

LETTER

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A combination of Bohr and Haldane effects provide a physiologic explanation for the increase in arterial oxygen saturation when a face mask is added to a high-flow nasal cannula in severely hypoxemic COVID-19 patients

Pablo Born and Ricardo Castro*

Dear editor:

We read with great interest the article by Dogani et al. on the potential effect of adding an oxygen mask –without supplemental oxygen– to a high-flow nasal cannula on the improvement of oxygenation, in patients with acute hypoxemic respiratory failure due to COVID-19 [1]. We would like to share some comments considering: (a) the improbability that the oxygenation improvement could be related to a real rise in PaO₂ by the use of a mask (although neither PaO₂ nor pH data were provided), and (b) the lack of a straightforward physiological mechanism for this observation. We think that the explanation for the observed increase in the arterial oxygen saturation (SaO₂) reported was due to a left shift on the hemoglobin dissociation curve, solely under the operation of Bohr and Haldane principles [2, 3].

We propose that an improvement in SaO₂ with a stable PaO₂ came secondary to a rising in arterial pH according to the Bohr effect, or to a displacement of CO₂ bound

to hemoglobin (the carbamino compound) by an increase on blood oxygenation (Haldane) (Figs. 1 and 2), while keeping the arterial CO₂ content relative stable. In fact, final PaCO₂ remained unchanged in the eighteen patients of the study.

If we assume an increase in alveolar ventilation by a more efficient high-flow nasal cannula performance (concurring with the authors on a significant reduction of ambient air entrainment), plasma alkalization came forth naturally: alongside with a ventilatory-driven PaCO₂ decrease, protonated hemoglobin released H⁺ which increased its affinity for O₂ (the Bohr effect), increasing SaO₂ consequently. On the CO₂ metabolic side, this effect shifted the bicarbonate buffer equilibrium towards CO₂ formation from carbonic acid, producing the release of this gas from erythrocytes that resulted in a slight rise in PCO₂. Furthermore, as hemoglobin carried more oxygen, amino group-bound CO₂ became displaced into its dissolved fraction (Haldane effect), all of which induced an increase in PaCO₂ which would match the previous ventilatory PaCO₂ decrease. As a final result, a slight or no major change in PaCO₂ was observed.

Moreover, progressive hypoxemia correction may have produced an adaptive decrease on

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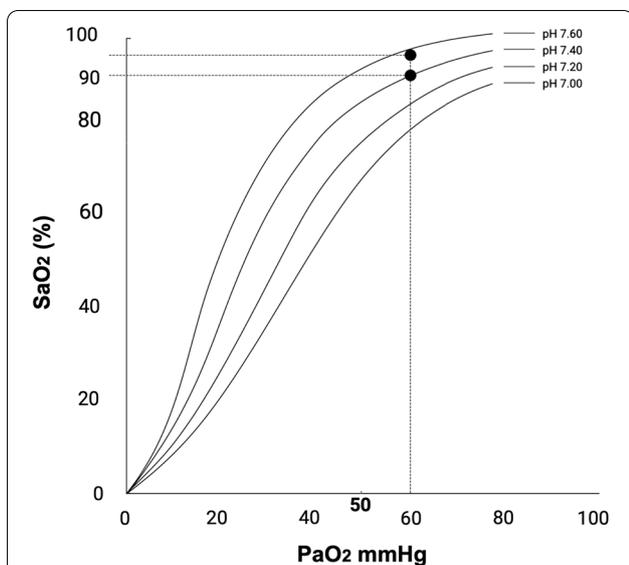


Fig. 1 Hemoglobin dissociation curves according to acid–base status. Figure shows the arterial oxygen saturation (SaO₂) variation (approximate values for the study by Dogani [1]) for a given PaO₂ depending on arterial pH. Note: Figures drawn by Ricardo Castro

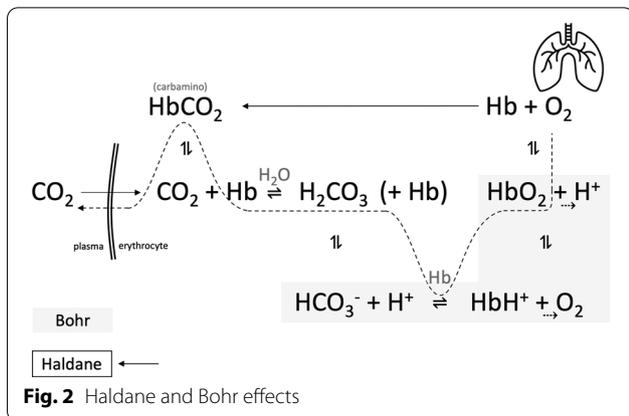


Fig. 2 Haldane and Bohr effects

2,3-diphosphoglycerate which left-shifted the hemoglobin dissociation curve further [4].

We acknowledge that we are presenting a theoretical model attempting to fill the gaps of an objectively documented observation, despite some lacking data. However, the combination of available data with classic physiologic principles provides another explanation for this interesting and clinically relevant phenomenon.

Authors’ response letter

Besarta Dogani, Fredrik Månsson, Fredrik Resman, Hannes Hartman, Johan Tham and Gustav Torisson

Dear editor,

We thank Dr. Born and Dr. Castro for the input on our research letter describing an increased SaO₂ when adding a mask to high-flow nasal cannula (HFNC) in patients with severe COVID-19 [1]. In a well-reasoned argument, Dr. Born and Dr. Castro propose that the increase in SaO₂ may be due to a left shift in the hemoglobin dissociation curve, i.e. an increase in SaO₂ with a stable PaO₂ [5]. To expand the discussion, we would like to provide data regarding PaO₂ and pH, from the arterial blood gases taken at baseline and after 30 min with mask.

In all participants, PaO₂ increased after 30 min, with a mean difference of 3.2 KPa (95% CI 2.2–4.2), equivalent to ~ 24 mmHg (95% CI 16–32), see Fig. 3. This result is in line with the study by Montiel et al., who applied a surgical mask on top of HFNC [6]. In their study, PaO₂ increased in all participants as well, with a mean difference of 20 mmHg (95% CI 13–26). Furthermore, in our study there was a slight decrease in the average pH after 30 min, from 7.480 to 7.471, with a mean difference of – 0.009 (95% CI – 0.018 to – 0.001). Therefore, we consider it unlikely that a left shift in the hemoglobin dissociation curve would fully explain the observed phenomenon.

We hypothesised that the mask could minimise entrainment of room air, especially when mouth-breathing, although we have no data to support this hypothesis. To the best of our knowledge, no studies have measured FiO₂ in COVID-19 patients with HFNC. Studies in healthy volunteers suggest that FiO₂ may decrease upon

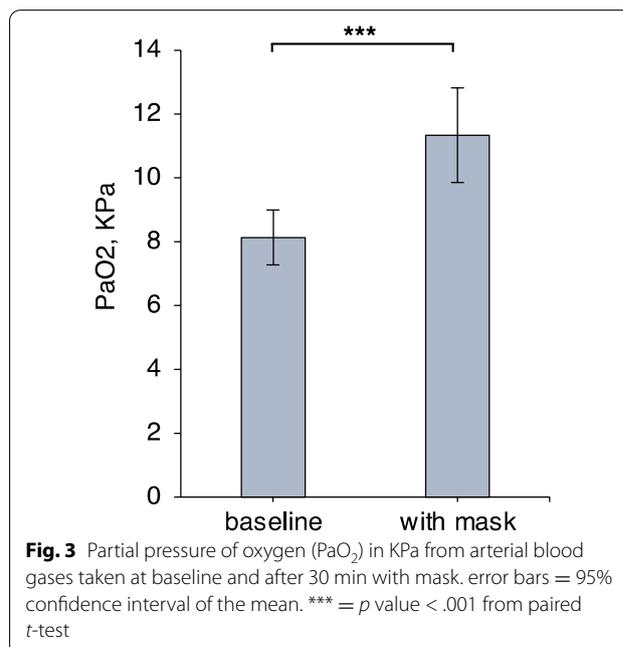


Fig. 3 Partial pressure of oxygen (PaO₂) in KPa from arterial blood gases taken at baseline and after 30 min with mask. error bars = 95% confidence interval of the mean. *** = p value < .001 from paired t-test

mouth-breathing or when exercise was used to simulate respiratory distress [7]. Whether this applies in COVID-19 is uncertain.

It was beyond the scope of our research letter to study the underlying mechanism, and several concurrent processes may contribute. Therefore, we are sincerely grateful for all input in this matter, including that of dr Swenson [8]. Hopefully, further research in oxygen delivery in severe COVID-19 will elucidate this matter.

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Authors' contributions

RC wrote and reviewed the manuscript. RC drawn the figures presented in this manuscript. PB wrote and reviewed the manuscript. All authors read and approved the final manuscript.

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Figures were drawn by the author/RC.

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Not applicable.

Consent for publication

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Competing interests

The authors declare that they have no competing interests.

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