Hypoxaemia in the early stage of COVID-19: prevalence of physical or biochemical factors?

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To the Editor:

We read with interest the reply from Busana *et al.* [1] to our correspondence [2]. We fully agree with the authors and with the cited references [3–6] stating that the affinity of haemoglobin (Hb) for oxygen (O_2) is not affected in the arteries or in the veins of coronavirus disease 2019 (COVID-19) patients. The confusion arises as our concept is based on the biochemical shunt due to the quaternary conformational change of Hb with a temporary decrease of Hb–O_2 affinity, which is applicable only to the affected alveolar-capillary bed.

In our previous article [7], we have answered Daniel *et al.* [4] detailing the physiological feasibility of substantial changes in Hb–O_2 affinity in the microcirculatory bed according to the overload of Hb by metabolites. That is, the oxyhaemoglobin dissociation curve (ODC) in arterial or venous blood is different from the ODC in the capillary blood. In addition, the same article explains the impotence of the ODC assessment technique using a Hemox Analyzer (TCS Scientific, New Hope, PA, USA).

To assess the effectiveness of a source in generating of hypoxaemia in COVID-19 patients, our group recommends observing the changes in O_2 and carbon dioxide (CO_2) gases at the same time in the alveolar-capillary bed: any physical shunt (*i.e.* opening of intrapulmonary or bronchopulmonary anastomosis, lung parenchymal consolidation, *etc.*) that rules out contact between blood and respiratory gas can explain a high gap between arterial carbon dioxide tension (P_{aCO_2}) and end-tidal carbon dioxide tension (P_{ETCO_2}), but it cannot explain the full recovery of blood oxygen saturation especially in the initial phase of COVID-19. Similarly, the pathological enlargement of alveolar capillaries can affect O_2 balance, but it will not cause a marked increase in the P_{aCO_2}–P_{ETCO_2} gap due to the high solubility of CO_2. From this point of view, the ventilation–perfusion mismatch can cause marked hypoxaemia, but it cannot cause a significant P_{aCO_2}–P_{ETCO_2} gap [1].

Interestingly, in a large multicentre study, Lazzari *et al.* [8] presented data on prospectively collected baseline characteristics in a cohort of 26 patients and data on a retrospective clinical cohort (n=638) of mechanically ventilated adults with non-COVID-19 related severe acute respiratory distress syndrome receiving veno-venous extracorporeal membrane oxygenation. It was found that a P_{aCO_2}–P_{ETCO_2} gap existed equal to 6.6 mmHg and 8.55 mmHg, respectively. For comparison: in L type COVID-19 patients the P_{aCO_2}–P_{ETCO_2} gap reaches 20.6 mmHg [9]; moreover, in critically ill COVID-19 patients this gap is at very high levels ∼33 mmHg [10]. Busana *et al.* [11] reported a P_{aCO_2}–P_{ETCO_2} difference of 15 mmHg in patients with COVID-19 who surprisingly achieved acceptable levels of arterial oxygenation with hyperoxia.

On the assumption that one can confirm that the ventilation–perfusion mismatch can't explain the high P_{aCO_2}–P_{ETCO_2} gap in the setting of COVID-19 induced hypoxaemia and cannot be considered as the sole pathophysiological basis for the treatment in the early stage of COVID-19, we discussed the prevalence of the biochemical shunt in the initial phase of COVID-19, which helps to explain the simultaneous changes in O_2 and CO_2 in the affected alveolar-capillary bed.

Shareable abstract (@ERSpublications)
The ventilation–perfusion mismatch can't explain the high P_{aCO_2}–P_{ETCO_2} gap in the setting of COVID-19 induced hypoxaemia and cannot be considered as the sole pathophysiological basis for the treatment in the early stage of COVID-19 https://bit.ly/3BKmGxJ

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Gurgen Harutyunyan[1], Rosa Isabel Benítez Bermejo[2], Varsenik Harutyunyan[3], Garnik Harutyunyan[3], Andrés Sánchez Gimeno[4], Artur Cherkezyan[5], Spartak Petrosyan[6], Anatoli Gnuni[6] and Suren Soghomonyan[7]

[1]Hospital 9 de Octubre, Urgency Department, Valencia, Spain. [2]Hospital General Universitario de Valencia, Valencia, Spain. [3]Universitat de València Facultat de Farmacia Valencia, Valencia, Spain. [4]Hospital 9 de Octubre, Valencia, Spain. [5]Erebouni Medical Center, Yerevan, Armenia. [6]Ministry of Health of the Republic of Armenia, Yerevan, Armenia. [7]The Ohio State University Wexner Medical Center, Columbus, OH, USA.

Corresponding author: Gurgen Harutyunyan (varsenik@hotmail.es)

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