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CORRESPONDENCE

Complexity and unanswered questions in the pathophysiology of COVID-19 ARDS

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We welcome the correspondence by Jha [1] who invites further elaboration on the findings reported in our manuscript [2]. In responding, it is well to keep in mind that the simplifications of classical physiology which often are helpful in other settings may give rise to misconceptions regarding the pathophysiology and observed behaviours of acute distress respiratory syndrome (ARDS) related to coronavirus disease 2019 (COVID-19).

Recent radiological studies using dual energy computed tomography (CT) scan and iodine maps have shown extensive heterogeneity in ventilation/perfusion mismatching, ranging from dead space, due to poor perfusion of ventilated lung parenchyma (as Dr Jha alludes to in the letter), to shunt due to increased perfusion in poorly or non-aerated lung regions [3].

Similarly, the dead space of COVID-19 pneumonia is not just due to microthromoboses—although these are much more prevalent than ARDS from other etiologies—but also to dysregulation of pulmonary perfusion, without overt thrombosis [4]. Therefore, shunt fraction and venous admixture is a composite element which derives from variable non-aerated lung tissue mass and neovascularisation in these regions, which further increases the perfusion in non-aerated lung [5]. The combination of these phenomena is reflected in the weak relationship between the quantity of non-aerated lung and observed venous admixture, and consequently hypoxaemia.

With these considerations in view, we are compelled to take serious issue with the flawed arguments posited by Jha regarding gas exchange in COVID-19. While we agree that the net effect on hypoxemia depends on a multitude of factors, large shunts are—by definition—refractory to inspired oxygen and to increases in minute ventilation. What is more, the alterations of respiratory drive in COVID-19 are complex and not necessarily due to absolute levels of hypoxaemia; many patients experience high levels of respiratory drive even when hypoxaemia is mild or corrected. It stands to reason, therefore, that the hypoxaemic stimulus is physiologically unlikely to cause high drive per se, nor is increased ventilation able to compensate for hypoxaemia (or improve the dead space fraction). This would seem self-evident, given the rather high number of patients requiring respiratory support. In addition, however desirable they might be, accurate and reproduceable measurements of lung mechanics and CT characteristics under standardised conditions are difficult to obtain in spontaneously breathing patients.

However, Jha is correct in saying that ventilation settings may influence ventilatory ratio [6], dead space and PaO_2/FiO_2 ratio. We note that this concern is an issue with all ARDS studies. The many interesting questions Jha raises, however, cannot be easily answered by any single study. Patient populations are inherently heterogeneous, both in terms of pathophysiology and timing of presentation; moreover, matching patients using certain variables of interest may pose insurmountable methodological challenges and limitations. We do hope, however, that our results have generated enough interest to stimulate further research into the complex pathophysiology of COVID-ARDS (CARDS).

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Compliance with ethical standards

Conflicts of interest
The authors have no conflict of interest to declare.

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