Author's response to reviews

Title: Cardiorespiratory effects of recruitment maneuvers and positive end expiratory pressure in an experimental context of acute lung injury and pulmonary hypertension

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

We would like to thank you for giving us the opportunity to revise our manuscript entitled “Cardiorespiratory effects of recruitment maneuvers and positive end expiratory pressure in an experimental context of acute lung injury and pulmonary hypertension” for consideration for publication in BMC Pulmonary Medicine.

Please find below point-by-point Reply to the Reviewer:

“Camille Doras et al. carried out a study aimed at evaluating how ALI and pulmonary hypertension influence the cardiorespiratory effect of recruitment manoeuvre and PEEP in animal model. The topic of the study is very interesting, since the “open the lung strategy” is still discussed. Some point need to be addressed.”

Reply 1: We thank the Reviewer for the thorough revision of our manuscript and for the positive feed-back and the highly pertinent comments.

“Major Compulsory Revisions
In general the “open the lung and keep it open” strategy is accepted. However, so far there is not clear evidence that a different PEEP level (or RM) can modify mortality in ARDS: please discuss.”

Reply 2: We agree with the Reviewer that limited evidence is available in the literature about the beneficial effect of high PEEP (or RM) to decrease mortality in ARDS patients. We reworded the relevant text in the introduction (Page 2, lines 82-84) to address this limitation.

“Introduction: “This hypothesis is based on the postulate that opening the lung in the presence of ALI will blunt the adverse pulmonary hemodynamic consequences of RM since the transmural pressure is expected to be lower”. This sentence should be clarified; since RM can compromise right heart function, why PH is expected to be protective? I think that the main concern is to better discuss PH (do you mean “post-capillary PH”, as indicate in your animal model?). If you mean “post-capillary PH”, please clarify this concept both in introduction and in discussion (otherwise the readers can be confused between pre- and post-capillary PH).”

Reply 3: Based on the Reviewer’s comment, the final paragraph of the Introduction has been substantially reworded. We clarify in the revised version of the manuscript the postulates behind the hypotheses how PHT and ALI may blunt the adverse pulmonary hemodynamic consequences of RM and PEEP (page 2-3, lines 101-105).

We apologize for the confusion about the use of “post-capillary” PHT following monocrotaline administrations. A thorough revision of the relevant literature revealed that such intervention leads to a plexogenic PHT with alterations in the alveolar pulmonary capillary tissue layers. This term has been corrected in the revised version of the manuscript (page 8, line 294).

“Results: “Over the initial pool of 19 rabbits, animals were excluded for some parameters, for technical or medical reasons. Seven rabbits were excluded for the right ventricle PV measurement due to defects of the catheter, and three animals were excluded from all data because of systemic failures during anesthesia.”: the final number of animals you evaluated should be clearly stated in this section.”

Reply 4: In agreement with the Reviewer’s comment, the final number of animals is now specified in the revised version of the manuscript (page 6, lines 231-233).
“Since the number of animals is limited, I will show single changes of the parameter you reported in figures.”

Reply 5: We are aware that the number of animals included in the main data set (n=8 in each group) is limited. This sample number was based on prediction statistics performed prior to the study to detect 20% difference at 0.05 significance level, with a power of 0.8.

As the Reviewer proposed, we modified the graphs to demonstrate individual animals (see below). Since each graph shows 4 conditions with 8 data sets in each, 32 lines (and 4 means) are displayed. The vast number of plots overloads the graph and masks the most important findings. Thus, we would like to keep the group mean and SEM representations for clarity.

“Discussion:
In ARDS patients, the effect of PEEP on gas exchange, evaluated by lung diffusion for carbon monoxide (DLCO), that allows to measure capillary lung volume (Vc), has been previously evaluated (I will include this in discussion).”

Reply 6: We added a section to discuss these earlier findings in the context of our results in the revised version of the manuscript (page 9, lines 337-340).

“A section about “study limitation” is missing; do you think the number of experiments you performed is enough to support your conclusion?”

Reply 7: The study limitations section is not included in the manuscript, however the Discussion addresses the limits of our findings. The most important limitations are related to the use of surfactant depletion as a model of ALI and the application of monocrotaline to induce PHT. The critical methodological considerations are included in the relevant part of the discussion (page 8, lines 300-304 and page 8 lines 307-308). As concerns the Reviewer’s question about the sufficient number of experiments, we would like to refer to our previous reply (Reply 5), where we describe the sample number prediction in the phase of the protocol design. Since the power of the statistical tests were exceeded 0.8 at p=0.05 level, we are confident about the reliability of our data to support our conclusions.

“These findings imply that adaptation of open lung strategy can be safely considered even in the presence of PHT.” Authors provided an animal model study; I would be more cautious in this conclusion.”

Reply 8: The quoted sentence in the Conclusions has been reworded to take into account the Reviewer’s comment (page 10, lines 357-359).