



## Letter to the Director

### About “Absence of Relevant Clinical Effects of SARS-CoV-2 on the Affinity of Hemoglobin for O<sub>2</sub> in Patients with COVID-19”



To the Director,

The SARS-CoV-2 virus damages the lungs and also the erythrocytes which often results in arterial hypoxia and severe anemia. Both factors typically cause a right shift of the hemoglobin oxygen dissociation curve (ODC) in man due to an increase in the concentration of 2,3-bisphosphoglycerate in the red cells. Consequently oxygen discharge to the consuming tissues is improved but the uptake in the lungs is hindered. Surprisingly, however, investigations in COVID-19 patients detected no changes or even a left shift of the ODC (reviewed in Ref. 1). Notably, COVID-19 effects on the ODC may depend on the severity of the illness: In mechanically ventilated patients with profound anemia<sup>2</sup> a clear left shift was observed. In contrast Gille et al.<sup>3</sup> detected no significant change in less severe cases without marked anemia, although the number of measurements might be too low for a decisive conclusion in our opinion.<sup>4</sup> In the recent publication of Pascual-Guardia et al. in this journal<sup>5</sup> the patients do on average not seem severely ill. Mechanical ventilation is not mentioned and anemia is mostly moderate with mean Hb concentrations of  $13.3 \pm 1.8$  SD g/dl in arterial samples from 139 patients, while unfortunately values are lacking for the 215 patients with venous samples. Notably, the authors did not detect a significant overall change in oxygen affinity but a very large scattering. Specifically, the difference between measured and calculated (from different standard curves) SO<sub>2</sub> in ca. 35 venous samples is larger than two times the standard deviation (approx.  $\pm 6\%$ ), in 22 of these samples the measured values exceed the calculated ones. The latter corresponds to a marked reduction of the standard P<sub>50</sub> by at least 5 mmHg compared to the normal value of approximately 27 mmHg. In view of these large deviations in some patients and the potential effect of disease severity on ODC discussed above, it would be of considerable interest to check whether P<sub>50</sub> depends on changes of the Hb-concentration or other indicators of severe illness (e. g. mechanical ventilation) in this patient cohort. One could expect that the results for critical illness with heavy anemia will be similar to those reported by Vogel et al.,<sup>2</sup> and thus explain the large scatter in the study by Pascual-Guardia et al.<sup>5</sup> In this context it is interesting that erythrocytes with injured membranes can often but not always be detected in lung biopsies from COVID-19 patients (W. Bloch, unpublished results). Without

an intact membrane the intraerythrocytic pH and therefore the oxygen affinity must be increased because of a disappearing Donnan equilibrium. Another cause for a left shift of the ODC in this scenario might be a loss of 2,3-bisphosphoglycerate (2,3-BPG) to the plasma.

A notable drawback of all papers cited here is that 2,3-BPG has not been measured in COVID-19 patients. The likely reason is that formerly used test kits are no longer available. In view of the current pandemic, there is now an urgent need for the reintroduction of 2,3-BPG measurements.

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### Conflict of interests

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Dieter Böning<sup>a,\*</sup>, Wilhelm Bloch<sup>b</sup>, Wolfgang M. Kuebler<sup>a</sup>

<sup>a</sup> *Institut für Physiologie, Campus Mitte, Charité – Universitätsmedizin Berlin, Virchowweg 6, 10117 Berlin, Germany*

<sup>b</sup> *Institut für Kreislaufforschung und Sportmedizin, Deutsche Sporthochschule Köln, Am Sportpark Müngersdorf 6, 50933 Köln, Germany*

Corresponding author.

E-mail address: [dieter.boening@charite.de](mailto:dieter.boening@charite.de) (D. Böning).