Regional lung opening and closing pressures in patients with acute lung injury

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Abstract. In acute lung injury, the application of positive end-expiratory pressure (PEEP) is known to prevent the alveoli from cyclic collapse and reopening and homogenize ventilation. The setting of adequate PEEP could be optimized by the knowledge of regional lung opening and closing pressures at the bedside. The aim of our study was to determine regional opening and closing pressures in mechanically ventilated patients by electrical impedance tomography (EIT). Eight supine patients with healthy lungs and eighteen patients with acute lung injury were studied. A low flow inflation and deflation manoeuvre with constant gas flow was performed. Regional opening and closing pressures were calculated for every pixel of the EIT scan. These pressures were defined as those values of global airway pressure at which the lung areas opened up or started to close. Injured lungs exhibited significantly higher regional opening pressures compared with healthy lungs (p<0.05). In acute lung injury, significantly higher opening pressures were found in the dependent lung regions. Regional closing pressures did not significantly differ between healthy and injured lungs. In conclusion, regional lung opening and closing pressures can be assessed by EIT. This information may facilitate the setting of adequate PEEP levels in patients in future.

Keywords: acute lung injury, electrical impedance tomography, EIT, regional lung opening pressure, regional lung closing pressure

1. Introduction

Positive end-expiratory pressure (PEEP) is applied in artificially ventilated patients with acute lung injury (ALI) with the aim of avoiding cyclic opening and closing of alveoli (Gattinoni et al 2006). It is postulated that cyclic recruitment and derecruitment is one of the main causes of lung tissue damage (Ranieri et al 1999) and an independent risk factor of mortality (Caironi et al 2010). The distribution of ventilation in patients with ALI is extremely inhomogeneous due to the gravity effect, regional surfactant dysfunction and uneven distribution of atelectatic lung regions (Slutsky 1999, Uhlig 2002). Consequently, there are different regional opening pressures needed to open up the alveoli (Crotti et al 2001, Pelosi et al 2001).

Finding the best level of PEEP in patients with injured lungs to avoid atelectasis and alveolar strain induced by inadequately high or low PEEP levels is a challenge. Moreover, the chosen PEEP level has to be constantly re-evaluated (Brower et al 2003). Several methods e.g. the low flow pressure-volume curve (Hickling 1998), PEEP trial (Borges et al 2006), stress index (Grasso et al 2004), computer tomography (CT) (Gattinoni et al 1993) and PEEP F_{O_2} table
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(2000) have been proposed for optimal PEEP setting. Except for the CT, the inability of detecting the regionally inhomogeneous distribution of ventilation is a central limitation of all these methods. CT is the only clinically available technique to assess regional lung function in patients with ALI. However, CT is not a bedside monitoring technique and it exposes the patients to radiation.

A promising method for monitoring regional ventilation distribution is the non-invasive, radiation-free technique of electrical impedance tomography (EIT). EIT offers the possibility of quantifying regional lung function with a high temporal resolution at the bedside. There is a high correlation between lung impedance changes measured by EIT compared with lung density changes determined by CT (Victorino et al 2004, Frerichs et al 2002, Wrigge et al 2008). There exist a few studies attempting to find EIT-derived measures which could be used to set PEEP (Zhao et al 2010, Meier et al 2008, Costa et al 2009).

In a study comparing CT and EIT, Victorino et al. have studied ALI/ARDS patients during low flow lung inflation (Victorino et al 2004). A sudden and delayed onset of regional ventilation was detected by EIT and CT, especially in the dependent lung areas after a time interval as long as 20-30s. These „inflation delays“ were found without detectable perturbation in the simultaneously registered pressure-time tracings.

We speculate that these „inflation delays“ are caused by regionally delayed opening of lung areas. The goal of this work was to develop a protocol to measure regional opening (ROP) and closing pressures (RCP) and to test whether these values differ between patients with ALI and patients with healthy lungs.

2. Methods

2.1. Patients

After the approval of the local ethics committee, 26 patients were enrolled from the surgical intensive care units or the operation theatres at the University Medical Centre Schleswig-Holstein, Campus Kiel. The patients or their legal representatives gave their written informed consent. We included eight lung healthy patients (age: 41 ± 12 years, height: 177 ± 8 cm, weight: 76 ± 8 kg, mean ± SD) and 18 patients (age: 58 ± 14 years, height 177 ± 9 cm, weight: 80 ± 11 kg) fulfilling the American-European Consensus criteria for ALI (rapid onset, PaO2/FIO2 ratio ≤ 300 mmHg, bilateral infiltrates and no clinical sign for left atrial hypertension) (Bernard et al 1994). Of the 18 ALI patients, ten patients had extra-pulmonary ALI and eight patients had ALI induced by pneumonia. All patients undergoing this study were sedated, paralyzed and artificially ventilated with a pressure-controlled mode in supine position.

2.2. Interventions

A low flow inflation and deflation pressure-volume manoeuvre was performed by the respirator (Evita XL, Draeger, Luebeck, Germany) with a constant gas flow of 4 l/min starting at a zero end-expiratory pressure up to a tidal volume of 2 l or until a maximum airway pressure of 35 cm H2O was reached. Gas flow, pressure and volume were measured by the respirator with a sampling rate of 126 Hz (Draeger Medical, Luebeck, Germany). The data acquisitions were synchronized via an Universal Serial Bus wire lead with the EIT device.

EIT examinations were performed with the Goethe MF II EIT device (CareFusion, Hoechberg, Germany) (Hahn et al 2000). Sixteen self-adhesive electrodes (Blue Sensor L-00-S, Ambu, Ballerup, Denmark) were attached on the chest circumference in one transverse plane lying approximately at the level of the 5th intercostal space. Electrical currents (50 kHz, 5 mA, peak) were...
applied through adjacent pairs of electrodes in a rotating mode. After each current injection, the
resulting potential differences were measured by the remaining electrode pairs. The EIT data
were acquired at a rate of 25 scans per second. Data evaluation was performed offline.

2.3. Data analysis
Cross-sectional images were calculated from the EIT data using a normalized difference
reconstruction algorithm based on GREIT (Adler et al. 2009). Images represent the change in
conductivity with respect to the data obtained immediately before the start of inflation. For
inflation and deflation, a region of interest (ROI) representing the lungs was identified as 25% of
the maximum conductivity change. For each pixel in the ROI, the ROP and RCP values were
determined as follows (see also figure 1): the pixel time course was smoothed by fitting to a
fourth order polynomial, then the time at which pixel crossed 10% of the maximum change was
identified, and the corresponding airway pressure at that time determined.

Our approach to the determination of ROP and RCP is schematically shown for two EIT
image pixels in figure 1. At first, the maximum impedance amplitudes were determined in all
pixels of the ROI during inflation and deflation and then the airway pressures were identified
from the global airway pressure tracing at which the ten percent thresholds of the local pixel
amplitudes were achieved. These pressure values were determined from the inspiratory and
expiratory limbs of the manoeuvre. In the final step, these values of ROP and RCP were plotted at
the corresponding image pixels showing their spatial distribution in the lung ROI (see also
figure 2).

For later quantitative analysis, the calculated ROP and RCP values of individual pixels
were averaged for the ventral, middle and dorsal lung areas.

2.4. Statistics
T-test for unpaired measures was used for testing the differences between the patients with
healthy lungs and the ALI patients. ANOVA for repeated measures with Bonferroni adjustment
was used for testing the differences between the different lung regions. Differences were
considered to be statistically significant when p < 0.05. All statistical analyses were performed
using the statistic program GraphPad Prism version 5.0 (GraphPad Software, San Diego, CA).
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Figure 1. Generation of functional scans of regional opening (ROP) and regional closing pressures (RCP) in a horizontal plane of the lung. The definition of ROP and RCP is based on simultaneous measurement of airway pressure and acquisition of a series of EIT scans. The three diagrams show the time course of global airway pressure and two local time courses of impedance change (rel. ΔZ) originating from two out of 806 pixels marked as (○/□). Regional lung opening and closing is identified in the regional time courses when 10% threshold of the maximum amplitude of impedance during the pressure-volume manoeuvre was reached. The corresponding global airway pressure at the moment of regional opening and closing is defined as ROP and RCP and is plotted in a functional scan.

3. Results

PaO2/FIO2 in the ALI group was 162 ± 52 mm Hg at a PEEP level of 12 ± 4 cm H2O. The lung healthy patients had no arterial line, so PaO2/FIO2 was not determined. These patients were ventilated at a PEEP of 5 cm H2O, a respiratory rate of 12 breaths/min with a tidal volume of 6 ml/kg.

3.1. Regional opening pressures

A more inhomogeneous distribution of ROP values was found in the lungs of ALI patients compared with the patients with healthy lungs (figure 3A). Significantly higher ROP values (ventral: p < 0.05; middle: p < 0.02; dorsal: p < 0.002) were found in the ALI patients compared with the patients with healthy lungs in all studied lung regions (figure 4A). In the lung healthy patients no differences in ROP values among the three lung areas were detected. In the ALI patients, lower ROP in the ventral lung regions and higher ROP values in the dorsal regions could be seen, with a significant difference between the ventral compared to the middle and dorsal lung regions.
3.2. Regional closing pressures
The frequency distribution of RCP in patients with healthy lungs and in ALI patients showed a more homogeneous distribution and lower values (figure 3B) than the corresponding distributions of ROP (figure 3A). The distribution of RCP in healthy lungs seemed to be slightly more homogeneous than in injured lungs.

Figure 4B shows the RCP values in the studied ventral, middle and dorsal ROIs. The ALI group showed significantly lower RCP values compared to the corresponding ROP values (p < 0.0001). In the lung healthy group, a significant difference between the ROP and RCP values was reached in all lung areas (p < 0.05). The ALI patients exhibited higher values of RCP than the lung healthy patients, however, a significant difference was only found between the ventral and the dorsal lung areas. No significant differences in RCP were found among the studied three regions in the lung healthy patients. The RCP values of the ALI patients showed, similarly to the ROP values, a trend from lower ventral to higher dorsal RCP. Only the difference between the ventral and dorsal lung areas was significant (figure 4B).

Figure 2. Functional EIT scans of regional lung ventilation, defined lung regions of interest (ROI) and functional images of regional opening (ROP) and closing pressures (RCP) in a patient with lungs (male, 34 years, pelvic fracture) and an ALI patient (female, 56 years, severe pneumonia).
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Figure 3. Frequency distribution of regional opening (ROP) (A) and regional closing pressures (RCP) (B) in eight patients with healthy lungs and eighteen ALI patients. Data are shown as mean values ± SD.
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Figure 4. Box plots of regional opening (ROP) (A) and regional closing pressures (RCP) (B) with mean values and 5% and 95% confidence intervals obtained in eight lung healthy (LH) patients and eighteen patients with acute lung injury (ALI) in the ventral, middle and dorsal lung areas. Significant differences between the lung healthy and the ALI patients and among the different lung areas are shown as * = p < 0.05 using a t-test for unpaired measures and as § = p < 0.05 using the ANOVA repeated measures test with Bonferroni adjustment.

4. Discussion
Identification and application of adequate PEEP in ALI/ARDS patients is very difficult because of the inhomogeneous distribution of lung damage (Gattinoni et al 2006). Therefore, the clinical evaluation of patient-specific PEEP values minimizing the occurrence of cyclic recruitment and derecruitment is essential for lung protective ventilator settings. PEEP adjustment based on the patients P\textsubscript{a}O\textsubscript{2} and F\textsubscript{I}O\textsubscript{2} may result in the correct mean value in the overall population of ALI/ARDS patients. However, in the individual patient, it may cause atelectasis or overdistension of lung tissue. We are convinced that this variation among the ALI/ARDS patients explains the better results in the study groups ventilated with an individually adjusted PEEP (Talmor et al 2008, Amato et al 1998). This leads to the idea of individual adjustment of PEEP based on regional lung function. With this intention, we studied whether the imaging technique of EIT may enable the assessment of ROP and RCP. These pressures could be used as parameters of regional lung function offering the possibility of individual PEEP adjustment guided by ROP and RCP.
The requirement for our ROP and RCP measurement was that EIT provided reliable data on regional opening and closing of alveoli. Victorino et al. found inflation delays in the dependent lung areas of ALI/ARDS patients that could be detected simultaneously by EIT and CT (Victorino et al. 2004). Wrigge et al. proved that the regional differences among the inspiratory data tracings are caused by regionally dissimilar opening of lung tissue in an experimental study in animals with artificial ARDS using EIT and CT (Wrigge et al. 2008). Thanks to parallel acquisition of EIT data and airway pressure, we could for the first time calculate and determine the ROP and RCP values within lung areas in a controlled trial.

The examined patients in the ALI group were suffering from a pronounced lung injury as indicated by the low $P_{A \text{O}_2}/F_{\text{IO}_2}$ ratios, so that they formed a representative group for measuring ROP and RCP in ALI. The patients with healthy lungs were measured before elective surgery shortly after induction of artificial ventilation. Lung damage and pronounced atelectasis were not expected in these patients.

Due to the marked lung injury and derecruitment in the dorsal lung areas significantly higher ROP values were noted in the ALI patients in comparison with the lung healthy group. The higher ROP values in the dependent lung areas were likely caused by the higher incidence of atelectasis. This preferential distribution of atelectasis predominantly in the dependent lung areas is known from previous CT studies (Puybasset et al. 1998,Gattinoni et al. 1986).

Similar to ROP, also the RCP values exhibited a gravity dependent behavior with higher values in the dorsal parts of the lung in the ALI group. This finding could also be considered as an indicator of damaged lung tissue in the dependent parts of the lung that needed higher superimposed pressures to avoid derecruitment. In contrast to the ALI patients, the patients with healthy lungs showed lower ROP and a more homogenous frequency distribution of these values with no significant differences among the lung areas. It seems obvious that the lack of low ROP is an indicator of injured lungs.

The higher values of ROP in the ALI group compared with RCP revealed that there were higher pressures needed to open the lung areas than to protect them from derecruitment. Similar findings were derived from previous EIT studies using animal models of ALI/ARDS with the dependent lung areas requiring higher pressure levels to open up (Wrigge et al. 2008, Frerichs et al. 2003).

We found only minimum differences between the lung healthy and ALI groups regarding RCP. The ALI patients would have needed only slightly higher end-expiratory pressure values to avoid regional alveolar closing compared to the lung healthy patients.

Other human studies, measuring the regional superimposed pressure using CT, found similar opening pressure values than in our study. In the dorsal lung areas, the mean pressure of 10.4 ± 0.7 cm H$_2$O was found in ALI patients (Gattinoni et al. 1993) and 3.8 ± 0.4 cm H$_2$O in lung healthy patients (Gattinoni et al. 1991). The corresponding values in our study were 10.5 ± 3.2 cm H$_2$O and 4.5 ± 2.2 cm H$_2$O, respectively. Our data show a wide variety of ROP values (figure 4 A) similar to other patient populations studied previously (Gattinoni et al. 2006). This large ROP variation among the patients may be interpreted as a hint that the ALI patients included in our study would have benefited from an individual PEEP setting.

Similar to a multicentre CT trial in patients with ALI/ARDS evaluating the amount of potentially recruitable lung tissue, we also found no differences in ROP and RCP depending on the type of ALI (Gattinoni et al. 2006).

We are convinced that the measurement of ROP and RCP as an indicator of regional lung function will help setting the PEEP level near to its optimal value. The clinical relevance of ROP
and RCP guided PEEP setting during artificial ventilation has to be established in future randomized trials.

4.1. Limitations of the study
Our calculation of ROP and RCP in every image pixel using a threshold of 10% of the maximum local pixel amplitude of relative impedance change may slightly overestimate the true pressure values. Nevertheless, this is a generally accepted and reliable procedure which has been used before (Wrigge et al 2008).

The low flow inflation and deflation manoeuvres were performed using the Draeger Evita XL respirator. The respirator automatically initiates one mechanical breath before starting the inflation/deflation manoeuvre. We can not exclude that this additional breath imposed by the ventilator did not induce lung recruitment. This effect could have an impact on the determined ROP values by lowering them.

We have not used any reference radiological examination in the studied patients. Due to the high radiation exposure dose of CT we believe that an additional CT of the thorax in this study would not have been ethically justified. Moreover, multiple studies have already shown the high correlation between EIT and nearly all established imaging techniques (Wrigge et al 2008, Frerichs et al 2002, Victorino et al 2004, Hinz et al 2003, Richard et al 2009, Kunst et al 1998).

We are aware that the low flow manoeuvre with an inspiratory pressure up to 35 cmH₂O is not an extensive recruitment manoeuvre. Lung regions recruitable only with high pressures above 35 cmH₂O applied for a longer period of time were not detected using the present ventilator protocol. The extent to which this limitation is of relevance in a clinical setting remains to be established.

4.2. Conclusion
EIT enables a non-invasive determination of ROP and RCP which could be easily performed repeatedly at the bedside. Individual PEEP setting based on ROP and RCP might help to avoid cyclic opening and closing of alveoli with reduced alveolar strain and potentially reduce the incidence of ventilator-induced lung injury.

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