Author’s response to reviews

Title: Relative cerebral hyperperfusion during cardiopulmonary bypass is associated with risk for postoperative delirium: a cross-sectional cohort study

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Author’s response to reviews:

Dear Prof. Biasucci,
dear reviewers,

we thank you for giving us the opportunity to submit a revised version of our manuscript. We have carefully studied the reviewers’ comments and gratefully acknowledge the helpful suggestions they made to further improve our report. In order to meet their demands, we have made comprehensive modifications within the text, which are further explained in a detailed point-to-point reply.

Reviewer #1:

- Really interesting topic but I did not quite understand the homogeneity of the population considered: what characteristics did the population have regarding the general risk factors for POD such as alcohol and drugs abuse, cognitive impairment, malnutrition, sleep disorder, duration of surgery, HES use, post-op pain to rest or basically the risk factors for POD in ICU (age, dementia, hypertension, pre-ICU emergency surgery or trauma, Acute Physiology and Chronic Health Evaluation II score, mechanical ventilation, metabolic acidosis, delirium on the prior day, and coma). If authors confirm that it is a prospective observational study combined with a cross-sectional study, it will be precious to use STROBE checklist as platform.
We thank the reviewer for his critical remark. Our manuscript now contains additional data from the patient charts as well as from the intraoperative period, giving a comprehensive overview of the patient’s general risk for POD. This information has been implemented into the results section as well as into Table 1.

Except for one individual in the no-POD cohort with a history of alcoholism, no patient suffered from chronic alcohol or drug abuse. No patient showed preexisting clinically relevant cognitive impairment or dementia, and prevalence of chronic arterial hypertension was equally distributed. Malnutrition is a risk factor for POD in cardiac surgery patients (see Ringaitienė et al. [1]). According to the WHO definition, the term refers to either undernutrition or overweight. We think, with his remark, the reviewer focuses on undernutrition. Unfortunately, a Nutritional Risk Screening (NRS), as it was used by Ringaitienė et al., was not performed preoperatively in our patients. However, we now provide the patients’ BMI values in Table 1, which all lie within a range from 20.5 to 39.3 kg/m^2 (with no intergroup differences), making severe undernutrition in our cohort highly unlikely. The fact that important possible confounders such as e.g. preexisting micronutrient deficiencies or clinically inconspicuous cognitive impairment cannot be ruled out with absolute certainty is now mentioned in the discussion section.

Duration of surgery as well as of aortic cross-clamping are now given in Table 1. Both parameters did not differ between the no-POD and the POD cohort. HES is not used in our department. The distribution of age among the groups has already been described and discussed. Patients receiving emergency surgery were not included into the observation, as explained in the methods section.

- As cross-sectional study, it is difficult for me follow the design when authors found 32% of hyperperfusion experience inside no-POD group and when analyze the 21 patients subcohort with lower MCAVbas: which of these patients are in the two begging groups? why the no-POD group patients with hyperperfusion don't develop POD?

We greatly acknowledge this critical remark. Analyzing our data revealed that MCAVbas (that was used to calculate the relative MCAV during CPB) was significantly lower in those patients that developed POD than in no-POD patients. Consequently, we wondered if a low MCAVbas alone poses an increased risk for POD to the patient, or if an additional cerebral hyperperfusion during CPB is necessary. We know that only a randomized trial with different intraoperative hemodynamic regimens will definitely answer this question. However, to get an idea of an underlying mechanism, we focused on those 21 patients with low MCAVbas (i.e. below the median of the whole cohort). Most of the POD patients (9 out of 12) belonged to this subcohort, but the majority (8 out of those 9 patients) was actually exposed to hyperperfusion during CPB, while only one had MVACrel values below 100 %. This, together with the fact that the duration
of hyperperfusion was likewise significantly associated with an increased risk for POD, suggests that not only reduced basal MCAV but rather an increased MCAVrel during CPB poses a risk for POD to the patient. We have updated our script to make this paragraph clearer.

We thank the reviewer for raising this critical question on why some patients with hyperperfusion do not develop POD. In fact, as to now, we cannot provide an answer. Duration of hyperperfusion might be one possible explanation, as our analyses suggest. Moreover, cerebral hyperperfusion during CPB may only be one of numerous risk factors, which often will result in POD only when coinciding.

- Do the "duration" of hyperperfusion experience have a more important physiopathological role in the POD development? Even the CPB management have an important role.

Our data suggest that the prevalence of POD was associated with the time the patients experienced hyperperfusion when being on CPB. A pathophysiological role seems reasonable, since others could demonstrate that duration of MAP above the upper cerebral autoregulation limit (see Hori et al. [2]) or that of CPB itself (see O’Neal et al. [3]) are risk factors for POD as well.

- Authors used AI (autoregulatory index) applying Zazulia's formula that look like to be tested on animal models with Alzheimer's disease; we love TCD and dynamic assessments, but we know the limits to assess CBF by TCD: probably will be usefull to specify that in a paragraph dedicated to the study's limitations.

We calculated the AI from a pressure-flow velocity relationship, similar to what was described by Zazulia et al. in human individuals with Alzheimer’s disease (not in animals) [4]. The same method has also been used in other clinical situations, e.g. subarachnoid hemorrhage (see Diringer et al. [5]). However, the reviewer is absolutely right pointing out the limits of deriving CBF from CBFV. Since Aaslid et al. first described the use of TCD to assess CBF in 1982, numerous authors aimed to validate this method for various clinical situations, including CPB (see also the recent review article by Caldas et al. [6]). During mild hypothermic CPB, results may be ambiguous, but it can be assumed that at least changes of flow velocity in the MCA reflect changes in CBF as long as arterial CO2 partial pressure remains constant (see Trivedi et al. [7], see Kirkham et al. [8]). In addition, although the impact of usual dosages of volatile anesthetics on this relationship seems to be small (see Kochs et al. [9]), we intentionally determined baseline MCAV in anesthetized and not in awake patients prior to CPB to exclude an
effect of anesthesia induction on TCD measurements. We now added a paragraph to the manuscript, discussing this potential limitation of our finding.

Reviewer #2:

- Page 3, lines 28,29. Substitute with "is an indirect measurement of"

Page 3, lines 59, "absence of acoustic window"

We changed our manuscript according to the suggestions.

- Page 5, line 6, can the authors specify where the 20% cutoff change of C02 was derived from?

Only time points with MAP changes ≥20 % were included into calculation of AI (see, e.g., Ti et al. [10]). Furthermore, although PaCO2 was held at a constant level during CPB, small changes occurred in 10 of the >290 measurements. To adjust for these changes, a cutoff value of 20 % was arbitrarily chosen (see also Numan et al. [11]). We added this information to the methods section.

- Page 5, was POCD excluded based just on the POD onset time? Explain.

As explained in the methods section, patients were rated as having developed POD if they were CAM-ICU positive for at least one single examination within 48 h after extubation.

- Since the authors performed static autoregulation testing every ten minutes, can they specify during which phase were the tests performed? Perioperative period, just during OR?

Static autoregulation was assessed during the CPB period, as explained in the methods section.
- A important way of differentiating Emergence Delirium, POD from POCD is most certainly the onset and duration (Silverstein J et al, Anesthesiology, 2007). While the authors refer to how they diagnosed POD, no mention is made on how they excluded POCD, which lasts for weeks or months. Was this performed through follow-up? Regarding the nomenclature I would suggest to include a few words while citing this reference:


We greatly thank the reviewer for this remark. Our observational window extended up to 48 h after extubation or until the patient was discharged from the ICU. Thus, occurrence of POCD was not assessed as this was not subject of investigation in our study. We now have cleared our diagnostic criteria and added a paragraph discussing this limitation, including the above mentioned reference as suggested by the reviewer.

Reviewer #3:

- Several different physiologic mechanism may be involved in cerebral flow velocity regulation during CPB. In fact, temperature may be reduced, hematocrit may change, and systemic flow can be artificially regulated by machine. Each parameter may influence not only cerebral blood flow, but even cerebral flow velocity, changing diameter of cerebral arteries. So, the equivalence between CBFV and CBF is not warranted after starting of CPB. The authors should report this important limitation of the study in the discussion.

We appreciate the reviewer’s critical comment on the limits of deriving CBF from CBFV. Hypothermia during CPB was very mild in our study, and PaCO2 values did not differ among no-POD and POD patients, respecting two important factors influencing CBF. We also mention the impact of HLM pump flow rate, which may be intentionally changed to titrate CBF, independent of other parameters such as the systemic blood pressure (see Moerman et al. [12]). However, we now have added a paragraph to the last section of our manuscript, discussing the difficulties and limitations of assessing CBF using TCD.

- The authors studied autoregulation during CPB in these patients, and found that autoregulation was preserved with no differences between patients with or without delirium. If this is true, CBF
must be independent from systemic parameters as pressure or flow. This cannot explain results. How can you explain hyperperfusion, when autoregulation is present?

Autoregulation was calculated as index derived from the relationship between systemic blood pressure (MAP) and MCAV. Since it can be assumed that changes of flow velocity in the MCA reflect changes in CBF (at least during mild hypothermia and stable arterial CO2 partial pressure, see Trivedi et al. [7]), the validity of this method has previously been evaluated (see also Caldas et al. [6]). According to this calculation, pressure autoregulation was intact in our patient cohort. However, as Moerman et al. [12] could demonstrate, during CPB, cerebral perfusion may be affected completely independent of systemic blood pressure, namely by changes in pump flow rate. Thus, our data underline the significance of a hemodynamic management that adapts blood pressure as well as pump flow rate dynamically to intraoperatively assessed cerebral perfusion indices. We have modified the wording in our manuscript to make this clearer to the reader.

- I think that the term hyperperfusion should be changed in increase of CBFV.

We appreciate this recommendation and understand that flow velocity is not necessarily the same as perfusion. However, in order not to impair the legibility of our manuscript, we kindly would like to avoid the somewhat unwieldy term ‘increase of CBFV’. Moreover, as we compared baseline with intraoperatively changed values, we think that ‘hyperperfusion’ transports well the message of our report. However, if the reviewer insists of the change, of course we will modify the whole text accordingly.

- Can you exclude that these results may be the consequences of increased cerebral metabolism? Have you any data about depth of anesthesia? Did you measure BIS or any other similar index? Did you measure regional oximetry to confirm that the increase of flow is related to hyperperfusion or not the effect of increase of increased metabolism, reduced viscosity or other?

According to recent guidelines, BIS monitoring is performed routinely during cardiac surgery procedures in our department. BIS values ranged from 30 to 55 in both subcohorts with no intergroup differences. We have added these data to the report. NIRS monitoring was unfortunately not performed regularly in all patients of the study cohort and thus cannot be reported.
- Did you measure hematocrit pre and during CPB? I think that this may be an important bias.

To follow the reviewer’s suggestion, pre- and postoperative hematocrit values are now given in Table 1. Both parameters as well as their delta did not differ between the no-POD and the POD cohort. However, preoperative hematocrit values were significantly higher than those obtained postoperatively. If hemodilution affects cerebral blood flow or oxygen consumption in a clinically relevant way is still uncertain. While some authors showed that during deep hypothermic CPB, CBFV increases with decreasing hematocrit [13], others have demonstrated that under conditions of laminar flow, the linear association between flow and velocity is not altered by changes in hematocrit in clinically relevant ranges [14]. Thus, the findings of Paut and Bissonnette “[...] support the use of transcranial Doppler sonography to estimate cerebral blood flow […] during bypass.”. Furthermore, it has been shown that cerebral autoregulation is preserved even with decreasing hematocrit as long as PaCO2 is held within normal ranges (see Ševerdija et al. [15]). Since hematocrit values in the POD group equaled those in the no-POD group, we might want to rule out a relevant effect of hemodilution on our findings. We added this to the discussion section of our manuscript.

- Is there any phase of CPB when CBFV was increased?

Did you measure CBFV after CPB?

In our manuscript, we report on increased CBFV (i.e., TCD-derived MCAV) during CPB, compared to baseline values obtained before CPB. These increases were significantly more pronounced in patients that later developed POD. However, they were not limited to any specific phase of CPB. We added this information to the text.

Unfortunately, we measured CBFV only before and during but not after CPB.

- Zazulia (ref 6 of the paper) reported an autoregulation index based on cbf measurements. In this case you measured flow velocity through tcd. Method should be standardized according with correct reference.

The reviewer is absolutely right stating that Zazulia et al. used the ratio of the percentage change in CBF (not CBFV) and the corresponding percentage change in MAP to calculate the AI. We refer to their work as we used a similar formula, calculating the ratio of the percentage change in
MCAV and the corresponding percentage change in MAP. We now modified this paragraph in our methods section, pointing to this significant difference. In addition, to underline the validity of our approach, we refer to the work of Trivedi et al. [7] as well as to the review article of Caldas et al. [6], which gives numerous examples of the validation of TCD-based autoregulation assessment against other methods.

We hope that these additional clarifications addressed all of your concerns sufficiently and that you agree that the changes improved our manuscript and helped to clarify the report. Please do not hesitate to contact us if you should have any more questions. We are very looking forward to your decision.

Thank you very much!

Sincerely,

PD Dr. med. Tobias Hilbert, MD, D.E.S.A.

References:


