Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Clinical Nutrition 39 (2020) 3842

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Letter to the Editor

Reply - Letter to the editor - Nutritional interventions to modulate haemoglobin-oxygen affinity in COVID-19 patients

We read with great interest the letter to the editor by Formenti et al. regarding our recent publication [1]. The authors partly support our proposition to consider drug-induced changes in the hemoglobin oxygen affinity (HbO_2 affinity) as a therapeutic target in COVID-19; on the other hand, some concerns were raised.

Recently, a left-shift of the oxygen dissociation curve (ODC) was shown in critically ill COVID-19 patients [2]. This is an interesting finding, as a decrease in HbO_2 affinity due to the low pH and high PCO_2 levels is expected to occur. Reductions in 2,3-diphosphoglycerate (2,3-DPG), a major contributor to the modification of the ODC, was thus suggested to play a critical role in the observed shift. Unfortunately, to the best of our knowledge, no data on 2,3-DPG concentrations are available in this patient group. We would like to emphasize that adaption to hypoxia (i.e., high altitude exposure) in general is found to increase 2,3-DPG [3,4]. Yet, the acidosis reported in this patient group might actually have reduced its content [4,5]. Overall, we think that the regulative role of 2,3-DPG in a hypoxemic situation such as COVID-19 requires further investigation.

We fully agree that a potential improvement of pulmonary oxygen loading by an increased HbO_2 affinity could result in an impaired oxygen release to the peripheral tissue, as was outlined in our opinion paper. During the passage of the blood through the peripheral capillaries, the blood is acidified mainly by CO_2 derived from metabolic activity [4]. Locally, this may counteract the negative effects of a systemic increase in HbO_2 affinity. Quantifying the overall effect is difficult, but must be addressed before making a final recommendation as to whether an agent that increases oxygen affinity might be beneficial.

Since the optimum degree of an ODC left shift is unknown, in addition to the P50, the Hill coefficient should also be considered. This parameter describes the cooperativity of oxygen binding or steepness of the slope of the ODC. Despite evidence from in vitro experiments that the Hill coefficient, similar to P50, can be changed by several effectors [6], less attention is given to it. The Hill coefficient cannot be measured by blood gas analyzers, thus knowledge about its impact in vivo is scarce. However, changes in the Hill coefficient might ameliorate or deteriorate the balance between improved pulmonary oxygen loading and impaired oxygen unloading in the tissue.

Overall, we agree that the supplementation of 5-HMF in COVID-19 patients needs further investigation. The effect of 5-HMF, the impact of the Hill coefficient and the regulative mechanisms in adaptive HbO_2 affinity increase of COVID-19 patients are worth further investigation, making ODC modification a possible future therapeutic target.

Conflict of interest

The authors declare no competing interests.

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Simon Woyke
Department of Anesthesiology and Intensive Care Medicine, Medical University of Innsbruck, Innsbruck, Austria

Hannes Gatterer*
Institute of Mountain Emergency Medicine, Eurac Research, Bolzano, Italy

Simon Rauch
Institute of Mountain Emergency Medicine, Eurac Research, Bolzano, Italy

Department of Anesthesia and Intensive Care Medicine, "F. Tappeiner" Hospital, Merano, Italy

Mathias Ströhle
Department of Anesthesiology and Intensive Care Medicine, Medical University of Innsbruck, Innsbruck, Austria

* Corresponding author. Institute of Mountain Emergency Medicine, Eurac Research, Hypatiastrasse 2, I-39100, Bolzano, Italy.
E-mail address: hannes.gatterer@eurac.edu (H. Gatterer).

23 October 2020

https://doi.org/10.1016/j.clnu.2020.10.049