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

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Author's response to reviews: see over
Dear Editor,

Please enclosed find our paper, entitled ‘Elevated central venous pressure is associated with impairment of microcirculatory blood flow in sepsis: a hypothesis generating post hoc analysis’. We thank you for considering our manuscript for publication in BMC Anesthesiology. Please enclosed find our answers to the comments of reviewers of Critical Care, as well as a revised version of our manuscript.

The majority of studies published in the field of microcirculation research focus on the (absence of) influence of upstream hemodynamic variables, such as blood pressure and cardiac output, on perfusion of the microcirculation. We invite the reader to observe microcirculatory perfusion from a downstream perspective. To this purpose, we examined the role of elevated central venous pressure (CVP) as a potential outflow obstruction of the microcirculation. Although the design of the study does not allow for making inferences regarding causality, we believe that the evaluation of the effect of elevated CVP has not been the subject of previous studies and is therefore an original hypothesis generating analysis. It must be stressed, however, that unraveling cause-effect relationships for this particular issue is extremely difficult in the clinical setting. We believe that the observed association between elevated CVP and impairment of microvascular perfusion could stimulate both researchers and clinicians to further elaborate on the role of CVP in sepsis resuscitation.

We hope for a positive result.

Yours truly,

Namkje Vellinga, MD
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Please refer to the following pages for our answers to the comments of the reviewers.

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Dear Editor, dear reviewers,
Please find below our answers to suggestions and comments of previous reviewers regarding our manuscript 'Elevated central venous pressure is associated with impairment of microcirculatory blood flow in sepsis: a hypothesis generating post hoc analysis'.
Sincerely,
Namkje Vellinga

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: 1
Referee's comments to the author(s)
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Summary
These investigators have measured macro-hemodynamics and parameters of sublingual microcirculatory blood flow in critically ill patients. In this post hoc analysis they find a statistical association between CVP and microcirculatory flow.

Major comments
The problem with a post hoc analysis, as opposed to an interventional trial, is that patients with an elevated CVP may have altered macro-hemodynamics, such as impaired ventricular function and decreased cardiac output. Thus, the relationship between CVP and microvascular flow may be a non-causal relationship due to a shared factor – decreased arterial flow, in this example. This problem is acknowledged by the authors but must be addressed with data to overcome the problem of potential confounding by, for example, severity of illness (as indicated by lactate and other baseline measures), cardiac dysfunction (possibly reflected by dopamine dose), or treatment (e.g. norepinephrine dose). This problem could potentially be rectified by adding additional experiments where CVP is changed by an intervention and the effect on microvascular flow is measured.

We agree with the reviewer that several factors could have interfered with our observations. Our aim was to present a merely hypothesis generating finding, without an intention to make statements about causality. Illness severity might have indeed been reflected by differences in inotrope dose or lactate levels and could have served as confounders. We have modified the text to underline the hypothesis generating purpose of this post-hoc analysis and we removed any reference to causality. Of course, further (experimental) research is needed to clarify the influence of elevated venous pressure on the microcirculation; however, this will be extremely difficult in the clinical setting.

Statistical associations will also likely be found between other clinical parameters.
and microcirculatory flow. What unbiased approach points to CVP as the most important association to explore?

We agree with the reviewer that a simple statistical association is a weak starting point for a study. However, in our review article (Boerma, Intensive Care Med 2010;36:2004) we already alluded to the strikingly absence of improvement of microcirculatory blood flow by a large variety of vasopressor agents. This observation was explained by us by a different view on physiological theory than as generally perceived in the clinical setting. Therefore, the starting point of this paper is not a statistical association, but the exploration of the aforementioned ideas.

Several clinical studies in the field of microcirculation research have already focused on the effects of (changes in) arterial pressure on microcirculatory perfusion. Main observation is that there seems to be no clear association between the microcirculation and upstream (i.e. arterial) pressure. We invite the reader to take a closer look at the microcirculation from a downstream perspective, i.e. from the venous side of the microcirculation. From the perspective of the microcirculation, the steep part of the blood pressure drop occurs upstream at the level of small arterioles (resistance vessels). The microcirculation itself may be considered as a very low pressure compartment. Therefore, mean capillary pressure is much closer to venous than to arterial pressure and CVP might become a major determinant of microcirculatory blood flow. This paper is the first exercise to explore this different view on physiological theory in the clinical setting with all the limitations that come with it.

We have rephrased the introduction accordingly.

Resuscitation to a pulmonary artery wedge pressure of 18 is not standard practice so that the results of this single center study may not be representative of standard resuscitation protocols.

We agree with the reviewer that is not standard practice. However, there seems to be a misunderstanding. We did not resuscitate until PAWP was 18 mmHg, but until patients no longer showed an increase > 10% in stroke volume, as long as resuscitation endpoints were not met. The upper limit of the wedge pressure was only used as an extra safety measurement to avoid fluid overload (despite being fluid responsive). This is in line with the literature.

We changed the text accordingly.

Minor comments

PPV is not defined in the Abstract.

This is changed in the abstract.
Reviewer's report

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

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Referee's comments to the author(s)

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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 patho-physiological 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.

We thank you for your interest in our manuscript and your valuable remarks. The sentence ‘The seemingly absence…’ was modified.

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 text is indeed unclear regarding the exact timing of the measurements. From the original dataset, we decided to analyze the first 2 measurements, being within the first hour after macrohaemodynamic resuscitation. Measurement 1 is the baseline measurement (one sequence of 3-5 clips of the sublingual area) obtained immediately after the resuscitation endpoints were fulfilled; measurement 2 (another sequence of 3-5 clips of the sublingual area) was obtained 30 minutes after the baseline measurements. All patients were resuscitated as soon as they arrived in the ICU, the pulmonary artery catheter was inserted within 4 hours of ICU admission. Immediately after insertion of the pulmonary artery
catheter, patients were included in the study. Therefore, all patients were considered to be in the early stage of sepsis. We changed the text accordingly.

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.

The data presented in table 1 are the data describing the patients at the moment of the first fulfillment of the resuscitation endpoints, which is the baseline of both this post hoc analysis and the original paper. SOFA score is the SOFA score of the 24 hours in which the original study took place. There is no reason to assume that SOFA score has changed significantly in a 30 minute time frame, and recalculation of SOFA scores in such a short time frame is unusual in the literature and not validated as such.

Our aim was to study the possibility of an association between CVP and microcirculatory perfusion, irrespective of (the influence) of PEEP-levels on CVP, because we were studying extra-thoracic microcirculation. Therefore, we decided beforehand not to eliminate the non-ventilated patient. Recalculation of the data after exclusion of the non-ventilated patient did not show any significant changes.

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.

In order to provide more details about the evolution of the patients during the study period, we have inserted an extra table. This table describes characteristics of all patients at baseline (i.e. directly after fulfillment of resuscitation endpoints) and at 30 minutes. APACHE II and SOFA scores (both APACHE II and SOFA for the day of the study, which was the first day of ICU admission) provided in table 1. All patients were ventilated in a pressure controlled mode, irrespective of the time point. We aimed for a sedation level to RASS -4 with midazolam/morphine. None of the patients received muscle relaxants. We have added PEEP settings to the tables. Text and tables were changed accordingly.

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.
We agree and have extensively rephrased the discussion of our main results and also added the change over time between the two timepoints.

Besides, I would like to know how many patients had increased intra-abdominal pressure/abdominal compartment syndrome.

We do not have data on intra-abdominal pressure for these patients. However, we do acknowledge the possibility of an influence of elevated intra-abdominal pressure on CVP in ICU patients. We have added this to the limitations of the study.

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.

We deliberately refrained from a multivariate analysis. Even if in a multivariate analysis for example norepinephrine dose and CVP point towards the same direction, this does not establish any causative relationship. It could still imply a CVP-related or a non-CVP related effect of norepinephrine. We have changed the text of our discussion accordingly.

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. Thank you.

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.

We have adjusted both title and abstract in order to underline the hypothesis generating purpose of this post-hoc analysis.

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

References: please update ref 6 and modify accordingly

Reference 6 was replaced by the most recent Surviving Sepsis Campaign guidelines (Intensive Care Med 2013, 39(2):165-228).
Reviewer's report

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

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Referee's comments to the author(s)
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While the analysis is interesting and relevant, the interpretation of the data seems hugely biased towards "finding something interesting". The correlation demonstrated is a very weak one. R = -0.19 and an r2 of 0.04 is a very weak relationship.

We agree with the reviewer that a simple statistical association is a weak starting point for a study and indeed, the association itself is also weak. However, in our review article (Boerma, Intensive Care Med 2010;36:2004) we already alluded to the strikingly absence of improvement of microcirculatory blood flow by a large variety of vasopressor agents. This observation was explained by us by a different view on physiological theory than generally perceived in the clinical setting. Therefore, the starting point of this paper is not a statistical association, but the exploration of the idea that the outflow pressure is an important determinant of microcirculatory perfusion pressure. This paper is the first exercise to explore this different view on physiological theory in the clinical setting with all the limitations that come with it.

Furthermore, if PPV and MFI are meant to be independent measures of the same physiological state how is it that the statistically significant correlation is being demonstrated with one and not the other.

This is explained by technicalities behind these variables. Microvascular flow index is solely a determinant of flow with four categories ranging from 0 (no flow) to 3 (continuous flow). PPV is not only a flow variable with only two categories (perfused (MFI 2-3) versus non-perfused (MFI 0-1)), but also incorporates the number of grid crossings of individual vessels. In other words, if the overall MFI is 2 (clearly abnormal), the PPV may be a 100% and if a single vessel crosses the grid many times a reduction in flow will lead to a substantial reduction in PPV, whereas a similar vessel with equal vessel length does not cross the grid so often, reduction in flow will lead to a comparatively lower reduction in PPV.

This being the case
how much significance can you attribute to this "significant correlation".

Indeed, the correlation is weak, suggesting that the CVP is not the only variable of influence to the MFI. We have omitted the part dealing with linear regression and have carefully rephrased the manuscript to avoid the possibility to claim more than we observed.

In the second analysis both MFI and PPV does suggest that flow is reduced in
patients with a high CVP....this is more convincing. However, even here the considerable number of confounding factors - particularly the differences in vasopressor requirement, suggests an association rather than causation. While the authors do not explicitly claim a causal relationship, the way the manuscript is presented/argued seems biased towards causation rather than association. In other words, the interpretation seems pretty biased towards demonstrating a relationship between CVP and microvascular flow.

We agree that this post-hoc analysis does not allow for making any inferences regarding causality and we merely intended to offer a hypothesis generating view on the microcirculation. We adjusted the text and the title to highlight the hypothesis generating purpose of this manuscript and we removed any references to causality.
Title: Elevated central venous pressure is associated with impairment of microcirculatory blood flow in sepsis: a post hoc analysis

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Referee's comments to the author(s)

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Dr Vellinga and co workers present the results of a post-hoc analysis of a prospective study in septic patients resuscitated according to non-CVP guided treatment protocol. Using the SDF technology they evaluated the sublingual microcirculatory blood flow immediately after fulfillment of resuscitation goals and 30 minutes thereafter. They conclude that “exist an association between elevated CVP and impairment of microvascular blood flow in septic patients, which is in line with physiological theory that microcirculatory perfusion pressure is predominantly determined by CVP as an outflow obstruction”. Furthermore, they propose those observations challenge the physiological ratio behind resuscitation guidelines. Finally, they admit that the study design does not allow for making assumptions regarding causality but they propose further research to clarify the role of elevated CVP in microvascular dysfunction in sepsis.

I found very interesting the data showed by Reynolds (Vellinga?) and co workers and their attempt to demonstrate the role of CVP as a key determinant of capillary blood flow. They hypothesized that increasing CVP may considerably influence the capillary driving pressure assuming that microcirculatory perfusion pressure is the net result of post arteriolar minus venular pressure. Despite this approach might make sense, I have some concerns which might be summarized as follows:

1. I must recognize that authors of this paper are known and well-respected researchers in the field. In fact, I keep a deep respect for them because their contributions to the knowledge on microcirculatory disturbances during critical illness.

We thank the reviewer for the interest in our manuscript and the valuable remarks as well as the detailed explanation of the regulation of capillary perfusion.

2. Regulation of capillary pressure is a complex issue described widely in the past. In a classic paper by Pappenheimer and Soto-Rivera (Am J Physiol 152:471-491, 1948) were described the governing forces of isogravimetric and isovolumetric capillary pressures determining capillary flows for whole-organ preparations. After their experiences in animal models, they proposed the following formula:

\[ P_{c iso} = \frac{[Rv/Ra] \cdot Pa + Pv}{1 + (Rv / Ra)} \]

Where \( P_{c iso} \) is isogravimetric / isovolumetric capillary pressure, \( Pa \) is mean arterial pressure, \( Pv \) is venous pressure, \( Ra \) is arterial resistance and \( Rv \) is venous resistance. Within a network of interconnected vessels, the distribution of
resistance or the location of main points of resistance can be inferred from the steepness of the fall in pressure in the direction of flow. Thus, there is a substantial pressure drop in arterial and venules # 100 μm in diameter, an intermediate through vessels between 40 – 60 μm and there is a small but not negligible drop across capillaries. Furthermore, resistance in venules and small veins seems to be comparable in magnitude to that of the capillaries.

In this order of ideas, physiologic proposal by Vellinga and co-workers sounds logical but largely inaccurate. In acutely ill patients, vascular resistances are largely changeful to consider that only CVP variations may explain changes in capillary pressure or capillary flows in a point of time.

We recognize the complexity of this issue and we acknowledge the shortcomings of CVP as a representative of venous pressure at the level of the microcirculation. On top of the suggested other factors that contribute to regulation of capillary perfusion, it is also of note that this is not a static process. In reality, vasomotion is the constant opening and closing of capillaries under influence of downstream hypoxic signals. However, this complexity of microcirculatory flow is a complete black box in the clinical setting. In previous papers, authors have tried to establish a relationship between the input signal (i.e. arterial pressure) and the microcirculation and were unable to do so. We however encourage the reader to pay attention to the outflow pressure of this black box. We have rephrased this important limitation of the study.

3. In fact, the changes in capillary pressures would be directly proportional to delta of pressures (of course including venous pressure!!) but indirectly proportional venous to arterial resistance ratios:

\[ \#Pc = \left( \frac{1}{1 + \left( \frac{Rv}{Ra} \right)} \right) \cdot \#Pv \] or, \[ \#Pc = \left( \frac{Ra}{Rv} \right) \cdot \#Pv \]

Again, the proposal by Vellinga et al has sense but is not accurate.

We agree with the reviewer that venous and arterial resistance also play a significant role in determining capillary blood flow. Unfortunately, it is impossible to measure vascular resistance in the clinical setting. Instead, the usual procedure is to calculate resistance from flow and pressure difference. This does not take into account the heterogeneity of blood flow that we typically observe with SDF imaging.

4. Authors can argue that SDF evaluates microvascular blood flows but not pressures. Thus, as microvascular bed responds passively to changes in perfusion pressures, the slope of a graph considering steady-state flow (Q) against perfusion pressure (Pa – Pv) increases with increasing the delta of pressure. However, the formula describing flow in capillary beds is more complex than it and blood flow equation might be described as follow:

\[ Q = k \cdot (Pa – Pv)^{exp.n} \]
where \( k = 1 \div R_{tot} \) when \( Pa – Pv = 1 \); and \( n \) is an index of resistance-vessels distensibility.

Again, resistance and capacitance are terms not considered in the paper given the difficulty of them during in vivo measurements. Thus, CVP could be a very thick determinant of microvascular blood flow when total vascular resistances are not considered.
As the reviewer notes, measurements of for instance resistance and capacitance as well as certain pressures are indeed difficult to incorporate in a clinical setting. Therefore, our aim was to present some hypothesis generating data, without the intention of establishing causative relationships between elevated CVP and microcirculatory perfusion. In order to emphasize the complexity of this issue we have incorporated a note regarding the complexity of regulation of capillary perfusion to the limitations of the study, including a reference to the article of Pappenheimer and Soto-Rivera. We agree that SDF evaluates flow rather than pressure, which is why this method is especially suitable for evaluating organ perfusion at the capillary level.

5. In the past, some papers on microcirculatory alterations evaluated by OPS or SDF technologies have shown microcirculatory blood flow improvements even CVP measurements moving in opposite directions. I.e., De Backer et al (Crit Care Med 2006; 34:1918–1924) demonstrated increased microcirculatory parameters after dotrecogin alpha-activated infusion even though this group had a higher CVP than control group. In the same way, Boerma et al. (Crit Care Med 2007; 35:1055–1060) demonstrated an increasing MFI at day 3 in patients with abdominal sepsis even in the presence of CVP values (day 1: 9 (7–14) vs. day 3: 12 (9–16)). This talks about the difficulties to interpret an isolated CVP as determinant of microvascular blood flow.

We agree with the reviewer that isolated measurements of any kind are difficult to interpret in terms of associations (or, if applicable, causality). As suggested by reviewer 2, we have now added the change over time in MFI in relation to change in CVP over time. In line with the observed association of the static measurements, we also observed an increase in MFI during a lowering of CVP and even perfusion pressure. We have changed the text of the discussion accordingly.

6. Time is a very important issue determining microvascular blood flow responses to different interventions. Thereby, Ospina-Tascón et al (Intensive Care Med (2010) 36:949–955) emphasized on importance of timing in microvascular response to fluids. In this paper, early but not late fluid challenges improve microcirculatory blood flow. Interestingly, even though CVP was increased in both groups (early: 11 [8–13] to 14 [11–17] and late: 11 [8–13] 12 [11–15]), only early fluids improve microvascular blood flow. Vascular resistance and distensibility are dynamic variables time-dependent. Even Vellinga et al. note that measurements were performed after achieving resuscitation, this could have happened in a wide window of time.

We agree that timing is indeed crucial when evaluating the microcirculation, which is elegantly demonstrated by the study of Ospina-Tascón and co-workers. Similar to the early group in this study, we aimed for the early phase of resuscitated sepsis, which was the first 30 minutes after fulfillment of resuscitation endpoints in our post-hoc analysis. Patients were included within 4 hours after ICU admission. Of course, we cannot rule out a potential
time-related effect, because every patient is in his own unique phase of sepsis (resolution) at the time of measurements.

7. Effects of vasopressors on microvascular blood flow have been widely discussed and contradictory results have been demonstrated maybe due to variable changes in vascular resistances conducting to different grades of microcirculatory blood flow derangements. Notoriously, data presented by Vellinga et al. demonstrated a higher number of patients and higher dose was received in elevated CVP group. It is not clear whether deeper microvascular derangement is explained by a more severe illness, a higher dose of vasopressors, or effectively, by a higher CVP (or even higher CVP reflects more severe cardiovascular challenge).

8. I agree that we need further research to clarify the role of elevated CVP in microvascular dysfunction in sepsis.

We agree with the reviewer that it is difficult to determine the relationship between microcirculatory abnormalities and the administration of vasoactive drugs. Regardless of the origin of elevated CVP, the only thing we wanted to draw attention to is that higher CVP is associated with impairment of microcirculatory blood flow irrespective of the origin. Studies like this one are by design unable to unravel the pathophysiological principles behind it.