Title: Use of interrupter technique in assessment of bronchial responsiveness in normal subjects.

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Author's response to reviews: see over
Point-by-point reply to reviewer NO II

Major Compulsory Revisions:

1. **Results:** Baseline PFT’s were not statistically significant according to gender. The lower FEV1%pred in females is in accordance with the higher Rint EI values and of course normalization by height could eliminate these small differences. So following reviewer’s comments we erased the word *in contrast* by the word *while* and we added in the paragraph the phrase *not statistically significant*.

2. The second sentence was corrected and an interpretation is given in the results section.

3. Since subjects were normals, not all of them of course showed measurable reactions by means of 20% fall in FEV1 or 100% increase in resistance. Our results as it is stated in detail in the discussion section are in accordance with the current bibliography. That is why we also checked the dose-response ratios. So we thought a figure might be redundant.

4. We agree with the reviewer about Rint values concerning children. Our data did not include children.

5. **Figure 2:** The Bland and Altman plot as it is explained in the legends section of course includes 2SD’s of the mean difference, so it allows good visualization of the values outside the 95% CI.

6. **Discussion:** we state that RintEI is more sensitive than mid or beginning of interruption. We feel that the paper by the reviewer concerning RintL is important, so we referenced the article in the last part of the discussion in a separate paragraph. Again our data did not include children and pressure equilibration in adults is explained accordingly.
7. **Conclusion:** Studies using RintEI in asthmatics have already been conducted (they are referenced) so we did not want to repeat the same paper, but a study in normals using this methodology has not been performed. Of course there are differences between RintEI and FEV1 in healthy and asthmatics (smooth muscle contraction), that is why we checked it and found very interesting data that are reported in the paper. The term useful refers not only to normals but also in all those situations (are many) where forced maneuvers cannot be performed.

**Minor essential revisions:**

8. Labels are included in the figures.

9. The reliability of Rint in sick persons is explained above.

10. **Materials and Methods:** We reported on that one person separately who responded to diluent control solution with both an FEV1 and RintEI change because we thought it would be interesting to know what that percentage is. Studies have concluded that is of no problem to omit the control phase, but our data disprove this.

11. Non evaluable means subjects with artifacts during measurement particularly glottis closure.

12. The sentence about FRC and RintEI was copied from the journal Respiration that is referenced.

13. P9 line 9-10: we think it is statistically sound that one hundred per cent in resistance comes from our normal data at baseline (1.96SD). The data are shown in the table 1.Also, following reviewer’s comment we replaced the word **fall** by the word **increase.**

**Discretionary revisions:**

14. The sample was a mixed population of adults representative of the general population
15. **Introduction**: nasal resistance measurement relies on the concept of pressure equilibration because nasal resistance is assessed by subtraction (total through the nose–airway).

16. The intraindividual variability of \( R_{\text{int}} \) measurement was small in the order of 6%-8%, but the 100% resistance increase was based on intersubject variability.

17. It is established knowledge about plethysmography being more expensive and cumbersome than any other method.

18. The sensitivity of DRR (reactivity) being better than threshold doses and its important consequences are explained in detail in the discussion section. Briefly DRR’s include two points of a measurement method, whereas PD’s are one point.