Author’s response to reviews

Title: Effects of lung protective mechanical ventilation associated with permissive respiratory acidosis on regional extra-pulmonary blood flow in experimental ARDS

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Point by point answers to the Reviewers’ comments:

Reviewer 1:

1. The title was changed as proposed by the reviewers

2. We stated in the Methods section that during instrumentation the animals were ventilated with a positive end-expiratory pressure set at 5 cm H2O, a peak inspiratory pressure (PAW) set at 15 cm H2O, and an inspiratory to expiratory ratio set at 1:1. After induction of lung injury pigs were paralyzed and mechanically ventilated using either an unchanged peak inspiratory PAW of 15 cm H2O resulting in low VT ventilation and hypercapnia or an increased peak inspiratory PAW resulting in an increase in VT and minute ventilation to compensate for respiratory acidosis. As both reviewers argued the PCV mode of mechanical ventilation in the setting of changing compliance is a limited model to compare distinct ranges of VT due to a significant overlap of VT in both study periods of limited or increased PAW. Therefore, it is certainly more precise to re-define the study periods as 1. mechanical ventilation with limited inspiratory PAW instead of low VT and 2. mechanical ventilation with increased PAW instead of increased VT. We are very greatful for this important comment of the reviewers and changed the respective wording throughout the manuscript (ventilation with limited PAW instead of low VT, and ventilation with increased PAW instead of high VT). As the reviewers proposed we also added Additional files with individual data of the experimental animals (see Additional file, and Results section)

3. Our study was designed as a cross-over study and the animals were randomized to start either with mechanical ventilation with limited or increased peak inspiratory pressure and then switched to the other mode. Therefore, we cannot present baseline characteristics according to
randomly assigned groups. However, baseline characteristics were collected for all animals during a stabilization period after induction of lung injury and before relaxation. During this period all animals were allowed to breathe spontaneously while being mechanically ventilated in a PCV mode (BIPAP). As the reviewer suggested we present these baseline data in the additional file.

4. See point 2 and Additional files: individual animal data.

5. We added the p-values in separate columns as proposed by the reviewer.

6. We clarified in the figure captions that mechanical ventilation with limited PAW targeted permissive respiratory acidosis and mechanical ventilation with increased PAW targeted normal pH.

7. See point 8 and Conclusion (“widely clinically accepted” deleted).

8. We deleted the second paragraph as suggested by the reviewer.

9. We markedly shortened the Discussion (see manuscript).

10. We agree with the reviewer that comparing high VT (increased PAW ) + normocapnia and low VT (limited PAW) + hypercapnia raises the problem that there is an interaction between effects caused by changes in CO2 and intrathoracic pressure. However, in our opinion and from a clinical point of view, this is a common scenario in the ICU and presumably better reflects the clinical practice of mechanical ventilation than experimentally separating the effects of changing CO2, pH and intrathoracic pressure. Therefore, we addressed this problem in the Limitations section: “Limiting inspiratory PAW resulted in a decrease in minute ventilation and moderate permissive respiratory acidosis which is common in daily clinical practice. Consequently, due to the combined variation of intrathoracic pressures and acid base balance we were not able to separate the effects of both parameters on the systemic and regional blood flows.”

11. As the reviewer suggested we addressed this point in the Limitations section: “Because direct measurement of regional perfusion is not possible in critical ill patients we used a porcine model of ARDS which was induced with oleic acid. Therefore, our findings are not generalizable to humans and may vary based on different etiologies of ARDS.”

12. See point 11.

13. We essentially shortened the Conclusion section.

Reviewer 2:

1. We added potential carry over effects due to the cross-over design in the Limitations section as follows: “Although gas exchange variables stabilized during equilibration periods before each measurement the time limits of our study probably were too short to elucidate potential carry over effects due to the cross-over design, e.g. long-term effects on a transcriptional/translational level and slow acting counter-regulatory effects.”

2. Please see answers to Reviewer 1, point 10.

3. Please see answers to Reviewer 1, points 8 and 9.

4. Please see answers to Reviewer 1, points 8 and 9.

5. We hypothesized that limiting inspiratory PAW associated with moderate respiratory acidosis results in an increase in systemic blood flow but an unequal distribution of blood flows to different organs and tissues (see Introduction section, last paragraph).

6. Please see answers to Reviewer 1, point 2.

7. Please see answers to Reviewer 1, point 4.

8. We amended the manuscript as the reviewer proposed and used “ARDS” instead of “acute lung injury.”