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LETTER TO THE EDITOR

# In response: Blood $CO_2$ exchange monitoring, Haldane effect and other calculations in sepsis and critical illness

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We want to thank Drs. Chiarla and Giovannini for their interest and their insightful comments on our study [1, 2]. We absolutely agree with the conclusion that $P_{cva}CO_2/C_{av}O_2$ reflects not only the ongoing anaerobic $CO_2$ production, but also the buffer power of blood [2], and we congratulate Chiarla and Giovannini for their concise physiological elucidation. We also believe that the combination of these effects is highly responsible for the enhanced prognostic significance of this variable.

In addition to their contribution to a deeper understanding of the magnifying effect of pH on $P_{cva}CO_2/C_{av}O_2$ prognostic value, the Authors emphasize their special interest in several cases where $C_{cva}CO_2/C_{av}O_2$ exceeded $P_{cva}CO_2/C_{av}O_2$. As the authors already comment, over the physiological range of $CO_2$ contents, where the relationship between $CO_2$ content and pressure remains quasi linear, the difference should be close to zero, but some variability could derive from the amplification of slight measurement errors. From a theoretical point of view, $C_{cva}CO_2$ will exceed $P_{cva}CO_2$ in those cases where the proportion of the free form of $CO_2$ is diminished, especially at the venous site, consequently narrowing the central venous-to-arterial $CO_2$ pressure difference, as compared to the $CO_2$ content. Since the decrease in the free form of $CO_2$ depends on pH and oxygen, this phenomenon should be expected in alkalosis and hypoxia situations. Indeed, our observations are in agreement with the effect of pH on this relationship (Fig. 2 of the original study [1]), and it becomes particularly relevant during metabolic acidosis. The effect of profound hypoxia can not be inferred from our data, but hypothesizing that tissue hypoxia would result in lower $P_{cva}CO_2$ as compared to $C_{cva}CO_2$ seems complicated, since in septic shock situations the effect of tissue hypoxia on the hemoglobin-$CO_2$ dissociation curve would not be isolated, and hypoxic conditions would also lead to anaerobic metabolism, causing metabolic acidosis, and therefore causing the contrary effect. Although increased $CO_2$ binding to hemoglobin in hypoxic conditions is a well-known effect that ensures $CO_2$ removal from the tissues (Haldane effect) [3], the shift in the $PCO_2/CCO_2$ relationship as results of metabolic acidosis is also determinant in the buffer capacity of blood, resulting in increased free $CO_2$ for a given $CCO_2$. Of note, as observed with pH, a significant and proportional magnifying effect in our study was observed in situations where hyperoxia was confirmed at the venous site, although this effect was limited in our range of venous oxygenation values.

However, to some extent, our observations are bad news for the clinicians. There are currently an infinity of prognostic variables in severe sepsis and septic shock, but what clinicians demand are variables that will help in taking decisions at the bedside. In the hemodynamic resuscitation process, detecting the oxygen consumption ($VO_2$)/supply ($DO_2$) dependency is crucial in order to decide to further increase oxygen delivery to the tissues. On that behalf, venous-to-arterial $CO_2$ (either content or pressure) to arterial–venous $O_2$ content difference ratios seemed powerful tools to detect the presence of ongoing anaerobic metabolism, with higher performance than lactate not only for anaerobic metabolism detection purposes, but also for short-term changes in response to hemodynamic interventions [4, 5]. Monnet et al. [5] observations reinforced the idea that $P_{cva}CO_2/C_{av}O_2$ could play an important role in the detection of $VO_2/DO_2$ dependency. Regrettably, our results suggest that elevations in $P_{cva}CO_2/C_{av}O_2$ might not only reflect this flow-dependent tissue hypoxia, and therefore, the interpretation of this variable might be much more complex.

To date, we do not dispose of a holy grail for $VO_2/DO_2$ dependency detection at the bedside, and further exploring and understanding the limitations of the few metabolic

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markers we have in our toolbox is still mandatory in order to ensure the appropriate utilization of these variables.

## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no competing interests.

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