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

Tobias Hermann Becher (tobias.becher@uksh.de)
Universitätsklinikum Schleswig-Holstein, Campus Kiel https://orcid.org/0000-0003-2026-7629
Valerie Buchholz
Universitätsklinikum Schleswig-Holstein Campus Kiel
Daniel Hassel
Christian-Albrechts-Universität zu Kiel
Timo Alexander Meinel
Universitätsklinikum Schleswig-Holstein, Campus Kiel
Dirk Schädler
Universitätsklinikum Schleswig-Holstein Campus Kiel
Inéz Frerichs
Universitätsklinikum Schleswig-Holstein Campus Kiel
Norbert Weiler
Universitätsklinikum Schleswig-Holstein, Campus Kiel

Research

Keywords: Electrical Impedance Tomography, lung-protective ventilation, ventilator-induced lung injury, personalized medicine, Acute respiratory failure

Posted Date: December 1st, 2020

DOI: https://doi.org/10.21203/rs.3.rs-115065/v1

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 (ΔP_{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 bed-side 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 (ΔP) for diagnostic purposes for about three consecutive breaths. If a reduction in regional C_{rs} during ventilation with lower ΔP was observed, this was interpreted as alveolar cycling, and PEEP was increased by 3 mbar. An increase in regional C_{rs} with lower ΔP 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

$V_{release}$ from V_{insp}: $FRC_{release} = V_{insp} - V_{release}$. Subsequently, global lung strain was calculated as the ratio of $V_{release}$ to FRC: Strain = $V_{release}$ / 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_{recr}) by first calculating the assumed PEEP volume by multiplying PEEP with global C_{rs} and subsequently subtracting this PEEP volume from EELV: $FRC_{recr} = EELV - (C_{rs} * PEEP)$.

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

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

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}, ΔP_{aw} and PaO_2/FiO_2. As exploratory endpoints, we analyzed changes in lung compliance (C_{lung}), transpulmonary driving pressure (ΔP_{TP}), total end-expiratory transpulmonary pressure ($P_{tp,exp}$), 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/m^2)	PaO_2/FiO_2 (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	puml	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 (± 18)	13 survivors

Definition of abbreviations: M = male; F = female; BMI = body mass index; PaO_2/FiO_2 = 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_T of 5.8 ± 0.5 ml/kg PBW. $P_{aw,plat}$ was 20.3 [IQR 18.5–22.4] mbar resulting in a ΔP_{aw} of 10.4 ± 2.2 mbar and C_{rs} of 38.2 ± 8.8 ml/mbar. PaO_2/FiO_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_{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_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_T remained similar, though with more intra-individual variability (5.7 ± 0.9 ml/kg PBW; $p = 0.96$; Fig. 2). $P_{aw,plat}$ increased to 27.9 [IQR 25.4–29.1] mbar ($p = 0.0001$), resulting in ΔP_{aw} of 10.4 ± 2.0 mbar ($p = 0.96$) and C_{rs} of 34.5 ± 10.3 ml/mbar ($p = 0.55$). PaO_2/FiO_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_{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_T, PaO_2/FiO_2 and ΔP_{TP} are presented in Fig. 2.

No significant changes were found for vasopressor dose, cardiac output, $PaCO_2$ 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_2/FiO_2 (mmHg)	151 ± 31	209 ± 53	0.0001
$PaCO_2$ (mmHg)	58 ± 11	61 ± 9	0.28
pH	7.31 ± 0.07	7.29 ± 0.05	0.17
V_T (ml/kg PBW)	5.8 ± 0.47	5.7 ± 0.92	0.96
$P_{aw.plat}$ (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_{rs} (ml/mbar)	38.2 ± 8.8	37.9 ± 11.4	0.83
C_{lung} (ml/mbar)	60.07 ± 23.48	63.53 ± 26.38	0.33
ΔP_{aw} (mbar)	10.4 ± 2.2	10.4 ± 2.0	0.96
ΔP_{TP} (mbar)	7.0 ± 2.3	6.6 ± 2.1	0.19
SD_{RVD} (%)	8.3 ± 2.8	6.6 ± 1.9	0.022
$P_{tp,plat}$ (mbar)	4.9 [1.4–6.9]	17.9 [15.6–19.0]	< 0.0001
$P_{tp,exp}$ (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
$FRC_{release}$ (ml)	1176 ± 439	1317 ± 443	0.17
$FRC_{recr.}$ (ml)	1267 [1141–1803]	1704 [1496–2512]	0.0001
Cardiac Index* ($l/min/m^2$)	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_2 = arterial partial pressure of oxygen; FiO_2 = inspired fraction of oxygen; C_{rs} = respiratory system compliance; C_{lung} = lung compliance; ΔP_{aw} = airway driving pressure; ΔP_{TP} = transpulmonary driving pressure; NE = norepinephrine dosage; $P_{aw.plat}$ = airway plateau pressure; PEEP = positive end-expiratory pressure (measured at airway opening); $P_{tp,plat}$ = transpulmonary plateau pressure (calculated as difference between $P_{aw.plat}$ and plateau esophageal pressure); $P_{tp,exp}$ = end-expiratory transpulmonary pressure (calculated as difference between PEEP and end-expiratory esophageal pressure); SD_{RVD} = standard deviation of regional ventilation delay; EELV = end-expiratory lung volume; $FRC_{recr.}$ = recruitment-adjusted functional residual capacity, calculated as EELV – C_{rs} * PEEP; $FRC_{release}$ = release-derived functional residual capacity, calculated as EELV – released volume during an exhalation to ambient pressure; PBW = predicted body weight; $Strain_{release}$ = release-derived strain, calculated as volume change above FRC_{rel}, normalized to FRC_{rel}; $Strain_{recr.}$ = recruitment-adjusted strain, calculated as volume change above $FRC_{recr.}$, normalized to FRC_{recr}; V_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_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 $P_{aw,plat}$ 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 opposite, 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 ΔP_{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

ABG	Arterial Blood Gas
ARDS	Acute Respiratory Distress Syndrome
C_{rs}	Respiratory System Compliance
C_{lung}	Lung Compliance
CT	Computed tomography
ΔP	Driving Pressure
ΔP_{aw}	Airway Driving Pressure
ΔP_{TP}	Transpulmonary driving pressure
EELV	End-Expiratory 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-Expiratory Pressure
PBW	Predicted body weight
SD_{RVD}	Standard Deviation of Regional Ventilation Delay
$Strain_{recr}$	Recruitment-adjusted strain

VILI	Ventilator-Induced Lung Injury
V_{insp}	Total inspiratory lung volume (= EELV + V_T)
$V_{release}$	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.

Funding

The study was financed by institutional funds.

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

Acknowledgements

We would like to express our gratitude to all patients and their relatives who volunteered to participate in this study. Furthermore, we would like to thank Eckhard Teschner for the inspiring exchange of ideas and his continuous valuable support.

References

1. Slutsky AS, Ranieri VM. Ventilator-induced lung injury. *N Engl J Med*. 2013;369:2126-2136. doi:10.1056/NEJMra1208707
2. Chiumello D, Carlesso E, Cadringher P, Caironi P, Valenza F, Polli F, Tallarini F, Cozzi P, Cressoni M, Colombo A, Marini JJ. Lung stress and strain during mechanical ventilation for acute respiratory distress syndrome. *Am J Respir Cit Care Med* 2008; 178(4):346-355.
3. Protti A, Cressoni M, Santini A, et al. Lung stress and strain during mechanical ventilation: any safe threshold? *Am J Respir Crit Care Med*. 2011; 183:1354-1362. doi:10.1164/rccm.201010-1757OC
4. Cressoni M, Cadringher P, Chiurazzi C, et al. Lung inhomogeneity in patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2014;189(2):149-158. doi:10.1164/rccm.201308-1567OC
5. Amato MB, Meade MO, Slutsky AS, et al. Driving pressure and survival in the acute respiratory distress syndrome. *N Engl J Med*. 2015;372(8):747-755. doi:10.1056/NEJMsa1410639
6. Writing Group for the Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial (ART) Investigators, Cavalcanti AB, Suzumura ÉA, et al. Effgect of Lung Recruitment and Titrated Positive End-Expiratory Pressure (PEEP) vs Low PEEP on Mortality in Patients with Acute Respiratory Distress Syndrome: A Randomized Clinical Trial. *JAMA*. 2017;318(14):1335-1345. doi:10.1001/jama.2017.14171
7. Gattinoni L, Caironi P, Cressoni M, et al. Lung recruitment in patients with the acute respiratory distress syndrome. *N Engl J Med*. 2006;354(17):1775-1786. doi:10.1056/NEJMoa052052
8. Grasso S, Terragni P, Mascia L, et al. Airway pressure-time curve profile (stress index) detects tidal recruitment/hyperinflation in experimental acute lung injury. *Crit Care Med*. 2004;32(4):1018-1027. doi:10.1097/01.ccm.0000120059.94009.ad
9. Chiumello D, Cressoni M, Carlesso E, et al. Bedside selection of positive end-expiratory pressure in mild, moderate, and severe acute respiratory distress syndrome. *Crit Care Med*. 2014;42(2):252-264. doi:10.1097/CCM.0b013e3182a6384f
10. Chiumello D, Coppola S, Froio S, et al. Time to reach a new steady state after changes of positive end expiratory pressure. *Intensive Care Med*. 2013;39(8):1377-1385. doi:10.1007/s00134-013-2969-x
11. Zick G, Elke G, Becher T, et al. Effect of PEEP and tidal volume on ventilation distribution and end-expiratory lung volume: a prospective experimental animal and pilot clinical study. *PLoS One*. 2013;8(8):e72675. Published 2013 Aug 22. doi:10.1371/journal.pone.0072675
12. Costa EL, Borges JB, Melo A, et al. Bedside estimation of recruitable alveolar collapse and hyperdistension by electrical impedance tomography. *Intensive Care Med*. 2009;35(6):1132-1137. doi:10.1007/s00134-009-1447-y
13. Muders T, Luepschen H, Zinserling J, et al. Tidal recruitment assessed by electrical impedance tomography and computed tomography in a porcine model of lung injury*. *Crit Care Med*. 2012;40(3):903-911. doi:10.1097/CCM.0b013e318236f452

14. Eronia N, Mauri T, Maffezzini E, et al. Bedside selection of positive end-expiratory pressure by electrical impedance tomography in hypoxemic patients: a feasibility study. *Ann Intensive Care*. 2017;7(1):76. doi:10.1186/s13613-017-0299-9
15. Rosemeier I, Reiter K, Obermeier V, Wolf GK. Mechanical Ventilation Guided by Electrical Impedance Tomography in Children With Acute Lung Injury. *Crit Care Explor*. 2019;1(7):e0020. Published 2019 Jul 1. doi:10.1097/CCE.0000000000000020
16. ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, et al. Acute respiratory distress syndrome: the Berlin Definition. *JAMA*. 2012;307(23):2526-2533. doi:10.1001/jama.2012.5669
17. Olegård C, Söndergaard S, Houltz E, Lundin S, Stenqvist O. Estimation of functional residual capacity at the bedside using standard monitoring equipment: a modified nitrogen washout/washin technique requiring a small change of the inspired oxygen fraction. *Anesth Analg*. 2005;101(1):. doi:10.1213/01.ANE.0000165823.90368.55
18. Brower RG, Lanken PN, MacIntyre N, et al. Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. *N Engl J Med*. 2004;351(4):327-336. doi:10.1056/NEJMoa032193
19. van der Staay M, Chatburn RL. Advanced modes of mechanical ventilation and optimal targeting schemes. Intensive Care Med Exp. 2018;6(1):30. Published 2018 Aug 22. doi:10.1186/s40635-018-0195-0
20. Gattinoni L, Tonetti T, Quintel M. Regional physiology of ARDS. *Crit Care* 2017; 21(Suppl 3):312. Published 2017 Dec 28. doi:10.1186/s13054-017-1905-9
21. Gulati G, Novero A, Loring SH, Talmor D. Pleural pressure and optimal positive end-expiratory pressure based on esophageal pressure versus chest wall elastance: incompatible results*. *Crit Care Med*. 2013;41(8):1951-1957. doi:10.1097/CCM.0b013e31828a3de5
22. Yoshida T, Amato MBP, Grieco DL, et al. Esophageal Manometry and Regional Transpulmonary Pressure in Lung Injury. *Am J Respir Crit Care Med*. 2018;197(8):1018-1026. doi:10.1164/rccm.201709-1806OC
23. Mauri T, Eronia N, Turrini C, et al. Bedside assessment of the effects of positive end-expiratory pressure on lung inflation and recruitment by the helium dilution technique and electrical impedance tomography. *Intensive Care Med*. 2016;42(10):1576-1587. doi:10.1007/s00134-016-4467-4
24. Frerichs I, Pulletz S, Elke G, Gawelczyk B, Frerichs A, Weiler N. Patient examinations using electrical impedance tomography--sources of interference in the intensive care unit. *Physiol Meas*. 2011;32(12):L1-L10. doi:10.1088/0967-3334/32/12/F01
25. Vogt B, Mendes L, Chouvarda I, et al. Influence of torso and arm positions on chest examinations by electrical impedance tomography. *Physiol Meas*. 2016;37(6):904-921. doi:10.1088/0967-3334/37/6/904
26. Becher T, Wendler A, Eimer C, Weiler N, Frerichs I. Changes in Electrical Impedance Tomography Findings of ICU Patients during Rapid Infusion of a Fluid Bolus: A Prospective Observational Study. *Am J Respir Crit Care Med*. 2019;199(12):1572-1575. doi:10.1164/rccm.201812-2252LE

27. Sobota V, Müller M, Roubík K. Intravenous administration of normal saline may be misinterpreted as a change of end-expiratory lung volume when using electrical impedance tomography. *Sci Rep*. 2019;9(1):5775. Published 2019 Apr 8. doi:10.1038/s41598-019-42241-7
28. Heines SJH, Strauch U, van de Poll MCG, Roekaerts PMHJ, Bergmans DCJJ. Clinical implementation of electric impedance tomography in the treatment of ARDS: a single centre experience. *J Clin Monit Comput*. 2019;33(2):291-300. doi:10.1007/s10877-018-0164-x
29. Sella N, Zarantonello F, Andreatta G, Gagliardi V, Boscolo A, Navalesi P. Positive end-expiratory pressure titration in COVID-19 acute respiratory failure: electrical impedance tomography vs. PEEP/FiO2 tables. *Crit Care. 2020*;24(1):540. Published 2020 Sep 1. doi:10.1186/s13054-020-03242-5
30. van der Zee P, Somhorst P, Endeman H, Gommers D. Electrical Impedance Tomography for Positive End-Expiratory Pressure Titration in COVID-19-related Acute Respiratory Distress Syndrome. *Am J Respir Crit Care Med*. 2020;202(2):280-284. doi:10.1164/rccm.202003-0816LE
31. Dargaville PA, Rimensberger PC, Frerichs I. Regional tidal ventilation and compliance during a stepwise vital capacity manoeuvre. *Intensive Care Med*. 2010 Nov;36(11):1953-61. doi: 10.1007/s00134-010-1995-1. Epub 2010 Aug 6.
32. Briel M, Meade M, Mercat A, et al. Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: systematic review and meta-analysis. *JAMA*. 2010;303(9):865-873. doi:10.1001/jama.2010.218
33. Bellani G, Laffey JG, Pham T, Fan E, Brochard L, Esteban A, Gattinoni L, van Haren F, Larsson A, McAuley DF, Ranieri M, Rubenfeld G, Thompson BT, Wrigge H, Slutsky AS, Pesenti A, LUNG SAFE Investigators; ESICM Trials Group. Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries. *JAMA*. 2016;315(8):788-800. doi:10.1001/jama.2016.0291
34. Fan E, Del Sorbo L, Goligher EC, Carol L Hodgson, Laveena Munshi, Allan J Walkey, Neill K J Adhikari, Marcelo B P Amato, Richard Branson, Roy G Brower, Niall D Ferguson, Ognjen Gajic, Luciano Gattinoni, Dean Hess, Jordi Mancebo, Maureen O Meade, Daniel F McAuley, Antonio Pesenti, V Marco Ranieri, Gordon D Rubenfeld, Eileen Rubin, Maureen Seckel, Arthur S Slutsky, Daniel Talmor, B Taylor Thompson, Hannah Wunsch, Elizabeth Uleryk, Jan Brozek, Laurent J Brochard, American Thoracic Society, European Society of Intensive Care Medicine, and Society of Critical Care Medicine. An Official American Thoracic Society/European Society of Intensive Care Medicine/Society of Critical Care Medicine Clinical Practice Guideline: Mechanical Ventilation in Adult Patients with Acute Respiratory Distress Syndrome. *Am J Respir Crit Care Med*. 2017;195(9):1253-1263. doi:10.1164/rccm.201703-0548ST
35. Mauri T, Lazzeri M, Bellani G, Zanella A, Grasselli G. Respiratory mechanics to understand ARDS and guide mechanical ventilation. *Physiol Meas*. 2017;38(12):R280-H303. Published 2017 Nov 30. doi:10.1088/1361-6579/aa9052

36. Bellani G, Grassi A, Sosio S, et al. Driving Pressure Is Associated with Outcome during Assisted Ventilation in Acute Respiratory Distress Syndrome. *Anesthesiology*. 2019;131(3):594-604. doi:10.1097/ALN.0000000000002846

Figures

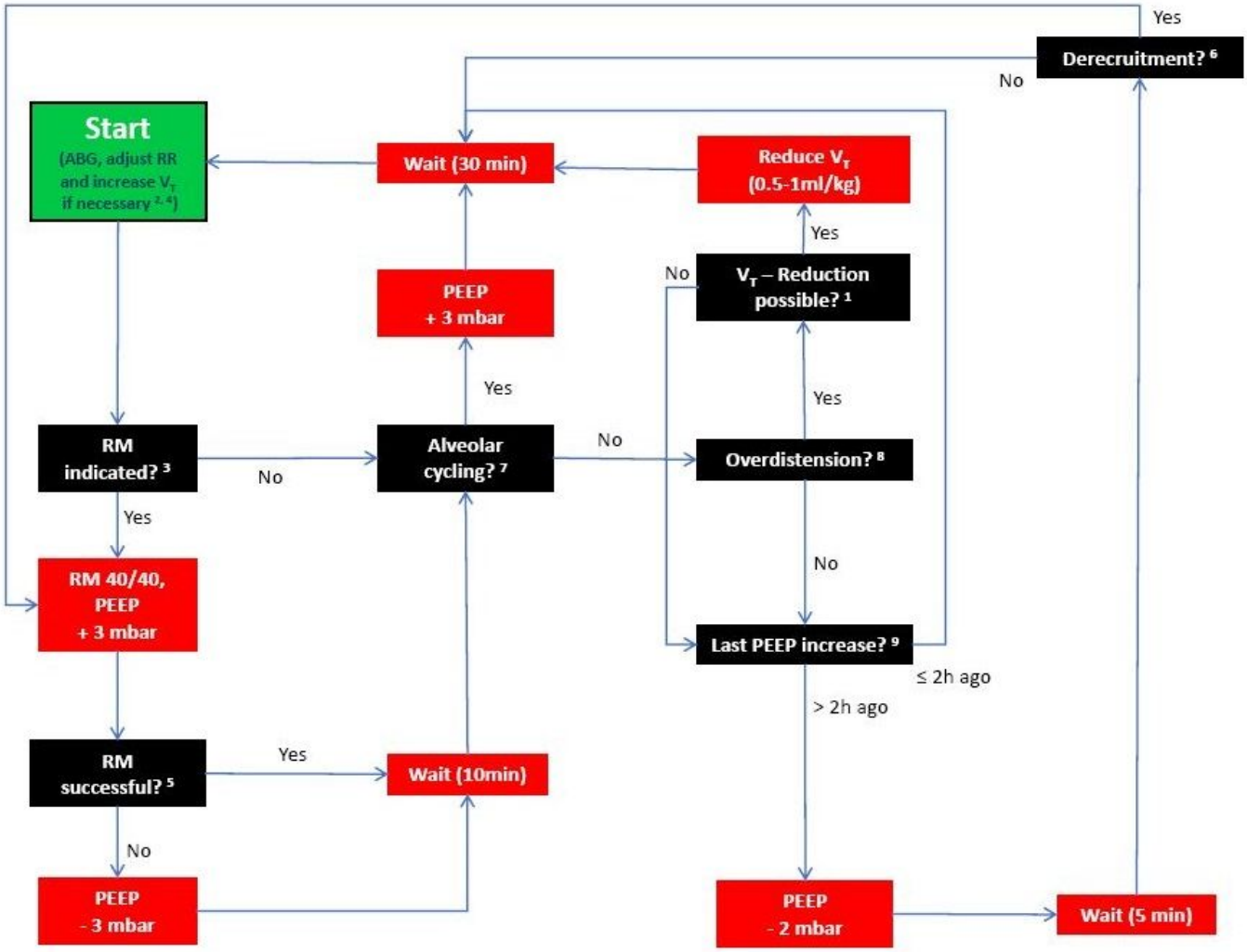

Figure 1

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.

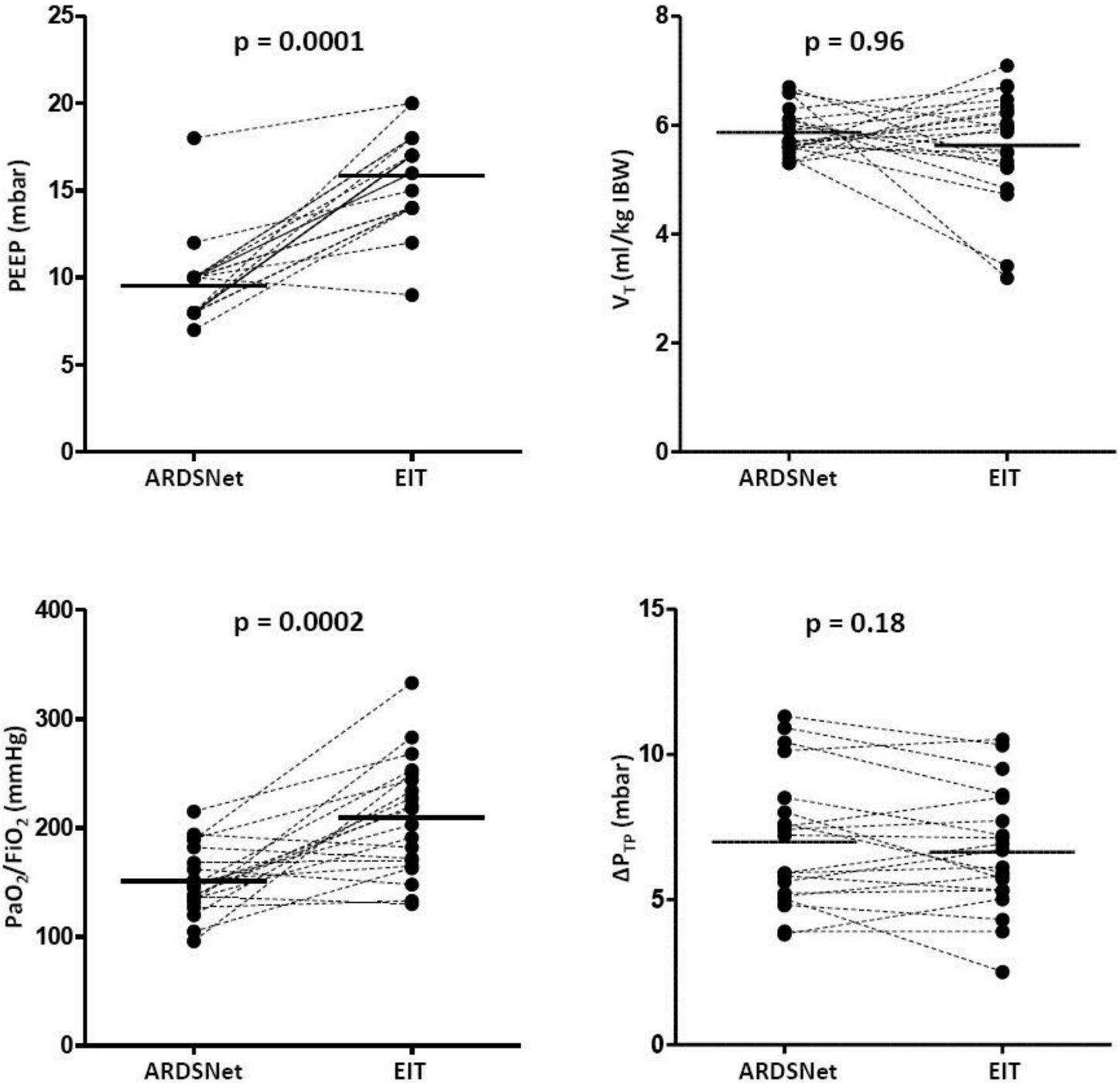

Figure 2

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.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- ElectronicSupplementaryMaterial.docx