Author’s response to reviews

Title: The effects of ventilation on left-to-right shunt and regional cerebral oxygen saturation: a self-controlled trial

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Author’s response to reviews:

We sincerely thank you for your constructive and valuable comments. We agree with these comments, and revised our manuscript considerably according to your comments and suggestions. If we have missed any one of the comments please let us know. This document includes our responses to your comments point by point:

Comments from Reviewer #1:

The manuscript is the result of a well designed study; however, some minor linguistic corrections are necessary.

Response: Thanks for your positive comments and suggestions on our manuscript. We have re-scrutinized to improve the English by a native English speaker and carefully revised the manuscript according to your comments.

Comments from Reviewer #2:
The enclosed study, “The effects of ventilation on Left to Right shunt and regional cerebral oxygen saturation: a self-controlled trial” is evaluating the effects of two ventilation modes on L-R shunt in patients undergoing congenital heart defect repair. As a main result the authors found that normo- to slight hypoventilation might prevent excessive L-R shunt. The study follows a prospective, cross-over, cohort interventional study design. Ethical approval was obtained and the study was registered.

Response: We have revised our manuscript according to your insightful comments and advice. Those comments are all valuable and very helpful for revising and modifying our paper, as well as the important guiding significance to our research. The answers for each comment were as summarized below.

General Comments 1: Figure 1a and 1b is not adding any information to the results and is showing a well-known and documented method. Figure 2, 3 and 4 is redundant because the information was already given by the tables.
Response: We have removed the Figure 2 and 4 from the manuscript. Considering figure is more visual and this is the first study for measuring the VTI of L-R shunt. the Figure 1a and 1b, Figure 3 were retained while the duplicate information associated with VTI in Table 2 was deleted. We also agree to delete these figures if your think that it is unnecessary.

General Comments2: Please check for English spelling and grammar. I am also not a native speaker therefore I would recommend to use one of these online scientific English editorial services.

Response: We have rewritten and revised the whole manuscript carefully and tried to avoid any grammar or spelling error. In addition, we have asked a native English speaker to check our language.

General Comments3: Overall the effects of different ventilation modes on L-R shunt are well described. I am not sure what exactly was a new information coming out of your study.

Response: Thank you for pointing this out. Increasing pulmonary vascular resistance (PVR) is a double-blade sword, since it would not only augment right ventricular afterload and lessen L-R shunt, but also lead to the insufficient pulmonary oxygenation and deteriorating tissue oxygenation. However, precisely measuring PVR and Qp/Qs is complicated and time-consuming in the operating room. PaCO2 which could be noninvasively measured via blood gases and adjusted by ventilation parameters is more likely to be an indicator of unstable PVR and Qp/Qs. Whereas, how to maintain a favorable level of PaCO2 by regulating mechanical ventilation parameters is still unclear, and largely derived from anesthesiologist’s personal experience to alleviate this unequal Qp/Qs distribution in patients with L-R shunt. According to your suggestions, we have re-written the background to clarify our aims as “Whereas, how to maintain a favorable level of PaCO2 by regulating mechanical ventilation parameters is still unclear, and largely derived from anesthesiologist’s personal experience to alleviate this unequal Qp/Qs distribution in patients with L-R shunt.” ..... “We attempted to find a perioperative ventilation strategy with a proper range of PaCO2 which could provide an appropriate Qp/Qs with optimal oxygen supply for children with L-R shunt.”

Specific Comments1: The citation on page 4 L 12 is about a case report of 2 cases and can therefore not proof general observations on the effect of PaCO2 modulating the QpQs.

Response: Thanks for your careful checks. As you suggested, the two case reports were unable to draw arbitrary conclusions that the clinical improvement of the two infants was evoked by improvement of Qp/Qs under the increased PaCO2. Therefore, the causality of increasing PaCO2, L-R shunt and Qp/Qs is one of the points that our experiment hope to explore. We have eliminated the case and revised this part as follows:

“In Reddy’s study, increased pulmonary vascular resistance (PVR), CO and reduced ratio of Qp/Qs through enhancing PaCO2 was testified[8], similar clinical phenomenon was also observed after four percent CO2 added to the fresh gas flow in a 6-year-old patient with a 4mm Blalock-Taussing shunt[9]. These indicated that PaCO2 which could be noninvasively measured via blood gases is more likely to be an indicator of unstable PVR and Qp/Qs[10].”
Specific Comments2: If one is letting to increase the PaCo2 to modulate i.e. the cerebral or peripheral circulation one automatically might decrease the blood PH. This will generate a pulmonary vasoconstriction (at least theoretically). This might influence the result of measuring QpQs. Bradley and co-workers were able to show these effects in children undergoing bidirectional superior cavopulmonary connection (DOI: 10.1016).

Response: Thanks for your recommending Prof Bradley’s article which helps us better understand of our results. The blood flow is equal to the multiple of flow velocity and cross-sectional area of blood vessel. As you concerned, pulmonary artery vasoconstriction caused by raised PaCO2 could affect the results of blood flow. However, we did not measure the cross-sectional area, mainly for two reasons. Firstly, the pulmonary blood flow was measured in the main pulmonary artery where the variation in cross-sectional area was slight under the fluctuating range of PaCO2 during our study. Secondly, the accuracy of the final result may be affected while simultaneously measuring the blood flow velocity and cross-sectional area at three locations in three modes confronting the constraints of measurement time. Comprehensive considering, we tend to give priority to the accuracy of blood flow velocity of blood flow. We also added “The velocity time integral (VTI) of L-R shunt, pulmonary artery (PA) and DA were measured respectively to represent blood flow assuming that the diameters of arteries changed subtly than arterioles by PaCO2[13, 14].” in the revised manuscript.

Specific Comments3: Moreover, the investigated cohort of patients is very heterogeneous regarding the underlying disease. Large VSDs with indication for operation may present in so many different hemodynamic variations regarding the pulmonary vascular system and reactivity. As the pulmonary arterioles involute, PVR falls with resultant increase in left-to-right shunt. The right ventricle (RV) and main and branch pulmonary arteries may also be dilated in moderate to large defects. Whereas pulmonary vascular obstructive disease (PVOD) does not manifest until adulthood in patients with ASD, patients with VSD are likely to develop PVOD as early as 18 months to 2 years of age if a large VSD is left unrepaired. That means that the effect of moderate increase or decrease of PaCO2 might will have less to no effect on L-R Shunt.

Response: We are extremely grateful to you for pointing out that heterogeneous patients regarding the variations in pulmonary vascular system and reactivity. We have removed the children over the age of 6 and re-analyzed results to prevent pulmonary arteriosclerosis from affecting outcomes as much as possible. Our results revealed that children with larger defects had weaker pulmonary vascular response to the elevated PaCO2, most likely due to pulmonary arteriosclerosis caused by their higher VTI of pulmonary blood flow. And we also found the younger children with defects>10mm in this study, which demonstrated that early surgery is needed for those to avoid pulmonary vascular obstructive disease as you comment. According to the latest results, we added a corresponding discussion in this part:

“The possible reason of the weaker vascular reactivity to higher PaCO2 in children with defect>10mm may accounted for their excessive pulmonary blood flow[33], which has been suggested produce alterations in the pulmonary vasculature, including vasoocclusive intimal
thickening and medical hypertrophy[34].”….. “Thus, we need realized that adjusting the ratio of Qp/Qs by increasing PaCO2 may not always be applicable to all patients, especially for children older than 18month with defect>10mm. Other measures of changing PVR or SVR should take into consideration individually.”….. “Therefore, further studies are still need to evaluate the effects of hypoventilation on children of different ages and defect types with L-R shunt, and develop individualized ventilation settings to optimize the Qp/Qs under various pulmonary vascular reactivity.”

Specific Comments4: In the "Discussion" on P9L7 the described effects of the citation were related to children with pHt and cannot be compared with those in this investigation although there might be some in this cohort with flow related pHt.

Response: we have deleted this reference as you suggested.

Specific Comments5: Please review the sentence on P11L 15ff "As shown in the results, pediatrics with defect>10mm had a larger flow of PA and 16 lower rSCO2 which may due to the relatively insufficient of cerebral blood flow" it's difficult to understand what you exactly want to say with it.

Response: We feel sorry that we didn’t provide explicit explanation. The new version is shown as follows: “For children with defect>10mm, their higher VTI of PA and lower intraoperative rSCO2 may result from the excessive pulmonary hyperperfusion and relatively insufficient of cerebral blood flow[31]. The prolonged length of stays in defect>10mm was consistent with previous postoperative follow-up study, in which an increased risk of postoperative cognitive impairment and a significantly prolonged LOS in patients with low intraoperative rSCO2 were revealed[32].”

Finally, let me reiterate and convey my sincerest gratitude to the reviewer for your hard work and constructive comments.