormalities [12] resulting in peculiar alterations of the distribution of the ventilation-perfusion ratio [13]. However, the study reminds us that an increased minute ventilation - and hypocapnia - is a sign of severity and it has a pathogenetic role in the worsening in ARF (P-SILI). We find, however, the use of this index debatable: other indices have been used to account for the effects of respiratory effort on the PaO_2/FiO_2 ratio, such as the ROX index [14,15]. Also, we believe that the calculation of alveolar-arterial oxygen gradient (AaO_2) may be more suited for this purpose, as it is a physiological entity including all the elements of the alveolar gas equation.

In conclusion, despite the limitations, the study highlights that respiratory effort is an important determinant of mortality and needs to be taken into consideration in the assessment and triage of the patients with COVID-19 ARF.

The standardised parameter put forward, however should be interpreted with caution when following the time course of patients with unpredictable lung parenchymal derangements.

Declaration of Competing Interest

The authors have declared that no conflict of interest exists.

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