Reply to Vogel et al.

Dieter Böning, Wilhelm Bloch, and Wolfgang M. Kuebler

Institut für Physiologie, Campus Mitte, Charité – Universitätsmedizin Berlin, Berlin, Germany and Institut für Kreislaufforschung und Sportmedizin, Deutsche Sporthochschule Köln, Cologne, Germany

TO THE EDITOR: We thank Dr. Vogel and colleagues for their letter (1) in response to our recent review on the oxygen dissociation curve (ODC) in COVID-19 (2). Indeed, we initially became interested in this topic when reading the paper by Vogel et al. (3), which showed a surprising left shift of the in vivo ODC in severe disease with marked anemia. Other investigators had not detected a significant change of the ODC in COVID-19, but only measured in vitro curves in small groups of patients with less anemia. Since it was previously reported that methemoglobin (MetHb) formation may cause a left shift of the ODC (4, 5), we had contacted Dr. Vogel in January 2021 regarding respective measurements in his patients and learned that these data at that time had not been evaluated yet. In our article finally submitted on April 26, 2021, we thus proposed increased levels of MetHb as a potential cause of the ODC left shift in COVID-19 (2). Dr. Vogel’s letter to the editor (1) now clarifies, however, that MetHb is not the underlying cause for the observed effect in the study by Vogel et al. (3). This does, however, not preclude that MetHb may contribute to a left shift of the ODC in other patients with COVID-19, in particular those treated with drugs that favor MetHb formation such as chloroquine and hydroxychloroquine.

As the patients of Dr. Vogel were severely anemic, one would in fact even expect a right shift of the ODC due to an adaptive increase in the concentration of 2,3-bisphosphoglycerate ([2,3-BPG]). Anemia, a frequent complication in SARS-CoV-2 infection, usually causes an increase in [2,3-BPG] in most cases except those with acidosis (reviewed in our article). Astonishingly, we could detect only one publication where 2,3-BPG had been measured in patients with COVID-19 (6). The authors found an increase in a slightly anemic group of patients with COVID-19 compared with a similar group without COVID-19. We contacted the corresponding author (Dr. A. D’Alessandro), who communicated that because of methodological reasons the concentrations are only given in arbitrary units, while the actual absolute concentrations in mmol/L red cells remain unknown. That notwithstanding, it seems fair to conclude that [2,3-BPG] should be increased in patients with COVID-19 given that the concentration was higher relative to the non-COVID control group also suffering from slight anemia in the study by D’Alessandro and colleagues (6).

We searched for other papers with [2,3-BPG] measurements in the past years until we were informed that the test kits are no longer produced, so that only specialized biochemistry laboratories still determine this substance quantitatively. Yet, only measurements of [2,3-BPG] will clarify with certainty whether the reported left shift of the ODC curve in COVID-19 with accompanying anemia (2) is facilitated by a lacking increase of [2,3-BPG] in these patients, or occurs despite elevated [2,3-BPG] by a so far unclear mechanism. A variety of substances that also influence oxygen affinity (e.g., ATP, Cl, La, glutathione) may play a role and should be studied, too. Finally, the role of nitric oxide (NO) should be reevaluated because its binding mechanism to Hb is similar to MetHb formation at high oxygen saturation in the lungs but changes in tissue capillaries (7).

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

D.B., W.B., and W.M.K. drafted manuscript; edited and revised manuscript; and approved final version of manuscript.

REFERENCES

1. Vogel DJ, Formenti F, Camporota L. The increased hemoglobin oxygen affinity in COVID-19. Am J Physiol Lung Cell Mol Physiol. In press. doi:10.1152/ajplung.00280.2021.
2. Böning D, Kuebler WM, Bloch W. The oxygen dissociation curve of blood in COVID-19. Am J Physiol Lung Cell Mol Physiol 321: L349–L357, 2021. doi:10.1152/ajplung.00079.2021.
3. Vogel DJ, Formenti F, Retter AJ, Vasques F, Camporota L. A left shift in the oxyhaemoglobin dissociation curve in patients with severe coronavirus disease 2019 (COVID-19). Br J Haematol 191: 390–393, 2020. doi:10.1111/bjh.17128.
4. Hrinczenko BW, Alayash AI, Wink DA, Gladwin MT, Rodgers GP, Schechter AN. Effect of nitric oxide and nitric oxide donors on red blood cell oxygen transport. Br J Haematol 110: 412–419, 2000. doi:10.1046/j.1355-2149.2000.02203.x.
5. Scholmann F, Restin T, Ferrari M, Quaresima V. The role of methemoglobin and carboxyhemoglobin in COVID-19: a review. J Clin Med 10: 50, 2020. doi:10.3390/jcm10010050.

6. Thomas T, Stefanoni D, Dzieciatkowska M, Issaian A, Nemkov T, Hill RC, Francis RO, Hudson KE, Buehler PW, Zimring JC, Hod EA, Hansen KC, Spitalnik SL, D’Alessandro A. Evidence of structural protein damage and membrane lipid remodeling in red blood cells from COVID-19 patients. J Proteome Res 19: 4455–4469, 2020. doi:10.1021/acs.jproteome.0c00606.

7. Premont RT, Reynolds JD, Zhang R, Stamler JS. Role of nitric oxide carried by hemoglobin in cardiovascular physiology: developments on a three-gas respiratory cycle. Circ Res 126: 129–158, 2020. doi:10.1161/CIRCRESAHA.119.315626.