Author’s response to reviews

Title: Flow-controlled ventilation (FCV) improves regional ventilation in obese patients – a randomized controlled crossover trial

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Author’s response to reviews:

Dear Dr. Grieco,

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

In the first section of this revision we will respond to the Editors comments of the current revision and in the second to the comments of the Reviewers. We have made every effort in revising our manuscript along the provided 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 hope that the revised manuscript will be acceptable for publication in BMC Anesthesiology.

Sincerely,

Dr. Jonas Weber

Editors’ comments

1. There are too many acronyms in the abstract and in the text. Please simplify to enhance readability.

Reply: We agree with the Editor that removing some acronyms would enhance the readability of the abstract and manuscript and thus replaced some acronyms in the revised version of the abstract and manuscript.
2. The essential results is that FCV increase EELV and mean airway pressure. The explanation for increased EELV is the increase mean airway pressure. Please state this clearly and include this information in the abstract.

Reply: We agree with the Editor that the essential result of an increased EELV and the potential underlying mechanism of the increased mean (tracheal) airway pressure (caused by the linearized pressure decline during expiration) should be stressed out more in the abstract. Therefore, we changed the conclusion section in the revised version of the abstract (pg. 2 line 23 to 25).

3. Remove the term “clearly” from line 22, page 2.

Reply: We deleted the word ‘clearly’ in the abstract in the revised version of the manuscript.


Reply: We adapted the word ‘reduces’ in the revised version of the manuscript (pg. 4 line 2).

5. Please include a figure in which it is clearly shown the difference between VCV and FCV (ventilator tracings would be optimal).

Reply: We included an additional Figure (new Figure 1) to the re-submission to show exemplary ventilator tracings to demonstrate the differences in pressure, flow rate and volume between VCV and FCV. Figure numberings were adapted, accordingly.

6. Page 5 line 27, include the unit of measure for 0.7. Move the section about sample size at the end of the methods section. The statistical analysis section is poor: please add further information (what test was used for the 2-group comparisons shown in the figures?). In table 2 you provide the p-value for 3-group comparison. You need to add the results of two-group comparisons for all the results (VCV vs FCV, BL vs. VCV and BL vs. FCV).

Reply: We would like to thank the Editor for this important comment. 0.7 is the assumed general effect size (being the quotient of differences in means and SD). This general effect size is dimensionless (pg. 9 line 10). For the two group comparisons shown in the figures, we used the Linear mixed effects model analyses as stated in the statistics section (pg. 9 line 18 to 20). In Table 2, we also used a linear mixed effect model to check for differences between the ventilation phases. The ventilation mode and the randomization both were factors. The mixed model was used to investigate whether one of these factors had any impact on the respective variable (dependent variable). If the p value of the linear mixed effect analysis (either p for ventilation mode or p for randomization) indicated that there is a significant effect of the respective factor on the dependent variable, we performed a post-hoc test. It follows that the chosen Linear mixed effect analysis is appropriate to compare between all ventilation modes (BL vs. VCV, BL. vs. FCV and VCV vs. FCV). As we feel that this may not have been clearly enough, we have enhanced the Statistics section accordingly (pg. 9 line 18 to 20).
7. What is the difference in the settings between BL and VCV: this is totally unclear. Please clarify. If there are no differences, how is it possible to explain the change in EELV?

Reply: Ventilation settings during baseline measurements and VCV were identical. However, BL characterizes the conditions of the respiratory system before the observation phase (pg. 7 line 11 to 12). During the observation period, we observed a decline in EELV in each patient (pg. 10 line 8). Interestingly, we found that EELV decreased significantly more during VCV compared to FCV (pg. 10 line 8 to 11). We attribute the observed differences between BL and VCV to the general tendency of the respiratory system to continued derecruitment during mechanical ventilation (Wirth et al. BJA 2015). This is discussed in the revised version of the manuscript (pg. 11 line 11 to 14).

8. What was the expiratory pressure set during FCV? Please include in the table 2 ‘mean expiratory pressure’ and ‘PEEP’. This is a study on EELV: the most important factor capable of affecting EELV is PEEP. If there is a difference between FCV and VCV in terms of expiratory pressure (as it is possible to suggest, since Pmean is increased but Pplat and RR are the same), the cause for increased EELV is the increased expiratory pressure caused by the technique.

Reply: According to the study protocol, (end) expiratory pressure during BL ventilation, VCV and FCV was maintained constant at 9 cmH2O (pg. 6 line 13, pg. 7 line 20 to 21) in all conditions. To avoid redundancy, we did not state the PEEP in table 2.

9. From the change in the expiratory pressure (if it is present) and the respiratory system compliance, it is possible to calculate the amount of lung recruitment from the deltaEELV (Mauri, ICM 2016, PMID 27518321). Please include this analysis in the results of the study, an analyze whether an heterogeneity in the response to FCV exists among enrolled patients.

Reply: The (end) expiratory pressure was comparable between all ventilation phases. Therefore, we omitted to include the suggested calculation in our present study.

10. Remove the p-order from table 2, which is confusing. Just include a sentence in the results stating that the randomization order did not affect any of the observed results.

Reply: Using a linear mixed effects model, we investigated the influence of different independent factors (ventilation sequence and randomization) on the primary and secondary endpoints. However, we agree with the Editor that it might improve readability if we just state in the description of Table 2 that the randomization had no significant effect on the measured respiratory and hemodynamic variables (pg. 23 line 7 to 10).

11. Please discuss in detail whether airway closure may affect the effect of FCV. This is not uncommon in obese patients after anesthesia (Grieco, Anesthesiology 2019).

Reply: We agree with the Editor that we should refer to the suggested reference in our manuscript and add this to the actual discussion where we state that the delayed expiration during FCV might delays the time point at which the lung volume falls below the closing capacity during expiration and thus improves lung aeration (pg. 4 line 5, pg. 11 line 23 to 24).
12. Discuss that 7 minutes for study phase may be short to observe any significant difference between treatments. This is a limitation of the study, especially because lung recruitment takes time.

Reply: We agree with the Editor that the duration of ventilation was too short to fully evaluate long term differences in recruitment and added this information to the limitations section in the revised version of the manuscript (pg. 13 line 5 to 9).

13. Do not include the response to reviewers among the submitted files.

Reply: We would like to apologize that we additionally included our response to the first revision as a separate file.

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.

Lucia Mirabella (Reviewer 1)

Alberto Fogagnolo (Reviewer 2)

Dear Authors,

thank you for the changes you made and the time you spend. I would make just a little, but necessary change: the static compliance, as calculated by authors, should be called more accurately "quasi-static" compliance (please see Henderson, Brochard ed al https://doi.org/10.1164/rccm.201612-2495CI )

Best regards

Reply: We would like to thank the Reviewer for his kind comment. We already stated that CRS is the abbreviation of the so called quasi-static compliance of the respiratory system (pg. 8 line 10, pg. 8 line 23, pg. 15 line 4).