Author’s response to reviews

Title: EFFECT OF PEEP AND I:E RATIO ON CEREBRAL OXYGENATION IN ARDS: AN EXPERIMENTAL STUDY IN ANESTHETIZED RABBIT

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Author’s response to reviews:

We thank the reviewers for their additional comments on our manuscript. We have done our best to clarify the remaining issues. Please find point-to-point responses below.

Nadja Carvalho (Reviewer 1)

1. Please include all comments for the authors in this box rather than uploading your report as an attachment. Please only upload as attachments annotated versions of manuscripts, graphs, supporting materials or other aspects of your report which cannot be included in a text format.
   Please overwrite this text when adding your comments to the authors.

R1. This comment does not seem to be addressed to the authors.

Pablo Cruces (Reviewer 2): Dear Dr. Bayat I agree with most of the answers and modifications made to the manuscript.
However, I have some queries

Dear Dr Cruces, thank you for your careful review of our manuscript. Please find responses to your additional queries below.

1. R5. Volume control mode was not used, because this ventilator mode is seldom used in patients with ARDS, because of the risk of ventilator-associated lung injury.
Whether pressure-controlled ventilation (PCV) can reduce ventilator-associated lung injury (VALI) compared to volume-controlled (VCV) ventilation is a matter of debate. A meta-analysis of three randomized controlled trials (RCTs) concluded that PCV was not superior to VCV [1]. Another systematic review which included 34 studies concluded that outcome is "unlikely influenced by simply using one breath type vs the other for all patients" [2]. Since flow, driving pressure, and frequency determine the power, and the factor by which ventilation injures the lungs, it seems unlikely that the manner in which this power is delivered (i.e., flow pattern) plays a major role. Despite their theoretical benefits, the clinical evidence of both techniques remains unproven and controversial for ARDS patients [3].

Undoubtedly it is much simpler to measure pulmonary mechanics (i.e. plateau pressure) in VCV mode.

R1. We take the reviewer’s point regarding ventilation mode. However, since we used oscillometry to measure respiratory mechanics in this study, the PCV mode posed no difficulty.

2. R9. As stated in the Methods section (page 7), the order of I:E ratios was randomized. What method was used to randomize the rats.

R2. Please note that the experiments were performed in rabbits. We used the random number function in Microsoft Excel; Rand(), to randomize the order of ventilation modes.

3. I understand the difficulties of measuring cardiac output by pulmonary thermodilution in subjects of 3.5 kg. However, the authors state that: "Arterial, central venous and respiratory pressure, ECG and CF signals were digitized and recorded at 1 kHz using an analog/digital interface (Powerlab model 8/35, ADInstruments)". Why not use dynamic preload markers (PPV or SPV) to estimate preload?

R3. The reason is that these indicators (PPV or SPV) reflect the position on the Frank-Starling curve. In the absence of hypovolemia, i.e.: on the flat portion of the Frank-Starling curve (which was the case in the present study), these parameters are insensitive to changes in preload or venous return induced by mechanical ventilation.

4. Table 1. Tables should be self-explanatory Vein SO2 is Jugular bulb saturation (SjO2) or central venous saturation (ScvO2)? When reading the manuscript I understand that the authors refer to SjO2. ScvO2 values were recorded? It would be interesting to have ScvO2. Parallel changes of SjO2 and ScvO2 reaffirm that hemodynamic deterioration due to inversed I:E ratio ventilation induces cerebral oxygenation deterioration. The homogeneity of venous lactate is surprising in the successive measurements.

R4. We apologize for the lack of clarity. As mentioned in the methods, the jugular catheter was placed cranially in order to better appreciate cerebral venous values. We therefore consider these blood gas parameters as peripheral venous values. This is consistent with what is stated in Table 1. We have clarified this further in the table and table legend.
Stefan Kreyer (Reviewer 3): The authors sufficiently replied to the comments and I have no further questions except for:

1. In the abstract on page 2, l.20 the authors said: ....the animals were ventilated with PEEP=9 or 6 cmH2O in random order......
The PEEP level was not randomized as stated in the replies and in the manuscript. Is this an error?

R1. Dear Dr Kreyer, thank you for catching this error. It is now corrected in the abstract.