Project name: Using electrical impedance tomography to monitor the effect of airway pressure release ventilation on the respiratory mechanism of acute respiratory distress syndrome

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1. Introduction

1.1 Background

1.1.1 Basic introduction

Acute respiratory distress syndrome(ARDS) is common syndrome in ICU which is characteristic by diffuse endothelial cell and epithelial damage,inflammatory edema,heterogeneous lung injury and refractory hyoxemia.Mechanical ventilation(MV) is the major treatment for ARDS.Lung protective MV including low tidal volume (LTV),appropriate positive end expiratory pressure(PEEP) and prone position ventilation(PPV) has been proved to improve outcome effectively. Despite these measures, the mortality of ARDS is still high, up to 30-50%.

Airway pressure release ventilation(APRV) is an kind of inverse ratio ventilation that provides consistently high mean airway pressure (mPaw) which preventing alveolar collapse/hyperventilation and recurrent opening/closure theoretically. Clinical trials have shown it to be effective to improve oxygenation and lung compliance in ARDS patients.Animal studies have also shown that compared with low tidal volume ventilation,APRV could improve oxygenation, reduce lung heterogeneity and alveolar over-expansion, reduce lung inflammation and histopathological damage.However, the ventilatory and blood flow changes on local lung tissues of ARDS patients during APRV have not

been confirmed.Moreover, due to the lung heterogeneity in ARDS patients, the increase of mPaw may lead to local lung over-expanded and collapsed simultaneously, which may result in the increase of pulmonry shunt fraction and dead space ventilation.Therefore, bedside monitoring of physiological effects of APRV in ARDS patients' lung would help to better understand the efficacy of APRV in clinical application.

Electrical impedance tomography (EIT) is a noninvasive, nonradiological, real-time bedside lung imaging technology which can monitoring local alveolar over-expansion and collapse.In recent years, EIT has been proposed to assess pulmonary perfusion by injecting saline.Therefore, EIT would be an ideal bedside tool to evaluate the effects of APRV on respiratory physiology. We hypothesized that EIT may help to clarify the effects of APRV on local lung ventilation, pulmonary shunt,dead space ventilation and V/Q ratio.

1.1.2 Preliminary Research Basis

In animal models of ARDS, APRV was found to reduce ventilation-induced lung injury (VILI) and improve alveolar heterogeneity.

RCT studies showed that compared with LTV, APRV improved oxygenation and lung compliance, and reduced duration of mechanical ventilation in ARDS patients significantly.

1.2 Study type

A single-center prospective observational study.

1.3 Study basis

ARDS is an acute, diffuse, inflammatory lung injury that results in increased alveolar capillary permeability and lung weight, and loss of aerated lung tissue.Current guidelines for ARDS include LTV for lung protective ventilation to improve oxygenation, which is recommended to all types of ARDS patients.However, the lung injury of ARDS is "heterogeneous", with alveolar collapse and atelectasis in gravity dependent area and over-expansion non-gravity dependent area. Besides, due to the geometric effects, parenchyma at the boundary between unidirectional and aerated parenchyma may bear greater strain and stress.APRV is an kind of inverse ratio ventilation that provides consistently high mean airway pressure (mPaw) to prevent alveolar collapse/hyperventilation and recurrent opening/closure theoretically. Clinical trials showed that APRV can improve oxygenation and lung compliance effectively, and reduce mechanical ventilation duration.Animal models of ARDS also showed that compared with LTV, APRV can improve oxygenation and reduce pulmonary heterogeneity and alveolar over-expansion, reduce lung inflammation and histopathological damage.However, up to now,the changes of ventilatory and blood flow in local lung tissue of ARDS patients during APRV have not been studied.In

addition, due to the high degree of respiratory heterogeneity in ARDS patients, the increase of mPaw may lead to simultaneous hyperexpansion and collapse of local lung tissues, which may be followed by an increase in pulmonary shunt fraction and dead space ventilation.Bedside monitoring of the physiological effects of APRV on the lungs would help to better understand the efficacy of APRV in clinical practice. EIT is a noninvasive,nonradioactive real-time bedside lung imaging tool for monitoring local alveolar over-expansion and collapse.In addition, EIT can be used to assess the V/Q ratio by injecting saline, contributing to a deeper understanding of the respiratory physiology of APRV on local lung tissues.

1.4 Risk and benefit

1.4.1 Known potential risks

Several animal experiments and clinical studies have demonstrated that APRV can effectively improve oxygenation and reduce MV duration. Compared with conventional MV, APRV is relatively safe. Therefore, there is no potential risk in this study.

1.4.2 Probability of injury

Mechanical ventilation is a routine treatment for patients with respiratory failure in the ICU, and its safety is well established.

1.4.3 Degree of injury

The subjects will suffer very minor injuries and have no fatal

adverse events.

1.4.4 Known potential benefits

MV is a routine treatment for ARDS patients. Compared with LTV, APRV ventilation can effectively improve oxygenation and reduce the duration of MV in ARDS patients.However, since APRV was classified as inverse ratio ventilation and relatively complex, it has not been widely applied in clinical practice. In this research, we will clarify the effect of APRV on pulmonary respiration mechanism in ARDS patients by EIT monitoring, and provide more clinical evidence for the application of APRV in ARDS patients.

1.4.5 Assessment of potential risks/benefits

MV is a routine treatment for ARDS patients. APRV is a classical mode of MV that has been used in the treatment for ARDS patients over 20 years. Animal and clinical studies have shown that it can effectively improve oxygenation, reduce the duration of MV and the length of ICU stay with less complications. However, due to the uncertainty of mechanism, Its application is still limited in clinical practice. We hope to further explore the mechanism of APRV through this study and provide sufficient evidence for its clinical promotion in ARDS patients.The potential risks of APRV are similar to those of other MV modes. It is a life-saving treatment for ARDS patients with minimal risks when conducted in appropriate indications and contraindications.

1.4.6 Discussion

APRV is a classical mode of MV that can effectively improve oxygenation in ARDS patients. Its unique characteristic of inverse radio ventilation helps to increase the time of alveolar gas exchange and effectively improve oxygenation. In addition, it can increase the mean airway pressure to promote the reaeration of collapsed alveoli. Because the airway pressure is set according to the platform pressure, there is less possibility of barotrauma during APRV.

At present, the effects of APRV on respiratory physiology are mostly limited to animal experimental models of ARDS, and its effects on respiratory physiology of ARDS patients still uncertain.For instance, whether it can improve the heterogeneity of lung lesions, or promote the reaeration of collapsed alveoli, or improve V/Q ratio in ARDS patients have not been supported by sufficient clinical evidence.EIT is a noninvasive,nonradioactive real-time bedside lung imaging tool for monitoring local alveolar.We hypothesized that EIT may help to clarify the effects of APRV on local lung ventilation, pulmonary shunt,dead space ventilation and V/Q ratio. We hope that this study will help clinicians to obtain a deeper understanding of APRV and promote its application in ARDS patients.

2. Objective and outcome

Objective: to clarify the effect of APRV on pulmonary ventilation

distribution and V/Q ratio in ARDS patients.

Primary outcome: Effect of 24h APRV on pulmonary ventilation distribution in ARDS patients.

Secondary outcome: Effects of APRV on lung ventilation distribution and V/Q ratio in ARDS patients at different times.

3. Study design

3.1 overall design

A Single center prospective observational study.

ARDS patients who received APRV were monitored by EIT at the time of before APRV and after APRV at 2h, 6h,12h,24h,48h and 72h. MV parameters, respiratory mechanics, results of arterial blood gas analysis, and hemodynamic status were recorded, and cardiac status was monitored by point-of care ultrasound.

Data collecting

(1) Demographic data:Sex, age, height, weight.

(2) Vital signs: Organ function including sequential organ function score (SOFA) score,acute physiology and chronic health evaluation Ⅱ (APACHE Ⅱ) score.

(3) physiological and laboratory test: Blood routine, Serum biochemical examination (total protein, albumin (ALB),total bilirubin (TB),aspartate aminotransferase (AST), alanine transaminase (ALT), gamma-glutamyl transpeptidase (GGT),blood urea nitrogen (BUN), serum creatinine (Scr)),

brain natriuretic peptide (BNP), C-reactive protein (CRP), respiratory mechanics, cardiac and hemodynamic status at the time of before APRV, APRV 24h, ARPV 48h and APRV 72h.

3.2 sample size

Referring to previous literatures, the number of patients is generally required to be 20, and the number of patients should be increased to 30 in consideration of shedding and withdrawal.

4. Study population

4.1 Diagnostic criteria

ARDS is diagnosed according to the 2014 Berlin definition.

4.2 Inclusion criteria

The following three items must be met simultaneously:

(1) Age: ＞18 years old and ＜80 years old

(2) ARDS was diagnosed as moderate to severe according to the 2014 Berlin definition.

(3) APRV duration is expected to exceed 72 hours.

4.3 Exclusion criteria

Any of the following exclusion criteria is an exclusion:

(1) APRV contraindications including pneumothorax, severe COPD, severe asthma, and intracranial hypertension

(2) Pregnancy and perinatal stage

(3) Severe cardiac dysfunction (NYHA classⅢor IV, acute coronary

syndrome or persistent ventricular tachyarrhythmia),chronic cardiopulmonary disease resulting in enlargement of the right heart, cardiogenic shock or cardiac perioperative period

(4) Refractory shock

(5) BMI>35 kg/m^2

5. The items and frequency of clinical and laboratory examinations to be performed

Pulmonary gas distribution, pulmonary shunt, and V/Q ratio were monitored by EIT before APRV and 2h,6h,12h,24h,48h and 72h after APRV. Blood routine, serum biochemistry test,BNP,CRP and arterial blood gas were recorded before APRV and 24h,48h and 72h after APRV. cardiac status was monitored by point-of-care ultrasound.

6. Evaluation

6.1 Primary and secondary outcome

Primary outcome: the effect of 24h APRV on pulmonary gas distribution monitored by EIT.

Secondary outcome: the effect of APRV on V/Q and pulmonary shunt at each time point monitored by EIT.

6.2 Safety evaluation

APRV is a mode of MV for ARDS patients and has been shown to be safe in animal and clinical studies.

7. Adverse events and severe adverse events

Adverse event reports: Adverse medical events that occur in patients receiving APRV, but are not necessarily causally related to treatment.

Reports of serious adverse events: patients receiving APRV experienced events requiring prolonged hospitalization, disability, incapacity to work, life-threatening events or death.

During a clinical trial, the clinical investigators are obligated to take necessary measures to ensure the safety of the patients and to document them timely.If serious adverse events occur during the clinical trial, the investigators should immediately administer appropriate treatment to the subject, and investigators should report to clinical trial unit Ethics committee,provincial or regional food and drug administration and state food and drug administration and sponsor by telephone or fax within 24 hours.At the same time, a written report shall be submitted to the above institutions within 15 days.The serious adverse event that occurred during study must be completed serious adverse event report form on the CRF.

All serious adverse events should be followed up until resolved and returned to baseline.Medical documentation of serious adverse events that proved to be irresolvable/permanent conversion to other treatment or death should be documented in the original documentation and follow-up form as well as results of laboratory and other tests.

The investigators and other responsible persons should analyze and determine the causal relationship between serious adverse events in the

subjects from a clinical perspective.

8. Statistical analysis and methods

Statistical analysis was performed by Prism 4.01. Due to the parameters are abnormal distributed, the data is showed as median (interquartile range).The data obtained at each step were compared using Friedman ANOVA of repeated measurements and, when appropriate, through Dunn post hoc tests using Bonferroni correction.Qualitative data were compared with Fisher's exact test.All comparisons were two-sided,P ＜0.05 indicates the existence of significant difference.

9. Medical treatment and protection of subjects

9.1 Risk assessment of subjects in the study and risk disposal plan

(1) Reporting methods: Any adverse events, such as subjects' subjective discomfort and abnormal laboratory testing, should be treated seriously and analyzed carefully, and immediate measures should be taken to protect the safety of subjects

(2) Processing procedures: detailed records, and according to the situation of retest, record the disappearance of its continuous turnaround and other circumstances.

(3) Follow-up for unmitigated adverse events. All adverse events should be followed up until they are properly resolved or the disease is stable.

9.2 Medical treatment and protection of subjects during the study

The rights and welfare of the subjects will be protected during the

study, and the quality of their medical care will not be affected by their refusal to participate or withdrawal from the study.

If the patient drops out of the study, we will no longer conduct study related tests.

The investigators will provide insurance for the subjects participating in the study program. If the subjects suffer any damage related to the study, they will receive timely free treatment and be compensated or compensated according to laws and regulations and mutual agreements.

9.3 Medical treatment and protection of subjects after study

APRV was administered in a investigational manner during the study, with inclusion/exclusion criteria clarified and efficacy and safety information recorded.Routine treatment was continued after the study.Subjects shall not be required to waive their right to free treatment and compensation for study related damages.

10. Supporting documents and notes

10.1 Informed consent process

Informed consent was completed before the subjects' relatives agreed to participate in the study and continued throughout the study.Informed consent was approved by the ETHICS committee, and the relatives of the study subjects should read the informed consent.Researchers explain the process and answer questions from

relatives; The subjects were also informed of possible risks to their relatives and their rights.

The investigator must inform the relatives that their participation is voluntary and that they may withdraw from the study at any time during the study.Copies of the informed consent can be provided to the relatives of the subjects for preservation.The rights and welfare of relatives will be protected and it is stressed that the quality of their medical care will not be affected by their refusal to participate.

10.2 privacy protection

The relevant data of the research object shall be kept by the project quality controller, who shall store the relevant form records and samples. All investigators should subject to the principle of confidentiality and relevant regulations, the ethics committee of the supervisor and the inspectors of the drug regulatory department may access the original medical records.No research information should be disclosed to unauthorized third parties without prior approval.

10.3 Collection and use of specimens and data

The blood samples collected by the institute are only used for routine medical tests in the treatment process, so there will be no residual specimens retained.

After the study, the retained image data and other data will be used for future research with the consent of the subjects.

10.4 Quality control and quality assurance

All physicians participating in this study were familiarized with APRV mechanical ventilation mode,EIT, and point-of-care ultrasound.

All physicians participating in this study should be aware of the time nodes for testing and blood collection.

The CRF form should be checked by two persons.

The project quality control leader shall conduct quality control on the study data every week to ensure the safety, accuracy and orderly progress of the test.

10.5 Data processing and record keeping

10.5.1 Data collection and management

The required data were collected from the medical records of patients who met the inclusion criteria and filled in the paper CRF.

Data collection will be conducted by the clinical investigator under the supervision of the superintendent, who will be responsible for the accuracy, completeness and timeliness of the reported data.All data shall be clear to ensure accurate interpretation and traceability.

Data entry: Remote data entry is carried out after the training of data entry staff, which is completed by two people independently by using the double-copy entry method.

Data review: Manual comparison of data in the case report form and the database to ensure that the data in the database are consistent with the

results in the CRF.

Data locking: In addition to the above data review, the principal investigator, statistician, data manager and sponsor representative shall further discuss and confirm the main content of the research proposal and the statistical analysis proposal. Investigator should audit to confirm that all data have been entered into the database, all questions have been resolved, and the analysis group has been defined and made a judgment before locking the data.

Clinical data will be stored in a database, which shall be password protected and logical collation procedures shall be set up when the database is established.

10.5.2 Research data retention

Specify minimum retention time for all data, original documents, and permission to be obtained prior to destruction.

10.5.3 Statement of conflict of interest

There is no conflict of interest between this study and any physician participating in this clinical study.