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LETTER TO THE EDITOR

Blood CO_2 exchange monitoring, Haldane effect and other calculations in sepsis and critical illness

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We would like to congratulate the Authors [1] for their interesting study and their effort to progressively determine the dominant factor (pH), among the many factors affecting $P_{cva}CO_2$ and $P_{cva}CO_2/C_{av}O_2$. Indeed, this is important also for clinical practice, because a busy ICU physician may be reluctant to deal with too many symbols, variables and equations, while simpler and well defined final messages are better accepted.

The group of the Authors previously emphasized in another article published in this same journal the importance of the Haldane effect in peculiar conditions (venous hyperoxia) [2]. There, they underscored the importance of the Haldane effect, and in our opinion their conclusions could be reinforced by the significant decrease in central venous pH in hyperoxia, an aspect that was not mentioned in the article. Indeed, another side of the Haldane effect is the O_2-linked H^+ exchange (which is related, although not quantitatively equivalent, to the O_2-linked CO_2 exchange) [3].

With regard to the present article [1] in which the Haldane effect (O_2-linked CO_2 exchange) [4] appears to have a secondary role, we believe that this is consistent with the fact that, with decreasing pH, the magnitude of the Haldane effect becomes smaller [5, 6] and this phenomenon amplifies both the impairment in CO_2 binding capacity of blood associated with low pH, and the widening of $P_{cva}CO_2$ for any given $C_{cva}CO_2$.

Presumably in this study [1] the high median RQ values reflected some still ongoing unsteady state with continuing anaerobic CO_2 production (and perhaps washout of CO_2 accumulated during the shock state). An aspect that we would like to comment regards Figs. 1, 2A and 2B, which show several negative values for the variable in the abscissae, where the difference between $P_{cva}CO_2$ and $C_{cva}CO_2$ (both divided by $C_{av}O_2$) is reported [1]. We are interested in such cases in which $C_{cva}CO_2$ exceeds $P_{cva}CO_2$, and would like to know more about them. In theory this could happen when the blood CO_2 equilibration curve is steeper (low PCO_2, elevated hemoglobin concentration, etc.) and/or with a prominent Haldane component, for instance at low RQ when O_2 exchange largely exceeds CO_2 exchange. In practice this should not be very likely to occur. By exploring the correlations described by the Authors in a partly suitable database of ours (unfit to well assess relationships with outcome) we basically reconfirmed their findings [1] therefore supporting reproducibility of their results. Some negative values were also obtained for the mentioned variable, and these were strictly associated with the smallest $P_{cva}CO_2$ values, and with an estimated Haldane component [6] which was disproportionately greater than the non-Haldane component. Therefore, these negative values seemed to result from the amplification of random approximations which are unavoidable when dealing with small CO_2 exchange and pH quantities, an issue that the Authors well address in their article [1] and with which we have long been familiar [6], also by using mathematical procedures that we deem well suitable also in unsteady state [7]. Only for instance, in a normo-hyperdynamic septic patient, a small measurement error yielding a $P_{cva}CO_2$ of 2.0 instead of 3.0 mmHg is clinically irrelevant, but it represents a 33% error to start with, when this $P_{cva}CO_2$ is used to derive other variables, despite any accurate calculation; moreover, approximations in pH are even exponentially amplified.

For completeness, the endeavor on our database also yielded a significant direct relationship between the mentioned variable and the estimated P_{50}, which was mediated by the changes in pH (it lost significance when tested together with pH in a multiple regression), and a weaker though significant inverse relationship with arterial CO_2 content [6]. This was explained by a tight correlation

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between $CaCO_2$ and blood base excess [8], whose linear approximation was: $BE = 0.46\ (CaCO_2) - 22.56$; $n = 599$; $r = 0.91$; $p < 0.0001$. As obvious as it may appear from the physico-chemical properties of blood and the conceptual/computational similarities between the two variables, this underscores the principle that CO_2 in combined form is the main component of the buffer power of blood [9]. A clinically relevant implication might be that an increase in the variable created by the Authors signaled the association of ongoing anaerobic CO_2 production (with or without simultaneous CO_2 washout from tissues) with the poorest buffer power of blood, a disadvantageous combination which is not so often recognized or emphasized, and needs deeper evaluation. Although our comments are in good part speculative, we may well be wrong and kindly ask the Authors [1] for their opinion, again congratulating them for their very nice study.

Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest.

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