Author’s response to reviews

Title: Effect of individualized PEEP titration guided by intratidal compliance profile analysis on regional ventilation assessed by electrical impedance tomography – a randomized controlled trial

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Author’s response to reviews:

BANE-D-19-00556R1

Individualized PEEP titration guided by intratidal compliance profile analysis improves regional ventilation – a randomized controlled trial

Jonas Weber, MD; Jan Gutjahr; Johannes Schmidt, MD; Sara Lozano-Zahonero; Silke Borgmann, Ph.D.; Stefan Schumann, Professor; Steffen Wirth, MD

BMC Anesthesiology
Dear Dr. Weber,

Your manuscript "Individualized PEEP titration guided by intratidal compliance profile analysis improves regional ventilation – a randomized controlled trial" (BANE-D-19-00556R1) has been assessed by our reviewers. They have raised a number of points which we believe would improve the manuscript and may allow a revised version to be published in BMC Anesthesiology.

Their reports, together with any other comments, are below. Please also take a moment to check our website at https://www.editorialmanager.com/bane/ for any additional comments that were saved as attachments.

If you are able to fully address these points, we would encourage you to submit a revised manuscript to BMC Anesthesiology.

Once you have made the necessary corrections, please submit online at:

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If you have forgotten your password, please use the 'Send Login Details' link on the login page at https://www.editorialmanager.com/bane/. For security reasons, your password will be reset.

Please include a cover letter with a point-by-point response to the comments, describing any additional experiments that were carried out and including a detailed rebuttal of any criticisms or requested revisions that you disagreed with. Please also ensure that all changes to the manuscript are indicated in the text by highlighting or using track changes.

Please also ensure that your revised manuscript conforms to the journal style, which can be found at the Submission Guidelines on the journal homepage.
A decision will be made once we have received your revised manuscript, which we expect by 11 Dec 2019.

Please note that you will not be able to add, remove, or change the order of authors once the editor has accepted your manuscript for publication. Any proposed changes to the authorship must be requested during peer-review, and adhere to our criteria for authorship as outlined in BioMed Central's policies. To request a change in authorship, please download the 'Request for change in authorship form' which can be found here – http://www.biomedcentral.com/about/editorialpolicies#authorship. Please note that incomplete forms will be rejected. Your request will be taken into consideration by the editor, and you will be advised whether any changes will be permitted. Please be aware that we may investigate, or ask your institute to investigate, any unauthorized attempts to change authorship or discrepancies in authorship between the submitted and revised versions of your manuscript.

I look forward to receiving your revised manuscript and please do not hesitate to contact us if you have any questions.

Best wishes,

Domenico Luca Grieco

BMC Anesthesiology

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Technical Comments:

Editor Comments:
Dear dr Weber,

thank you for submitting a revised version of your manuscript. The manuscript has improved. However, both myself and the reviewers still have great concerns on the relevance of your results. We believe there is original information in the data you have: however, in the way data are presented and because of some methodological inconsistencies, the original information is really difficult to catch. We would like to give you another opportunity to thoroughly revise the manuscript to improve its content. Please, be aware that, in case you should be unable to do so, the manuscript will be rejected despite re-submission.

In particular, please be sure that you have responded in detail not only to reviewers' comments but also to the points that I address. Unfortunately, in your previous response to the decision letter, there was no mention to responses to editor comments. Moreover, please check carefully the numbers in the tables, there are some relevant inconsistencies (noted by reviewer 2) that will hamper the publication of the manuscript.

I also have great concerns on the research question: in this study, the intervention group received PEEP tailored to optimize intratidal linear compliance, which also is the primary endpoint of the study. Isn't it obvious that an approach optimizing intratidal compliance yields improved intratidal compliance. This aspect should be discussed in details the choice of the primary endpoint justified. Accordingly in the background of the study you state that your aim is to demonstrate that the approach allows to"improve respiratory system mechanics and regional ventilation during perioperative mandatory ventilation, compared to a non-personalized PEEP ventilation technique", which is deeply different from your primary endpoint. Study endpoints are important and guide methodology.

Please check carefully figure 2, which (again) is not detailed enough (60 participants assessed and randomized?) and also numbers are not correct (23 patients randomized to treatment and 25 received?).

BMC Anesthesiology operates a policy of open peer review, which means that you will be able to see the names of the reviewers who provided the reports via the online peer review system. We encourage you to also view the reports there, via the action links on the left-hand side of the page, to see the names of the reviewers.
Dear Dr. Grieco,

we would like to thank you and the Reviewers very much for the time and effort spent in reviewing our manuscript and for the very constructive and helpful comments and criticisms.

First we would like to apologize for the delay of re-submission and that we have overseen to reply to the Editors’ comments. In the first section of this revision we will respond to the Editors comments of the first and the current revision. We have made every effort in revising our manuscript along yours’ and the Reviewer’s suggestions and remaining concerns and we feel that the manuscript has further improved. Again, for better overview within the revision process, we numbered the Reviewer’s comments.

We apologize for the misleading flow diagram and corrected it.

We hope that the revised manuscript will be acceptable for publication in BMC Anesthesiology.

Sincerely,

Dr. Jonas Weber
Editors’ comments (first revision)

Please carefully follow reviewers' instructions. In particular, pay attention to the need to clearly identify a primary endpoint for your study, and fully justify the assumptions for sample size calculation; please also specify the time-period of patients' enrolment.

Reply: We clarified the primary endpoint and the sample size calculation in the methods section in the revised version of the manuscript (pg. 10 line 20 to pg. 11 line 12). Patients were recruited from November, 5th 2015 to January, 29th 2016 (pg. 12 line 2).

You will also need to better characterize your population: the consort diagram you are reporting is too simplistic (60 patients assessed for eligibility and randomized?).

Reply: We attached a corrected version of the flow diagram to the re-submission.

Please consider that your study is clearly underpowered (60 patients to be studied, 48 analyzed). This has to be acknowledged and discussed.

Reply: We acknowledged the fact that the study is underpowered in the limitations section in the revised version of the manuscript (pg. 18 line 8 to 12).

Reviewer 2 and myself have great concerns on the way EIT signals were analyzed. EIT can provide a lot of information, plenty of data are available for analysis, that should be done according to the current state of the art (Chest electrical impedance tomography examination, data analysis, terminology, clinical use and recommendations: consensus statement of the TRanslational EIT developmeNt stuDy group. Thorax 2017). The results section is poor, inadequate for the amount of results you could get.
Reply: We agree with the Editor and Reviewer 2 that the EIT recordings should be more exploited. Therefore, we further investigated and calculated measurements of regional ventilation, and added the results and corresponding information to the discussion and limitations section to the revised version of the manuscript (pg. 9 line 19 to pg. 10 line 18, pg. 12 line 22 to pg. 13 line 5, pg. 17 line 1 to line 24).

Editors’ comments (second revision)

Unfortunately, in your previous response to the decision letter, there was no mention to responses to editor comments. Moreover, please check carefully the numbers in the tables, there are some relevant inconsistencies (noted by reviewer 2) that will hamper the publication of the manuscript.

Reply: We apologize for not having replied appropriately on the Editors’ comments in our first revision. Therefore, we performed a point-by-point revision of the Editors comments of the first and the current revision. We kindly would like to refer to our reply on comment #8 and comment #9 of Reviewer 2.

I also have great concerns on the research question: in this study, the intervention group received PEEP tailored to optimize intratidal linear compliance, which also is the primary endpoint of the study. Isn't it obvious that an approach optimizing intratidal compliance yields improved intratidal compliance. This aspect should be discussed in details the choice of the primary endpoint justified.

Reply: We agree with the Editor that the fact that the nonlinear intratidal compliance profile was the primary determinant of the PEEP adjustments and the primary endpoint is a limitation of the present study. However, it should be noted that with the individualized PEEP adjustments performed in the intervention group, compliance profiles did not improve significantly during mechanical ventilation. We adapted the discussion section according to the Editors suggestions in the revised version of the manuscript (pg. 18 line 8 to 12).
Accordingly in the background of the study you state that your aim is to demonstrate that the approach allows to "improve respiratory system mechanics and regional ventilation during perioperative mandatory ventilation, compared to a non-personalized PEE ventilation technique", which is deeply different from your primary endpoint. Study endpoints are important and guide methodology.

Reply: We want to apologize for not having formulated the primary study aim correctly. We adapted the formulation in the background section of the revised version of the manuscript (pg. 6 line 8 to 9).

Please check carefully figure 2, which (again) is not detailed enough (60 participants assessed and randomized?) and also numbers are not correct (23 patients randomized to treatment and 25 received?).

Reply: Actually, all 60 consecutive patients who were assessed for eligibility matched the inclusion criteria (and did not indicate exclusion criteria), agreed to participate in the study and were randomized to one of the two investigated groups. We apologize for the misleading flow diagram and attached a revised version of figure 2 to the re-submission.

Elena Spinelli (Reviewer 1)

The major limitations of the study are the study population and (related to this) the sample size calculation. The study indicates that when the incidence of nonlinear compliance profile is very low (less than 20% in control group), an individualized PEEP titration approach results in few minor PEEP adjustment. As a consequence, the study might be underpowered to detect significant changes in ventilation distribution: the differences in regional gain and loss values might suggest that the individualized approach could decrease the loss of ventilation in the dependent areas (and the subsequent relative increase of ventilation in the non-dependent regions), but the effect is very limited, thus resulting in a not detectable difference in ventilation distribution (as indicated by not different TVv and TVd values between groups).
Reply: We agree with the Reviewer that the study turned out to be underpowered since we expected a large effect from the experience of our earlier studies. This is stated in the limitations section of the revised version of the manuscript (pg. 18 line 8 to 12). We also adapted the discussion (pg. 17 line 1 to 24) and conclusion (pg. 19 line 4 to 9) section according to the Reviewers’ suggestions.

Even if "there are no data available concerning the variance of frequencies of compliance profiles", the sample size calculation should be based on the expected difference in the frequency of nonlinear intratidal CRS profiles, which is the study endpoint. These drawbacks in the study design hinder the interpretation of the results.

Reply: We further agree with the Reviewer that it is a limiting fact that the sample size calculation is based on an assumed general large effect and not on an expected difference of compliance profiles frequencies. This is stated as limitation in the respective section of the revised version of the manuscript (pg. 19 line 4 to 9).

Additional comments:

1. Methods: You state that "regional ventilation was measured via electrical impedance tomography (EIT, PulmoVista 500, Dräger 11 Medical) every 10 minutes for a duration of 2 minutes". It is not clear which f-EIT recordings were used and compared to assess tidal variation, gain and loss. Did you refer to images obtained at the beginning and at the end of surgery? Or did you average parameters from the comparisons of all images obtained at 10 minutes intervals?

Reply: We apologize for not having clearly stated that we used the first and last measured f-EIT to assess tidal variation, gain and loss. This was corrected in the methods (pg. 9 line 23 to pg. 10 line 1, pg. 10 line 3 to 5) and discussion (pg. 17 line 1 to 2) section in the revised version of the manuscript

2. Tidal variation is actually defined as the difference between gain and loss (AT = TVG - TVL) (ref 28), while what you are reporting is the percentage of tidal volume going to ventral and dorsal areas, based on the fraction of impedance values in ventral (TVv) and dorsal areas (TVd).
Reply: We agree with the Reviewer that we did not correctly state the calculation of the tidal variation TVv and TVd. We corrected the methods, results and discussion section in the revised version of the manuscript (pg. 10 line 5 to 8, pg. 17 line 14 to 24).

3. Results: You need to report p values for baseline characteristics (Table 1) to exclude confounding differences between the study groups

Reply: We added p values to table 1 in the revised version of the manuscript.

Gaetano Scaramuzzo (Reviewer 2):

I would like to congratulate dr. Weber and all the coauthors for the work done to improve the manuscript. Specifically, I appreciated the new EIT analysis and the modification of the manuscript's conclusions. The technique and the results are interesting, but I still have some concerns about the overall manuscript.

General comment: the primary aim of the study (compare two groups) is not in line with the variable selected to calculate the sample size (frequency of intratidal profiles). This should be stated in the limitation section. Moreover, the results coming from the new EIT analysis were not fully discussed in the paper and do not justify the title and the abstract conclusions. Finally, the abstract's conclusion and the manuscript's conclusion are in conflict.

Reply: We thank the reviewer for appreciating our first revision. In the revised manuscript we state that our sample size calculation had limitations since there were no appropriate data available as a limitation of our study. This is reflected in the limitations section of the revised version of the manuscript according to the Reviewer’s suggestion (pg. 19 line 4 to 9). In this context, please find also our response on comment #9. Further, we enhanced the discussion of the EIT analyses (pg. 17 line 1 to 24). Finally, we would like to apologize for not having aligned the conclusion appropriately. We have aligned the conclusions of the abstract and the manuscript and corrected the title of the manuscript. Please find our detailed comments in the following point-by-point response.
Specific comments

1. Please revise the title of your manuscript according to your findings which are not completely converging on the improvement of ventilation (Effect of PEEP titration guided by intratidal compliance analysis on regional ventilation assessed by electrical impedance tomography, for example).

Reply: We would like to thank the Reviewer for this advice and changed the title in the revised version of the manuscript (pg. 1 line 1 to 3).

2. page 2, line 22: the abstracts conclusion and the manuscript conclusion are in conflict ("promising approach to patient-individual ventilation settings" and "limited importance in patients without impaired respiratory mechanics"). Please fix.

Reply: We would like to excuse for the inconsistent formulation in the conclusion section of the manuscript and adapted it to be consistent with the conclusion section of the abstract in the revised version of the manuscript.

3. Page 7 line 13: baseline measurements. Which measurement? Was EIT recorded also in this step? Is this the baseline step you refer to when you calculate the gain/loss of regional ventilation?

Reply: After tracheal intubation and prior to the operation procedure, we performed baseline measurements in each patient while holding the respiratory variables constant according to the study protocol (pg.8 line 13). During this phase, we also performed the first EIT measurement to calculate gain and loss of ventilation between this first and the last measured EIT sequence. To avoid any interference with the surgical procedure (especially by electrical currents applied during electrosurgery) the last EIT measurement was performed after the surgical procedure was finished (pg. pg. 9 line 25 to pg. 10 line 4 to 6).
4. Page 8, line 22. It is not clear which where the two time points to calculate gain/loss of ventilation. Baseline/end of surgery?

Reply: We agree with the Reviewer that we should state the time points to calculate gain and loss measurements. We used the first (baseline measurement, before the start of the surgical procedure) and the last (after the surgical procedure was finished) EIT recording to calculate gain and loss of ventilation (pg. 17 line 1 to 3).

5. Page 9, line 18: please specify when data collection was conducted.

Reply: Intratidal compliance profiles, respiratory and hemodynamic variables were recorded continuously during the study protocol. EIT measurements were performed every 10 minutes for a duration of 2 minutes (pg. 11 line 4 to 6).

6. Page 11 line 21: in the results, loss of ventral ventilation in the intervention group is 29.3(17.6)% while in the table 4 is 29.7(17.6%). Please correct.

Reply: We would like to excuse for the typo and corrected the corresponding part of the results section in the revised version of the manuscript (pg. 12 line 24).

7. Page 14, line 25. The authors report an improvement in regional ventilation. This improvement was shown only by one of the parameters analyzed (gain/loss of ventilation) but no differences were seen in impedance distribution and tidal ventilation in the dorsal and ventral lung. Can the authors discuss this point in the paper? How do they justify a gain in regional ventilation also in the control group where PEEP was kept the same throughout all the surgery? Can they add two representative EIT images for the patients in the 2 groups?

Reply: We agree with the author that the discussion section of the manuscript should be adapted to pay more attention to the extended EIT measurements and therefore elaborated the discussion section in the revised version of the manuscript (pg. 17 line 1 to 24). We added an additional figure (Figure 3) including representative functional EIT images of two exemplary patients to the re-submission.
8. Table 1, gender, intervention. Summing the patients (21+6=27) the number of patients in the intervention group does not correspond the one stated by the authors (25). Please correct.

Reply: We apologize for having given the wrong number of male patients in the intervention group and corrected table 1 in the revised version of the manuscript.

9. Table 4: it seems that the loss of ventilation both in the intervention and in the control group was more pronounced in the ventral lung (41% vs 25.9% and 29.7% vs 16.4%) while atelectasis usually distributes in the dorsal lung. How do the authors justify this finding?

Reply: We agree with the Reviewer that atelectasis usually is more pronounced in the dependent (dorsal) lung areas. One possible explanation may be the limited because of the poor spatial resolution of the EIT. Further, it should be noted that we found almost equal gain in both, ventral and dorsal, lung areas in both groups. We further extented this discussion to differentiate between gain and loss and tidal variation in the discussion section in the revised version of the manuscript (pg. 17 line 1 to 24).

10. Figure 3: please consider putting this data in table 4 and substitute it with gain/loss of ventilation, which is the main positive finding of your study.

Reply: Since the variables TVv and TVd show the percentage tidal volume distribution in the ventral and dorsal lung areas, we did not add the data of figure 3 to table 4 to avoid redundancy. We agree with the Reviewer that the data presented in figure 3 includes only little information and thus deleted figure 3 in the revised version of the manuscript.

11. Please specify in the tables’ description how data are expressed (mean (SD)?).

Reply: All data in the tables are expressed as mean (SD). This is stated in the tables descriptions in the revised version of the manuscript.