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The effects of increased positive end-expiratory pressure on intracranial pressure and different respiratory mechanics in acute respiratory distress syndrome: a protocol of a prospective observational study

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Abstract

Introduction: There are concerns that the use of positive end-expiratory pressure (PEEP) in patients with brain injury may potentially elevate intracranial pressure (ICP). However, the transmission of PEEP into the thoracic cavity depends on the properties of the lungs and the chest wall. When chest wall compliance is low, PEEP can significantly increase intrathoracic pressure. In the present study, we investigate the effects of PEEP on the intrathoracic pressure and ICP by oesophageal pressure measurement.

Methods and analysis: This study is a prospective, single-centre, observational study of severe brain injury patients. Acute respiratory distress syndrome patients with ventricular drainage will be enrolled. An oesophageal balloon catheter will be inserted to measure oesophageal pressure. Patients will be sedated and paralyzed; airway pressure and oesophageal pressure will be measured during end-inspiratory occlusion and end-expiratory occlusion. Compliance of the chest wall, the lungs and the respiratory system will be calculated. We will classify each patient based on whether the difference in ICP in response to high or low PEEP levels is above or below the median for the study population. Two groups will thus be compared.

Ethics and dissemination: The study protocol and consent forms were approved by the Institutional Review Board of Fujian Provincial Hospital. Study findings will be disseminated through peer-reviewed publications and conference presentations.

Trail registration: The study was registered on January 26, 2016, at ClinicalTrials.org (ClinicalTrials.gov Identifier: NCT02670733)

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4 **Key words:** *Oesophageal* pressure; acute respiratory distress syndrome; positive
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6 end-expiration pressure; intracranial pressure
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STRENGTHS AND LIMITATIONS OF THIS STUDY

- We will investigate the effects of PEEP on intrathoracic pressure and ICP via oesophageal pressure measurements.
- We also consider the lung recruitability which may affect the interaction between PEEP and ICP via the measurement of PEEP volume.
- The main limitation of this study is the absence of widely accepted thresholds to identify the responsiveness of ICP to increased PEEP, and we therefore arbitrarily divided patients into two groups using the median of the study population.

INTRODUCTION

Acute respiratory distress syndrome (ARDS), which is characterized by severe hypoxemia and alterations in lung function, is common in critically ill patients. Numerous authors have reported that a significant portion of brain injury patients can develop pulmonary complications, including ARDS and neurogenic pulmonary edema (NPE).[1-6] Ventilation strategies to protect the lungs should be applied in patients with ARDS.[7] The mainstays of lung-protective ventilation strategies are to (1) limit tidal volume; (2) limit end-inspiratory plateau pressure (P_{plat}); and (3) provide adequate positive end-expiratory pressure (PEEP) to keep the lungs open and prevent alveolar collapse.

There are concerns that the use of PEEP for the treatment of pulmonary complications in patients with a brain injury could elevate ICP and deteriorate neurological status. Both respiratory system compliance and ventricular compliance are thought to contribute to the elevation of ICP when PEEP increases.[8-11] In theory, PEEP may increase ICP by increasing intrathoracic pressure and diminishing venous return. However, the transmission of PEEP into the thoracic cavity depends on the properties of the lungs and chest wall. An experimental study conducted by Chapin et al. showed that when chest wall compliance is low, PEEP can significantly increase intrathoracic pressure, whereas low lung compliance can minimize airway pressure transmission.[12] Lung compliance is generally recognized to decrease in ARDS patients due to extensive alveolar collapse. However, it has been reported that the elastance ratio (the ratio between the elastance of the chest wall and the respiratory

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4 system, where elastance is the reciprocal of compliance) may vary from 0.2 to 0.8.[13]

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6 Therefore, it is important to distinguish between the compliance of the chest wall and
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8 the lungs when investigating the effects of PEEP on ICP.
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11 Intrathoracic pressure (pleural pressure) is difficult to measure in clinical situations,
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13 and oesophageal pressure (P_{es}) is considered a surrogate of intrathoracic pressure.[14

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15 15] In the present study, we will investigate the effects of PEEP on intrathoracic
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17 pressure and ICP by measuring P_{es} .
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METHODS

Study design overview

The present study is a prospective, single-centre, observational study of patients with severe brain injuries.

Study setting and population

The study setting is the surgical intensive care unit (SICU) (22 beds), at Fujian Provincial Hospital (2500 beds), Fujian Provincial Clinical College of Fujian Medical University, Fuzhou, China.

All patients admitted to the SICU will be consecutively screened for study eligibility.

Inclusion criteria are as follows:

- 1) Aged 18 years or above;
- 2) Glasgow Coma Score ≤ 8 ;
- 3) Ventricular ICP monitor placement for ICP monitoring and cerebrospinal fluid (CSF) drainage;
- 4) Need for mechanical ventilation with PEEP; and
- 5) ARDS diagnosis according to the Berlin Definition.[7]

Exclusion criteria are as follows:

- 1) Hemodynamic instability requiring more than 10 $\mu\text{g}/\text{kg}/\text{min}$ dopamine or more than 0.5 $\mu\text{g}/\text{kg}/\text{min}$ norepinephrine;[10]
- 2) ICP > 25 mmHg;

- 3) Oesophageal varices;
- 4) History of oesophageal or gastric surgery;
- 5) Evidence of active air leak from the lung, including bronchopleural fistula, pneumothorax, pneumomediastinum, or existing chest tube; and
- 6) History of chronic obstructive pulmonary disease.

Baseline data collection

After enrolment, the following baseline data will be collected:

Demographic data: age, gender, height, and predicted body weight, which is calculated as $50 + 0.91 * (\text{centimetres of height} - 152.4)$ for males and $45.5 + 0.91 * (\text{centimetres of height} - 152.4)$ for females.[16]

Clinical data: primary diagnosis, type of brain injury (traumatic brain injury, stroke, postoperation for brain tumour), type of brain lesion (bilateral or unilateral), Acute Physiology and Chronic Health Evaluation II score (APACHE II) at the time of ICU admission, Simplified Acute Physiology Score II (SAPS II) on the day of enrolment, and duration of mechanical ventilation prior to enrolment.

Mechanical ventilation and blood gas at baseline: PEEP, FiO_2 , partial pressure of oxygen in arterial blood (PaO_2), $\text{PaO}_2/\text{FiO}_2$ (P/F ratio), PaCO_2 and pH.

Baseline ICP and haemodynamic parameters: HR, blood pressure, central venous pressure (CVP) and CVP change during the passive leg raising test.

Ventricular compliance measurement

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3
4 ICP will be measured with a ventricular ICP monitor (Codman, Johnson & Johnson,
5
6 Raynham, MA, USA). To measure ventricular compliance, 2 mL of CSF will be
7
8 drained, and the ICP value before and after CSF drainage will be recorded. Ventricular
9
10 compliance will be calculated as follows:
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14 Ventricular compliance = $2 / (\text{ICP before CSF drainage} - \text{ICP after CSF drainage})$

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16 (Formula 1).
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21 **Placement of oesophageal balloon catheter**

22
23 We will use the SmartCath-G adult nasogastric tube with an oesophageal balloon
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25 (7003300, CareFusion Co., Yorba Linda, CA, USA) in this study. Patients will remain
26
27 in a supine position with the head of the bed elevated to 30° during the study period.
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30 After anesthetizing the nose and oropharynx with 10% lidocaine spray, the
31
32 oesophageal balloon catheter will be inserted through the nostril to a depth of 60 cm.
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36 The intra-gastric position of the distal part of the catheter will be confirmed by
37
38 aspiration of gastric juice and auscultation of air insufflations into the stomach. After
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41 confirmation of the catheter position, the balloon will be inflated with 1.5 mL of air
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43 [17 18], and the proximal part of the catheter will be connected to the pressure
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46 transducer. Subsequently, the catheter will be slowly withdrawn, and the dynamic
47
48 occlusion test will be performed.[19] An end-expiratory occlusion will be performed
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50
51 until three to five spontaneous inspiratory efforts are made against the end-expiratory
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53 occlusion. The ratio of the change in P_{es} to the change in airway pressure ($\Delta P_{es}/\Delta P_{aw}$)
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56 will be calculated. The catheter will be considered correctly positioned when the
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4 $\Delta P_{es}/\Delta P_{aw}$ ratio during the occlusion test is in the range of 0.8 to 1.2.[20-22] In
5
6 paralyzed patients, the occlusion test will be performed by applying manual
7
8 compression on the rib cage during the end-expiratory occlusion.
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11 12 13 14 **Pressure measurements**

15
16 Flow will be measured with a Fleisch pneumotachograph (Vitalograph Inc., Lenexa,
17
18 KS, USA) inserted between the Y-piece of the ventilator circuit and the endotracheal
19
20 tube. The volume will be obtained by electrical integration of the flow signal. Airway
21
22 pressure (P_{aw} , located distal to the pneumotachograph) and P_{es} will be measured with
23
24 two differential pressure transducers (KT 100D-2, Kleis TEK di Cosimo Micelli, Italy,
25
26 range: +/- 100 cmH₂O). The Fleisch pneumotachograph and pressure transducers will
27
28 be connected to an ICU-Lab Pressure Box (ICU Lab, KleisTEK Engineering, Bari,
29
30 Italy) by 80 cm tube lines. The signals will be displayed continuously and saved
31
32 (ICU-Lab 2.5 Software Package, ICU Lab, KleisTEK Engineering, Bari, Italy) on a
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34 laptop for further analysis at a sample rate of 200 Hz. The pressure transducer will be
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36 calibrated with a water column. The pneumotachograph will be calibrated with a 1-L
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38 calibration syringe (SN: 554-2266, Hans Rudolph, Inc. Shawnee, KS, USA).
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49 **Respiratory mechanics measurements**

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51 After placement of the oesophageal balloon catheter, patients will be sedated and
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53 paralyzed via intravenous infusion of 5 mg of midazolam, 0.1 mg of fentanyl, and 50
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55 mg of rocuronium. Mechanical ventilation will be set at a volume control ventilation,
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4 constant flow, an inspiratory–expiratory ratio of 1:2, and a tidal volume of 6 to 8
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6 mL/kg of predicted body weight. The initial respiratory rate will be set at 20/min and
7
8 will be adjusted to maintain the partial pressure of carbon dioxide (PaCO₂) value at
9
10 approximately 35 to 40 mmHg. PEEP will be set as the baseline level. The
11
12 oxygenation goal will be maintained constant at a pulse oxygen saturation (SpO₂)
13
14 above 90% by adjusting the fraction of inspired oxygen concentration (FiO₂). After a
15
16 30 min stabilization period, ICP and ventricular compliance will be measured at these
17
18 baseline mechanical ventilation settings. Data on blood gas will also be obtained. An
19
20 end-inspiratory occlusion and an end-expiratory occlusion will be performed, and
21
22 plateau pressure (P_{plat}) and total PEEP (PEEP_{tot}) will be recorded. P_{es} during
23
24 end-inspiratory occlusion and end-expiratory occlusion will also be recorded.
25
26 Expiratory tidal volume (V_{te}) will also be recorded, and the compliance of the lungs
27
28 (C_l), the chest wall (C_{cw}) and the respiratory system (C_{rs}) will be calculated as
29
30 follows:
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$$39 \quad C_{rs} = V_{te} / (P_{plat} - PEEP_{tot}) \text{ (Formula 2)}$$

$$40 \quad C_{cw} = V_{te} / (P_{es-plat} - P_{es-PEEP}) \text{ (Formula 3)}$$

$$41 \quad C_l = V_{te} / [(P_{plat} - P_{es-plat}) - (PEEP_{tot} - P_{es-PEEP})] \text{ (Formula 4)}$$

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46 P_{es-plat}: oesophageal pressure at end-inspiration; P_{es-PEEP}: oesophageal pressure at
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48 end-expiration.
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51 If the patient's PEEP level is below 15 cmH₂O, the PEEP will be adjusted to 15
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53 cmH₂O. If the PEEP level is equal to or greater than 15 cmH₂O, the PEEP will be
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55 remained unchanged. The PEEP level will be maintained for 30 min, and ICP,
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4 ventricular compliance, haemodynamic status (HR, BP and CVP), blood gas analysis,
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6 and respiratory mechanic data will be collected as described above.
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9 Thereafter, the recruitment volume induced by PEEP will be measured as follows:

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11 The RR will be decreased to 6 breaths/min with the inspiratory time unchanged, and

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13 PEEP will be decreased to 5 cmH₂O. The PEEP volume will be measured as follows:

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15 PEEP volume = (the first V_{te} after PEEP adjustment) – (the last V_{te} before PEEP
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17 adjustment). (Formula 5)
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21 After the measurement of PEEP volume, RR will be increased to the baseline level
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23 with PEEP remaining at 5 cmH₂O. After a 5 min stabilization period, data on ICP,
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25 ventricular compliance, haemodynamic status (HR, BP and CVP), blood gas analysis,
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27 and respiratory mechanics will be obtained as described above.
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31 Recruitment volume induced by PEEP will be defined as follows:

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33 Recruitment volume = PEEP volume – ΔPEEP * C_{rs} at PEEP_{Low} (Formula 6)

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35 Where “10 * C_{rs} at low PEEP” is the minimal predicted increase in lung volume,
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37 which is the smallest possible increase in lung volume induced by PEEP.[23]
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41 A flow chart of the study procedure is shown in Figure 1.
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44 45 46 **Adverse event management and emergency termination of the study** 47

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49 Patients will be closely monitored during the study period. Taking into account the
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51 potential adverse effects of PEEP, emergency interventions will be provided when the
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53 following occur:
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57 1. Abrupt increase of ICP greater than 25 mmHg that persists for > 5 minutes. A bolus
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4 of 125 mL mannitol infusion will be administered.

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6 2. BP decrease to below 90/60 mmHg or a systolic BP decrease of > 40 mmHg; 100
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8 mL of crystalloid fluid infusion will be administered.

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11 The study will be continued if the patient is responsive to the interventions (i.e., ICP
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13 decreases or BP increases); otherwise, the study will be terminated and further
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15 interventions for increased ICP or decreased BP will be provided.
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20 21 **Study endpoints**

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23 The primary endpoint is the influence of PEEP on ICP. There are two PEEP
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25 adjustments during the study procedure as follows: from baseline PEEP to high-level
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27 PEEP (15 cmH₂O) and from high-level PEEP to low-level PEEP (5 cmH₂O). We will
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29 calculate the change in ICP per 1 cmH₂O change in PEEP to standardize the influence
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31 of PEEP on ICP during the increase or decrease of PEEP.
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35 Secondary endpoints include the identification of possible contributors to the effects
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37 of PEEP on ICP and the investigation of the influence of PEEP on haemodynamic
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39 parameters, including CVP, MAP and cerebral perfusion pressure.
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45 46 **Statistical analysis**

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48 We will classify each patient into one of two groups according to the median value of
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50 ICP responsiveness to PEEP in the overall study population. The two groups will
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52 consist of patients with ICP responsiveness below the median value and ICP
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54 responsiveness above the median ICP value.
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4 Baseline characteristics will be evaluated by univariate analysis. Categorical variables
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6 will be presented as numbers and percentages and analysed by the χ^2 -test. Continuous
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8 variables will be assessed for normal distribution and presented as the mean and
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10 standard deviation or median and inter-quartile range as appropriate. Comparisons of
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12 continuous variables will be performed using Student's t-test for normally distributed
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14 variables and the Mann-Whitney U test for non-normally distributed variables. A
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16 multivariate logistic regression analysis will be performed using forward procedures
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18 with factors demonstrating $P < 0.20$ in univariate logistic regression analysis. All tests
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20 of significance will be at the 5% significance level and will be two-sided. Analyses
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22 will be performed with SPSS 19.0 (IBM Corporation, New York, USA).
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31 **Sample size calculation**

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33 Prospective sample size calculations are performed using G*Power Software (sample
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35 size calculating software package provided by the G*Power Team, Germany,
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37 downloaded from <http://www.gpower.hhu.de/en.html>). We will need to study 30
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39 subjects to be able to reject the null hypothesis that the means of the two groups are
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41 equal with a probability (power) of 0.8. The Type I error probability with testing this
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43 null hypothesis is 0.05.
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Trial registration, ethical aspects and informed consent

The study protocol and consent forms were approved on September 30, 2015, by the Institutional Review Board of Fujian Provincial Hospital. The study was registered on January 26, 2016, at ClinicalTrials.org (ClinicalTrials.gov Identifier: NCT02670733).

After patients' eligibility for the study is confirmed, the study coordinator will be introduced to the patients' families. The ICU physician will emphasize the credentials of the study coordinator and communicate that this person will discuss a research programme for which the patient is qualified to participate. Every relevant aspect of the project will be described. The study coordinator will stop frequently, ask if there are any questions, and request that the family repeat back in their own words what is being discussed to ensure that the family understands the study. The study coordinator will be especially careful to assure the family that they are free to decline consent without consequences and that they can withdraw consent at any time without impact on treatment. Family members will be provided with contact information for the study coordinator, the local co-investigator and the local Ethical Committee. Written consent will be obtained in the presence of a witness.

Dissemination plan

Results of the trial will be submitted to an international peer-reviewed journal. The results will also be presented at national and international conferences relevant to the subject fields.

DISCUSSION

Previous studies have demonstrated that in patients with low Crs, PEEP exerts no significant effects on cerebral haemodynamics.[10] However, compliances of the chest wall and the lungs were not distinguished in that previous study. In another study that examined chest wall and lung compliance, the authors did not investigate the effects of increased PEEP on ICP.[12] In the present study, we aim to investigate the effects of PEEP on intrathoracic pressure and ICP by measuring P_{es} .

Lung recruitment may occur when PEEP is adjusted from 5 cmH₂O to 15 cmH₂O, which may contribute to variations in lung compliance. Therefore, we will measure PEEP volume to estimate whether a patient's lung is recruitable or non-recruitable.[23]

We speculate that increased PEEP can have a greater effect on ICP in patients with greater recruitability.

We will classify each patient with a high or low responsiveness of ICP to increased PEEP based on whether the difference between ICP at 5 cmH₂O and ICP at 15 cmH₂O is above or below the median for the study population. Because there is no widely accepted threshold to identify the responsiveness of ICP to increased PEEP, the division of patients into two groups is reasonable and enables us to compare differences between the two groups of patients.

Authors' contributions

HC, RGY and JXZ participated in the design of the study and drafted the manuscript.

MX, YLY, KC, JQX and YRZ participated in the design of the study. All authors edited the manuscript and read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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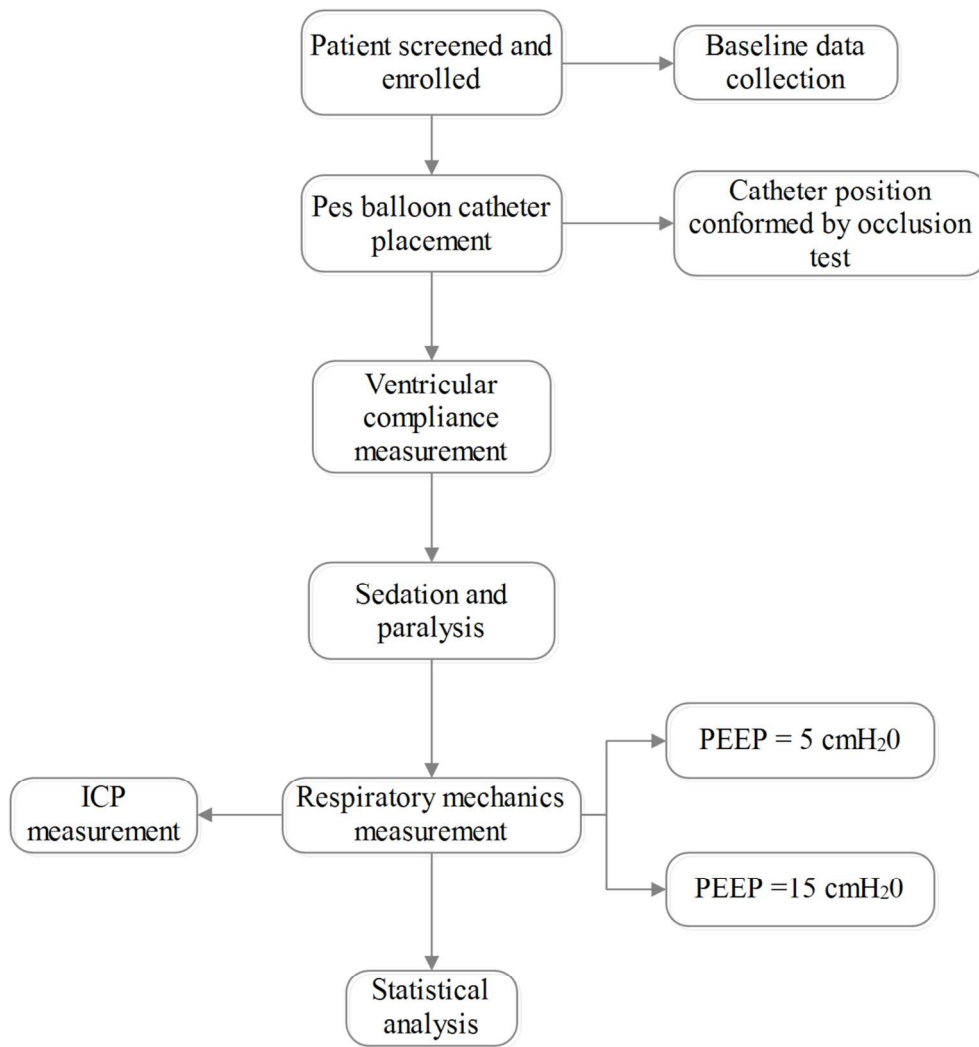
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The effects of increased positive end-expiratory pressure on intracranial pressure in acute respiratory distress syndrome: a protocol of a prospective physiological study

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6 **in acute respiratory distress syndrome: a protocol of a prospective physiological**
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8 **study**
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Abstract

Introduction: There are concerns that the use of positive end-expiratory pressure (PEEP) in patients with brain injury may potentially elevate intracranial pressure (ICP). However, the transmission of PEEP into the thoracic cavity depends on the properties of the lungs and the chest wall. When chest wall compliance is low, PEEP can significantly increase pleural pressure. In the present study, we investigate the different effects of PEEP on the pleural pressure and ICP in different respiratory mechanics.

Methods and analysis: This study is a prospective, single-centre, physiological study of severe brain injury patients. Acute respiratory distress syndrome patients with ventricular drainage will be enrolled. An oesophageal balloon catheter will be inserted to measure oesophageal pressure. Patients will be sedated and paralyzed; airway pressure and oesophageal pressure will be measured during end-inspiratory occlusion and end-expiratory occlusion. Compliance of the chest wall, the lungs and the respiratory system will be calculated at the PEEP level of 5 cmH₂O, 10 cmH₂O and 15 cmH₂O. We will classify each patient based on the maximal Δ ICP/ Δ PEEP is above or below the median for the study population. Two groups will thus be compared.

Ethics and dissemination: The study protocol and consent forms were approved by the Institutional Review Board of Fujian Provincial Hospital. Study findings will be disseminated through peer-reviewed publications and conference presentations.

Trial registration: The study was registered on January 26, 2016, at ClinicalTrials.org (ClinicalTrials.gov Identifier: NCT02670733)

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4 **Key words:** *Oesophageal* pressure; acute respiratory distress syndrome; positive
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For peer review only

STRENGTHS AND LIMITATIONS OF THIS STUDY

- We will investigate the effects of PEEP on pleural pressure and ICP via oesophageal pressure measurements.
- We also consider the lung recruitability which may affect the interaction between PEEP and ICP via the measurement of recruitment volume.
- The main limitation of this study is the absence of widely accepted thresholds to identify the responsiveness of ICP to increased PEEP, and we therefore arbitrarily divided patients into two groups using the median of the study population.

INTRODUCTION

Acute respiratory distress syndrome (ARDS), which is characterized by severe hypoxemia and alterations in lung function, is common in critically ill patients. Numerous authors have reported that a significant portion of brain injury patients can develop pulmonary complications, including ARDS and neurogenic pulmonary edema (NPE).[1-6] Ventilation strategies to protect the lungs should be applied in patients with ARDS.[7] The mainstays of lung-protective ventilation strategies are to (1) limit tidal volume; (2) limit end-inspiratory plateau pressure (P_{plat}); and (3) provide adequate positive end-expiratory pressure (PEEP) to keep the lungs open and prevent alveolar collapse.

There are concerns that the use of PEEP for the treatment of pulmonary complications in patients with a brain injury could elevate intracranial pressure (ICP) and deteriorate neurological status. Both respiratory system compliance and ventricular compliance are thought to contribute to the elevation of ICP when PEEP increases.[8-11] In theory, PEEP may increase ICP by increasing pleural pressure and diminishing venous return. However, the transmission of PEEP into the thoracic cavity depends on the properties of the lungs and chest wall. An experimental study conducted by Chapin et al. showed that when chest wall compliance is low, PEEP can significantly increase intrathoracic pressure, whereas low lung compliance can minimize airway pressure transmission.[12] Lung compliance is generally recognized to decrease in ARDS patients due to extensive alveolar collapse. However, it has been reported that the elastance ratio (the ratio between the elastance of the chest wall and the respiratory

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4 system, where elastance is the reciprocal of compliance) may vary from 0.2 to 0.8.[13]

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6 Therefore, it is important to distinguish between the compliance of the chest wall and
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8 the lungs when investigating the effects of PEEP on ICP.
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11 We hypothesise that PEEP have greater influence on ICP in patients with higher
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13 elastance ratio (e.g. the lung compliance is high and/or the chest wall compliance is
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15 low). To test the hypothesis, we need to measure the airway pressure and pleural
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17 pressure to calculate the compliances of the lung and the chest wall. However,
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19 pleural pressure is difficult to measure in clinical situations, and oesophageal pressure
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21 (P_{es}) is considered a surrogate of pleural pressure.[14 15] In the present study, we will
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23 investigate the effects of PEEP on pleural pressure and ICP by measuring P_{es} .
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METHODS

Study design overview

The present study is a prospective, single-centre, physiological study of patients with severe brain injuries.

Study setting and population

The study setting is the surgical intensive care unit (SICU) (22 beds), at Fujian Provincial Hospital (2500 beds), Fujian Provincial Clinical College of Fujian Medical University, Fuzhou, China.

All patients admitted to the SICU will be consecutively screened for study eligibility.

Inclusion criteria are as follows:

- 1) Aged 18 years or above;
- 2) Glasgow Coma Score ≤ 8 ;
- 3) Ventricular ICP monitor placement for ICP monitoring and cerebrospinal fluid (CSF) drainage;
- 4) Need for mechanical ventilation with PEEP; and
- 5) ARDS diagnosis according to the Berlin Definition.[7]

Exclusion criteria are as follows:

- 1) Hemodynamic instability requiring more than 10 $\mu\text{g}/\text{kg}/\text{min}$ dopamine or more than 0.5 $\mu\text{g}/\text{kg}/\text{min}$ norepinephrine;[10]
- 2) ICP > 25 mmHg;

- 3) Decompressive craniectomy was performed;
- 4) Oesophageal varices;
- 5) History of oesophageal or gastric surgery;
- 6) Evidence of active air leak from the lung, including bronchopleural fistula, pneumothorax, pneumomediastinum, or existing chest tube; and
- 7) History of chronic obstructive pulmonary disease.

Baseline data collection

After enrolment, the following baseline data will be collected:

Demographic data: age, gender, height, and predicted body weight, which is calculated as $50 + 0.91 * (\text{centimetres of height} - 152.4)$ for males and $45.5 + 0.91 * (\text{centimetres of height} - 152.4)$ for females.[16]

Clinical data: primary diagnosis, type of brain injury (traumatic brain injury, stroke, postoperation for brain tumour), type of brain lesion (bilateral or unilateral), Acute Physiology and Chronic Health Evaluation II score (APACHE II) at the time of ICU admission, Simplified Acute Physiology Score II (SAPS II) on the day of enrolment, and duration of mechanical ventilation prior to enrolment.

Mechanical ventilation and blood gas at baseline: PEEP, FiO_2 , partial pressure of oxygen in arterial blood (PaO_2), $\text{PaO}_2/\text{FiO}_2$ (P/F ratio), PaCO_2 and pH.

Baseline ICP and haemodynamic parameters: HR, blood pressure, central venous pressure (CVP) and CVP change during the passive leg raising test.

Ventricular compliance measurement

ICP will be measured with a ventricular ICP monitor (Codman, Johnson & Johnson, Raynham, MA, USA). To measure ventricular compliance, 2 mL of CSF will be drained, and the ICP value before and after CSF drainage will be recorded. Ventricular compliance will be calculated as follows:

Ventricular compliance = $2 / (\text{ICP before CSF drainage} - \text{ICP after CSF drainage})$
(Formula 1).

Placement of oesophageal balloon catheter

We will use the SmartCath-G adult nasogastric tube with an oesophageal balloon (7003300, CareFusion Co., Yorba Linda, CA, USA) in this study. Patients will remain in a supine position with the head of the bed elevated to 30° during the study period. After anesthetizing the nose and oropharynx with 10% lidocaine spray, the oesophageal balloon catheter will be inserted through the nostril to a depth of 60 cm. The intra-gastric position of the distal part of the catheter will be confirmed by aspiration of gastric juice and auscultation of air insufflations into the stomach. After confirmation of the catheter position, the balloon will be inflated with 1.5 mL of air [17 18], and the proximal part of the catheter will be connected to the pressure transducer. Subsequently, the catheter will be slowly withdrawn, and the dynamic occlusion test will be performed.[19] An end-expiratory occlusion will be performed until three to five spontaneous inspiratory efforts are made against the end-expiratory occlusion. The ratio of the change in P_{es} to the change in airway pressure ($\Delta P_{es}/\Delta P_{aw}$)

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4 will be calculated. The catheter will be considered correctly positioned when the
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6 $\Delta P_{es}/\Delta P_{aw}$ ratio during the occlusion test is in the range of 0.8 to 1.2.[20-22] In
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8 paralyzed patients, the occlusion test will be performed by applying manual
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10 compression on the rib cage during the end-expiratory occlusion.
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13 14 15 16 **Pressure measurements**

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18 Flow will be measured with a Fleisch pneumotachograph (Vitalograph Inc., Lenexa,
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20 KS, USA) inserted between the Y-piece of the ventilator circuit and the endotracheal
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22 tube. The volume will be obtained by electrical integration of the flow signal. Airway
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24 pressure (P_{aw} , located distal to the pneumotachograph) and P_{es} will be measured with
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26 two differential pressure transducers (KT 100D-2, Kleis TEK di Cosimo Micelli, Italy,
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28 range: +/- 100 cmH₂O). The Fleisch pneumotachograph and pressure transducers will
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30 be connected to an ICU-Lab Pressure Box (ICU Lab, KleisTEK Engineering, Bari,
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32 Italy) by 80 cm tube lines. The signals will be displayed continuously and saved
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34 (ICU-Lab 2.5 Software Package, ICU Lab, KleisTEK Engineering, Bari, Italy) on a
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36 laptop for further analysis at a sample rate of 200 Hz. The pressure transducer will be
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38 calibrated with a water column. The pneumotachograph will be calibrated with a 1-L
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40 calibration syringe (SN: 554-2266, Hans Rudolph, Inc. Shawnee, KS, USA).
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51 52 **Respiratory mechanics measurements**

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54 After placement of the oesophageal balloon catheter, patients will be sedated and
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56 paralyzed via intravenous infusion of 5 mg of midazolam, 0.1 mg of fentanyl, and 50
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mg of rocuronium. Mechanical ventilation will be set at a volume control ventilation, constant flow, an inspiratory–expiratory ratio of 1:2, and a tidal volume of 6 to 8 mL/kg of predicted body weight. The initial respiratory rate will be set at 20/min and will be adjusted to maintain the partial pressure of carbon dioxide (PaCO₂) value at approximately 35 to 40 mmHg. PEEP will be adjusted to 5 cmH₂O. The oxygenation goal will be maintained constant at a pulse oxygen saturation (SpO₂) above 90% by adjusting the fraction of inspired oxygen concentration (FiO₂). After a 30 min stabilization period, blood gas will be obtained. Mean P_{aw} and P_{es} will also be recorded. An end-inspiratory occlusion and an end-expiratory occlusion will be performed, and plateau pressure (P_{plat}) and total PEEP (PEEP_{tot}) will be recorded. P_{es} during end-inspiratory occlusion and end-expiratory occlusion will also be recorded. Expiratory tidal volume (V_{te}) will also be recorded, and the compliance of the lungs (C_l), the chest wall (C_{cw}) and the respiratory system (C_{rs}) will be calculated as follows:

$$C_{rs} = V_{te} / (P_{plat} - PEEP_{tot}) \text{ (Formula 2)}$$

$$C_{cw} = V_{te} / (P_{es-plat} - P_{es-PEEP}) \text{ (Formula 3)}$$

$$C_l = V_{te} / [(P_{plat} - P_{es-plat}) - (PEEP_{tot} - P_{es-PEEP})] \text{ (Formula 4)}$$

P_{es-plat}: oesophageal pressure at end-inspiration; P_{es-PEEP}: oesophageal pressure at end-expiration.

Thereafter, PEEP will be stepwise increased. 10 and 15 cmH₂O of PEEP will be applied. The measurements of ICP, ventricular compliance, haemodynamic status (HR, BP and CVP), blood gas analysis, and respiratory mechanics will be repeated at these

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4 two PEEP levels. PEEP will be then adjusted from 15 cmH₂O to 5 cmH₂O and the RR
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6 will be decreased to 4 breaths/min with the inspiratory time unchanged to measure the
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8 PEEP volume. The PEEP volume will be calculated as follows:
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11 PEEP volume = (the first V_{te} after PEEP adjustment) – (the last V_{te} before PEEP
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13 adjustment). (Formula 5)
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16 We will use recruitment volume to assess the recruitability. Recruitment volume
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18 induced by PEEP will be defined as follows:
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21 Recruitment volume = PEEP volume – ΔPEEP * C_{rs} at PEEP₅ (Formula 6)
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24 Where “ΔPEEP * C_{rs} at PEEP₅” is the minimal predicted increase in lung volume,
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26 which is the smallest possible increase in lung volume induced by PEEP.[23]
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29 A flow chart of the study procedure is shown in Figure 1.
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31 32 33 **Adverse event management and emergency termination of the study**

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35 Patients will be closely monitored during the study period. Taking into account the
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37 potential adverse effects of PEEP, emergency interventions will be provided when the
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39 following occur:
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43 1. Abrupt increase of ICP greater than 25 mmHg and/or decrease of cerebral perfusion
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45 pressure less than 50 mmHg that persists for > 2 minutes. A bolus of 125 mL mannitol
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47 infusion will be administered.
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50 2. BP decrease to below 90/60 mmHg or a systolic BP decrease of > 40 mmHg; 100
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52 mL of crystalloid fluid infusion will be administered. The study will be continued if
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54 the patient is responsive to the interventions (BP increases); otherwise, the study will
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be terminated and further interventions for decreased BP will be provided.

3. The procedure will be stopped if ICP is too high or BP is too low when 15 cmH₂O PEEP is applied. The data obtained at 5 and 10 cmH₂O PEEP will be collected.

Study endpoints

The primary endpoint is the influence of PEEP on ICP. There are two PEEP increases during the study procedure as follows: from 5 cmH₂O to 10 cmH₂O and from 10 cmH₂O to 15 cmH₂O. We will calculate $\Delta\text{ICP}/\Delta\text{PEEP}$ to standardize the influence of PEEP on ICP during the increase of PEEP for each step.

Secondary endpoints include the identification of possible contributors to the effects of PEEP on ICP and the investigation of the influence of PEEP on haemodynamic parameters, including CVP, MAP and cerebral perfusion pressure.

Statistical analysis

We will classify each patient into one of two groups according to the median value of $\Delta\text{ICP}/\Delta\text{PEEP}$ in the overall study population. The two groups will consist of patients with ICP responsiveness below the median value and ICP responsiveness above the median value. Since there will be two $\Delta\text{ICP}/\Delta\text{PEEP}$ values in one patient (except those who are intolerant to 15 cmH₂O PEEP), the greater one will be used to determine the grouping.

Baseline characteristics will be evaluated by univariate analysis. Categorical variables will be presented as numbers and percentages and analysed by the χ^2 -test. Continuous variables will be tested for normal distribution and presented as the mean and

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4 standard deviation or median and inter-quartile range as appropriate. Comparisons of
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6 continuous variables will be performed using Student's t-test for normally distributed
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8 variables and the Mann-Whitney U test for non-normally distributed variables.
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11 Wilcoxon signed-rank test will be performed to compare the difference of
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13 Δ ICP/ Δ PEEP between the two PEEP increases. A multivariate logistic regression
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15 analysis will be performed using forward procedures with factors demonstrating $P <$
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17 0.20 in univariate logistic regression analysis. All tests of significance will be at the 5%
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19 significance level and will be two-sided. Analyses will be performed with SPSS 19.0
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21 (IBM Corporation, New York, USA).
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29 **Sample size calculation**

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31 Prospective sample size calculations are performed using G*Power Software (sample
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33 size calculating software package provided by the G*Power Team, Germany,
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35 downloaded from <http://www.gpower.hhu.de/en.html>). We will need to study 30
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37 subjects to be able to reject the null hypothesis that the means of elastance ratio of the
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39 two groups are equal with a probability (power) of 0.8. The Type I error probability
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41 with testing this null hypothesis is 0.05.
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Trial registration, ethical aspects and informed consent

The study protocol and consent forms were approved on September 30, 2015, by the Institutional Review Board of Fujian Provincial Hospital. The study was registered on January 26, 2016, at ClinicalTrials.org (ClinicalTrials.gov Identifier: NCT02670733).

After patients' eligibility for the study is confirmed, the study coordinator will be introduced to the patients' families. The ICU physician will emphasize the credentials of the study coordinator and communicate that this person will discuss a research programme for which the patient is qualified to participate. Every relevant aspect of the project will be described. The study coordinator will stop frequently, ask if there are any questions, and request that the family repeat back in their own words what is being discussed to ensure that the family understands the study. The study coordinator will be especially careful to assure the family that they are free to decline consent without consequences and that they can withdraw consent at any time without impact on treatment. Family members will be provided with contact information for the study coordinator, the local co-investigator and the local Ethical Committee. Written consent will be obtained in the presence of a witness.

Dissemination plan

Results of the trial will be submitted to an international peer-reviewed journal. The results will also be presented at national and international conferences relevant to the subject fields.

DISCUSSION

Previous studies have demonstrated that in patients with low Crs, PEEP exerts no significant effects on cerebral haemodynamics.[10] However, compliances of the chest wall and the lungs were not distinguished in that previous study. In another study that examined chest wall and lung compliance, the authors did not investigate the effects of increased PEEP on ICP.[12] In the present study, we aim to investigate the effects of PEEP on pleural pressure and ICP by measuring P_{es} .

Lung recruitment may occur when PEEP is adjusted to a higher level, which may contribute to variations in lung compliance. Therefore, we will measure PEEP volume and calculate recruitment volume to estimate whether a patient's lung is recruitable or non-recruitable.[23] We speculate that increased PEEP can have a greater effect on ICP in patients with greater recruitability.

We will classify each patient with a high or low responsiveness of ICP to increased PEEP based on whether the $\Delta ICP/\Delta PEEP$ is above or below the median for the study population. Because there is no widely accepted threshold to identify the responsiveness of ICP to increased PEEP, the division of patients into two groups is reasonable and enables us to compare differences between the two groups of patients.

Authors' contributions

HC, RGY and JXZ participated in the design of the study and drafted the manuscript.

MX, YLY, KC, JQX and YRZ participated in the design of the study. All authors edited the manuscript and read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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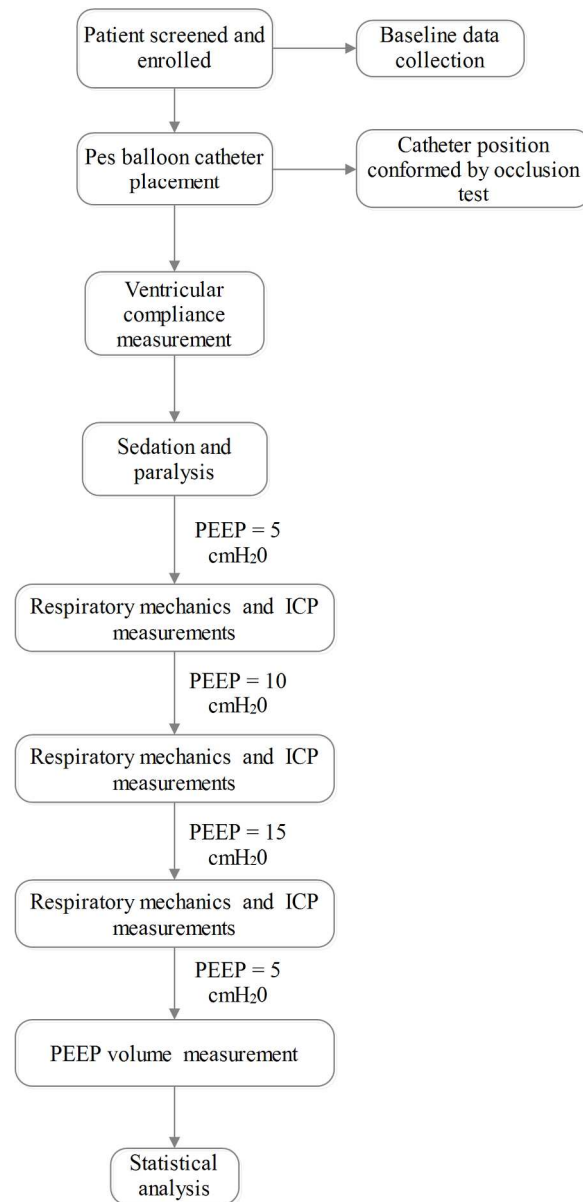


Figure 1 The flow chart of the study procedure.

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	___ 1 ___
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	___ 1 ___
	2b	All items from the World Health Organization Trial Registration Data Set	___ None ___
Protocol version	3	Date and version identifier	___ None ___
Funding	4	Sources and types of financial, material, and other support	___ 18 ___
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	___ 1,2 ___
	5b	Name and contact information for the trial sponsor	___ 18 ___
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	___ 18 ___
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	___ None ___

1
2
3 **Introduction**

4				
5	Background and	6a	Description of research question and justification for undertaking the trial, including summary of relevant	_____6,7_____
6	rationale		studies (published and unpublished) examining benefits and harms for each intervention	
7				
8		6b	Explanation for choice of comparators	_____14_____
9				
10	Objectives	7	Specific objectives or hypotheses	_____7_____
11				
12	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group),	
13			allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	_____8_____
14				
15				
16	Methods: Participants, interventions, and outcomes			
17				
18	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will	_____8_____
19			be collected. Reference to where list of study sites can be obtained	
20	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and	_____8,9_____
21			individuals who will perform the interventions (eg, surgeons, psychotherapists)	
22				
23	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be	_____10-13_____
24			administered	
25		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose	_____13_____
26			change in response to harms, participant request, or improving/worsening disease)	
27		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence	_____None_____
28			(eg, drug tablet return, laboratory tests)	
29		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	_____None_____
30				
31	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood	_____14_____
32			pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg,	
33			median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen	
34			efficacy and harm outcomes is strongly recommended	
35				
36	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for	_____13_____
37			participants. A schematic diagram is highly recommended (see Figure)	
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Sample size 14 Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations 15

Recruitment 15 Strategies for achieving adequate participant enrolment to reach target sample size None

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation 16a Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions 14

Allocation concealment mechanism 16b Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned None

Implementation 16c Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions None

Blinding (masking) 17a Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how None

17b If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial None

Methods: Data collection, management, and analysis

Data collection methods 18a Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol 9-13

18b Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols None

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3	Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	_____None_____
4				
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6	Statistical methods			
7		20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	====_14-15=====
8				
9				
10		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	___ _None__ _
11				
12		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	___ _None__ _
13				_____
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16	Methods: Monitoring			
17				
18	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	====_None=====
19				
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23		21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	___ _None__ _
24				
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26	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	___ _None__ _
27				
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29	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	====_None=====
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33	Ethics and dissemination			
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35	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	====_16=====
36				
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38	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	___ _None__ _
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3	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	_____ 16 _____
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6		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	_____ None _____
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8	Confidentiality			
9		27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	_____ None _____
10				
11				
12	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	_____
13				
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15	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	_____ 18 _____
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18	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	_____ None _____
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21	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	_____ 16 _____
22				
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26		31b	Authorship eligibility guidelines and any intended use of professional writers	_____ None _____
27				
28		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____ None _____
29				
30	Appendices			
31				
32	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	_____ None _____
33				
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35	Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	_____ None _____
36				
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38 *It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.
 39 Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons
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BMJ Open

The effects of increased positive end-expiratory pressure on intracranial pressure in acute respiratory distress syndrome: a protocol of a prospective physiological study

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Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Neurology, Surgery
Keywords:	Oesophageal pressure, Acute respiratory distress syndrome, Positive end-expiration pressure, Intracranial pressure

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Manuscripts

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4 **The effects of increased positive end-expiratory pressure on intracranial pressure**
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6 **in acute respiratory distress syndrome: a protocol of a prospective physiological**
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8 **study**
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Abstract

Introduction: There are concerns that the use of positive end-expiratory pressure (PEEP) in patients with brain injury may potentially elevate intracranial pressure (ICP). However, the transmission of PEEP into the thoracic cavity depends on the properties of the lungs and the chest wall. When chest wall elastance is high, PEEP can significantly increase pleural pressure. In the present study, we investigate the different effects of PEEP on the pleural pressure and ICP in different respiratory mechanics.

Methods and analysis: This study is a prospective, single-centre, physiological study in severe brain injury patients. Acute respiratory distress syndrome patients with ventricular drainage will be enrolled. An oesophageal balloon catheter will be inserted to measure oesophageal pressure. Patients will be sedated and paralyzed; airway pressure and oesophageal pressure will be measured during end-inspiratory occlusion and end-expiratory occlusion. Elastance of the chest wall, the lungs and the respiratory system will be calculated at the PEEP level of 5 cmH₂O, 10 cmH₂O and 15 cmH₂O. We will classify each patient based on the maximal Δ ICP/ Δ PEEP being above or below the median for the study population. Two groups will thus be compared.

Ethics and dissemination: The study protocol and consent forms were approved by the Institutional Review Board of Fujian Provincial Hospital. Study findings will be disseminated through peer-reviewed publications and conference presentations.

Trial registration: The study was registered on January 26, 2016, at ClinicalTrials.org

(ClinicalTrials.gov Identifier: NCT02670733)

Key words: Oesophageal pressure; acute respiratory distress syndrome; positive end-expiratory pressure; intracranial pressure

For peer review only

STRENGTHS AND LIMITATIONS OF THIS STUDY

- We will investigate the effects of PEEP on pleural pressure and ICP via oesophageal pressure measurements.
- We will try to identify the possible contributors of the influence of PEEP on ICP.
- The main limitation of this study is the absence of widely accepted thresholds to identify the responsiveness of ICP to increased PEEP, and we therefore arbitrarily divided patients into two groups using the median of the study population.

INTRODUCTION

Acute respiratory distress syndrome (ARDS), which is characterized by severe hypoxemia and alterations in lung function, is common in critically ill patients. Numerous authors have reported that a significant portion of patients with brain injury can develop pulmonary complications, including ARDS and neurogenic pulmonary edema (NPE).[1-6] Ventilation strategies to protect the lungs should be applied in patients with ARDS.[7] The mainstays of lung-protective ventilation strategies are to (1) limit tidal volume and driving pressure; (2) limit end-inspiratory plateau pressure (P_{plat}); and (3) provide adequate positive end-expiratory pressure (PEEP) to keep the lungs open and prevent alveolar collapse.

There are concerns that the use of PEEP for the treatment of pulmonary complications in patients with brain injury could elevate intracranial pressure (ICP) and deteriorate neurological status. Both respiratory system elastance and ventricular compliance are thought to contribute to the elevation of ICP when PEEP increases.[8-11] In theory, PEEP may increase ICP by increasing pleural pressure and diminishing venous return. However, the transmission of PEEP into the thoracic cavity depends on the properties of the lungs and chest wall. An experimental study conducted by Chapin et al. showed that when chest wall elastance is high, PEEP can significantly increase intrathoracic pressure, whereas high lung elastance can minimize airway pressure transmission.[12] Lung elastance is generally recognized to increase in ARDS patients due to extensive alveolar collapse. However, it has been reported that the chest wall elastance ratio (the ratio between the elastance of the chest wall and the respiratory system) may vary

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4 from 0.2 to 0.8.[13] Therefore, it is important to distinguish between the elastance of
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6 the chest wall and the lungs when investigating the effects of PEEP on ICP.
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9 We hypothesise that PEEP has greater influence on ICP in patients with higher chest
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11 wall elastance ratio (e.g. the lung elastance is low and/or the chest wall elastance is
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13 high). To test the hypothesis, we need to measure the airway pressure and pleural
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15 pressure to calculate the elastance of the lung and the chest wall. However, pleural
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17 pressure is difficult to measure in clinical situations, and oesophageal pressure (P_{es}) is
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19 considered a surrogate of pleural pressure.[14 15] In the present study, we will
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21 investigate the effects of PEEP on pleural pressure and ICP by measuring P_{es} .
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METHODS

Study design overview

The present study is a prospective, single-centre, physiological study in patients with severe brain injury.

Study setting and population

The study setting is the surgical intensive care unit (SICU) (22 beds), at Fujian Provincial Hospital (2500 beds), Fujian Provincial Clinical College of Fujian Medical University, Fuzhou, China.

All patients admitted to the SICU will be consecutively screened for study eligibility.

Inclusion criteria are as follows:

- 1) Aged 18 years or above;
- 2) Glasgow Coma Score ≤ 8 ;
- 3) Ventricular ICP monitor placement for ICP monitoring and cerebrospinal fluid (CSF) drainage;
- 4) Need for mechanical ventilation with PEEP; and
- 5) ARDS diagnosis according to the Berlin Definition.[7]

Exclusion criteria are as follows:

- 1) Hemodynamic instability requiring more than 10 $\mu\text{g}/\text{kg}/\text{min}$ dopamine or more than 0.5 $\mu\text{g}/\text{kg}/\text{min}$ norepinephrine;[10]
- 2) ICP > 25 mmHg;

- 3) Decompressive craniectomy was performed;
- 4) Oesophageal varices;
- 5) History of oesophageal or gastric surgery;
- 6) Evidence of active air leak from the lung, including bronchopleural fistula, pneumothorax, pneumomediastinum, or existing chest tube; and
- 7) History of chronic obstructive pulmonary disease.

Baseline data collection

After enrolment, the following baseline data will be collected:

Demographic data: age, gender, height, and predicted body weight, which is calculated as $50 + 0.91 \times (\text{centimetres of height} - 152.4)$ for males and $45.5 + 0.91 \times (\text{centimetres of height} - 152.4)$ for females.[16]

Clinical data: primary diagnosis, type of brain injury (traumatic brain injury, stroke or postoperation for brain tumour), type of brain lesion (bilateral or unilateral), Acute Physiology and Chronic Health Evaluation II score (APACHE II) at the time of ICU admission, Simplified Acute Physiology Score II (SAPS II) on the day of enrolment, and duration of mechanical ventilation prior to enrolment.

Mechanical ventilation and blood gas at baseline: PEEP, FiO_2 , partial pressure of oxygen in arterial blood (PaO_2), $\text{PaO}_2/\text{FiO}_2$ (P/F ratio), PaCO_2 and pH.

Baseline ICP and haemodynamic parameters: HR, blood pressure, central venous pressure (CVP) and CVP change during the passive leg raising test.

Ventricular compliance measurement

ICP will be measured with a ventricular ICP monitor (Codman, Johnson & Johnson, Raynham, MA, USA). To measure ventricular compliance, 2 mL of CSF will be drained, and the ICP value before and after CSF drainage will be recorded. Ventricular compliance will be calculated as follows:

Ventricular compliance = $2 / (\text{ICP before CSF drainage} - \text{ICP after CSF drainage})$
(Formula 1).

Placement of oesophageal balloon catheter

We will use the SmartCath-G adult nasogastric tube with an oesophageal balloon (7003300, CareFusion Co., Yorba Linda, CA, USA) in this study. Patients will remain in a supine position with the head of the bed elevated to 30° during the study period. After anesthetizing the nose and oropharynx with 10% lidocaine spray, the oesophageal balloon catheter will be inserted through the nostril to a depth of 60 cm. The intra-gastric position of the distal part of the catheter will be confirmed by aspiration of gastric juice and auscultation of air insufflations into the stomach. After confirmation of the catheter position, the balloon will be inflated with 1.5 mL of air [17 18], and the proximal part of the catheter will be connected to the pressure transducer. Subsequently, the catheter will be slowly withdrawn, and the dynamic occlusion test will be performed.[19] An end-expiratory occlusion will be performed until three to five spontaneous inspiratory efforts are made against the end-expiratory occlusion. The ratio of the change in P_{es} to the change in airway pressure ($\Delta P_{es}/\Delta P_{aw}$)

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4 will be calculated. The catheter will be considered correctly positioned when the
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6 $\Delta P_{es}/\Delta P_{aw}$ ratio during the occlusion test is in the range of 0.8 to 1.2.[20-22] In
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8 paralyzed patients, the occlusion test will be performed by applying manual
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10 compression on the rib cage during the end-expiratory occlusion.
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13 14 15 16 **Pressure measurements**

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18 Flow will be measured with a Fleisch pneumotachograph (Vitalograph Inc., Lenexa,
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20 KS, USA) inserted between the Y-piece of the ventilator circuit and the endotracheal
21
22 tube. The volume will be obtained by electrical integration of the flow signal. Airway
23
24 pressure (P_{aw} , located distal to the pneumotachograph) and P_{es} will be measured with
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26 two differential pressure transducers (KT 100D-2, Kleis TEK di Cosimo Micelli, Italy,
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28 range: +/- 100 cmH₂O). The Fleisch pneumotachograph and pressure transducers will
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30 be connected to an ICU-Lab Pressure Box (ICU Lab, KleisTEK Engineering, Bari,
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32 Italy) by 80 cm tube lines. The signals will be displayed continuously and saved
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34 (ICU-Lab 2.5 Software Package, ICU Lab, KleisTEK Engineering, Bari, Italy) on a
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36 laptop for further analysis at a sample rate of 200 Hz. The pressure transducer will be
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38 calibrated with a water column. The pneumotachograph will be calibrated with a 1-L
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40 calibration syringe (SN: 554-2266, Hans Rudolph, Inc. Shawnee, KS, USA).
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51 52 **Respiratory mechanics measurements**

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54 After placement of the oesophageal balloon catheter, patients will be sedated and
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56 paralyzed via intravenous infusion of 5 mg of midazolam, 0.1 mg of fentanyl, and 50
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4 mg of rocuronium. Mechanical ventilation will be set at a volume control ventilation,
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6 constant flow, an inspiratory–expiratory ratio of 1:2, and a tidal volume of 6 to 8
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8 mL/kg of predicted body weight. The initial respiratory rate will be set at 20/min and
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10 will be adjusted to maintain the partial pressure of carbon dioxide (PaCO₂) value at
11
12 approximately 35 to 40 mmHg. PEEP will be adjusted to 5 cmH₂O. The oxygenation
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14 goal will be maintained constant at a pulse oxygen saturation (SpO₂) above 90% by
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16 adjusting the fraction of inspired oxygen concentration (FiO₂). After a 30 min
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18 stabilization period, blood gas analysis will be performed. Mean P_{aw} and P_{es} will also
19
20 be recorded. An end-inspiratory occlusion and an end-expiratory occlusion will be
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22 performed, and plateau pressure (P_{plat}) and total PEEP (PEEP_{tot}) will be recorded. P_{es}
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24 during end-inspiratory occlusion and end-expiratory occlusion will also be recorded.
25
26 Expiratory tidal volume (V_{te}) will also be recorded, and the elastance of the lungs (E_l),
27
28 the chest wall (E_{cw}) and the respiratory system (E_{rs}) will be calculated as follows:
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$$36 \quad E_{rs} = (P_{plat} - PEEP_{tot}) / V_{te} \text{ (Formula 2)}$$

$$37 \quad E_{cw} = (P_{es-plat} - P_{es-PEEP}) / V_{te} \text{ (Formula 3)}$$

$$38 \quad E_l = [(P_{plat} - P_{es-plat}) - (PEEP_{tot} - P_{es-PEEP})] / V_{te} \text{ (Formula 4)}$$

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44 P_{es-plat}: oesophageal pressure at end-inspiration; P_{es-PEEP}: oesophageal pressure at
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46 end-expiration.
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49 Thereafter, PEEP will be stepwise increased to 10 and 15 cmH₂O. The measurements
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51 of ICP, ventricular compliance, haemodynamic status (HR, BP and CVP), blood gas
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53 analysis, and respiratory mechanics will be repeated at these two PEEP levels.
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57 Changes in end-expiratory lung volume (ΔEELV) will also be measured, which is
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3 determined as the cumulative difference between inspiratory and expiratory tidal
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5 volumes, during the first 30 breaths following a change in PEEP level, with a
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7 systematic difference (namely V_T offset) corrected.[23-25]
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11 A flow chart of the study procedure is shown in Figure 1.
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14 15 16 **Adverse event management and emergency termination of the study**

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18 Patients will be closely monitored during the study period. Taking into account the
19
20 potential adverse effects of PEEP, emergency interventions will be provided when the
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22 following occur:
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26 1. Abrupt increase of ICP greater than 25 mmHg and/or decrease of cerebral perfusion
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28 pressure less than 50 mmHg that persists for > 2 minutes. A bolus of 125 mL mannitol
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30 infusion will be administered.
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34 2. BP decrease to below 90/60 mmHg or a systolic BP decrease of > 40 mmHg; 100
35
36 mL of crystalloid fluid infusion will be administered. The study will be continued if
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38 the patient is responsive to the interventions (BP increases); otherwise, the study will
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40 be terminated and further interventions for decreased BP will be provided.
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44 3. The procedure will be stopped if ICP is too high or BP is too low when 15 cmH₂O
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46 PEEP is applied. The data obtained at 5 and 10 cmH₂O PEEP will be collected.
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49 50 51 **Study endpoints**

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53 The primary endpoint is the influence of PEEP on ICP. There are two PEEP increases
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55 during the study procedure as follows: from 5 cmH₂O to 10 cmH₂O and from 10
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cmH₂O to 15 cmH₂O. We will calculate Δ ICP/ Δ PEEP to standardize the influence of PEEP on ICP during the increase of PEEP for each step.

Secondary endpoints include the identification of possible contributors (see statistical analysis part for detail) to the effects of PEEP on ICP and the investigation of the influence of PEEP on haemodynamic parameters, including CVP, MAP and cerebral perfusion pressure.

Statistical analysis

We will classify each patient into one of two groups according to the median value of Δ ICP/ Δ PEEP in the overall study population. The two groups will consist of patients with ICP responsiveness below the median value and ICP responsiveness above the median value. Since there will be two Δ ICP/ Δ PEEP values in one patient (except those who are intolerant to 15 cmH₂O PEEP), the greater one will be used to determine the grouping.

Categorical variables will be presented as numbers and percentages and analysed by the χ^2 -test. Continuous variables will be tested for normal distribution and presented as the mean and standard deviation or median and inter-quartile range as appropriate.

Comparisons of continuous variables will be performed using Student's t-test for normally distributed variables and the Mann-Whitney U test for non-normally distributed variables. Wilcoxon signed-rank test will be performed to compare the difference of Δ ICP/ Δ PEEP between the two PEEP increases. Possible confounders of the ICP responsiveness to PEEP including demographic data, type of brain injury

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4 (traumatic brain injury, stroke, postoperation for brain tumour), type of brain lesion
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6 (bilateral or unilateral), ventricular compliance, respiratory mechanics (elastance of
7
8 the lung, the chest wall and the respiratory system, $\Delta EELV$, chest wall elastance ratio
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10 and change of elastance) and changes of PaO_2 and $PaCO_2$ will be collected in this
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12 study. First, univariate analysis will be performed. Thereafter, a multivariate logistic
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14 regression analysis will be performed using forward procedures with factors
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16 demonstrating $P < 0.20$ in univariate analysis. All tests of significance will be at the 5%
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18 significance level and will be two-sided. Analyses will be performed with SPSS 19.0
19
20 (IBM Corporation, New York, USA).
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29 **Sample size calculation**

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31 Prospective sample size calculations are performed using G*Power Software (sample
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33 size calculating software package provided by the G*Power Team, Germany,
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35 downloaded from <http://www.gpower.hhu.de/en.html>). We will need to study 30
36
37 subjects to be able to reject the null hypothesis that the means of chest wall elastance
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39 ratio of the two groups are equal with a probability (power) of 0.8. The Type I error
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41 probability with testing this null hypothesis is 0.05.
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Trial registration, ethical aspects and informed consent

The study protocol and consent forms were approved on September 30, 2015, by the Institutional Review Board of Fujian Provincial Hospital. The study was registered on January 26, 2016, at ClinicalTrials.org (ClinicalTrials.gov Identifier: NCT02670733).

After patients' eligibility for the study is confirmed, the study coordinator will be introduced to the patients' families. The ICU physician will emphasize the credentials of the study coordinator and communicate that this person will discuss a research programme for which the patient is qualified to participate. Every relevant aspect of the project will be described. The study coordinator will stop frequently, ask if there are any questions, and request that the family repeat back in their own words what is being discussed to ensure that the family understands the study. The study coordinator will be especially careful to assure the family that they are free to decline consent without consequences and that they can withdraw consent at any time without impact on treatment. Family members will be provided with contact information for the study coordinator, the local co-investigator and the local Ethical Committee. Written consent will be obtained in the presence of a witness.

Dissemination plan

Results of the trial will be submitted to an international peer-reviewed journal. The results will also be presented at national and international conferences relevant to the subject fields.

DISCUSSION

Previous studies have demonstrated that PEEP exerts no significant effects on cerebral haemodynamics in patients with high respiratory system elastance.[10] However, elastance of the chest wall and the lungs were not distinguished in that previous study.

In another study that examined chest wall and lung compliance, the authors did not investigate the effects of increased PEEP on ICP.[12] In the present study, we aim to investigate the effects of PEEP on pleural pressure and ICP by measuring P_{es} .

Respiratory mechanics may change when PEEP is adjusted to a higher level. End-expiratory lung volume can also increase with an increase of PEEP, as a result of recruitment of non-aerated lung units and distension of already aerated alveoli.

Moreover, PaO_2 and $PaCO_2$ can also change with PEEP adjustments. All these may contribute to the influence of PEEP on ICP. Therefore, we will measure the respiratory mechanics, $\Delta EELV$ and blood gas to determine the possible contributors.

We will classify each patient with a high or low responsiveness of ICP to increased PEEP based on whether the $\Delta ICP/\Delta PEEP$ is above or below the median for the study population. Because there is no widely accepted threshold to identify the responsiveness of ICP to increased PEEP, the division of patients into two groups is reasonable and enables us to compare differences between the two groups of patients.

Authors' contributions

HC, RGY and JXZ participated in the design of the study and drafted the manuscript.

MX, YLY, KC, JQX and YRZ participated in the design of the study. All authors edited the manuscript and read and approved the final manuscript.

Funding statement:

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Competing interests

The authors declare that they have no competing interests.

Acknowledgement

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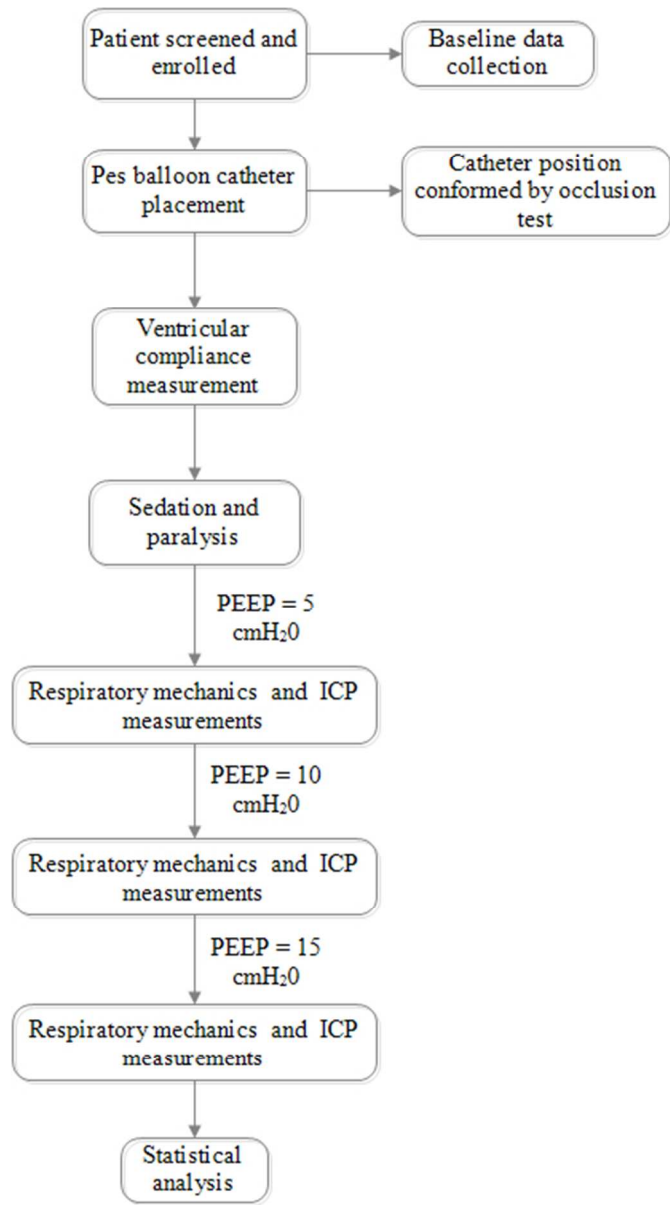


Figure 1 Flow Chart of the study procedure

35x63mm (300 x 300 DPI)



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	___ 1 ___
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	___ 1 ___
	2b	All items from the World Health Organization Trial Registration Data Set	___ None ___
Protocol version	3	Date and version identifier	___ None ___
Funding	4	Sources and types of financial, material, and other support	___ 18 ___
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	___ 1,2 ___
	5b	Name and contact information for the trial sponsor	___ 18 ___
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	___ 18 ___
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	___ None ___

1
2
3 **Introduction**

4				
5	Background and	6a	Description of research question and justification for undertaking the trial, including summary of relevant	_____6,7_____
6	rationale		studies (published and unpublished) examining benefits and harms for each intervention	
7				
8		6b	Explanation for choice of comparators	===== 14 _____
9				
10	Objectives	7	Specific objectives or hypotheses	_____ 7 _____
11				
12	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group),	
13			allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	_____ 8 _____
14				
15				
16	Methods: Participants, interventions, and outcomes			
17				
18	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will	===== 8 _____
19			be collected. Reference to where list of study sites can be obtained	
20	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and	_____ 8,9 _____
21			individuals who will perform the interventions (eg, surgeons, psychotherapists)	
22				
23	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be	_____ 10-13 _____
24			administered	
25		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose	_____ 13 _____
26			change in response to harms, participant request, or improving/worsening disease)	
27		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence	_____ None _____
28			(eg, drug tablet return, laboratory tests)	
29		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	_____ None _____
30				
31	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood	===== 14 _____
32			pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg,	
33			median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen	
34			efficacy and harm outcomes is strongly recommended	
35				
36	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for	===== 13 _____
37			participants. A schematic diagram is highly recommended (see Figure)	
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3 Sample size 14 Estimated number of participants needed to achieve study objectives and how it was determined, including _____ 15_____
4 clinical and statistical assumptions supporting any sample size calculations

5 Recruitment 15 Strategies for achieving adequate participant enrolment to reach target sample size _____ None_____
6
7

8 **Methods: Assignment of interventions (for controlled trials)**
9

10 Allocation:

11
12 Sequence generation 16a Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any _____ 14_____
13 factors for stratification. To reduce predictability of a random sequence, details of any planned restriction
14 (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants
15 or assign interventions

16
17 Allocation concealment mechanism 16b _____ None_____
18 Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered,
19 opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
20

21
22 Implementation 16c _____ None_____
23 Who will generate the allocation sequence, who will enrol participants, and who will assign participants to
24 interventions

25 Blinding (masking) 17a _____ None_____
26 Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome
27 assessors, data analysts), and how

28 17b _____ None_____
29 If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's
30 allocated intervention during the trial
31

32 **Methods: Data collection, management, and analysis**
33

34 Data collection methods 18a _____ 9-13_____
35 Plans for assessment and collection of outcome, baseline, and other trial data, including any related
36 processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of
37 study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known.
38 Reference to where data collection forms can be found, if not in the protocol

39 18b _____ None_____
40 Plans to promote participant retention and complete follow-up, including list of any outcome data to be
41 collected for participants who discontinue or deviate from intervention protocols
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3	Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	_____None_____
4				
5				
6	Statistical methods			
7		20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	====_14-15=====
8				
9				
10		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	___ _None__ _
11				
12		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	___ _None__ _
13				
14				
15				
16	Methods: Monitoring			
17				
18	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	====_None=====
19				
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23		21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	___ _None__ _
24				
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26	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	___ _None__ _
27				
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29	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	====_None=====
30				
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33	Ethics and dissemination			
34				
35	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	====_16=====
36				
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38	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	___ _None__ _
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3	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	_____ 16 _____
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6		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	_____ None _____
7				
8	Confidentiality			
9		27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	_____ None _____
10				
11				
12	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	_____
13				
14				
15	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	_____ 18 _____
16				
17				
18	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	_____ None _____
19				
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21	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	_____ 16 _____
22				
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26		31b	Authorship eligibility guidelines and any intended use of professional writers	_____ None _____
27				
28		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____ None _____
29				
30	Appendices			
31				
32	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	_____ None _____
33				
34				
35	Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	_____ None _____
36				
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*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.

BMJ Open

The effects of increased positive end-expiratory pressure on intracranial pressure in acute respiratory distress syndrome: a protocol of a prospective physiological study

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2016-012477.R3
Article Type:	Protocol
Date Submitted by the Author:	21-Oct-2016
Complete List of Authors:	Chen, Han; Beijing Tiantan Hospital, Capital Medical University, Department of Critical Care Medicine Xu, Ming; Beijing Tiantan Hospital, Capital Medical University, Department of Critical Care Medicine Yang, Yan-Lin; Beijing Tiantan Hospital, Capital Medical University, Department of Critical Care Medicine Chen, Kai; Fujian Provincial Hospital Fuzhou, China, Xu, Jing-Qing; Fujian Provincial Hospital, Surgical intensive care unit Zhang , Ying-Rui; Fujian Provincial Hospital, Surgical intensive care unit Yu, Rong-Guo; Fujian Provincial Hospital, Zhou, Jian-Xin; Beijing Tiantan Hospital, Capital Medical University, Department of Critical Care Medicine
Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Neurology, Surgery
Keywords:	Oesophageal pressure, Acute respiratory distress syndrome, Positive end-expiration pressure, Intracranial pressure

SCHOLARONE™
Manuscripts

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4 **The effects of increased positive end-expiratory pressure on intracranial pressure**
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6 **in acute respiratory distress syndrome: a protocol of a prospective physiological**
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8 **study**
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Word count: 2641

Abstract

Introduction: There are concerns that the use of positive end-expiratory pressure (PEEP) in patients with brain injury may potentially elevate intracranial pressure (ICP). However, the transmission of PEEP into the thoracic cavity depends on the properties of the lungs and the chest wall. When chest wall elastance is high, PEEP can significantly increase pleural pressure. In the present study, we investigate the different effects of PEEP on the pleural pressure and ICP in different respiratory mechanics.

Methods and analysis: This study is a prospective, single-centre, physiological study in severe brain injury patients. Acute respiratory distress syndrome patients with ventricular drainage will be enrolled. An oesophageal balloon catheter will be inserted to measure oesophageal pressure. Patients will be sedated and paralyzed; airway pressure and oesophageal pressure will be measured during end-inspiratory occlusion and end-expiratory occlusion. Elastance of the chest wall, the lungs and the respiratory system will be calculated at the PEEP level of 5 cmH₂O, 10 cmH₂O and 15 cmH₂O. We will classify each patient based on the maximal Δ ICP/ Δ PEEP being above or below the median for the study population. Two groups will thus be compared.

Ethics and dissemination: The study protocol and consent forms were approved by the Institutional Review Board of Fujian Provincial Hospital. Study findings will be disseminated through peer-reviewed publications and conference presentations.

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4 **Trial registration:** The study was registered on January 26, 2016, at ClinicalTrials.org
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6 (ClinicalTrials.gov Identifier: NCT02670733)
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10 **Key words:** Oesophageal pressure; acute respiratory distress syndrome; positive
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12 end-expiratory pressure; intracranial pressure
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STRENGTHS AND LIMITATIONS OF THIS STUDY

- Oesophageal pressure will be measured in this study and thereby we will be able to differentiate the possible contributions of the lungs and the chest wall to the influence of PEEP on ICP.
- The main limitation of this study is the absence of widely accepted thresholds to identify the responsiveness of ICP to increased PEEP, and we therefore arbitrarily divided patients into two groups using the median of the study population.

INTRODUCTION

Acute respiratory distress syndrome (ARDS), which is characterized by severe hypoxemia and alterations in lung function, is common in critically ill patients. Numerous authors have reported that a significant portion of patients with brain injury can develop pulmonary complications, including ARDS and neurogenic pulmonary edema (NPE).[1-6] Ventilation strategies to protect the lungs should be applied in patients with ARDS.[7] The mainstays of lung-protective ventilation strategies are to (1) limit tidal volume and driving pressure; (2) limit end-inspiratory plateau pressure (P_{plat}); and (3) provide adequate positive end-expiratory pressure (PEEP) to keep the lungs open and prevent alveolar collapse.

There are concerns that the use of PEEP for the treatment of pulmonary complications in patients with brain injury could elevate intracranial pressure (ICP) and deteriorate neurological status. Both respiratory system elastance and ventricular compliance are thought to contribute to the elevation of ICP when PEEP increases.[8-11] In theory, PEEP may increase ICP by increasing pleural pressure and diminishing venous return. However, the transmission of PEEP into the thoracic cavity depends on the properties of the lungs and chest wall. An experimental study conducted by Chapin et al. showed that when chest wall elastance is high, PEEP can significantly increase pleural pressure, whereas high lung elastance can minimize airway pressure transmission.[12] Lung elastance is generally recognized to increase in ARDS patients due to extensive alveolar collapse. However, it has been reported that the chest wall elastance ratio (the ratio between the elastance of the chest wall and the respiratory system) may vary

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4 from 0.2 to 0.8.[13] Therefore, it is important to distinguish between the elastance of
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6 the chest wall and the lungs when investigating the effects of PEEP on ICP.
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10 We hypothesise that PEEP has greater influence on ICP in patients with higher chest
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12 wall elastance ratio (e.g. the lung elastance is low and/or the chest wall elastance is
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14 high). To test the hypothesis, we need to measure the airway pressure and pleural
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16 pressure to calculate the elastance of the lung and the chest wall. However, pleural
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18 pressure is difficult to measure in clinical situations, and oesophageal pressure (P_{es}) is
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20 considered a surrogate of pleural pressure.[14 15] In the present study, we will
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22 investigate the effects of PEEP on pleural pressure and ICP by measuring P_{es} .
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METHODS

Study design overview

The present study is a prospective, single-centre, physiological study in patients with severe brain injury.

Study setting and population

The study setting is the surgical intensive care unit (SICU) (22 beds), at Fujian Provincial Hospital (2500 beds), Fujian Provincial Clinical College of Fujian Medical University, Fuzhou, China.

All patients admitted to the SICU will be consecutively screened for study eligibility.

Inclusion criteria are as follows:

- 1) Aged 18 years or above;
- 2) Glasgow Coma Score \leq 8;
- 3) Ventricular ICP monitor placement for ICP monitoring and cerebrospinal fluid (CSF) drainage;
- 4) Need for mechanical ventilation with PEEP; and
- 5) ARDS diagnosis according to the Berlin Definition.[7]

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4 Exclusion criteria are as follows:
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- 7 1) Hemodynamic instability requiring more than 10 µg/kg/min dopamine or more
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9 than 0.5 µg/kg/min norepinephrine;[10]
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12 2) ICP > 25 mmHg;
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15 3) Decompressive craniectomy was performed;
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18 4) Oesophageal varices;
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21 5) History of oesophageal or gastric surgery;
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24 6) Evidence of active air leak from the lung, including bronchopleural fistula,
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26 pneumothorax, pneumomediastinum, or existing chest tube; and
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29 7) History of chronic obstructive pulmonary disease.
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Baseline data collection

After enrolment, the following baseline data will be collected:

Demographic data: age, gender, height, and predicted body weight, which is calculated as $50 + 0.91 \times (\text{centimetres of height} - 152.4)$ for males and $45.5 + 0.91 \times (\text{centimetres of height} - 152.4)$ for females.[16]

Clinical data: primary diagnosis, type of brain injury (traumatic brain injury, stroke or postoperation for brain tumour), type of brain lesion (bilateral or unilateral), Acute

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4 Physiology and Chronic Health Evaluation II score (APACHE II) at the time of ICU
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6 admission, Simplified Acute Physiology Score II (SAPS II) on the day of enrolment,
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8 and duration of mechanical ventilation prior to enrolment.
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11 Mechanical ventilation and blood gas at baseline: PEEP, FiO₂, partial pressure of
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13 oxygen in arterial blood (PaO₂), PaO₂/FiO₂ (P/F ratio), PaCO₂ and pH.
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17 Baseline ICP and haemodynamic parameters: HR, blood pressure, central venous
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19 pressure (CVP) and CVP change during the passive leg raising test.
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27 **Ventricular compliance measurement**

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29 ICP will be measured with a ventricular ICP monitor (Codman, Johnson & Johnson,
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31 Raynham, MA, USA). To measure ventricular compliance, 2 mL of CSF will be
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33 drained, and the ICP value before and after CSF drainage will be recorded. Ventricular
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35 compliance will be calculated as follows:
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41 Ventricular compliance = 2/ (ICP before CSF drainage – ICP after CSF drainage)

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43 (Formula 1).
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51 **Placement of oesophageal balloon catheter**

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53 We will use the SmartCath-G adult nasogastric tube with an oesophageal balloon
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55 (7003300, CareFusion Co., Yorba Linda, CA, USA) in this study. Patients will remain
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4 in a supine position with the head of the bed elevated to 30° during the study period.
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6 After anesthetizing the nose and oropharynx with 10% lidocaine spray, the
7
8 oesophageal balloon catheter will be inserted through the nostril to a depth of 60 cm.
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10 The intra-gastric position of the distal part of the catheter will be confirmed by
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12 aspiration of gastric juice and auscultation of air insufflations into the stomach. After
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14 confirmation of the catheter position, the balloon will be inflated with 1.5 mL of air
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16 [17 18], and the proximal part of the catheter will be connected to the pressure
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18 transducer. Subsequently, the catheter will be slowly withdrawn, and the dynamic
19
20 occlusion test will be performed.[19] An end-expiratory occlusion will be performed
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22 until three to five spontaneous inspiratory efforts are made against the end-expiratory
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24 occlusion. The ratio of the change in P_{es} to the change in airway pressure ($\Delta P_{es}/\Delta P_{aw}$)
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26 will be calculated. The catheter will be considered correctly positioned when the
27
28 $\Delta P_{es}/\Delta P_{aw}$ ratio during the occlusion test is in the range of 0.8 to 1.2.[20-22] In
29
30 paralyzed patients, the occlusion test will be performed by applying manual
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32 compression on the rib cage during the end-expiratory occlusion.
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46 **Pressure measurements**

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48 Flow will be measured with a Fleisch pneumotachograph (Vitalograph Inc., Lenexa,
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50 KS, USA) inserted between the Y-piece of the ventilator circuit and the endotracheal
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52 tube. The volume will be obtained by electrical integration of the flow signal. Airway
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54 pressure (P_{aw} , located distal to the pneumotachograph) and P_{es} will be measured with
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4 two differential pressure transducers (KT 100D-2, Kleis TEK di Cosimo Micelli, Italy,
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6 range: +/- 100 cmH₂O). The Fleisch pneumotachograph and pressure transducers will
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8 be connected to an ICU-Lab Pressure Box (ICU Lab, KleisTEK Engineering, Bari,
9
10 Italy) by 80 cm tube lines. The signals will be displayed continuously and saved
11
12 (ICU-Lab 2.5 Software Package, ICU Lab, KleisTEK Engineering, Bari, Italy) on a
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14 laptop for further analysis at a sample rate of 200 Hz. The pressure transducer will be
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16 calibrated with a water column. The pneumotachograph will be calibrated with a 1-L
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18 calibration syringe (SN: 554-2266, Hans Rudolph, Inc. Shawnee, KS, USA).
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28 **Respiratory mechanics measurements**

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31 After placement of the oesophageal balloon catheter, patients will be sedated and
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33 paralyzed via intravenous infusion of 5 mg of midazolam, 0.1 mg of fentanyl, and 50
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35 mg of rocuronium. Mechanical ventilation will be set at a volume control ventilation,
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37 constant flow, an inspiratory–expiratory ratio of 1:2, and a tidal volume of 6 to 8
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39 mL/kg of predicted body weight. The initial respiratory rate will be set at 20/min and
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41 will be adjusted to maintain the partial pressure of carbon dioxide (PaCO₂) value at
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43 approximately 35 to 40 mmHg. PEEP will be adjusted to 5 cmH₂O. The oxygenation
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45 goal will be maintained constant at a pulse oxygen saturation (SpO₂) above 90% by
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47 adjusting the fraction of inspired oxygen concentration (FiO₂). After a 30 min
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49 stabilization period, blood gas analysis will be performed. Mean P_{aw} and P_{es} will also
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51 be recorded. An end-inspiratory occlusion and an end-expiratory occlusion will be
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4 performed, and plateau pressure (P_{plat}) and total PEEP (PEEP_{tot}) will be recorded. P_{es}
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6 during end-inspiratory occlusion ($P_{\text{es-ei}}$) and end-expiratory occlusion ($P_{\text{es-ee}}$) will also
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8 be recorded. Expiratory tidal volume (V_{te}) will also be recorded, and the elastance of
9
10 the lungs (E_{l}), the chest wall (E_{cw}) and the respiratory system (E_{rs}) will be calculated
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12 as follows:
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$$14 \quad E_{\text{rs}} = (P_{\text{plat}} - \text{PEEP}_{\text{tot}}) / V_{\text{te}} \text{ (Formula 2)}$$

$$15 \quad E_{\text{cw}} = (P_{\text{es-ei}} - P_{\text{es-ee}}) / V_{\text{te}} \text{ (Formula 3)}$$

$$16 \quad E_{\text{l}} = [(P_{\text{plat}} - P_{\text{es-ei}}) - (\text{PEEP}_{\text{tot}} - P_{\text{es-ee}})] / V_{\text{te}} \text{ (Formula 4)}$$

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27 Thereafter, PEEP will be stepwise increased to 10 and 15 cmH₂O. The measurements
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29 of ICP, ventricular compliance, haemodynamic status (HR, BP and CVP), blood gas
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31 analysis, and respiratory mechanics will be repeated at these two PEEP levels.
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Changes in end-expiratory lung volume (ΔEELV) will also be measured, which is
determined as the cumulative difference between inspiratory and expiratory tidal
volumes, during the first 30 breaths following a change in PEEP level, with a
systematic difference (namely V_{T} offset) corrected.[23-25]

A flow chart of the study procedure is shown in Figure 1.

Adverse event management and emergency termination of the study

Patients will be closely monitored during the study period. Taking into account the
potential adverse effects of PEEP, emergency interventions will be provided when the

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4 following occur:

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7 1. Abrupt increase of ICP greater than 25 mmHg and/or decrease of cerebral perfusion
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9 pressure less than 50 mmHg that persists for > 2 minutes. A bolus of 125 mL mannitol
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11 infusion will be administered.
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15 2. BP decrease to below 90/60 mmHg or a systolic BP decrease of > 40 mmHg; 100
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17 mL of crystalloid fluid infusion will be administered. The study will be continued if
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19 the patient is responsive to the interventions (BP increases); otherwise, the study will
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21 be terminated and further interventions for decreased BP will be provided.
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25 3. The procedure will be stopped if ICP is too high or BP is too low when 15 cmH₂O
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27 PEEP is applied. The data obtained at 5 and 10 cmH₂O PEEP will be collected.
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35 **Study endpoints**

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38 The primary endpoint is the influence of PEEP on ICP. There are two PEEP increases
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40 during the study procedure as follows: from 5 cmH₂O to 10 cmH₂O and from 10
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42 cmH₂O to 15 cmH₂O. We will calculate $\Delta\text{ICP}/\Delta\text{PEEP}$ to standardize the influence of
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44 PEEP on ICP during the increase of PEEP for each step.
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49 Secondary endpoints include the identification of possible contributors (see statistical
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51 analysis part for detail) to the effects of PEEP on ICP and the investigation of the
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53 influence of PEEP on haemodynamic parameters, including CVP, MAP and cerebral
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55 perfusion pressure.
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Statistical analysis

We will classify each patient into one of two groups according to the median value of $\Delta\text{ICP}/\Delta\text{PEEP}$ in the overall study population. The two groups will consist of patients with ICP responsiveness below the median value and ICP responsiveness above the median value. Since there will be two $\Delta\text{ICP}/\Delta\text{PEEP}$ values in one patient (except those who are intolerant to 15 cmH₂O PEEP), the greater one will be used to determine the grouping.

Categorical variables will be presented as numbers and percentages and analysed by the χ^2 -test. Continuous variables will be tested for normal distribution and presented as the mean and standard deviation or median and inter-quartile range as appropriate. Comparisons of continuous variables will be performed using Student's t-test for normally distributed variables and the Mann-Whitney U test for non-normally distributed variables. Wilcoxon signed-rank test will be performed to compare the difference of $\Delta\text{ICP}/\Delta\text{PEEP}$ between the two PEEP increases. Possible confounders of the ICP responsiveness to PEEP including demographic data, type of brain injury (traumatic brain injury, stroke, postoperation for brain tumour), type of brain lesion (bilateral or unilateral), change in mean arterial pressure, ventricular compliance, respiratory mechanics (elastance of the lung, the chest wall and the respiratory system, ΔEELV , chest wall elastance ratio and change of elastance) and changes of PaO₂ and PaCO₂ will be collected in this study. First, univariate analysis will be performed.

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4 Thereafter, a multivariate logistic regression analysis will be performed using
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6 forward procedures with factors demonstrating $P < 0.20$ in univariate analysis. All
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8 tests of significance will be at the 5% significance level and will be two-sided.
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11 Analyses will be performed with SPSS 19.0 (IBM Corporation, New York, USA).
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14 15 16 17 18 **Sample size calculation** 19

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21 Prospective sample size calculations are performed using G*Power Software (sample
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23 size calculating software package provided by the G*Power Team, Germany,
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25 downloaded from <http://www.gpower.hhu.de/en.html>). We will need to study 30
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27 subjects to be able to reject the null hypothesis that the means of chest wall elastance
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29 ratio of the two groups are equal with a probability (power) of 0.8. The Type I error
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31 probability with testing this null hypothesis is 0.05.
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Trial registration, ethical aspects and informed consent

The study protocol and consent forms were approved on September 30, 2015, by the Institutional Review Board of Fujian Provincial Hospital. The study was registered on January 26, 2016, at ClinicalTrials.org (ClinicalTrials.gov Identifier: NCT02670733).

After patients' eligibility for the study is confirmed, the study coordinator will be introduced to the patients' families. The ICU physician will emphasize the credentials of the study coordinator and communicate that this person will discuss a research programme for which the patient is qualified to participate. Every relevant aspect of the project will be described. The study coordinator will stop frequently, ask if there are any questions, and request that the family repeat back in their own words what is being discussed to ensure that the family understands the study. The study coordinator will be especially careful to assure the family that they are free to decline consent without consequences and that they can withdraw consent at any time without impact on treatment. Family members will be provided with contact information for the study coordinator, the local co-investigator and the local Ethical Committee. Written consent will be obtained in the presence of a witness.

Dissemination plan

Results of the trial will be submitted to an international peer-reviewed journal. The results will also be presented at national and international conferences relevant to the subject fields.

For peer review only

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DISCUSSION

Previous studies have demonstrated that PEEP exerts no significant effects on cerebral haemodynamics in patients with high respiratory system elastance.[10] However, elastance of the chest wall and the lungs were not distinguished in that previous study.

In another study that examined chest wall and lung compliance, the authors did not investigate the effects of increased PEEP on ICP.[12] In the present study, we aim to investigate the effects of PEEP on pleural pressure and ICP by measuring P_{es} .

Respiratory mechanics may change when PEEP is adjusted to a higher level. End-expiratory lung volume can also increase with an increase of PEEP, as a result of recruitment of non-aerated lung units and distension of already aerated alveoli. Moreover, PaO_2 and $PaCO_2$ can also change with PEEP adjustments. All these may contribute to the influence of PEEP on ICP. Therefore, we will measure the respiratory mechanics, $\Delta EELV$ and blood gas to determine the possible contributors.

We will classify each patient with a high or low responsiveness of ICP to increased PEEP based on whether the $\Delta ICP/\Delta PEEP$ is above or below the median for the study population. Because there is no widely accepted threshold to identify the responsiveness of ICP to increased PEEP, the division of patients into two groups is reasonable and enables us to compare differences between the two groups of patients.

Authors' contributions

HC, RGY and JXZ participated in the design of the study and drafted the manuscript.

MX, YLY, KC, JQX and YRZ participated in the design of the study. All authors edited the manuscript and read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

Acknowledgement

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Figure legends

Figure 1 Flow chart of the study procedure.

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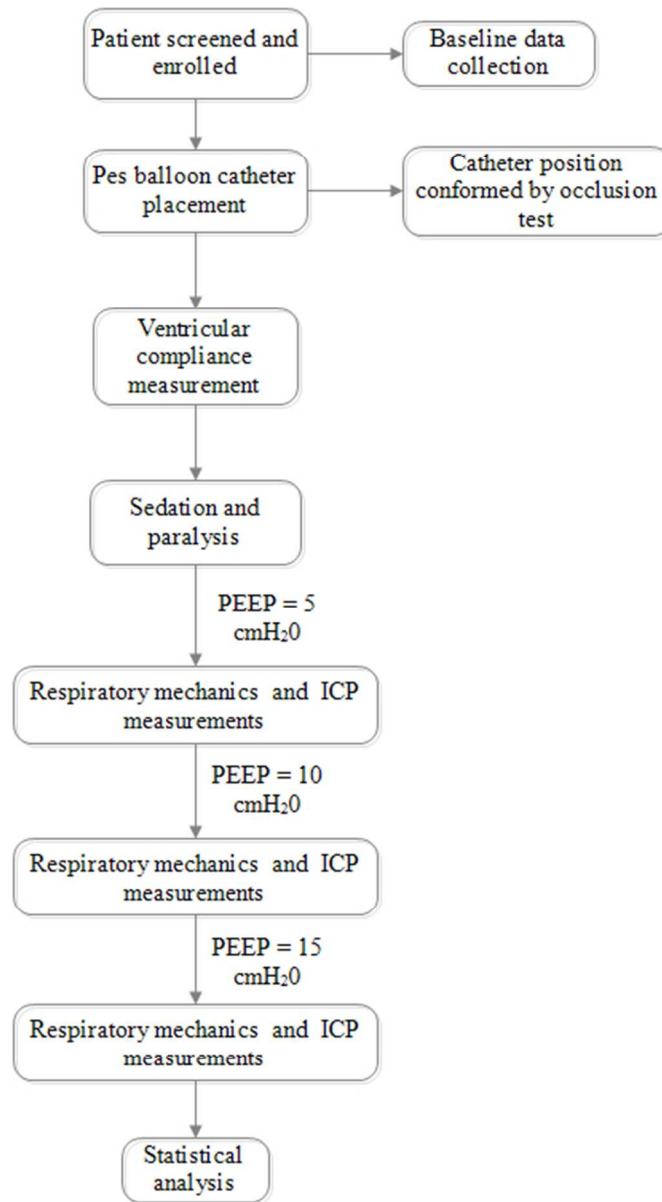


Figure 1 Flow Chart of the study procedure

35x63mm (300 x 300 DPI)



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	___ 1 ___
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	___ 1 ___
	2b	All items from the World Health Organization Trial Registration Data Set	___ None ___
Protocol version	3	Date and version identifier	___ None ___
Funding	4	Sources and types of financial, material, and other support	___ 18 ___
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	___ 1,2 ___
	5b	Name and contact information for the trial sponsor	___ 18 ___
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	___ 18 ___
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	___ None ___

1
2
3 **Introduction**

4				
5	Background and	6a	Description of research question and justification for undertaking the trial, including summary of relevant	_____6,7_____
6	rationale		studies (published and unpublished) examining benefits and harms for each intervention	
7				
8		6b	Explanation for choice of comparators	===== 14 _____
9				
10	Objectives	7	Specific objectives or hypotheses	_____7_____
11				
12	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group),	
13			allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	_____8_____
14				
15				
16	Methods: Participants, interventions, and outcomes			
17				
18	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will	===== 8 _____
19			be collected. Reference to where list of study sites can be obtained	
20				
21	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and	_____8,9_____
22			individuals who will perform the interventions (eg, surgeons, psychotherapists)	
23				
24	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be	_____10-13_____
25			administered	
26		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose	_____13_____
27			change in response to harms, participant request, or improving/worsening disease)	
28		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence	_____None_____
29			(eg, drug tablet return, laboratory tests)	
30		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	_____None_____
31				
32				
33	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood	===== 14 _____
34			pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg,	
35			median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen	
36			efficacy and harm outcomes is strongly recommended	
37				
38	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for	===== 13 _____
39			participants. A schematic diagram is highly recommended (see Figure)	
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3 Sample size 14 Estimated number of participants needed to achieve study objectives and how it was determined, including 15
4 clinical and statistical assumptions supporting any sample size calculations

5 Recruitment 15 Strategies for achieving adequate participant enrolment to reach target sample size None
6
7

8 **Methods: Assignment of interventions (for controlled trials)**
9

10 Allocation:

11
12 Sequence generation 16a Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any 14
13 factors for stratification. To reduce predictability of a random sequence, details of any planned restriction
14 (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants
15 or assign interventions

16
17 Allocation concealment mechanism 16b Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, None
18 opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
19
20

21
22 Implementation 16c Who will generate the allocation sequence, who will enrol participants, and who will assign participants to None
23 interventions

24
25 Blinding (masking) 17a Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome None
26 assessors, data analysts), and how

27
28 17b If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's None
29 allocated intervention during the trial
30
31

32 **Methods: Data collection, management, and analysis**
33

34 Data collection methods 18a Plans for assessment and collection of outcome, baseline, and other trial data, including any related 9-13
35 processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of
36 study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known.
37 Reference to where data collection forms can be found, if not in the protocol

38
39 18b Plans to promote participant retention and complete follow-up, including list of any outcome data to be None
40 collected for participants who discontinue or deviate from intervention protocols
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3	Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	_____None_____
4				
5				
6	Statistical methods			
7		20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	====_14-15=====
8				
9				
10		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	___ _None__ _
11				
12		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	___ _None__ _
13				_____
14				
15				
16	Methods: Monitoring			
17				
18	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	====_None=====
19				
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23		21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	___ _None__ _
24				
25				
26	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	___ _None__ _
27				
28				
29	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	====_None=====
30				
31				
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33	Ethics and dissemination			
34				
35	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	====_16=====
36				
37				
38	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	___ _None__ _
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3	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	_____ 16 _____
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5				
6		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	_____ None _____
7				
8	Confidentiality			
9		27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	_____ None _____
10				
11				
12	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	_____
13				
14				
15	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	_____ 18 _____
16				
17				
18	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	_____ None _____
19				
20				
21	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	_____ 16 _____
22				
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26		31b	Authorship eligibility guidelines and any intended use of professional writers	_____ None _____
27				
28		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____ None _____
29				
30	Appendices			
31				
32	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	_____ None _____
33				
34				
35	Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	_____ None _____
36				
37				

38 *It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.
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