Author's response to reviews

Title: High tidal volume mechanical ventilation-induced lung injury in rats is greater after acid instillation than after sepsis-induced acute lung injury, but does not increase systemic inflammation: an experimental study.

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Author's response to reviews: see over
Dear Dr. Harris,

We are very grateful to the editorial board to appoint an extra reviewer and thereby give us the opportunity to clarify any ambiguities and further improve our manuscript.

We hereby submit our revised manuscript entitled “High tidal volume mechanical ventilation-induced lung injury in rats is greater after acid instillation than after sepsis-induced acute lung injury, but does not increase systemic inflammation: an experimental study.” by Jan Willem Kuiper, Frans B Plötz, AB Johan Groeneveld, Jack J Haitsma, Serge Jothy, Rosanna Vaschetto, Haibo Zhang and Arthur S Slutsky.

As requested, and to avoid confusion, we solely answered to the issues raised by reviewer 3. Needless to say, if requested to do so, we will be happy to answer to the issues raised by reviewer 2. Below you will find our answers to the comments made by reviewer 3. In particular those comments concerning the study design, specifically the choice of high and low tidal volumes and control groups. We therefore comment more extensively in the discussion in the second paragraph concerning the experimental models. In the paragraph on the limitations we discuss the control groups in more detail.

The changes are marked yellow in the revised version. On separate pages we have addressed the comments point by point in more detail as requested.
We would like to take the opportunity to thank the reviewers for reviewing our manuscript. We hope that the aforementioned changes have improved the manuscript in accordance to their recommendations.

I certify that the revised manuscript, or part of it, has not been published nor is currently under consideration for publication by any other journal. The co-authors have read the revised manuscript and approved its submission to BMC Anesthesiology.

Sincerely,

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REPLY

“High tidal volume mechanical ventilation-induced lung injury in rats is greater after acid instillation than after sepsis-induced acute lung injury, but does not increase systemic inflammation: an experimental study.” by Jan Willem Kuiper, Frans B Plötz, AB Johan Groeneveld, Jack J Haitsma, Serge Jothy, Rosanna Vaschetto, Haibo Zhang and Arthur S Slutsky. We thank the reviewers for their valuable comments.

Reviewer number: 3

Major revisions:

The absence of control animals that would have received mechanical ventilation with high and low tidal volume and no lung injury should be discussed.

This study was designed to test the hypothesis that the harmful effects of different ventilation strategies depend on the type of underlying lung injury. Since most ICU patients requiring MV have underlying lung injury we compared direct and indirect forms of lung injury, but not healthy lungs. In our opinion adding more groups of sham-instrumentated rats receiving either high or low tidal volume ventilation would not add to testing the hypothesis nor to the conclusion. We therefore further clarified the hypothesis and objectives of this study in the last paragraph of the introduction on page 5. We added a paragraph to the discussion, further explaining the abovementioned. Additionally, in the paragraph addressing the limitations of the study we have added additional sentences to clarify this.

The discussion section should be improved to better present previously published evidence that would support the choice of levels of high and low tidal volume.

In this study we aimed to induce lung injury by using a high tidal volume previously shown to do so. In the material and methods section on the experimental protocol we briefly commented on the chosen tidal volume, and provided references [refs 15-17]. As stated by the reviewer in his report, tolerable tidal volumes in animals with lung injury would lie somewhere between 6 ml/kg and 15 ml/kg. However, Herrera et al., stated that during sepsis tidal volumes of at least 20 ml/kg were needed to induce lung injury. In contrast during acid aspiration tidal volumes exceeding 16 ml/kg without PEEP likely increases
premature death of experimental animals [Chiumello et al., 1999). Additionally, one of the references provided by the reviewer indicate that even a tidal volume of 8 ml/kg may be harmful to healthy lungs [Vanecker et al., 2007 and 2008]. We therefore chose a high tidal volume of 15 ml/kg, balancing injury and mortality. We added a section in the second paragraph of the discussion. We apologize for the misunderstanding concerning our statement that 15 ml/kg does not injure normal lungs. In the discussion we referred to a study by Altemeier et al. showing that MV with a tidal volume of 15 ml/kg following systemic lipopolysaccharide does not cause gross histological changes. We subsequently meant to suggest that during sepsis MV with 15 ml/kg may still not be sufficient to induce significant lung injury. We removed this sentence from the discussion. We did never mean to suggest in our manuscript that, in general, MV with 15 ml/kg will never lead to lung injury. In contrast, in this study, we set out to induce lung injury by using tidal volumes of 15 ml/kg.

**Discretionary revisions:**

Usage of a single style, either UK or US.

*We edited the manuscript.*

What is meant by “one animal was ventilated per experiment”.

*In some experimental set ups it is possible to use one ventilator to ventilate several animals at the same time, however, we did not.*

Validation of the histology score mentioned on page 8 and 9.

*This histology score has been used and published before by our lab. We provided a reference.*

Comment on the evolution and comparison of the mean arterial pressure at baseline.

*We rewrote the paragraph on mean arterial pressure in the results section on page 9. We first analyzed the effect of the model, second we analyzed the effects of MV and third we analyzed the interaction between model and MW. At baseline, model did not have an effect on MAP, but when analyzing the whole experiment MAP was higher after acid*
Instillation than during sepsis. When analyzing interaction at baseline, MAP after acid instillation and LVt ventilation was higher than in the HVt sepsis group.

Comment on the evolution and comparison of the mean arterial pressure at 4 hrs. We rewrote the paragraph on mean arterial pressure in the results section on page 9. In all groups MAP decreased during the experiment. However, in the LVt sepsis group MAP decreased by 4 points as compared to baseline, in contrast in the HVt sepsis group MAP decreased by 9 points. In our analysis of interaction between model and MV, MAP in the LVt acid group was higher than in the HVt sepsis group.

Delete 5 first lines of page 12. We deleted the requested sentences.

Explain decompartmentalization. The term decompartmentalization has been used before and describes the transfer of, for example, cytokines from the intra-pulmonary compartment to the systemic circulation. We clarified the term on page 13, second paragraph.