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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-expiration 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)

Key words: *Oesophag*eal pressure; acute respiratory distress syndrome; positive end-expiration pressure; intracranial pressure

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

system, where elastance is the reciprocal of compliance) may vary from 0.2 to 0.8.[13] Therefore, it is important to distinguish between the compliance of the chest wall and the lungs when investigating the effects of PEEP on ICP.

Intrathoracic pressure (pleural pressure) is difficult to measure in clinical situations, and oesophageal pressure (P_{es}) is considered a surrogate of intrathoracic pressure.[14 15] In the present study, we will investigate the effects of PEEP on intrathoracic pressure and ICP by measuring P_{es}.

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 μg/kg/min dopamine or more than 0.5 μg/kg/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 * (centimetres of height−152.4) for males and 45.5 + 0.91 * (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), PaO_2/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/ (ICP before CSF drainage – 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 ($\Delta P_{es}/\Delta P_{aw}$) will be calculated. The catheter will be considered correctly positioned when the

$\Delta P_{es}/\Delta P_{aw}$ ratio during the occlusion test is in the range of 0.8 to 1.2.[20-22] In paralyzed patients, the occlusion test will be performed by applying manual compression on the rib cage during the end-expiratory occlusion.

Pressure measurements

Flow will be measured with a Fleisch pneumotachograph (Vitalograph Inc., Lenexa, KS, USA) inserted between the Y-piece of the ventilator circuit and the endotracheal tube. The volume will be obtained by electrical integration of the flow signal. Airway pressure (P_{aw}, located distal to the pneumotachograph) and P_{es} will be measured with two differential pressure transducers (KT 100D-2, Kleis TEK di Cosimo Micelli, Italy, range: +/- 100 cmH_2O). The Fleisch pneumotachograph and pressure transducers will be connected to an ICU-Lab Pressure Box (ICU Lab, KleisTEK Engineering, Bari, Italy) by 80 cm tube lines. The signals will be displayed continuously and saved (ICU-Lab 2.5 Software Package, ICU Lab, KleisTEK Engineering, Bari, Italy) on a laptop for further analysis at a sample rate of 200 Hz. The pressure transducer will be calibrated with a water column. The pneumotachograph will be calibrated with a 1-L calibration syringe (SN: 554-2266, Hans Rudolph, Inc. Shawnee, KS, USA).

Respiratory mechanics measurements

After placement of the oesophageal balloon catheter, patients will be sedated and paralyzed via intravenous infusion of 5 mg of midazolam, 0.1 mg of fentanyl, and 50 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 ($PaCO_2$) value at approximately 35 to 40 mmHg. PEEP will be set as the baseline level. The oxygenation goal will be maintained constant at a pulse oxygen saturation (SpO_2) above 90% by adjusting the fraction of inspired oxygen concentration (FiO_2). After a 30 min stabilization period, ICP and ventricular compliance will be measured at these baseline mechanical ventilation settings. Data on blood gas will also be obtained. 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:

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

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

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

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

If the patient's PEEP level is below 15 cmH_2O, the PEEP will be adjusted to 15 cmH_2O. If the PEEP level is equal to or greater than 15 cmH_2O, the PEEP will be remained unchanged. The PEEP level will be maintained for 30 min, and ICP,

ventricular compliance, haemodynamic status (HR, BP and CVP), blood gas analysis, and respiratory mechanic data will be collected as described above.

Thereafter, the recruitment volume induced by PEEP will be measured as follows:

The RR will be decreased to 6 breaths/min with the inspiratory time unchanged, and PEEP will be decreased to 5 cmH_2O. The PEEP volume will be measured as follows:

PEEP volume = (the first V_{te} after PEEP adjustment) – (the last V_{te} before PEEP adjustment). (Formula 5)

After the measurement of PEEP volume, RR will be increased to the baseline level with PEEP remaining at 5 cmH_2O. After a 5 min stabilization period, data on ICP, ventricular compliance, haemodynamic status (HR, BP and CVP), blood gas analysis, and respiratory mechanics will be obtained as described above.

Recruitment volume induced by PEEP will be defined as follows:

Recruitment volume = PEEP volume – $\Delta PEEP * C_{rs}$ at $PEEP_{Low}$ (Formula 6)

Where "10 * C_{rs} at low PEEP" is the minimal predicted increase in lung volume, which is the smallest possible increase in lung volume induced by PEEP.[23]

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 following occur:

1. Abrupt increase of ICP greater than 25 mmHg that persists for > 5 minutes. A bolus

of 125 mL mannitol infusion will be administered.

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

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

Study endpoints

The primary endpoint is the influence of PEEP on ICP. There are two PEEP adjustments during the study procedure as follows: from baseline PEEP to high-level PEEP (15 cmH_2O) and from high-level PEEP to low-level PEEP (5 cmH_2O). We will calculate the change in ICP per 1 cmH_2O change in PEEP to standardize the influence of PEEP on ICP during the increase or decrease of PEEP.

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 ICP responsiveness to 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 ICP value.

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 assessed 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. A multivariate logistic regression analysis will be performed using foreword procedures with factors demonstrating $P < 0.20$ in univariate logistic regression analysis. All tests of significance will be at the 5% significance level and will be two-sided. Analyses will be performed with SPSS 19.0 (IBM Corporation, New York, USA).

Sample size calculation

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

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 cmH_2O to 15 cmH_2O, 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 cmH_2O and ICP at 15 cmH_2O 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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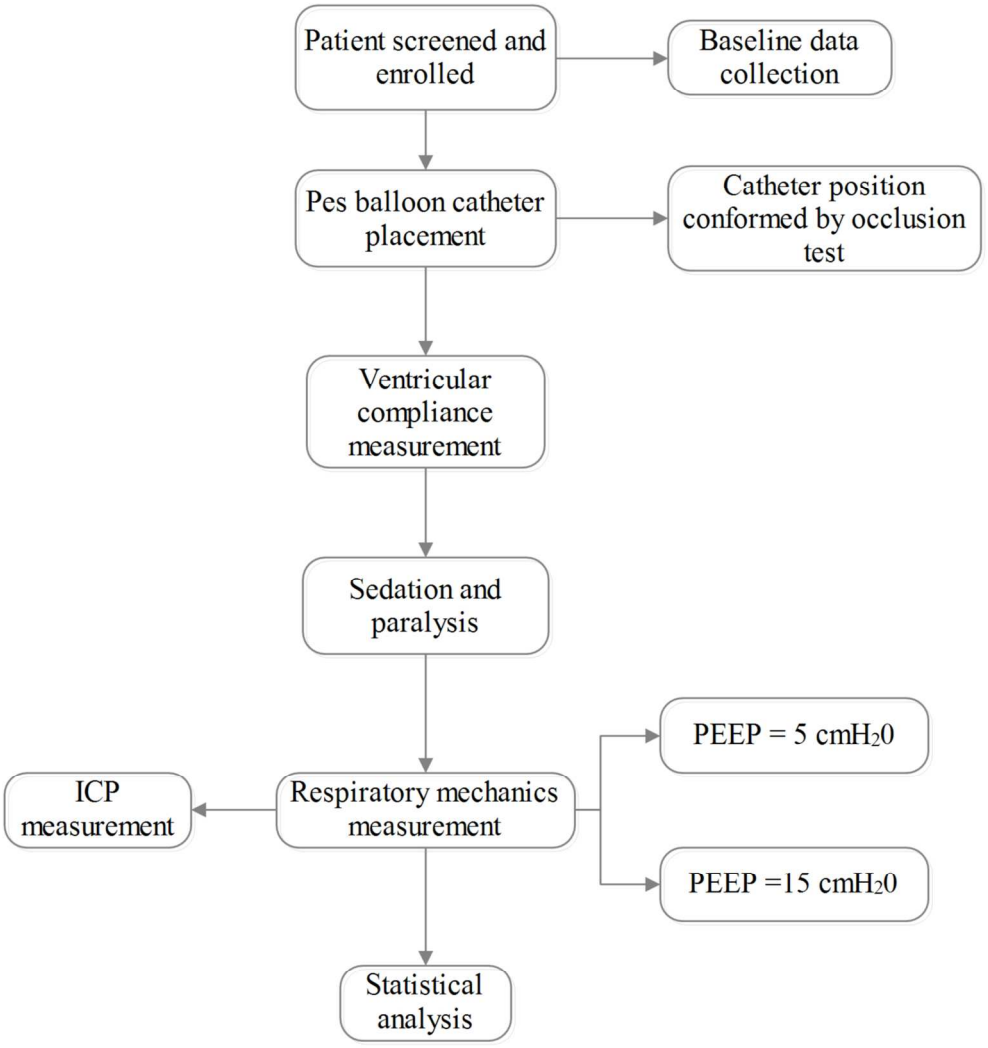

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Abstract

Introduction: There are concerns that the use of positive end-expiration 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 cmH_2O, 10 cmH_2O and 15 cmH_2O. We will classify each patient based on the maximal $\Delta ICP/\Delta PEEP$ 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.

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- 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

system, where elastance is the reciprocal of compliance) may vary from 0.2 to 0.8.[13] Therefore, it is important to distinguish between the compliance of the chest wall and the lungs when investigating the effects of PEEP on ICP.

We hypothesis that PEEP have greater influence on ICP in patients with higher elastance ratio (e.g. the lung compliance is high and/or the chest wall compliance is low). To test the hypothesis, we need to measure the airway pressure and pleural pressure to calculate the compliances of the lung and the chest wall. However, pleural pressure is difficult to measure in clinical situations, and oesophageal pressure (P_{es}) is considered a surrogate of pleural pressure.[14 15] In the present study, we will investigate the effects of PEEP on pleural pressure and ICP by measuring P_{es}.

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 μg/kg/min dopamine or more than 0.5 μg/kg/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 * (centimetres of height−152.4) for males and 45.5 + 0.91 * (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), PaO_2/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/ (ICP before CSF drainage – 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 ($\Delta P_{es}/\Delta P_{aw}$)

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

Pressure measurements

Flow will be measured with a Fleisch pneumotachograph (Vitalograph Inc., Lenexa, KS, USA) inserted between the Y-piece of the ventilator circuit and the endotracheal tube. The volume will be obtained by electrical integration of the flow signal. Airway pressure (P_{aw}, located distal to the pneumotachograph) and P_{es} will be measured with two differential pressure transducers (KT 100D-2, Kleis TEK di Cosimo Micelli, Italy, range: +/- 100 cmH_2O). The Fleisch pneumotachograph and pressure transducers will be connected to an ICU-Lab Pressure Box (ICU Lab, KleisTEK Engineering, Bari, Italy) by 80 cm tube lines. The signals will be displayed continuously and saved (ICU-Lab 2.5 Software Package, ICU Lab, KleisTEK Engineering, Bari, Italy) on a laptop for further analysis at a sample rate of 200 Hz. The pressure transducer will be calibrated with a water column. The pneumotachograph will be calibrated with a 1-L calibration syringe (SN: 554-2266, Hans Rudolph, Inc. Shawnee, KS, USA).

Respiratory mechanics measurements

After placement of the oesophageal balloon catheter, patients will be sedated and paralyzed via intravenous infusion of 5 mg of midazolam, 0.1 mg of fentanyl, and 50

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 ($PaCO_2$) value at approximately 35 to 40 mmHg. PEEP will be adjusted to 5 cmH_2O. The oxygenation goal will be maintained constant at a pulse oxygen saturation (SpO_2) above 90% by adjusting the fraction of inspired oxygen concentration (FiO_2). 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:

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

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

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

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

Thereafter, PEEP will be stepwise increased. 10 and 15 cmH_2O 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

two PEEP levels. PEEP will be then adjusted from 15 cmH_2O to 5 cmH_2O and the RR will be decreased to 4 breaths/min with the inspiratory time unchanged to measure the PEEP volume. The PEEP volume will be calculated as follows:

PEEP volume = (the first V_{te} after PEEP adjustment) – (the last V_{te} before PEEP adjustment). (Formula 5)

We will use recruitment volume to assess the recruitability. Recruitment volume induced by PEEP will be defined as follows:

Recruitment volume = PEEP volume – ΔPEEP * C_{rs} at $PEEP_5$ (Formula 6)

Where "ΔPEEP * C_{rs} at $PEEP_5$" is the minimal predicted increase in lung volume, which is the smallest possible increase in lung volume induced by PEEP.[23]

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 following occur:

1. Abrupt increase of ICP greater than 25 mmHg and/or decrease of cerebral perfusion pressure less than 50 mmHg that persists for > 2 minutes. A bolus of 125 mL mannitol infusion will be administered.

2. BP decrease to below 90/60 mmHg or a systolic BP decrease of > 40 mmHg; 100 mL of crystalloid fluid infusion will be administered. The study will be continued if the patient is responsive to the interventions (BP increases); otherwise, the study will

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 cmH_2O PEEP is applied. The data obtained at 5 and 10 cmH_2O 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 cmH_2O to 10 cmH_2O and from 10 cmH_2O to 15 cmH_2O. We will calculate $\Delta ICP/\Delta PEEP$ 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 $\Delta ICP/\Delta PEEP$ 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 $\Delta ICP/\Delta PEEP$ values in one patient (except those who are intolerant to 15 cmH_2O 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

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 ΔICP/ΔPEEP between the two PEEP increases. A multivariate logistic regression analysis will be performed using foreword procedures with factors demonstrating $P <$ 0.20 in univariate logistic regression analysis. All tests of significance will be at the 5% significance level and will be two-sided. Analyses will be performed with SPSS 19.0 (IBM Corporation, New York, USA).

Sample size calculation

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

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 ΔICP/ΔPEEP 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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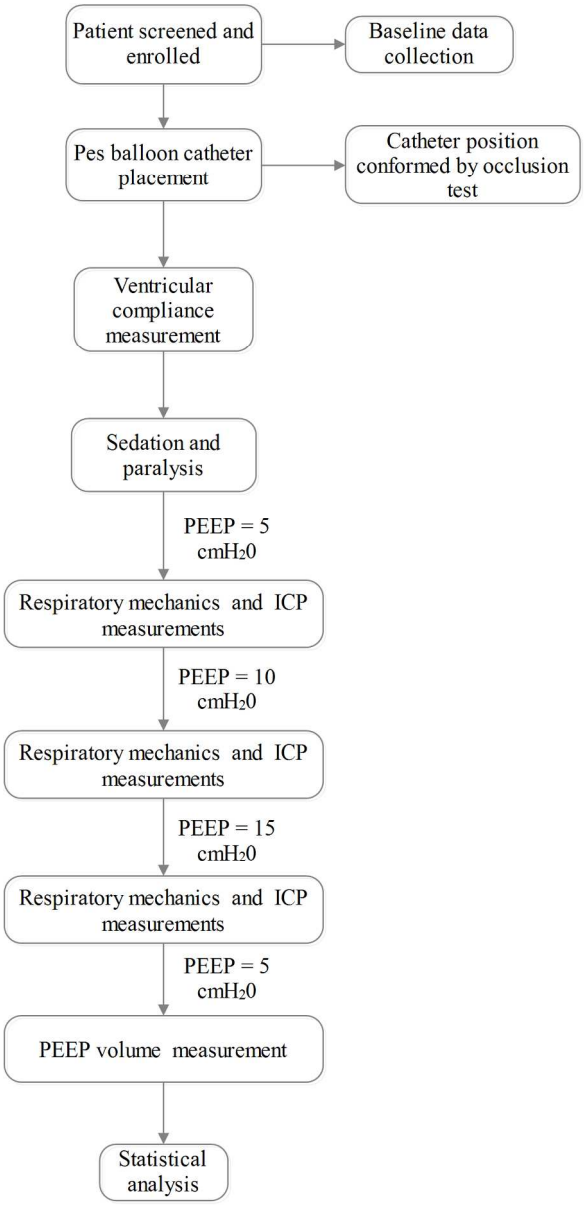

Figure 1 The flow chart of the study procedure.

110x227mm (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

Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	6,7
	6b	Explanation for choice of comparators	14
Objectives	7	Specific objectives or hypotheses	7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	8

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8,9
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10-13
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	13
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	None
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	None
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	14
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	13

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

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
Statistical methods	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
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	None
	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
Methods: Monitoring			
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
	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
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
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	None
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	16
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

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	16
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	None
Confidentiality	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
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	
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
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
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
	31b	Authorship eligibility guidelines and any intended use of professional writers	None
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	None
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	None
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

*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" license.

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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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Keywords:	Oesophageal pressure, Acute respiratory distress syndrome, Positive end-expiration pressure, Intracranial pressure

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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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 cmH_2O, 10 cmH_2O and 15 cmH_2O. We will classify each patient based on the maximal $\Delta ICP/\Delta PEEP$ 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

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

from 0.2 to 0.8.[13] Therefore, it is important to distinguish between the elastance of the chest wall and the lungs when investigating the effects of PEEP on ICP.

We hypothesise that PEEP has greater influence on ICP in patients with higher chest wall elastance ratio (e.g. the lung elastance is low and/or the chest wall elastance is high). To test the hypothesis, we need to measure the airway pressure and pleural pressure to calculate the elastance of the lung and the chest wall. However, pleural pressure is difficult to measure in clinical situations, and oesophageal pressure (P_{es}) is considered a surrogate of pleural pressure.[14 15] In the present study, we will investigate the effects of PEEP on pleural pressure and ICP by measuring P_{es}.

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 μg/kg/min dopamine or more than 0.5 μg/kg/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 × (centimetres of height−152.4) for males and 45.5 + 0.91 × (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), PaO_2/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/ (ICP before CSF drainage – 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 ($\Delta P_{es}/\Delta P_{aw}$)

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

Pressure measurements

Flow will be measured with a Fleisch pneumotachograph (Vitalograph Inc., Lenexa, KS, USA) inserted between the Y-piece of the ventilator circuit and the endotracheal tube. The volume will be obtained by electrical integration of the flow signal. Airway pressure (P_{aw}, located distal to the pneumotachograph) and P_{es} will be measured with two differential pressure transducers (KT 100D-2, Kleis TEK di Cosimo Micelli, Italy, range: +/- 100 cmH_2O). The Fleisch pneumotachograph and pressure transducers will be connected to an ICU-Lab Pressure Box (ICU Lab, KleisTEK Engineering, Bari, Italy) by 80 cm tube lines. The signals will be displayed continuously and saved (ICU-Lab 2.5 Software Package, ICU Lab, KleisTEK Engineering, Bari, Italy) on a laptop for further analysis at a sample rate of 200 Hz. The pressure transducer will be calibrated with a water column. The pneumotachograph will be calibrated with a 1-L calibration syringe (SN: 554-2266, Hans Rudolph, Inc. Shawnee, KS, USA).

Respiratory mechanics measurements

After placement of the oesophageal balloon catheter, patients will be sedated and paralyzed via intravenous infusion of 5 mg of midazolam, 0.1 mg of fentanyl, and 50

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 ($PaCO_2$) value at approximately 35 to 40 mmHg. PEEP will be adjusted to 5 cmH_2O. The oxygenation goal will be maintained constant at a pulse oxygen saturation (SpO_2) above 90% by adjusting the fraction of inspired oxygen concentration (FiO_2). After a 30 min stabilization period, blood gas analysis will be performed. 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 elastance of the lungs (E_l), the chest wall (E_{cw}) and the respiratory system (E_{rs}) will be calculated as follows:

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

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

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

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

Thereafter, PEEP will be stepwise increased to 10 and 15 cmH_2O. The measurements of ICP, ventricular compliance, haemodynamic status (HR, BP and CVP), blood gas analysis, and respiratory mechanics will be repeated at these two PEEP levels.

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 following occur:

1. Abrupt increase of ICP greater than 25 mmHg and/or decrease of cerebral perfusion pressure less than 50 mmHg that persists for > 2 minutes. A bolus of 125 mL mannitol infusion will be administered.

2. BP decrease to below 90/60 mmHg or a systolic BP decrease of > 40 mmHg; 100 mL of crystalloid fluid infusion will be administered. The study will be continued if the patient is responsive to the interventions (BP increases); otherwise, the study will 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 cmH_2O PEEP is applied. The data obtained at 5 and 10 cmH_2O 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 cmH_2O to 10 cmH_2O and from 10

cmH_2O to 15 cmH_2O. We will calculate ΔICP/ΔPEEP 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 ΔICP/ΔPEEP 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 ΔICP/ΔPEEP values in one patient (except those who are intolerant to 15 cmH_2O 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 ΔICP/ΔPEEP 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), 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 PaO_2 and $PaCO_2$ will be collected in this study. First, univariate analysis will be performed. Thereafter, a multivariate logistic regression analysis will be performed using foreward procedures with factors demonstrating $P < 0.20$ in univariate analysis. All tests of significance will be at the 5% significance level and will be two-sided. Analyses will be performed with SPSS 19.0 (IBM Corporation, New York, USA).

Sample size calculation

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

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, ΔEELV 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 ΔICP/ΔPEEP 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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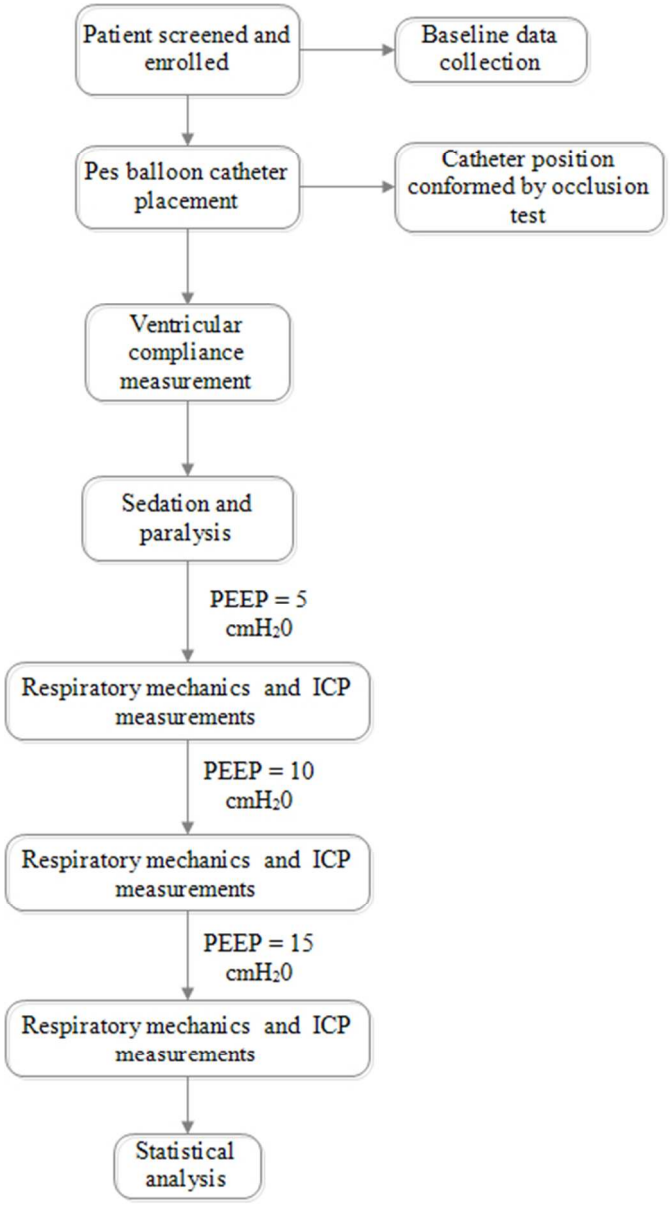

Figure 1 Flow Chart of the study procedure

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

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

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

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
Statistical methods	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
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	None
	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
Methods: Monitoring			
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
	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
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
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	None
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	16
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

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	16
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	None
Confidentiality	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
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	
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
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
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
	31b	Authorship eligibility guidelines and any intended use of professional writers	None
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	None
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	None
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

*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" 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

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Keywords:	Oesophageal pressure, Acute respiratory distress syndrome, Positive end-expiration pressure, Intracranial pressure

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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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 cmH_2O, 10 cmH_2O and 15 cmH_2O. We will classify each patient based on the maximal $\Delta ICP/\Delta PEEP$ 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

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

from 0.2 to 0.8.[13] Therefore, it is important to distinguish between the elastance of the chest wall and the lungs when investigating the effects of PEEP on ICP.

We hypothesise that PEEP has greater influence on ICP in patients with higher chest wall elastance ratio (e.g. the lung elastance is low and/or the chest wall elastance is high). To test the hypothesis, we need to measure the airway pressure and pleural pressure to calculate the elastance of the lung and the chest wall. However, pleural pressure is difficult to measure in clinical situations, and oesophageal pressure (P_{es}) is considered a surrogate of pleural pressure.[14 15] In the present study, we will investigate the effects of PEEP on pleural pressure and ICP by measuring P_{es}.

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 μg/kg/min dopamine or more than 0.5 μg/kg/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 × (centimetres of height−152.4) for males and 45.5 + 0.91 × (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), PaO_2/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/ (ICP before CSF drainage – 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 ($\Delta P_{es}/\Delta P_{aw}$) will be calculated. The catheter will be considered correctly positioned when the $\Delta P_{es}/\Delta P_{aw}$ ratio during the occlusion test is in the range of 0.8 to 1.2.[20-22] In paralyzed patients, the occlusion test will be performed by applying manual compression on the rib cage during the end-expiratory occlusion.

Pressure measurements

Flow will be measured with a Fleisch pneumotachograph (Vitalograph Inc., Lenexa, KS, USA) inserted between the Y-piece of the ventilator circuit and the endotracheal tube. The volume will be obtained by electrical integration of the flow signal. Airway pressure (P_{aw}, located distal to the pneumotachograph) and P_{es} will be measured with

two differential pressure transducers (KT 100D-2, Kleis TEK di Cosimo Micelli, Italy, range: +/- 100 cmH_2O). The Fleisch pneumotachograph and pressure transducers will be connected to an ICU-Lab Pressure Box (ICU Lab, KleisTEK Engineering, Bari, Italy) by 80 cm tube lines. The signals will be displayed continuously and saved (ICU-Lab 2.5 Software Package, ICU Lab, KleisTEK Engineering, Bari, Italy) on a laptop for further analysis at a sample rate of 200 Hz. The pressure transducer will be calibrated with a water column. The pneumotachograph will be calibrated with a 1-L calibration syringe (SN: 554-2266, Hans Rudolph, Inc. Shawnee, KS, USA).

Respiratory mechanics measurements

After placement of the oesophageal balloon catheter, patients will be sedated and paralyzed via intravenous infusion of 5 mg of midazolam, 0.1 mg of fentanyl, and 50 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 ($PaCO_2$) value at approximately 35 to 40 mmHg. PEEP will be adjusted to 5 cmH_2O. The oxygenation goal will be maintained constant at a pulse oxygen saturation (SpO_2) above 90% by adjusting the fraction of inspired oxygen concentration (FiO_2). After a 30 min stabilization period, blood gas analysis will be performed. 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 ($P_{es\text{-}ei}$) and end-expiratory occlusion ($P_{es\text{-}ee}$) will also be recorded. Expiratory tidal volume (V_{te}) will also be recorded, and the elastance of the lungs (E_l), the chest wall (E_{cw}) and the respiratory system (E_{rs}) will be calculated as follows:

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

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

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

Thereafter, PEEP will be stepwise increased to 10 and 15 cmH_2O. The measurements of ICP, ventricular compliance, haemodynamic status (HR, BP and CVP), blood gas analysis, and respiratory mechanics will be repeated at these two PEEP levels. 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

following occur:

1. Abrupt increase of ICP greater than 25 mmHg and/or decrease of cerebral perfusion pressure less than 50 mmHg that persists for > 2 minutes. A bolus of 125 mL mannitol infusion will be administered.

2. BP decrease to below 90/60 mmHg or a systolic BP decrease of > 40 mmHg; 100 mL of crystalloid fluid infusion will be administered. The study will be continued if the patient is responsive to the interventions (BP increases); otherwise, the study will 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 cmH_2O PEEP is applied. The data obtained at 5 and 10 cmH_2O 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 cmH_2O to 10 cmH_2O and from 10 cmH_2O to 15 cmH_2O. We will calculate $\Delta ICP/\Delta PEEP$ 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 ΔICP/ΔPEEP 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 ΔICP/ΔPEEP values in one patient (except those who are intolerant to 15 cmH_2O 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 ΔICP/ΔPEEP 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 PaO_2 and $PaCO_2$ will be collected in this study. First, univariate analysis will be performed.

Thereafter, a multivariate logistic regression analysis will be performed using foreward procedures with factors demonstrating $P < 0.20$ in univariate analysis. All tests of significance will be at the 5% significance level and will be two-sided. Analyses will be performed with SPSS 19.0 (IBM Corporation, New York, USA).

Sample size calculation

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

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, ΔEELV 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 ΔICP/ΔPEEP 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:

The study was supported by grants from the Beijing Municipal Administration of Hospital (ZYLX201502, DFL20150502). The sponsor had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Competing interests

The authors declare that they have no competing interests.

Acknowledgement

We thank Lauren W. from American Journal Experts for language editing.

Figure legends

Figure 1 Flow chart of the study procedure.

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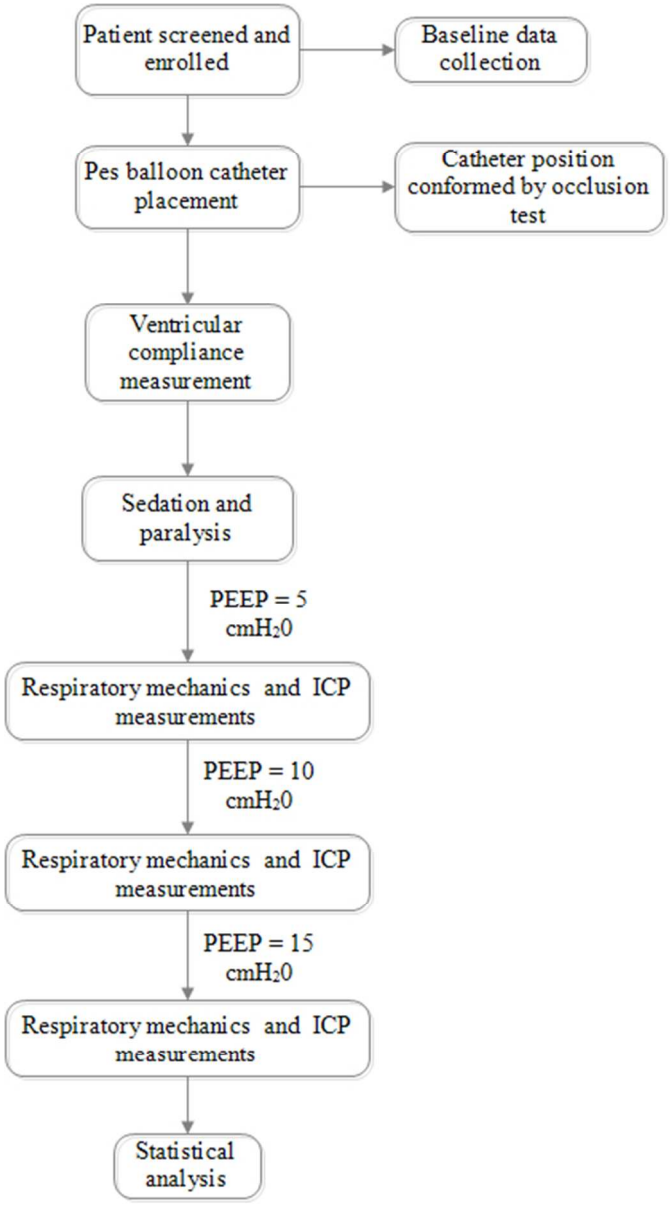

Figure 1 Flow Chart of the study procedure

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

Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	6,7
	6b	Explanation for choice of comparators	14
Objectives	7	Specific objectives or hypotheses	7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	8

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8,9
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10-13
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	13
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	None
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	None
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	14
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	13

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

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
Statistical methods	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
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	None
	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
Methods: Monitoring			
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
	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
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
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	None
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	16
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

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	16
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	None
Confidentiality	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
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	
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
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
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
	31b	Authorship eligibility guidelines and any intended use of professional writers	None
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	None
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	None
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

*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" license.