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Opinion paper

Modulation of Hb-O_2 affinity to improve hypoxemia in COVID-19 patients

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SUMMARY

This opinion paper aims at discussing the potential impact of modulating the Hb-O_2 affinity by the nutritional supplement 5-HMF on patients affected by COVID-19. The paper describes the critical role of the oxygen affinity in hypoxemic COVID-19 patients and the potential positive effect of 5-HMF, a compound shown to increase the Hb-O_2 affinity.

1. Introduction and discussion

The oxygen dissociation curve (ODC) describes the dependency of the oxygen saturation on the oxygen partial pressure (PO_2) [1]. With its sigmoid shape, the curve is subjected to right or left shifts, thereby changing hemoglobin-O_2 affinity. An increase in the partial pressure of carbon dioxide (PCO_2), in 2,3-diphosphoglycerate (2,3 DPG) and in temperature as well as a decrease in pH lead to a right-shift of the ODC, decreasing oxygen affinity, and vice versa [1,2]. In hypoxemic conditions, a shift of the ODC can significantly alter arterial oxygen saturation (SaO_2) and consequently arterial oxygen content (CaO_2). With a PO_2 of 60 mmHg, for instance, SaO_2 may be around 81% [1] at a pH of 7.27 (corresponding to a PCO_2 of 60 mmHg according to Siggaard-Andersen nomogram) and normal body temperature (37 °C), or about 90% at a pH of 7.4, 37 °C body temperature and an PCO_2 of 40 mmHg [3]. Assuming a hemoglobin concentration of 12 g/dl, this corresponds to an increase in CaO_2 from 13.0 to 14.5 ml/dl. Further assuming a cardiac output of 6 l/min, the delivery of oxygen (DO_2) increases from 780 to 870 ml/min. This increase in DO_2 by augmenting CaO_2 is equivalent to a DO_2 increase by rising cardiac output by approximately 0.7 l/min. This approximates the effect of low-to medium-dose Dobutamine, a commonly used inotrope [4]. The difference in SpO_2 may even widen with lower PO_2, due to the shape of the ODC, or changes in body temperature, leading to an even greater effect on DO_2 as outlined before.

Coronavirus disease 2019 (COVID-19) is a respiratory tract infection caused by a newly emergent coronavirus [5]. The disease is characterized by symptoms of cough and high fever and causes primarily interstitial lung changes and is characterized by a dissociation between relatively well preserved lung mechanics and the severity of hypoxemia [5]. Intrapulmonary ventilation-perfusion mismatch, probably due to impaired hypoxic vasoconstriction, results in hypoxemic respiratory failure [6]. Oxygen administration via face mask or nasal cannula, high-flow-nasal oxygen or non-invasive ventilation are common first-line interventions to improve oxygenation and dyspnea in these patients [5]. In case of persistent hypoxemia or clinical deterioration, endotracheal intubation and invasive ventilation is required. In mechanically ventilated adults with COVID-19, gentle ventilation with low tidal volume is recommended in order not to further damage the lungs [7,8]. Low tidal volume ventilation often results in hypercapnia, which is tolerated to pH levels as low as 7.2 (permissive hypercapnia) [9]. As outlined above, the consequence of the high PCO_2 and increased body temperature is a shift of the ODC to the right, worsening hypoxemia. In these patients, the PO_2 levels are on the steep part of the ODC, so that a small shift of the ODC may have a large effect on the oxygen affinity and thus on SpO_2. The question arises whether shifting the ODC back to the left would improve oxygenation of COVID-19 patients.

5-hydroxymethylfurfural (5-HMF) is an agent able to shift the oxygen dissociation curve to the left. 5-HMF reduces the P50 (PO_2

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at which 50% of hemoglobin is saturated with oxygen, a parameter indicating the position of the ODC) via allosteric modification of the hemoglobin [10]. Animal studies showed that under severe hypoxia conditions (FiO_2: 5%), 5-HMF increased hemoglobin affinity, preserved systemic O_2 delivery and partially was able to maintain microvascular oxygenation (i.e., by protecting arteriolar and venular vasodilation and blood flow) [10]. In swine exposed to severe hypoxia, 5-HMF treatment decreased P50, improved SaO_2, and mitigated increases in pulmonary artery pressure [11]. Moreover, a recent study indicated that the substance might have cardiac protective properties by inhibiting L-type Ca^{2+} channels [12]. However, not only in animal and in vitro models beneficial effects were reported. 5-HMF was also found to increase the oxygen affinity in healthy subjects exposed to hypoxia and in sickle cell disease patients [13,14]. Additionally, the combined oral intake of 5-HMF and α-ketoglutaric acid increased SpO_2 during cycling exercise at 3500 m in healthy subjects [15]. The oral intake of these 2 substances was also shown to reduce oxidative stress, to increase exercise capacity and to reduce ICU and hospitalization time in patients admitted for lung resection [16]. It is important to mention that these substances are available as nutritional supplements and that no relevance for humans concerning carcinogenic and genotoxic effects have been found for 5-HMF supplementation [17].

This makes 5-HMF a potential therapeutic agent for the treatment of hypoxemic COVID-19 patients. By facilitating oxygen loading and increasing SaO_2, breathing exertion might be reduced. This could delay or even prevent invasive ventilation and hence save valuable intensive care capacity in a crisis like this. In ARDS patients undergoing lung protective ventilation with permissive hypercapnia, a left-shift of the ODC induced by 5-HMF might ameliorate oxygenation by counteracting the hypercapnia effect on the oxygen affinity. On the other hand, a left-shift of the ODC might impair peripheral O_2 unloading, leading to an unchanged cellular oxygen supply despite an increased DO_2. Even though comparability might be questioned, recent data on hypoxic exercise show that a high O_2-affinity and hence enhanced oxygen uptake in the lungs, outweighed deficits in peripheral O_2 unloading [2,18]. Additionally, it was reported previously that in hypoxic conditions O_2 unloading from Hb does not require a right-shift of the ODC [19].

In conclusion, the modulation of hemoglobin-oxygen affinity by 5-HMF might be worth investigating as a potential therapeutic target in hypoxemic respiratory failure, e.g. due to COVID-19.

Conflict of interest

None.

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