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

Authors:
Xue-Fei Li (kikyou015@163.com)
Dan Jiang (631688232@qq.com)
Yu-Lian Jiang (liano5@foxmail.com)
Hong Yu (happyjia1990@foxmail.com)
Jia-Li Jiang (834143383@qq.com)
Lei-Lei He (171764169@qq.com)
Xiao-Yun Yang (cdyangxiaoyun@163.com)
Hai Yu (yuhaishan117@yahoo.com)

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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. Trial Registration
As the authors aim to publish in an international journal, I would to also register their trial on an international site (such as ClinicalTrials.gov or other)
Response: Special thanks for your good suggestion. Chinese Clinical Trial Registry (ChiCTR) is an international clinical trials registry platform and meets the requirements of the ICMJE (https://www.who.int/ictrp/network/primary/en/). A staff member suggested us to register our trial on
ChiCTR when applied for an account on ClinicalTrials.gov.

2. Throughout the manuscript sentences are written in the past tense. However, as this is the protocol of a trial that has not been finished yet, it is more logical to use present or even future tense. Please adjust. Some examples, but there are more in the text:

- Abstract: 'Postoperative pulmonary complications (PPCs) have been the most common peri-operative complication following surgical site infection'
- p.8 L1: '…and ventilation settings were permitted to alter until acquiring the satisfied oxygenation…' settings are permitted to alter.

Response: Thanks for you suggestion. We have rewritten some parts. Details are as follows:

- Abstract: we have revised "… (PPCs) have been the…" to "... (PPCs) is the…".
- Abstract: we have revised "…patients are randomly…" to "... patients will be randomly…".
- p.5 L.36: we have revised "…who accept abdominal surgery are…” to “…who will undergo abdominal surgery are…”.
- p.6 L.45: we have revised " Pre-oxygenation and induction are prescribed for…” to "Pre-oxygenation and induction will be prescribed for…”.
- p.6 L.47: we have revised "…the participants are randomized to…” to "…the participants will be randomized to…”.
- p.8 L.1: we have revised "…ventilation settings were permitted to…” to "... ventilation settings are permitted to…”.
- p.9 L.17: we have revised "The study is conducted in the operating room…” to "The study will be conducted in the operating room... ”.
- p.9 L.23-24: we have revised "…participants is visited…” to "…participants will be visited... “.
- p.9 L.44: we have revised "…anesthesia-associated data is recorded…” to "... anesthesia-associated data will be recorded…".
- p.9 L.59: we have revised "Postoperative visits are conducted daily…” to "Postoperative visits will be conducted daily…”.

3. The manuscript (especially abstract, introduction, methods) needs to be revised by a native English speaker.
Response: Thanks for your comments and we have made correction according to the comments:

- Abstract: We have revised "...within the first 7 days postoperatively. " to "...within the first postoperative 7 days".
- Abstract: We have revised "...within the first 7 and 30 days postoperatively. " to "...within the first postoperative 7 and 30 days. ".
- Abstract: In the sentence "PROVIO trial specially assesses the effect of low versus high FiO₂", we deleted word "specially".
- p. 3 L.8 - 14: We have revised "About 2.0% to 5.6% developed postoperative pulmonary complications (PPCs) in more than 234 million patients accepting surgery, up to 40% in general and vascular surgery, which is the most common perioperative complications following surgical site infection (SSI) " to "About 2.0% to 5.6% of more than 234 million patients undergoing surgery developed postoperative pulmonary complications (PPCs), especially after general and vascular surgery (approximately 40%), which makes PPCs the most common perioperative complications following surgical site infection (SSI) ".
- p.3 L.18 - 20: "Preventing the PPCs has been a major indicator to evaluate the safety and quality of healthcare". We mean reduction of pulmonary complications in hospital is an important part of medical quality management. We revised it to "Reduction of pulmonary complications is a very important evaluation index of medical quality management. ".
- p.3 L.20 - 22: We have revised "…increasing morbidity PPCs is that mechanical ventilation…” to "…
increasing morbidity in patients that develop PPCs is that mechanical ventilation..."

- p.3 L.47 – 49: We have revised "The inspiratory oxygen fraction (FiO₂), as a significant factor of ventilation parameters, has not been regarded as a clinical standard." to "Setting FiO₂ intraoperatively is a significant task of anesthetists, but has not based on evidence-based guidelines."

- p.7 L.28 - 31: We have revised "Vasoactive agent therapy is permitted when the hemodynamics get instability with the discretion of the attending anesthetist" to "Vasoactive drugs can be used in patients with unstable hemodynamics as appropriate."

- p.11 L.47: We have revised "Any ventilatory settings play a critical..." to "The optimal intraoperative FiO₂ is more highly debated."

4. p.4 L.2 - 5: 'Evidence is lacking for a regular application of a high FiO₂ in abdominal surgery suggested by a Cochrane review [20]'
   Please add the most recent evidence on hyperoxia, published in BJA 2019
   Response: Thanks for your suggestion. We have added the most recent evidence, and provided references on p.19.

5. p.4 L.20 - 24: 'Higher FiO₂ seems to be associated with pulmonary complications and adverse clinical outcomes, but the existing evidence is insufficient to warrant its effect to promote PPCs'
   Please add references here.
   Response: We have added references on p.20.

6. p.6 L. 50: '...perioperatively (from intubation to extubation).'
   Response: Thanks for your suggestion. "perioperatively (from intubation to extubation)" was corrected as "during mechanical ventilation."

7. p.5 L57: 'Emergency unblinding is permissible if hypoxemia occurs.' How is hypoxemia defined? Which SpO₂ and for what duration?
   Response: Hypoxemia is defined in the part "Rescue strategies for intraoperative hypoxemia" (p.7 L.45-48) and we made the necessary complement.

8. p.6 L2-6: "...in Catalonia (ARISCAT) risk score...
   What will the ARISCAT score be used for? Is a high ARISCAT score one of the inclusion criteria? If so, please state this in the chapter 'Study Population' and in the Abstract
   Response: The ARISCAT score is not used as one of the inclusion criteria and it will help us to analyze the effect of FiO₂ on the patients of intermediate-high risk. We have made the necessary complement on p.6 L.3-14.

9. p.7 L5: 'Other settings are shown in table 1.' Or do the authors mean Table 2?
   Response: We are sorry for our negligence. We have revised "table 1" to "table 2".

10. p.7 L43-45: 'In general, surgery patients rarely require adjustment of the FiO₂ in 30% FiO₂ group according to the previous trials and clinical practice.' Please provide references.
   Response: We mean the safety of around 30% FiO₂ is proved by previous trials and our pilot trial. We revised it to "Around 30% FiO₂ has proved to be safe in mechanically ventilated patients and rarely causes hypoxemia " and provided references.

11. p.5 L57: 'Emergency unblinding is permissible if hypoxemia occurs.' How is hypoxemia defined? Which SpO₂ and for what duration?
   Response: The comments is the same as comment 7.
12. p.9 L10 - 15: 'After extubation, patients will be sent to the PACU or ward where they will be oxygenated with 2L/min, pure oxygen via a nasal tube in 24 hours. At the same time, they will accept standard monitoring.'

Did the authors define a minimal SpO2? If patients are hypoxic, will they receive higher flows of oxygen?
Response: Thanks for your comment. When hypoxemia (defined as SpO2 < 92%) occurs, the primary task is to search for reasons (airway problems, lung injury, or haemodynamic impairment). Removing induced factors to deal with hypoxemia is effective.

13. p.10 L8: Will the DSMB remain blinded to the study intervention?
Response: Thanks for your comment. The DSMB is not part of our research group, so they are not blinded to study intervention and we added supplementary information on p.10 L.15.

14. p. 13 L12-13: 'The PROXI trial demonstrates that the incidence of PPCs, PONV, and SSI after abdominal surgery were not significantly different in patients receiving 80% or 30% FiO2'
If in the PROXI trial, which included 1400 patients, there was no difference in PPCs, how do the authors expect to find a significant effect on PPCs in their study sample of 252 patients? Shouldn't the authors consider increasing their sample size?
Response: Thanks for your comment. Firstly, the sample size required for the PROXI trial was based on the frequency of SSI (its primary outcome). Patients who developed atelectasis and respiratory failure tended to be less in 30% FiO2 group, but the power to detect a proper relative risk reduction was low, as reflected in the wide confidence intervals. And, because of few researches to reference, our sample size was estimated based on our pilot trial, which may increase credibility as a single-center study. Our subsequent multicenter trial will increase the sample size according to results of PROVIO trial or other future researches.

15. 'Emergency surgery population were not excluded in PROXI trial, which is an independent risk factor of pulmonary complications' But the PROVIO trial aims to include only elective surgery.
Response: Thanks for your question. It is because emergency procedure is an independent risk factor of PPCs which may influence results, we designed the trial to unify baseline characteristics and reduce selection bias.

16. p.13 L.50-52: 'The iPROVE-O2 trial is an ongoing randomized controlled trial (clinicaltrials.gov identifier: NCT02776046)…'
The iPROVE trial has been published in 2018, please alter your Discussion.
Response: Thanks for your comment. The iPROVE trial has been published yet and cited in the manuscript. We mean the iPROVE-O2 trial is ongoing and unpublished.

Reviewer #2:
1. Please revise the manuscript by an English speaker. There are several unclear sentences and very long sentences.
Response: We really appreciate your advice and comments. We have rewritten some parts:
1) Abstract: We have revised "The role of inspiratory oxygen fraction (FiO2) in the strategy is currently not clear and remains disputable, despite liberal oxygen administration and hyperoxia is demonstrated to be associated with respiratory mechanism changes and increased mortality in ventilated patients." to "However, the role of inspiratory oxygen fraction (FiO2) in the strategy remains disputable. Previous trials have focused on reducing SSI by increasing inhaled oxygen concentration but an elevated FiO2 (80%) was found to be associated with a greater incidence of atelectasis and mortality in recent
researches."

2) on page 4, L.9 - 15: We have rewritten the sentence ("there’s no significant difference in pulse oximetry, oxygenation index and functional residual capacity for several time-points with 30% or 80% FiO₂ intraoperatively.") and inserted it on p.3 L.55.

3) on page 5, L.17 - 28: We have rewritten the exclusion criteria: "Other exclusion criteria are: diagnosis of heart failure (New York Heart Association classes, NYHA IV), chronic renal failure (glomerular filtration rate < 30 ml/min), serious hepatic diseases (e.g., hepatic failure), scheduled for reoperation or postoperative mechanical circulatory support, known pregnancy, participation in another interventional study, and with a body mass index (BMI) of > 30 kg/m².".

4) on page 5, L.49 - 51: We have revised " Researchers including the data collector and the data analyzer will all be blinded to the randomization arm, in addition to the investigator in the operating room." to " Researchers including the investigator in the operating room, the data collector and the data analyzer will all be blinded to the randomization arm. ".

5) on page 5, L.55: We have revised "…outcome assessment will be taken by…” to "…outcome assessment will be performed by…”.

6) on page 7, L.15: We have revised "…they will accept standard monitoring." to "…they will receive standard monitoring.".

2. Methods: On page 7: you describe your rescue recruitment maneuver with: Paw 30 cmH₂O for 30s. On which reference does this maneuver base?
Response: Thanks for your comments. Most commonly, recruitment maneuvers are performed by “bag squeezing” using the airway pressure-limiting valve of the anesthesia machine. Considering the use of pneumoperitoneum in a proportion of patients, pressures of up to 40 cm H₂O may result in overpressure with the risk of barotrauma, we choose the 30 cm H₂O as the airway pressure. A randomized clinical trial also set the airway pressures of 30 cm H₂O in recruitment maneuvers. We have provided the references.

3. Please add a section for SPIRIT checklist item #27.
Response: Thanks for your comments. We have rewritten the section (confidentiality) on page 11, L.35-40 and inserted it on page 15.

4. Figure 1: Why are you presenting the postop FU only for day 1,3,7,30 ? I thought you will follow up the patient daily until POD 7?
Response: We are very sorry for our negligence. In the section " Data collection and follow-up" and figure 2, we pointed out that the primary and secondary outcomes will be measured on postoperative 1, 2, 3, 5, 7 or at discharge by interview. Revised figure 1 has been uploaded.

5. SPIRIT checklist: Please add item page numbers for # 3, #5c. Please update the indicated page numbers according to your manuscript
Response: Thanks for your advice. We have uploaded an updated SPIRIT checklist.

Additional Changes
We find some other grammatical and format problems after carefully inspection. Listed as followed:
- Abstract: "…following surgical site infection…” to "…following surgical site infection (SSI)…”
The trial aims at exploring the effect of FiO₂ in lung-protective ventilation strategy on PPCs. The trial aims at comparing the effect of FiO₂ added to lung-ventilation strategy on reducing the incidence of PPCs during general anesthesia for abdominal surgery.

We have deleted a word "first" on line 33 and 38.
We have added "for abdominal surgery patients" on line 44.
We have added a word "as" on line 11.
"waste resource" to "resources utilization".
"have been" to "are".
" Knowledge about hyperoxia caused by high FiO₂ is stressed by clinicians over the past few decades." to "Obtaining comprehensive knowledge about hyperoxia caused by high FiO₂ has been stressed by clinicians over the past few decades."
"has been shown to be" to "is".
"under" to "undergoing".
"controlled, two-arm" to "controlled and two-arm ".
"Trial" to "The trial".
We have added a word "patients".
"accept" to "receive".
"Also, they will be…" to " Moreover, the participants will be…".
"accept" to "receive".
"In cases of hypoxemia, defined as SpO₂ < 92% or PaO₂ < 60 mmHg, the rescue strategies will be performed immediately to treat." to We design a rescue strategy for patients in whom SpO₂ measured by pulse oximetry fell to less than 92% or PaO₂ less than 60 mmHg.
We have deleted a sentence "Finding out the underlying causes of hypoxemia matters.".
"above" to "underlying ".
"first" to "postoperative".
"…and death rate in the 7 and 30 postoperative days." to "…and death rate in the postoperative 7 and 30 days.".
"in the postoperative 7 and 30 days ".
"We deleted a word "independent".
"… will be send to DSMB… " to "… will be sent to DSMB… ".
"is set to watch over the overall…" to "…is set to supervise the overall…"
"rounded" to "round".
"done" to "performed".
"Besides" to "In addition".
We have added a word "that".
"demonstrates" to "demonstrated".
"…ventilation strategy to patients was not specified…” to "…ventilation strategy to patients is not specified…".
"is complex to implement clinically and hard to popularize, when comparing to…” to "is more complex to implement clinically, when comparing to…”
"on PPCs, whose results may provide guidance of routine oxygen management and an optimal choice of FiO₂ application to protect from pulmonary complications." to "The results of the trial will support anesthetists in routine oxygen management during general anesthesia in an attempt to prevent PPCs."
"use of high FiO₂ is essential to surgery population…” to "…use of an elevated FiO₂ is essential to all intubated patients…”

There is a growing concern about oxygen affecting lung capillary endothelial function and facilitating oxidative stress. Concerns on potential detrimental effects such as impairing lung capillary endothelial function and facilitating oxidative stress due to the use of high FiO₂ were raised.

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.