Individualization of PEEP and Tidal Volume in ARDS Patients with Electrical Impedance Tomography

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Research

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Abstract

Background

In mechanically ventilated patients with acute respiratory distress syndrome (ARDS), electrical impedance tomography (EIT) provides information on alveolar cycling and overdistension as well as assessment of recruitability at the bedside. We developed a protocol for individualization of positive end-expiratory pressure (PEEP) and tidal volume ($V_T$) utilizing EIT-derived information on recruitability, overdistension and alveolar cycling. The aim of this study was to assess whether the EIT-based protocol allows individualization of ventilator settings without causing lung overdistension, and to evaluate its effects on respiratory system compliance, oxygenation and alveolar cycling.

Methods

20 patients with ARDS were included. Initially, patients were ventilated according to the recommendations of the ARDS-Network with a $V_T$ of 6 ml per kg predicted body weight and PEEP adjusted according to the fraction of inspired oxygen. Subsequently, ventilator settings were adjusted according to the EIT-based protocol once every 30 minutes for a duration of 4 hours. To assess global overdistension, we determined whether lung stress and strain remained below 27 and 2.0, respectively.

Results

We found that prospective optimization of mechanical ventilation with EIT led to global lung stress below 27 mbar in all patients and global strain below 2.0 in 19 out of 20 patients. Compliance remained similar while oxygenation was significantly improved and alveolar cycling was reduced after EIT-based optimization.

Conclusions

Adjustment of PEEP and $V_T$ using the EIT-based protocol led to individualization of ventilator settings with improved oxygenation and reduced alveolar cycling without promoting global overdistension.

Trial registration

This study was registered at clinicaltrials.gov (NCT02703012) on March 9, 2016 before including the first patient.

Background

Mechanical ventilation is a life-saving treatment for critically ill patients suffering from acute respiratory distress syndrome (ARDS). The morphological features of ARDS, namely regional atelectasis, overdistension and presence of lung inhomogeneities pose patients at an increased risk of developing ventilator-induced lung injury (VILI). Cyclic opening and closing of lung units may lead to atelectrauma,
whereas ventilation at high lung volumes may lead to overdistension and barotrauma [1]. The potentially detrimental effects of ventilation at high absolute lung volumes can be quantified using the concept of stress and strain: When the lungs are inflated with elastance-based transpulmonary pressure (stress) of 27 mbar, they typically reach a strain of 2.0, corresponding to an inflation to twice their resting volume (functional residual capacity, FRC) [2]. Conceivably, any further inflation to even higher volumes increases the risk of VILI development because of global overinflation [3]. Regionally, detrimental levels of stress may be reached at even lower values of global transpulmonary pressure due to the presence of regional inhomogeneities which act as local pressure multipliers (“stress raisers“, [4]).

In theory, the negative effects of both overdistension and alveolar cycling could be counterbalanced by adjusting positive end-expiratory pressure (PEEP) according to global respiratory system compliance ($C_{rs}$), which would then lead to ventilation with minimized airway driving pressure ($\Delta P_{aw}$) and presumably less harm to the lungs [5]. However, PEEP titration according to global $C_{rs}$ has failed to show beneficial results in a large multi-center trial [6]. This could, in part, be explained by the fact that changes in global $C_{rs}$ with PEEP are a weak predictor of recruitability [7]. Adjusting PEEP according to the stress index, which is a measure of intratidal changes in global $C_{rs}$ [8] does not lead to higher PEEP levels in patients with higher recruitability [9]. Global $C_{rs}$ primarily reflects changes in the mechanical properties of lung tissue already open for ventilation; atelectasis formation and -reopening are comparatively slow processes that may take some time to translate into global changes in $C_{rs}$ [10].

Electrical impedance tomography (EIT) allows bedside assessment of regional changes in $C_{rs}$. This information can be used to identify cyclic opening and closing of lung units [11] as well as regional overdistension [11, 12] and for early detection of even small changes in lung recruitment [12]. EIT-derived regional ventilation delay inhomogeneity (standard deviation of regional ventilation delay, $SD_{RVD}$) is closely correlated to alveolar cycling as assessed by end-expiratory and end-inspiratory computed tomography (CT) scans [13]. Despite this potential, reports on prospective optimization of mechanical ventilation with EIT are scarce. Previous studies using EIT to guide mechanical ventilation have focused primarily on adjustment of PEEP [14, 15] without individual adjustment of tidal volumes ($V_T$). Here, we describe a protocol for individual optimization of both PEEP and $V_T$ with EIT and we report its effects on global lung stress and strain, oxygenation, lung recruitment, $SD_{RVD}$ and other physiologic variables in a clinical cross-over study including 20 mechanically ventilated intensive care unit (ICU) patients.

**Methods**

We conducted a clinical cross-over study (clinicaltrials.gov NCT02703012) including 20 adult ICU patients ventilated in pressure-controlled mode with no spontaneous breathing activity. All patients had ARDS according to the Berlin Definition [16]. Exclusion criteria were severe hemodynamic instability, thoracic skin lesions, pregnancy, severe chronic obstructive pulmonary disease, esophageal pathologies, duration of ARDS more than 72 hours and inspired oxygen fraction (FiO$_2$) of more than 80%. Informed consent was obtained from the patients’ legal representatives.
Measurements

The EIT device (Pulmovista 500, Dräger, Lübeck, Germany) was connected to the ventilator (Evita XL or V500, Dräger). Synchronized ventilator and EIT data were recorded at sampling rates of 50 Hz. Hemodynamic data, air flow, airway pressure ($P_{aw}$), esophageal pressure as well as inspired and expired $O_2$ and $CO_2$ were additionally recorded with an S/5 monitoring system (Datex-Ohmeda, Helsinki, Finland) and stored electronically. The validity of esophageal pressure measurements was confirmed using an expiratory hold maneuver with gentle manual chest compressions. Cardiac output was assessed by transpulmonary thermodilution (PiCCO, Pulsion, München, Germany), where available.

EIT protocol

Recruitability was assessed using a sustained-inflation maneuver with $P_{aw}$ of 40 mbar followed by a PEEP increase of 3 mbar. Regional $C_{rs}$ was assessed by dividing the EIT image in four horizontal regions of interest (ROIs) and by multiplying global $C_{rs}$ with the relative tidal impedance change in each of the ROIs. If a regional increase in $C_{rs}$ was identified following a sustained-inflation maneuver and PEEP increase, the higher PEEP level was kept. Alveolar cycling and overdistension were analyzed by halving inspiratory driving pressure ($\Delta P$) for diagnostic purposes for about three consecutive breaths. If a reduction in regional $C_{rs}$ during ventilation with lower $\Delta P$ was observed, this was interpreted as alveolar cycling, and PEEP was increased by 3 mbar. An increase in regional $C_{rs}$ with lower $\Delta P$ was interpreted as overdistension. In this case, $V_T$ was decreased by 1 ml/kg predicted body weight (PBW) provided this did not lead to severe acidosis ($pH < 7.2$). PEEP was decreased by 2 mbar if no recruitability and no alveolar cycling had been identified during the last two hours. The details of the EIT protocol are presented in Fig. 1 and in the electronic supplementary material.

Assessment of ventilation delay, stress and strain

A low-flow pressure-volume maneuver (inspiratory flow: 6 l/min) starting at PEEP up to a $V_T$ of 12 ml per kg was performed to allow assessment of $SD_{RVD}$ as described by Muders and coworkers [13]. $SD_{RVD}$ was calculated offline by analyzing the EIT data obtained during the low-flow pressure-volume maneuver with the “Diagnostics” view of the PC version of Pulmovista 500 Software 1.2 (Dräger Medical, Lübeck, Germany).

Subsequently, $FiO_2$ was increased by 10% and decreased to its original value after 10 minutes to allow calculation of end-expiratory lung volume (EELV) according to [17]. Total inspiratory lung volume ($V_{insp}$) was calculated by adding $V_T$ to EELV: $V_{insp} = EELV + V_T$.

For assessment of FRC, we performed an expiratory release maneuver by setting PEEP to zero and allowing complete exhalation of inspired air to ambient pressure. Expired volume during this maneuver (release volume, $V_{release}$) was then used to calculate release-derived FRC ($FRC_{release}$) by subtracting...
$V_{\text{release}}$ from $V_{\text{insp}}$: $FRC_{\text{release}} = V_{\text{insp}} - V_{\text{release}}$. Subsequently, global lung strain was calculated as the ratio of $V_{\text{release}}$ to FRC: $\text{Strain} = V_{\text{release}} / FRC$.

This approach may lead to an underestimation of actual FRC because of alveolar derecruitment that may occur during complete exhalation to ambient pressure. Therefore, we additionally calculated recruitment-adjusted FRC ($FRC_{\text{recr}}$) by first calculating the assumed PEEP volume by multiplying PEEP with global $C_{rs}$ and subsequently subtracting this PEEP volume from EELV: $FRC_{\text{recr}} = EELV - (C_{rs} \times \text{PEEP})$.

Recruitment-adjusted strain (strain$_{\text{recr}}$) was then calculated as the ratio of end-inspiratory lung volume to FRC$_{\text{recr}}$: $\text{Strain}_{\text{recr}} = V_{\text{insp}} / FRC_{\text{recr}}$.

For assessment of airway plateau pressure and transpulmonary plateau pressure ($P_{aw,\text{plat}}$, $P_{tp,\text{plat}}$), we performed an end-inspiratory airway occlusion of 3–4 seconds. Respiratory system elastance ($E_{rs}$) and lung elastance ($E_{\text{lung}}$) were calculated from the ratio of $V_T$ to $P_{aw,\text{plat}}$ and $P_{TP,\text{plat}}$, respectively. Stress was calculated from $P_{aw,\text{plat}}$ multiplied with the ratio between lung elastance ($E_{\text{lung}}$) and respiratory system elastance ($E_{rs}$): $\text{Stress} = P_{aw,\text{plat}} \times E_{\text{lung}} / E_{rs}$.

**Study Procedure**

During the first two hours of measurement, ventilation was adjusted according to the recommendations of the ARDS Network protocol with $V_T$ of 6 ml / kg PBW and PEEP setting according to the low PEEP/FiO$_2$ table [18]. Subsequently, an arterial blood gas (ABG) sample was taken and the first assessment of SD$_{RVD}$, stress and strain was performed. Ventilator settings were then optimized according to the EIT-based protocol once every 30 minutes for a total of four hours. At the end of the four hour period, another assessment of SD$_{RVD}$, stress and strain was performed.

**End points and statistical analysis**

The primary end point was the number of patients with stress below 27 mbar and release-derived strain below 2.0 after four hours of ventilation according to the EIT-based protocol. Secondary endpoints included changes in SD$_{RVD}$, $C_{rs}$, $\Delta P_{aw}$ and PaO$_2$/FiO$_2$. As exploratory endpoints, we analyzed changes in lung compliance ($C_{\text{lung}}$), transpulmonary driving pressure ($\Delta P_{TP}$), total end-expiratory transpulmonary pressure ($P_{tp,\text{exp}}$), tidal power [19], recruitment-adjusted strain and cardiac output, where available. Statistical analysis was performed with GraphPad Prism 5.0 (GraphPad, LaJolla, USA). Normal distribution was assessed with Shapiro-Wilk-Test. Continuous variables are presented as mean ± standard deviation if normally distributed or as median [interquartile range, IQR] if not normally distributed. Comparisons were performed with two-sided paired t-test or Wilcoxon matched-pairs-test, as appropriate.

**Results**
20 patients (11 male, 9 female; age 65 ± 15 years, height 172 ± 9 cm, weight 77 ± 20 kg) were included. One patient had mild ARDS, 18 patients presented with moderate ARDS and one patient fulfilled the criteria for severe ARDS. The average duration of mechanical ventilation prior to study inclusion was 47 ± 18 hours. 14 patients had cardiac output measurements using the PiCCO device. Baseline patient characteristics are presented in Table 1:
Table 1
Main characteristics of the study population.

| Patient No. | Age (years) | Sex (M/F) | BMI (kg/m²) | PaO₂/FiO₂ (mmHg) | ARDS Type (pulmonary / extrapulmonary) | Hours of MV before enrollment | 28 day survivor? |
|-------------|-------------|-----------|-------------|------------------|---------------------------------------|-----------------------------|-----------------|
| 1           | 65          | F         | 21          | 137              | pulm.                                 | 31                          | No              |
| 2           | 72          | F         | 29          | 148              | extrapulm.                            | 61                          | Yes             |
| 3           | 80          | M         | 29          | 120              | extrapulm.                            | 32                          | Yes             |
| 4           | 44          | F         | 23          | 132              | extrapulm.                            | 43                          | Yes             |
| 5           | 78          | F         | 24          | 148              | extrapulm.                            | 34                          | Yes             |
| 6           | 28          | M         | 32          | 189              | pulm.                                 | 33                          | Yes             |
| 7           | 71          | M         | 26          | 162              | pulm.                                 | 30                          | Yes             |
| 8           | 54          | M         | 16          | 215              | pulm.                                 | 30                          | Yes             |
| 9           | 78          | M         | 25          | 168              | pulm.                                 | 55                          | Yes             |
| 10          | 53          | M         | 22          | 152              | pulm.                                 | 62                          | No              |
| 11          | 69          | M         | 28          | 194              | extrapulm.                            | 72                          | Yes             |
| 12          | 59          | F         | 26          | 135              | pulm.                                 | 54                          | No              |
| 13          | 76          | M         | 27          | 138              | pulm.                                 | 70                          | Yes             |
| 14          | 86          | M         | 25          | 138              | pulm.                                 | 42                          | No              |
| 15          | 70          | F         | 27          | 182              | extrapulm.                            | 18                          | Yes             |
| 16          | 74          | F         | 23          | 190              | pulm.                                 | 35                          | No              |
| 17          | 73          | F         | 24          | 127              | extrapulm.                            | 72                          | No              |
| 18          | 49          | M         | 40          | 105              | extrapulm.                            | 62                          | Yes             |
| 19          | 50          | F         | 21          | 145              | pulm.                                 | 72                          | Yes             |
| 20          | 73          | M         | 29          | 96               | pulm.                                 | 24                          | No              |
| Mean (± SD) | 65 (± 15)   | 11 M, 9 F | 26 (± 5)    | 151 (± 31)       | 12 pulm., 8 extrapulm.                | 47                          | 13 survivors    |

Definition of abbreviations: M = male; F = female; BMI = body mass index; PaO₂/FiO₂ = ratio of arterial partial pressure of oxygen to inspired fraction of oxygen; ARDS = acute respiratory distress syndrome; pulm. = pulmonary; extrapulm. = extrapulmonary; MV = mechanical ventilation.
After adjusting mechanical ventilation according to the ARDS Network protocol, patients were ventilated with a median PEEP level of 10 [IQR 8–10] mbar and an expiratory V\textsubscript{T} of 5.8 ± 0.5 ml/kg PBW. P\textsubscript{aw,plat} was 20.3 [IQR 18.5–22.4] mbar resulting in a ΔP\textsubscript{aw} of 10.4 ± 2.2 mbar and C\textsubscript{rs} of 38.2 ± 8.8 ml/mbar. PaO\textsubscript{2}/FiO\textsubscript{2} was 151 ± 31 mmHg. Lung stress was within the physiological range for all patients (14.1 ± 3.9 mbar). End-Expiratory lung volume (EELV) was 1637 [IQR 1450–2228] ml, corresponding to a release-derived FRC of 1176 ± 439 ml and recruitment-adjusted FRC of 1267 [IQR 1141–1803] ml. Release-derived strain was above 2.0 for 2 patients (2.2 and 3.4, respectively) with a median value of 0.80 [IQR 0.70–1.10]. Recruitment-adjusted strain was below 2.0 for all patients with an average value of 0.56 ± 0.14. The ventilation-delay index SD\textsubscript{RVD} was 8.3 ± 2.8%.

During the first assessment of recruitability with EIT, we found recruitable lung tissue in 15 patients. The first assessment of overdistension and alveolar cycling with EIT revealed regional overdistension in 15 patients and alveolar cycling in 5 patients. A median of 3 [IQR 3–4] assessments of recruitability, 6 [IQR 5–6] assessments of overdistension and 6 [IQR 5–6] assessments of alveolar cycling were performed over the four-hour period of optimization of ventilator settings according to the EIT based protocol, resulting in 3 [IQR 3–4] adjustments of PEEP and 2 [IQR 1–2] adjustments of V\textsubscript{T}.

At the end of optimization of ventilator settings according to the EIT based protocol, EIT identified regional overdistension in 10 patients and alveolar cycling in 0 patients. The set PEEP level had increased to 16.5 [IQR 14–18] mbar (p = 0.0001) while the average expiratory V\textsubscript{T} remained similar, though with more intra-individual variability (5.7 ± 0.9 ml/kg PBW; p = 0.96; Fig. 2). P\textsubscript{aw,plat} increased to 27.9 [IQR 25.4–29.1] mbar (p = 0.0001), resulting in ΔP\textsubscript{aw} of 10.4 ± 2.0 mbar (p = 0.96) and C\textsubscript{rs} of 34.5 ± 10.3 ml/mbar (p = 0.55). PaO\textsubscript{2}/FiO\textsubscript{2} increased to 209 ± 53 mmHg (p = 0.0002). Stress increased significantly to 17.2 ± 4.4 mbar (p = 0.0007 in comparison to ARDS Network strategy) but remained below 27 mbar in all patients. Similarly, release-derived strain increased significantly to a median value of 1.13 [IQR 0.96–1.59] (p = 0.015) and was above 2.0 in one patient (3.4). Recruitment-adjusted strain remained unchanged despite the higher PEEP levels selected with our EIT based strategy (0.55 ± 0.19; p = 0.77). SD\textsubscript{RVD} decreased significantly to 6.6 ± 1.9% (p = 0.02). Tidal power decreased from 4.96 ± 1.87 to 4.24 ± 1.24 J/min (p = 0.047). Individual patient values of PEEP, V\textsubscript{T}, PaO\textsubscript{2}/FiO\textsubscript{2} and ΔP\textsubscript{TP} are presented in Fig. 2.

No significant changes were found for vasopressor dose, cardiac output, PaCO\textsubscript{2} and pH. All results are summarized in Table 2:
Table 2
Ventilator data and physiological parameters after mechanical ventilation according to the ARDS Network protocol low positive end-expiratory pressure (PEEP) table (ARDSNet) and after four hours of mechanical ventilation according to the electrical impedance tomography based protocol (EIT Protocol). Normally distributed variables are presented as mean ± standard deviation whereas non-normally distributed variables are presented as median [interquartile range].

| Parameter (unit)          | ARDSNet   | EIT Protocol | p       |
|--------------------------|-----------|--------------|---------|
| Stress (mbar)            | 14.1 ± 3.9| 17.2 ± 4.4   | 0.0007  |
| Strain
release (ratio)     | 0.80 [0.70–1.10] | 1.13 [0.96–1.59] | 0.015   |
| Strain
recr. (ratio)        | 0.56 ± 0.14 | 0.55 ± 0.19  | 0.77    |
| PaO\textsubscript{2}/FiO\textsubscript{2} (mmHg) | 151 ± 31 | 209 ± 53 | 0.0001  |
| PaCO\textsubscript{2} (mmHg)    | 58 ± 11   | 61 ± 9      | 0.28    |
| pH                       | 7.31 ± 0.07 | 7.29 ± 0.05 | 0.17    |
| V\textsubscript{T} (ml/kg PBW) | 5.8 ± 0.47 | 5.7 ± 0.92  | 0.96    |
| P\textsubscript{aw,plat} (mbar) | 20.3 [18.5–22.4] | 27.9 [25.4–29.1] | 0.0001  |
| PEEP (mbar)              | 10 [8–10]  | 16.5 [14–18] | 0.0001  |
| C\textsubscript{rs} (ml/mbar) | 38.2 ± 8.8 | 37.9 ± 11.4 | 0.83    |
| C\textsubscript{lung} (ml/mbar) | 60.07 ± 23.48 | 63.53 ± 26.38 | 0.33    |
| ΔP\textsubscript{aw} (mbar) | 10.4 ± 2.2 | 10.4 ± 2.0  | 0.96    |
| ΔP\textsubscript{TP} (mbar) | 7.0 ± 2.3  | 6.6 ± 2.1   | 0.19    |
| SD\textsubscript{RVD} (%) | 8.3 ± 2.8  | 6.6 ± 1.9   | 0.022   |
| P\textsubscript{tp,plat} (mbar) | 4.9 [1.4–6.9] | 17.9 [15.6–19.0] | < 0.0001 |
| P\textsubscript{tp,exp} (mbar) | -3.5 [-5.9–1.1] | 3.25 [-0.7–4.7] | 0.0002  |
| Tidal Power (J/min)      | 4.96 ± 1.87 | 4.24 ± 1.24 | 0.047   |
| EELV (ml)                | 1637 [1450–2228] | 2348 [2034–3201] | < 0.0001 |
| FRC\textsubscript{release} (ml) | 1176 ± 439 | 1317 ± 443  | 0.17    |
| FRC\textsubscript{recr.} (ml) | 1267 [1141–1803] | 1704 [1496–2512] | 0.0001  |
| Cardiac Index* (l/min/m\textsuperscript{2}) | 3.4 [2.4–4.5]* | 3.4 [2.5–5.0]* | 0.19*   |
| NE (µg/kg/min)           | 0.12 [0.01–0.26] | 0.12 [0.01–0.26] | 0.55    |
Definition of abbreviations: PaO\textsubscript{2} = arterial partial pressure of oxygen; FiO\textsubscript{2} = inspired fraction of oxygen; C\textsubscript{rs} = respiratory system compliance; C\textsubscript{lung} = lung compliance; ΔP\textsubscript{aw} = airway driving pressure; ΔP\textsubscript{TP} = transpulmonary driving pressure; NE = norepinephrine dosage; P\textsubscript{aw,plat} = airway plateau pressure; PEEP = positive end-expiratory pressure (measured at airway opening); P\textsubscript{tp,plat} = transpulmonary plateau pressure (calculated as difference between P\textsubscript{aw,plat} and plateau esophageal pressure); P\textsubscript{tp,exp} = end-expiratory transpulmonary pressure (calculated as difference between PEEP and end-expiratory esophageal pressure); SD\textsubscript{RVD} = standard deviation of regional ventilation delay; EELV = end-expiratory lung volume; FRC\textsubscript{recr.} = recruitment-adjusted functional residual capacity, calculated as EELV – C\textsubscript{rs} * PEEP; FRC\textsubscript{release} = release-derived functional residual capacity, calculated as EELV – released volume during an exhalation to ambient pressure; PBW = predicted body weight; Strain\textsubscript{release} = release-derived strain, calculated as volume change above FRC\textsubscript{rel}, normalized to FRC\textsubscript{rel}; Strain\textsubscript{recr.} = recruitment-adjusted strain, calculated as volume change above FRC\textsubscript{recr.}, normalized to FRC\textsubscript{recr.}; V\textsubscript{T} = tidal volume. * cardiac output measurements were available in 14 patients.

Discussion

The main finding of this prospective clinical cross-over study was that adjustment of PEEP and V\textsubscript{T} according to the EIT-based protocol led to individualized ventilator settings with improved oxygenation and reduced alveolar cycling without causing excessive lung stress and strain. Global lung stress remained below 27 mbar in all patients, while release-derived strain was below 2.0 in 19 out of 20 patients. We chose 27 mbar as upper threshold for stress and 2.0 as upper threshold for strain because these values represent the upper limit of the physiological range postulated for human patients in previous publications [2, 20].

In one patient, we found an unphysiologically high value of release-derived strain of 3.4 after adjusting mechanical ventilation with the EIT-based protocol. However, this patient had relatively moderate P\textsubscript{aw,plat} of 29 mbar and lung stress of 21 mbar. Recruitment-adjusted strain amounted to 1.5, which is still within the physiological range. These findings support the assumption that the unphysiologically high strain observed in this patient was largely due to derecruitment during the release maneuver that was performed for calculating strain and FRC from the measured end-expiratory lung volume (EELV).

For assessing global lung stress in this study, we used the concept of elastance-based transpulmonary pressure which is based on the assumption that at zero airway pressure, transpulmonary pressure also equals zero and that transpulmonary pressure can therefore be calculated using the ratio between the elastance of the lung and the respiratory system multiplied with airway plateau pressure. Obviously, this assumption may not always be valid, especially in patients with increased lung weight and ARDS. Indeed, it has been found that elastance-based methods for estimating transpulmonary pressure yield very different results when compared to the more widely applied method that uses absolute values of esophageal pressure for directly calculating transpulmonary pressure [21]. However, the assumption of transpulmonary pressure close to zero at zero airway pressure may be an acceptably accurate
approximation for the non-dependent lung regions [22], where overdistension primarily occurs. Therefore, our results of stress < 27 mbar in all patients indicate that adjusting PEEP and $V_T$ according to our EIT-based protocol did not lead to overinflation of non-dependent lung areas.

Furthermore, we found significant improvements in oxygenation and lower values of $SD_{RVD}$ consistent with a reduction in alveolar cycling. The average value of absolute end-expiratory transpulmonary pressure was negative before optimizing ventilation according to the EIT-based approach but became positive after 4 hours of its use. We found no changes in cardiac output and vasopressor dosing, indicating that there was no relevant hemodynamic compromise despite the higher PEEP levels applied after EIT-based optimization.

Our protocol for prospective optimization of PEEP and $V_T$ with EIT was largely based on bedside assessment of changes in regional $C_{rs}$. An increase in regional $C_{rs}$ following a sustained-inflation recruitment maneuver was interpreted as indicator for alveolar recruitment and a higher PEEP level was selected to keep the recruited lung volume. With this approach, we identified alveolar recruitment in 15 out of 20 patients after the initial recruitment maneuver, indicating a high potential for recruitment in a large proportion of patients studied.

If regional $C_{rs}$ decreased during a brief reduction in $V_T$, this was interpreted as an indicator for regional alveolar cycling and PEEP was increased by a further 3 mbar to counteract this phenomenon. On the contrary, an increase in regional $C_{rs}$ during a brief reduction in $V_T$ was interpreted as overdistension with the previously applied $V_T$. In this case, the therapeutic consequence was to decrease $V_T$, provided this did not lead to severe acidosis. In a surprisingly large proportion of patients, we still identified regional overdistension with a $V_T$ of 6 ml/kg PBW. This EIT finding led to further reductions of $V_T$ to levels below 6 ml/kg PBW in 10 out of 20 patients.

Our $C_{rs}$-based approach differs from the approach that was employed for prospective optimization of PEEP with EIT in a study published by Eronia and Coworkers [14]. In this study, the time-course of end-expiratory lung impedance was analyzed for determining changes in EELV associated with PEEP. A slow decrease in end-expiratory lung impedance following a recruitment maneuver was interpreted as derecruitment, and PEEP was increased to counteract this phenomenon until a stable level of end-expiratory impedance was achieved. As end-expiratory lung impedance appears to be a reasonably accurate measure for changes in EELV [23], this approach allows straightforward bedside assessment of recruitment and derecruitment. However, it is highly susceptible to artifacts: For instance, the pulsation therapy with inflatable mattresses can cause substantial artifacts in end-expiratory impedance [24]; the same applies to changes in torso and arm position [25] and even intravenous fluid therapy, which is a rather common intervention in ICU patients [26, 27]. These interferences render EIT-based analyses of EELV difficult to interpret and error-prone. Moreover, while observing end-expiratory lung impedance may facilitate bedside assessment of recruitment and derecruitment, it provides no information on regional overdistension, which can be easily identified by analyzing regional changes in $C_{rs}$ [11, 12].
Another $C_{rs}$-based approach that has been applied for EIT-based optimization of PEEP in patients with ARDS [28] and with Covid-19 induced acute respiratory failure [29, 30] relies on analyzing pixel-wise changes in $C_{rs}$ during a decremental PEEP-trial [12, 31]. The main disadvantage of this approach is that it requires a decremental PEEP trial that must be started at relatively high PEEP levels that may be associated with overdistension while applied. The PEEP trial must then be carried on until very low PEEP levels (that may lead to alveolar collapse and atelectasis formation) are reached. Therefore, it cannot be repeated on a regular basis to adapt ventilator settings to the changing conditions of a patient's lung. In contrast, our approach is primarily based on brief changes in $V_T$ for diagnosing regional overdistension and alveolar cycling, and can thus be repeated whenever a new assessment of these phenomena is clinically required.

Our study has several limitations. First, it was not a randomized study. Therefore, we can make no assumptions on whether individualized optimization of mechanical ventilation with our EIT-based protocol has an influence on actual clinical outcomes. Instead, we tried to carefully monitor and describe the physiologic effects of individualized adjustment of ventilator settings using the EIT-based protocol by analyzing changes in transpulmonary pressure and EELV.

Also, we did not directly measure recruitment and alveolar cycling with a reference method like CT. Our measurements of EELV using the modified nitrogen dilution technique [17] indicate that recruitment-adjusted FRC that was derived by subtracting the assumed PEEP volume from EELV, was significantly increased. The ventilation delay index $SD_{RVD}$, that was not used for optimization of ventilation but served as a secondary outcome parameter, indicated a possible reduction in alveolar cycling with our EIT-based optimization. Nevertheless, independent reference methods like CT might be necessary to confirm a reduction in alveolar cycling following optimization of mechanical ventilation with the EIT-based protocol.

The majority of patients included in this study presented with moderate ARDS. Following a meta-analysis by Briel and coworkers [32], recent recommendations suggest using a higher PEEP / FiO$_2$ strategy for patients with moderate to severe ARDS [33]. Nevertheless, comparatively low levels of PEEP in patients with moderate to severe ARDS are still common clinical practice in many centers around the world [34].

Valid assessment of $C_{rs}$, which is a prerequisite for our EIT-based approach for individualization of PEEP and $V_T$, typically requires a paralyzed patient, even though it is possible to assess $C_{rs}$ and $\Delta P_{aw}$ in many patients on assisted ventilation using an inspiratory-hold maneuver [35, 36]. The patients included in our study exhibited no spontaneous breathing activity. It is uncertain whether a $C_{rs}$-based approach using inspiratory hold maneuvers during assisted modes of ventilation will yield similar results in patients with spontaneous breathing activity.

In conclusion, we presented a protocol for prospective adaption of PEEP and $V_T$ taking into account EIT-derived information on recruitability, overdistension and alveolar cycling. Mechanical ventilation adjusted according to the EIT protocol resulted in global values of lung stress and strain within the physiological
limits and was associated with improvements in oxygenation and a reduction in regional ventilation delay inhomogeneity.

List Of Abbreviations
| Abbreviation | Definition |
|--------------|------------|
| ABG          | Arterial Blood Gas |
| ARDS         | Acute Respiratory Distress Syndrome |
| $C_{rs}$     | Respiratory System Compliance |
| $C_{lung}$   | Lung Compliance |
| CT           | Computed tomography |
| $\Delta P$  | Driving Pressure |
| $\Delta P_{aw}$ | Airway Driving Pressure |
| $\Delta P_{TP}$ | Transpulmonary driving pressure |
| EELV         | End-Expansible Lung Volume |
| EIT          | Electrical Impedance Tomography |
| etCO$_2$     | End-tidal Carbon Dioxide |
| FiO$_2$      | Inspired Fraction of Oxygen |
| FRC          | Functional Residual Capacity |
| FRC$_{recr}$ | Recruitment-adjusted Functional Residual Capacity |
| HR           | Heart Rate |
| ICU          | Intensive Care Unit |
| IQR          | Interquartile range |
| MV           | Mechanical Ventilation |
| NE           | Norepinephrine |
| PaCO$_2$     | Arterial Partial Pressure of Carbon Dioxide |
| PaO$_2$      | Arterial Partial Pressure of Oxygen |
| $P_{aw}$     | Airway pressure |
| $P_{aw,plat}$ | Airway plateau pressure |
| PEEP         | Positive End-Expansible Pressure |
| PBW          | Predicted body weight |
| SD$_{RVD}$   | Standard Deviation of Regional Ventilation Delay |
| Strain$_{recr}$ | Recruitment-adjusted strain |
| VILI | Ventilator-Induced Lung Injury |
|------|------------------------------|
| $V_{\text{insp}}$ | Total inspiratory lung volume (= EELV + $V_T$) |
| $V_{\text{release}}$ | Release volume |
| $V_T$ | Tidal Volume |

**Declarations**

**Ethics approval and consent to participate**

The study was approved by the Ethics Committee of the Medical Faculty of the Christian Albrechts University in Kiel (A126/14). Written informed consent was obtained from the patient’s legal representatives prior to study inclusion.

**Consent for publication**

Consent for publication of pseudonymized data was obtained with the written informed consent to participate in the study.

**Availability of data and material**

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

**Competing interests**

DS and TB received lecture fees from Drägerwerk AG & Co. KGaA. The other authors report no competing interests.

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**Authors' contributions**

**Conception and design:** T.B., D.S., I.F., T.M., N.W.; **Data acquisition:** T.B., D.H., V.B.; **Analysis and interpretation of data:** T.B., D.H., V.B., N.W., I.F.; **Drafting the manuscript for important intellectual content:** T.B., D.S., I.F., N.W.; **Revision and final approval of the manuscript:** All authors

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**Figures**

![Diagram](image)

**Figure 1**

Clinical protocol for prospective optimization of ventilator settings with electrical impedance tomography (EIT). Optimization started with an arterial blood gas (ABG) analysis and, if necessary, adjustments of respiratory rate (RR) and tidal volume (VT), followed by a recruitment maneuver (RM) and subsequent adaptations of positive end-expiratory pressure (PEEP) and VT. The footnotes are explained in the online data supplement.
Changes in positive end-expiratory pressure (PEEP), tidal volume (VT), ratio of arterial partial pressure of oxygen to inspired fraction of oxygen (PaO₂/FiO₂) and transpulmonary driving pressure (ΔPTP) after individualization of ventilator settings according to the electrical impedance tomography (EIT) protocol. ARDSNet = Ventilator settings according to acute respiratory distress syndrome network recommendations with low PEEP/FiO₂ table; EIT = ventilator settings after 4 hours of adjustment according to EIT-based protocol.
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