Author’s response to reviews

Title: Regulating Autonomic Nervous System Homeostasis improves Pulmonary Function in rabbits with Acute Lung Injury

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Version: 3 Date: 08 Jun 2017

Author’s response to reviews:

Manuscript ID: PULM-D-16-00357R2

Title: Regulating Autonomic Nervous System Homeostasis improves Pulmonary Function in rabbits with Acute Lung Injury

Dear editor,

Dear editor and reviewers,

Thank you very much for your letter and comments concerning our manuscript entitled “Regulating Autonomic Nervous System Homeostasis improves Pulmonary Function in rabbits with Acute Lung Injury” (Manuscript ID: PULM-D-16-00357R2). Those comments are all valuable and helpful to improve our research.

We have studied the comments carefully and have made corrections which we are hope meet with approval. Revised portions are highlighted by track changes mode in MS word in the paper. The point-by point responses to comments are listed below.

We are looking forward to getting your approval for its publication. If you have any additional questions, please contact us without hesitation.

Sincerely yours,

Wenzhi Li and Yulong Bo

Responses to comments
1) Although you stated that "All data were expressed as mean ± standard deviation (SD)" you did not make those changes in your graphs. Therefore, we require that you make edits to your graphs.

Response: Thank you very much for your comment. We have revised the figures to present with mean ± standard deviation, and the new revised figures have been affiliated in this revised version.

2) It does not appear that you addressed Reviewer 3’s comments about bupivacaine dose in that you only addressed the pentobarbital dose. The original comment by Reviewer 3 was "A bolus of 5 ml bupivacaine 0.25% seems rather high to me, due the fact that the maximum dose for humans should not exceed 2 mg/kg and the rabbits in the current study received doses of 4.6 - 3.9 mg/kg. What’s the rationale for this high dose? How do the doses in rabbits compare with humans? Have any adverse events been noted (see also ARRIVE checklist)?"

Response: Thank you very much for your comment. We are sorry that we did not carefully response to this point. In this revised version, we have responded to this comment of Reviewer 3 as follows:

Because of the difference between humans and rabbits, the dose of bupivacaine applied in humans was only provided a reference for our study. The final dose of bupivacaine applied in this study was determined via several different intensity of invasive manipulation in preliminary experiments. Because there is a very strong impulse to insert a tracheal catheter into dissected trachea, insufficient of anesthesia can induce a strong excitation in sympathetic nerve. This result is not advantage for us to investigate the balance of autonomic nervous system homeostasis. Therefore, according to several trial with different anesthetic concentration, the final usage of bupivacaine was determined. No adverse events were identified in this short-term research.

3) Page 3 line 24, there is a typo where you write "inflammayion" instead of "inflammation". Please change this and go over the manuscript to make sure there are no other typos.

Response: Thank you very much for your comment. We have revised “inflammation” to “inflammation” in the manuscript. Meanwhile, the other typos were also revised. The revised proportions are highlighted by rack changes mode in MS word.

Reviewer reports:

Tobias Piegeler (Reviewer 3): Thank you for letting me review the second revised version of the manuscript "Regulating Autonomic Nervous System Homeostasis improves Pulmonary Function in rabbits with Acute Lung Injury", authored by Yan Liu et al. I appreciate the authors’ efforts to improve their manuscript, but unfortunately there are still some issues with this manuscript, which I think have not been clarified yet.
1. Statistics and Figures: The authors now state that they had already changed SEM to SD in the previous version. Looking at the figures from the initial submission as well as from the versions R1 and R2, I really have to say that the size of the error bars in figures 1-5 look very similar in most of the cases when comparing the three versions of the manuscript. What's the explanation for this? Please comment.

Response: Thank you very much for your comment. We are sorry that we didn't revise the figures in the previous revised versions. At this time, we have revised the figures to present with mean ± standard deviation. The new revised figures have been affiliated.

2. In my previous review of Version R1 I had asked about the bupivacaine dose. Unfortunately, the point-by-point response by the authors only includes information about pentobarbital (which I didn't ask about).

The original comment was "A bolus of 5 ml bupivacaine 0.25% seems rather high to me, due the fact that the maximum dose for humans should not exceed 2 mg/kg and the rabbits in the current study received doses of 4.6 - 3.9 mg/kg. What's the rationale for this high dose? How do the doses in rabbits compare with humans? Have any adverse events been noted (see also ARRIVE checklist)"

Response: Thank you very much for your comment. Because of the difference between humans and rabbits, the dose of bupivacaine applied in humans was only provided a reference for our study. The final dose of bupivacaine applied in this study was determined via several different intensity of invasive manipulation in preliminary experiments. Because there is a very strong impulse to insert a tracheal catheter into dissected trachea, insufficient of anesthesia can induce a strong excitation in sympathetic nerve. This result is disadvantage for us to investigate the balance of autonomic nervous system homeostasis. Therefore, according to several trials with different anesthetic concentrations, the final usage of bupivacaine was determined. No adverse events were identified in this short-term research, and this statement was also added in the manuscript.