Author's response to reviews

Title: Higher cerebral oxygen saturation may provide higher urinary output during continuous regional cerebral perfusion

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Author's response to reviews: see over
Dear Vipin Zamvar

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Thank you very much for reviewing our manuscript number: MS: 5216423921949676.
We extensively revised it according to the pertinent remarks and comments of the reviewers. The main changes are red marked in the text. The points raised by the reviewers have been addressed as following:

#1 For Reviewer PM Lemmers:

First, the number of patients is rather small, limited to such an extent that statistical analysis of any result is highly questionable.
---- We quite agree with you in regard to small number. We feel that it is important to evaluate both cerebral perfusion and cerebral oxygen saturation on NIRS. We believe our data is much clearer.

We also have our doubts about the cut-off point of 75% to identify groups. Normal cerebral oxygen saturation ranges from 60 to 80% in babies and young infants. Therefore a cut-off point of 75% seems rather high, and authors have not been able to provide evidence for their choice.
---- Although absolute thresholds of rSO2 for neurological injury are not known in human neonates, I think that aerobic metabolism is impaired when cerebral rSO2 decreases below 50% from previous reports. We subsequently targeted a cerebral rSO2 greater than 75% during moderate hypothermic RCP as a cut point in the present study because this kind of rSO2 ensures a good collateral blood flow in the sub-diaphragmatic viscera and lower limbs.

In addition, it appears that 2 patient groups of patients have thus been defined that have significantly different ages at operation. Consequently, although no thoracic surgeons, we suspect that major circulatory differences have played a role in who was selected for operation at what time. Finally, there are significant differences in both renal function and pharmacokinetics of a variety of vasoactive drugs between the newborn (<1 week old) and older infants. We presume that not
just the cerebral oxygenation but the overall clinical condition and the age of the patient may be at the basis of reported findings.

We quite agree with you in regard to different ages at operation, renal function and pharmacokinetics of a variety of vasoactive drugs between the newborn and older infants. I think that the widespread network of arterial collaterals from vessels (such as the arterial circle of Willis, internal thoracic and intercostals arteries etc.) are well grown in older infants. Furthermore, renal function and pharmacokinetics of a variety of vasoactive drugs may have increase in early infant than neonate. According to this speculation, urinary output might be higher in Group B than that in Group A. However, the results were counter to this speculation. We think that there are not significant differences in both renal function and pharmacokinetics of a variety of vasoactive drugs between the newborn and older infants.

#2 For Reviewer Klaus PhD. Valeske:

1. Introduction: The hypothesis is: Higher cerebral oxygen saturation is correlated with pump flow rate. Table 2 says: no difference in pump flow rate.
   ----- At the reviewer’s suggestion, we rewrote it in the revised manuscript.

2. Page 6: You describe the administration of phenoxybenzamine. In the discussion you state, that higher urinary output depends on higher cerebral oxygen saturation and a large dose of chlorpromazin. What about phenoxybenzamin? Can chlorpromazin provide additional vasodilatation in patients treated with phenoxybenzamin?
   ----- We didn’t use phenoxybenzamin in this study.

3. Page 6: Standart hemodynamic monitoring...
   ----- Arterial blood pressure, ECG, SaO₂, Central venous pressure, Rectal temperature, Systemic venous oxygen saturation etc.

4. Page 7: Table 2 says: Pump flow rate during RCP is 79+/−23ml. If a mean bypass flow of 141+/−37 ml was required to reach a mean radial arterial pressure of between 30 and 50 mmHg, how did you reach a pressure of 37,9+/−9.6mmHg with a reduced flow rate? What is the mean rSo2 in both groups? We know only about more than 75% in group A and less in group B, but no exact data.
   ----- We had 2 cases with a mean radial arterial pressure less than 30 mmHg.
   ----- The mean rSo2 during RCP (81.8 ± 4.2 % vs 62.4 ± 8.9 %, p=0.0012) was significantly higher in Group A than that in Group B.

Page 11: In our opinion...
Page 11: You suppose that decreased cerebral vascular resistance requires higher blood flow rates although Your results show no difference in blood flow rates. What was the hematocrit during RCP? Was it different in between the groups?
   ----- The mean Hct during RCP (28.5 ± 2.4 % vs 28.0 ± 3.3 %, p=0.80) was not significantly between the groups.

Page 12: Also on page 12: Your pump flow rate shows no statistical difference.
   ----- Generally, higher pump flow rate may provide higher blood flow. However, the pump flow
rate shows no statistical difference in my study.

Page 13: smooth muscle, liver,...
Page 13: Isn’t there a significant rise in group B compared to group A because here the rSO2 is lower than in group A?
---- There is a significant rise in group B compared to group A. Text was corrected accordingly. I think the somatic rSO\textsubscript{2} is lower than in group A.

Page 14: In my opinion the authors cannot show that a cerebral saturation of more than 75% or a pressure of between 10 and 15 mm Hg should be targeted as a sign of a better perfusion of the lower body, but this study That shows flow during RCP should target on a high rSO2 controlled by NIRS.
----- At the reviewer’s suggestion, we rewrote it in the revised manuscript.

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The whole manuscript has been rewritten.
We tried to improve English language.

We hope to have met your requirements that greatly improved this manuscript.

Yours gratefully and faithfully,

Takashi Miyamoto, PhD, MD.