Reviewer's report

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

Version: 0 Date: 23 Jul 2017

Reviewer: Jeremy Beitler

Reviewer's report:

COMMENTS TO AUTHORS

Thank you for giving me the privilege of reviewing your interesting manuscript. My comments and suggested revisions, intended only to build upon your interesting findings are as follows:

1. TITLE: Consider using the phrase "regional extrapulmonary blood flow" in the title. When I first saw the title, I expected to read about regional blood flow in the lungs, not other organs. Also, the title is excessively long and could be shortened by deleting "a crossover randomized trial" and deleting "systemic," since the effects of hypercapnia on cardiac output are well-described in existing literature.

2. METHODS: Because the pressure-control mode was used, tidal volume will decrease as lung injury (and lung compliance) worsens. Thus, the crossover design becomes problematic. Indeed, the standard deviations for "high" and "low" tidal volume demonstrate considerable overlap between groups. If the animal was already near 6 mL/kg during "high Vt," how was the ventilator changed during low Vt?

3. RESULTS: Please present baseline characteristics according to randomly assigned group, either in the main manuscript or an online supplement.

4. RESULTS: Since there are only 9 animals, please also present individual-animal data, perhaps in an online supplement. It would be helpful to see differences in Vt.

5. TABLES 1-4: Please present all p-values in a separate column.

6. Figures 1-2: Clarify in the Figure captions that high Vt targeted eucapnia and low Vt targeted hypercapnia.
7. DISCUSSION, 2nd paragraph: ARDSnet was not a trial of permissive hypercapnia. Average PaCO2 in the low-Vt arm was 40 mmHg on day 1. By contrast, Amato NEJM 1998 did allow permissive hypercapnia. Permissive hypercapnia remains controversial and is not universally accepted among clinicians. Please address/revise.

8. DISCUSSION: The 2nd paragraph of the Discussion is almost identical to the Introduction and could be deleted or at least significantly modified.

9. DISCUSSION: The Discussion is exceedingly long, especially relative to the amount of original data presented in the manuscript. Much of it is a review of well-known CO2 effects in other organs and is not specific to the data presented.

10. METHODS & LIMITATIONS: Why did the authors compare high Vt + eucapnia with low Vt + hypercapnia? A design more relevant to their question would have been to compare low Vt with vs without hypercapnia. Using high Vt raises the possibility that ventilation-induced lung injury and biotrauma, or changes in intrathoracic pressure, perturbed regional blood flow independent of CO2.

11. LIMITATIONS: Findings in pigs regarding regional blood flow may not be generalizable to humans. Please address in your limitations.

12. LIMITATIONS: Findings were tested only in an oleic acid model. The effects of hypercapnia may vary based on etiology of ARDS. Please address in your limitations.

13. CONCLUSION: I disagree with the statement "the increase in splanchnic and intestinal perfusion during low Vt ventilation and hypercapnia without any doubt is advantageous in critically ill patients." I am not aware of any clinical data supporting this claim. Please provide references supporting this claim and modify this statement as appropriate.

14. CONCLUSION: Much of the Conclusion repeats text in the Discussion and is not relevant to the data presented but rather is a review of established physiology. The Discussion and Conclusion also should be careful not to conflate findings from a small pig study to those of critically ill patients.
Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Yes

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

Quality of written English
Please indicate the quality of language in the manuscript:

Acceptable

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