Author’s response to reviews

Title: PROtective Ventilation with a low versus high Inspiratory Oxygen fraction (PROVIO) and its effects on postoperative pulmonary complications: protocol for a randomized controlled trial

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Responses to the reviewers’ comments
We would appreciate the editor and reviewers very much for their positive and constructive comments and suggestions on our manuscript. Our point-by-point responses to the reviewers’ comments are as follows:

Reviewer #1:
1. p.5, L42-54: 'Setting FiO₂ intraoperatively is a significant task of anesthetists, but has not based on evidence-based guidelines. Obtaining comprehensive knowledge about hyperoxia caused by high FiO₂ has been stressed by clinicians over the past few decades. Potentially preventable hyperoxia and substantial oxygen exposure are common in clinical practice to maintain satisfactory oxygenation [17]. However, there’s no significant difference in pulse oximetry, oxygenation index and functional residual capacity for several time-points with 30% or 80% FiO₂ intraoperatively [18]"  
>> I assume that the authors suggest hyperoxia to be deleterious for the lung, but it is not clear in this
paragraph. The authors mention it further down, but I would advise to make this clear in this paragraph too, as it is the main pathologic issue which their study examines.
Response: Thanks for your suggestion. We have rewritten this paragraph.

2. I would also advise the authors to add a small paragraph on background of hyperoxia induced lung injury. What is the mechanism?
Response: Thanks for your advice. We have added some explanations of hyperoxia induced lung injury. And more mechanisms are mentioned in discussion.

3. p.6, L1: The recent systematic review revealed'
Response: Thank for your suggestion and we have deleted "the".

4. p.8, L 9-10: 'The ARISCAT score will help to analyze the effect of FiO₂ to intermediate high risk patients who get a score of more than 26.'
Response: Thanks for your correction and supplementary explanation has been made.

Reviewer #2:
1. Please correct the sign after NYHA on page 6. It is presented as a square.
Response: Thanks for your correction. We have revised the sign.

2. Please delete one punctuation on p 6 after "(defined as SpO₂ < 92% or PaO₂ < 60 mmHg)"
Response: Thanks for your correction. We have deleted one punctuation.

3. Page 8 "Intraoperative care": Please write Vasoactive instead of "vasoactive" at the beginning of the sentence
Response: Thanks for your correction. We have revised "vasoactive" to "Vasoactive".

4. Page 8 "Rescue strategies for intraoperative hypoxemia" I think you mean „We designed" instead of „We design".
Response: Thanks for your correction. We have revised "design" to "designed".

5. Page 10 „Data collection and follow-up“ Please write …on postoperative day 1, 2, 3, 5, 7 or…
Response: Thanks for your correction. We have added the word “day”.

6. page 10 last sentence: please write „include" instead of „includes"
Response: Thanks for your correction. We have revised "include" to "includes".

7. page 11: „DSMB have access to patient allocation, but the results of interim analysis will be treated as strictly confidential." You should write : DSMB members have... or DSMB has....
Response: Thanks for your correction. We have revised " DSMB have..." to " DSMB has...".

8. page 11 „Study drop-out“ Please write: „Both situations“ without „two".
Response: Thanks for your correction. We have deleted the word "two".

9. page 12: I think you mean „In a descriptive analysis of population..." instead of „In a descriptive
analysis to population...
Response: Thanks for your correction. We have revised "...analysis to population..." to "...analysis of population...".

10. page 13: I think you mean „A multicenter observational trial collecting the ventilator data 1h after induction found .... the elderly [41].” Please change find and elder!
Response: Thanks for your correction. We have revised two words.

11. page 14, please add a comma after Yet: „Yet no direct evidence revealed...."
Response: Thanks for your correction. We have added a comma.

12. page 14: „The major differences from PROVIO trial are: the appearance of pulmonary complications...” please write: compared to the PROVIO...
Response: Thanks for your correction. We have rewritten the sentence.

Additional Changes
We find some other grammatical and format problems after carefully inspection. Listed as followed:
- Abstract: We have rewritten the last sentence in background.
- Abstract: We have revised "under" to "undergoing".
- Abstract: We have added a word "group".
- Abstract: We have revised "in" to "added to".
- Abstract. L.11: We have deleted a word "as".
- p.5 L.1: We have added a word "the".
- p.5 L.5: We have revised "surgery" to "surgeries".
- p.5 L.11: We have revised "," to "and".
- p.5 L.13: We have revised "pulmonary complications" to "PPCs".
- p.5 L.25: We have revised " which refers to " to "referring".
- p.5 L.29: We have revised "ICU" to " intensive care unit (ICU)".
- p.5 L.31-32: We have revised "A decrease of PPCs, mortality and health system costs ..." to " The decreases of PPCs, mortality and health care costs...".
- p.6 L1: We have added " the effects of ".
- p.6 L.17-23: We have revised "We hypothesize that compared with high FiO₂ (80%), a low level of FiO₂ (30%) would decrease the incidence of PPCs in patients undergoing abdominal surgery when both are treated with lung-protective ventilation strategy. " to "."
- p.6 L.41: We have added a word "etc".
- p.7 L.40-42: We have deleted "and observe".
- p.8 L.13: We have deleted "general".
- p.8 L.21: We have revised "...depending on individuals and clinical routines. " to "...according to clinical routines.".
- p.8 L.23-25: We have deleted "Moreover, the participants will be managed intraoperatively with the anesthetic plan drew up by the attending anesthetist. "
- p.8 L.27: We have added a sentence "...and individualized health care will be performed intraoperatively.".
- p.8 L.42: We have deleted "and induction".
- p.8 L.46: We have revised "...low FiO₂ (30% FiO₂) or high FiO₂ (80% FiO₂) during mechanical ventilation. " to "...low (30%) or high (80%) FiO₂ throughout the whole period of intraoperative mechanical ventilation after tracheal intubation."
We have revised "Ventilatory parameters will be monitored by the anesthesia machine and recorded: tidal volume, minute volume (MV), Paw, plateau pressure (Pplat), fresh gas flow, PEEP and FiO₂. " to " Ventilatory parameters, including tidal volume, minute volume (MV), Paw, plateau pressure (Pplat), fresh gas flow, PEEP and FiO₂, will be monitored."

- p.9 L.39: We have added a word "been".
- p.10 L.53: We have added a word "criteria".
- p.11 L.9: We have revised "...during the screening period, hospitalization period and follow-up period." to "...during the screening, hospitalization and follow-up periods.".
- p.11 L.17: We have revised "body mass index" to "BMI".
- p.11 L.42: We have deleted "anesthetic procedure".
- p.12 L.1: We have deleted "which is ".
- p.12 L.45: We have added "80%".
- p.13 L.23: We have revised "was" to "is".
- p.13 L.45: We have revised "find" to "show".
- p.14 L.27: We have revised "there is still contradiction not confirming..." to "there is contradictory view on...".
- p.14 L.45-46: We have deleted "(VA/Q) which poorly ventilated relatively to perfusion.".
- p.14 L.48: We have revised "lower" to "lowers".
- p.14 L.50: We have revised "synthetic" to "synergetic".
- p.14 L.50: We have revised "which" to "that".
- p.15 L.9: We have revised "about" to "in".
- p.15 L.19: We have revised "found" to "showed".
- p.15 L.31: We have revised "complications" to "complication".
- p.17 L.19: We have deleted "VA/Q: ventilation/perfusion-ratio; ".
- p.16 L.1-13: We have added "Firstly" and "Thirdly ".
- p.16 L.11: We have revised "which" to "that".
- p.16 L.17: We have revised "relation of" to "relationship between".
- p.16 L.19: We have revised "in" to "added to".

We thank you very much for giving us an opportunity to revise our manuscript. We have studied reviewers’ comments carefully and tried our best to have made revision which marked in red in the paper.