Ventilation/perfusion mismatch is not the sole reason for hypoxaemia in early stage COVID-19 patients

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To the Editor:

It was a pleasure reading the work of Gattinoni *et al.* [1] dedicated to the pathophysiological mechanisms of hypoxaemia observed in coronavirus disease 2019 (COVID-19) patients. The authors recommend treating the hypoxaemia observed in the early stages of COVID-19 based on ventilation/perfusion (V'_A/Q') mismatch.

According to the laws of physics, increasing fractional concentration of oxygen in inspired gas (F_{IO_2}) can increase arterial blood oxygen saturation (S_{aO_2}) in case of V'_A/Q' <1. Also, it should be recognised that oxygen, as an important homotropic allosteric effector, favours the stabilisation of the quaternary R (relaxed) state of haemoglobin (Hb) allowing for an increase in S_{aO_2} by a positive feedback mechanism (binding of oxygen to Hb facilitates binding of new oxygen molecules). These biochemical processes may improve the S_{aO_2} in patients with decreased Hb–O_2 affinity in alveolar capillaries without any V'_A/Q' mismatch. Therefore, in cases of "happy" hypoxia or silent hypoxaemia, an exaggerated increase in S_{aO_2} with minimal hyperoxia may take place due to the allosteric effects of oxygen rather than V'_A/Q' maldistribution. Also, a high level of oxygen dependency is commonly seen in all stages of COVID-19 with frequent use of high F_{IO_2} without of development of atelectasis in the hypoventilated areas of the lungs, which also can't be explained by the V'_A/Q' mismatch.

A discussion of CO_2 gas exchange mechanisms will further clarify the course of events resulting in hypoxaemia in COVID-19 patients. The remarkable increase in tidal volume in a patient with COVID-19 can be understood from the biochemical point of view: elimination of CO_2, which is a strong heterotropic allosteric effector, will result in stabilisation of Hb's R state and assists its complete oxygenation.

As we know, during hypoventilation, the gases are balanced in the alveolar-capillary space. Hence, a decreased V'_A/Q' ratio will result in a higher alveolar (P_{ACO_2}) and arterial carbon dioxide tension (P_{aCO_2}), but won't change the P_{aCO_2} and end-tidal carbon dioxide tension (P_{ETCO_2}) gap [2]. Also, due to the low resistance to diffusion of CO_2, P_{aCO_2}–P_{ETCO_2} gap is maintained unchanged in cases when patients have oxygen diffusion limitations [3].

Surprisingly, COVID-19 patients may achieve a high P_{aCO_2}–P_{ETCO_2} gap, sometimes exceeding the predicted cut-off values of mortality in non-COVID-19 acute respiratory distress syndrome (ARDS) patients (*i.e.* 10–15 mmHg) [4]. Observing the data presented by Viola *et al.* [5] in type L COVID-19 pneumonia patients, we have found a median P_{aCO_2}–P_{ETCO_2} gap for supine position of 20.6 mmHg and 14.9 mmHg for prone position. Busana *et al.* [6] reported a P_{aCO_2}–P_{ETCO_2} gap of 15 mmHg in COVID-19 patients who need a high F_{IO_2} to maintain S_{aO_2}. In critically ill COVID-19 patients, as presented by Chen *et al.* [7], the P_{aCO_2}–P_{ETCO_2} gap is reached at very high levels of 33 mmHg (18–40 mmHg).

So, considering excessively high levels of the P_{aCO_2}–P_{ETCO_2} gap in COVID-19 patients, excluding important right-to-left shunt and massive microthrombosis as a possible cause of huge dead space (pulmonary microthrombi were reported in 57% of COVID-19 autopsy cases) [8], one may not conclude that the main cause of hypoxaemia is solely a V'_A/Q' mismatch.

Shareable abstract (@ERSpublications)
The transformation of alveolar microcirculation to a peripheral circulation type in COVID-19 patients leads to important decreases in haemoglobin–oxygen affinity and provokes biochemical shunt https://bit.ly/3jE53pe

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We believe that the main cause of hypoxaemia in COVID-19 patients is the decrease in Hb–O_2 affinity in the affected alveolar-capillary bed [9] due to the decrease in the Hill coefficient (n), a measure of cooperativity in a binding process. This process usually occurs in non-alveolar capillaries and it is more accentuated in the cerebral microcirculation [10]. Normobaric hyperoxia in apparently healthy tissue leads to a dramatic elevation of brain oxygen partial pressure to levels up to 147±36 mmHg, but an increase in regional cerebral oxygen saturation assessed by near-infrared spectroscopy is negligible (2.8±1.82%) and within the venous blood oxygen saturation range [11]. Thus, it is possible to encounter situations with venous levels of blood oxygen saturation and a coexisting high oxygen tension in the microcirculation.

According to our concept, the transformation of alveolar microcirculation to a type of peripheral circulation in COVID-19 patients leads to important decreases in Hb–O_2 affinity. Additional oxygen concentration and/or hyperventilation are required to fully oxygenate the haemoglobin in the affected areas of the lungs through stabilisation of Hb in its R state.

Other measures that may increase Hb's oxygen affinity will also improve the oxygenation values, such as transfusion of red blood cells (decreasing 2,3-diphosphoglycerate concentration with stabilise Hb in the R state), increases in the concentration of carboxyhaemoglobin, 5-hydroxymethylfurfural, *etc.* [9].

In mild and moderate COVID-19 cases, when the Hill coefficient is $1<n<2.7$, an increase in F_{IO_2}, elimination of CO_2 by hyperventilation, as well as application of dead space washout, will stabilise the R state of Hb. More problems occur when $n\leqslant 1$: the Hb will change its quaternary state from R to T, which has a very low Hb–O_2 affinity and the highest buffer capacity (*i.e.* it contains a high amount of CO_2 and protons) [12].

As a result of decreased Hill coefficient, a biochemical shunt will be created: Hb will become much less saturated with oxygen and won't release enough CO_2. The blood from the affected capillaries, after mixing with the blood from normal capillaries, will restore the Hb's R state with a subsequent release of CO_2 and a significant increase in the P_{aCO_2}–P_{ETCO_2} gap without any true shunt or dead space.

V'_A/Q' mismatch cannot be the only cause of hypoxaemia in COVID-19 patients. For treatment, it is also important to take into account the Hb's oxygen affinity and the presence of the biochemical shunt in the alveolar-capillary bed.

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