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8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242 Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com http://www.wjgnet.com

Name of Journal: *World Journal of Critical Care Medicine*
ESPS Manuscript NO: 21989
Manuscript Type: REVIEW

Dear Editor,

Please find enclosed our revised manuscript entitled " **The use of venous-to-arterial carbon dioxide tension difference to guide resuscitation therapy in septic shock**". We have addressed the Reviewer' comments in the revised version and have included a point-by-point response to the comments. We have checked the format of our references and their accuracy. Changes within the text of the revised manuscript are indicated in red.

We hope that you will find this revised version suitable for publication in *World Journal of Critical Care Medicine*.

Name of Journal: *World Journal of Critical Care Medicine*
ESPS Manuscript NO: 21989

Reviewer's code: 02454185

Comment: This is a timely review to give readers an overview of clinical values of delta-Pa-vCO2 in patients with septic shock. It is generally well written.

Response: We thank the Reviewer for the positive and encouraging comments regarding our review.

Comment: I have several small suggestions for this review.

1.Between the first and second paragraphs of the introduction, there is a transition from SvO2 to ScvO2, but without any specifications. As we all know, the latter is a good substitute of the former, but these two do not measure the same thing. Therefore, some lines specifying that the two have similar clinical meaning should be added.

Response: We agree with the reviewer's comment. We have now added to the introduction (page 5, text in red) some lines as suggested by the reviewer: "Since the measurement of central venous oxygen saturation ($ScvO_2$) can be performed more easily, and is less risky than from pulmonary artery catheter, it would be useful if $ScvO_2$ could function as an accurate reflection of SvO_2. In fact, SvO_2 is not similar to $ScvO_2$ because the latter primarily reflects the oxygenation of the upper part of the body. In normal patients, $ScvO_2$ is lower than SvO_2 by about 2 to 3%, largely because of the less rate of oxygen extraction by the kidneys[6.]. In shock state, the absolute value of $ScvO_2$ was more often reported to be higher than $ScvO_2$, probably due to the oxygen extraction increases in splanchnic and renal tissues[7-11]. This suggests that the presence of a low $ScvO_2$ indicates an even smaller SvO_2. Because of the lack of agreement regarding absolute values, some authors questioned the clinical utility of $ScvO_2$[12,13]. However, despite absolute values differ, trends in $ScvO_2$ closely mirror trends in SvO_2[8,9], suggesting that monitoring $ScvO_2$ makes sense in critically ill patients".

Comment: 2. High/normal ScvO2 may be a result of disturbances in tissue oxygen extraction, this point should be clearly stated in the third paragraph of INTRODUCTION. In discussing the lactate clearance as an end point for resuscitation. Additional citations may be of interests: (1. Intensive Care Med. 2015 Jul 8. Early lactate clearance-guided therapy in patients with sepsis: a meta-analysis with trial sequential analysis of randomized controlled trials. 2. Crit Care Med. 2014 Sep;42(9):2118-25. BMJ Open. 2014 May 23;4(5):e004752.

Response: In response to the first point: we have already mentioned in the introduction (page 6) that normal/high $ScvO_2$ may be a result of disturbances in tissue oxygen extraction: "In septic conditions, normal/high $ScvO_2$ values might be due to the heterogeneity of the microcirculation that generates capillary shunting and/or mitochondrial damage responsible of disturbances in tissue oxygen extraction". We have just removed "poor" from the older version and replaced it by "disturbances in tissue" to make the sentence clearer.

In response to the second point: we have now added the first two references suggested by the reviewer (Intensive Care Med. 2015, and Crit Care Med. 2014) (Ref: 23, and 24) in discussing the lactate clearance as an endpoint for resuscitation in the introduction section. We have not added the third reference (BMJ Open) because it was a study that described only the methodology and statistical analysis of the second study published in Crit Care Med.

Comment: 3. I appreciate figure 4 very much. I think this decision tree is of great value for clinicians and should be highlighted.

Response: We thank the Reviewer for this supportive comment. We have now highlighted the figure 4 by explaining it in more details in the conclusion paragraph (text in red): "In such situation, the presence of low $ScvO_2$ (< 70%) should push the physician to increase DO_2, and if ΔPCO_2 is increased (≥ 6mmHg), that indicates that increasing cardiac output is the rational choice to achieve this target (Figure 4). In the presence of a normal/high $ScvO_2$ (≥ 70%), an elevated ΔPCO_2 still suggests that rising cardiac output can be indicated with the purpose of reducing global tissue hypoxia (Figure 4). However, if both $ScvO_2$ and ΔPCO_2 are normal in a state of global anaerobic metabolism, manipulating the macrocirculation will probably be ineffective to reduce oxygen deficit (Figure 4)".

Comment: 4. I think the clinical study section should highlight three main points: 1) as the authors have already well described, the P[v - a]CO2 is highly correlated with cardiac output; 2) variations in P[v - a]CO2 is associated with clinical outcomes such as mortality, ICU length of stay or days free of organ failure; 3) P[v - a]CO2, when used as a resuscitation endpoint, should be associated with improved outcomes.

Response: In response to the first point: we have now added in the clinical study section (text in red) some lines to highlight the correlation between P[v - a]CO_2 and cardiac output: "Moreover, the changes in cardiac output induced by volume expansion was correlated with changes in P[v-a]CO_2 ($r=0.46$, $p< 0.01$)". And: "Bakker et al.[48] similarly found a significant negative correlation between P[v-a]CO_2 and cardiac output in a series of 64 septic shock patients. Thus, a strong relationship between P[v-a]CO_2 and cardiac output is also well documented in septic shock". However, we would like to stress out that not all clinical studies have found a good correlation between P[v - a]CO_2 and cardiac output. Indeed, recently, Ospina-Tascon et al. (*Crit Care* 2013; **17**:R294) found a very weak correlation between these two variables in septic shock patients ($r^2= 0.025$).

In response to the second point: actually, there is only one observational report that looked at the variations in P[v - a]CO_2 (mixed-gap) in the early resuscitation period of septic shock (*Crit Care* 2013; **17**:R294), and found that the persistence of high P[v - a]CO_2 was associated with poor outcomes. We have now added (page 14, text in red) some lines explaining the main results of that study: "Recently, Ospina-Tascon et al. have shown that the persistence of high P[v-a]CO_2 (≥ 6mmHg) during the first six hours of resuscitation of septic shock patients was associated with more severe multi-organ failure and higher mortality rate[50] (relative risk= 2.23, $p=0.01$)".

In response to the third point: there is no randomized clinical study yet that has tested whether hemodynamic optimization using P[v - a]CO_2 or ΔPCO_2 as an endpoint is associated with improvement outcomes. Thus, we are sorry

but we cannot add what the Reviewer required: "P[v - a]CO2, when used as a resuscitation endpoint, should be associated with improved outcomes". We have just added (Page 4, text in red): "However, further studies are required to test if P[v-a]CO_2 used as a resuscitation endpoint would be associated with improved outcomes".

We thank the Reviewer for his/her very constructive and comprehensive comments that have helped to improve the quality of the manuscript.

Thank you again for publishing our manuscript in the *World Journal of Critical Care Medicine*.

Sincerely yours,

Jihad Mallat, M.D.

Department of Anesthesiology and Critical Care Medicine, Centre Hospitalier du Dr. Schaffner de Lens, France.

mallatjihad@gmail.com

Telephone: +33-321-691088

Fax: +33-321-691839