Effect of PEEP and Tidal Volume on Ventilation Distribution and End-Expiratory Lung Volume: A Prospective Experimental Animal and Pilot Clinical Study

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Abstract

Introduction: Lung-protective ventilation aims at using low tidal volumes (VT) at optimum positive end-expiratory pressures (PEEP). Optimum PEEP should recruit atelectatic lung regions and avoid tidal recruitment and end-inspiratory overinflation. We examined the effect of VT and PEEP on ventilation distribution, regional respiratory system compliance (CRS), and end-expiratory lung volume (EELV) in an animal model of acute lung injury (ALI) and patients with ARDS by using electrical impedance tomography (EIT) with the aim to assess tidal recruitment and overinflation.

Methods: EIT examinations were performed in 10 anaesthetized pigs with normal lungs ventilated at 5 and 10 ml/kg body weight VT and 5 cmH2O PEEP. After ALI induction, 10 ml/kg VT and 10 cmH2O PEEP were applied. Afterwards, PEEP was set according to the pressure-volume curve. Animals were randomized to either low or high VT ventilation changed after 30 minutes in a crossover design. Ventilation distribution, regional CRS and changes in EELV were analyzed. The same measures were determined in five ARDS patients examined during low and high VT ventilation (6 and 10 (8) ml/kg) at three PEEP levels.

Results: In healthy animals, high compared to low VT increased CRS and ventilation in dependent lung regions implying tidal recruitment. ALI reduced CRS and EELV in all regions without changing ventilation distribution. Pressure-volume curve-derived PEEP of 21±4 cmH2O (mean±SD) resulted in comparable increase in CRS in dependent and decrease in non-dependent regions at both VT. This implied that tidal recruitment was avoided but end-inspiratory overinflation was present irrespective of VT. In patients, regional CRS differences between low and high VT revealed high degree of tidal recruitment and low overinflation at 3±1 cmH2O PEEP. Tidal recruitment decreased at 10±1 cmH2O PEEP and was further reduced at 15±2 cmH2O PEEP.

Conclusions: Tidal recruitment and end-inspiratory overinflation can be assessed by EIT-based analysis of regional CRS.

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Introduction

It is well known that mechanical ventilation leads to lung injury. Dreyfuss and coworkers comprehensively showed the relationship between mechanical ventilation and pathologic lung tissue changes [1]. Liable factors inducing lung injury are high plateau pressures (Pplat), high tidal volumes (VT) and cyclic opening and closing of alveoli (tidal recruitment) [2].

To minimize ventilator-induced lung injury the concept of lung-protective ventilation was introduced comprising the limitation of Pplat, reduction of VT and optimization of positive end-expiratory pressure (PEEP) [3–5]. The current recommendations advocate VT of 6 ml/kg predicted body weight and Pplat lower than 30 cm H2O in patients with acute lung injury (ALI) and acute respiratory distress syndrome (ARDS). Whether this recommended VT is optimal or whether the risk of ventilator-induced lung injury can be reduced by further reduction of VT is still under debate. However, VT lower than 6 ml/kg predicted body weight poses the risk of impaired alveolar ventilation and oxygenation [6,7].

Proposed measures to avoid derecruitment are increased PEEP and repeated recruitment maneuvers [8]. The effectiveness of these strategies to improve oxygenation was demonstrated in
Mechanical ventilation and induction of ALI

Throughout the experiment, the animals were ventilated in a volume-controlled mode (Avea, CareFusion, Hochberg, Germany) at 20 breaths/min with the ratio of inspiration and expiration times (I:E) of 1:1.5. ALI was induced by repeated bronchoalveolar lavage with 1.5 L of warm saline solution until arterial partial pressure of oxygen ($P_{\text{aO}_2}$) remained stable below 100 torr at an inspired oxygen fraction ($F_{\text{iO}_2}$) of 1.0 and PEEP of 10 cm H$_2$O for 30 min. The animals were ventilated with $V_T$ of 5 and 10 ml/kg BW both before and after ALI induction. These are referred to as low and high $V_T$ throughout the text.

A constant low-flow (2.5 l/min) inflation (pressure-volume (PV)) maneuver with an inspiratory volume limit of 1.5 l was performed starting at zero end-expiratory pressure. Afterwards, positive end-expiratory pressure (PEEP) was set 2 cm H$_2$O above the lower inflection point (LIP) identified in the PV curve. An additional image file shows the PV curve obtained from a representative animal (Figure S2).

Interventional lung assist device

A pumpless extracorporeal interventional lung assist device (ILA, Novalung, Hechingen, Germany) was applied in all animals allowing control of arterial partial pressure of carbon dioxide ($P_{\text{aCO}_2}$) independent of the ventilator pattern [27,28]. A 13 Fr cannula was inserted into the iliac artery with ultrasound guidance and a 15 Fr cannula into the iliac vein using Seldingers technique. The ILA device was prefilled with saline solution and connected to both cannulae. 5000 units of heparin were given after the instrumentation was completed. ILA was only used after induction of ALI during low $V_T$ ventilation. Oxygen flow was set to 10 l/min to achieve a $P_{\text{aCO}_2}$ of 40 mmHg.

Electrical Impedance Tomography

EIT measurements were performed with the Goe-MF II system (CareFusion, Hochberg, Germany) using a set of 16 electrodes (Blue Sensor BR-50-K, Ambu, Olstykke, Denmark) placed on the thoracic circumference at the fifth-sixth intercostal space. EIT data were acquired with a scan rate of 25 Hz. EIT images were generated using the filtered back-projection algorithm [29]. The data were filtered using a digital low-pass filter with a cut-off frequency of 1 Hz to eliminate small impedance changes synchronous with the heart beat.

Experimental protocol

A flowchart of the experimental protocol is provided in Figure 1. EIT scanning was performed during baseline conditions and at six subsequent measurement time points as described below:

- **Baseline:** Pigs were ventilated with $F_{\text{iO}_2}$ of 0.5, $V_T$ of 5 ml/kg BW and PEEP of 5 cm H$_2$O. ILA was inactive.
- **Time point 1:** $V_T$ was set to 10 ml/kg BW while other settings remained unchanged.
- **Time point 2:** After induction of ALI, $F_{\text{iO}_2}$ was set to 1.0, $V_T$ 10 ml/kg BW, PEEP 10 cm H$_2$O and ILA inactive.

Animals were then allocated to either ventilation with low $V_T$ and active ILA or to ventilation with high $V_T$ and inactive ILA in randomized order (5 animals in each randomization arm). After 30 minutes, the applied $V_T$/ILA pattern was changed in a crossover design where each animal served as its own control.

- **Time points 3 and 5:** 5 minutes after ventilation with the set $V_T$/ILA pattern.
Time points 4 and 6: 30 minutes after ventilation with the set VT/ILA pattern.

At baseline and at each measurement time point, heart rate, mean arterial pressure, inspiratory peak pressure (P_{insp}), plateau pressure (P_{plat}) and end-expiratory partial pressure of CO₂ (P_{CO₂}) were determined and EIT data acquired during 60 seconds. To account for the crossover design, the data obtained at identical VT/ILA settings were combined. This resulted in the merged time points 5/3 and 6/4 for low VT and 3/5 and 4/6 for high VT ventilation.

Blood gases were measured at time point 1, after ALI induction (i.e. time point 2), immediately after the pressure-volume maneuver was performed (during ventilation with high VT and PEEP set 2 cmH₂O above LIP) and at the end of the experiment to check for the stability of the ALI model.

**EIT data analysis**

Functional EIT scans were generated from each measurement using an established approach [19]. They showed the distribution of regional VT in the chest cross-section by calculating the tidal amplitudes of relative impedance change in 912 image pixels (Figure 2).

Ventrodorsal profiles of fractional VT in 32 layers were generated from the functional ventilation scans and the geometrical centers of ventilation were calculated in relation to the ventrodorsal chest diameter as previously described [30–32]. To compare and display changes in ventilation distribution between the baseline and individual measurement time points, EIT ventilation difference images [33] and regional ventilation difference profiles were generated (Figures 2 and 3). Changes in EELV between individual time points and baseline were analyzed by calculating the differences between the minimum (end-expiratory) values of ventilation-related relative impedance change.

Finally, global C_{RS} was calculated as V_{T}/(P_{plat}−PEEP) and regional C_{RS} determined in each of the 32 layers as ((fraction of VT)/P_{plat}−PEEP). Corresponding to the ventilation profiles described above, regional C_{RS} and C_{RS} difference profiles were generated (Figure 3).

**Pilot patient study**

The study was approved by the Ethics committee of the Christian-Albrechts University, Kiel, Germany (“Bestimmung der globalen und regionalen Atemmechanik bei unterstutzter Spontanatmung” Permit Number: A 125/12). Written informed consent was obtained from each patient or their legal representative, respectively.

We included five adult patients (age 74±6 years, height 174±5 cm, weight 77±15 kg) with mild and moderate ARDS...
according to the Berlin definition [34] treated in our surgical intensive care unit. ARDS resulted from severe sepsis (n = 4) and pneumonia (n = 1). Anaesthesia was performed with sufentanile and propofol and if required for an intervention or intubation muscle paralysis was induced with rocuronium. Patients were ventilated with Evita XL (Dräger Medical AG & Co., Lübeck, Germany) in the pressure-controlled mode. During the study period volume-controlled mode was used. A low-flow (4 L/min) PV maneuver was started at PEEP of 0 cm H2O with an inspiratory volume limit of 2 L and a pressure limit of 35 cm H2O. Afterwards, PEEP was set at three different levels according to the LIP. We started with a PEEP of LIP + 2 cm H2O followed by LIP + 5 cm H2O and LIP + 7 cm H2O. At each PEEP level, patients were first ventilated with low VT (6 ml/kg BW) followed by high VT (10 ml/kg BW) for 5 minutes. The lowest PEEP was second in order to avoid unnecessary long derecruitment and followed by the highest PEEP. We a priori decided not to exceed a pressure limit of 40 cm H2O at this PEEP level and, therefore, we reduced VT to 8 ml/kg BW.

EIT examinations and data analyses were performed exactly as described above in sections on the experimental study. (The only difference was that we used the L-00-S electrodes (Ambu, Ølstykke, Denmark) in patients.) We calculated C\textsubscript{RS} at each PEEP level and each VT and the C\textsubscript{RS} differences between high and low VT at each PEEP level.

**Statistical analysis**

Since normal distribution assumption was not violated (Shapiro-Wilk-test), data are presented as means±SD and analyzed parametrically with paired t test or repeated-measures ANOVA as appropriate. The pilot patient data were analyzed using descriptive statistics as means±SD.

The statistical analysis was conducted using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA). All statistical tests were two-sided and the level of significance was set at 5%.

**Results**

**Experimental study**

**Hemodynamics and global respiratory system mechanics.** All animals studied were included in the final analyses. Hemodynamic and respiratory data are summarized in Table 1. Pco\textsubscript{2} increased to about 60 torr during ventilation with high VT and inactive ILA whereas ventilation with low VT and active ILA resulted in normocapnia. Increasing VT from 5 to 10 ml/kg BW did not significantly change global C\textsubscript{RS} in the healthy lungs. ALI reduced C\textsubscript{RS} markedly to about 50% of baseline values despite PEEP increase to 10 cm H2O. Application of PEEP according to LIP restored C\textsubscript{RS} only partially.

**Regional distribution of ventilation and respiratory system compliance.** Increasing VT in the healthy lung from 5 to 10 ml/kg BW led to a small but significant redistribution of ventilation in favor of the dependent lung regions. The geometrical center of ventilation moved slightly but significantly downwards (Figure 4). This went along with an increase in regional C\textsubscript{RS} in the dependent parts of the lung (Figure 3). Increasing PEEP to 2 cm H2O above the LIP of the pressure-volume curve restored regional C\textsubscript{RS} to initial values in the dependent lung regions and reduced it in the non-dependent ones. Accordingly, distribution of ventilation was directed more toward the dependent lung regions as reflected by the downward shift in geometrical centers of ventilation. There was no difference in ventilation distribution and

![Figure 2. Regional ventilation distribution.](https://www.plosone.org/fig2.png)
regional $C_{RS}$ between ventilation with 5 or 10 ml/kg BW at the four measurement time points with PEEP increased to 2 cm H$_2$O above LIP (Figures 3 and 4).

End-expiratory lung volume. Regardless of the applied $V_T$, EELV did not change in the healthy lung (Figure 5). ALI led to a pronounced loss in EELV despite PEEP of 10 cm H$_2$O. This volume loss could only partially be regained when increased PEEP was set according to the pressure-volume curve with high variability among the animals (Figure 5).

Stability of the model. There were no significant differences in gas exchange between the initial measurement after induction of ALI and the final measurements at the end of the experimental protocol (Table 2).

Pilot patient study

Respiratory and hemodynamic data are given in Table 3. LIP was identified at $8 \pm 2$ cm H$_2$O. Regional $C_{RS}$ differences at the respective PEEP levels are shown in Figure 6. At the lowest PEEP of $3 \pm 1$ cm H$_2$O we found a pronounced increase in $C_{RS}$ in the dorsal regions and a small decrease in the ventral regions with high $V_T$. At PEEP of $10 \pm 1$ cm H$_2$O, high $V_T$ led to a smaller increase in $C_{RS}$ in the dorsal regions and more pronounced reduction in the ventral parts than at the lowest PEEP. At PEEP of $15 \pm 2$ cm H$_2$O, the $C_{RS}$ difference between high and low $V_T$ was even smaller.

Discussion

Our study examined regional ventilation, $C_{RS}$ and EELV using EIT at different $V_T$ and PEEP in lung healthy animals and after
induction of ALI. The protocol was designed to reflect clinical decision-making regarding the choice of PEEP and V̇T in ARDS patients. It tested the hypothesis that a variation of tidal volume at a preset PEEP could be used to assess tidal recruitment and therefore guide the choice of adequate (optimum) PEEP. We subsequently applied this EIT-based approach developed in the

| Table 1. Respiratory and hemodynamic data. |
|------------------------------------------|
| Time point | Baseline | 1 | 2 | 3/5 | 4/6 | 5/3 | 6/4 |
| FIO₂ | 0.5 | 0.5 | 1 | 1 | 1 | 1 | 1 |
| V̇T [ml] | 252±35 | 494±59 | 487±67 | 466±95 | 466±95 | 255±31 | 255±31 |
| PIP [cm H₂O] | 13±2 | 20±2 | 35±3 | 42±6 | 41±6 | 31±4 | 31±4 |
| Plateau pressure | 12±2 | 17±3 | 32±4 | 36±9 | 36±8 | 27±7 | 28±7 |
| PEEP [cm H₂O] | 5 | 5 | 10 | 21±4 | 21±4 | 21±4 | 21±4 |
| CRs [ml/cm H₂O] | 40±10 | 42±10 | 22±7 | 27±8 | 28±8 | 29±9 | 28±8 |
| Pco₂ [torr] | 83±18 | 77±12 | 72±15 | 76±13 | 71±9 | 71±7 | 67±5 |
| MAP [mm Hg] | 95±14 | 99±13 | 132±16 | 131±21 | 132±17 | 125±13 | 132±16 |
| HR [1/min] | 95±14 | 99±13 | 132±16 | 131±21 | 132±17 | 125±13 | 132±16 |

Data are shown as mean values ± standard deviation. V̇T: tidal volume, FIO₂: fraction of inspired oxygen, PEEP: positive end-expiratory pressure, PIP: peak inspiratory pressure, CRs: respiratory system compliance, Pco₂: end-expiratory partial pressure of carbon dioxide, MAP: mean arterial pressure, HR: heart rate. Due to the crossover design data obtained at identical V̇T/ILA settings were combined resulting in the merged time points 5/3 and 6/4 for low V̇T and 3/5 and 4/6 for high V̇T ventilation.

*: vs. baseline (P<0.05).
**: vs. baseline (P<0.01).
***: vs. time point 1 (P<0.001).
**: vs. time point 1 (P<0.0001).
**: vs. time point 1 (P<0.0001).
**: vs. time point 2 (P<0.01).
&: vs. time point 2 (P<0.05).

Figure 4. Center of ventilation. Ventilation distribution during individual measurement time points represented by the geometrical center of ventilation. The center of ventilation is given in percent of the anteroposterior chest diameter. Values above 50 indicate a location in the dorsal half of the chest cross-section. The median, the 25th and the 75th percentile, minimum and maximum values of ten animals are shown. The gray areas in the diagram show the positive end-expiratory pressure (PEEP) values during the individual measurement time points. Significant differences between corresponding high V̇T and low V̇T are indicated. Every group with ALI and high PEEP is significantly different from normal lung and ALI with PEEP 10 cm H₂O (Time point 2). Left Y axis: center of ventilation, right Y axis: PEEP. High V̇T, ventilation with 10 ml/kg BW, low V̇T, ventilation with 5 ml/kg BW.

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In the experimental study, we found that an increase in VT from 5 to 10 ml/kg BW led to an increase in regional C RS and fractional ventilation in the dependent parts of the healthy lung. This is in accordance with our hypothesis that the application of different VT at a distinct PEEP can be used in combination with EIT to assess the recruitment potential of the lung. The increase in CRS in the dependent parts of the lung with high VT is hereby interpreted as an increase in ventilated volume in these parts of the lung (Figure S1). With identical mechanical properties, an increase in ventilated volume leads to an increase in compliance. ALI induced a profound reduction in EELV accompanied by low global and regional CRS despite the application of a PEEP of 10 cm H2O. Surprisingly, the distribution of ventilation was similar to the healthy lung. The subsequent further PEEP increase according to the identified LIP of the pressure-volume curves restored CRS to near baseline values in the dependent lung regions. However, CRS in the ventral regions of the lung was markedly decreased implying overinflation. The fact that there was no difference in regional C RS and distribution of ventilation between VT of 5 and 10 ml/kg BW suggests that no tidal recruitment occurred. The fact that EELV did not reach the level observed in the normal lung even with the high PEEP has to be interpreted with caution, since the induction of ALI may have changed the electrical conductivity of the lung tissue [35].

Recruitment and derecruitment

Our finding of dorsally directed shift in ventilation and increase in regional C RS in the dependent lung regions at a PEEP of 5 cm H2O and high VT in normal lungs is in accordance with previous findings. Sinclair et al. who examined the effect of different PEEP (0 and 8 cm H2O) and VT (6 and 12 ml/kg) on cyclic airway collapse and recruitment using aerosolized fluorescent microspheres in a rabbit model revealed that cyclic tidal recruitment occurred with low PEEP in the healthy lung [36]. Improved ventilation in the dorsocaudal lung regions with high PEEP in that study was attributed to local recruitment with a postulated increase in regional C RS.

In our study, a PEEP of 10 cm H2O was not sufficiently high to prevent derecruitment after ALI induction as reflected by overall decrease in regional C RS. This derecruitment could be reversed after the pressure-volume maneuver and subsequent application of higher PEEP of about 21 cm H2O. At the same time, however, regional C RS fell in the non-dependent regions when compared with baseline. Thus, although PEEP had the beneficial effect of recruiting the lung in the dependent regions and thereby avoiding tidal recruitment it also lead to regional overdistension. This phenomenon was also identified by Grasso et al. in three different pig models of ALI, including the lavage model, where overinflation was present in the baby lung despite recruited lung areas [6]. The concomitant existence of lung regions exhibiting recruitment and overinflation was also determined in patients with ALI [37], which renders the selection of adequate PEEP so difficult in individual patients.

End-expiratory lung volume

In our study, ALI led to a pronounced reduction in EELV, which could not be offset by PEEP of 10 cm H2O. By further increasing PEEP according to the pressure-volume curve, EELV increased.

Several studies have proven the ability of EIT to detect PEEP-dependent changes in EELV by analysis of end-expiratory impedance values [19,38–40] as used in our analysis. The fall in end-expiratory impedance values associated with ALI development has previously been described, although in an oleic acid ALI model [33]. Previous EIT studies using either two [41] or three electrode planes [19] demonstrated that EIT-based evaluation of EELV requires a cautious selection of the electrode plane. Therefore, we chose the midthoracic plane for our EIT.
measurements. With this approach, most of the lung tissue was included in the analysis because the examined chest slice was approximately 10 to 15 cm thick [42].

Ventilation distribution

To characterize regional ventilation distribution by EIT, we have generated ventrodorsal ventilation profiles derived from the functional EIT scans and calculated the centers of ventilation [30,32,43]. This is a relatively simple but sensitive procedure that was previously applied to determine the effects of ventilation mode, PEEP, recruitment maneuvers or surfactant administration on ventilation distribution [30,31,43].

The redistribution of ventilation occurring between the individual measurement time points resulted in shifts of the centers of ventilation in the ventrodorsal direction. The dorsal shift identified in the animals ventilated with high VT compared with low VT before ALI implied tidal recruitment in the dependent lung regions. The centers of ventilation exhibited the dorsal most locations during ventilation with high PEEP set according to the pressure-volume curve after ALI. This was consistent with reduced ventilation in the non-dependent regions caused by overinflation accompanied by an increase in ventilation in the dependent regions caused by recruitment.

To better visualize the changes in regional ventilation induced by the study interventions (i.e., ALI, PEEP and VT changes), we also calculated ventrodorsal profiles showing the differences in regional VT at individual time points in comparison with baseline. These profiles highlighted the ventilation changes identified by the centers of ventilation by showing the respective changes in 32 chest layers.

Regional respiratory system compliance

Although the topographical distributions of regional VT and CRS have to be identical by virtue of the underlying calculation of regional CRS, the absolute values of regional CRS reflect the changing respiratory system mechanics in the course of the experiment. This was detected especially after the induction of ALI (measurement time point 2) where a dramatic loss in regional CRS was observed in all analyzed lung layers, whereas regional tidal volumes remained fairly unchanged (Figure 3).

The profiles of differences in regional CRS detected the changing CRS when compared with baseline. After the induction of ALI during ventilation at 10 cm H2O of PEEP (time point 2), a marked decrease in CRS was found. Higher regional CRS in the dependent lung regions at high PEEP in the later phase after ALI could be attributed to recruitment of lung tissue as shown by Sinclair et al. [36]. The simultaneous decrease in regional CRS in the ventilated, non-dependent regions reflected regional overinflation. These results indicate that the distribution of regional CRS and regional differences in CRS are crucial for the interpretation of the PEEP and VT effects and that the threshold PEEP, where tidal recruitment begins or ceases, might be the optimal PEEP to achieve best possible recruitment and minimal overinflation.

The importance of regional CRS has also been highlighted by two recent EIT studies. Bikker et al. calculated CRS in four horizontal chest layers at 15, 10, 5 and 0 cm H2O of PEEP during a decremental PEEP trial [41]. They found that high PEEP led to an increase in regional CRS in the dependent part of the lung indicating recruitment but also to a decrease in CRS in the non-dependent part suggesting overinflation. Dargaville et al. examined regional CRS in three horizontal layers of the lungs during an incremental/decremental PEEP trial using a total of 11 PEEP steps [44]. Regional recruitment, derecruitment and overinflation could be detected and the PEEP value identified at which the most homogeneous CRS distribution was achieved during the deflation limb of the maneuver. Our results show that a change in regional CRS with different VT can be used to determine recruitment potential, implying that tidal recruitment occurs and the choice of a higher PEEP could be advantageous.

Interventional lung assist

Based on former studies [28,45], we presumed that ventilation with low VT of 5 ml/kg BW would lead to CO2 accumulation in our animal model of ALI which would not allow us to maintain the ventilatory pattern constant. Since we focused on the measurement of lung mechanics we considered it essential to keep the pattern constant throughout the whole experiment. The technique of interventional lung assist is easily available in our animal laboratory, therefore, we used it for CO2 removal in the phases of ventilation with low VT. When we designed the experimental protocol, we expected from our previous experience that the ventilation with high VT during ALI would result in a PCO2 of about 40 mmHg. During the experiments we saw it was slightly higher, nevertheless, we decided to adhere to our original protocol.

### Table 2. Gas exchange data.

| Time point               | Normal lung (time point 1) | ALI (time point 2) | PV maneuver | End of experiment |
|--------------------------|---------------------------|--------------------|-------------|-------------------|
| FIO2                     | 0.5                       | 1                  | 1           | 1                 |
| PO2 [torr]               | 234±40*                   | 120±27**           | 420±110     | 133±27†           |
| Pco2 [torr]              | 47±10                     | 58±11*             | 58±15       | 60±18*            |

Data are shown as mean values ± standard deviation. ALI: acute lung injury, FIO2: arterial oxygen saturation, PO2: arterial partial pressure of oxygen, Pco2: arterial partial pressure of carbon dioxide, P: pressure, V: volume.

At the time point ‘PV maneuver’ data was obtained immediately after the low-flow inflation maneuver during ventilation with high VT and with PEEP set 2 cmH2O above the lower inflection point.

* vs. time point 1 (P<0.05).
** vs. time point 1 (P<0.001).
† vs. PV maneuver (P<0.0001).

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In the animal experimental phase we could not identify any significant differences in CRS between the low and high VT after ALI because the lungs were already maximally inflated by the applied high PEEP. Therefore, we could not test our EIT-based approach of identifying tidal recruitment and end-inspiratory overinflation in the injured lungs of the studied animals. However, our pilot patient EIT data acquired at three PEEP levels, allowed us to apply this analysis. At the lowest PEEP, tidal recruitment in the dependent regions could clearly be identified. At the two higher PEEP values, progressive reduction in tidal recruitment was seen. End-inspiratory overinflation in the non-dependent regions was present already at the PEEP level of 2 cm H₂O above LIP. At the highest PEEP, regional overdistention at the higher of the two VT values was blunted by the already present PEEP-induced overinflation. We postulate that the individual optimum PEEP could be derived from similar EIT examinations at the bedside in the future: the variation of VT at different PEEP levels could identify the settings with minimum tidal recruitment and minimum overinflation.

Limitations

1) We chose a lavage model of ALI well aware of the fact that it does not closely reflect the clinical situation because it is recruitable with PEEP and high VT [46]. However, this was a desired feature of the model in our study in order to evaluate the ability of EIT to detect VT-dependent tidal recruitment. We could show that our ALI model was stable during the experiment and did not exhibit spontaneous recruitment in the course of time.

2) We limited the experiment to the crucial measurement time points to exclude the influence of time, and therefore, we applied only the high but not the low VT after ALI induction.

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### Table 3. Respiratory and hemodynamic data of the studied patients.

| Time point | Baseline | Low VT | High VT | Low VT | High VT | Low VT | High VT |
|-----------|----------|--------|---------|--------|---------|--------|---------|
|           | LIP−5    | LIP−5  | LIP+2   | LIP+2  | LIP+7   | LIP+7  |
| P_{O_2}/F_{O_2} [torr] | 213±63 | 183±52 | 244±62 | 277±61 |
| VT [ml]    | 418±40  | 705±68 | 418±41 | 709±61 | 419±34 | 554±46 |
| PIP [cm H₂O] | 16±1   | 26±2   | 24±2   | 34±4   | 30±2   | 37±2   |
| Plateau pressure | 13±1    | 19±1   | 20±2   | 28±3   | 28±1   | 33±3   |
| PEEP [cm H₂O] | 3±1     | 3±1    | 10±1   | 10±1   | 15±2   | 16±2* |
| C₅₃ [ml/cm H₂O] | 43±7   | 44±8   | 42±7   | 39±9   | 36±8   | 36±10 |
| P_{CO_2} [torr] | 99±23  | 85±13  | 114±21 | 130±30 |
| P_{CO_2} [torr] | 51±12   | 59±12   | 59±13  | 64±10 |
| HR [1/min]  | 90±20  | 85±15  | 79±18  | 84±15  | 80±17  | 84±16  | 77±11 |

Data are shown as mean values ± standard deviation. VT: tidal volume, F_{O_2}: fraction of inspired oxygen, PEEP: positive end-expiratory pressure, PIP, peak inspiratory pressure, C₅₃: respiratory system compliance, P_{CO_2}: end-expiratory partial pressure of carbon dioxide, HR: heart rate.

*The measurement at LIP+7 and high VT was not conducted in patient 1 due to excess of peak inspiratory pressure limit of 40 cm H₂O (see Methods for further details). doi:10.1371/journal.pone.0072675.t003
with a PEEP of 10 cm H2O. We did not expect lacking tidal recruitment during ventilation at high PEEP set according to the pressure-volume curve, otherwise, we would have studied both VT at the lower PEEP of 10 cm H2O. Since the data analysis was performed offline it was too late to change the protocol. However, our pilot patient data acquired at lower PEEP values than in animal experiments could show that tidal recruitment could be reliably assessed by EIT-derived regional CRs.

3) EIT measurements were not compared with another established radiological imaging modality like computed tomography. This might be regarded as a limitation, however, the feasibility of EIT to assess regional ventilation has been previously validated with multiple standard imaging techniques [47–49].

4) EIT does not measure absolute lung volumes and thus we were only able to report relative changes in EELV. The validity of using relative instead of absolute lung volumes was previously confirmed by using the nitrogen washout technique [40].

Conclusions

1) With a PEEP of 5 cm H2O, tidal recruitment was determined by EIT in the normal lung implying recruitment potential at this PEEP value.

2) PEEP set according to the pressure-volume curve at 2 cm H2O above LIP proved to be too high in the experimentally injured lung since no tidal recruitment was detected but pronounced regional overinflation was present in the non-dependent lung regions.

3) Regional tidal recruitment and end-inspiratory overinflation was identified in patients with ARDS with EIT by calculation of regional CRs differences from measurements acquired at different VT and PEEP.

4) Concomitant analysis of regional VT, EELV and CRs using EIT holds substantial potential to titrate lung protective ventilation by facilitating choice of adequate PEEP to avoid tidal recruitment and adequate VT to prevent overdistension.

Supporting Information

Figure S1 Explanation of the model. Schematic presentation of postulated changes in regional lung ventilation and regional respiratory system mechanics during different phases of the study protocol. Each large circle symbolizes ventilated lung volume. The small blue and large red circles represent normally aerated and overdistended lung regions, respectively. The oval dark grey symbols indicate atelectatic lung regions. The transparent grey circles represent atelectatic lung regions.

Overdistension occurs in the non-dependent regions (increasing number of red circles). On the right, the decrease in compliance in the non-dependent ROI and its increase in the dependent ROI is explained in a P-V diagram. Additionally, the observed changes in the distribution of regional CR is shown. Middle panel: The effect of acute lung injury (ALI) with an increase in atelectatic lung (higher number of dark grey oval symbols) and the decrease in regional compliance is shown. Lower panel: Applying high levels of PEEP after ALI results in reduction of atelectasis (reduction of the number of dark grey symbols) along with an increase in compliance in the dependent ROI but also leads to a higher degree of overdistension in the non-dependent ROI (higher number of large red circles).

(TIF)

Figure S2 Low-flow inflation maneuver. Low-flow inflation maneuver (pressure-volume (PV) maneuver) with the lower inflection point (LIP) identified on the inflation limb of the curve at the airway pressure of 20 cmH2O. Original tracing obtained in one of the studied animals (animal 7). The values of inhaled air volume and airway pressure by the end of inflation are indicated in the grey boxes. Paw, pressure at the airway opening, VT, tidal volume.

(DOC)

Text S1 Hypothesis.

Author Contributions

Conceived and designed the experiments: GZ GE NW. Performed the experiments: GZ GE TB DS SP. Analyzed the data: GZ GE TB DS SFW IF NW. Wrote the paper: GZ GE. Other: Carried out the EIT examination for the patient study and participated in the analysis and interpretation of data: TB. Interpretation of the data: IF NW. Performed the statistical analysis: SFW. Read, revised and approved the final version of the manuscript: GZ GE TB DS SP SFW IF NW.

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