Reviewer's report

Title: Comparison of the Effects of Moderate and Severe Hypercapnic Acidosis on Ventilation-Induced Lung Injury

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Reviewer: John Laffey

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Yang et al present data from an in vivo animal experiment in which they elucidate the dose response characteristics of acute hypercapnic acidosis in the setting of VILI in the rat. The authors find that moderate hypercapnic acidosis is more protective than severe hypercapnic acidosis, and is better tolerated in terms of haemodynamic and oxygenation indices. I have a number of comments.

Major compulsory Revisions

1. It would be helpful if the authors could clarify why they selected their ventilator settings. What made them decide on these particular ventilator settings, particularly the PIP and the FiO2? VILI studies usually quantify their inflation settings as tidal volumes in ml/kg, but there is no mention of tidal volume here.

2. Please clarify whether the in vivo experiments were carried out as a single 5 group series or as 1 series of 2 groups [Sham and NV groups] and 1 series of 3 groups [NC, MHA, SHA].

3. The authors should graph some of the key physiology data, including BAL protein, BAL cell counts, and Wet:Dry weight ratios, and perhaps 1-2 exemplar cytokines.

4. Can the authors include data for the NV group in Figure 1? This would help the reader understand the extent of the protection from injury conferred by MHA.

5. The authors suggest that their anesthesia regimen for the animals was ‘inappropriate’. I am unsure what this statement means, but the authors need to provide some reassurance that the animals were adequately anesthetized throughout the experimental protocol, and that this was tested at regular intervals, such as by confirmation of the absence of a motor or hemodynamic response to paw clamp.

Minor essential Revisions

1. Please give some actual experimental data in the results section of the abstract rather than just giving statements and p values about the results.

Discretionary Revisions

1. I would rephrase the opening line of the abstract. A number of groups have
demonstrated protective effects of hypercapnic acidosis in the setting of VILI, and did so prior to the work of the current authors.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests