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Short Commentary

Clinical Considerations on the Potential Interaction between SARS-Cov-2 and Hemoglobin

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SARS-CoV-2 is a new virus that appeared in China at the end of last year [1], and has recently caused a pandemic outbreak worldwide. The infection of SARS-CoV-2 causes CoVid-19 disease and a significant portion of patients develop lung involvement that combines elements of pneumonia, inflammatory cytokine storm and alterations in the pulmonary circulation [2, 3]. All these abnormalities can lead to hypoxemia, which is sometimes very severe, and even to the development of an Acute Respiratory Distress Syndrome (ARDS) [4]. The diagnosis and management of these processes implies the periodic obtaining of arterial blood gases to adapt oxygen supplementation to the needs of the patient. In the most severe cases, the use of invasive or non-invasive ventilator support may also be necessary. Partial pressure of oxygen in arterial blood (PaO_2) is the variable commonly used in clinics to assess the level of hypoxemia, as well as the index that relates this parameter to the inspiratory fraction of oxygen received by the patient (PaO_2/FIO_2), currently known as PaFi [5]. This was described approximately half a century ago and allows the grading of the severity of the disease in ARDS patients receiving oxygen supplements, although it has also been used in assessing the level of hypoxemia in other entities [6, 7]. However, the use of PaO_2 as the main oxygenation index is based on the fact that its relationship with the oxygen saturation of hemoglobin (SaO_2) is quite predictable under normal circumstances. This relationship takes the form of an italic 'S' and shows that in the intermediate part of the curve even small decreases in PaO_2 have important consequences in SaO_2, which in turn conditions a deficiency of oxygen supply to the tissues. This is due to the fact that approximately 95% of oxygen circulates bound to hemoglobin [8], and only a very small portion does so dissolved in plasma. Although the relationship between PaO_2 and SaO_2 may vary somewhat in clinical circumstances, depending on factors such as the partial pressure of CO_2 in arterial blood ($PaCO_2$), acid-base balance or temperature, it is generally accepted that they are minor changes with relatively little impact on patient status and management.

As previously mentioned, the main oxygen carrier in blood is hemoglobin, a complex molecule of 54 kD formed by four subunits or groups called 'heme', consisting of a porphyrin with an iron atom (Fe), attached to a globin. The Fe ion in particular is the hemoglobin element capable of reversibly binding to oxygen.

A very recent and controversial study using *in silico* methodologies has shown that certain proteins of the SARS-CoV-2 virus, such as ORF8, would be able to interfere with the Fe to oxygen binding (figure 1) [9]. Moreover, other viral proteins (orf1ab, ORF3a and ORF10) could directly destroy the heme group, and therefore hemoglobin, by releasing the Fe ion, with similar pathophysiological consequences [9]. These results would tally with the fact that many CoVid-19 patients show a reduced amount of hemoglobin in their blood [10], a finding that is associated with an increase in serum

ferritin (perhaps to buffer Fe ions released from destroyed hemoglobin) [11], and inflammatory markers [12].

From viral and immunological levels, iron is crucial for viral replication and many viruses can directly disrupt iron homeostasis [13]. However, whether this holds true also for SARS-CoV-2 needs experimental evidence. Moreover, on the one hand macrophages play a pivotal role in the regulation of iron homeostasis by preventing the release of hemoglobin from red blood cells. On the other, an excess of heme can act as an alarmin to activate the innate immune system and induce a pro-inflammatory polarization in macrophages [14, 15]. It is not yet known whether these cells can get productively infected with SARS-CoV-2, but they have been suggested as drivers for the cytokine storm observed in COVID-19 patients [16]. High ferritin levels together with the cytokine profiles observed in severe COVID-19 patients correlate with Haemophagocytic Lympho-Histiocytosis (HLH), a macrophage activation syndrome that leads to the dysregulation of the macrophage function with an excessive immune activation and tissue damage. The potential involvement of some SARS-CoV-2 proteins on disrupting iron metabolism and causing an excessive immune response in the case of COVID-19 needs to be taken with caution but raises interesting questions that exceed the clinical setting.

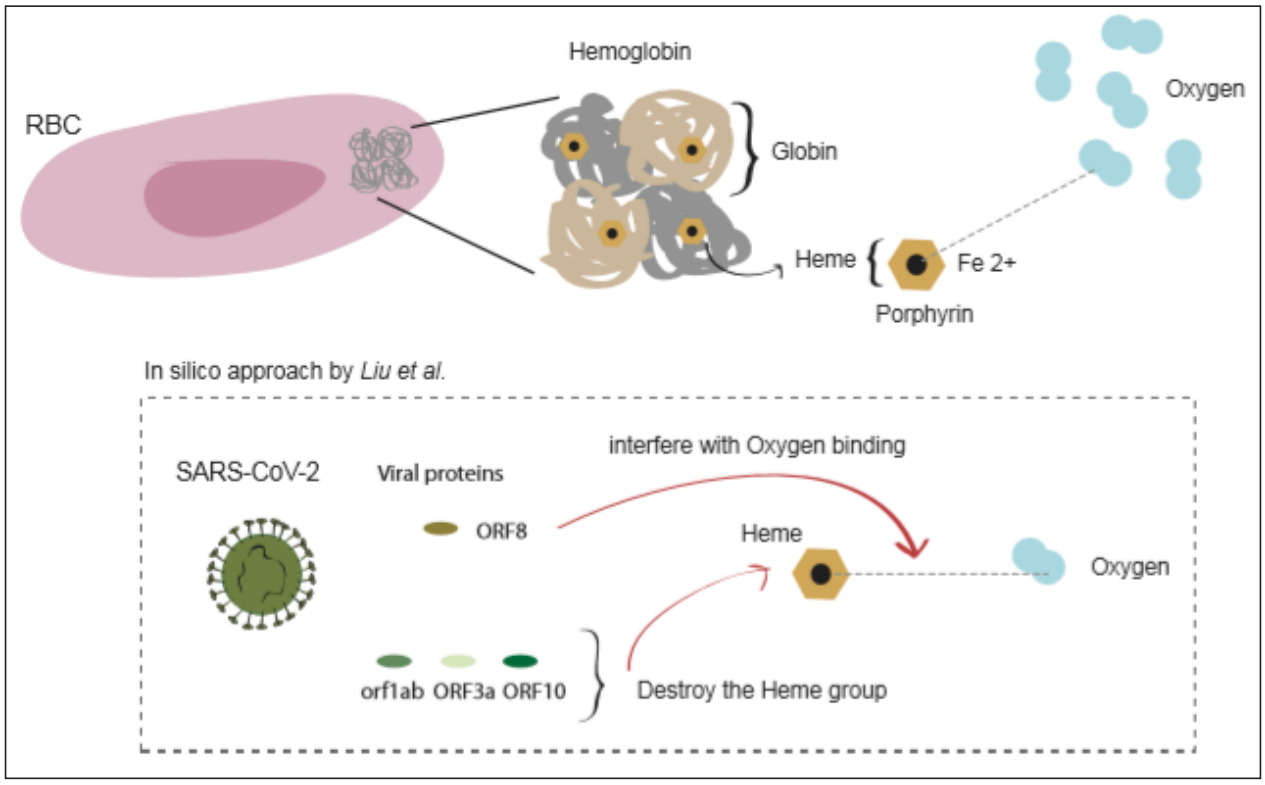

Figure 1: Graphical representation of the interactions between viral proteins and the hemoglobin molecule (see the text). Red Blood Cell.

If Liu et al.'s *in silico* approach is confirmed *in vivo* it could have important consequences in the management of CoVid-19 patients. Under these circumstances, PaO_2 would no longer be a good indicator of the patient's oxygenation status, as we already know that it occurs for instance in carbon monoxide poisoning, and, as a logical consequence neither would PaFi be appropriate for this purpose. It would be more coherent to use the real value of SaO_2 and its derivative, the SaO_2/FiO_2 index (or SaFi) as oxygenation markers. More controversial would be the use of saturation measured with the oximeter (or SpO_2) for this same purpose [17, 18], since this instrument only gives an approximation to the real SaO_2, which is based on the absorption of light through relatively translucent areas of the patients' body. Fortunately, most blood gas analyzers are today equipped with cooximetry, which allows obtaining the true value of SaO_2. Therefore, the calculations, sometimes erroneous, that were previously

used to calculate the approximate value of SaO_2 (through Kelman subroutine or the Severinghaus nomogram)[8] have been excluded in most care centers.

In conclusion, until further data on the effects of SARS-CoV-2 on the hemoglobin molecule (an essential oxygen transporter to maintain aerobic metabolism) is available, caution should be taken with the weight that clinicians give to PaO_2 and PaFi in patients with CoVid-19. This is especially true if there is an obvious discrepancy between the values of measured PaO_2 and measured SaO_2, since the former could lead to underestimating the severity of the patient's actual blood and tissue oxygenation status.

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