Author's response to reviews

Title: The effect of changing ventilator settings on indices of ventilation inhomogeneity in small ventilated lungs

Authors:

Gerd Schmalisch (gerd.schmalisch@charite.de)
Hans Proquitte (hans.proquitte@charite.de)
Charles C Roehr (christoph.roehr@charite.de)
Roland R Wauer (roland.wauer@charite.de)

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Author’s response to reviews: see over
Dear Editors,

Thank you very much for the review of our manuscript. We have revised the manuscript to meet all suggestions of both reviewers. Changes are listed in detail in the attached protocol.

The authors assure that the work is original and that the manuscript is being submitted only to BMC-Pulmonary Medicine, that it will not be submitted elsewhere while under consideration, that it has not been published elsewhere, and, should it be published in BMC-Pulmonary Medicine, that it will not be published elsewhere.

The authors assure that they are responsible for reported research and that they have participated in the concept and design; analysis and interpretation of the data; drafting or revision of the manuscript, and that they have approved the manuscript as submitted. They are disclosing any affiliation, financial agreement, or other involvement of any author with any company whose product figures prominently in the submitted manuscript.

Sincerely

Dr. Gerd Schmalisch
**Protocol of Review**

We would like to thank you for inviting us to revise our manuscript. We thank the editor and all reviewers for their critical and helpful comments and do acknowledge their valuable suggestions that helped to improve the quality of our manuscript. We have revised the manuscript according the suggestions of all reviewers, changes are listed in detail below.

**Reply to the editor** (Matt Hodgkinson-Barett)

- For the calculation of the VI indices of a well mixed volume a computer program was developed for this study and, as suggested by the editor, is attached to the revised manuscript. It is a simple to use Excel-worksheet which contains a macro to calculate the indices.

- Between our first publication in this field


  and the submitted manuscript are important differences. Our first study was done about 3 years ago and aimed to describe a new technique to measure the FRC in ventilated small lung and to validate this method in-vitro as well in-vivo. The measurements in piglets were performed before and after surfactant depletion by lung lavage. In these measurements the tidal volume and, so far, the ratio VD/VT were kept constant (after lavage PIP and PEEP were increased simultaneously) so that the differences in FRC and VI indices can mainly be attributed to the lung lavage. As shown in the present study the effect of changing FRC by lung lavage on the VI indices is relatively small. The present study was performed in the last year and all measurements were performed in healthy piglets. The aim of this study was to demonstrate the fact (proved theoretically for the well mixed volume) that changes in ventilator settings can lead to significant changes in VI indices. Changes in the VT have the strongest effect on VI indices. Therefore in this study PIP was increased and PEEP was kept constant.

  Thus the aims and the messages of both studies are quite different. The clarify the difference between both studies a new paragraph was added (see first point of reply to reviewer 3)
Major points

- The effect of breathing rate on FRC measurements and alveolar ventilation is a very interesting question and should be addressed to further studies. In our model we assume an ideal gas mixing without any time delay. This model is only adequate for relatively low breathing rates.

In our study we have used a constant respiratory rate of 40/min (commonly used in the neonatal ICU). For this rate we had an stable end-expiratory tracer gas concentration and we could show an unexpected good agreement between the model and the gas mixing in our healthy lungs, likely due to the low time constants of these small lungs. In lungs with higher respiratory time constants much lower respiratory rates are possible.

- The extension of our theoretical model to consider dynamic effects of gas mixing is an unsolved problem (see last point of the reply to Hjalmarson). Up to now no accepted model which would be easy to apply is known and more research is necessary.

Besides physical and physiological aspects we also have to consider the limited response time of the gas analyzer. In our in-vitro studies the washout curves were independent of the respiratory rate up to 60 breaths/min.

- All measurements were performed with the same ventilator (Babylog 8000) because hard- and software for MBW with HFP were developed only for this ventilator. It is likely that VI indices will differ more or less from ventilator to ventilator due to the differences in the functional active dead space of the ventilator circuit. This functional active deadspace would not necessarily be identical with the geometrical deadspace. Thus, deadspace corrections are often difficult.

- We agree with the referee that the consideration of all aspects of gas mixing within the lung would increase the expense of such a study dramatically. The aim of the present study was to demonstrate in theory and by in-vivo measurements that the conventionally used VI indices can change with changing ventilator settings and that they do not always reflect changes in the homogeneity of alveolar ventilation. This is an important aspect for monitoring mechanical ventilation in the near future, because MBW techniques with traces gases hopefully will be soon an integrated part of ventilator monitors.
• Thank you very much for the interesting discussion and hints. We completely agree with Prof. Hjalmarson that the dependency of most VI indices on VD/VT and VT/FRC is an important disadvantage, often overlooked and a source of error when trying to interpret the indices as markers of ventilation inhomogeneity. Therefore the aim of this study was to demonstrate it both in theory and animal experiments.

• It is a very interesting point of view to interpret the conventional VI indices as measures of air mixing within the lung. However, air mixing in the lung is a very complex process and up to now not well understood. Furthermore a theoretical analysis is very difficult (see Fuller et al. Gas-mixing efficiency in a mathematical model of the lung. Clin. Phys. Physiol. Meas. 11 (1990) 149-158; Tsuda et al. Chaotic mixing deep in the lung. PNAS 15 (2002) 101713-10178)

We believe that more basic research is necessary before we can describe the relationship between gas mixing and VI indices.

Reply to reviewer 3 (Frans B. Plötz)

Major points

• In contrast to our first publication in CCM 2006 (see 2nd point of the reply to editor) in this study the lungs were healthy and unaffected so that the effect of changed ventilator settings could be demonstrated. To further clarify this difference we have added in the text:

“In a previous study [13], we have shown that by this technique the effect of surfactant-depletion by lung lavage on the FRC and the VI indices is reliably measured: before and after lavage VD/VT was not significant different. Therefore, the significant increase of the VI indices has to be predominantly attributed to the effect of lung lavage. In the present study the measurements were performed in healthy lungs and VD/VT was distinctly changed by an increase of the PIP. As shown in Fig. 5 the changes of the VI indices are mainly caused by physical laws of gas mixing

• Please excuse that the ventilator data were not described. These were now inserted in “Material and Methods”:
Healthy newborn piglets do not tolerate an increased PEEP well. Therefore, all measurements were performed with zero PEEP and the measured end-expiratory lung volume is equal to the FRC.

As already mentioned the study aimed to demonstrate the effect of changes in ventilator settings on VI indices according to physical laws of gas mixing. The strongest influence is given by changing the ratio VD/VT and this most simply is obtained by increasing PIP and leaving PEEP unchanged. Thus, only PIP was changed.

The effect of changes of PEEP on VD/VT and VT/FRC is difficult to predict. There are significant differences between healthy and sick lungs. If PIP were kept constant an increase of PEEP causes commonly a decrease in VT. In sick lungs an increase of the PIP can improve considerably the lung mechanics and VT increases. Furthermore earlier studies have shown that there is a high intersubject variability in the reaction of changes of PEEP. Therefore, in this study the effect of changed PEEP on VI indices was not investigated. In the theoretical model (not in-vivo) there is no difference whether changes in VD/VT and VT/FRC were generated by changes in PIP or PEEP or both.

The computer program for calculating VI indices of a well-mixed volume used in this study was described more in detail and attached to the manuscript.

"A computer program written in Visual Basic (Microsoft Corpor., USA) as a macro of an EXCEL worksheet (Microsoft Office 2000, Microsoft Corpor., USA) was developed to compare the VI indices measured in the piglets with the VI indices of a uniformly ventilated volume using the same ventilator settings (see attached file). The program calculates the washout curve according equation 2 and the corresponding VI indices according equations 1, 3 and 5."

**Minor points**

- The referee suggested an adjustment of the title. The study was not aimed to investigate the physiological effects of changes in PIP, PEEP and FRC on alveolar ventilation. The aim of this study was to demonstrate that changes in ventilator settings can (but must not) lead to significant changes in VI indices, which can be partly explained by the physics of gas mixing. Therefore, we would like to maintain the current formulation.

- A statement of the high intra-subject variability of VI indices was added to the abstract.
"The within-subject variability of the VI indices (coefficient of variation in brackets) was distinctly higher (LCI (9.8%), M1/M0 (6.6%), M2/M0 (14.6%), AMDN1 (9.1%)) compared to FRC measurements (5.6%)."

- Data from the literature were added to describe the significantly higher VD/VT ratios in ventilated newborns.

  "In ventilated newborns the dead space fraction VD/VT is often markedly higher [9] depending on the ventilator settings. Typical values lie between 0.4 and 0.6 [10] and in preterm or surfactant-depleted lungs VD/VT can rise up to 0.7 [11]."

- Fig 4 was quoted in the results.

- All figures were revised. In figure 2 the arrows were removed and a legend was added.
- The legend of figure 4 was corrected