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Multicentre, parallel, open-label, two-arm, randomised controlled trial on the prognosis of electrical impedance tomography-guided versus low PEEP/FiO2 table-guided PEEP setting: a trial protocol

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ABSTRACT

Introduction Previous studies suggested that electrical impedance tomography (EIT) has the potential to guide positive end-expiratory pressure (PEEP) titration via quantifying the alveolar collapse and overdistension. The aim of this trial is to compare the effect of EIT-guided PEEP and acute respiratory distress syndrome (ARDS) network low PEEP/fraction of inspired oxygen (FiO_2) table strategy on mortality and other clinical outcomes in patients with ARDS.

Methods This is a parallel, two-arm, multicentre, randomised, controlled trial, conducted in China. All patients with ARDS under mechanical ventilation admitted to the intensive care unit will be screened for eligibility. The enrolled patients are stratified by the aetiology (pulmonary/extrapulmonary) and partial pressure of arterial oxygen/FiO_2 (≥150 mm Hg or <150 mm Hg) and randomised into the intervention group or the control group. The intervention group will receive recruitment manoeuvre and EIT-guided PEEP titration. The EIT-guided PEEP will be set for at least 12 hours after titration. The control group will not receive recruitment manoeuvre routinely and the PEEP will be set according to the lower PEEP/FiO_2 table proposed by the ARDS Network. The primary outcome is 28-day survival.

Analysis Qualitative data will be analysed using the χ^2 test or Fisher's exact test, quantitative data will be analysed using independent samples t-test or Mann-Whitney U test. Kaplan-Meier analysis with log-rank test will be used to evaluate the 28-day survival rate between two groups. All outcomes will be analysed based on the intention-to-treat principle.

Ethics and dissemination The trial is approved by the Institutional Research and Ethics Committee of the Peking Union Medical College Hospital. Data will be published in peer-reviewed journals.

Trial registration number NCT05307913.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Subgroup analyses will be performed according to the acute respiratory distress syndrome aetiologies and severity.
⇒ Clinicians will not be blinded to the group allocations as interventions are obvious.
⇒ The intervention of electrical impedance tomography (EIT)-guided positive end-expiratory pressure (PEEP) setting will be kept for 3 days only at the early stage.
⇒ Recruitment manoeuvre is performed routinely only in the intervention group and so further analyses are needed to reduce biases.
⇒ The EIT-based regional compliance method may not be appropriate to guide PEEP in some patients in which the overall best compromised PEEP level may indicate unacceptable high overdistention or collapse of alveolar.

INTRODUCTION

Background and rationale

Mechanical ventilation is an essential supportive management for patients with acute respiratory distress syndrome (ARDS), but it could also exacerbate lung injury.[1] The mechanisms of ventilator-induced lung injury (VILI) involve volutrauma caused by regional alveolar overdistention, shear injury caused by tidal recruitment, oxygen toxicity, etc.[2 3] Previous studies have shown that ventilation strategy with low tidal volume ventilation (tidal volume ≤6 mL/kg predicted body weight), application of positive end-expiratory pressure (PEEP) and

limited plateau pressure (<30 cmH_2O) reduces VILI and improves ARDS survival.[4–6] However, the mortality rate of ARDS is still exceedingly high under the current lung-protective ventilation strategies. Further effective strategies are warranted.[7]

Studies have demonstrated that alveolar derecruitment is notable in ARDS.[8 9] How to recruit the collapsed alveoli while limiting overinflation in well-ventilated alveoli is an important goal in clinical practice. To achieve this, the combination of recruitment manoeuvres (RM) and PEEP titration is of great importance. Several studies have shown that a maximal recruitment strategy (PEEP of 45 cmH_2O and peak pressure of 60 cmH_2O for 2 min) can adequately achieve lung recruitment and improve oxygenation in the studied ARDS patients without causing serious complications and adverse events.[10 11] However, there is still controversy over the setting of PEEP. The application of PEEP has been demonstrated to improve oxygenation and reduce the risk of VILI in ARDS patients, possibly by its potential to recruit collapsed alveolar, improve lung static compliance, prevent cyclic atelectasis and reduce static stress and strain.[5] Nonetheless, inadequate setting of PEEP might be associated with worsened oxygenation, increased risk of VILI and acute cor pulmonale, via different mechanisms including alveolar overdistention, ventilation-perfusion mismatch due to increased shunting and dead space, increased pulmonary vascular resistance, etc.[12] Hence, an optimal PEEP would be high enough to prevent collapse of alveolar and tidal recruitment, and low enough to avoid overinflation of alveoli and elevation of right ventricular afterload.[13] Furthermore, clinical studies have shown heterogeneity in the effect of PEEP on individual patients.[14–16] Some clinical studies suggested that compared with traditional lung protective ventilation strategies, RM along with a high PEEP strategy failed to significantly reduce the mortality of patients with ARDS.[17 18] One possible reason could be that the PEEP setting was not individualised in these studies, leading to a growing interest in the research of individualised PEEP-setting strategies. Various methods were proposed to individualise optimal PEEP, but they have failed to show significant benefits compared with the conventional PEEP strategies.[13 19] Electrical impedance tomography (EIT) is a bedside imaging tool to monitor ventilation and perfusion distribution.[20] Since EIT quantifies the collapse and overdistension of lung tissues in real time, it has the potential to guide PEEP titration. Two single-centre randomised controlled studies demonstrated mortality rate reduction in ARDS patients with EIT-guided PEEP.[21 22]

We have designed a multicentre clinical randomised controlled trial (RCT) to compare the effect of EIT-guided PEEP and ARDS network-table[23] strategy on the prognosis of patients with ARDS.

Objective

This study aims to explore if EIT-guided PEEP could improve outcomes compared with the PEEP setting according to the PEEP/fraction of inspired oxygen (FiO_2) table (Table-PEEP) from the ARDS network[23] in ARDS patients.

Trial design

This is a parallel, two-arm, open-label, multicentre, randomised, controlled trial approved by the Institutional Research and Ethics Committee of the Peking Union Medical College Hospital (JS-2425). The trial was registered on the website https://clinicaltrials.gov/ with the registration number NCT05307913. Patients recruited will be randomised into two parallel groups: the intervention group or the control group, with an allocation ratio of 1:1. Designation of the trial follows the Standard Protocol Items: Recommendations for International Trials (SPIRIT) reporting guidelines,[24] the SPIRIT checklist is provided as online supplemental Additional file 1.

METHODS: PARTICIPANTS, INTERVENTIONS AND OUTCOMES

Study setting

The trial is conducted at diverse levels of hospitals in China, in order to enhance external validity. Until October 2023, there are 29 clinical centres of a variety of levels participating in this trial, this includes university-affiliated hospitals, provincial hospitals, municipal hospitals and county hospitals. A list of participating centres is provided as online supplemental Additional file 2.

Eligibility criteria

Inclusion criteria

- Intubated, mechanically ventilated patients with the diagnosis of ARDS according to ARDS Berlin definition.[25]

Exclusion criteria

- Age <18 years old or >90 years old.
- Pregnancy.
- EIT contradictions (presence of a pacemaker or automatic implantable cardioverter defibrillator).
- Severe intracranial hypertension.
- Pneumothorax, pneumomediastinum, subcutaneous emphysema or at high risk for pneumothorax (eg, pneumatocele, interstitial lung disease).
- Unstable haemodynamic status that is intolerable to lung recruitment and PEEP titration, judged by an attending intensivist. (This may be a transient criterion since patients meeting this criterion might be included later if haemodynamics improves).
- End status of disease.
- Patients or their families refused to participate in the study.

Eligibility for study centres

- A participating study centre must have experienced in managing ARDS patients, able to provide critical care and specialised clinical management to ARDS patients, equipped with an EIT machine and experienced in

Table 1 The lower PEEP/FiO_2 table according to the ARDS Network

FiO_2 (%)	30	40	40	50	50	60	70	70	70	80	90	90	90	100
PEEP (cmH_2O)	5	5	8	8	10	10	10	12	14	14	14	16	18	18–24

ARDS, acute respiratory distress syndrome; FiO_2, fraction of inspired oxygen; PEEP, positive end-expiratory pressure.

performing PEEP titration for patients with ARDS guided by EIT, despite its level.

Who will take informed consent?

Information regarding the trial will be provided to the patient's next of kin in written form and verbally explained by the intensivist in charge after the patient is screened to be eligible. If the patient's next of kin agrees to participate, an informed consent signed by one of them will be obtained by the intensivist in charge before data are included in the study. These processes will be done within the first 24 hours after admission to intensive care unit (ICU).

Additional consent provisions for collection and use of participant data and biological specimens

No additional data or biological specimens will be obtained.

Interventions

Explanation for the choice of comparators

The PEEP setting for the control group will follow the lower PEEP/FiO_2 table proposed by the ARDS Network study.[23] Despite the numerous PEEP titration approaches that have been proposed for individualised PEEP setting, none has to date shown superiority over the others regarding patient-centred outcomes.[13 19] The PEEP/FiO_2 (table 1), therefore, still recommended as a standard approach worldwide and justifies its selection as the comparator in this trial. Previous clinical studies comparing the higher and lower PEEP/FiO_2 table showed no difference in ARDS mortality.[23 26] Moreover, we chose the lower PEEP/FiO_2 table rather than the higher one as it is a more popular and widely available practice in China. One possible explanation that lower PEEP is more preferred in the Chinese population is that the average body mass index (BMI) of the Chinese population is relatively low compared with that of the western populations,[27] a previous study has shown that obesity is associated with a higher risk of atelectasis and thus higher PEEP may be more beneficial in managing respiratory failure in obese patients.[28] Therefore, we preferred the lower PEEP/FiO_2 table as the comparator in order to keep it in accordance with the local practice.

Intervention description

Different managements will be implemented on the day of randomisation according to the grouping situation.

Intervention group

The intervention group will adopt an EIT-guided PEEP titration strategy.

Procedures:

1. Preparation: Patients will be sedated, with Richmond Agitation-Sedation Scale ≤−3, no spontaneous breathing, and sufficient airway suction of secretion will be performed. RM and PEEP titration process will be monitored by an EIT device (Pulmovista 500, Dräger Medical, Lübeck, Germany). A silicon belt with 16 surface electrodes will be placed around the patient's thorax transversely at the 4th–5th intercostal space according to the manufacturer's instructions.
2. RM: All patients will be ventilated under pressure control (PC) mode, and the following three different levels of recruitment pressure will be applied according to the patient's condition: (A) PC 15 cmH_2O+PEEP 24 cmH_2O (for patients with pressure of arterial oxygen (PaO_2)/FiO_2<100 mm Hg); (B) PC 15 cmH_2O+PEEP 21 cmH_2O (for patients with a PaO_2/FiO_2≥100 and <200 mm Hg); (C) PC 15 cmH_2O+PEEP 18 cmH_2O (for patients with a PaO_2/FiO_2≥200 and <300 mm Hg); these parameters will be maintained for 2 min and FiO_2 will be adjusted to 100% during this process. The lower pressure B or C will be applied to patients who are clinically evaluated to be intolerant to the higher pressure A or B.
3. PEEP titration: A decremental PEEP titration strategy will be applied after RM. The initial and final PEEP level will be set according to the previously applied RM pressure level: (A) For patients with PaO_2/FiO_2<100 mm Hg, the initial PEEP is 24 cmH_2O and the final PEEP level is 6 cmH_2O. (B) For patients with a PaO_2/FiO_2≥100 and <200 mm Hg, the initial PEEP is 21 cmH_2O and the final PEEP level is 6 cmH_2O. (C) For patients with a PaO_2/FiO_2≥200 and <300 mm Hg, the initial PEEP is 18 cmH_2O and the final PEEP level is 3 cmH_2O. The decremental PEEP trial will be conducted stepwise (3 cmH_2O each step) until reaching the final PEEP level. Each PEEP step will be maintained for 2 min before the next decrease.
4. EIT data recording: EIT data will be recorded continuously during the whole PEEP titration process and analysed offline with a customised software designed specifically for this trial (Matlab 2023, MathWorks, Natick, Massachusetts, USA). The percentages of regional collapse and overdistention will be estimated based on the regional compliance curve that is computed and recorded during the decremental PEEP

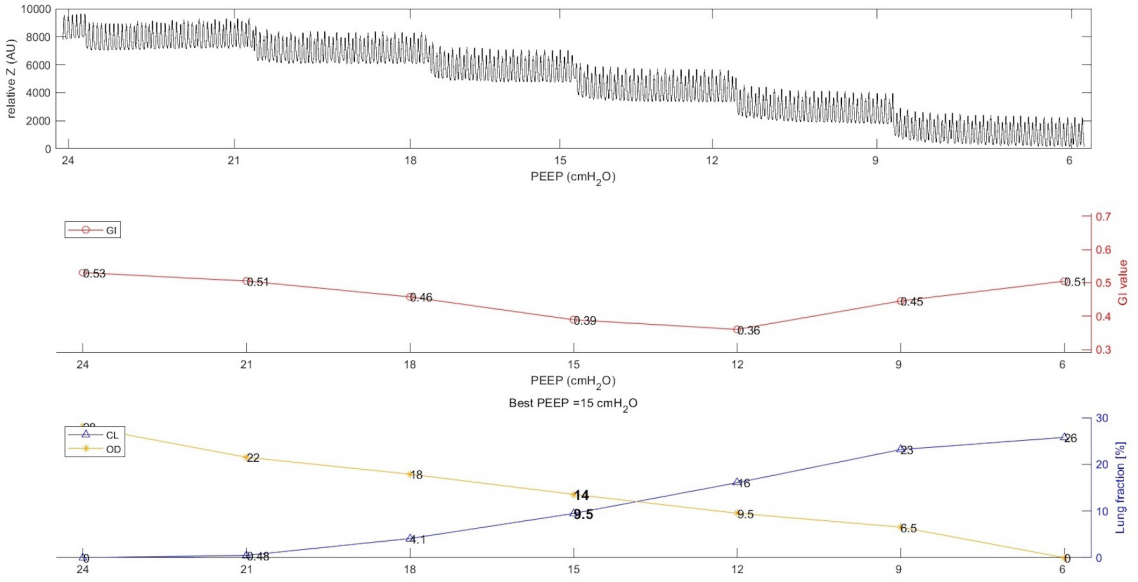

Figure 1 An example of an individualised positive end-expiratory airway pressure titration curve guided by electrical impedance tomography. In this case, the optimal PEEP is 15 cmH_2O. PEEP, positive end-expiratory pressure; GI, global inhomogeneity index.

titration.[29] The optimal PEEP level guided by EIT is defined as the PEEP level that corresponds to the intercept point of the cumulated collapse and overdistension percentage curves, which indicates the best compromise between regional collapse and overdistention. If the intercept point presents between two PEEP steps, the PEEP level that corresponds with a lower global inhomogeneity index is considered as the optimal PEEP.[30] An example of an individualised PEEP titration curve guided by EIT is shown in figure 1. RM will be performed once again after the PEEP titration process. After that, PEEP is set according to the optimal value guided by EIT for at least 12 hours.

5. Adjustment: PEEP is assessed daily according to the clinical situation. RM and EIT-guided PEEP titration are recommended once daily with the above procedures for the first 2 days (days 1 and 2) after the first RM and PEEP titration (day 0), but not mandatory. If clinical conditions do not allow further RM/PEEP titration (haemodynamic unstable or barotrauma, etc) or the attending clinician judges that further adjustment is unnecessary (satisfied with the current condition, etc), only once RM+EIT-guided PEEP titration at day 0 is also acceptable. The necessity for PEEP adjustment could be evaluated after at least 12 hours from the end of each time of EIT-guided PEEP titration. If PaO_2/FiO_2> 250 mm Hg and improves > 50 mm Hg compared with the previous day, PEEP is reduced gradually (by 2–3 cmH_2O every 4–8 hours). If the clinical manifestation or PaO_2/FiO_2 deteriorates after adjusting PEEP, derecruitment might occur and the PEEP setting will return to the optimal level determined by EIT. RM is performed again if PaO_2/FiO_2 does not improve and derecruitment is still considered after setting the PEEP to the previous level before adjustment. EIT-guided PEEP titration could be performed again after RM if necessary.

Control group

The practice of sedation will be the same as the intervention group. RM will not be performed as routine for the control group. PEEP will be set directly according to the lower PEEP/FiO_2 table from the ARDSNet table, as shown in table 1.

PEEP is adjusted according to the table. The times of RM performed as rescue therapy within the first 7 days are recorded if it is required due to clinical conditions.

Mechanical ventilation parameters and oxygenation goals for the two groups

The mechanical ventilation parameters and oxygenation goals for the two groups (refer to ARDSNet ventilation strategy) are shown in table 2.

Strategies to maintain oxygenation goals:

1. Prone positioning will be considered when PaO_2/FiO_2 ratio <150 mm Hg, or when PEEP > 10 cm H_2O, or when FiO_2 >60% in supine position.[31] Duration of prone positioning will be >12 hours per day,[32] the termination of prone positioning will be decided according to clinical situations by the clinician in charge.
2. Inhaled nitric oxide, if available, will be considered if oxygenation is not improved after receiving prone positioning.
3. If oxygenation goal cannot be maintained despite performing the above interventions, extracorporeal membrane oxygenation (ECMO) will be considered as rescue therapy.

Table 2 Mechanical ventilation parameters and oxygenation goals for the two groups

	Intervention EIT-PEEP	Control Table-PEEP
Recruitment manoeuvre	Once at day 0, then any time if necessary	Only as rescue therapy
Ventilation mode	VC/PC/PS	VC/PC/PS
Plateau pressure	≤ 30 cmH_2O	≤ 30 cmH_2O
Tidal volume	4–6 mL/kg PBW	4–6 mL/kg PBW
Respiratory rate and pH target	RR ≤35 bpm Adjust RR to maintain pH≥7.3	RR ≤ 35 bpm Adjust RR to maintain pH≥7.3
I:E	1:1~1:3	1:1~1:3
Oxygenation goals		
PaO_2	55–80 mm Hg	55–80 mm Hg
SpO_2	88%–95%	88%–95%

EIT, electrical impedance tomography; FiO_2, fraction of inspired oxygen; I:E, inspiratory to expiratory ratio; PaO_2, partial pressure of oxygen; PBW, predicted body weight; PC, pressure control; PEEP, positive end-expiratory pressure; RR, respiratory rate; SpO_2, blood oxygen saturation; VC, volume control.

Criteria for discontinuing or modifying allocated interventions

RM and PEEP titration for the intervention group will be discontinued if one of the following criteria is met: persistent drop of mean arterial pressure (MAP) > 20–30 mm Hg from baseline level; SpO_2<88%; new-onset arrhythmia. Data of these patients will be reserved for intention-to-treat analysis.

Strategies to improve adherence to interventions

Not applicable.

Relevant concomitant care permitted or prohibited during the trial

Relevant concomitant care such as low tidal volume ventilation and adjuvant therapies of ARDS will be the same for both groups according to the local ARDS therapy regulation in China.

Provisions for post-trial care

Ancillary and post-trial care will be the same as the standard local ARDS therapy. Adverse events will be monitored and managed timely according to the best-known practice. Compensation for trial-related harm will be provided in accordance with the corresponding national regulations.

Outcomes

- Primary outcome:
  1. Survival within 28 days from randomisation.
- Secondary outcomes:
  1. Length of ICU stay from randomisation to ICU discharge.
  2. Length of hospital stay from randomisation to hospital discharge.
  3. 28-day ventilator-free days from randomisation.
  4. Newly developed barotrauma: any newly developed pneumothorax, pneumomediastinum, subcutaneous emphysema or pneumatocele >2 cm detected on imaging studies within 7 days from randomisation, except those judged to be caused by invasive procedures.
  5. Survival at ICU discharge.
  6. Survival at hospital discharge.
  7. Change of Sequential Organ Failure Assessment (SOFA) score from baseline within first 2 days.

The plan for assessment and collection of outcomes and other trial data are discussed in the 'Plans for assessment and collection of outcomes and other trial data' section.

Participant timeline

The schedule of enrolment and intervention is shown in figure 2.

Sample size

The sample size is estimated using the sample size calculation formula for two-sample rates comparison.

The test level α is defined as 0.05, the type II error probability β is defined as 0.2. The ARDS mortality rate of the control group is estimated to be 45% according to a reported literature.[33] The ARDS mortality rate of the intervention group is estimated to be reduced to 34% (HR=0.75).[13] The sample size ratio of the intervention group and the control group is assumed to be 1:1, the required sample size calculated according to PASS V.15 software (PASS V.15.0.13, NCSS) is 614 subjects. Assuming a 10% drop-out rate, the final sample size of this study is 680, with 340 in each of the intervention group and the control group.

Recruitment

Any hypoxaemic patient admitted to the ICU will be screened for eligibility by the attending intensivist at the time of admission. Details of recruitment are mentioned in the 'Who will take informed consent' section. We intend to enrol a total of 680 patients. To achieve this target, we initially invited 28 centres to participate in this trial and attempt to invite more to join as the trial

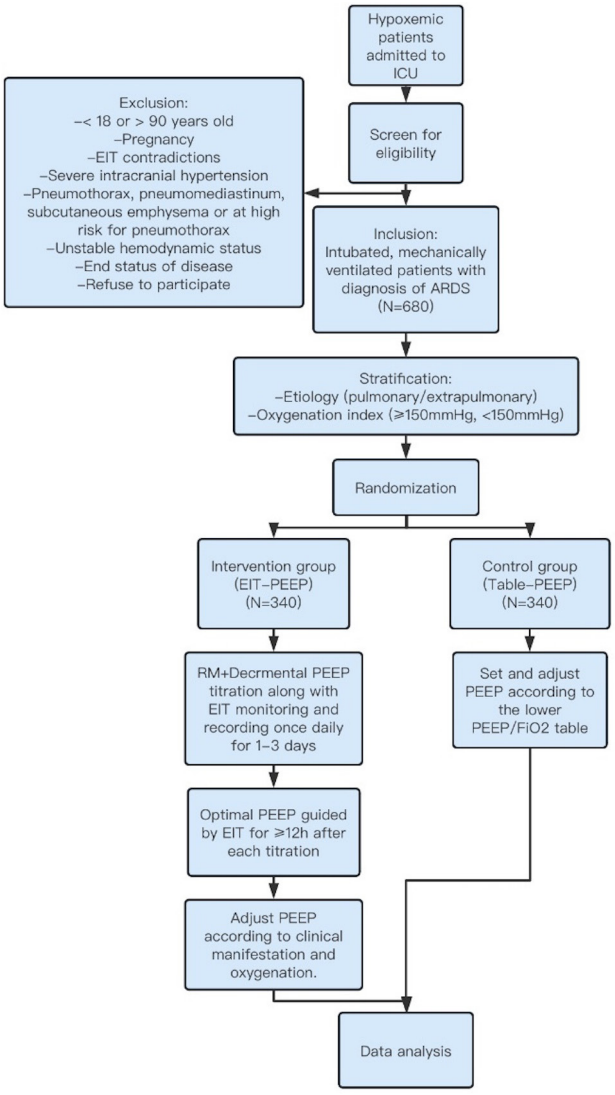

Figure 2 The schedule of enrolment and intervention. ARDS, acute respiratory distress syndrome; EIT, electrical impedance tomography; FiO_2, fraction of inspired oxygen; ICU, intensive care unit; PEEP, positive end-expiratory pressure.

proceeds. Online conferences with the trialists of all centres will be held once per month to discuss the existing problems regarding recruitment and other aspects of the trial, allow sharing experience about patient recruitment. Around 220 patients have been recruited by May 2023 and the estimation of complete recruitment is April 2025.

Assignment of interventions: allocation

Sequence generation, concealment mechanism, implementation

Patients will be assigned randomly in a 1:1 ratio to the intervention group (EIT-PEEP) and the control group (Table-PEEP). A website specifically for this RCT to achieve randomisation and allocation concealment was developed by a team of programmers who are not involved in this trial. Every investigator and independent clinician in charge will be provided with an account and password to access this website but with limited authorisation. After recruitment, the independent clinician in charge will fill in the patient's information on the website. The included patients will then be stratified according to the aetiology (pulmonary/extrapulmonary) and PaO_2/FiO_2 (≥150 mm Hg or <150 mm Hg). On the same website, randomisation and allocation concealment will be conducted. The group assignment will not be disclosed until after the patient is enrolled in the study and related information is recorded in the system.

Assignment of interventions: blinding

Who will be blinded

Intensivists and other care providers will not be blinded as the intervention will be obvious. The patients will not be aware of the intervention applied to them until the trial is finished, as they will be under mechanical ventilation and fully sedated during the intervention.

Procedure for unblinding if needed

There will be no circumstance under which emergency unblinding is essential to maintain trial safety, since the intensivist in charge and other care providers will not be blinded to the group assignment.

Data collection and management

Plans for assessment and collection of outcomes and other trial data

Data collection time points and parameters

1. Baseline data of patients (day 0)
   - Name of the clinical centre, admission number, name, gender, age, height, weight.
   - Admission time, ICU admission time, enrolment time, patient type (medical/surgical).
   - Primary diagnosis (the three major diagnoses that occasion ICU admission).
   - ARDS aetiology (pulmonary/extrapulmonary), time interval between ARDS onset and enrolment.
   - Acute Physiology and Chronic Health Evaluation (APACHE) II score, SOFA score.
   - Baseline respiratory parameters (tidal volume, respiratory rate, PEEP, FiO_2, plateau pressure, PaO_2/FiO_2).
2. 1 hour after intervention on day 0 (T1h)
   - Respiratory parameters (tidal volume, respiratory rate, PEEP, FiO_2, plateau pressure, PaO_2, $PaCO_2$, pH).
   - Haemodynamic parameters (heart rate, MAP, dosage of vasopressors if used).
   - Intervention group specified records: the highest PEEP level during the RM; the initial and final PEEP level during the PEEP titration process; whether PEEP titration is interrupted (if interrupted, record the reason); the best PEEP guided by EIT; EIT analysis diagram of the PEEP titration; whether the optimal PEEP determined by the EIT-guided PEEP titration is applied strictly within 24 hours after titration.
   - Control group specified record: whether RM is performed inevitably as rescue therapy due to worsened oxygenation.

3. Days 1–2
   - Respiratory parameters (tidal volume, respiratory rate, PEEP, FiO_2, plateau pressure, PaO_2, $PaCO_2$, pH).
   - Haemodynamic parameters (heart rate, MAP, dosage of vasopressors if used, intake-output balance).
   - Other: SOFA score.
   - Intervention group specified records: the highest PEEP level during the RM; the initial and final PEEP level during the PEEP titration process; whether PEEP titration is interrupted (if interrupted, record the reason); the best PEEP guided by EIT; whether the optimal PEEP determined by the EIT-guided PEEP titration is applied strictly within 12 hours after titration; whether RM and EIT-guided PEEP titration are repeated daily for day 1–2, if yes, archive the EIT analysis diagram.
   - Control group specified record: whether RM is performed inevitably as rescue therapy due to worsened oxygenation.
4. Day 7
   - Respiratory parameters (FiO_2, PaO_2, $PaCO_2$, pH).
   - If the patient is still on mechanical ventilation, include the followings (tidal volume, respiratory rate, PEEP, plateau pressure).
   - Use of additional treatments during the period: (1) prone positioning; (2) muscle relaxants (if yes, record the number of days using muscle relaxants); (3) ECMO; (4) use of norepinephrine or dopamine (if yes, record the number of days using norepinephrine or dopamine); (5) the number of days using sedative drugs; and (6) the number of days using analgesics.
   - Adverse event: occurrence of barotrauma during the period.
   - Intervention group specified record: the number of days that RM and PEEP titration are performed within 7 days.
   - Control group specified record: the number of days that RM is performed as rescue therapy within 7 days.
5. Day of discharge/death/withdrawal
   - Discharge date, ICU discharge date, death (if yes, record the date of death), days of mechanical ventilation within 28 days, total days of mechanical ventilation; record the reason if withdrawn from the trial.

A table of the schedule of enrolment, interventions and assessments can be seen in figure 3.

Measurement of outcomes: Most clinical data including respiratory parameters, haemodynamic parameters, survival at different time points, length of ICU and hospital stay, length of ventilation, use of vasopressor or muscle relaxant or sedative drug, implementation of additional treatment (eg, pronation, ECMO), implementation of RM and PEEP titration, could be retrieved directly from hospitalised medical records. SOFA scores and APACHE II scores will be evaluated by the clinician in charge. Arterial blood gas analysis will be performed

	STUDY PERIOD							
	Enrolment	Allocation	Post-allocation					
TIMEPOINTS	Day 0	Day 0	T0	T1h	Day1	Day2	Day7	Discharge/Death
Enrolment :								
Eligibility screen	×							
Informed consent	×							
Random allocation		×						
Interventions:								
Intervention group:								
Recruitment maneuver			×		×	×		
EIT-guided PEEP titration			×		×	×		
Control group:								
ARDSNet table			×	×	×	×	×	
Assessments:								
APACHE II & SOFA	×				×	×		
Respiratory parameters	×			×	×	×		
Hemodynamic parameters				×	×	×		
ABGA				×	×	×		
I/O					×	×		
Intervention group:								
Initial PEEP during titration				×	×	×		
Final PEEP during titration				×	×	×		
EIT-determinded optimal PEEP				×	×	×		
EIT-PEEP titration curve analysis				×	×	×		
Duration of setting optimal PEEP				×	×	×		
RM+PEEP titration(frequency)				×	×	×		
Control group:								
RM as rescue therapy (frequency)			×	×	×	×	×	
ECMO or Pronation(frequency & duration)	×		×	×	×	×	×	
Use of muscle relaxant(days)			×	×	×	×	×	
Use of NE or DA(days & dose)			×	×	×	×	×	
Use of sedative drugs(days)			×	×	×	×	×	
Use of analgesic(days)			×	×	×	×	×	
Assess for de novo barotrauma			×	×	×	×	×	
Assess for other ADEs			×	×	×	×	×	×
Survival			×	×	×	×	×	×
Total ventilation days								×

Figure 3 The schedule of enrolment, interventions and assessments. ABGA, arterial blood gas analysis; ADE, adverse events; APACHE, Acute Physiology and Chronic Health Evaluation; ARDS, acute respiratory distress syndrome; DA, Dopamine; ECMO, extracorporeal membrane oxygenation; EIT, electrical impedance tomography; NE, Norepinephrine; PEEP, positive end-expiratory pressure; RM, recruitment manoeuvre; SOFA, Sequential Organ Failure Assessment.

to obtain PaO_2, $PaCO_2$ and pH. For de novo barotrauma, chest imaging (X-ray or CT) will be performed if barotrauma is suspected according to clinical manifestations (diminished breath sounds, absent tactile or vocal fremitus, hyper-resonant percussion, subcutaneous emphysema, etc). As for EIT data, an EIT analysing software developed specifically for this trial will be provided uniformly to each trial centre by the lead centre, analysis diagram of the EIT-PEEP titration result will be generated automatically by the software after the titration process, and these analysis diagrams are then uploaded immediately by the clinician in charge to the specific website for further statistical analysis.

Plans to promote participant retention and complete follow-up

Not applicable.

Data management

Data will be input to the same specific website mentioned above, right after every single time point of data collection according to the above procedures. On the website, an electronic case report form (CRF) for each patient is created, clinicians in charge will input the data as required from the CRF. To ensure accuracy, a range check for data value is set for each item of input data.

The backup will be made automatically after each time of data entry. After reaching the research endpoint, data will be retrieved from the system and input to an EXCEL database (EXCEL 2019, Microsoft, Washington, USA) for further statistical analysis by the researcher from the lead centre. Incomplete data will be filled in according to medical records. The paper form of the CRF will be uniformly kept and stored by the researchers from the lead centre.

Confidentiality

In-depth explanation of the research purpose and assurance of confidentiality will be presented to the patient's family/legal representative before having them signed the informed consent and data collection. The web-based CRF system where data are input requires a personal account and password to access. Only clinicians in charge for data collection/input and investigators from the data monitoring committee (DMC) (see the 'Composition of the DMC, its role and reporting structure' section) have access. The authorisation is strictly limited. A coded ID number for each of the participants is used as identification, instead of their real name. The database is password protected. Paper form of the CRF and all other participant information will be stored in locked file cabinets at the lead centre and will be kept for 10 years without being disclosed to a third party. Participants are, at any time, authorised to correct, delete and restrict the use of their information if they are willing to.

Plans for collection, laboratory evaluation and storage of biological specimens for genetic or molecular analysis in this trial/future use

Not applicable, no biological specimens will be obtained for genetic or molecular analysis in this trial/future use.

Statistical methods

Statistical methods for primary and secondary outcomes

Statistical analysis will be conducted by using SPSS software (SPSS V.21.0, IBM).

1. Descriptive statistics: qualitative data such as gender and diagnosis will be described as frequency and percentage; quantitative data such as age, APACHE II score, SOFA score, BMI, haemodynamic and respiratory parameters, duration of ICU stay and mechanical ventilation will be described as means±SD or quartiles after confirming normality.
2. Qualitative data such as gender and diagnosis of the two groups will be analysed using the χ^2 test or Fisher's exact test; quantitative data including age, APACHE II score, BMI, haemodynamic and respiratory parameters, duration of ICU stay and mechanical ventilation of the two groups will be analysed using independent samples t-test or Mann-Whitney U test.
3. The 28-day mortality rate and occurrence of safety conditions (such as barotrauma) in the two groups will be described as frequency and percentage. Kaplan-Meier analysis with log-rank test will be used to evaluate the 28-day survival rate between two groups.
4. The outcomes will be measured based on the intention-to-treat principle, taking into account any protocol deviations.
5. Statistical significance is defined as $p \leq 0.05$ in the above statistical analyses.

Interim analyses

Interim analyses will be performed on the defined study endpoints when one or two patients in each arm have been randomised. A DMC will review and discuss the results in a blinded fashion with the trial steering committee (TSC) from which decisions on the continuation of the study or modification of the study protocol will be made.

Methods for additional analyses (eg, subgroup analyses)

Further evaluation of the treatment effect on the same primary endpoint will be performed in the following subgroups: (1) $PaO_2/FiO_2 \geq 150$ mm Hg vs <150 mmHg; (2) aetiology (pulmonary ARDS vs extrapulmonary ARDS), using Cox proportional hazards models.

Plans to give access to the full protocol, participant-level data and statistical code

The protocol can be obtained from https://clinicaltrials.gov/, datasets used and/or analysed during the current study and statistical results are available from the corresponding author on reasonable request.

Oversight and monitoring

Composition of the coordinating centre and TSC

The coordinating centre is the Department of Critical Care Medicine, State Key Laboratory of Complex Severe and Rare Diseases, Peking Union Medical College Hospital, Peking Union Medical College, Chinese Academy of Medical Sciences, Beijing, China. Its responsibility includes but not limited to the design and refinement of the study protocol, identifying eligible centres and providing necessary instructions for participating centres, preparation of the web-based randomisation software and CRF, establishment of the TSC and the DMC, organising meeting among centres, publication of study reports. The TSC is composed of the lead investigators from the leading centre, they monitor the progress of the study, communicate with the DMC and adjust the study protocol if needed, decide the continuation or termination of the study after discussing the results of interim analyses with the DMC.

Composition of the DMC, its role and reporting structure

A DMC is composed of statisticians and clinicians independent from the sponsor and other trial investigators. DMC will oversee the data collection regularly, ensure data consistency, check for missing data, provide advice from the perspective of data quality on refinement of the trial conduct to the TSC, as well as regarding the continuation of the study based on interim analyses. Only the DMC is allowed to unblind the results before the end of the trial.

Adverse event reporting and harms

All trial-related adverse events should be reported to the leading centre within 24 hours. The events will be managed timely according to the best-known practice. Details will be recorded and reported to the Endpoint Adjudication Committee at once.

Frequency and plans for auditing trial conduct

A dedicated auditing team independent from the sponsor and trial investigators is formed to perform trial audit considering all participating centres mainly by exploring existing data once per month. From which they verify inclusion and exclusion criteria of each enrolled participants, monitor adherence of study procedures and adverse event reporting. Access to participants' medical records will be provided as required. Site visit will be considered in centres which have anomalous rates of enrolment, withdrawal or reported adverse events.

Plans for communicating important protocol amendments to relevant parties (eg, trial participants, ethical committees)

Important protocol amendments will be communicated to the ethics committee of the participating hospitals before implementation, any modification will be recorded and updated at https://clinicaltrials.gov/.

Ethics and dissemination

The trial is approved by the Institutional Research and Ethics Committee of the Peking Union Medical College Hospital. Registered at ClinicalTrials.gov, with the registration number NCT05307913. The study design follows the principles of the Declaration of Helsinki. Signed informed consent is obtained from all participating patients or the next of kin after they are provided with written and oral information about the trial, and before enrolment. The RCT results will be disseminated via journal publications after the manuscript is finished regardless of the statistical significance of the result.

Patient and public involvement

Patients or the public are not involved in the design, or conduct, or reporting, or dissemination plans of this clinical trial.

DISCUSSION

The result of a recent multicentre RCT draws attention to the necessity to align mechanical ventilation strategies with lung morphology.[34] Lung CT scan, among the several imaging methods that have been used to evaluate PEEP-induced lung recruitment, is the reference method.[35] But the time consumption and risk of transferring patient make CT scan inefficient and less feasible to practice routinely for critically ill patients in ICU. An early experimental study has found that relative change of regional impedance assessed by EIT strongly correlated with the recruited lung volume measured by CT.[36] Several clinical studies have proven the feasibility and shown potential benefits of EIT-based PEEP titration in patients with ARDS, including improved oxygenation and respiratory system compliance, higher weaning success rate and reduced mortality.[22 37] A recent meta-analysis that included 8 clinical trials with a total of 222 patients has demonstrated that EIT-based PEEP titration was associated a with higher PaO_2/FiO_2 ratio as compared with conventional PEEP setting strategies.[38] But the included studies are small-sample trials and only two out of eight are RCT. Moreover, selection and measurement biases are also concerned in all the studies. Our research team has performed a single-centre RCT including 117 ARDS patients which showed a 6% absolute decrease in mortality in the EIT-guided PEEP titration group when compared with the low PEEP/FiO_2-table group.[21] This statistically insignificant result warrants further large sample RCT to validate the EIT-guided PEEP setting in ARDS with less heterogeneity.

This is a multicentre clinical randomised controlled study that aims to compare the effect of EIT-guided PEEP titration strategy and traditional lung protective ventilation strategy on the prognosis of ARDS patients. With an estimated sample size of 680, this RCT is to date the first of its size regarding the efficacy of EIT-guided PEEP titration. If our study demonstrates that the PEEP titration guided by EIT significantly reduces mortality, duration of mechanical ventilation and ICU length stay, without increasing the incidence of barotrauma, it would provide evidence of great importance to alter the current mechanical ventilation strategies for ARDS patients, improving the prognosis and reducing treatment expense.

There are several limitations in this protocol. The role of RM on ARDS mortality is controversial. Some studies showed that RM did not reduced mortality and may lead to clear harmful effect.[13] Latest guideline recommended against performing RM routinely in patients with ARDS.[39] Therefore, we have no reasons to perform RM routinely when PEEP titration is not performed. To reduce the biases that may occur in such design, further analysis that concerns the differences between the outcomes of the control group with or without RM performed would be considered. Furthermore, a limitation with the method was that the optimal PEEP at the intercept point of the cumulated alveolar collapse and overdistension does not exclude the presence of alveolar collapse nor overdistension. A possible subanalysis could be performed to identify the subgroup with a high level of overdistension in combination of a high level of collapse at the optimal PEEP. The proposed intercept between overdistension and collapse might be not appropriate to these patients. With the improvement of the evidences for prone positioning, its implementation will become increasingly proactive. However, the specific execution may vary across different centres. The indications for prone positioning in this protocol are not a mandatory standard but rather recommendations. Considering the actual execution differences at various subcentres, subsequent analyses may be considered to evaluate the influence of prone positioning as a potential variable.

Trial status

The trial was registered on the website https://clinicaltrials.gov/ with the registration number NCT05307913 on 1 April 2022. The study is actively proceeding at 29 sites in China, recruitment began on 10 April 2022 and is planned to be finished by April 2025, the whole study is estimated to be completed by April 2025. A total of 220 patients had already been recruited until 31 May 2023, we are passionately inviting more centres to join us. This is protocol version 4.1, dated December 2023.

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