Hypoxaemia in COVID-19: many pieces to a complex puzzle

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Reply to G. Harutyunyan and co-workers:

We read with interest the comments from G. Harutyunyan and co-workers on our coronavirus disease 2019 (COVID-19) pathophysiology review [1]. Without doubt we recognise that new data emerge every day and present knowledge must be reassessed in the face of new evidence. In this regard, the authors dive deep into the putative effects of pathological changes in the oxygen–haemoglobin dissociation curve (OHDC) as an additional cause of hypoxaemia in COVID-19. While interesting, this aspect is not completely new. Indeed, since the early days of COVID-19 some authors have speculated over the very same issue and conducted clinical and preclinical studies. Renoux *et al.* [2], for example, described no changes in the OHDC between seven COVID-19 patients and 14 comparable matched non-COVID-19 (control and septic) subjects. The findings of Daniel *et al.* [3] are along the same line: no change in the OHDC. Gille *et al.* [4] published a larger study on 100 COVID-19 patients and also found no deviation of the P_{50} (the partial pressure of oxygen at which haemoglobin is 50% saturated) in COVID-19. The largest study (3518 patients) by Vogel *et al.* [5] even found a left shift (increased affinity) of the OHDC with a P_{50} of 23.4 mmHg. Therefore, we are quite confident to say that the theory of haemoglobin with altered oxygen affinity is not significant enough to be responsible for the severity of hypoxaemia seen in patients with COVID-19.

Nevertheless, the pathophysiology of hypoxaemia in COVID-19 still has some secrets that are waiting to be revealed. We published a computational study showing that even an extreme degree of ventilation–perfusion mismatch is *per se* not sufficient to completely explain the hypoxaemia [6]. It is therefore likely that other mechanisms, or a combination of mechanisms, play a role. Interestingly, some recent evidence coming from autoptic studies show, among the other mechanisms, openings of intrapulmonary bronchopulmonary anastomosis [7, 8] that may well be the source of intrapulmonary shunt not associated with lung parenchymal consolidation. Moreover, the pathological enlargement of COVID-19 pulmonary vessels would cause an increase in oxygen equilibration time within the capillary, a phenomenon commonly called “diffusion limitation”. We believe that only through a rigorous measurement of ventilation–perfusion distribution, we may deepen our understanding of the problem and close the circle, explaining why in COVID-19 the degree of lung consolidation is often not proportional to hypoxaemia severity.

Shareable abstract (@ERSpublications)
Hypoxaemia from COVID-19 is likely a consequence of multiple causes https://bit.ly/3yXCJGZ

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