Reviewer’s report

Title: Elevated central venous pressure is associated with impairment of microcirculatory blood flow in sepsis: a post hoc analysis

Version: 3

Reviewer number: 2

Referee's comments to the author(s)

Only this section of the report will be returned to the authors. Do not comment in this section on the interest/importance level of the manuscript, or whether or not the manuscript should be accepted.

Dear Authors,

I read with interest the manuscript you submitted to ICM, evaluating the association between high central venous pressure and altered sublingual microcirculation in sepsis. Despite the pathophysiological background of the study and the profound experience on microcirculatory disturbancies of a part of the Authors, I would recommend major revisions of your manuscript. I feel that a more extensive, precise and better defined analysis of the data should be provided in order to well support the hypothesis.

The question posed is not original but discrepancies are still present in literature about the association between micro- and macro-dynamics; apart from a little unnecessary speculation in the introduction on page 4 (“the seemingly absence…”), the background of the study is quite well established; thus, the aim of the study is per se important and well defined.

As far as the methods are considered I might propose the following concerns.

Even if most of the data are contained in the previous paper (Boerma EC et al, CCM 2010), the details about the 2 measurements used for this post-hoc study should be better described. Patients were included in the study within 24 hrs from ICU admission, but the SDF images used in the analysis were collected during the first 24 hrs from the achievement of the resuscitation protocols. This could lead to great variability in patients’ characteristics that should be taken into account (early vs late shock, solved shock, septic myocardial dysfunction…).

When evaluating SDF images I would ask to the Authors if they performed 1 or 2 baseline set of measurements at time 0.

The data presented seem however partial and not exhaustively analyzed; I would appreciate the analysis of the evolution of the patients before the analysis of mere numbers, in order to have a context.

Patients (with reference to the table 1)

Time 0 is considered as the baseline of this study; are presented data the ones
after the achievement of the resuscitation protocol or the ones of ICU admission/previous study inclusion? I make reference obviously to the SOFA score; I would eliminate the non ventilated patient.

Table 2: before considering the data pooled in the 2 different set of pressures I would add a table (and/or figure for some parameters) with the values at 0 and at 30 minutes for the totality of patients; in the actual table 2 I would add some data in order to better define the groups (admission APACHE II score, SOFA at the time of measurement, presence/quality and quantity of sedation/muscle relaxant drugs, type of mechanical ventilation, levels of PEEP): the group CVP>12 seem to be more severely ill and with important cardiac/circulatory failure. Before saying that the alterations in microcirculation are associated to increased CVP I would exclude other determinants. Indeed, the Authors underline the differences in some haemodynamic variables at the end of the result section on page 7, but this is not well discussed thereafter. Besides, I would like to know how many patients had increased intra-abdominal pressure/abdominal compartment syndrome. Moreover, I would consider a multivariate analysis appropriate.

That means that the interpretation of the data could be also modified and balanced in a different way.

Nevertheless, I might say that the study has the potential to be very appealing: even if the Authors present the post-hoc analysis of a previous study, they probably have the material to perform an appropriate analysis able to well support a physiologically based hypothesis that has no straightforward answer yet.

Title and abstract are appropriate if the manuscript is considered in this “quite skinny” version, if ever modifications were provided, they should be modified accordingly.

Some parts need minimum English editing/typo editing, whereas the table/figure part need to be improved (see above).

References: please update ref 6 and modify accordingly