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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Abstract

Background

Application of positive end-expiratory pressure (PEEP) improves lung aeration and reduces mechanical stress during mechanical ventilation. Although numerous approaches for PEEP titration have been proposed, there is no accepted strategy to titrate optimal PEEP. By analyzing the intratidal compliance profiles, PEEP may be titrated patient-individually.

Methods

After obtaining informed consent, we measured respiratory system mechanics, regional ventilation in 60 consecutive patients undergoing elective surgery, randomly allocated to the control group (PEEP = 5 cmH 2 O) or the intervention group receiving individually titrated PEEP, guided by intratidal compliance profile analysis. Primary endpoint was the frequencies of nonlinear intratidal compliance (C RS ) profiles of the respiratory system (horizontal, increasing, decreasing and mixed). We further investigated respiratory and hemodynamic variables and regional ventilation.

Results

Frequencies of C RS profiles were comparable between the groups. Besides PEEP [control: 5.0 (0.0), intervention: 5.8 (1.1) cmH 2 O, p<0.001] respiratory and hemodynamic variables were comparable between the two groups. The compliance profile analysis showed no significant differences between the two groups. The loss of ventral and dorsal regional ventilation was higher in the control [ventral: 41.0 (16.3) %, dorsal: 25.9 (13.8) %] than in the intervention group [ventral: 29.3 (17.6) %, dorsal: 16.4 (12.7) %, p (ventral) = 0.039, p (dorsal) = 0.028].

Conclusions

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. However, differences in dorsal to ventral ventilation distribution were not found. Unfavorable compliance profiles indicating tidal derecruitment were found less often than in earlier studies.

Background
During mechanical ventilation, it is widely accepted that the application of low tidal volume and low driving pressure [i.e. the difference between plateau pressure (P\text{Plat}) and (positive) end-expiratory pressure (PEEP)] protect the lung from destructive effects of alveolar overdistension [1–4]. In combination with low tidal volumes, application of adequate PEEP and the performance of recruitment maneuvers was shown to improve postoperative pulmonary function, arterial oxygenation and to reduce health care utilization [2, 5]. However, there are conflicting data regarding the setting of adequate PEEP during general anesthesia [6]. With regard to the conflicting clinical data, many techniques were developed to determine adequate PEEP [7–10]. One of these techniques, first described in 1979 for patients with severe lung injury [11], is based on setting the PEEP slightly above the lower inflection point of the inspiratory limb of the static pressure-volume (PV) curve [7, 12, 13]. Other techniques focus on the respiratory system compliance (C_{RS}). For example, PEEP can be titrated to reach the maximum quasi-static compliance, calculated by dividing V_T by the driving pressure [10, 14, 15]. However, a single value compliance cannot reflect the non-linearity of intratidal respiratory system mechanics during the breathing cycle [16, 17] and therefore always a maneuver is required to identify the PEEP for maximal compliance. To cope with the non-linearity of the intratidal C_{RS} under the dynamic conditions of mechanical ventilation, the gliding-SLICE method [18, 19] was introduced, enhancing the classical SLICE method [20, 21]. In brief, the pressure-volume curve is subdivided in several volume steps and the volume dependent compliance is calculated on the base of data points within a certain volume range (‘slice’) around the current step via multiple linear regression analysis (Fig. 1). The resulting compliance-volume curve can then be classified as follows: An increasing compliance profile is interpreted to indicate intratidal recruitment, suggesting an increase of PEEP. A decreasing compliance profile indicates overdistension, suggesting a decrease of PEEP. A horizontal compliance profile is assumed preferable as it does not indicate either of both unwished conditions. According to these three basic compliance profiles, combinations may be observed [19] (Fig. 1). A previously described Decision Support System with a Graphical User Interface (GUI) implements the gliding-SLICE method into a user-friendly tool to recommend a bedside patient-individual PEEP.
titration during mandatory ventilation [22]. Using exemplary data from patients ventilated in the volume- and pressure-controlled mode, a theoretical study demonstrated that the Decision Support System allows to estimate the intratidal compliance-profiles and that the recommended PEEP adjustments directed to ventilation with horizontal compliance profiles [22].

The primary hypothesis of this randomized controlled clinical trial is that individualized PEEP titration based on the analysis of the intratidal compliance profile improves frequencies of preferable compliance profiles (i.e. compliance profiles that indicate neither tidal lung derecruitment nor overdistension), respiratory system mechanics and regional ventilation during perioperative mandatory ventilation, compared to a non-personalized PEEP ventilation technique. Therefore we determined frequencies of nonlinear intratidal compliance (C_{RS}) profiles, regional ventilation, and respiratory and hemodynamic variables in 60 mandatory ventilated consecutive patients undergoing otorhinolaryngeal surgery.

Methods

Ethics, consent and permission

The study was approved by the Ethics Committee of the University Medical Centre of Freiburg (vote # 268/15) on 29th June 2015 and registered at the German Register for Clinical Trials (DRKS00008924). This study adheres to CONSORT guidelines.

Study design and patient population

After obtaining written informed consent from all individual participants included in the study, we studied respiratory mechanics, hemodynamic variables and regional ventilation in 60 consecutive patients with American Society of Anesthesiologists (ASA) physical status I-III, undergoing otorhinolaryngeal surgery at the Medical Center of the University of Freiburg, Germany. The study was performed as a prospective parallel arm, randomized, controlled trial with an allocation ratio of 1:1. Randomization was carried out in blocks of 30 by a computer generated allocation sequence. Participants were enrolled and assigned to the interventions by a study related anesthetist. Exclusion criteria were ASA physical status > III, age < 18 years, pregnancy, emergency procedure, cardiac
pacemaker and other active implants, obesity (BMI ≥ 30 kg·m⁻²) history of pulmonary disease, laparoscopic surgery or refusal of participation.

**Procedure**

After primary recruitment and preoperative evaluation, the patients received routine monitoring (electrocardiography, SpO₂, noninvasive blood pressure measurement; Infinity Delta XL, Dräger Medical, Lübeck, Germany). After preoxygenation to an expiratory fraction of oxygen of 0.8, anesthesia was induced and maintained as total intravenous anesthesia with a continuous infusion of propofol (Propofol 1%, Fresenius Kabi, Bad Homburg, Germany; target controlled infusion, effect site target concentration for induction: 6–8 µg·mL⁻¹, target concentration for maintenance: 3–5 µg·mL⁻¹, Agilia, Schnider Model; Fresenius Kabi) and remifentanil (TEVA GmbH, Ulm, Germany; induction: 1–2 µg·kg⁻¹, maintenance: 0.15–0.3 µg·kg⁻¹·min⁻¹). During the study protocol, a Bispectral Index™ (BIS™) monitoring (Medtronic, Minneapolis, USA) was used as an additional monitor of depth of anesthesia (BIS value target 40–60). Tracheal intubation was facilitated with 0.15 mg·kg⁻¹ predicted body weight (PBW) [23] cisatracurium (Fresenius Kabi). Potential hypotension (defined as mean arterial pressure < 65 mmHg) was treated with a continuous infusion of norepinephrine (0.03–0.2 µg·kg⁻¹·min⁻¹). Volume requirements were addressed individually according to clinical judgement with a crystalloid solution (Jonosteril; Fresenius Kabi). For tracheal intubation, we used tracheal tubes with low pressure cuffs (internal diameter of 7.0–7.5 mm for women and 8.0 mm for men; Mallinckrodt Hallo-Contour; Covidien, Neustadt an der Donau, Germany). All patients were ventilated in the volume-controlled mode with a tidal volume (V₇) of 7 mL·kg⁻¹ PBW. Ventilation frequency was set to maintain an end-tidal carbon dioxide partial pressure between 35 and 40 mmHg. The initial PEEP was set to 5 cmH₂O, according to our local standard. Following these baseline measurements, the randomization was disclosed. In the control group, this PEEP was maintained for the whole procedure, in the intervention group, the PEEP was adjusted dynamically according to the recommendations resulting from the intratidal compliance profile analysis (see below).
Gliding-SLICE

To calculate nonlinear intratidal $C_{RS}$ profiles of via the gliding-SLICE method, we chose a number of 21 equidistant slices as a tradeoff between calculation effort and reasonable resolution. The resulting intratidal compliance curves were classified into six different compliance profiles, as described earlier [21, 24, 25]. In brief, a second order polynomial was fit into the compliance-volume curve, and the resulting segment of a parabola was assumed to represent the compliance-volume curve in a filtered form. If the segment showed an increase of more than 20% of the compliance maximum, the profile was classified as containing an increasing part. A segment decreasing by more than 20% of the compliance maximum was classified as containing a decreasing part. A segment containing the angular point of the parabola was classified as containing the horizontal part. A compliance profile with less than 20% change was classified as horizontal (Fig. 1) [22]. The Decision Support Systems suggested a PEEP increase of 2 cmH$_2$O in case of a merely increasing compliance profile, 1 cmH$_2$O in case of an increasing compliance profile with horizontal component, a PEEP decrease of 2 cmH$_2$O in case of a merely decreasing compliance profile and 1 cmH$_2$O in case of a decreasing compliance profile with horizontal component. A merely horizontal compliance profile resulted in the suggestion to maintain PEEP as it is.

Electrical impedance tomography

Regional ventilation was measured via electrical impedance tomography (EIT, PulmoVista 500, Dräger Medical) every 10 minutes for a duration of 2 minutes. EIT recordings were offline evaluated using software developed in Matlab (MATLAB R2014a, The Mathworks Inc., Natick, MA, USA). As a first step, the relevant lung areas were determined for each patient by applying the lung area estimation method [26, 27] to the raw EIT data. Therefore, functional region of interest was selected by deleting all pixels with impedance change smaller than 20% of maximum tidal impedance change. Subsequently, the remaining pixels were mirrored to compensate for potential atelectatic areas. The obtained lung area was then applied to all recorded raw EIT images. After this preprocessing, functional impedance images were generated. This was done by subtracting the frames.
corresponding to the start of inspiration from the frames corresponding to the end of inspiration. Thus, these functional images (f-EIT) represent the distribution of the tidal volume for each breath. To assess potential changes in regional ventilation, tidal variation as well as a gain and loss calculation was performed and compared between the two groups. Gain and loss calculation is based on subtracting functional impedance images of different time points in order to directly compare differences in ventilation between them. In our case, the averaged f-EIT images of the first EIT recording (baseline measurement, prior to the surgical procedure) and the averaged f-EIT images of the last EIT recording (after the surgical procedure was finished) were subtracted for each patient. Subsequently, the resulting differential images were split into ventral and dorsal parts and the number of positive (‘gain’) and negative (‘loss’) pixels were calculated for each such region. Thus, gain represents the amount of pixels that exhibit an increase in aeration in the last measured EIT sequence compared to the first (baseline) measured EIT sequence and loss the decrease in aeration accordingly. The results were then compared between the two different groups. The change in tidal volume ($\Delta V_T$) was then calculated as difference between gain ($TV_G$) and loss ($TV_L$) ($\Delta V_T = TV_G - TV_L$) for the previous defined ventral ($\Delta V_{T,v}$) and dorsal ($\Delta V_{T,d}$) lung areas. This ultimately provides a measure for changes in regional ventilation. If this difference was positive, we assumed an increase in regional ventilation in the respective lung area whereas a negative difference indicates a decrease in regional ventilation [28].

Tidal variation (impedance distribution) is the percentage of tidal volume going to ventral ($TV_v$) and dorsal areas ($TV_d$). This has been calculated for all functional impedance images using Equation 1,

$$TV_v = \frac{\sum x_{i,v}}{\sum x_i} \quad \text{or} \quad TV_d = \frac{\sum x_{i,d}}{\sum x_i}$$

where $x_{i,v}$ are the impedance values in the ventral region, $x_{i,d}$ the impedance values in the dorsal region and $x_i$ the sum of all impedance values of the functional impedance image under consideration. Tidal variation was calculated for each averaged f-EIT image of each two minute EIT
End points and data collection

Frequencies of nonlinear intratidal $C_{RS}$ profiles (measured using the gliding-SLICE method) was the primary endpoint of this study. Secondary endpoints were regional ventilation (ventral and dorsal ventilation distribution, ventral and dorsal gain and loss, tidal variation), the respiratory system variables [peak inspiratory pressure (PIP), $P_{Plat}$, mean tracheal pressure ($P_{mean}$), PEEP] and hemodynamic variables [systolic blood pressure ($BP_{sys}$), diastolic blood pressure ($BP_{dias}$), heart rate and mean arterial pressure (MAP)]. Intratidal compliance profiles, respiratory and hemodynamic variables were recorded continuously during the study protocol. EIT measurements were performed every 10 minutes for a duration of 2 minutes.

Sample size calculation and statistical evaluation

There are no data available concerning the variance of frequencies of compliance profiles. Therefore, we based our sample size calculation on estimation of a general standardized effect size $e$, being the quotient of differences in means and SD. With regard to our approach, adapting PEEP according to the measured compliance profile, we assumed a large effect size and therefore chose $e = 0.8$ [29]. In regard to the trial design (unpaired test conditions) and an assumed $e$ of 0.8, 50 patients were required to reach a test power of 0.8 with a desired level of significance of 0.05.

To compensate for potential incomplete data sets, a total of 60 patients were recruited. Data are presented as mean (SD). Differences between the two groups were assessed with unpaired Students t-test, respectively. Statistical significance was considered for $p < 0.05$. Preceding, Shapiro-Wilk tests were used to confirm that the assumed normal distribution cannot be rejected. For not normally distributed data, differences between the two groups were assessed with Mann-Whitney U tests.

Results

Patients were enrolled from November, 5th 2015 to January, 29th 2016. In total, 60 patients were included. 12 patients had to be excluded due to incomplete data sets (Fig. 2). During the study recording.
protocol, no adverse or serious events occurred. Age, gender, ASA physical status, PBW, actual body weight (ABW) and BMI were comparable between the two groups (Table 1).

Respiratory and hemodynamic variables

In 12 patients in the intervention group (48%) the PEEP was adjusted according to the intratidal compliance profile analysis. In 11 patients (44%), the PEEP was increased as the corresponding compliance profile analysis showed increasing compliance profiles. In 7 of these patients (28%) the PEEP was thenceforward held constant. In 3 of the patients in the intervention group (12%) the PEEP was adjusted twice. In 2 patients (8%), the PEEP was adjusted three times. PEEP was higher in the intervention group compared to the control group [control: 5.0 (0.2) cmH₂O, intervention: 5.8 (1.1) cmH₂O, p < 0.001; range control: 5.0–5.0 cmH₂O, range intervention: 3.9–8.5 cmH₂O]. In total, a PEEP adaption was performed in 12 patients in the intervention group (48%). These individualized PEEP adaptations had no significant effect on the other measured respiratory system or hemodynamic variables (Table 2). The frequencies of nonlinear intratidal Cₐₐₚₚₚₚ profiles showed no significant difference between the two groups (Table 3).

EIT measurements

Regional impedance distribution showed no significant difference in ventilation distribution between the two groups (Table 4). Gain and loss calculations showed a significant decrease in loss of ventral regional ventilation between the two groups [loss of ventral regional ventilation of 41.0 (16.3) % in the control group and 29.7 (16.8) % in the intervention group, p = 0.039]. In the dorsal lung area, the gain in regional ventilation was higher in the intervention group [14.3 (11.9) %] than in the control group [24.6 (13.0) %, p = 0.013] (Fig. 3). In the intervention group, the loss of dorsal regional ventilation was less pronounced [16.4 (12.7) %] than in the control group [25.9 (13.9) %, p = 0.028] (Table 4). TVᵥ and TV₅ showed no significant difference between the two groups. ΔVᵥ indicate a lower difference between gain and loss in the intervention than in the control group in the ventral lung area (ΔVᵥ (control group) = -22.2 (31.1) %, ΔVᵥ (intervention group) = -0.4 (34.2) %, p = 0.044). ΔV₅ indicate a lower difference between gain and loss in the intervention than in the control
group in the ventral lung area ($\Delta V_{T,d}$ (control group) = -11.6 (24.6) %, $\Delta V_{T,d}$ (intervention group) = 8.25 (25.4) %, $p = 0.017$) (Table 4).

**Discussion**

In this study, we compared the effects of an individualized PEEP titration according to bedside analysis of the frequencies nonlinear intratidal $C_{RS}$ profiles (measured using the gliding-SLICE method). 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.

**Respiratory and hemodynamic variables**

Besides PEEP, none of the respiratory and hemodynamic variables differed between the two investigated patient groups. PEEP is generally associated with recruitment and one might expect that $C_{RS}$ increases with increasing PEEP. However, in agreement with earlier studies [16, 30] $C_{RS}$ remained unchanged besides PEEP related changes in regional ventilation. Compared to lungs with severe lung-injury and impaired respiratory system mechanics, healthy lungs are in a well recruited state, thus compliance may barely depend on lung volume. In particular, in our study, patients showed respiratory system mechanics that were mostly characterized by a horizontal compliance profile and consequently PEEP adaptations were performed less frequent than we had expected. It follows that the observed improvement in regional ventilation may have increased $C_{RS}$, if the studied patient collective would have included more patients with impaired respiratory system mechanics and/or surgical procedures associated with an increased risk for alterations of respiratory functions (e.g. laparoscopic surgery, patient positioning, obesity). Since this is the first study in which we applied individualized PEEP titration according to the compliance profile analysis, we did not include patients at risk for impaired respiratory system performance. One might speculate further that the comparably high alveolar recruitment in the studied patients was the reason that we did not find significant differences in $C_{RS}$. This hypothesis can be supported by two clinical trials to provide preliminary investigations of the gliding-SLICE method [16, 30]. In both studies, lower levels of PEEP (such as 5
and 7 cmH₂O) did not prevent from C_{RS} profiles indicating recruitment/derecruitment. In both studies, intratidal compliance profile analysis was used as a bedside measurement for predefined PEEP settings. In the present study, this analysis was used to guide PEEP titration individually. One might speculate that the higher duration of surgical procedure [mean duration of surgery of 120 min [30] and 184 min [16] vs. 83.2 min (control group) and 87.5 min (intervention group) in the present study] lead to a more pronounced impairment of respiratory system mechanics and thus of intratidal C_{RS} profiles. Further, in the present study, obesity was an exclusion criterion. In one of the previous studies [16], obese patients were included. Since obesity is associated with a low respiratory system compliance, early expiratory alveolar collapse, consecutive atelectasis and increased airway resistance [31], it seems obvious that the results from intratidal compliance profile analysis differs from them in the present study. It follows that further studies are needed to provide more detailed information about the impact of an individualized PEEP titration strategy based on the gliding-SLICE method on respiratory function in patients with impaired respiratory system mechanics.

By increasing the intrathoracic pressure, PEEP was shown to affect the cardiac performance by altering the left ventricular preload, afterload and cardiac contractility [32]. Previous studies found that in case of increasing intratidal compliance profiles, a small increase in PEEP directed to ventilation with horizontal compliance [16, 30]. Since the overall increase of PEEP in our intervention group was comparably low, it is not surprising that our individualized PEEP titration had no effect on the measured hemodynamic variables. With regard to the unaffected respiratory and hemodynamic variables, it is even more remarkable that our ventilation strategy improved regional ventilation, anyway.

Further, it should be noticed that our PEEP titration strategy is based on analyses of the intratidal compliance profiles utilizing only data which are available from standard monitoring. In contrast, previously described techniques for titrating PEEP (decremental PEEP trial [33], dead space fraction [34], indices of regional ventilation [35–37], esophageal pressure [38] or other imaging techniques [39]) require additional equipment, involve additional burden for the patient or may per se not be
available at the bedside. The techniques based on the determination of best PEEP from static respiratory system variables, such as the static PV curve, did not contribute to the dynamic intratidal changes in respiratory system mechanics [40], required sedation and often muscle relaxation [7]. Moreover, they required a prolonged maneuver during which the patient is not sufficiently ventilated. During a decremental PEEP trial, adequate ventilation is warranted however, to identify the PEEP for maximum $C_{RS}$, the optimal PEEP must necessarily be exceeded during the maneuver. Thus, both PEEP titration methods bear the risk for overdistension and cannot be applied continuously. By contrast, PEEP titration based on the intratidal compliance profile does not require a maneuver, may be applied on a breath-by-breath analysis and is applicable for consecutive PEEP adjustment.

**Regional ventilation**

Even in patients without impaired respiratory function, induction of general anesthesia and consecutive mechanical ventilation bear the risk for atelectrauma [41]. Studies that focus on perioperative lung-protective ventilation strategies in patients without severe lung-injury showed that the rate of postoperative pulmonary complications was lower when the ventilation strategy included low tidal volume, high PEEP and repetitive recruitment maneuvers [2, 5]. The application of low PEEP levels was shown to promote tidal small airway closure and consecutive atelectasis [42]. As a non-invasive, radiation-free method, EIT can be used to monitor regional ventilation and the formation of atelectasis [43]. Further, EIT can be used to evaluate differences between the measured PV curve from the respirator and regional ventilation [44]. This recently introduced technique to assess these differences may help to understand the heterogeneity of the respiratory system mechanics, especially in patients with impaired respiratory function. In contrast to other studies that showed that the EIT can be used to titrate PEEP individually [36, 37], we used the EIT as an external measurement and could demonstrate that an individualized PEEP titration guided by the intratidal compliance profile analysis improved regional ventilation.

Comparing the two scenarios of baseline measurements (EIT sequence before the surgical procedure) and the last EIT sequence (after the end of the surgical procedure) with gain and loss calculation
showed a significant increase in aeration in the intervention group. This is not surprising, since PEEP was higher in the intervention group which leads to an increase in aeration [45]. The detected changes in regional gain and loss calculations might suggest that the individualized PEEP titration strategy according to the gliding-SLICE reduces the loss of ventilation in the dependent lung areas. However, the detected effect is very limited (comparable frequencies of compliance profiles, TV_v and TV_d values and respiratory system mechanics).

Tidal variation did not differ significantly between the two groups. The larger part of ventilation remained for both groups in the ventral region of the lung at all times. Again, this is expected for mechanically ventilated patients [46]. However, one has to keep in mind that a shift in tidal variation from ventral to dorsal regions would indicate recruitment. This would be very unlikely in lung healthy patients, since their lungs are already very well recruited.

It might seem that the results from our gain and loss calculation contradict the findings for tidal variation development. However, we found almost equal gain in both ventral and dorsal areas for both groups. We would argue that this does not necessarily change the fraction of ventilation in these parts. Consider as an example an hourglass at a certain time point where there will be more sand in the top compartment than in the bottom compartment. If one would increase now the amount of sand in the top compartment but also increase the diameter of the connecting tube accordingly, there will be more sand in both compartments, but the fraction of sand in the top compartment would not change. In contrast to this analogy, the tidal volume was held constant in both groups but one has to keep in mind that with increasing PEEP, the residual capacity of the lung is increased as well [47]. At this point we would also speculate that redistribution of volume either based on pendelluft effects or from areas outside our observation plane might contribute to the surplus in aeration as well.

Limitations of the study

We did not perform invasive blood pressure measurement to evaluate hemodynamic performances with a higher temporal resolution and arterial blood gas analyses. Placing an arterial line is not part of our standard treatment in the patients conducted in the present study. We felt that the risks of an
arterial line placement would not outweigh the potential benefits of such measurement. Since the intention of our study was to investigate the impact of comparable new patient-individual PEEP titration strategy in non-injured respiratory system, we did not include patients at high risk to the formation of atelectasis. Based on our earlier study we expected a large effect size, however without having any data on variability of the frequencies of compliance profiles available. Therefore, it should be noted that the study has turned out to be underpowered for detecting differences in frequencies of compliance profiles between the two groups. This may have been caused by our choice for an approach utilizing a general standardized effect size for the sample size calculation. This may limit the interpretation of our results.

Thus, further studies are required to investigate the potential impact of PEEP titration based on bedside analysis of non-linear intratidal compliance on the respiratory system mechanics in patients prone to an impaired respiratory function.

Conclusions
This is the first study to investigate regional ventilation during PEEP titration guided by intratidal compliance profile analysis in patients. In lung-healthy patients undergoing short surgical procedures associated with a low risk of pulmonary impairment, unfavorable compliance profiles indicating tidal derecruitment were found less often than in earlier studies. Bedside analysis of non-linear intratidal mechanics of the respiratory system did not improve respiratory system mechanics and compliance profiles. 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. However, the overall effects were very limited and showed no detectable differences in ventilation distribution.

List Of Abbreviations

\( ABW \), actual body weight

\( ASA \), American Society of Anesthesiologists

\( BMI \), body mass index

\( C_{RS} \), compliance of the respiratory system

\( C_{stat} \), quasi-static compliance of the respiratory system
Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the University Medical Centre of Freiburg (Engelbergstr. 21, 79106 Freiburg, Germany, Ethical Committee N° 268/15) on 29th June 2015 (Chairperson Prof. Dr. R. Korinthenberg). Written informed consent was obtained from all participants.

Consent for publication

Not applicable

Availability of data and material
The datasets used and analyzed during the current study are available from the corresponding author on request. Please note that EIT data files require large memory. A separate data transfer service will be used to transfer EIT data files.

**Competing interests**

J. W., J. G., J. S., S. L.-Z., S. B. and S. W declare no conflicts of interest. S. S. has a consulting contract with Gründler GmbH, Freudenstadt (no relationship to this study).

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**Author’s contributions**

Planning the study: S. S., S. W.

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All authors have read and approved the manuscript.

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Tables

Table 1: Patients characteristics (n = 48).
### Table 2: Respiratory and hemodynamic variables.

| Parameter      | Control (n = 23) | Intervention (n = 25) | p-value |
|----------------|------------------|-----------------------|---------|
| Age (yr)       | 50.1 (17.0)      | 45.0 (16.0)           | 0.150   |
| Gender (n), female/male | 12/11            | 6/19                  | 0.226   |
| ASA I/II/III (n) | 10/12/1          | 8/17/0                | 0.506   |
| PBW (kg)       | 47.4 (2.6)       | 48.3 (2.6)            | 0.491   |
| ABW (kg)       | 73.7 (13.7)      | 79.6 (14.5)           | 0.249   |
| BMI (kg·m⁻²)   | 24.5 (3.3)       | 26.5 (5.2)            | 0.178   |

ASA, physical status according to the American Association of Anesthesiologists; PBW, predicted body weight; ABW, actual body weight; BMI, body mass index. Data are expressed as mean (SD).
| Variable       | Control \((n = 23)\) | Intervention \((n = 25)\) | p-value |
|---------------|----------------------|---------------------------|---------|
| \(V_T\) (mL) | 541.9 (71.9)         | 552.6 (61.9)              | 0.565   |
| \(V_T\) PBW (mL·kg\(^{-1}\)) | 7.4 (0.9)          | 7.1 (0.9)                 | 0.300   |
| \(V_F\) (·min\(^{-1}\)) | 11.8 (1.3)        | 11.7 (1.7)                | 0.843   |
| PIP (cmH\(_2\)O) | 16.6 (2.7)         | 17.1 (3.1)                | 0.722   |
| \(P_{\text{Plat}}\) (cmH\(_2\)O) | 14.0 (2.3)        | 14.3 (2.4)                | 0.656   |
| \(P_{\text{mean}}\) (cmH\(_2\)O) | 8.6 (0.9)          | 8.3 (0.9)                 | 0.400   |
| PEEP (cmH\(_2\)O) | 5.0 (0.0)          | 5.8 (1.1)                 | <0.001  |
| \(\Delta P\) (cmH\(_2\)O) | 8.9 (2.3)          | 8.5 (2.0)                 | 0.695   |
| \(C_{RS}\) (mL·cmH\(_2\)O\(^{-1}\)) | 63.2 (14.0)      | 67.8 (15.9)               | 0.508   |
| FiO\(_2\) | 60.6 (1.6)           | 60.4 (1.5)                | 0.802   |
| SpO\(_2\) | 99.1 (0.8)           | 98.8 (0.9)                | 0.177   |
| PetCO\(_2\) (mmHg) | 37.4 (1.5)        | 38.9 (4.6)                | 0.296   |
| Heart rate (·min\(^{-1}\)) | 54.9 (7.8)        | 55.4 (9.0)                | 0.796   |
| BP\(_{sys}\) (mmHg) | 101.1 (10.2)      | 100.4 (11.6)              | 0.236   |
| BP\(_{dias}\) (mmHg) | 62.8 (12.5)       | 61.7 (12.3)               | 0.667   |
| MAP (mmHg) | 75.6 (11.0)          | 74.6 (11.1)               | 0.296   |
| Duration of anesthesia (min) | 83.2 (33.3)      | 87.5 (28.7)               | 0.378   |
$V_T$, tidal volume; $V_T\text{PBW}$, tidal volume per predicted body weight; $VF$, ventilation frequency; $PIP$, peak inspiratory pressure; $P_{\text{plat}}$, plateau pressure; $P_{\text{mean}}$, mean airway pressure; PEEP, positive end-expiratory pressure; $\Delta P$, driving pressure; $C_{RS}$, respiratory system compliance; $FiO_2$, fraction of inspired oxygen; $SpO_2$, peripheral oxygen saturation; $PetCO_2$, end-tidal carbon dioxide partial pressure; $BP_{\text{sys}}$, systolic blood pressure; $BP_{\text{dias}}$, diastolic blood pressure; MAP, mean arterial pressure.

Data are expressed as mean (SD).

**Table 3**: Frequencies of compliance profiles from 48 patients.

| Compliance profile          | Control $(n = 23)$ | Intervention $(n = 25)$ | p-value |
|-----------------------------|-------------------|-------------------------|---------|
| Horizontal (%)              | 85.5 (28.1)       | 92.8 (9.6)              | 0.1162  |
| Merely Increasing (%)       | 9.6 (20.8)        | 3.5 (6.4)               | 0.1727  |
| Increasing-horizontal (%)   | 3.8 (8.5)         | 2.9 (4.8)               | 0.6626  |
| Merely Decreasing (%)       | 0.2 (0.5)         | 0                       | 0.4379  |
| Horizontal-decreasing (%)   | 0.2 (0.8)         | 0.6 (1.9)               | 0.0797  |
| Mixed (%)                   | 0.7 (3.0)         | 0.4 (1.6)               | 0.6816  |

Differences between the two groups were assessed with Mann-Whitney U tests. Frequencies were adapted to the duration of mechanical ventilation. Data are expressed as mean (SD).

**Table 4**: Measurements of regional ventilation.
| Measurements of regional ventilation | Control \( (n = 23) \) | Intervention \( (n = 25) \) | p-value |
|------------------------------------|-----------------------|--------------------------|---------|
| Gain ventral [%]                   | 18.8 (15.5)           | 29.3 (17.6)              | 0.056   |
| Loss ventral [%]                   | 41.0 (16.3)           | 29.7 (16.8)              | 0.039   |
| Gain dorsal [%]                    | 14.3 (11.9)           | 24.6 (13.0)              | 0.013   |
| Loss dorsal [%]                    | 25.9 (13.8)           | 16.4 (12.7)              | 0.028   |
| \( \Delta V_{T,v} \) [%]          | -22.2 (31.1)          | -0.4 (34.2)              | 0.044   |
| \( \Delta V_{T,d} \) [%]          | -11.6 (24.8)          | 8.25 (25.4)              | 0.017   |
| TV\textsubscript{v} [%]           | 63.9 (13.1)           | 60.2 (15.1)              | 0.368   |
| TV\textsubscript{d} [%]           | 36.1 (13.1)           | 39.8 (15.1)              | 0.368   |

Differences between the two groups were assessed with Mann-Whitney U tests. \( \Delta V_{T,v} \), change in tidal volume (difference between gain and loss) for the ventral lung area; \( \Delta V_{T,d} \), change in tidal volume (difference between gain and loss) for the dorsal lung area; TV\textsubscript{v}, percentage of tidal volume in ventral lung areas; TV\textsubscript{d}, percentage of tidal volume in dorsal lung areas. Data are expressed as mean (SD).
Figure 1

Intratidal compliance profile analysis during a single breathing cycle according to the gliding-SLICE method[25]. The tidal pressure-volume curve is divided into 21 equidistant slices. For each slice, the compliance profile is determined based on multiple linear regression analysis and matched to the respective tidal volume. The resulting intratidal compliance curves were classified into six different compliance profiles (H = horizontal compliance profile, I/IH = increasing compliance profile, D/HD = decreasing compliance profile, IHD = mixed compliance profiles).
Assessed for eligibility (n = 60)

Randomized (n = 60)

Allocated to control group (n = 30)
- Received allocated control (n = 30)

Analysed (n = 23)
- Excluded from analysis (incomplete data set) (n = 7)

Allocated to control group (n = 30)
- Received allocated control (n = 30)

Analysed (n = 25)
- Excluded from analysis (incomplete data set) (n = 5)

Figure 2

Flow diagram of the study population.

Figure 3
Functional impedance images (f-EIT) of two respective exemplary patients. According to the study protocol, volume-controlled ventilation was started with a PEEP of 5 cmH2O. In the exemplary patient in the intervention group (A-C), the PEEP was then increased to 7 cmH2O as the intratidal compliance profile analysis indicated a merely increasing compliance profile. In the patient in the control group (D-F), the PEEP was maintained at 5 cmH2O. f-EIT images were generated by subtracting the frames corresponding to the start of inspiration from the frames corresponding to the end of inspiration. A, f-EIT image of the exemplary patient of the intervention group initially ventilated with PEEP 5 cmH2O; B, f-EIT image of the exemplary patient of the intervention group during the last EIT measurement after the surgical procedure was finished; C, Illustration of gain (red) and loss (blue) for the patient in the intervention group; D, f-EIT image of the exemplary patient of the control group during baseline measurements; E, f-EIT image of the exemplary patient of the control group during the last EIT measurement after the surgical procedure was finished; F, Illustration of gain (red pixels) and loss (blue pixels) for the patient in the control group. Gain represents the amount of pixels that exhibited an increase in ventilation in the end compared to the beginning and loss the decrease in ventilation accordingly.

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