Author’s response to reviews

Title: Hypoxia preconditioning attenuates lung injury after thoracoscopic lobectomy in patients with lung cancer: a prospective randomized controlled trial

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Author’s response to reviews:

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Thank you for your letter and the reviewers’ comments concerning our manuscript entitled “Hypoxia preconditioning enhances recovery after thoracoscopic lobectomy in patients with lung cancer: a prospective randomized controlled trial”. Your comments are very valuable and helpful for revising and improving our manuscript, as well as the important guiding significance to our research. We have studied your comments carefully and have made corrections which we hope meet with your approval. All changes to the manuscript are marked in yellow in the text. The responds to your comments are at the following:

The editor:

1. Please explain why did you choose PaO2/FiO2 as your primary outcome.

Response: PaO2/FiO2 is a good oxygenation parameter in acute lung injury. It is a useful indicator for detecting impaired gas exchange and oxygenation among patients receiving a wide range of FiO2 (PMID: 17573487). It can be used to indicate the preventive effect of HPC. As Reviewer #3 suggested that the major limitation of our study is PaO2/FiO2 should be measured more often, not only 30 min after OLV and 7 days after the surgery. It deserves to be studied in the further study.
2. Please explain why PEEP was not used for controlled ventilation during the trial.
Response: Mechanical ventilation during surgery was provided without PEEP in this study. Excessive PEEP may cause lung pressure injury and low PEEP does not effectively dilate collapsed alveoli. It’s key to choose proper PEEP. Considering it’s complex and correct position of DLT was confirmed by fiberoptic bronchoscope, we didn’t choose PEEP to improve oxygenation.

3. Explain why the length of postoperative stay was longer than reported in other studies.
Response: It is really true that the average postoperative stay of both groups in our study was a little longer than reported in other studies. The average postoperative stay is also affected by other factors, for example, different payment methods and postoperative stay costs. And we don’t have a very large number of cases.

4. Provide detailed information on the technique of thoracic paravertebral block.
Response: Thanks to your valuable suggestion. The thoracic paravertebral block is a very important thoracic postoperative analgesia technique. The detailed information of thoracic paravertebral block should be attached. We have added it on Page 5, line 109, highlighted in yellow.

Reviewer #1:
1. I think that in Table 2 should be included the value of the FiO2 used in each group and analyze if there is any difference in this aspect between the two groups.
Response: It is really a detail which should not be neglected as Reviewer suggested. The FiO2 is a very important factor and was initially set at 60%, and in case of low SpO2, FiO2 was increased to 100%. Only two patients’ FiO2 of the HPC group was not increased. The value of the FiO2 used in each group has been added in Table 2 and highlighted in yellow.

2. I suppose that only lobectomies and not bilobectomies are included in this study. If there were also bilobectomies, they should also be included in this same table to see if there are differences between groups.
Response: We are very grateful to Reviewer for reviewing this paper so carefully. Considering very few patients required bilobectomies and possible adverse effects of bilobectomies on postoperative pulmonary function, we didn’t include bilobectomies.

3. The average postoperative stay of both groups seems a bit long with respect to the literature. Do you have any reason to explain it?
Response: Thanks for reviewing our manuscript carefully. It is really true that the average postoperative stay of both groups is a bit long with respect to the literature. The average postoperative stay is also affected by other factors, for example, different payment methods and postoperative stay costs. And we don’t have a very large number of cases.
4. Finally, lung injury is very important in thoracic surgery with unipulmonary ventilation. From the results of this study it can not be concluded that there are differences in pulmonary complications between both groups so there is not enough evidence in this study to conclude that hypoxic hypoxic preconditioning is associated with lower incidence of lung injury.

Response: Thanks for your valuable comments. We concluded that hypoxic preconditioning is associated with lower incidence of lung injury for the reason of significantly increased PaO2/FiO2 ratio in HPC group at 30 min after one-lung ventilation and 7 days after operation. PaO2/FiO2 is a good oxygenation parameter in acute lung injury. However, there was no differences in pulmonary complications between both groups in our study. We speculated that this may be due to the low number of cases.

Reviewer #2:

1. Although this is a well-designed study with a smart intention, there was no statistical difference in BIS values between both sides. BIS has a usual trend esp during the operation and more often in position changes, where changes within 3-5 do not play usually a clinically relevant role.

Response: I’m sorry! We didn’t monitor BIS intraoperative.

2. Do you think that the (insignificant) difference between both sides can have a relevant role in anesthetic approach? If yes, I think this should be speculated in Discussion.

Response: Thanks for your suggestion. We assessed the protective effect of hypoxia preconditioning on lung injury in patients undergoing thoracoscopic lobectomy. During this study, we strive to control the effects of anesthetic approach on lung injury. We used a standardized perioperative anesthetic management protocol and mechanical ventilation during the surgery was provided without PEEP in our study.

Reviewer #3:

MAJOR COMMENTS

1. Major limitation of the study is the choice of primary outcome parameters. PaO2/FiO2 is a good parameter but probably more measurements (i.e., not only 30 min after the start of OLV and 7 days after the surgery, but more often; it could be extremely interesting to see the values just before and after HPC intervention). The same apply for parameters from spirometry. How were 7-days values obtained in the patients discharged before 7 days (see Table 4 for postoperative hospital stay)? Moreover, it is strange that no difference in morbidity translated into significant difference in hospital length of stay. Furthermore, the patients were excellently fit (see spirometry values in Table 1, i.e., before the surgery), and this should be listed also as limitation of the study.

Response: It is really true as Reviewer suggested that PaO2/FiO2 and parameters from spirometry should be measured more often, not only 30 min after OLV and 7 days after the surgery, especially just before and after HPC intervention. It deserves to be studied in the further research. Few people discharged before 7 days. We didn’t get their 7-days values. It is really strange that no difference in morbidity but translated into significant difference in hospital length of stay. This is a limitation of this
study. We speculate that it maybe due to the low number of cases in our study, and we expect more studies to verify the preventive effect of HPC on lung injury.

2. I would suggest to modify the title of the manuscript, e.g., HPC attenuates lung injury after …
Response: We appreciate it very much for this good suggestion, and we have modified the title of the manuscript according to your idea and highlighted in yellow.

3. P4/L2. The authors state that there is little clinical evidence regarding protective effect of HPC on lung injury - still it should be cited and discussed here, i.e., what research has been done until now with appropriate references. Moreover, the authors should explain how this limited evidence currently available influenced the design of their clinical study.
Response: We are very sorry for our inaccurate statement. As far as we know, the studies we have found on the protection of hypoxia preconditioning on lung injury are mainly at the animal level, and the relevant clinical studies are lacking (PMID: 21599636, PMID: 30622474). We modified it to directly introduce our conjecture.

4. In Methods section, there is detailed description of anesthesia provided, followed by the description of intervention (HPC). The intervention should be certainly described with more details, e.g., how was the other lung ventilated during HPC (OLV to non-operated lung) - was the same protocol used as described in methods as general approach to all patients, or where there any differences? Precise specification of tidal volume, FiO2, PEEP, concentration of sevoflurane etc. for HPC is needed as it represents the crucial part of the study.
Response: As Reviewer suggested that it is important to add how was the other lung ventilated during HPC. The non-operated lung received normal mechanical ventilation as general approach to all patients (Page 6, line 119). Precise specification of tidal volume, respiratory rate, FiO2, concentration of sevoflurane in the HPC group has also been added on page 6, line 117 and highlighted in yellow. In our study, mechanical ventilation during HPC and the surgery was provided without PEEP in the HPC group.

5. The authors stated that mechanical ventilation during the surgery was provided without PEEP - was it really the case? The duration of OLV was approx 2.5 h in both groups thus one could expect problems with desaturation (i.e., decrease in SpO2 values) during OLV in some patients. Was FiO2 1.0 only measure needed to keep the patients adequately oxygenated or other measures to improve oxygenation were used (e.g., CPAP to non-dependent lung)?
Response: It was really true that mechanical ventilation during the surgery was provided without PEEP in this study. Excessive PEEP may cause lung pressure injury and low PEEP does not effectively dilatate collapsed alveoli. It’s key to choose proper PEEP. Considering its complex and correct position of DLT was confirmed by fiberoptic bronchoscope, we didn’t choose PEEP to improve oxygenation. FiO2 1.0 was not only measure to keep the patients adequately oxygenated. Intermittent two-lung ventilation was used when saturation of pulse oxygenation (SpO2) less than 90%.

6. There is no information about extubation, duration of postoperative ventilation, early postoperative care, time in ICU/standard ward etc.
Response: We are very sorry for our negligence of extubation, duration of postoperative ventilation, early postoperative care, time in ICU/standard ward etc. Although we focus on postoperative complications, these details should not be neglected as Reviewer suggested. Our clinical trial design was not scientific enough to collect these data.

7. P10/L219: I would suggest to mention only „prevention“, not „treatment“ of lung unjury (as HPC is a preventive measure certainly).
Response: Thanks for careful reviewing our manuscript. The HPC is a preventive option. We have deleted “treatment” on page 10, line 218.

MINOR COMMENTS
1. In Figure 1, 6 patients were excluded due to open thoracotomy - it was realized probably during the surgery (in inclusion criteria there was thoracoscopic procedure) thus should be moved below randomization (?).
Response: We are very grateful to Reviewer for reviewing our paper so carefully. The flow diagram of this study we made was wrong and we didn’t examine it carefully. We have repainted Figure 1.

2. P5/L110. A little bit more detail about thoracic paravertebral block could be provided.
Response: Thanks to your valuable suggestion. The detail of thoracic paravertebral block should be attached. We have added it on Page 5, line 107-109, highlighted in yellow.

3. Table 1. I would suggest to divide „Smoking“ to 3 categories: non-smoker, ex-smoker, current smoker.
Response: Thank you for reading carefully. We have modified it according to your suggestion in Table 1.

4. Table 1. The values depicted as „Predicted FVC and FEV“ should be marked as measured values expressed as % of predicted values (depending on patient's characteristics).
Response: We are very grateful to your work! We didn’t find this mistake when checking. It has been modified and highlighted in yellow in Table 1.

TECHNICAL COMMENTS
1. Table 3. The columns for Control and HPC groups should be exchanged to follow the pattern of other three tables where first column is for HPC group.
Response: We deeply appreciate this comment. The columns for Control and HPC groups have been exchanged to follow the pattern of other three tables according to your idea and highlighted in yellow.

We have tried our best to improve this manuscript and made some changes in the manuscript.
appreciate for Editor and Reviewers’ warm work earnestly, and hope that the corrections will meet with approval. Once again, thank you very much for your comments and suggestions.

Yours sincerely,

Yan Zhang