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A cross-sectional study of acute cor pulmonale in acute respiratory distress syndrome patients in China

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Abstract

Background: Increased right ventricle afterload during acute respiratory distress syndrome (ARDS) may induce acute cor pulmonale (ACP), which is associated with a poor clinical outcome. Echocardiography is now considered as a rapid and non-invasive tool for diagnosis of ACP. The aims of this study were to investigate the morbidity and mortality rates of ACP in ARDS patients in intensive care units (ICUs) across the mainland of China and to determine the severity and prognosis of ACP in ARDS patients through an ultrasound protocol (TRIP). And the association between ACP related factors and the ICU mortality will be revealed.

Methods: This study is a multicenter and cross-sectional study in China which will include ICU participants when diagnosed as ARDS. The ultrasound protocol, known as the TRIP, is proposed as severity assessment for ACP, which includes tricuspid regurgitation velocity (T), right ventricular size (R), inferior vena cava diameter fluctuation (I), and pulmonary regurgitation velocity (P). The 28-day mortality, ICU/hospital mortality, the length of stay in ICU, mechanical ventilation days, hemodynamic parameters and lab parameters of liver function and kidney function are all recorded.

Discussion: This large-scale study would give a sufficient epidemic investigation of ACP in ARDS patients in China. In addition, with the TRIP protocol, we expect that we could stratify ACP with more echocardiography parameters.

Trial registration: NCT03827863, https://clinicaltrials.gov/ct2/show/NCT03827863

Keywords: Acute respiratory distress syndrome; Acute cor pulmonale; Echocardiography; Outcome

Introduction

Acute respiratory distress syndrome (ARDS) is an acute inflammatory lung injury, characterized by progressive dyspnea and refractory hypoxemia.[1] The mortality rate of ARDS remains high although we have implemented protective ventilation strategy for many years.[2] Improper use of positive pressure mechanical ventilation may increase right ventricle afterload and increase the morbidity in ARDS patients.[3] It has been recognized that acute cor pulmonale (ACP) is an independent risk factor for the poor prognosis of ARDS patients.[4] Therefore, understanding the pathophysiological effect of positive pressure mechanical ventilation on right heart function in ARDS patients and early identification of ACP is important for ARDS patients.[5]

ACP, characterized by pulmonary vascular dysfunction, is related to the severity of lung injury in ARDS patients.[6] The alveolar edema and collapse, hypoxic pulmonary vasoconstriction or vasospasm, and pulmonary microthrombus formation, could all increase pulmonary arterial pressure and participate in the development of ACP.[7] Positive end expiratory pressure (PEEP), aiming to prevent alveoli collapse, would increase both mean intra-alveolar pressure and right ventricle afterload. Different studies have found that the incidence of ACP in ARDS patients

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ranged from 22% to 60%.[8-13] Jardin *et al*[14] found that ARDS patients had a significantly increased ACP morbidity and mortality when airway pressure was greater than 26 cm H_2O, which means different mechanical ventilation settings would have a significantly different effect on right heart function in ARDS patients. Mekontso *et al*[13] proposed a simple clinical risk score for early identification of patients at high risk of ACP, which includes four variables: pneumonia as the cause of ARDS, driving pressure $\geq$18 cm H_2O (1 mmH_2O=0.00981kPa), partial pressure of oxygen in arterial blood (PaO_2)/Fraction of inspiration O2(FiO_2) ratio <150 mmHg, and $PaCO_2 \geq$ 48 mmHg, with three out of four are related to ventilation strategy. This risk score has shown to be useful in clinical practice to select those ARDS patients who should be assessed by echocardiography. However, the exact morbidity and mortality of ACP in ARDS patients are not sure due to different risk factors, diagnostic criteria, and etiologies of ARDS. For these reasons, we established a national prospective observational cohort study to determine morbidity and mortality rate of ACP in ARDS patients in intensive care units (ICUs) across the mainland China. Additionally, a protocolized ultrasonography strategy (TRIP protocol) is designed to assess the severity and prognosis of ACP in ARDS patients. Furthermore, the association between ACP related factors and the ICU mortality will be revealed.

Methods

Ethical approval

This study received approval from the Ethics Committee of the Peking Union Medical College Hospital (No. HS-1615) and from all participating hospitals. This study is also registered in the US National Institutes of Health Clinical Trials Register (No. NCT03827863). The requirement for patient's consent will be waived, a written consent will be provided to the next-of-kin. Participants can withdraw from the study anytime with no restriction. All data are collected anonymously and managed confidentially.

Study design

This is a multicenter and cross-sectional study in Chinese ARDS patients. Chinese Critical Ultrasound Study Group (CCUSG) is responsible for organizing study implementation. ICUs in more than 20 hospitals from different cities will participate in this study.

Population

All the participants will be recruited from November 2019 to April 2020. We will include patients diagnosed as moderate-to-severe ARDS in each ICU.

We choose ARDS Berlin definition[1] criteria in this study: acute respiratory failure within 1 week of a known clinical insult or new or worsening respiratory symptoms; bilateral chest opacities not fully explained by effusions, lobar/lung collapse, nodules, or cardiac failure or fluid overload. ARDS is classified as mild (200 mmHg < PaO_2/FIO_2 $\leq$300 mmHg), moderate (100 mmHg < PaO_2/FIO_2 $\leq$200 mmHg) or severe ($PaO_2/FIO_2 \leq$ 100 mmHg) with a PEEP value of at least 5 cmH_2O.

We will exclude participants if they meet any of the following criteria (1) diagnosed as cardiogenic pulmonary edema; (2) diagnosed as acute exacerbation of idiopathic pulmonary fibrosis; (3) diagnosed as chronic pulmonary hypertension, or if they have the comorbidity such as pulmonary embolism, chronic thromboembolic pulmonary hypertension (CPETH), chronic obstructive pulmonary disease (COPD) or other diseases that could cause chronic right heart dysfunction.

According to previous literatures,[8-13] we set the incidence of ACP at 22%, the allowable error is 0.05, α is set to 0.05, and the calculated sample size is 323. In addition, considering the rate of loss of follow-up, the sample size increased by 10%, and the final sample size was 355.

Ultrasound diagnostic criteria for ACP and TRIP assessment

ACP in this study is defined as a dilated right ventricle (RV) in apical four chamber view [right ventricular end-diastolic (RVED)/left ventricular end-diastolic (LVED) > 0.6] associated with the presence of septal dyskinesia. We successively screen each ARDS patient with transthoracic echocardiogram (TTE).[15] Based on the ESC/ERS2015 sixth World Symposium on Pulmonary Hypertension and Cologne Consensus Conference 2018,[16-18] we propose a critical ultrasound protocol, which combines tricuspid regurgitation velocity (T), right ventricle size (R), inferior vena cava diameter fluctuation (I), and pulmonary regurgitation velocity (P), known as TRIP protocol [Figure 1]. With the ultrasonic parameters in TRIP protocol, we could combine the tricuspid regurgitant velocity (TRV), right ventricular size, interventricular septal function, inferior vena cava (IVC) diameter fluctuations within respiratory cycle, systolic right atrial area, pattern of pulmonary arterial systolic flow velocity and early diastolic pulmonary regurgitant velocity, and diameter of the pulmonary artery to stratify the severity of ACP and assess prognosis.

The abnormal ranges for these parameters are defined as follows according to their normal reference range: tricuspid regurgitation (TR) >2.8 m/s; right ventricle/left ventricle basal diameter ratio >1.0, late systole interventricular septal flattening and paradoxical motion, tricuspid annular plane systolic excursion (TAPSE) <17 mm, IVC > 2 cm with decreased inspiratory collapse; pulmonary regurgitation velocity >2.2 m/s. Here, late systole interventricular septal flattening and paradoxical motion are subjected to the subjective influence of the operator, the systolic eccentricity index (sEI) is used for specification. sEI defined as the ratio of anteroposterior diameter of left ventricular and left and right diameter of free wall of interventricular septum at papillary muscle level on parasternal short axis. So the abnormal value is less than 1. All the mentioned indicators in the article, including TR > 2.8 m/s, right ventricle/left ventricle basal diameter ratio >1.0, late systole interventricular septal flattening and paradoxical motion (yes or no), TAPSE < 17 mm, IVC > 2 cm with decreased inspiratory collapse; pulmonary

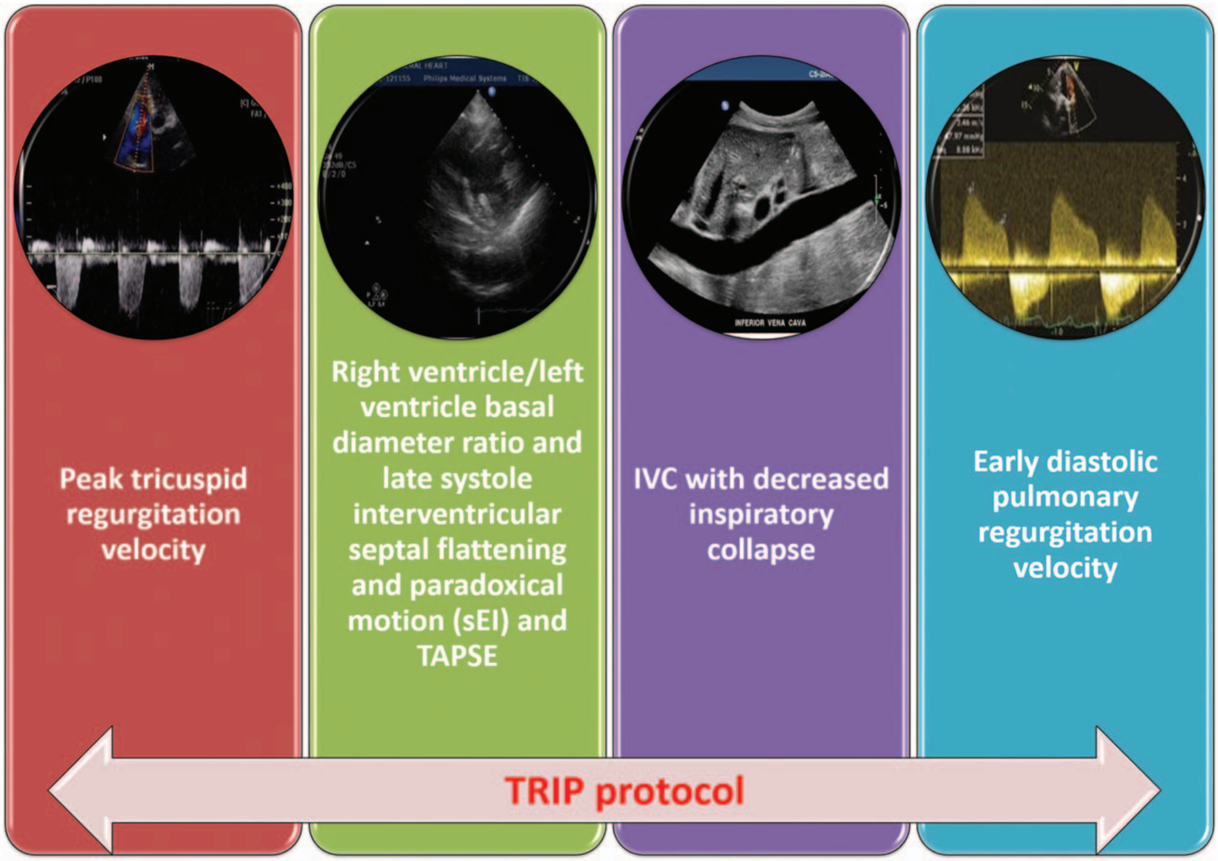

Figure 1: The ultrasound protocol, known as the TRIP, is proposed as severity assessment for ACP, which includes tricuspid regurgitation velocity (T), right ventricular size (R), inferior vena cava diameter fluctuation (I), and pulmonary regurgitation velocity (P); IVC: Inferior vena cava; TAPSE: Tricuspid annular plane systolic excursion.

regurgitation velocity >2.2 m/s, and sEI<1 were constitute the ACP's severity scoring system. The above indicators in abnormal range will be recorded as 2 points each. If ultrasound imaging is not clear to read the indicators, recorded as 1 point. The indicators within normal range will be recorded as 0 point. The total TRIP scores of each patient will be calculated.

Screening and enrolment

Screening for potential eligible participants will be conducted by two intensivists at each clinical center who is well trained in critical care ultrasound and qualified by CCUSG. When there are some disagreements between these two, we also have panel specialists from CCUSG to settle it and as a quality control, all the videos and scans used in TRIP protocol for each enrolled patient will be recorded. The ultrasonic assessment must be completed in each patient within two hours when ARDS suspected. When eligible, an informed consent is required before officially entering the study. And then the participants will register in a mobile app (https://www.pgyer.com/jKRf).

Data collection

Detailed demographics and clinical characteristics including age, sex, main diagnosis, clinical etiology of ARDS (if known), comorbidities, history of medication, will be collected and recorded. All parameters mentioned below will be recorded after diagnosed as ARDS within 2 hours in ICU.

Clinical and laboratory data being collected includes body temperature, heart rate, respiratory rate, blood pressure, Glasgow coma score, white blood cell count, neutrophil count, platelet count, procalcitonin, G-test, total bilirubin, serum creatinine, radiological imaging, vasopressor dosage.

Mechanical ventilation parameters being collected include: tidal volume, peak pressure (P_{peak}), plateau pressure (P_{plat}), positive end-expiratory pressure (PEEP), dynamic compliance, fraction of inspired oxygen (FiO_2), saturation of pulse oxygen (SPO_2), and partial pressure of arterial oxygen (PO_2).

Ultrasound parameters being collected include: TRV; right ventricle/left ventricle basal diameter ratio, (sEI) and TAPSE; IVC; pulmonary regurgitation velocity; systolic D sign; E/E'; mitral annular plane systolic excursion (MAPSE); left ventricular ejection fraction (LVEF); and velocity time integral (VTI).

Hemodynamic parameters being collected include central venous pressure (CVP), central venous-arterial blood carbon dioxide partial pressure difference ($Pv\text{-}aCO_2$), central venous oxygen saturation ($ScvO_2$), and lactate concentration.

The prime outcome is mortality rate in 28-day, ICU and hospital. The secondary outcome is length of stay in ICU, and mechanical ventilation days.

All efforts will be made to prevent dropout of the participants from the study. All data will be collected in electronic CRF which is integrated into a mobile app.

Data statistical analysis

Continuous variables will be presented as the mean ± standard deviation (SD). Student's *t* test was used to compare means between two groups. Results for qualitative variables were expressed as percentages and compared between groups using a Chi-square test. The morbidity and mortality of ARDS patients with ACP will be calculated. All the mentioned indicators above, including TR >2.8 m/s, right ventricle/left ventricle basal diameter ratio >1.0, late systole interventricular septal flattening and paradoxical motion (yes or no), TAPSE <17 mm, IVC > 2 cm with decreased inspiratory collapse; pulmonary regurgitation velocity >2.2 m/s, and sEI < 1 were constitute the ACP's severity scoring system. If each indicator exceeds the normal value, record 2 points. If you cannot see the ultrasound imaging section clearly and can't read it, then record 1 point. If it is normal range, it records 0 point. The scores of survivors and non-survivors were compared. Areas under receiver operating characteristic curves were used to evaluate how well the model distinguished non-survivors from all patients used TRIP score. Univariate logistic regression was used for related factors that associate to poor outcome of ACP.

Public involvement

To increase public awareness of ACP in ARDS patients, the results of this study will be open and available on the Chinese Critical Ultrasound Study Group website (http://www.ccusg.cn/).

Discussion

ARDS is a life-threatening form of respiratory failure,[19] with limited effective therapeutic approaches, such as protective ventilation strategy. The severity of lung injury and improper mechanical ventilation setting could both contribute to the incidence of ACP in ARDS patients, which was up to 60% prior to the implementation of protective ventilation strategy.[9,10,12,20] It has been confirmed that the occurrence of ACP is independently associated with mortality of ARDS patients.[4,20] Accordingly, it is very important to identify ACP at the initial stage of ARDS so as to tailor a personalized therapy to these patients other than harming them by upregulating mechanical ventilation parameters according to current clinical guidelines.

ACP is characterized by acute pulmonary vascular dysfunction, which means a rapid increase of right ventricular afterload. The assessment of right heart function together with its preload and afterload has a key value. Pulmonary artery catheter (PAC) and echocardiography are the two most commonly used tools to assess right heart function. PAC is a classic method to assess right ventricular function and pulmonary circulation, which has been widely used for several decades because it enables clinicians to obtain much more information regarding right heart function; thus, it is regarded as the golden standard.[21] However, PAC is invasive, expensive and complicated to operate. In addition, some studies have proved that the application of PAC does not improve the prognosis of critically ill patients.[22,23] In recent years, with the broad application of echocardiography in critically ill patients, echocardiography has become the primary tool to diagnose ACP with great accuracy and efficacy.[24] ACP is then defined as ventricular septal dyskinesia with a dilated RV [RVEDA/LVEDA >0.6, (≥1 for severe dilatation)].[13] In addition to the RVEDA/LVEDA ratio, there are some other echocardiographic parameters which could further evaluating right heart dysfunction. For example, TAPSE ⩽ 16 mm, two-dimensional fractional area change (FAC) < 35%, TR velocity > 2.8 m/s, a tricuspid E/A ratio (the ratio of peak velocity blood flow from gravity in early diastole (the E wave) to peak velocity flow in late diastole caused by atrial contraction (the A wave)) < 0.8 and a pulmonary regurgitation velocity >2.2 m/s, etc.[25] We propose a convenient, effective and easy-to-operate ultrasound protocol, TRIP, for assessing the severity of ACP. The TRIP protocol may be a potential tool for rapid ACP stratification, and differential diagnosis.

Under physiological conditions, pulmonary circulation is a low-resistant, high-compliant system. The right ventricle has poor tolerance to afterload, that is, a mild increase in pulmonary vascular resistance (PVR) can lead to right ventricular overload. Meanwhile, due to the high compliance of the right ventricle, an excessive load can easily cause acute right ventricular dilatation. In ARDS, the direct damage to the lung will cause inflammatory mediators released and pulmonary vascular endothelial cell injury, microvascular thrombosis and occlusion, hypoxic pulmonary vasoconstriction, pulmonary vascular remodeling, which may all lead to decreased pulmonary vascular compliance and increased PVR, finally increasing right ventricle afterload and clinically causing acute pulmonary hypertension with right heart dysfunction. The purpose of mechanical ventilation is to recruit collapsed alveoli and increase functional residual capacity. The latter will ideally lower PVR and decrease right ventricle afterload. However, due to inhomogeneous lung injury in ARDS, the use of lung recruitment and high PEEP may lead to the recruitment of collapsed alveoli as well as overextension of normal alveoli. From this perspective, whether PVR is decreased depends on the balance between recruitment and overextension of the alveoli. Some studies have found that a PEEP at 4 to 6 cmH_2O had the lowest PVR but a PEEP more than 12 cmH_2O increased alveolar capillary pressure and led to a gradual increase in PVR.[26,27] When tidal volume or PEEP is increased, regional transpulmonary pressure (even more than the pressure in the pulmonary veins or the pulmonary artery) may lead to the increase of the PVR, and so does to the right ventricular afterload.[28] In many studies that assessed right ventricular function during mechanical ventilation, a CVP greater than PAOP was defined as right heart dysfunction, and a RV stroke volume index less than 30 mL/m^2 with a pulmonary artery pressure more than 30 mmHg was defined as right ventricular failure.[29] One study found that during the first day of mechanical ventilation, plateau pressure exceeding 30 cmH_2O significantly increased the incidence of pulmonary hypertension and right heart dysfunction in the early stage of mechanical ventilation and could significantly reduce right cardiac output, leading to right ventricular congestion.[10] We aimed at early detection of ACP and identification of associated factors of ACP which may in the future help to prevent development of ACP in ARDS patients by modification of clinical treatments.

In conclusion, the goals of this study were to investigate the morbidity and mortality rates and assess the severity of ACP in ARDS patients in ICUs across the mainland of China by using an assessment ultrasound protocol, TRIP. We expect that this cross-sectional study will provide a detailed epidemiological information of ACP in ARDS patients, including clinical associated factors for development of ACP, and further analysis of ultrasound parameters would help to better treat ARDS patients in the future.

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Conflicts of interest

None.

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