Project name: The Effect of APRV on Right Ventricular Function Assessed by Transthoracic Echocardiography

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1.The introduction

1.1 Research Background

1.1.1 Basic Overview

Acute Respiratory Distress Syndrome (ARDS) often complicated with Right Ventricular Dysfunction (RVD), the incidence of which can be as high as 64%. Acute cor pulmonale is the most serious form of ARDS complicated with RVD.The mechanisms include pulmonary vascular dysfunction and right ventricular systolic dysfunction.Excessive inflammation, hypoxic pulmonary vasoconstriction, hypercapnia, elevated pulmonary vascular resistance due to hyperventilation or pulmonary collapse, pulmonary capillary microthrombosis and pulmonary vascular remodeling are important factors leading to right heart dysfunction in ARDS.RVD often leads to low cardiac displacement and hemodynamic failure in patients[1].ARDS patients with RVD have a worse prognosis and a significantly higher risk of death, which is an independent risk factor for death in ARDS patients[2-4].

Mechanical ventilation is an important treatment for moderate/ severe ARDS.Mechanical ventilation has a significant effect on hemodynamics by affecting the right ventricle by increasing intrathoracic positive pressure.On the one hand, periodic (moist respiration) or continuous (PEEP application) changes in transpulmonary pressure caused by respiratory support directly affect the right ventricular outflow impedance.On the other hand, increased intrathoracic pressure caused by respiratory support can limit right ventricular diastole.In addition, during mechanical ventilation, alveolar pressure will directly act on the outside of pulmonary capillary bed. If alveolar pressure exceeds venous pressure, pulmonary blood flow will be obstructed.Therefore, mechanical ventilation may significantly increase the right cardiac afterload by increasing intrathoracic or alveolar pressure, resulting in right cardiac dysfunction and hemodynamic disorders[5].

APRV is an inversely proportional mechanical ventilation mode with transient pressure release under continuous positive airway pressure.

Studies have shown that APRV can improve oxygenation and is very safe compared with lung protective ventilation with low tidal volume [6]. It is worth

noting that randomized controlled studies have shown that APRV can increase average airway pressure compared with low tidal volume ventilation [7], which may theoretically increase intrathoracic and alveolar pressure, increase external pericardium pressure, thereby affecting venous return, increasing pulmonary circulation resistance, and leading to right heart dysfunction and even hemodynamic deterioration.However, the actual effect of APRV on right heart function in ARDS patients has not been reported.In this study, transthoracic cardiac ultrasound was used to evaluate right heart function, pulmonary artery pressure, tricuspid regurgitation and hemodynamics related indicators in ARDS patients receiving APRV mechanical ventilation, so as to fully understand the influence of APRV mechanical ventilation mode on right heart function and hemodynamics, which is more conducive to clinical application and avoid the occurrence of adverse reactions.

1.1.2 Research Types

Prospective single-center observational study

1.1.3 Research Basis

ARDS is often complicated with RVD, and the incidence can be as high as 64%.ARDS patients with RVD have a worse prognosis and a significantly higher risk of death, which is an independent risk factor for death in ARDS patients.Randomized controlled studies have shown that compared with low tidal volume ventilation, APRV can increase average airway pressure [7], which may theoretically increase intrathoracic pressure and extrapericardial pressure, thereby affecting venous return, increasing pulmonary circulation resistance, leading to right heart dysfunction and even hemodynamic deterioration.However, the actual effect of APRV on right heart function in ARDS patients has not been reported.

1.2 Risk/benefit assessment

1.2.1 Known potential risks

Several animal and clinical studies have confirmed that APRV can effectively improve oxygenation and reduce the duration of mechanical

ventilation compared with traditional mechanical ventilation mode, and the clinical application of APRV is somewhat safe.Therefore, there is no potential risk in this study.

1.2.2 Probability of injury

Mechanical ventilation is the most important and necessary treatment for patients with respiratory failure, and its safety has been proven.Mechanical ventilation does far more good than harm when compared to severe life-threatening respiratory failure.

1.2.3 Degree of injury

The subjects suffered very minor injuries and had no fatal adverse events.

1.2.4 Known potential benefits

ARDS is an acute, diffuse, inflammatory lung injury that results in increased alveolar capillary permeability, lung weight gain, and loss of aerated lung tissue.Mechanical ventilation is the primary treatment for ARDS patients.APRV ventilation can effectively improve oxygenation in ARDS patients and reduce the duration of mechanical ventilation, which is very safe compared to other mechanical ventilation modes.

1.2.5 Assessment of potential risks/benefits

Mechanical ventilation is the main treatment for ARDS patients. APRV mechanical ventilation is a mode of mechanical ventilation that has been used in the treatment of ARDS patients for more than 20 years. Animal and clinical studies have shown that APRV mechanical ventilation can safely and effectively improve oxygenation, reduce the duration of mechanical ventilation and ICU stay, which can benefit ARDS patients.The potential risks of APRV are similar to those of other mechanical ventilation modes. With indications and contraindications, APRV has little risk and is a life-saving treatment for patients with ARDS.

1.3 Discussion

Acute Respiratory Distress Syndrome (ARDS) often complicated with Right Ventricular Dysfunction (RVD), and the incidence of RVD was as high as 64%.RVD often leads to low cardiac displacement and hemodynamic failure in patients[1].ARDS patients with RVD have a worse prognosis and a significantly higher risk of death, which is an independent risk factor for death in ARDS patients[2-4].

Mechanical ventilation is an important treatment for ARDS patients.Mechanical ventilation has a significant effect on hemodynamics by influencing right ventricular function through intrathoracic positive pressure, especially in patients with existing right ventricular insufficiency.

APRV is an inversely proportional mechanical ventilation mode with transient pressure release under continuous positive airway pressure (CPAP). APRV is commonly used in the treatment of ARDS patients.APRV improves oxygenation and is safe compared to low tidal volume lung protective ventilation and SIMV, but randomized controlled studies have not shown that APRV improves mortality.It is not clear whether the reason is related to APRV increasing average airway pressure [7], thus increasing pulmonary circulation resistance, leading to right heart dysfunction, or even hemodynamic deterioration.However, the actual effect of APRV on right heart function in ARDS patients has not been reported.In this study, transthoracic cardiac ultrasound was used to evaluate right heart function, pulmonary artery pressure, tricuspid regurgitation and hemodynamics related indicators in ARDS patients receiving APRV mechanical ventilation, so as to fully understand the influence of APRV mechanical ventilation mode on right heart function and hemodynamics, which is more conducive to clinical application and avoid the occurrence of adverse reactions.

2. Study Objective/end point

Objective: To study the effect of APRV on right ventricular function in ARDS patients.

Primary endpoint/outcome: Effect of APRV mechanical ventilation for 24 hours on right heart function in ARDS patients.

Secondary end point/outcome: Effects of APRV ventilation at 6h, 12h, 48h, 72h and 24h after APRV ventilation on right heart function in ARDS patients.

Effects of APRV ventilation at 6h, 12h, 24h, 48h, 72h and 24h after APRV ventilation on hemodynamics of ARDS patients.

Mortality rate of ARDS patients on APRV mechanical ventilation at 28 days after enrollment, length of stay in ICU, length of stay, and mortality rate in hospital.

3.Study design

3.1 Overall Design

(1). A single center prospective observational study.

(2).In ARDS patients receiving APRV mechanical ventilation, right heart function was monitored at 6, 12, 24, 48, 72 hours after APRV mechanical ventilation, and 24 hours after APRV mechanical ventilation. Mechanical ventilation parameters, respiratory mechanics and arterial blood gas analysis were recorded, and hemodynamic indexes were recorded at the same time.

3.2 Collect the following data:

（1）Demography: sex, age, height, weight

（2）Vital signs: SOFA score and APACHE II score were measured 24 hours after admission to ICU and randomness.

（3）Physiological and biochemical indexes: blood routine, blood biochemistry (total protein, ALB, total bilirubin, AST, ALT, GGT, blood urea nitrogen, serum creatinine), TNI, BNP, CRP before APRV, APRV24h, 48h, 72h and at the end of APRV24h.

(4)Respiratory mechanical parameters before APRV, APRV6h, 12h, 24h, 48h, 72h and end APRV24h.

(5)Cardiac ultrasound and hemodynamic indexes before, after, and after APRV at 6, 12, 24, 48, 72, and 24h.

(6)Fatality rate at 28 days after inclusion, length of stay in ICU, length of stay, and

fatality rate in hospital.

3.3 Sample size

This study is to study the effect of APRV on right heart function. Referring to previous literatures, the number of subjects is generally required to be 40, and the number of subjects should be increased to 50 in consideration of shedding and withdrawal, etc.

4.Study population

4.1 Diagnostic criteria

According to the Berlin 2012 ARDS diagnostic criteria

4.2 The inclusion criteria

(1). Patients who met the 2012 Berlin ARDS diagnostic criteria and underwent invasive mechanical ventilation

(2). PEEP≥5cmH2O, oxygenation index ≤200mmHg

(3). The duration of endotracheal intubation and mechanical ventilation was less than 48h at the time of inclusion

(4). Age ≥18 and ≤80 years old

4.3 Exclusion criteria

(1). Younger than 18 years old or older than 80 years old

(2). BMI of obese patients ≥35kg/m2;

(3). Pregnant and lactating women

(4). The expected time of invasive mechanical ventilation is less than 48h

(5). Neuromuscular diseases known to require prolonged mechanical ventilation

(6). Severe chronic obstructive pulmonary disease

(7). Intracranial hypertension

(8). Pulmonary bullae or pneumothorax, subcutaneous emphysema, mediastinum emphysema

(9). ECMO treatment was performed when admitted to ICU

(10). Refractory shock

(11). Severe cardiac dysfunction (New York Heart Association Class iii or iv, acute coronary syndrome or persistent ventricular tachyarrhythmia), enlargement of the right heart due to chronic cardiopulmonary disease, cardiogenic shock or major cardiac surgery;

(12). Informed consent was not signed

Note: All subjects meeting either of the exclusion criteria at baseline will be excluded from the study

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

Cardiac ultrasound examination was performed before APRV mechanical ventilation, 6h, 12h, 24h, 48h, 72h after APRV mechanical ventilation, and 24h after APRV mechanical ventilation. Mechanical ventilation parameters were recorded, respiratory mechanics and arterial blood gas analysis were measured, and hemodynamic indexes were recorded.

Collect the following data:

(1). Demography: sex, age, height, weight

(2). Vital signs: 24h SOFA score and APACHE II score after admission to ICU and randomization

(3). Physiological and biochemical indicators: echocardiographic right heart function monitoring, hemodynamic parameters and arterial blood gas were performed before APRV or LTV mechanical ventilation, 6h, 12h, 24h, 48h, 72h after mechanical ventilation, and 24h after mechanical ventilation.

(4). Blood routine examinations, blood biochemistry (total protein, ALB, total bilirubin, AST, ALT, GGT, blood urea nitrogen, serum creatinine), TNI, BNP and CRP were performed at 24, 48 and 72 hours after admission to ICU and randomization.

()Respiratory mechanical parameters before and after randomization at 24h, 48h and 72h.

Case fatality rate at 28 days after inclusion, length of stay in ICU, length of stay, and in-hospital case fatality rate.

6.evaluation

6.1Primary and secondary end point/outcome evaluation

Primary endpoint: Effect of APRV mechanical ventilation for 24 hours on right heart function in ARDS patients

Secondary endpoint: Effects of APRV ventilation at other time points on right heart function in ARDS patients.

Effects of APRV ventilation at different time points on hemodynamics of ARDS patients.

Mortality rate of ARDS patients on APRV mechanical ventilation at 28 days after enrollment, length of stay in ICU, length of stay, and mortality rate in hospital.

6.2 Safety evaluation

APRV mechanical ventilation is a mode of mechanical ventilation for ARDS patients, which has been proved to be safe in animal and clinical studies.

7.Adverse events and serious adverse events

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

Reports of serious adverse events: events requiring hospitalization, prolonged hospitalization, disability, inability to work, life threatening or death occurred during APRV mechanical ventilation.

During a clinical trial, the clinical investigator is obligated to take necessary measures to ensure the safety of the subject and to document them.Such as serious adverse events during the process of clinical trials, researchers should immediately treatment for participants to take appropriate measures, and report by phone or fax within 24 hours of the main researchers, the clinical test units of ethics committee, the province, municipality directly under the central government or autonomous region food and drug administration and the state food and drug administration and bidders.At the same time, a written report shall be submitted to the above institutions within 15 days.All serious adverse events must be completed in the CRF Serious adverse Event Report Form.

All serious adverse events should be followed up until resolved, returned to baseline, and proved unsolvable/ Permanent, change to other treatment, or death. Medical documentation of serious adverse events should be documented in the original documentation and follow-up tables, including results of laboratory and ancillary tests.

The investigator 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 statistical methods

Prism 4.01 was used for statistical analysis software.Because all the parameters are non-normally distributed, the data is represented as the median (quartile range;Head).Friedman ANOVA of repeated measurements was used to compare the data obtained at each step and, where appropriate, through Dunn post hoc tests using Bonferroni correction.Qualitative data were compared with Fisher's exact test.All comparisons were double-tailed, with $P<0.05$ indicating the existence of significant differences.

9.Medical treatment and protection of subjects

9.1 Risk assessment of subjects and risk disposal measures and plans

(1) Reporting method: 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: record in detail, and retest according to the situation, record its persistence, return, disappearance and other conditions.

(3) Follow-up of unalleviated adverse events. All adverse events should be followed up until they are properly resolved or the condition 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 investigator 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 and 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 study manner during the study, with inclusion/exclusion criteria clearly defined, 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.

Relatives of the study subjects may discuss it with other family members or guardians before agreeing to participate.The investigator must inform relatives that study 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 of the study subjects will be protected and it is stressed that the quality of their medical care will not be affected by their refusal to participate in the study.

10.2 Privacy protection

Research object information kept by member of project quality control, by the relevant forms, records and samples for storage, without violating confidentiality and related laws and regulations, arbitrator, ethics committee and the pharmaceutical supervisory and administrative department inspectors can check original medical records, in not approved consent before any research information cannot be disclosed to unauthorized third party.

10.3 Collection and use of specimens and data

Blood samples collected by the institute are only used for routine medical tests during treatment, so no residual specimens will be 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 required to familiarize themselves with the APRV mechanical ventilation pattern and the use of bedside ultrasound.All physicians participating in this study should master respiratory mechanics measurement methods.

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 order of the test.

10.5 Data processing and record keeping

10.5.1 Data collection and management

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

Data collection will be carried out by clinical researchers under the supervision of the director, 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 shall be carried out after the training of data entry staff, which shall be completed by two persons 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 case report form.

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 study proposal and the statistical analysis proposal.Conduct 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 judged before locking the data.

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

10.5.2 Research data retention

The minimum retention time of all data and original documents should be 1 year and permission should be obtained before destruction.

10.6 Declaration of conflict of interest

There is no conflict of interest between this study and any physician

participating in this clinical study