Author’s response to reviews

Title: Protective ventilation with high versus low positive end-expiratory pressure during one-lung-ventilation for thoracic surgery (PROTHOR): Study protocol for a randomized controlled trial

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Protective ventilation with high versus low positive end-expiratory pressure during onelung-ventilation for thoracic surgery (PROTHOR): Study protocol for a randomized controlled trial

--Manuscript Draft--

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Response: We appreciated very much the constructive comments from the editor and the reviewers and are thankful for the effort and time spent in the revision of the manuscript. Please find below the detailed point-by-point responses to all comments. Since the reordering and restructuring of the manuscript was substantial, we have written bullet points of our major changes to the manuscript, rather than included a ‘track changes’ document.
Summary of major changes:

• More detail on pulmonary embolism and lung hemorrhage in the discussion section are provided

• The revised manuscript now incorporates all data corresponding to a detailed statistical analysis plan

• We added the information that the use of almitrine is depending on national/institutional approval

• Funding information has been completed

• High and low PEEP rescue procedures as well as recruitment maneuvers are displayed as tables

• The section “Study endpoints” has been reformatted and converted to a bulleted list, allowing for better readability

• Reordering of figures and tables

• We have corrected spelling mistakes in the entire text

Reviewer #1:

Kiss et al propose a protocol for a currently recruiting, multicenter, randomized IIT investigating a high PEEP with recruitment maneuvers (RM) vs. low PEEP without RM protocol in patients undergoing thoracic surgery with one lung ventilation (OLV).

The study aims to recruit 2378 patients and the primary endpoint and secondary is a collapsed composit for postoperative pulmonary complications (PPC). Postinterventional observation period is 1-5 days concerning endpoints and the 90d mortality to be assessed via phone interview.

Response: Thank you for your thoughtful and thorough review of our manuscript.
Comments:

1.) Overall the PROTHOR protocol aims to test high PEEP + RM and low PEEP without RM. According to the protocol, a standardized RM shall be executed in the high PEEP group at distinct occasions. The protocol also provides strategies for intraoperative scenarios like hypoxemia. Therein, the authors recommend the standardized RM for the high PEEP group but also for the low PEEP group after initially increasing the FiO2 (page10, line9). The authors state in their step by step procedure to increase the PEEP up to 7cmH2O. But in between the stepwise increase the standardized RM is placed where, according to the procedure, the PEEP can be increased up to a maximum of 20cmH2O. In Figure 3 the authors show the procedure of the RM and display a PEEP of 10cmH2O at the beginning (not below or any recommendations for the low PEEP group). This algorithm is proposed for TLV as well as for OLV, but in the OLV setting, CPAP therapy is recommended for both groups up to 20 cmH2O and this is clearly stated for both groups.

It is of course clear that under hypoxia, state-of-the-art rescue strategies must be established to ensure patients' safety. Nevertheless, a clarification is needed to explain if the standardized RM is adapted for the low PEEP group or if statistical analysis will be able to distinguish patients in the low PEEP group with hypoxic rescue using the high peep RM from the rest of the low PEEP group, or if such a patient will be excluded at all from analysis.

Response: Thank you very much for your important comment. A related comment has been raised by Reviewer #2 stating that the manuscript is very extensive what makes it in part difficult to follow. As you commented, we have now reformatted the hypoxia rescue maneuvers section for better readability. The high and low PEEP procedures are displayed as tables, which makes it easier to see the differences between the groups. It should be more clear now, that in the high PEEP group, in case of hypoxia, the sequence of interventions is as follows: apply recruitment maneuver, increase PEEP, increase FiO2, whereas in the low PEEP group the steps are as follows: increase FiO2, apply supplemental oxygen, apply recruitment maneuver, increase PEEP. Statistical analysis will follow the intention-to-treat principle, thus, independent of hypoxemia or need of rescue, patients will be analyzed in the group they were randomized. However, the number of patients needing RM as a rescue for hypoxemia will be reported as a secondary endpoint, as reported in the Study endpoints section. We have extended our statistics section for clarification, as a result of your suggestion.

2.) Page 13/14 postoperative extrapulmonary complications: Define Sepsis (life-threatening organ dysfunction caused by a dysregulated host response to infection) and sepsis shock (vasopressor requirement to maintain a mean arterial pressure of 65 mm Hg or greater and serum lactate level greater than 2 mmol/L (>18 mg/dL) in the absence of hypovolemia)
Accordingly. According to the current Sepsis guidelines, the term "severe sepsis" should be avoided.

Response: We appreciated this comment. When the new SEPSIS-3 definition was published, the trial was already submitted to the Institutional Review Board at Istanbul University (Turkey). We agree that new studies should be designed according to the new SEPSIS definition. For this project, we are not able to change the proposed point as this would involve a change in the study protocol. We will report this task when publishing the final results.

3.) As far as I know, almitrine is not approved in every European country, this should be stated in the protocol.

Response: This is correct. As you pointed out, we have now added a sentence at two occurrences to clarify this aspect, which now read as: “Consider administration of inhaled nitric oxide or prostacyclin, or intravenous almitrine (provided the drug is approved in your country/institution)”

4.) Funding: This seems inaccurate. Even if funding is based only on institutional money this should be stated for each participating study center.

Response: Thank you very much for the suggestion. As you suggested, we have completed Funding information in the text now.

5.) Suggestion: page 19, 3rd line: you might want to consider rephrasing "[..]if the trial is going nowhere"

Response: The sentence has been rephrased.

6.) Typos: page 23 line 37/38 space and full stop between "[...]did not achieve the same effect." and "Furthermore...."

   page 24 line19/20 "[...] but also the incidence of each element separately. f" delete

Response: The sentences have been corrected.
Reviewer #2:

Thank you for giving me the opportunity to review this interesting and well written manuscript for the large randomized controlled PROTHOR trial. The nature of the trial design together with the large patient cohort will bring enough evidence to gain new insights. The topic of the trial deals with an important issue for anesthesia management in mechanically ventilated patients.

Response: Thank you for your thoughtful suggestions and thorough review of our manuscript.

I would recommend to include the study protocol as part of the supplements. Moreover, here are some thoughts the authors might like to address:

The manuscript is well written but very extensive what makes it in part difficult to follow. Therefore, I would recommend to shorten some sections and translate some sections to the supplements.

Response: Thank you very much for the suggestion. As you suggested, we have reformatted large parts of the manuscript. The high and low PEEP rescue procedures are displayed as tables, which make it easier to see the differences between the groups. Also the section “Study endpoints” has been reformatted. Simple justified text has now been converted to bulleted list, allowing for better readability.

For instance:

- Rescue strategies for intraoperative hypoxemia: maybe it would be an idea to show the different strategies in a Table (for better elucidation).

Response: We thank the Reviewer for this suggestion. The strategies have been summarized in tables.

- Study endpoints: if the authors include the study protocol, the specific definition of the endpoints, especially postoperative extrapulmonary complications, can be deleted.

Response: Thank you very much for your comment. The present manuscript is intended to be published as a study protocol without putting the original study protocol as a supplement. We have attached a supplemental file which shows all participating centers and their investigators. All other information should be available in the main manuscript, including postoperative extrapulmonary complications.

- Study visits and data collection: Figure 4, which is actually not referred to in the manuscript, shows similar details as written in the study visits and data collection section. The section should be deleted or greatly shortened and referred to Figure 4.
Response: Thank you very much for your comment. References to Tables and Figures have been updated, as you requested. We see the point, that Figure 4 (now Figure 3 - Schedule of enrolment, interventions, and assessments) shows redundant data and could be deleted. In this specific case, this Figure is required by the Journal as stated in the “Guidelines for Authors” document.

- Sub-studies: can be deleted since it is surely part of the study protocol.

Response: Thank you very much for your comment. The separate declaration of substudies is mandatory as stated in the “Guidelines for Authors” document.

- Trial organization: Please add a list of participating centers and DSMB partners in the supplements instead of mentioning the different persons in the main text.

Response: Thank you very much for your comment. In the main manuscript authors of this manuscript (steering committee members) and their affiliations are listed as required by the journal’s instructions, which indeed appears as a long list in the current layout, but will be condensed in the final layout. We opted to keep the members of the DSMB in the main manuscript text, particularly to pay respect and honor their contribution to our project. All participating centers and their investigators are listed in the supplemental file.

Please include a separate section ethics and consent.

Response: We fully understand the concerns of the Reviewer, but Journal rules request a section labelled “Ethics approval and consent to participate”.

In the text, it is referred to Figure 3 before mentioning Figure 2 and there is no reference to Table 1. Please check this and revise.

Response: The references to the Table/Figures have been revised. Thank you for this suggestion.

Reviewer #3:

The authors should be congratulated for designing and conducting a large-scale multicenter clinical trial that will undoubtedly inform intraoperative anesthesia practice for thousands of patients per year around the world.

Response: We thank the reviewer for careful reading of the manuscript and constructive remarks.
The manuscript is well compiled and the methods are clear. I am recommending publication, but would like the authors to consider a few points.

1) Definition of postoperative pulmonary complications

The ESA and ESICM in 2015 created a consensus definition of postoperative pulmonary complications in part to aid in strengthening the quality of perioperative research through the use of standard definitions.


The authors have chosen a similar but ultimately different set of complications to include in their definition of PPCs that is inconsistent with this consensus definition. Although there are many recent trials that have been performed with a non-standard composite outcome (ie pulmonary and non-pulmonary complications IMPROVE, PPV), this can create a few issues.

a) Using a non-standard definition of PPCS could limit the generalizability of the findings of the proposed trial with regards to comparison between other intraoperative mechanical ventilation trials using PPCs as an outcome (ie PROVHILO, iPROVE,).

Response: We appreciated these comments very much. We know the publication mentioned and individual members of our steering committee are coauthors of this paper. Although the authors of this paper propose a general definition of the composite outcome of postoperative pulmonary complications, this definition is valid for a general surgical population only. The difficulties in defining PPC in this surgical population were addressed in the following book chapter:


Our steering committee has put a lot of effort into the task of creating a composite outcome measure that meets the needs for a study on patients undergoing thoracic anesthesia. Our steering committee is set up of a huge number of experts in the field of thoracic surgery/anesthesia and the current definition of PPC constitutes the consensus of this group.

b) Including additional non-standard complications into their primary outcome will likely increase the event rate within their study. This has the obvious beneficial effects, leading to narrower confidence intervals and potentially enough power to detect a difference between groups. However, the sample size calculation performed using a baseline PPC incidence from LAS VEGAS is inaccurate. LAS VEGAS’ definition of PPC is more consistent with
the ESICM definition, but contains fewer variables than the proposed composite PPC outcome in this proposed study. The event rate in the control group in the proposed study, using these additional endpoints, is likely to be higher than 23%. This could lead to inaccuracies in the sample size calculation which would then lead to a potentially excessive amount of patients being enrolled in the study and subjected to potential risk than what is truly needed to accomplish the study goals.

Response: We appreciate and acknowledge your comments. We discussed this issue exhaustively during the meetings of the steering committee. The statistical basis for our sample size calculation was based on unpublished data of the LAS VEGAS trial. The incidence of PPC in LAS VEGAS was accounted for by a great extent of “mild respiratory failure” (PaO2 < 60 mmHg or SpO2 < 90% breathing at least 10 min of room air but responding to supplemental oxygen = 2 l/min, excluding hypoventilation). For the PROTHOR trial, the steering committee decided to exclude “mild respiratory failure” from being part of the composite primary endpoint and moved it to the secondary endpoints section (extended PPC). We decided to rather assume a lower incidence of PPC resulting in a larger sample size than to risk an underpowered study and eventually ending up with a corrected sample size. For this trial we have used the group sequential methods design which gives us the possibility for early stopping the study if the experimental treatment shows a statistically significant therapeutic advantage at an interim look. Our study design contains interim analysis points when reaching 20, 40, 60, 80 and 100% of patient data. At each interim point all existing datasets will be analyzed focusing on the primary endpoint and presented in a blinded manner to the DSMB. Provided that the experienced PPC rate will well be higher than expected, the study can be stopped prematurely on recommendation of the DSMB.

c) The authors have potentially included complications that are not related directly to VILI. Pulmonary embolism and lung hemorrhage come to mind. If there were a significant contribution from these endpoints in the composite outcome, this would limit the potential argument that a protective ventilator strategy was responsible for a difference in the primary outcome.

Response: We appreciate your comments and agree that pulmonary embolism and lung hemorrhage are not directly related to VILI, but they may be related to ventilation practice itself. Both, ventilation and PEEP tend to decrease right and left ventricular preload, increase right ventricular afterload and decrease left ventricular afterload. The sum of these effects is that the cardiac output may fall, especially in the presence of hypovolaemia or in those with impaired cardiovascular reflexes. Consequent exacerbation of venous stasis will increase venous thromboembolism risk. https://journals.sagepub.com/doi/pdf/10.1177/175114371301400109
Actually, mechanical ventilation has been identified as an independent ICU-acquired venous thromboembolism risk factor (Cook D, Attia J, Weaver B et al. Venous thromboembolic disease: an observational study in medical-surgical intensive care unit patients. J Crit Care 2000;15:127-32). Lung hemorrhage is defined as bleeding through the chest tubes requiring reoperation, or transfusion of at least three red blood cell packs. Lung inflation of a collapsed lung, recruitment maneuvers but also distribution of lung perfusion during one and two lung ventilation may facilitate lung hemorrhage. Taken these points together, we must consider also such possible complications as resulting from mechanical ventilation, even if it is not a consequence of VILI. Given your comments, we decided to explain this topic in more detail in the discussion section.

Due to these issues, I would recommend using the standard definition of PPCs as the primary outcome in this study. It would lead to a more generalizable, biologically plausible result and make the sample size calculation more accurate. The additional outcomes which are currently included in the composite outcome could be treated as secondary endpoints, or used to create a separate composite outcome (such as “expanded PPCs” or the like). Alternatively, the authors could name the composite outcome something other than PPC to avoid confusion with the standard definition.

Response: We thank the reviewer for the critical appraisal. We are aware that the interpretation of the final study results may not be generalizable according to the consensus definition of postoperative pulmonary complications. All the raised points have been intensively discussed by the members of the steering committee. As mentioned before, PPC definition for thoracic surgery does currently not exist. The expert group has agreed on the current definition. Mild respiratory failure has been excluded from the PROTHOR primary outcome composite, resulting in a thoracic surgery specific definition. Mild respiratory failure is treated as secondary endpoint, which is in line with the reviewer’s recommendation. The study has started 2 years ago. Currently, we are not able to change the proposed points as this would involve a change in the study protocol.

2) Application of recruitment maneuvers in the low PEEP group

It is understood that RMs will only be used during certain times in the low PEEP group for surgical reasons or in the incidence of hypoxia, here defined as an SPO2 for more than 1 minute. One concern is if these conditions might be quite frequent in this population, especially when OLV is first initiated, and this could lead to frequent RMs being performed in the group with low PEEP. If the RMs (or a subsequent increase in PEEP) are applied frequently in the low PEEP/no RM group, this could result in contamination of interventions between study groups and thus bias the results of the study towards the null. Since this protocolized response to hypoxia is designed to prevent patient harm, it is understandable why it has been designed this way.
Alternatives could be to adjust the definition of hypoxia to a more severe setpoint (lower SpO2 or longer period of desaturation), or at a time further from the initiation of OLV, after hypoxic vasoconstriction has occurred. Because this could potentially increase patient risk, this is something merely for the authors to consider given that the potential sacrifices they would be making in terms of achieving a positive study result the way the protocol is currently defined. It is also noted that the first intervention listed for hypoxia in the low PEEP/no RM group is to increase FiO2.

Response: Thank you for this comment which addresses a topic that has been questioned in a slightly different manner by Reviewer #1. The design of hypoxia rescue maneuvers has been debated intensively by the members of the steering committee. We discussed the duration (1 minute) the cutoff level (SpO2 < 90%) and also the sequence of interventions to counteract hypoxemia. Due to the sigmoidal shape of the Oxygen Dissociation Curve, a saturation of 90% may promptly drop to substantially low levels endangering the patient inadvertently. The idea of the proposed recruitment maneuvers was primarily not to harm the study patients, even at the risk of having a negative study. We must remember that increasing the PEEP in the low PEEP group may lead to better oxygenation and reduces the need for recruitment maneuvers. However, the mean airway pressure will be lower in the low PEEP group, even with multiple recruitment maneuvers.

3) Statistical considerations

a) Page 11, line 40 - Please describe how the authors plan on treating missing data for a 90d endpoint, which is prone to a significant amount of loss to follow up

Response: Since this is not the primary endpoint, patients with missing data will be excluded from the secondary analyses. Your comment is now considered in the statistics section, which has been extended.

b) Page 19, line 36 - I would encourage the authors to use this publication as the means to publish their detailed statistical plan, in the interest of transparency of methods. Any changes in the statistical analysis plan that occur after this publication, and after one or more interim analyses, would be scrutinized by future reviewers.

Response: Thank you very much for the suggestion. As you suggested, we have completed the statistics section which now contains all elements of the detailed statistical plan according to this checklist (https://jamanetwork.com/journals/jama/fullarticle/2666509).
4) Minor points

a) Page 6, lines 125 and 133 - please specify the "outcomes" you are referring to

Response: Thank you for this note. You are referring to a sentence in the introduction of the manuscript. This paragraph is referenced to 3 publications. In the abstract (the abstract is free for all readers) of these publications all outcomes are listed: lung injury development, mortality, incidence of pulmonary infection, mean hospital length of stay, mean PaCO2 levels, mean pH values, atelectasis, better pulmonary functional tests up to day 5, alterations on chest x-ray up to day 3, arterial oxygenation in air at days 1, 3, and 5, modified Clinical Pulmonary Infection Score. The results of these studies are closely correlated to the specific design of the studies. To our opinion, readability does not improve by specifying the outcomes in more detail, as the context to those specific results is missing. Also, concerns have been raised by Reviewer #2, criticizing the extent and readability of our manuscript. Thus, we would refrain from expanding the manuscript.

b) Page 7, line 51 - please define persistent hemodynamic instability or intractable shock

Response: Thank you for this suggestion. This directive is part of the exclusion criteria of the study. It should emphasize that patients who are at risk to develop life threatening hypotonia during a recruitment maneuver should not be included. We intentionally avoided numbers here. For better understanding we reworded this sentence, which now reads as follows: “show persistent hemodynamic instability or intractable shock (as judged by the treating physician)”.

c) Page 13, line 34 - please specify the outcome "high dosage of vasoactive drugs" or consider using dosage as a continuously measured variable

Response: We appreciate your comment and your suggestion to measure the dosage of vasoactive drugs as a continuous variable. During surgery, several events can be marked, which are summarized within the secondary composite endpoint “intraoperative complications”. This event is currently designed as binary variable, therefore metric data is not recorded. Vasoactive therapy is highly variable from center to center, including epinephrine, norepinephrine, dobutamine, dopamine and vasopressin, among others. One must note that patients with an epidural anesthesia per se may need a higher dosage of vasoactive drugs, than patients with general anesthesia alone, which makes comparison between these patients difficult. Analysis of such data would require a simple conversion to a common scale such as those for opioids or steroids. In our study, this variable stands for a highly subjective event. The treating physician is able to report whether the patient was difficult to manage or not. For latter portability of the results to daily routine this procedure seems practicable. For better understanding, we changed
this sentence, which now reads as follows: “..need for high dosage of vasoactive drugs (a dosage at the tolerance limit of the treating physician).”

d) Page 16, line 35 - Use of a method of lung separation other than a DLT (i.e endobronchial blocker) is listed as an exclusion criteria, and therefore shouldn't be present in your list of collected data for enrolled patients

Response: We see the point by the Reviewer. We included this question in the CRF to double check for protocol adherence. Also, preexisting pleural effusion is an exclusion criterion, which is scanned for in the preoperative CRF.

e) Page 22, line 48 - One could argue that this trial does not focus on the independent effects of PEEP, but rather PEEP and RMs. Consider revising this statement.

Response: We appreciate your comments very much. From a physiological point a view, treatment of atelectasis is based on a transient rise in airway pressure (higher than alveolar opening pressure in heterogeneous lung tissue) and transpulmonary pressure, respectively, combined with a persistent airway pressure to keep the lung open. From our point of view, high PEEP should be preceded by recruitment maneuvers with the purpose of expanding lung units. We have revised this statement according to your request, which now reads as follows: “We opted for testing the impact of two ventilation strategies at the same low VT in order to focus on the independent effects of different airway pressures, especially PEEP.”