Dependency of respiratory system mechanics on positive end-expiratory pressure and recruitment maneuvers in lung healthy pediatric patients—A randomized crossover study

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Funding
This work was supported by institutional funding.

Editor: Britta von Ungern-Sternberg

Abstract

Background: The lungs of pediatric patients are subjected to tidal derecruitment during mechanical ventilation and in contrast to adult patients this unfavorable condition cannot be resolved with small c increases. This raises the question if higher end-expiratory pressure increases or recruitment maneuvers may resolve tidal derecruitment in pediatric patients.

Aims: We hypothesized that higher PEEP resolves tidal derecruitment in pediatric patients and that recruitment maneuvers between the pressure changes support the improvement of respiratory system mechanics.

Methods: The effects of end-expiratory pressure changes from 3 to 7 cmH₂O and vice versa without and with intermediate recruitment maneuvers on respiratory system mechanics and regional ventilation were investigated in 57 mechanically ventilated pediatric patients. The intratidal respiratory system compliance was determined from volume and pressure data before and after PEEP changes and categorized to indicate tidal derecruitment.

Results: Tidal derecruitment occurred comparably frequently at PEEP 3 cmH₂O without (13 out of 14 cases) and with recruitment maneuver (14 out of 14 cases) and at PEEP 7 cmH₂O without (13 out of 14 cases) and with recruitment maneuver (13 out of 15 cases).

Conclusions: We conclude that contrary to our hypothesis, PEEP up to 7 cmH₂O is not sufficient to resolve tidal derecruitment and that recruitment maneuvers may be dispensable in mechanically ventilated pediatric patients.

Keywords
children, compliance-volume curve, functional residual capacity, lung compliance, mechanical ventilation, protective ventilation, respiratory system mechanics
1 | INTRODUCTION

Positive end-expiratory pressure (PEEP) is supposed to counteract tidal lung derecruitment during mechanical ventilation. However, in pediatric patients PEEP is usually set lower compared with adults and high closing capacity promotes intraoperative atelectasis and tidal derecruitment in pediatric patients. In an earlier study, lungs of mechanically ventilated pediatric patients showed signs of tidal derecruitment at PEEP 2 cmH\textsubscript{2}O which was not dissolved when PEEP was increased to 5 cmH\textsubscript{2}O. Therefore, we aimed to investigate if a higher PEEP of 7 cmH\textsubscript{2}O and recruitment maneuvers would be adequate measures for preventing tidal derecruitment during mechanical ventilation of pediatric patients. For this purpose, we ventilated pediatric patients subsequently at PEEP 3 or 7 cmH\textsubscript{2}O or vice versa and without and with recruitment maneuvers between the PEEP changes, respectively, and evaluated global respiratory system mechanics from recordings of respiratory data and regional ventilation from electrical impedance tomography (EIT).

2 | MATERIALS AND METHODS

The study protocol was approved by the ethics committee of the University of Freiburg (EK03/15) and registered at the German Register for Clinical Studies (DRKS00008545) before inclusion of the first patient. Written informed consent was obtained from all parents prior to the procedure. 60 pediatric patients (ASA status I-II, age 9-149 months), scheduled for elective surgery between June 2015 and December 2016 at the University Medical Center Freiburg participated in the study. Exclusion criteria were age over 12 years or below 6 months, known lung disease, cardiac pacemaker, implantable cardioverter or defibrillator, or other active implants, intracardiac heart defects, planned oblique or prone position, surgery close to the thorax, and abdominal procedures.

For induction of anesthesia, Midazolam (0.2 mg·kg\textsuperscript{-1}, Roche Pharma AG, Grenzach-Wyhlen, Germany) was administered as oral premedication about 30 minutes before inducing anesthesia. Routine monitoring (ECG, SpaO\textsubscript{2}, noninvasive blood pressure measurement, Infinity Delta XL, Dräger Medical) was established, an intravenous line was placed and the anesthesia was induced according to a standard protocol. Remifentanil (Janssen-Cilag) 0.3-0.5 μg·kg\textsuperscript{-1}·min\textsuperscript{-1} and Propofol 1% (Fresenius Kabi, Germany) 2-3 mg·kg\textsuperscript{-1} were administered. Cisatracurium (0.2 mg·kg\textsuperscript{-1}, Nimbecx®, GlaxoSmithKline, Munich, Germany) was administered for relaxation during tracheal intubation. After anesthesia was established, an EIT electrode belt was placed around the rib cage at the level of the 5th intercostal space. Maintenance of anesthesia was provided total intravenously by administration of Propofol 100-150 μg·kg\textsuperscript{-1}·min\textsuperscript{-1} and continuous infusion of Remifentanil 0.1-0.2 μg·kg\textsuperscript{-1}·min\textsuperscript{-1}. Intraoperative fluids were administered as a crystalloid solution (8 mL·kg\textsuperscript{-1}·h\textsuperscript{-1}, Jonosteril, Fresenius Kabi, Germany). Bispectral index (BIS, Aspect Medical Systems) electrodes were placed on the patient’s forehead to control the depth of anesthesia. The BIS index was maintained between 40 and 60 during the entire measurement procedure. The ventilation protocol consisted of volume-controlled ventilation (Fabius Tiro in case of ENT surgery or Primus IE in case of urological surgery, Dräger Medical) with an inspiratory to expiratory time ratio of 1:2, tidal volume of 8 mL·kg\textsuperscript{-1}, and respiratory rate set to maintain end-tidal carbon dioxide partial pressure between 4 and 5.3 kPa. After transfer to the operation theatre, the children were randomly assigned to one of four crossover groups receiving mechanical ventilation either with a PEEP of 3 cmH\textsubscript{2}O for 20 minutes followed by a PEEP of 7 cmH\textsubscript{2}O for 20 minutes without or with recruitment maneuver or vice versa. Random assignment was based on disclosure of an item of a beforehand self-generated (Matlab, R 2014) randomization list. The recruitment maneuver followed a modified scheme according to Tusman et al. In brief, PEEP was stepwise increased to 15 cmH\textsubscript{2}O, then tidal volume was increased until peak pressure was 35 cmH\textsubscript{2}O. This setting was maintained for 10 breaths, and then tidal volume was reset to 8 mL·kg\textsuperscript{-1} and PEEP stepwise decrease to the, respectively, required level. The position of the patients remained unchanged during the measurement period. Flow rate and airway pressure curves as measured by the ventilator were recorded via the ventilator’s serial port with a sample rate of 62.5 Hz throughout the intervention period. Five min. EIT (PulmoVista 500, Dräger Medical) recordings were performed at the end of the first, and at the beginning and the end of the second ventilation periods at a frame rate of 50 1/s. Respiratory data analyses were performed according to these time points.

Offline data analyses were performed using Matlab. The dynamic compliance of the respiratory system ($C_{R\ell}$) at the different PEEP levels was calculated for every patient via multilinear regression analysis. Using the gliding-SLICE method, the volume-dependent compliance curves were calculated from which the respective compliance profile was determined as described earlier. In brief, the intratidal pressure-volume curve was subdivided into 21 equidistant volume segments. The segment-specific compliance was then calculated from the data surrounding each segment (SLICE) within the...
range of ±1/12 of the tidal volume. The resulting compliance-volume
curves were classified and assigned to one of six compliance profiles
as follows4: A merely increasing profile was considered to indicate
strong tidal derecruitment. A merely decreasing profile was consid-
ered to indicate strong overdistension. A horizontal profile was con-
sidered to indicate that neither derecruitment nor overdistension
was present. From these basic profiles, three other possible profiles
result from their combinations: An increasing turning into horizontal
profile was considered to indicate moderate tidal derecruitment, a
horizontal turning into decreasing profile was considered to indicate
moderate tidal overdistension and a profile ranging from increasing
via horizontal to decreasing was considered to indicate both, tidal
derecruitment and overdistension.

Functional EIT images were generated by averaging the pix-
el-wise differences between raw images corresponding to start and
end of expiration for each recorded sequence in each patient.

From these functional images, regional tidal variation was deter-
mined as a measure for ventilation distribution in the ventral (TVv)
region.5 In brief, the functional impedance images were first split
into ventral and dorsal parts.5 Subsequently, impedance values were
summed up separately in these regions of interest (xi,v and xi,d) and
related to the sum of impedances (xi) of the whole functional EIT image:

\[
TV_v = \frac{\Sigma x_{i,v}}{\Sigma x_i}
\]  

(1)

Additionally, regional ventilation gain and loss7 were calculated
for each group by subtracting the functional EIT images from the
second PEEP phase from those of the first PEEP phase and splitting
them into ventral and dorsal regions. In order to achieve meaning-
ful results, the lung area of each patient was determined using the
lung area estimation method6 for this purpose. Subsequently, this
area was applied to all functional impedance images. Furthermore,
a threshold of 10% for relevant gain and loss pixels was used and
applied similar to the lung area estimation. In brief, the highest gain
or loss value was determined and only pixels with more than 10%
of this value were included into the gain and loss calculation. This
mitigates the drawback of gain and loss calculation to some extent,
since in its original form very small fluctuations with no relevant in-
formation in ventilation would result in a gain or loss.

2.1  |  Statistical analysis

Data are given as mean (SD), actual differences as mean [95% lower
to upper CI] if not indicated otherwise. A sample size estimation
was based on Fisher’s exact test for comparison of proportions. From
earlier data from adult patients, frequency of compliance profiles
with an increasing part decreased from 92% to 36% by increasing
PEEP by 4 cmH2O. At an alpha level of 0.05, a sample size of 11
patients per group would be required to achieve a power of 0.8 in a
group wise post hoc comparison. To compensate for potential drop-
outs, particularly with respect to the EIT recordings, we planned to
include 15 patients per group. Statistical analyses were performed
using StatView (version 5.0, SAS Institute Inc, Second edition).
Scalable data were compared using multifactorial repeated meas-
urement ANOVA, followed by Fisher’s PLSD post hoc comparisons,
if appropriate. Frequencies of compliance profiles were compared
via Fisher’s exact test. Tidal variations between groups were com-
pared using one-way ANOVA followed by a Student’s t test as a post
hoc test when indicated. For pixel-wise comparisons of EIT images,
Student’s t test was performed with Bonferroni correction for mul-
tiple comparisons. A P < .05 was considered statistically significant.

3  |  RESULTS

In the offline analysis, we detected large ventilation leakage in
the data of one patient which prevented meaningful analysis of
For two patients, we detected violations of the protocol after the measurements. Data from these patients were also excluded from the analyses (Figure 1). Characteristics of the 57 patients included in the study are given in Table 1. All patients were sufficiently ventilated with average oxygen saturation of 99.7 (0.6)% and endtidal CO\textsubscript{2} partial pressure of 38.4 (2.8) mmHg, which were comparable in all ventilation conditions (Table 2).

In four patients hypotension and bradycardia occurred during the first recruitment maneuver and volume substitution was administered, two patients received additionally akrinor (1) or aterenol (1). No further hemodynamic instabilities were observed.

When PEEP was increased from 3 to 7 cmH\textsubscript{2}O peak pressure increased by 3.2 [95% CI 3.0-3.4] cmH\textsubscript{2}O without recruitment maneuver and by 2.8 [95% CI 2.5-3.0] cmH\textsubscript{2}O with recruitment maneuver (pRecruitment = 0.388, Table 2). A reduction of PEEP from 7 to 3 cmH\textsubscript{2}O decreased peak pressure by 3.4 [95% CI 3.2-3.6] cmH\textsubscript{2}O without and comparably by 3.2 [95% CI 2.9-3.6] cmH\textsubscript{2}O with recruitment maneuver (pRecruitment = 0.869).

Independent of a preceding recruitment maneuver peak pressure increased by (0.8 [95% CI 0.3-1.1] cmH\textsubscript{2}O, during 20 minutes ventilation with PEEP 3 cmH\textsubscript{2}O (pTime = 0.0003, pRecruitment = 0.835) and by 0.3 [95% CI 0.1-0.5] cmH\textsubscript{2}O with PEEP 7 cmH\textsubscript{2}O (pTime = 0.008, pRecruitment = 0.604) (Table 2).

Respiratory system compliance was 14% [95% CI 10% to 17%] higher with PEEP 7 cmH\textsubscript{2}O than with PEEP 3 cmH\textsubscript{2}O (pPEEP = 0.0416) but recruitment was not a significant factor for compliance.
Independent of a preceding recruitment ($P_{\text{Recruit}} = 0.775$), respiratory system compliance decreased by $1.4 \, [95\% \text{ CI 0.6-2.2}] \, \text{mL-cmH}_2\text{O}^{-1}$ during 20 minutes ventilation with PEEP $3 \, \text{cmH}_2\text{O}$ ($P = .026$) but remained comparable with PEEP $7 \, \text{cmH}_2\text{O}$ (compliance loss = $0.4 \, [95\% \text{ CI 0.3-1.1}] \, \text{mL-cmH}_2\text{O}^{-1}$, $P = .316$).

Strong tidal derecruitment occurred in 66% of all conditions, moderate derecruitment in 29% and no derecruitment and no overdistension in 3% of all measurement phases (Figure 1). Profiles indicating overdistension occurred only three times (D: 1x, IHD 2x, in two different patients), in all those occasions PEEP was $7 \, \text{cmH}_2\text{O}$. Increasing PEEP was associated with improved tidal derecruitment condition in 1 of 13 cases of strong or moderate tidal derecruitment without and in 4 of 15 cases of strong or moderate tidal derecruitment with intermediate recruitment while decreasing PEEP was associated with more tidal derecruitment in 4 of 4 cases and 4 of 8 cases, respectively, without and with intermediate recruitment.

Changes in compliance profiles during ventilation on the second PEEP level occurred unspecifically and PEEP or recruiting maneuvers had no significant influence on the distributions of compliance profiles (Figure 2).

Electrical impedance tomography could not be performed when the surgical procedure required cautering. Reasoned by that, EIT recordings were not complete for 12 patients.

The ventral share of ventilation was $>55\%$ throughout the measurements in all groups. Tidal variations were comparable between all groups (Table 3).

Impedance gains and losses were significantly different between PEEP increases and PEEP decreases but not between PEEP changes in the same direction with or without intermediate recruitment maneuver (Table 4).

The main results of our study demonstrate that in mechanically ventilated pediatric patients respiratory system compliance is moderately higher with PEEP $7 \, \text{cmH}_2\text{O}$ than with $3 \, \text{cmH}_2\text{O}$ but the lung’s tidal derecruitment status is not considerably improved by PEEP or by recruitment maneuvers.

A preceding study found that tidal derecruitment persisted when PEEP was increased from 2 to $5 \, \text{cmH}_2\text{O}$.\textsuperscript{2} By contrast, in mechanically ventilated adult patients small PEEP increases shifted clearly the derecruitment condition of the lung from strong derecruitment toward moderate derecruitment or from moderate toward no derecruitment.\textsuperscript{4,8} We therefore assumed that tidal derecruitment might be resolvable in pediatric patients if PEEP would be increased to $7 \, \text{cmH}_2\text{O}$, particularly if supported by a recruitment maneuver. However, our results demonstrate that tidal derecruitment persisted.

![Figure 2](image-url)
in clinical routine are questionable, due to the associated higher peak pressure and the potential side effects of higher PEEP levels on the hemodynamic conditions. However, one might speculate that a certain tidal derecruitment in the pediatric lung is a rather physiological condition without necessity of a countermeasure. In this context, studying the intratidal respiratory system mechanics in spontaneously breathing awake pediatric patients might be interesting but difficult as it would require placement of an esophageal catheter and cooperation of the patient.

### 5 | LIMITATIONS OF THE STUDY

Our results are limited to children with healthy lungs during anesthesia and controlled mechanical ventilation. In case of pathologic lung conditions, for example, in case of intraoperative atelectases or lung disease, recruitment maneuvers and higher PEEP values may have relevant effects. We included pediatric patients in a wide range of age promoted a large variability of the results, particularly those which are related to tidal volume; on the other hand the investigated respiratory systems were in different states of development. However, the crossover design of this study allows to diminish the effects of large variability and furthermore, clinical practice in pediatrics is characterized by such bandwidth of age and weight. Respiratory mechanics of children < 1 year are different from those of older children and adults. It might be interesting to investigate at which age the respiratory system passes from the pediatric to the adult PEEP dependent tidal derecruitment behavior. Aiming to prevent from interfering with standard clinical routine as least as possible, we did not account for potential effects of medication. The premedication with midazolam and the decline of muscle relaxant might have influenced our study results; however, since our analyses covered a total duration range of about 25 minutes we would not assume a major impact of medication on our results.

In our study, we determined peak pressure instead of the more relevant plateau pressure. However, since not all pressure curves contained a well-defined plateau phase, plateau pressure could not be determined for all measurements. Since tidal volume was constant throughout the measurements, inspiratory flow

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**TABLE 3** Tidal variations of ventilation in the ventral region (TVv)

| Group 3-7/X | Group 3-7/R | Group 7-3/X | Group 7-3/R |
|------------|------------|------------|------------|
| TVv (%)    | TVv (%)    | TVv (%)    | TVv (%)    |
| T1         | 58.7 (2.8) | 56.1 (4.5) | 60.6 (3.0) | 61.5 (6.5) |
| T2         | 58.8 (3.3) | 55.6 (5.1) | 61.6 (4.4) | 60.8 (8.0) |
| T3         | 58.7 (3.4) | 57.0 (4.5) | 61.1 (4.4) | 61.2 (9.3) |

Note: First number of group indicates first PEEP level (before PEEP change = T1), second number of group indicates second PEEP level (immediately after PEEP change = T2, and after 20 min ventilation at this PEEP = T3). X indicates that PEEP change was performed without recruitment maneuver, R indicates that PEEP change was performed with intermediate recruitment maneuver. Values represent mean (SD). No significant differences were found between groups at any timepoint.

**TABLE 4** Ventilation gain and loss in ventral and dorsal areas. Significant differences could only be found for different PEEP levels. The intermediate recruitment maneuver had no effect

| Group 3-7/X | Group 3-7 R | Group 7-3/X | Group 7-3 R |
|------------|------------|------------|------------|
| Gain (%)   | Loss (%)   | Gain (%)   | Loss (%)   |
| Ventral    | 6.9 (4.7)  | 12.6 (4.9) | 4.2 (4.7)* | 16.0 (6.0)* |
| Dorsal     | 3.0 (4.2)  | 11.1 (6.5) | 0.8 (0.7)* | 13.4 (5.4)* |

Note: First number of group indicates first PEEP level (before PEEP change = T1), second number of group indicates second PEEP level (immediately after PEEP change = T2, and after 20 min ventilation at this PEEP = T3). X indicates that PEEP change was performed without recruitment maneuver, R indicates that PEEP change was performed with intermediate recruitment maneuver. Values represent mean (SD).

*P < .05 to group 3-7/X.

#Schumann et al

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at even this PEEP and was not ameliorated by the application of a recruitment maneuver. A PEEP of 7 cmH2O was only superior to 3 cmH2O in terms of a moderately higher compliance and in a better maintenance of compliance over a 20 minutes ventilation period. In this focus, once more it becomes clear that pediatric patients are not simply small adult patients. In this context is the missing effect of the recruitment maneuver of particular interest. Neither compliance nor the derecruitment status nor the regional ventilation was necessarily permanent atelectasis, persisting at the end of inspiration. Consequently, tidal derecruitment would not be resolvable by moderate PEEP levels—with or without recruitment maneuvers—but might require PEEP levels clearly above 7 cmH2O whose applicability...
and thus resistive pressure during inspiration was similar, too. Therefore, we assume that changes in peak pressure paralleled those of plateau pressure. As further the changes of respiratory system compliance were in accordance with the changes of peak pressure, we feel that peak pressure measurements were reliable in our study.

6 | CONCLUSION

Lung recruitment maneuvers have limited effects on respiratory system mechanics in healthy children while a moderate increase in PEEP may improve lung compliance.

CONFLICT OF INTEREST

The authors report no conflict of interest.

AUTHOR’S CONTRIBUTION

SS: involved in study design, data analysis, and writing up of the first draft of the paper. AF: involved in patient recruitment, data collection and data analysis and writing of the paper. SB: involved in data analysis and writing of the paper. SW: involved in study design, patient recruitment, data collection, data analysis, and writing up of the first draft of the paper.

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How to cite this article: Schumann S, Feth A, Borgmann S, Wirth S. Dependency of respiratory system mechanics on positive end-expiratory pressure and recruitment maneuvers in lung healthy pediatric patients—A randomized crossover study. Pediatr Anaesth. 2020;30:905–911. https://doi.org/10.1111/pan.13927