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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Effect of individualized PEEP titration guided by intratidal compliance profile analysis on regional ventilation assessed by electrical impedance tomography – 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 "Effect of individualized PEEP titration guided by intratidal compliance profile analysis on regional ventilation assessed by electrical impedance tomography – a randomized controlled trial" (BANE-D-19-00556R2) has been assessed by our reviewers. Based on these reports, and my own assessment as Editor, I am pleased to inform you that it is potentially acceptable for publication in BMC Anesthesiology, once you have carried out some essential revisions suggested by our reviewers.
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.

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

https://www.editorialmanager.com/bane/

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.

We request that a point-by-point response letter accompanies your revised manuscript. This letter must provide a detailed response to each reviewer/editorial point raised, describing what amendments have been made to the manuscript text and where these can be found (e.g. Methods section, line 12, page 5). If you disagree with any comments raised, please provide a detailed rebuttal to help explain and justify your decision.

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 28 Jan 2020.
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.

We 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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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.

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 yours’ and the Reviewer’s comments.

We further would like to inform you that we used an academic proofreading service to improve syntax and grammatic of our manuscript.

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

Sincerely,

Dr. Jonas Weber

Editors’ comments

1. Abstract: line 3. PEEP never reduces stress, it always increases it (See stresses and strain AJRCCM). It may reduce dynamic strain if successfully increases the aerated volume by recruitment of collapsed alveoli. Please Fix it.

Reply: We agree with the Editor and corrected this sentence in the abstract session in the revised version of the manuscript according to the Editor’s suggestion (pg. 2 line 3 to 4).

2. Abstract: state in the background that the study was performed during general anesthesia

Reply: We state that the study was performed during general anesthesia in the revised version of the abstract (pg. 2 line 8).

3. Abstract: Methods: please simplify and state that you used EIT to assess regional ventilation.
Reply: We simplified the methods section in the abstract and state that we used EIT to assess regional ventilation (pg. 2 line 13 to 14).

4. Abstract: please simplify your conclusions and provide 1-2 key messages related to your primary endpoint and EIT analysis. Avoid any speculation not supported by your data.

Reply: The conclusion section in the revised version of the abstract (pg. 2 line 23 to pg. 3 line 1) and the manuscript (pg. 18 line 3 to 7) according to the Editor’s and the first Reviewer’s suggestions.

5. Line 4: protect$S$. Please, have your manuscript grammar and syntax thoroughly professionally revised. There are a lot of mistakes across the entire manuscript.

Reply: We want to apologize for the grammatical and syntax errors and corrected them throughout the revised version of the manuscript. We also used a professional academic proofreading to improve syntax and grammar of our manuscript.

6. Line 5-7: there are no conclusive data supporting the use of high PEEP and RM during general anesthesia. Please rephrase, or delete.

Reply: We agree with the Editor and deleted the respective sentence in the Background section of the revised version of the manuscript.

7. Line 14-16: revise syntax, long sentence and difficult to follow.

Reply: We revised the sentence by eliminating the second part of it (pg. 5 line 5 to 6).

8. Mandatory ventilated is an unusual term: please modify ‘fully controlled ventilation’.

Reply: We replaced the term ‘mandatory’ by ‘fully controlled’ throughout the revised version of the manuscript.

9. Please shorten and simplify your discussion, also avoiding speculations not supported by your results.
Reply: The discussion section in the revised version of the manuscript was shortened and thereby simplified. Speculations not supported by our results were deleted.

10. Please carefully revise the grammar and syntax of the manuscript and tune down the discussion and conclusions of the manuscript, as also suggested by dr. Spinelli.

Reply: We revised the entire discussion and conclusion section and used a professional academic proofreading service as mentioned above.

Elena Spinelli (Reviewer 1)

I truly appreciated the efforts that the authors put into this revision of the manuscript.

Three major issues were raised by the peer-review:

1. Research question not appropriate/not clearly stated: In the current version of the manuscript, the authors decided to maintain the intratidal linear compliance as the main endpoint. Respiratory mechanics and regional ventilation were defined secondary endpoints. Of note, the intratidal linear compliance is also the target of intervention, so it might be expected to be different in the two groups by study design. Nevertheless, it did not differ between the two groups. I think that both the methodological issue and the unexpected result are disclosed and discussed in the manuscript.

Reply: We thank the Reviewer for approving our secondly revised version of the manuscript.

2. EIT analysis underexploited/not clearly described: The current version of the manuscript has greatly improved in this respect. The methods and the results of EIT analysis are now clear and quite detailed.

Reply: Again, we thank the Reviewer for her positive assessment of our efforts in revising our manuscript.
3. Interpretation of results and inconsistent conclusions: This remain the major drawback of the current version. I think that none of the study endpoint was positive: intratidal linear compliance, respiratory mechanics and regional ventilation did not differ between the two groups. I think that global increase in aeration indicated by the calculations of regional gain and loss and change in tidal volume might just indicate the slight increase in aeration cue to the small PEEP increase in the intervention group. The authors seem to suggest this interpretation in the discussion (page 17), while in other parts of the manuscript (mainly in the conclusions) this result is overemphasized and it is used to support the idea that the intervention (PEEP titration according to the intratidal compliance profile) was effective. For example: Page 2: "Individualized PEEP titration according to bedside compliance profile analysis improves regional ventilation in terms of global aeration gain without affecting respiratory and hemodynamic variables negatively and might be a promising approach to patient-individual ventilation settings." Page 14: "The main findings are that only small PEEP adaptations are required to transfer increasing to horizontal compliance profiles and that the individualized PEEP titration improved regional ventilation without affecting impedance distribution and respiratory or hemodynamic variables negatively" Page 19: "Differences in regional ventilation gain and loss might suggest that the individualized PEEP titration could reduce the loss of ventilation in the dependent lung areas." All these sentences are misleading and they confuse the message of the manuscript. They should be deleted/rewritten in order to be consistent with the study data.

Reply: We appreciate again the kind rating of our manuscript. Willingly, we have addressed the final remarks of the Reviewer. And in agreement with the Editor’s suggestion to shorten the Discussion section we have deleted the mentioned sentences and in this context we have rephrased the Conclusion of the Abstract and of the main text. We feel that this has once more improved our manuscript.

Gaetano Scaramuzzo (Reviewer 2):

I congratulate the authors for improving the manuscript and I have no further comment.