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Cerebrovascular autoregulation and neurocognitive outcome in patients with acute respiratory distress syndrome

Dissertation

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Contents

List of abbreviations

ARDS	Acute respiratory distress syndrome
ABP	Arterial blood pressure
AECC	American-European Consensus Conference
ALI	Acute lung injury
CVA	Cerebrovascular autoregulation
CBF	Cerebral blood flow
CFQ	Cognitive failures questionnaire
CO_2	Carbon dioxide
COVID-19	Coronavirus disease 2019
COx	Cerebral oxygenation index
CPAP	Continuous positive airway pressure
CPC	Cerebral performance category
CPP	Cerebral perfusion pressure
CT	Computed tomography
CVR	Cerebrovascular resistance
ECMO	Extracorporeal membrane oxygenation
FiO_2	Fraction of inspired oxygen
HRQL	Health-related quality of life
ICP	Intracranial pressure
ICU	Intensive care unit
MAP	Mean arterial pressure
MAC	Minimum alveolar concentration
NIRS	Near infrared spectroscopy
NO	Nitric oxide
$PaCO_2$	Arterial partial pressure of carbon dioxide
PaO_2	Arterial partial pressure of oxygen
PEEP	Positive end expiratory pressure
PTSD	Post-traumatic stress disorder
RASS	Richmond agitation and sedation scale

rSO_2	Regional oxygen saturation
SF-36	Short form 36-item health survey
SOFA	Sequential organ failure assessment
TBI	Traumatic brain injury
TCD	Transcranial Doppler
va-ECMO	veno-arterial extracorporeal membrane oxygenation
VILI	Ventilator-induced lung injury
vv-ECMO	veno-venous extracorporeal membrane oxygenation

1. Introduction

1. 1 Acute respiratory distress syndrome

Acute respiratory distress syndrome (ARDS) is a common respiratory criterial illness characterized by severe hypoxemia (ARDS Definition Task Force et al., 2012). Due to the coronavirus disease 2019 (COVID-19) pandemic, ARDS has become better known globally. Because ARDS is one of the most common and severe complications of the COVID-19 (Chen et al., 2020). The hospital mortality for severe ARDS patients remains as high as 46.1% (Bellani et al., 2016). Although the mortality has declined over the past few decades with the improvements of treatment strategies, ARDS patients still have a high mortality and long-term sequelae (Cochi et al., 2016; Mart and Ware, 2020).

1. 1. 1 History and definition

In 1967, ARDS was first proposed by Ashbaugh et al. who reported 12 patients with a similar pattern of acute respiratory distress (Ashbaugh et al., 1967). These 12 patients, including one child and 11 adults, presented clinical, physiological, and pathological features that were remarkably similar to neonatal respiratory distress syndrome (Ashbaugh et al., 1967). Pulmonary hyaline membranes which were thought to be present only in respiratory distress syndrome of neonates, appeared on six of seven patients at autopsy (Ashbaugh et al., 1967). Therefore, the term ‘adult respiratory distress syndrome’ was proposed. Later ‘adult’ was changed to ‘acute’, because the respiratory distress syndrome occurred not only in adults, but also in children (Ashbaugh et al., 1967).

The definition and diagnosis of ARDS have been developed gradually. In 1988, Murray et al. attempted to define ARDS with a ‘lung injury score’ (Murray et al., 1988). The lung injury score consisted of four components, which included chest radiograph, arterial partial pressure of oxygen (PaO_2)/fraction of inspired oxygen (FiO_2) ratio, positive end expiratory pressure (PEEP), and respiratory system compliance (Murray et al., 1988). Each component was scored from 0 (no lung injury) to 4 (severe lung injury), and ARDS was defined an average score of these components above 2.5 (Murray et al., 1988). In 1994, the first widely accepted ARDS diagnosis criteria was published in an American-European Consensus Conference (AECC) statement (Bernard et al., 1994). In the statement, diagnosis criteria of ARDS included acute onset, severe hypoxemia (PaO_2/FiO_2 ratio ≤ 200 mmHg), bilateral infiltrates on chest radiographs, no clinical evidence of left atrial hypertension and acute lung injury (ALI) was defined as PaO_2/FiO_2 ratio ≤ 300 mmHg (Bernard et al., 1994). In 2012, the ARDS Definition Task Force updated the definition of ARDS, referred to as ‘Berlin definition’

(ARDS Definition Task Force et al., 2012). In the Berlin definition, acute hypoxemia was defined as “within one week”, and ARDS severity was classified according to the degree of hypoxemia (ARDS Definition Task Force et al., 2012) (Table 1).

Table 1 The Berlin definition of acute respiratory distress syndrome

Timing		Within 1 week of a known clinical insult or new or worsening respiratory symptoms
Chest imaging[a]		Bilateral opacities—not fully explained by effusions, lobar/lung collapse, or nodules
Origin of edema		Respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (eg, echocardiography) to exclude hydrostatic edema if no risk factor present
Oxygenation[b]		
	Mild	200 mmHg < PaO_2/FiO_2 ≤ 300 mmHg with PEEP or CPAP ≥ 5cmH_2O[c]
	Moderate	100 mmHg< PaO_2/FiO_2 ≤ 200 mmHg with PEEP ≥ 5 cmH_2O
	Severe	PaO_2/FiO_2 ≤ 100 mmHg with PEEP ≥ 5 cmH_2O

Table 1 The Berlin definition of acute respiratory distress syndrome. [a] Chest radiograph or computed tomography scan. [b] If altitude is higher than 1000 m, the correction factor should be calculated as follows [PaO_2/FiO_2(barometric pressure/760)]. [c] This may be delivered noninvasively in the mild acute respiratory distress syndrome group. CPAP continuous positive airway pressure, FiO_2 fraction of inspired oxygen, PaO_2 arterial partial pressure of oxygen, PEEP positive end expiratory pressure.

From ARDS Definition Task Force et al. Acute respiratory distress syndrome: the Berlin Definition. JAMA. 2012;307:2526–33.

1. 1. 2 Clinical presentation

Acute onset, progressive hypoxemia, and respiratory distress are major clinical characteristics of ARDS. The early presentations of ARDS are shortness of breath, hypoxemia and respiratory alkalosis. These manifestations usually worsen within 48 hours with respiratory failure and diffuse pulmonary infiltrates on chest radiographs (Mortelliti and Manning, 2002). In addition to these typical clinical manifestations, ARDS patients also present with symptoms of co-morbidities, such as systemic inflammatory response syndrome in patients with sepsis-induced ARDS and peripheral perfusion deficit in ARDS patients with shock.

Chest X-ray can appear normal shortly after a clinical insult, but widespread opacities will become evident with the development of ARDS (Chiumello et al., 2013).The classic computed tomography (CT) presentation of ARDS in the acute phase is a dense consolidation or ground-glass opacities in gravity-dependent areas and normal or hyper-inflated lungs in non-gravity-dependent areas (Sheard et al., 2012). Thus, ARDS patients have been described with two radiological patterns: a focal and a diffuse one. The focal

pattern refers to the area of lung attenuations that are in the lower lobe or gravity-dependent areas, while in the diffuse pattern, the attenuations are throughout the lung which is known as ‘white lung’ (Chiumello et al., 2013). Patients with cardiogenic pulmonary edema can present with similar clinical manifestations to ARDS, and need to be identified by assessing the cardiac function as well as fluid load (ARDS Definition Task Force et al., 2012).

1. 1. 3 Epidemiology

There is a huge variability of ARDS incidence in various population-based studies. The estimates of ARDS incidence was 3.7–81/100,000 person-years in the general population (Pham and Rubenfeld, 2017). In a prospective screening program according to Berlin definition, ARDS incidence was 27.6/100,000 person-years in Canada (Parhar et al., 2019). In a nationwide cohort study in France, the crude national incidence of ARDS using Berlin definition was 24.6/100,000 person-years in 2017 (Papazian et al., 2020). Besides, in a multicenter international study, the incidence of ARDS was 10.4% in patients admitted to the intensive care unit (ICU) and 23.4% in mechanically ventilated patients (Bellani et al., 2016). Additionally, in patients hospitalized with COVID-19 or influenza in Germany, ARDS incidence was much higher in patients with COVID-19 (9%) than in those with influenza (1%) (Ludwig et al., 2021).

The incidence of ARDS seems to be age and gender related. In a population-based cohort study, the incidence of ALI was higher in patients 75–84 years old than those 15–19 years old (306 vs.16/100,000 person-years) (Rubenfeld et al., 2005). Besides, in a study of four ICUs in Canada, men had a higher crude incidence of ARDS than women (33.9 vs 21.4/100,000 person-years) (Parhar et al., 2019).

Notably, the relative low recognition of ARDS need to be considered. In a large global observational study, clinical recognition of ARDS increased with ARDS severity, with 51.3%, 65.3% and 78.5% in mild, moderate, and severe ARDS patients, respectively (Bellani et al., 2016). The clinical recognition of ARDS is also low in low-income countries, where chest radiographs and arterial blood gas testing resources are insufficient. In Rwanda, Kigali modification of the Berlin definition was used to define ARDS (Riviello et al., 2015). In this modification of Berlin definition, PEEP was not required, and oxygen saturation measured using pulse oximetry as a substitute of PaO_2.

1. 1. 4 The etiology and risk factors

There are many etiologies of ARDS, and the AECC committee defined two pathways of pathogenesis (Bernard et al., 1994). One was the pulmonary etiology, which refers to a direct effect of insult on lung parenchyma. The other was an extrapulmonary etiology, which

corresponds to an indirect insult from an acute systemic inflammatory response (Bernard et al., 1994). The main pulmonary etiology of ARDS is pneumonia caused by bacterial, viral, fungal infections (Bernard et al., 1994). In addition to pneumonia, other pulmonary etiologies include aspiration, near drowning, and pulmonary contusion. Extrapulmonary causes of ARDS include sepsis of non-pulmonary source, severe non-thoracic trauma, severe burn injury, and massive transfusion of blood products (Thompson et al., 2017). Furthermore, ARDS is categorized as community-acquired or hospital-acquired based on whether it occurs within 48 hours of hospital admission (Kao et al., 2015).

Most ARDS patients have risk factors. In a 9-year retrospective study in the United States, more than 80% of patients with ARDS had major ARDS-specific risk factors, including sepsis, pneumonia, shock, blood transfusion, aspiration of gastric contents, and trauma (Eworuke et al., 2018). In addition, mechanical ventilation might also be a risk factor of ARDS. In an international, multicenter study, 30% mechanically ventilated patients were at risk for ARDS (Neto et al., 2016).

1. 1. 5 Pathophysiology

The typical pathophysiological characteristics of ARDS are diffuse alveolar injury and increased capillary permeability (Kaku et al., 2020). The pathological process of ARDS has been outlined as three overlapping phases: an acute exudative phase (0–7 day), followed by a proliferative phase(7–21 day), and a fibrotic phase (from day 10) (Vasudevan et al., 2004).

1. 1. 5. 1 The acute exudative phase

This phase is characterized by damage of pulmonary capillary endothelium and alveolar epithelial barriers and large amounts of edema fluid accumulating in the alveolar interstitium and alveoli (Figure 1) (Thompson et al., 2017). The innate immune system is activated when microbial products bind to receptors on the alveolar macrophages (Huppert et al., 2019). Activated macrophages lead to the release of potent pro-inflammatory mediators such as tumor necrosis factor-α, interleukin-1, interleukin-6, which can further impair the lung (Thompson et al., 2017). The tumour necrosis factor-α mediated tissue factor expression promotes platelet aggregation and the formation of micro-thrombus and hyaline membranes (Thompson et al., 2017). Imbalance between anticoagulants and procoagulants leads to tissue factor-dependent coagulation (Thompson et al., 2017). Furthermore, neutrophil migration results in epithelial injury due to disruption of intercellular junctions (Huppert et al., 2019). These injuries lead to the disruption of the pulmonary capillary endothelial and alveolar epithelial barriers and interstitial and intra-alveolar flooding (Thompson et al., 2017).

Figure 1 The healthy lung and the exudative phase of ARDS

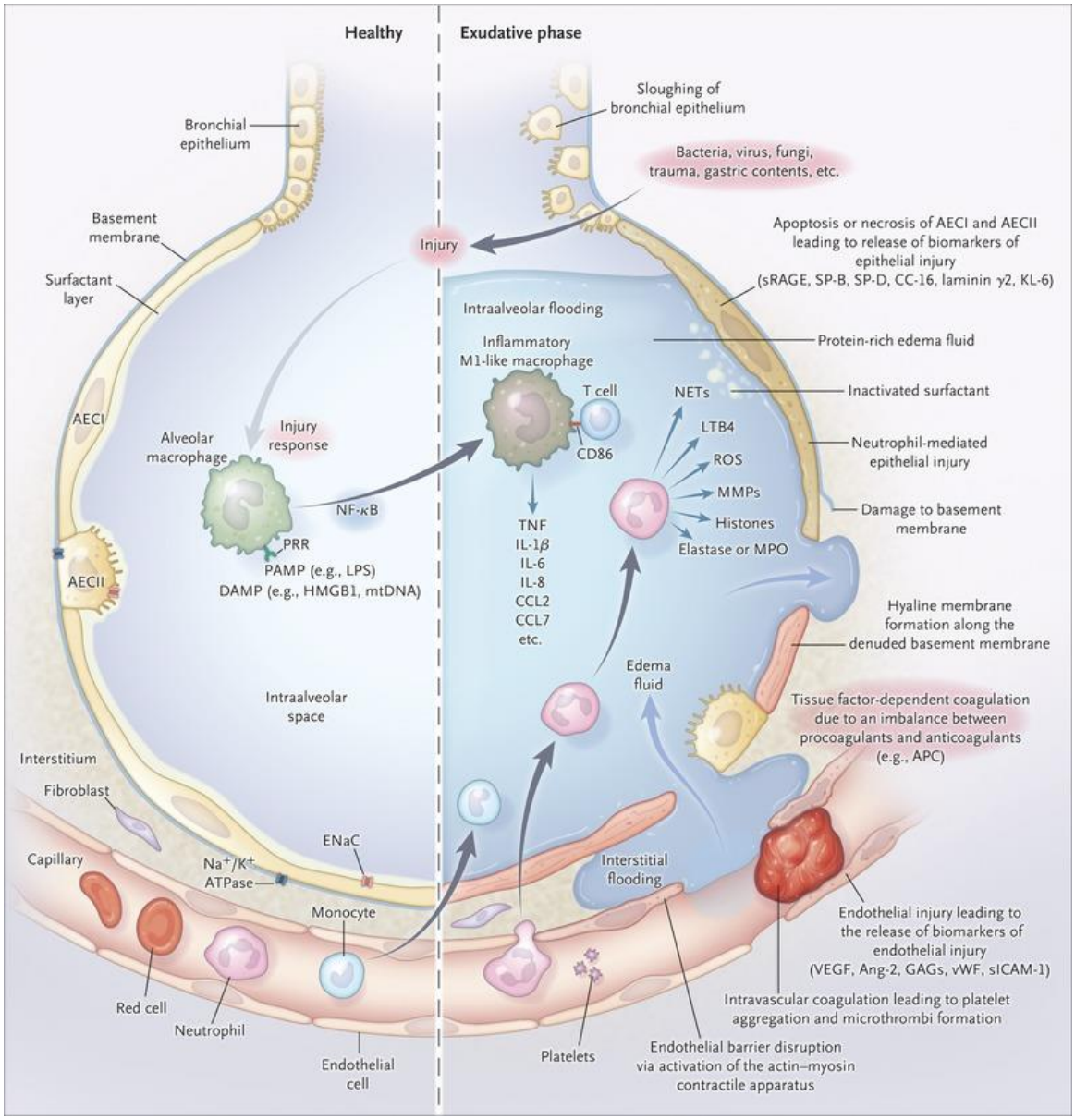

Figure 1 The healthy lung and the exudative phase of ARDS. Reproduced with permission from (Thompson et al., 2017), Copyright Massachusetts Medical Society.

From Thompson, B.T., Chambers, R.C., Liu, K.D., 2017. Acute Respiratory Distress Syndrome. N. Engl. J. Med. 377, 562–572. https://doi.org/10.1056/NEJMra1608077

1. 1. 5. 2 The proliferative phase and the fibrotic phase

The proliferative phase is a stage of repair marked by intense cellular proliferation, particularly of type II alveolar epithelial cells and fibroblasts (Thille et al., 2013). The proliferative phase mainly includes the following processes (Thompson et al., 2017). Airway progenitor and type II alveolar epithelial cell proliferate and differentiate into type I alveolar epithelial cell (Thompson et al., 2017). Endothelial barrier function is restored by reestablishment of tight junctions and adherens junctions, as well as endothelial cell

proliferation (Thompson et al., 2017). The re-expression of alveolar ion channels and aquaporin 5 can reabsorb alveolar edema fluid and reduce pulmonary edema (Thompson et al., 2017). The proliferative phase is crucial as it aims to restore tissue homeostasis (Thompson et al., 2017). The regeneration of a functioning epithelial layer allows the clearance of exudative fluid, and improves the alveolar function (Sweeney and McAuley, 2016).

Of adult ARDS patients, 30–50% develop pulmonary fibrosis and limited lung function (Yang et al., 2018). The fibrosis phase is followed by a series of host responses, including the resolution of injury and restoration of normal alveolar structure and function (Hendrickson et al., 2015). However, lung repair can be more difficult when there is severe structural damage to the lungs which may be due to ventilator-induced lung injury (VILI) (Burnham et al., 2014). Failure to repair the lung injury and restore normal alveolar structure timely are the main causes of pathological fibroproliferative reaction (Burnham et al., 2014). Unresolved inflammatory response allows the accumulation of macrophages, fibrocytes, fibroblasts and myofibroblasts, further causing excessive deposition of fibronectin and collagen (Burnham et al., 2014). The Inadequate repair of endothelial and epithelial barrier function and massive deposition of the extracellular matrix promote alveolar interstitial and intra-alveolar fibrosis (Thompson et al., 2017).

1. 1. 6 Treatment

The treatment of ARDS includes general treatment measures, mechanical ventilation strategies, adjunctive therapies, and treatment of the underlying conditions. The cornerstone of ARDS management is mechanical ventilation (Fan et al., 2018). Maintaining adequate gas exchange and avoiding VILI are the major concerns of mechanically ventilated patients with ARDS (Fan et al., 2018). Mechanical ventilation strategies of ARDS are according to its severity.

For patients with mild ARDS, non-invasive ventilation is recommended when patients are clinically stable (Fan et al., 2018). Controlled mechanical ventilation with lung-protective ventilation is recommended for moderate and severe ARDS patients. Lung-protective ventilation refers to a target tidal volume of 6 ml/kg predicted body weight and plateau pressure less than or equal to 30 cmH_2O (Fan et al., 2018). In a prospective trial, lung protective strategies for ARDS patients improved 28-day survival as well as mechanical ventilation weaning rate (Amato et al., 1998). Also, High PEEP is considered for adult patients with moderate or severe ARDS. As evidence showed patients with high PEEP had significantly better oxygenation and lower mortality than those with low PEEP in moderate or severe ARDS patients (Briel et al., 2010).

When PaO_2/FiO_2 is less than 150 mmHg, deep sedation, prone ventilation, neuromuscular blocking agents, and lung resuscitation should be considered (Fan et al., 2018). Prone position allows for the opening of collapsed alveoli in gravity-dependent areas, which can reduce the amount of atelectatic regions (Pelosi et al., 2002). For patients with severe ARDS, prone position is strongly recommended for more than 12 hours per day (Fan et al., 2017). Besides, in a multicenter prospective, randomized, controlled trial, prone position longer than 16 hours significantly reduced the mortality in severe ARDS patients (Guérin et al., 2013). Lung recruitment maneuvers were demonstrated to reduce atelectasis, and ARDS patients with attenuations widely throughout the lungs in CT had a better response to the recruitment maneuver (Coppola et al., 2021).

When PaO_2/FiO_2 is less than 80 mmHg, extracorporeal membrane oxygenation (ECMO) therapy is considered (Fan et al., 2018). Technological advances have made ECMO devices safer and more easier to implement, largely driving the rapid growth of ECMO use in patients with respiratory failure (Abrams and Brodie, 2017). But in an international randomized trial in 2018, ECMO did not reduce the 60-day mortality compared with conventional mechanical ventilation (Combes et al., 2018). Conversely, in a meta-analysis in 2019, the treatment of veno-venous extracorporeal membrane oxygenation (vv-ECMO) was associated with decreased 60-day mortality in severe ARDS patients (Munshi et al., 2019). However, in this meta-analysis, ARDS patients with vv-ECMO support had a moderate risk of major bleeding. More evidence is still needed to support ECMO treatment in ARDS patients.

Another treatment for ARDS patients is inhaled nitric oxide (NO). Inhaled NO has been shown to cause a remarkable decrease in pulmonary arterial pressure (Rossaint et al., 1993). This study also demonstrated that NO improved arterial oxygenation by reducing intrapulmonary shunting in ARDS patients (Rossaint et al., 1993). In addition, inhaled NO is a salvage therapy in patients with severe hypoxemia and to buy time for other therapies such as ECMO, prone position (Rossaint et al., 2014). However, in a retrospective cohort study, inhaled NO was not observed to reduce mortality and ventilator-free days in pediatric ARDS patients (Bhalla et al., 2018).

1. 1. 7 Hypercapnia in acute respiratory distress syndrome

ARDS patients are at high risk of developing hypercapnia. There are two major factors that contribute to hypercapnia in ARDS patients. The first factor is impaired gas exchange in ARDS patients due to decreased lung volume, increased pulmonary dead space, disordered ventilation-to-blood flow ratio, and reduced lung compliance (Wohlrab et al., 2018). They can result in carbon dioxide (CO_2) retention. The second factor is lung-protective ventilation strategies, which are strongly recommended for ARDS patients (Fan et al., 2018). Due to the

reduced alveolar ventilation caused by low tidal volume and limited plateau pressure, lung-protective ventilation has strong potential to increase CO_2 levels.

The exact effect of hypercapnia in ARDS patients is still unclear, and whether hypercapnia in ARDS patients should be accepted, or avoided remains controversial (Morales-Quinteros et al., 2019). Hypercapnia may affect the repair of impaired tissue and alveolar fluid clearance (Morales-Quinteros et al., 2019). Also, hypercapnia may impair alveolar epithelial cells and neutrophil function (Nin et al., 2018). Besides, more complications and organ failures during mechanical ventilation were observed in patients with severe hypercapnia compared with patients without severe hypercapnia (Nin et al., 2017). Moreover, severe hypercapnia was associated with increased mortality in this multicenter international study according to Nin et al. (Nin et al., 2017).

However, hypercapnia was thought to be protective, and permissive hypercapnia was proposed in 1990s, which referred to the acceptance of a non-physiologically high arterial partial pressure of carbon dioxide ($PaCO_2$) to allow for lung-protective ventilation (Hickling et al., 1990). In an animal model of ALI, hypercapnia was demonstrated to preserve lung mechanics, reduce protein leakage and pulmonary edema, as well as improve oxygenation (Laffey et al., 2000). Furthermore, in an experimental model, hypercapnic acidosis was shown to attenuate the pulmonary edema caused by VILI (Kapetanakis et al., 2011). In a prospective randomized study, hypercapnic acidosis was observed to attenuate VILI as well as reduce mechanical stretch-induced epithelial injury and death (Contreras et al., 2012).

1. 1. 8 Prognosis

Patients with ARDS have a high mortality in the ICU, as well as the long-term neurocognitive sequelae. In a multicenter international study, hospital mortality was 34.9%, 40% and 46.1% in patients with mild, moderate and severe ARDS, respectively (Bellani et al., 2016). In a secondary analysis of randomized controlled trials conducted by the ARDS network, the crude mortality declined from 35.4% in 1996 to 28.3% in 2013 (Zhongheng Zhang et al., 2019). In that study, ARDS mortality was lower for patients admitted between 2005 and 2010 and those admitted after 2010 compared to patients admitted before 2000. The decline in mortality was probably due to the implementation of a conservative fluid management, lung protective ventilation strategies, and high PEEP into clinical practice (Zhongheng Zhang et al., 2019). Despite the declining trend of hospital mortality in ARDS patients, ARDS patients are still at risk of death after ICU discharge (Mart and Ware, 2020). In a prospective cohort study, Wang et al. showed that the 1-year mortality for ARDS survivors admitted to the ICU between 2006 and 2020 was 22% (Wang et al., 2014). Furthermore, severe hypercapnia may increase ICU mortality, with a mortality of 62.5% in ARDS patients with severe

hypercapnia compared with 49.6% in patients without severe hypercapnia in a multicenter study (Nin et al., 2017).

Additionally, ARDS patients are at risk for delirium. In a randomized controlled trial, 72% of sepsis-related ARDS patients developed delirium (Needham et al., 2016). Furthermore, in a prospective cohort study, 73% of intubated ARDS patients developed delirium during the first two weeks in ICU, compared with 21% of the non-intubated ARDS patients and 52% of the intubated patients without ARDS (Hsieh et al., 2015).

The long-term sequelae of ARDS include cognitive impairment, psychological disorders, neuromuscular weakness, and reduced health-related quality of life (HRQL) (Mart and Ware, 2020). Survivors of ARDS may experience cognitive impairment with poor functional status, which often persists months after hospital discharge (Sasannejad et al., 2019). The incidence of cognitive impairment in ARDS patients was 70%–100% at discharge, 46%–80% one year after discharge (Herridge et al., 2016).

Patients of ARDS can suffer from psychological morbidities including anxiety, depression, and post-traumatic stress disorder (PTSD) (Bienvenu et al., 2018; Huang et al., 2016). In a 1-year multicenter study of ARDS patients, 66% had psychological symptoms at the 1-year follow-up, and the incidence of depression, anxiety, and PTSD was 36%, 42%, and 23%, respectively (Huang et al., 2016). Besides, in a 5-year longitudinal study, 38%, 32%, and 23% of ARDS survivors developed prolonged anxiety, depression, and PTSD symptoms, respectively (Bienvenu et al., 2018). Moreover, another common complication of ARDS patients is ICU acquired weakness, which was initially described as a muscle wasting and weakness in severe ARDS patients (Herridge et al., 2003). In a retrospective analysis, 60% ARDS patients were diagnosed with polyneuropathy and/or myopathy by clinical assessment of muscular strength (Bercker et al., 2005).

1. 2 Cerebrovascular autoregulation

1. 2. 1 Definition

The term cerebrovascular autoregulation (CVA), proposed by Lassen in 1959, describes the tendency of cerebral blood flow (CBF) to remain relatively constant even though cerebral perfusion pressure (CPP) changes over a wide range (Lassen, 1959). To be more exact, CVA is a homeostatic mechanism that reduces fluctuations in CBF when CPP varies within a certain range (Aaslid et al., 1989). Cerebral blood vessels constrict in reaction to CPP rising and dilate when CPP falls to maintain a relatively stable CBF (Meng and Gelb, 2015).

To further understand this definition, CVA can be visualized as a CVA curve, with CPP on the x-axis and CBF on the y-axis (Meng and Gelb, 2015). The ideal CVA curve is shown in Figure 2. There are three major elements of CVA curve: lower limit, plateau, and upper limit (Meng and Gelb, 2015). The upper and lower limits of CVA are approximately at CPP of 150 mmHg, 60 mmHg respectively, and the plateau is at CBF of around 50 ml/min per 100 g (Figure 2) (Paulson et al., 1990). When CPP fluctuates during the plateau, CBF remains approximately constant. While when CPP is outside the plateau, CBF changes with CPP. Notably, the lower limit and upper limit vary individually (Meng and Gelb, 2015). The shape of CVA curve may be influenced by many factors, such as chronic hypertension, CO_2 or cardiac output (Meng et al., 2015; Meng and Gelb, 2015; Moerman and De Hert, 2019).

Figure 2 The idealized cerebrovascular autoregulation curve

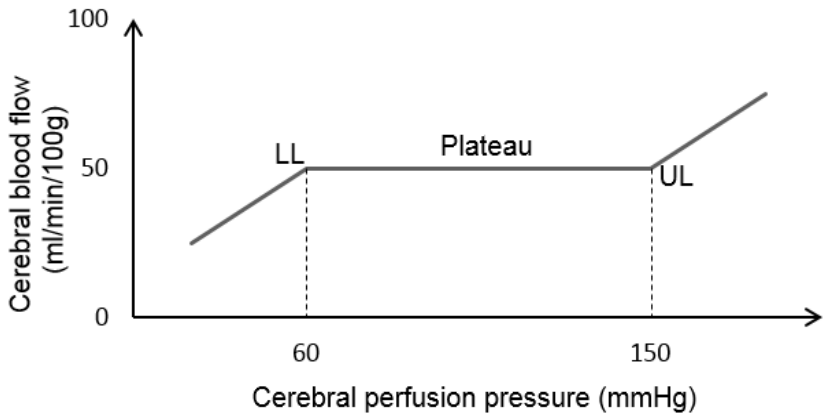

Figure 2 The idealized cerebrovascular autoregulation curve. LL Lower limit, UL Upper limit. According to Meng, L., Gelb, A.W., 2015. Regulation of cerebral autoregulation by carbon dioxide. Anesthesiology 122, 196–205.

1. 2. 2 Physiology

The human brain has a high energy demand, representing only a small percentage (2%) of the entire body mass, but accounting for approximately 20% of the total energy consumption

in normal adults at rest (Fantini et al., 2016). Furthermore, cerebral perfusion is responsible for delivering oxygen and glucose to the brain, which are crucial for the neuronal oxidative metabolism (Fantini et al., 2016). Both hypoperfusion (CBF deficiency) and hyperperfusion (CBF excess) can lead to brain injury (Fantini et al., 2016). Thus, CVA is essential for maintaining a relatively stable cerebral perfusion to provide the brain with the necessary oxygen and energy substrates (Fantini et al., 2016).

The three key factors of CVA are CBF, CPP, and cerebrovascular resistance (CVR). Notably, CPP depends on the pressure difference between the cerebral arterial and venous systems (Donnelly et al., 2016). Cerebral arterial pressure approaches arterial blood pressure (ABP) and cerebral venous pressure closes to intracranial pressure (ICP). Furthermore, CVR depends on the diameter of small cerebral arteries; the smaller the diameter, the greater the resistance (Donnelly et al., 2016). This relationship can be simplified as follows:

$\text{CBF} = \frac{\text{CPP}}{\text{CVR}} = \frac{\text{ABP-ICP}}{\text{CVR}}$ (Donnelly et al., 2016).

Although decades of research have elucidated some underlying mechanisms, the exact physiological mechanisms of CVA remain elusive (Silverman and Petersen, 2020). The traditional hypotheses of physiological mechanisms involve metabolic, neurogenic, myogenic, and endothelial responses. In a retrospective study of healthy volunteers, Hamner and Tian demonstrated that neurogenic and myogenic mechanisms together accounted for 62% of the cerebral pressure-flow relationship (Hamner and Tan, 2014). Several major physiological mechanisms of CVA are described below.

1. 2. 2. 1 Metabolic mechanism

The major metabolic control of CVA is CO_2, which is a powerful modulator of cerebral vascular tone (Salinet et al., 2019). When the CO_2 level decreases, the cerebral blood vessels constrict. Conversely, when the CO_2 level increases, the cerebral blood vessels dilate. For every 1 mmHg increase or decrease in CO_2 within 20–80 mmHg, the flow in the middle cerebral artery changes by 4% (Salinet et al., 2019).

Hypercapnia might reduce the effectiveness of CVA by reducing cerebral vascular tone, while it increases CBF by cerebral vasodilation (Meng and Gelb, 2015). As described by Meng and Gelb, hypercapnia affects the upper and lower limits of CVA. The effect of hypercapnia on CVA is illustrated in Figure 3. When CPP decreases, cerebral resistance vessels dilate in order to prevent hypoperfusion. In the case of hypercapnia, due to the additional dilation it imposes, maximum dilation is reached while CPP is higher than the normal lower limit (Meng and Gelb, 2015). Therefore, the lower limit is shifted to the right during hypercapnia (Meng and Gelb, 2015). When CPP is elevated, cerebral vasoconstriction occurs to prevent

hyperperfusion. However, in hypercapnia, the CVA-induced vasoconstriction is antagonized by the hypercapnia-induced vasodilation (Meng and Gelb, 2015). Thus, the upper CVA limit shifts to the left during hypercapnia, meaning that the upper limit is lower than that in normocapnia (Meng and Gelb, 2015). Since the lower limit shifts to the right and the upper limit to the left, the plateau shortens during hypercapnia (Meng and Gelb, 2015). The more severe the degree of hypercapnia, the more the lower limit shifts to the right, the upper limit shifts to the left, and the shorter the plateau. During severe hypercapnia, when cerebral blood vessels are dilated to the maximum limit, the plateau disappears and the CVA curve becomes linear (Meng and Gelb, 2015).

Figure 3 Effect of hypercapnia on cerebrovascular autoregulation

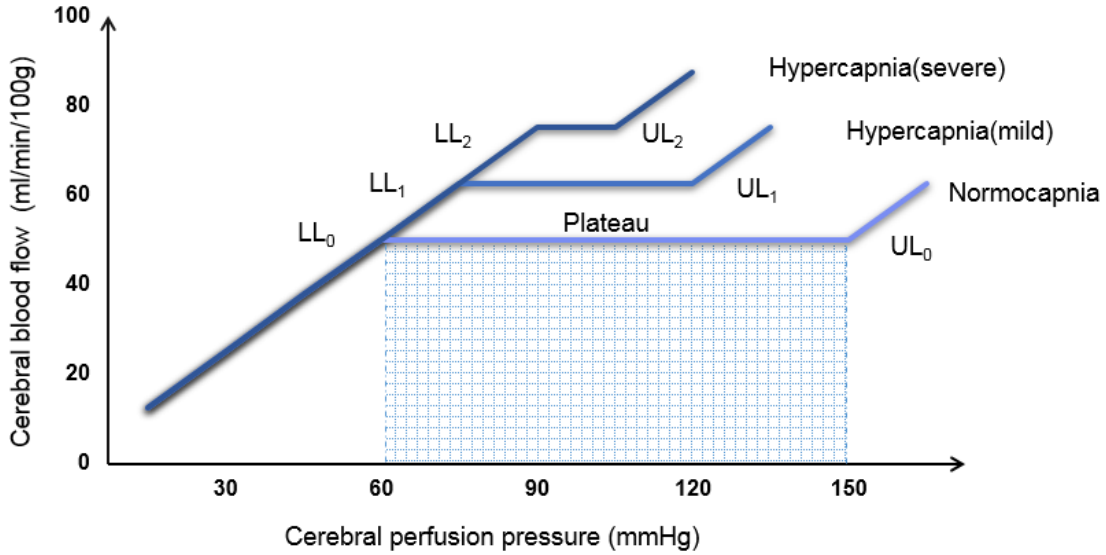

Figure 3 Effect of hypercapnia on cerebrovascular autoregulation (CVA). Curves of CVA are in light blue at normocapnia, blue at mild hypercapnia, and dark blue at severe hypercapnia. The light blue grid is the area where CVA works in normocapnia. LL_0, LL_1, and LL_2 are the lower limits of normocapnia, mild hypercapnia, and severe hypercapnia, respectively. UL_0, UL_1, and UL_2 are the upper limits of normocapnia, mild hypercapnia, and severe hypercapnia, respectively.

According to Meng, L., Gelb, A.W., 2015. Regulation of cerebral autoregulation by carbon dioxide. Anesthesiology 122, 196–205.

Hypocapnia reduces CBF through cerebral vasoconstriction (Meng and Gelb, 2015). The effect of hypocapnia on the CVA curve is more complicated and still not well understood. Because a decrease in CPP causes vasodilatation and hypocapnia constricts cerebral resistance vessels with opposite effects. In contrast, both CPP rise and hypocapnia cause cerebral vasoconstriction. According to Meng and Gelb, the plateau of the CVA curve shifts downward at hypocapnia (Meng and Gelb, 2015). Besides, in the case of hypocapnia, changes in the lower limit are unremarkable, and it is still not clear how the upper limit moves (Meng and Gelb, 2015).

The effect of hypocapnia to CVA remains controversial in previously reported studies. In one study including 12 patients undergoing elective surgery, hypocapnia due to increased respiratory rate or tidal volume was able to restore CVA during isoflurane-induced CVA impairment (McCulloch et al., 2005). Similarly, in intubated patients with traumatic brain injury (TBI), 30 minutes of moderate hypocapnia (33 mmHg) induced by hyperventilation, showed to improve the function of CVA (Haubrich et al., 2012). However, in mechanically ventilated septic patients, hypocapnia induced by short-term hyperventilation did not enhance CVA (Berg and Plovsing, 2016). Short-term hypocapnia is used in the treatment of acute brain injury to reduce ICP, but it may lead to cerebral ischemia and damage (G. Curley et al., 2010). Moreover, in patients with severe brain injury, CVA was preserved during a mean $PaCO_2$ of 34.2 mmHg and impaired after $PaCO_2$ decreased to a mean value of 23.1 mmHg (Cold et al., 1981).

In addition to CO_2, hypoxemia also exerts an effect on CVA. Hypoxemia has a powerful stimulating effect on arterial dilation (Johnston et al., 2003). As the PaO_2 decreases from 50 to 25 mmHg, CBF doubles due to cerebral vasodilatation in anaesthetized dogs (Johnston et al., 2003). In a model of cerebral hypoxia caused by carotid artery and jugular vein ligation in newborn lambs, CVA was impaired during the recovery phase after two hours of severe hypoxia (Short et al., 1994). Similarly, in a cohort study, CVA was impaired in healthy volunteers under four hours of hypobaric hypoxia (Subudhi et al., 2010).

1. 2. 2. 2 Neurogenic mechanism

It is well known that large amount of nerve fibers are along the cerebral vessels (Edvinsson, 1975). Earlier studies on the neurogenic response of CVA were conducted in animals. In an animal study, after removal of the carotid sinus nerve in experimental canines, the experimental canines showed a linear relationship between CPP and CBF, suggesting the loss of CVA (Sagawa and Guyton, 1961).

The neurologic control of CVA has been shown to play a key part in human studies using the corresponding blocking agents. In a study with healthy subjects, trimethaphan was used as a ganglion blockade, showing the function of CVA to minimize pressure fluctuations was reduced (Zhang et al., 2002). Single sympathetic blocking agents had similar effects. In 12 healthy subjects, Hamner et al. used α-adrenergic sympathetic blockade, phentolamine, and found the ability of CVA to buffer against blood pressure fluctuations was impaired (Hamner et al., 2010). Similarly, the use of cholinergic blockades in healthy volunteers also showed with impaired dynamic CVA (Hamner et al., 2012). Moreover, in a retrospective study in 43 healthy subjects, neurologic control was confirmed to have an crucial effect on CVA when ABP fluctuated during the plateau of the CVA curve (Hamner and Tan, 2014). These studies

found a reduced effect of CVA using sympathetic or cholinergic blockers, which illustrated the role for the neurologic mechanisms of CVA.

1. 2. 2. 3 Myogenic mechanism

Myogenic mechanisms have a major role in the physiological effects of CVA. When CPP increases, the myogenic reflex causes vasoconstriction, and conversely, when CPP decreases, myogenic tone relaxes, leading to vasodilation (Silverman and Petersen, 2020). The cerebrovascular arterial muscle is regulated by the level of membrane potential which mainly includes the following processes according to Harder et al. (Harder et al., 1998). First, the increasing CPP promotes the expression of cytochrome P-450 4A enzymes, leading to the production of 20-hydroxyeicosatetraenoic acid. Second, 20-hydroxyeicosatetraenoic acid activates protein kinase C. Third, protein kinase C inhibits potassium channels, which decreases the membrane potential of the cerebrovascular smooth muscle. Thus, decreased membrane potential contributes to an influx of calcium and cerebrovascular constriction (Harder et al., 2011). Additionally, early studies have described that myogenic mechanisms of CVA may be calcium-dependent (Harder et al., 1998). In a vitro study, human isolated cerebral resistance arteries produced spontaneous intrinsic tone when pressure stimulation was at 20–90 mmHg (Wallis et al., 1996). But in the absence of extracellular calcium, the spontaneous intrinsic tone was not evident (Wallis et al., 1996).

Moreover, the myogenic control of CVA has also been shown in human studies. In a study of 16 healthy subjects, the effective pressure range of CVA was halved after the use of calcium channel blockades compared to baseline. Besides, the slope of CVA curve increased almost fivefold after the use of calcium channel blockades, suggesting an important role of myogenic mechanisms in CVA (Tan et al., 2013). Notably, when ABP fluctuated outside the plateau of the CVA curve, myogenic effectors were the largest determinants of CVA (Hamner and Tan, 2014).

1. 2. 2. 4 Endothelial mechanism

Endothelial mechanisms refer to the regulation of cerebrovascular function by endothelial cells through the production or release of vasoactive substances, including endothelial relaxing factors, such as NO, and endothelial contracting factors, such as endothelin (Faraci, 1992). Previous studies were mainly on the effect of NO on CVA. Endothelial NO has been shown to have a protective effect on CVA in both animal and human studies. In 24 anesthetized cats, CBF become dependent on changes in blood pressure during nitric oxide synthase inhibitor infusion, suggesting an association between reduced NO and impaired CVA (Kobari et al., 1994). Similarly, in healthy subjects, CVA function was affected during

nitric oxide synthase inhibitor infusion, indicating that NO mediated part of the CVA process in human (White et al., 2000). Moreover, in newborn and juvenile pigs with TBI, inhaled NO had a protective effect on CVA (Hekierski et al., 2019).

1. 2. 3 Methods of measuring cerebrovascular autoregulation in clinical practice

Measuring CVA requires a continuous measurement of CPP, a real-time estimate of CBF and a mathematical method of calculating CVA function between CPP and CBF. For TBI patients, CPP can be easily calculated based on direct ICP monitoring, while in patients without ICP monitoring, ABP is thought to be an alternative to CPP for CVA measurement (Moerman and De Hert, 2019). The most accurate method to obtain ABP is through invasive arterial cannulation, which can provide a stable and continuous ABP measurement.

Besides, CVA can be measured in two different ways, measuring relative CBF fluctuations in response to steady state changes of ABP or rapid changes of ABP (Fantini et al., 2016). The former is defined as static CVA, and the latter is dynamic CVA. The static CVA method assesses CVA during relatively steady-state changes in ABP, such as an increase in ABP over time due to hypertension or a decrease in ABP over time after hypertension treatment. By contrast, the dynamic CVA investigates how transient changes in ABP affect CBF (Tiecks et al., 1995). Pressure changes can be induced by using stimuli such as thigh-cuff release, lower body negative pressure, postural changes or more commonly, vasoactive drug injection (Fantini et al., 2016; Tiecks et al., 1995). Since pressure manipulations in critically ill patients are potentially harmful, one alternative approach is to measure the CBF response to spontaneous fluctuations of ABP.

Researchers have developed some methods of the CVA measurement. Invasive techniques include jugular venous oximetry, brain tissue oxygen monitoring, laser Doppler and thermal diffusion flowmetry (Fantini et al., 2016). Non-invasive methods include CBF velocity measured by transcranial Doppler (TCD) and regional oxygen saturation (rSO_2) by near infrared spectroscopy (NIRS). Researchers used a continuous, moving correlation coefficient to evaluate CVA function, mean velocity index in TCD-based CVA measurement or cerebral oxygenation index (COx) in NIRS based CVA measurement (Masahiro Ono et al., 2012; Schramm et al., 2012). The mean velocity index refers to the correlation coefficient between ABP and CBF velocity and the CO_X is the correlation coefficient between ABP and rSO_2. The following is a detailed introduction of NIRS based CVA measurement.

In NIRS based CVA measurement, rSO_2 is used as an alternative for CBF. In 1985, Brazy et al. first used NIRS in clinical practice to assess cerebral oxygenation (Brazy et al., 1985). It

is a diffuse optical method sensitive to tissue concentrations of oxyhemoglobin and deoxyhemoglobin, because oxyhemoglobin and deoxyhemoglobin absorb near-infrared light differently (Fantini et al., 2016). The ratio of oxyhemoglobin to total hemoglobin is the hemoglobin oxygen saturation of brain tissue. Since the majority of oxygen in the blood is bound to hemoglobin and all blood albumin is in the red blood cells, the total hemoglobin concentration is proportional to the cerebral blood volume (Fantini et al., 2016). Cerebral oxygen saturation is determined by arterial blood oxygen content, cerebral oxygen consumption, oxygen-tissue diffusivity, and CBF (Moerman and De Hert, 2017). The NIRS method of CVA measurement is based on the assumption that fluctuations in rSO_2 can represent changes in CBF when other determinants remain constant (Bush et al., 2019). If the NIRS electrode is placed on the patients' forehead, the cerebral NIRS signal reflects the oxygenation of mixed arterial and venous of the frontal lobe tissue in the path of the emitted light (Bush et al., 2019). Thus, NIRS is an attractive choice for CVA measurement because of its noninvasiveness, uncomplicated manipulation and continuous measurement.

Studies have compared NIRS-based with the TCD-based CVA measurement. The results showed that they were correlated and in good agreements (K. Brady et al., 2010; Ono et al., 2013). In a study monitoring CVA during cardiac surgery, the correlation between mean velocity index and COx was highly consistent at r = 0.55 (K. Brady et al., 2010). These two different methods of monitoring CVA also demonstrated consistent agreement in a diverse population with acute coma and large intracranial lesions (Rivera-Lara et al., 2017). One difference between TCD and NIRS-based CVA measurement is continuity. It is easy to measure CVA continuously with sensors at the forehead in NIRS-based CVA measurement. In the TCD-based method, continuous measurement is a technical challenge, so it is usually used for intermittent CVA measurements (Moerman and De Hert, 2019).

1. 2. 4 Effects of vasoactive medications and sedatives on cerebrovascular autoregulation

Many medications used in the ICU can affect CVA function. The most representative medications are sedatives and vasoactive medications. Sedatives include intravenous midazolam and propofol, inhaled isoflurane and sevoflurane. Vasoactive medications include dopamine and noradrenalin. The effects of these medications on CVA are described below.

Propofol sedation seems to keep the CVA intact in patients without brain injury. In adult patients undergoing non-neurosurgical procedures during administration of 250–300 μg/kg/min propofol, no significant fluctuations in CBF velocity were observed with increasing ABP, indicating that CVA remained intact (Matta et al., 1995). Similarly, in preterm neonates, the use of propofol for endotracheal intubation did not disrupt the integrity of CVA while

causing hypotension (Thewissen et al., 2018). Cerebrovascular effects of propofol differ in patients with and without TBI. In adult patients with TBI, deterioration of CVA was observed after increasing the dose of propofol (Steiner et al., 2003). Unlike propofol, midazolam has been shown to improve CVA in previous studies. In a randomized, single-blind, crossover study, steady-state CBF velocity decreased significantly with administration of midazolam and propofol in healthy male subjects (Ogawa et al., 2010). However, in this study, dynamic CVA improved only after midazolam administration. Moreover, midazolam caused the CVA improvement in the other study in healthy subjects, and a smaller change of CBF was observed in response to pressure fluctuations after midazolam administration (Ogawa et al., 2015).

The effect of isoflurane on CVA is dose-dependent, with low doses of isoflurane maintaining the integrity of CVA and high doses leading to impaired CVA. In adult patients undergoing lumbar disc surgery, CVA was intact in most patients at 1 minimum alveolar concentration (MAC) of isoflurane and impaired at 2 MAC of isoflurane (Olsen et al., 1994). Similarly, in adult patients undergoing elective orthopedic surgery, low doses of isoflurane (0.5 MAC) did not impair dynamic CVA, whereas 1.5 MAC of isoflurane damaged dynamic CVA (Strebel et al., 1995). The effect of sevoflurane on CVA is similar to isoflurane, depending on its concentration. In patients undergoing general anesthesia, CVA was intact under 1 MAC of sevoflurane (Juhász et al., 2019). In a rabbit study, CVA function was intact with 1 MAC and impaired with 2 MAC sevoflurane (Lu et al., 1998).

Vasoactive medications including noradrenalin, adrenalin, and dopamine might affect CVA function. The effect of dopamine on CVA varies across studies. In juvenile pigs after brain injury, dopamine was observed with protective effect on CVA (Curvello et al., 2017). Conversely, in a secondary analysis study of preterm neonates, patients with dopamine treatment had much longer time of injured CVA than those without dopamine treatment (Solanki and Hoffman, 2020). In addition, CO_X was significantly higher in hypotensive preterm infants treated with dopamine than in those not treated with dopamine, suggesting an association between dopamine treatment and CVA impairment (Eriksen et al., 2014). The protective effect of noradrenalin on CVA was observed in an animal study. In this study, noradrenalin protected CVA in female piglets after brain injury but not in male piglets (Armstead et al., 2016).

1. 2. 5 Cerebrovascular autoregulation impairment in patients without primary intracranial disorders

When it comes to CVA impairment, a key point is to understand how it has been defined in previous studies. However, previous studies had different definitions of impaired CVA

(Schramm et al., 2012; M. Ono et al., 2012; Lee et al., 2019). Schramm et al. evaluated impaired CVA based on a calculated mean CO_X above 0.3 during the measurement. Lee et al. used the percentage of time with CVA impairment during the measurement in critically ill patients. Ono et al. using TCD-based CVA measurement, impaired CVA was defined as a mean velocity index between ABP and CBF above 0.4. Going back to the CVA curve, CVA is intact when the CPP changes during the plateau. However, when CPP is above the upper limit or below the lower limit of CVA, CVA is impaired.

The impairment of CVA has been observed in patients with sepsis (Bindra et al., 2016; Crippa et al., 2018; Schramm et al., 2012). In a prospective, observational multicenter study of TCD based CVA measurement, Crippa et al. demonstrated that CVA was impaired in half of the patients with sepsis (Crippa et al., 2018). The CVA function which was assessed by mean flow index between CBF and ABP independently predicted sepsis-associated brain dysfunction, indicating that CVA impairment might contribute to the sepsis-associated encephalopathy (Crippa et al., 2018). In a study including severe sepsis or septic shock patients, CVA was impaired in 60% patients during the first two days of sepsis. As described by Schramm and colleagues, impaired CVA was associated with the incidence of sepsis associated delirium (Schramm et al., 2012). Furthermore, in a prospective observational study, CVA impairment in the first three days of septic shock was independently associated with mortality three months after ICU admission (Bindra et al., 2016).

Recent studies have suggested an association between cardiac surgery and CVA impairment, with the majority of studies reporting that impaired CVA was observed during cardiac surgery (Caldas et al., 2018). The incidence of CVA impairment during cardiac surgery ranged from 20% to 70% in previously reported studies (Murkin et al., 2015; Masahiro Ono et al., 2012; M. Ono et al., 2012). Patients undergoing cardiac surgery have some risk factors for developing impaired CVA, such as hypothermia, hypotension. In adult patients undergoing cardiopulmonary bypass, Joshi et al. demonstrated that hypothermic cardiopulmonary bypass was associated with abnormal CVA, and CVA worsened with rewarming (Joshi et al., 2010). In a prospective, observational pilot study, hypotension was associated with impaired CVA in pediatric patients undergoing cardiac surgery with cardiopulmonary bypass (K. M. Brady et al., 2010). Besides, patients undergoing cardiac surgery with evidence of impaired CVA were more likely to have a stroke than those with functional CVA (Joshi et al., 2010; M. Ono et al., 2012).

1. 3 Cerebrovascular autoregulation in patients with acute respiratory distress syndrome

Many factors that are known to affect CVA function frequently occur in ARDS patients. First, ARDS patients have hypoxemia and a high probability of developing dyscapnia due to pulmonary ventilation and gas exchange dysfunction. As previously described, both hypoxemia and abnormal CO_2 levels affect the CVA function. Furthermore, in order to maintain lung-protective ventilation settings or treat patient-ventilator asynchrony, sedatives are often used during the treatment of ARDS patients (Chanques et al., 2020). However, commonly used sedative medications such as isoflurane, which was shown to influence CVA function in a dose-dependent manner (Olsen et al., 1994). Moreover, ARDS can be caused by sepsis or septic shock. Impaired CVA was observed in 50% of sepsis patients and the majority of patients with septic shock (Crippa et al., 2018; Taccone et al., 2010).

Numerous studies about CVA in patients with or without neurological disorders have been performed in recent years (Brown et al., 2019; Gaasch et al., 2018). However, there are few studies on CVA in ARDS patients. To date, two studies which focused on the influence of PEEP on CVA in adult ARDS patients, indicated that around 50% of adult ARDS patients had CVA impairment (Schramm et al., 2013; Yang et al., 2014). In a prospective observational study conducted by Schramm et al., CBF velocity was measured by TCD, and the mean velocity index between CBF velocity and ABP was calculated to obtain the CVA function. In 11 of 20 ARDS patients had impaired CVA with mean velocity index above 0.3 (Schramm et al., 2013). The other prospective study by Yang et al. demonstrated that 47% ARDS patients had CVA impairment, and a high level of PEEP would not further damage CVA (Yang et al., 2014). In a study with NIRS-based CVA measurement, preterm infants with ARDS exhibited longer duration with CVA impairment in the first 72 hours after birth compared to patients without ARDS (Lemmers et al., 2006).

A case report showed hypercapnia or the rapid change of CO_2 in ARDS patients may compromise the CVA function (Muellenbach et al., 2014). This hypercapnic ARDS patient was treated with ECMO. After the initiation of ECMO, $PaCO_2$ decreased rapidly, pH levels gradually returned to normal, PaO_2 increased, and mean arterial pressure (MAP) decreased slightly, while rSO_2 dropped by about 20% from baseline levels. It is likely that the patient's CVA was affected or even compromised during this process, as the change in rSO_2 was disproportionate to the change in MAP.

In very low birth weight respiratory distress syndrome infants, hypercapnia was shown to be associated with CVA (Kaiser et al., 2005). In this study, CVA was measured during tracheal

suctioning procedures, and the correlation coefficient between CBF and ABP increased significantly when $PaCO_2$ > 45 mmHg, indicating the impairment of CVA.

However, it is still unclear how hypercapnia affects CVA in adult ARDS patients, and the relationship between impaired CVA and neurological outcomes.

2. Aim of the study

1) The first aim is to compare CVA function between patients with and without early hypercapnia during the acute phase of ARDS.

2) The second aim is to explore the association between impaired CVA and neurocognitive outcome in ARDS patients three months after ICU discharge.

3. Hypothesis

1) CVA impairment is more severe in ARDS patients with early hypercapnia than those without early hypercapnia.

2) Impairment of CVA in ARDS patients is associated with neurocognitive dysfunction three months after ICU discharge.

4. Material and methods

4. 1 Study registration and ethical information

To provide public access and increase the transparency in clinical research, this study was registered at ClinicalTrials.gov on May 14, 2019, the registration number was NCT03949738. Ethical approval was achieved from the ethics committee of the Hamburg Chamber of Physicians on November 8th, 2018 under serial number PV5872. Informed consent was obtained from the patient or legal guardian prior to enrollment in our study. If the patient was unable to give consent at the time of ARDS diagnosis and had no legal guardian, the initial decision to participate in the study was made after the presumed patient's wishes with next of kin and in consultation with an independent physician. Written consent for the study was obtained as soon as the legal guardian was identified.

4. 2 Participants and study design

This prospective observational cohort study was conducted at the Department of Intensive Care Medicine of the University Medical Center Hamburg-Eppendorf from December 2018 to March 2020. Patients with ARDS who met the inclusion criteria and none of exclusion criteria were enrolled between December 2018 and November 2019. The CVA was monitored twice during the acute stage of ARDS. The first CVA measurement was performed immediately after enrollment. The time point of the second measurement was determined based on a relevant change in disease severity and/or adjunctive therapy. The adjunctive therapies included new position, new inhaled NO, new vv-ECMO, or new invasive ventilation. Patients were followed up three months after discharge from the ICU. The study procedure is shown in Figure 4.

4. 2. 1 Inclusion and exclusion criteria

Patients who met ARDS diagnosis criteria based on Berlin definition and were older than 18 years were included. Patients were not in the acute phase of ARDS (within 6 days of ARDS diagnosis) and those with pre-ICU diagnosis of neurological diseases were excluded. In addition, patients with chronic hypercapnia ($PaCO_2$ ≥ 50 mmHg, PH > 7.35) or a life expectancy < 24 hours or patients not fluent in German were also excluded.

4. 2. 2 Definition of hypercapnia

$PaCO_2$ was assessed multiple times during the course of the study.

Early hypercapnia

If ARDS was diagnosed at our department, arterial blood gas information for the first 24 hours after ARDS diagnosis was collected from the electronic patient data management system (ICM, Drägerwerk AG & Co. KGaA, Lübeck, Germany). For patients who were referred from another hospital and with a preexisting diagnosis of ARDS before admission to our ICU, arterial blood gas analyses within 24 hours after ARDS onset were obtained from the referring hospital.

Early hypercapnia was defined as the maximum $PaCO_2$ ≥ 50 mmHg and a corresponding pH < 7.35 within the 24 hours after ARDS diagnosis (Kahl et al., 2021). The cut-off value for hypercapnia was based on Nin et al (Nin et al., 2017). According to Nin et al, severe hypercapnia was the highest $PaCO_2$ ≥ 50 mmHg within 48 hours of the initiation of mechanical ventilation (Nin et al., 2017).

$PaCO_2$ during the CVA measurement

Two arterial blood analyses were taken during each measurement period, one at the beginning of CVA measurement, the other one at the end. $PaCO_2$ during the CVA measurement was the averaged $PaCO_2$ value from the two arterial blood gas analyses. Values of $PaCO_2$ during CVA measurement were classified as 'hypocapnia' (< 35 mmHg), 'normocapnia' (35–50 mmHg), and 'hypercapnia' (> 50 mmHg) (Kahl et al., 2021).

Figure 4 Schematic presentation of the study design and study-related procedures

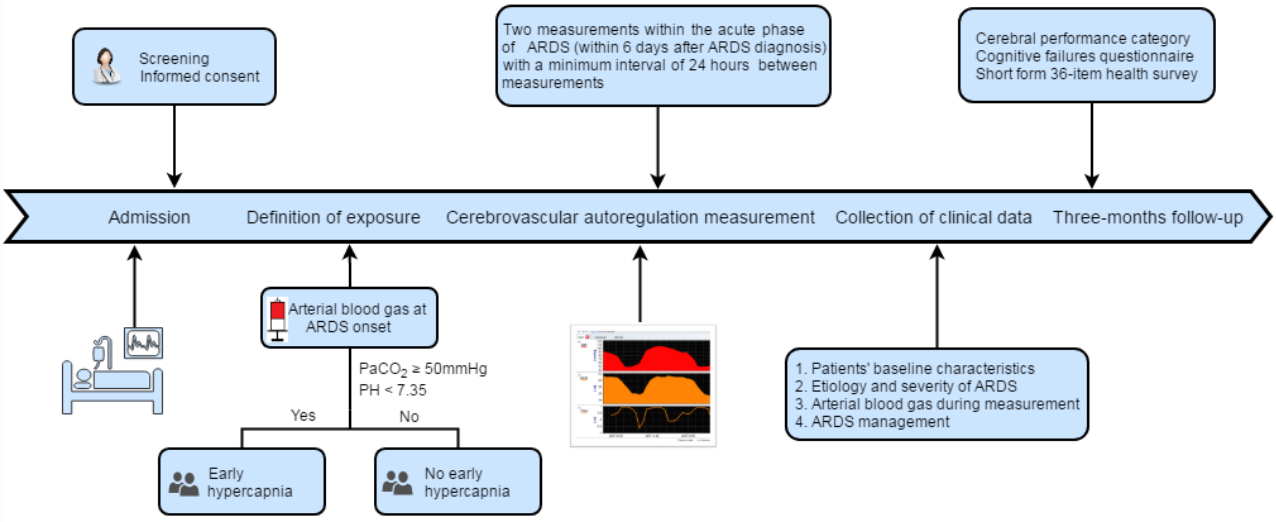

Figure 4 Schematic presentation of the study design and study-related procedures. ARDS acute respiratory distress syndrome, $PaCO_2$ arterial partial pressure of carbon dioxide, ECMO extracorporeal membrane oxygenation. This Figure is made by Xunjie Flowchart Maker Software, Shanghai Hudun Information Technology Co., Ltd

4. 3 Measurement of cerebrovascular autoregulation

4. 3. 1 Cerebrovascular autoregulation monitoring

CVA was assessed using COx, a correlation coefficient that used ABP as a surrogate for CPP and rSO_2 as a surrogate for CBF, which has been described previously (Andersen et al., 2018; Kainerstorfer et al., 2015; Steiner et al., 2009). Unilateral rSO_2 was monitored with a NIRS monitor (INVOS™ 5100 Cerebral Oximeter, Medtronic, Minneapolis, Minnesota, USA). A compatible sensor (INVOS™ Cerebral/Somatic Oximetry Adult Sensors, Medtronic, Minneapolis, Minnesota, USA) was attached to one side of patient's forehead. The sensors used infrared wavelengths to provide real-time data of rSO_2 values. Spontaneous fluctuations of ABP were monitored continuously by intra-arterial catheters (Leader-Cath, VYGON GmbH & Co KG, Aachen, Germany). Intra-arterial catheter was placed by the clinician in the radial or femoral artery. The rSO_2 and ABP were processed to calculate COx using ICM+®software (Smielewski et al., 2008)(University of Cambridge, Cambridge, UK).

Twice episodes of CVA were monitored during the acute stage of ARDS with at least 24 hours between measurements. Duration of each measurement was 60–90 minutes. To prevent artifacts by changes of ventilation settings (FiO_2, respiratory rate, tidal volume, PEEP), CVA was measured while the respiratory status was stable. A member of our study team was at the bedside to supervise the measurement and guaranteed that the ventilation settings did not change from 30 minutes prior to CVA monitoring until the end of the measurement. The measurement was suspended if ventilation settings had to be adjusted for clinical reasons and restarted as soon as the respiratory status was stable again. The schematic diagram of CVA measurement is shown in Figure 5.

Figure 5 Schematic diagram of bedside patient cerebrovascular autoregulation measurement

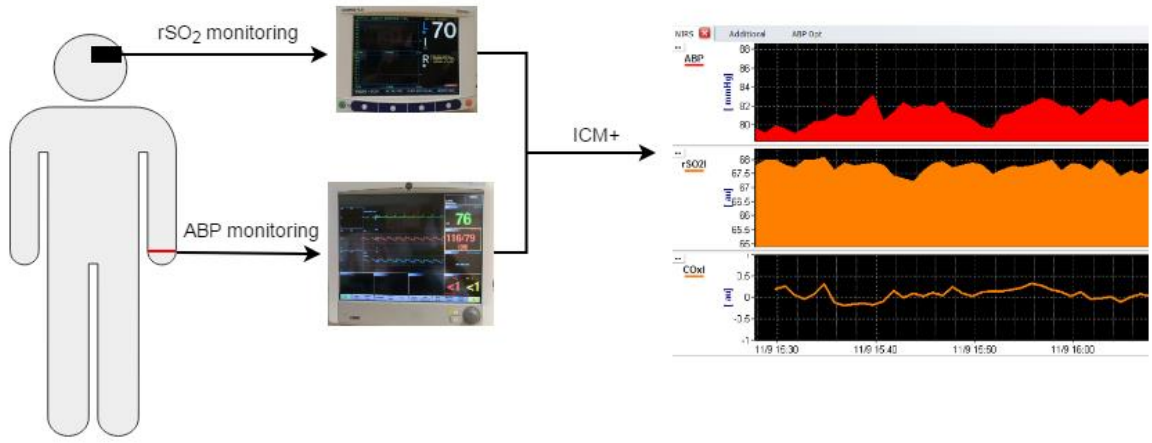

Figure 5 The measurement of cerebrovascular autoregulation. rSO_2, regional oxygen saturation, ABP, arterial blood pressure. ICM+ software was from University of Cambridge, Cambridge, UK (Smielewski et al., 2008).

4. 3. 2 Cerebral oxygenation index

First described by Brady et al. in 2007, COx was found to be sensitive to impaired CVA in hypotensive piglets (Brady et al., 2007). In this study, COx was calculated by ICM+, and it was used to evaluate the function of CVA. When CVA is intact, there is no correlation between rSO_2 and ABP, and COx approaches 0. However, when CVA is impaired, COx values approach 1 (Figure 6). The cut-off for distinguishing COx between intact and impaired CVA ranged from 0.3 to 0.5 in different studies (K. M. Brady et al., 2010; Gilmore et al., 2011; Hori et al., 2014). We used the cut-off of 0.3 to define the impaired CVA, according to previous reports (Hori et al., 2016; Masahiro Ono et al., 2012).

Figure 6 An example of cerebrovascular autoregulation impairment

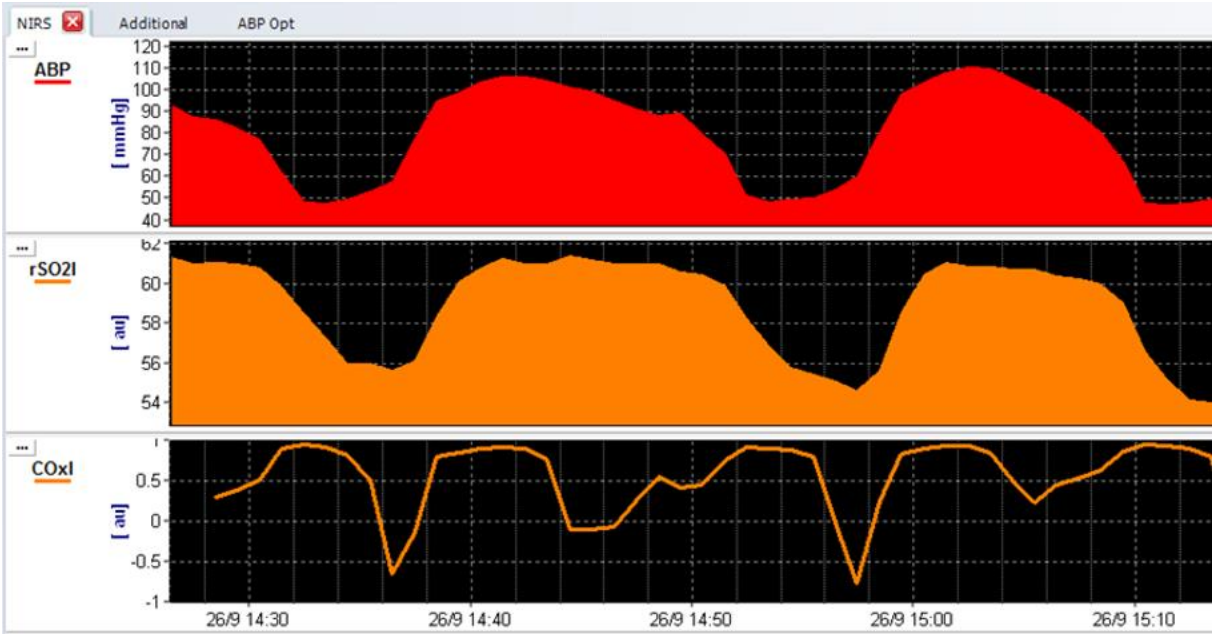

Figure 6 This measurement clearly indicated the impairment of cerebrovascular autoregulation, rSO_2 was in line with the trend of ABP change (Smielewski et al., 2008). The majority of COx was above 0.3 throughout the measurement. ABP Arterial blood pressure, rSO_2 regional oxygen saturation, COx cerebral oxygenation index.

4. 4 Management of acute respiratory distress syndrome

The management of ARDS was based on current guidelines and the ARDS standard operating procedure in our ICU (Fan et al., 2017). The treatment strategies of ARDS included many aspects, such as mechanical ventilation, sedatives and adjunctive therapies as described in detail below.

4. 4. 1 Mechanical Ventilation

In mild ARDS patients, non-invasive ventilation or high-flow oxygen therapy was attempted, and intubation was performed in patients who could not tolerate non-invasive ventilation (Fan et al., 2018). In moderate and severe ARDS patients, invasive ventilation was primarily considered (Fan et al., 2018). Mechanical ventilation parameters followed the principles of lung-protective ventilation, which included the following points (Fan et al., 2017):

- Tidal volume ≤ 6 ml/kg predicted body weight
- Platform pressure ≤ 30 cmH_2O
- Tolerating hypercapnia (up to pH 7.2)
- Driving pressure (platform pressure minus PEEP) ≤ 15 cmH_2O
- Oxygen saturation ≥ 90% (maximum 94%)
- Inspiratory time extension (I: E 1:1 to 1:1.5)
- PEEP settings according to the ARDS network table (Table 2) (Acute Respiratory Distress Syndrome Network et al., 2000)

Table 2 Acute respiratory distress syndrome (ARDS) network table

FiO_2	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.7	0.7	0.8	0.9	0.9	0.9	1
PEEP	5	5	8	8	10	10	10	12	14	14	14	16	18	18–24

Table 2 ARDS network table of positive end expiratory pressure (PEEP) settings, according to required fraction of inspired oxygen (FiO_2).

From Acute Respiratory Distress Syndrome Network, Brower, R.G., Matthay, M.A., Morris, A., Schoenfeld, D., Thompson, B.T., Wheeler, A., 2000. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N. Engl. J. Med. 342, 1301–1308.

4. 4. 2 Sedation strategies

If required, sedative medication was titrated to achieve a score of 0 or -1 on Richmond Agitation and Sedation Scale (RASS). For patients requiring neuromuscular blockade to facilitate mechanical ventilation and reduce patient-ventilator asynchrony, the goal of sedation was a relatively low RASS score (Chanques et al., 2020). Propofol, midazolam, isoflurane, or a combination of these substances were used for sedation.

4. 4. 3 Adjunctive therapies

4. 4. 3. 1 Prone position

For invasively ventilated ARDS patients with PaO_2/FiO_2 ≤ 150mmHg, prone position was continuously performed for at least 16 hours (Fan et al., 2017). Deep sedation was used for ARDS patients during prone position (Fan et al., 2018). Prone position was stopped after an

improvement in oxygenation, which was defined as a PaO_2/FiO_2 ≥ 150 mmHg, with PEEP ≤ 10 cmH_2O and FiO_2 ≤ 0.6 (Guérin et al., 2013).

4. 4. 3. 2 Nitric oxide inhalation

Patients with ARDS with severe hypoxemia requiring FiO_2 ≥ 0.8 or PaO_2/FiO_2 < 60mmHg were treated with inhaled NO in a dosage of 10–40ppm. Treatment ceased as soon as FiO_2 < 0.8 or extracorporeal therapy was started.

4. 4. 3. 3 Extracorporeal membrane oxygenation

Severe ARDS patients with refractory hypoxemia (PaO_2/FiO_2 ≤ 80mmHg) were considered with ECMO after all other measures had been exhausted (Fan et al., 2018). A transthoracic echocardiography was carried out before ECMO implantation. Veno-arterial extracorporeal membrane oxygenation (va-ECMO) was considered for patients with a combination of cardiac failure. In ARDS patients with hypercapnia, $PaCO_2$ was slowly reduced after the initiation of ECMO therapy. Extracorporeal veno-venous 'low-flow' systems were used in the case of refractory hypercapnia with respiratory acidosis or in cases where ventilation was no longer protective.

4. 5 Neurocognitive and functional outcome assessment

We did a follow-up of ARDS patients three months after discharge from the ICU. Neurologic functional outcome, cognitive function, and HRQL were assessed. The cerebral performance category (CPC) was used for evaluating functional outcomes. Self-reported cognitive function was evaluated by cognitive failures questionnaire (CFQ), and HRQL was assessed by the short form 36-item health survey (SF-36). Details on neurocognitive and functional outcomes assessment are described below.

4. 5. 1 Cerebral performance category

Originally, CPC scores were developed for patients with severe brain injury (Jennett and Bond, 1975). They were adapted to evaluate cerebral performance in the brain resuscitation clinical trial (Brain Resuscitation Clinical Trial I Study Group, 1986). CPC score ranges from 1 to 5, and cerebral performance gradually deteriorates as the CPC score increases, with CPC 5 representing brain death (Kiehl et al., 2017)(Table 3). These scores are frequently measured for neurological function after cardiac arrest (Pachys et al., 2014). In this study, CPC score was used to evaluate functional outcome. A detailed description of the CPC score is listed in Table 3.

Table 3 Cerebral performance category

Cerebral performance category (CPC)		
1	Good cerebral performance	conscious, alert, able to work, might have mild neurologic or psychological deficit;
2	Moderate cerebral disability	conscious, sufficient cerebral function for independent activities of daily life, able to work in sheltered environment;
3	Severe cerebral disability	Conscious, dependent on others for daily support because of impaired brain function, ranges from ambulatory state to severe dementia or paralysis;
4	Coma/Vegetative State	Any degree of coma without the presence of all brain death criteria. Unawareness, even if appears awake without interaction with environment; may have spontaneous eye opening and sleep/awake cycles, cerebral unresponsiveness;
5	Brain Death	apnea, areflexia, electroencephalogram silence, etc.

Table 3 The detailed cerebral performance category score.
From Kiehl et al. C-GRApH: A validated scoring system for early stratification of neurologic outcome after out-of-hospital cardiac arrest treated with targeted temperature management. J Am Heart Assoc. 2017;6:e003821

4. 5. 2 Cognitive failures questionnaire

In 1982, the CFQ was described by Broadbent et al. (Broadbent et al., 1982). This version of the CFQ consisted of 25 items of self-assessed failures in perception, memory, and motor function (Broadbent et al., 1982). These items are small mistakes that people make in their daily lives. The German version of CFQ consists of 32 items developed from the Broadbent CFQ with an additional 7 items (Klumb, 1995). The German CFQ version was used in this study. For each item, respondents were asked to indicate the frequency of failures happening to them. All items had to be answered on 5-point scales ranging from ‘never’ to ‘very often’. The total CFQ score was calculated by adding up each item level, with higher scores indicating more cognitive difficulties. Frequently, CFQ was used to identify cognitive function of ICU survivors (Brück et al., 2019).

4. 5. 3 36-item short-form health survey

The SF-36 was first made available in a standard form by Ware and colleagues in 1992 (Ware and work(s):, 1992). Most SF-36 items are derived from instruments used since the 1970s and 1980s, including the General Mental Health Scale, various measures of physical and role functioning, and the Health Perception Questionnaire (Ware, 2000). The SF-36 is a self-administered questionnaire, which consists of eight dimensions: vitality, physical function, bodily pain, general health, physical role function, emotional role function, social role function and mental health (Ware, 2000). The score for each dimension can be calculated by aggregating the item responses. The scores for each dimension range from 0 to 100, with a high score representing good health and a low score indicating poor health (Ware, 2000). These eight dimensions are commonly combined to calculate two summary

measures (Ware, 2000). Physical function, bodily pain, general health, and physical role function can be combined into a physical component score, and the mental component score consists of vitality, social function, emotional role, and mental health (Ware, 2000). The SF-36 is the most common and valid tool to measure general HRQL (Stewart, 2007).

4. 6 Power calculation

A power calculation was performed by PASS Version 15.0.3. The module “Two-Sample t-Tests using Effect Size” (NCSS, LLC. Kaysville, Utah, USA) was used. According to a study examining the effect of postural changes on CVA, a standard deviation of 0.21 and a mean difference of 0.17 in COx between groups would have statistical significance (Schramm et al., 2014). Assuming a type I error of 5% (two-tailed hypothesis) and a power of 80%, we required a minimum sample size of 50 patients to obtain an effect size of 0.81 (Kahl et al., 2021).

4. 7 Data collection

We obtained medical history information from patients, their relatives, or the referring physicians. Data was extracted from the electronic patient data management system (ICM, Drägerwerk AG & Co. KGaA, Lübeck, Germany). Baseline characteristics including sex, age, weight, height, comorbid conditions were collected. Arterial blood gas analyses were recorded before and after CVA measurement. Besides, treatment measures for ARDS patients were documented, including mechanical ventilation parameters, sedatives, ECMO therapy, and other details on ARDS management. On the CVA measurement day, the sequential organ failure assessment (SOFA) score was collected to evaluate the severity of organ failure.

4. 8 Statistical analysis

The descriptive statistics of continuous numeric variables were given as means and standard deviations, and categorical variables were shown as numbers and percentages. Baseline demographic and clinical data between ARDS patients with and without early hypercapnia was compared with Mann-Whitney-U tests, Chi-square tests and Fisher’s exact as applicable.

The dependent variable was the percentage of time with impaired CVA, which was a continuous numerical variable. Each participant had one or two CVA measurements and clinically relevant variables were collected in the repeated CVA measurements. Therefore, a linear mixed model was built in this study. The main independent variable was the presence of early hypercapnia. The clinically relevant variables included age, SOFA score, ARDS

severity, ARDS etiology, sedation mode, $PaCO_2$ during CVA measurement, prone position, inhaled NO, and ECMO during the measurement. All independent variables were fixed effects in the model. The model was gradually reduced with a stepwise-backwards method. Variables that resulted in a change of parameter estimates > 10% or were statistically significant remained in the model. Residuals for normal distribution were evaluated with Q-Q and residual plots. Besides, a leave-one-out cross-validation was conducted to confirm the final model (Kahl et al., 2021).

Two sensitivity analyses were performed. In one sensitivity analysis, considering the inconsistent definition of hypercapnia in studies, the model was recalculated using a different definition of early hypercapnia, which was defined as a $PaCO_2 \geq 60$ mmHg with a corresponding pH < 7.35 within the first 24 hours of ARDS diagnosis. In the other sensitivity analysis, the independent variable of primary interest was delta $PaCO_2$, which was defined as the difference of $PaCO_2$ between ARDS onset and CVA measurement.

We conducted an exploratory subgroup analysis to compare CVA during measurements with and without ECMO treatment with Mann-Whitney-U tests. Correlation analysis was performed to examine the relationship between impaired CVA and the self-assessed cognitive function as well as the HRQL three months after discharge from the ICU. The impaired CVA was also compared in ARDS survivors and non-survivors with the Mann-Whitney-U test. Multivariable analysis for neurocognitive and functional outcomes was not performed due to low patient numbers.

All analyses were conducted using SPSS Version 24 (IBM SPSS Statistics, IBM Corporation). The figures were drawn through Prism 8, Version 8.4.3 (GraphPad Software Inc., San Diego, CA, USA) or Xunjie Flowchart Maker Software (Shanghai Hudun Information Technology Co., Ltd, China) or Microsoft Office 2016 (Microsoft Corporation, USA)

5. Results

5. 1 Study population

Figure 7 Flow chart of patient identification, enrollment and follow up

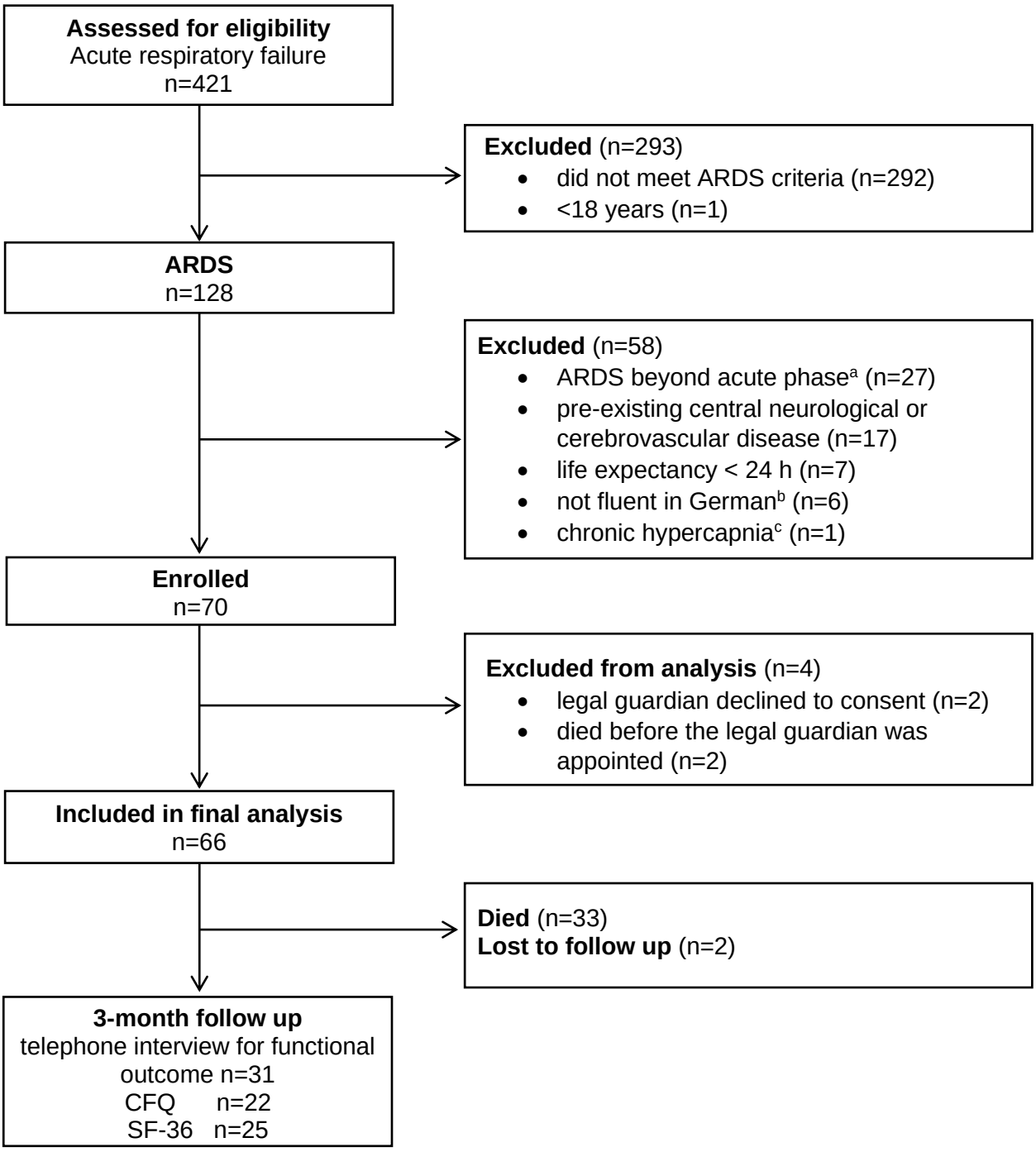

Figure 7 [a] > 6 days from the onset of ARDS, [b] it is difficult to follow up for these patients, [c] patients with $PaCO_2$ > 50 mmHg and pH ≥ 7.35. ARDS Acute respiratory distress syndrome, CFQ cerebral failures questionnaire, SF-36 Short Form 36-item Health Survey.

According to Kahl, U., Yu, Y., Nierhaus, A., Frings, D., Sensen, B., Daubmann, A., Kluge, S., Fischer, M., 2021. Cerebrovascular autoregulation and arterial carbon dioxide in patients with acute respiratory distress syndrome: a prospective observational cohort study. Ann. Intensive Care 11,47.

We screened all patients admitted to one of our ICUs between December 2018 to November 2019 who required mechanical ventilation and had a PaO_2/FiO_2 ratio ≤ 300mmHg. In total, 128 patients with ARDS were identified, and 63 patients were excluded. The exclusion was mainly due to ARDS beyond the acute phase or pre-existing central neurological or cerebrovascular disease. Thus, 66 ARDS patients were included in the analysis for Hypothesis 1. The flow chart of patient identification, enrollment, and follow up is shown in Figure 7.

5. 2 Baseline characteristics of study participants

The majority of included ARDS patients were male (n = 52, 78.8%). The mean age of study participants was 58.5 (±16) years. Most patients had severe (n = 28, 42.4%) or moderate (n = 28, 42.4%) ARDS. A few patients (n = 10, 15.2%) were diagnosed with mild ARDS. The major comorbid conditions of ARDS patients were hypertension (n = 26, 39.4%), arrhythmia (n = 10, 15.2%), coronary heart disease (n = 10, 15.2%), malignant hematologic disease (n = 10, 15.2%) (Table 4).The most common etiologies of ARDS were community-acquired pneumonia and hospital-acquired pneumonia (Figure 8).

Figure 8 Detailed etiology of acute respiratory distress syndrome

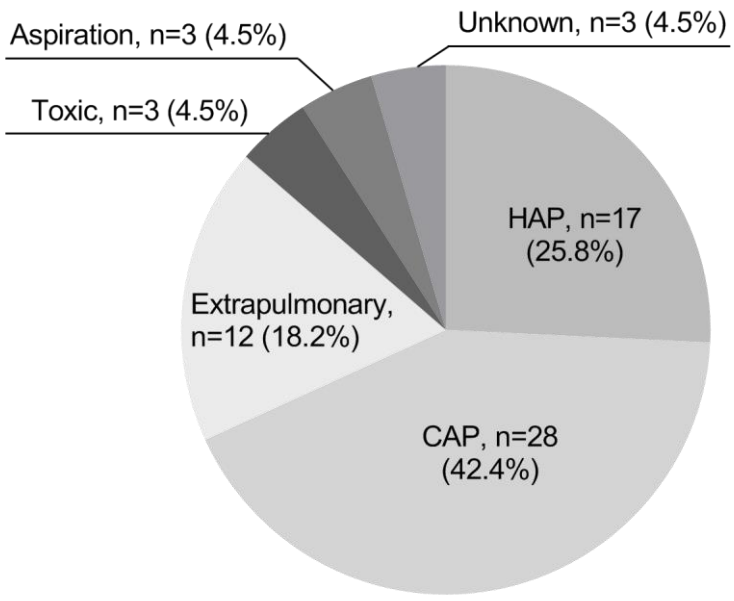

Figure 8 The detailed etiology of acute respiratory distress syndrome. CAP, community-acquired pneumonia, HAP, hospital-acquired pneumonia.

Table 4 Baseline characteristics of study participants

		No early hypercapnia (n=27)	**Early hypercapnia** (n=39)	*p*-value
Age, years		62 ± 17	55 ± 15	0.040[c]
Gender, female		5 (18.5)	9 (23.1)	0.765[c]
Height,m		1.76 ± 0.1	1.77 ± 0.1	0.703[c]
Weight, kg		83.2 ± 14.7	96.2 ± 34.0	0.039[c]
Body mass index, kg/m^2		26.8 ± 4.4	30.8 ± 11.3	0.334[c]
SOFA score[a]		9 ± 4	10 ± 3	0.854[c]
ARDS Etiology[b]	Community-acquired	12 (44.4)	29 (74.4)	0.020[d]
	Hospital-acquired	15 (55.5)	10 (25.6)	
Comorbid conditions				
Arterial hypertension		10 (37.0)	16 (41.0)	0.802[d]
Diabetes mellitus		1 (3.7)	8 (20.5)	0.071[d]
Coronary heart disease		3 (11.1)	7 (17.9)	0.508[d]
Arrhythmia		7 (25.9)	3 (7.7)	0.077[d]
Chronic obstructive pulmonary disease		2 (7.4)	6 (15.4)	0.455[d]
Asthma		0 (0)	2 (5.1)	0.509[d]
Malignant haematologic disease		7 (25.9)	3 (7.7)	0.077[d]
Autoimmune disorder		3 (11.1)	2 (5.1)	0.393[d]
Solid organ transplantation		2 (7.4)	2 (5.1)	1.000[d]
AIDS		0 (0)	1 (2.6)	1.000[d]

Table 4 Baseline characteristics of study participants. Data are presented in n (%) or mean ± SD. Patients were stratified according to the presence of early hypercapnia. [a] Highest score during measurement of cerebrovascular autoregulation. [b] Community-acquired, patients diagnosed with acute respiratory distress syndrome (ARDS) within 48 hours of hospital admission; hospital acquired, patients diagnosed with ARDS more than 48 hours of hospital admission. [c] Based on Mann-Whitney-U tests, [d] based on Chi-square tests or Fisher's exact tests. SOFA sequential organ failure assessment score AIDS acquired immune deficiency syndrome.

From Kahl, U., Yu, Y., Nierhaus, A., Frings, D., Sensen, B., Daubmann, A., Kluge, S., Fischer, M., 2021. Cerebrovascular autoregulation and arterial carbon dioxide in patients with acute respiratory distress syndrome: a prospective observational cohort study. Ann. Intensive Care 11, 47.

In total, 39 (59.1%) study participants had early hypercapnia. The majority of early hypercapnia patients had severe ARDS, while more patients without early hypercapnia had moderate ARDS (Figure 9). Patients with early hypercapnia were younger and had a higher body mass index than patients without early hypercapnia (Table 4). ARDS in the early hypercapnia group was more often caused by community-acquired factors. In contrast, patients without early hypercapnia presented more often with hospital-acquired ARDS. Other baseline characteristics such as gender, SOFA score, and comorbid conditions did not differ significantly between ARDS patients with and without early hypercapnia (Table 4).

Figure 9 ARDS severity

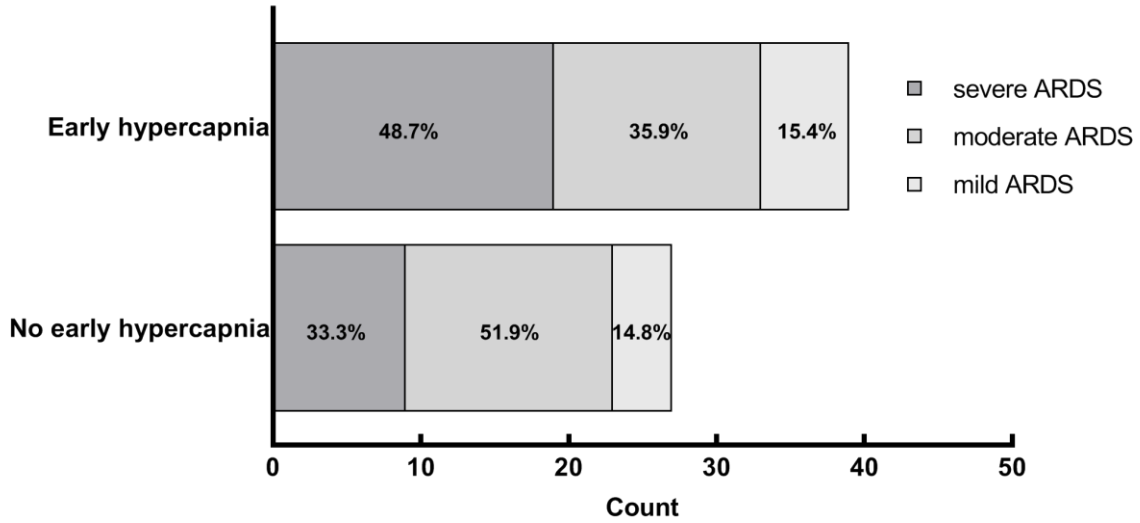

Figure 9 The severity of acute respiratory distress syndrome (ARDS). Patients were stratified by the presence of early hypercapnia. The percentage in the figure represents the proportion of mild, moderate and severe ARDS in patients with or without early hypercapnia. Severe ARDS $PaO_2/FiO_2 \leq 100$ mmHg, moderate ARDS 100 mmHg < $PaO_2/FiO_2 \leq 200$, mild ARDS 200 mmHg < $PaO_2/FiO_2 \leq 300$ mmHg (ARDS Definition Task Force et al., 2012).

5. 3 Management of acute respiratory distress syndrome

Of all study participants, 59 (89.4%) required invasive ventilation, and 7 (10.6%) patients received non-invasive ventilation. Around one half of all patients (n=34, 51.5%) required renal replacement therapy, and 25 (37.9%) patients were treated with prone position. Furthermore, 19 (28.8%) patients required extracorporeal organ support with vv-ECMO, and no patient received va-ECMO. Additionally, 15 (22.7%) patients received inhaled NO (Figure 10).

Figure 10 The management of acute respiratory distress syndrome

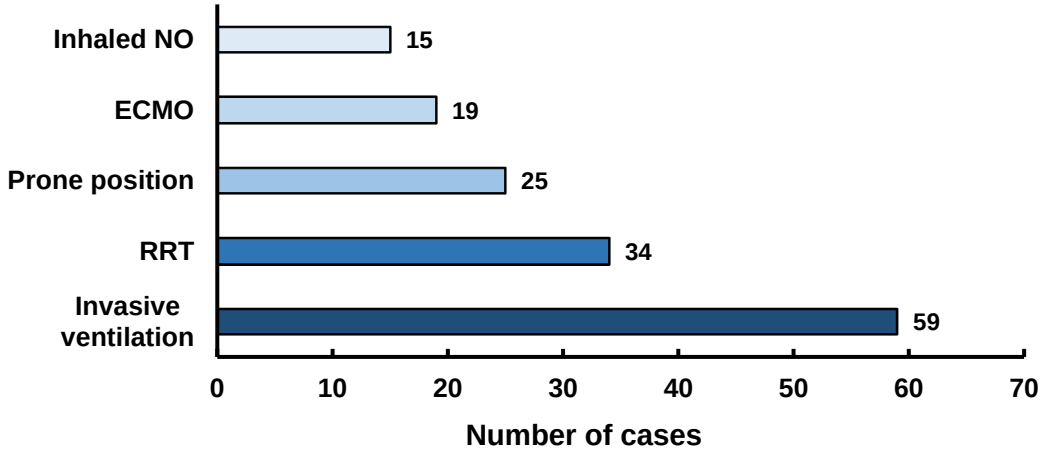

Figure 10 The management of acute respiratory distress syndrome. NO nitric oxide, ECMO extracorporeal membrane oxygenation, RRT renal replacement therapy.

Propofol, midazolam, and isoflurane were the main sedative drugs used for ARDS patients in our ICU. In patients with early hypercapnia, propofol or midazolam combined with isoflurane sedation was the most frequently used sedation mode. In contrast, in patients without early hypercapnia, intravenous sedation with propofol or midazolam was the most frequently used mode of sedation (Table 5).

Table 5 Mechanical ventilation and adjunctive therapies in patients with acute respiratory distress syndrome (ARDS)

	No early hypercapnia (n=27)	**Early hypercapnia** (n=39)	*p*-value
Sedation[a]			0.048[g]
Intravenous[b]	13(48.1)	17(43.6)	
Combined[c]	10(37.0)	20(51.3)	
none	4(14.8)	0(0)	
Inhaled[d]	0(0)	2(5.1)	
Ventilation parameters			
Non-invasive ventilation	7(25.9)	0(0.0)	<0.001[g]
Invasive ventilation	20(74.1)	39(100)	
Respiratory rate, breath/min	25 ± 5	21 ± 6	<0.001[g]
Tidal volume, ml	434 ± 185	395 ± 133	0.485[f]
Tidal volume, ml/ideal body weight	6.3 ± 2.7	5.6 ± 2.0	0.336[f]
Difference from Ideal tidal volume[e], ml	19 ± 192	-36 ± 142	0.264[f]
PEEP, mbar	10 ± 4	13 ± 4	0.001[f]
Driving pressure, mbar	15 ± 4	14 ± 3	0.231[f]
inspiration time/expiratory time	1:1.57 ± 0.38	1:1.62 ± 0.50	0.306[f]
Inhaled nitric oxide	6(22.2)	9(23.1)	1.000[g]
Prone position	11(40.7)	14(35.9)	0.798[g]
ECMO	3(11.1)	16(41.0)	0.012[g]
ECMO duration, days	8.83 ± 2.51	35.93 ± 63.27	0.045[f]
Sweep gas flow, l/min	3.75 ± 0.50	4.37 ± 1.61	0.388[f]
Blood flow, l/min	4.31 ± 0.68	4.52 ± 0.82	0.637[f]
FiO_2	0.94 ± 0.13	0.98 ± 0.07	0.418[f]
Renal replacement therapy	11(40.7)	23(59.0)	0.145[g]
ICU duration, days	21.9 ± 17.3	32.0 ± 23.4	0.056[f]

Table 5 Ventilation parameters and adjunctive therapies are stratified by the presence of early hypercapnia. Data are presented in n (%) or mean ± SD. [a] Sedation was titrated to obtain a RASS of 0 or -1. [b] Intravenous: propofol or midazolam. [c] Combined: propofol/midazolam + isoflurane. [d] Inhalational: isoflurane. [e] Ideal tidal volume: 6 ml/ideal body weight. [f] Based on Mann-Whitney-U tests, [g] Based on Chi-square tests or Fisher's exact tests. PEEP positive end-expiratory pressure, ECMO extracorporeal membrane oxygenation, FiO_2 fraction of inspired oxygen, ICU intensive care unit.

From Kahl, U., Yu, Y., Nierhaus, A., Frings, D., Sensen, B., Daubmann, A., Kluge, S., Fischer, M., 2021. Cerebrovascular autoregulation and arterial carbon dioxide in patients with acute respiratory distress syndrome: a prospective observational cohort study. Ann. Intensive Care 11, 47.

The most common ventilation mode was pressure-controlled ventilation (n = 104/117 CVA assessments, 88.9%). In 3/117 (2.6%) of the measurements, pressure-support ventilation was used. Patients with early hypercapnia had significantly higher PEEP and lower respiratory rates than those without early hypercapnia (Table 5). No significant differences were observed in tidal volume, driving pressure, and inspiratory/expiratory time ratios between patients with and without early hypercapnia. Patients with early hypercapnia required ECMO more frequently. There were no statistically significant differences in adjuvant therapies (prone position, inhaled NO, renal replacement therapy) between patients with and without early hypercapnia (Table 5).

Patients with early hypercapnia and without early hypercapnia had high inflammatory parameters. Inflammatory and coagulation parameters on the day of CVA measurements in ARDS patients are listed in Table 6.

Table 6 Selected laboratory parameters of inflammation and coagulation

	No early hypercapnia (n=27)	**Early hypercapnia** (n=39)
Procalcitonin, ug/l	3.15 ± 6.76	12.15 ± 30.36
Leukocytes, Mrd/l	15.35 ± 8.99	15.15 ± 7.56
C-reaction protein, mg/dl	166.9 ± 88.5	194.0 ± 107.0
Platelets, Mrd/l	175.3 ± 173.7	202.6 ± 131.6
aPTT, second	34.4 ± 9.6	38.9 ± 12.9
Quick, %	71.1 ± 19.5	77.0 ± 16.9
Fibrinogen, g/l	5.44 ± 1.90	5.87 ± 1.46
ATIII, %	67.56 ± 27.60	76.26 ± 28.21

Table 6 Selected laboratory parameters of inflammation and coagulation Data are given in mean ± SD, which are the average value of Inflammation and coagulation indicators on the day of CVA measurement stratified by the presence of early hypercapnia. aPTT activated partial thromboplastin time, ATIII Antithrombin III activity.

5. 4 Cerebrovascular autoregulation in patients with or without early hypercapnia

In total, 117 measurements of CVA were conducted. Most patients (n = 51, 77.2%) had two measurements. The mean percentage of time with impaired CVA was 27.45 in patients without early hypercapnia and 22.95 in patients with early hypercapnia (Table 7, Figure 11).

Table 7 Hemodynamic parameters and arterial blood gas analyses during measurement of cerebrovascular autoregulation

	No early hypercapnia (n=27) Measurement periods=47	**Early hypercapnia (n=39)** Measurement periods=70
Time with impaired CVA, %	27.45 ± 18.51	22.95 ± 18.75
Duration of measurement, minutes	77 ± 12	77 ± 15
Time with impaired CVA, minutes	21 ± 15	18 ± 15
Cerebral oxygenation index, COx	0.11 ± 0.15	0.06 ± 0.18
Regional oxygen saturation, rSO_2, %	59.81 ± 12.03	67.32 ± 10.20
Mean arterial pressure, mmHg	76.34 ± 10.84	74.85 ± 9.12
Heart rate, bpm	81.25 ± 18.80	90.45 ± 19.10
Body temperature, °C	37.1 ± 0.8	37.1 ± 0.9
Hemoglobin, g/dL	9.20 ± 1.42	9.79 ± 1.63
Mean pH[a]	7.41 ± 0.08	7.39 ± 0.09
Mean $PaCO_2$[a], mmHg	45.2 ± 11.1	47.7 ± 9.6
Mean PaO_2[a], mmHg	80.6 ± 18.4	85.9 ± 16.4
Mean PaO_2/FiO_2[a], mmHg	152.55 ± 57.16	151.38 ± 75.27
Mean Bicarbonate, HCO_3^-[a], mmHg	27.28 ± 4.62	28.0 ± 5.65
Mean Lactate[a], mmol/L	1.6 ± 0.9	2.3 ± 2.5
Hypocapnia[b] (< 35 mmHg)	8 (17)	3 (4.3)
Normocapnia[b] (35-50 mmHg)	28 (59.6)	43 (61.4)
Hypercapnia[b] (> 50 mmHg)	11 (23.4)	24 (34.3)
Δ[c] pH	0.01 ± 0.02	0.01 ± 0.02
Δ[c] $PaCO_2$, mmHg	1.29 ± 1.76	1.79 ± 3.23
Δ[c] PaO_2, mmHg	4.92 ± 7.45	5.91 ± 9.97
Δ[c] PaO_2/FiO_2 ratio	8.20 ± 12.86	9.86 ± 19.73
From ARDS diagnosis until first measurement		
Time from ARDS diagnosis to first measurement, days	4 ± 4	2 ± 2
Mean $PaCO_2$, mmHg	41.6 ± 8.6	47.8 ± 17.9
$PaCO_2$ variability[d], mmHg	32.1 ± 40.3	115.1 ± 168.8
From first measurement until second measurement		
Time from ARDS diagnosis to second measurement, days	8 ± 3	5 ± 3
Mean $PaCO_2$, mmHg	49.2 ± 10.9	49.0 ± 7.3
$PaCO_2$ variability[d], mmHg	68.6 ± 65.2	57.8 ± 50.2

Table 7 Hemodynamic parameters and arterial blood gas analyses during measurement of cerebrovascular autoregulation (CVA). Data are presented in n (%) or mean ± SD, mean values during the first and second measurement, stratified according to the presence of early hypercapnia. [a] 'Mean value' refers to the mean value of two blood gas analyses during each CVA measurement. [b] $PaCO_2$ was categorized as 'hypocapnia', 'normocapnia' 'hypercapnia' during each CVA measurement. [c] △values refer to the mean difference between the first and the second CVA measurement in one study subject. [d] Calculated as the variance.

From Kahl, U., Yu, Y., Nierhaus, A., Frings, D., Sensen, B., Daubmann, A., Kluge, S., Fischer, M., 2021. Cerebrovascular autoregulation and arterial carbon dioxide in patients with acute respiratory distress syndrome: a prospective observational cohort study. An n. Intensive Care 11, 47.

The variability of $PaCO_2$ from ARDS diagnosis to the first CVA measurement were higher in patients with early hypercapnia than in those without early hypercapnia (Table 7). The absolute change in arterial CO_2 from ARDS diagnosis to CVA measurement was 33.8 mmHg in ARDS patients with early hypercapnia, and 1.9 mmHg in patients without early hypercapnia. Compared with patients without early hypercapnia, early hypercapnia patients had a significantly higher rSO_2 (Figure 12, $p < 0.001$). The cerebrovascular hemodynamic parameters and arterial blood gas parameters in patients with or without early hypercapnia are listed in Table 7.

Figure 11 Percentage of time with impaired cerebrovascular autoregulation in patients with and without early hypercapnia

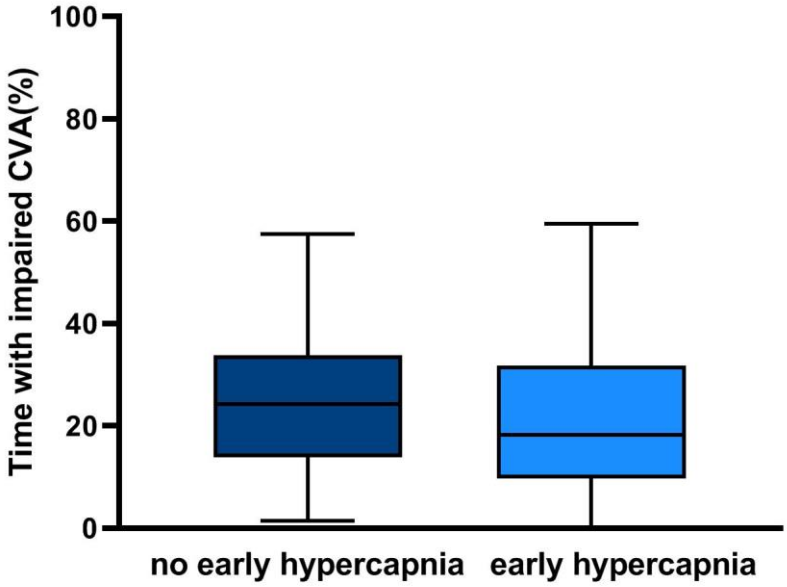

Figure 11 Percentage of time with impaired cerebrovascular autoregulation (CVA) (in % of the total monitoring time) is shown for patients with and without early hypercapnia (Kahl et al., 2021). Impaired CVA was defined as a cerebral oxygenation index > 0.3. Data are shown as median (boxes) with Tukey whiskers.

According to Kahl, U., Yu, Y., Nierhaus, A., Frings, D., Sensen, B., Daubmann, A., Kluge, S., Fischer, M., 2021. Cerebrovascular autoregulation and arterial carbon dioxide in patients with acute respiratory distress syndrome: a prospective observational cohort study. Ann. Intensive Care 11, 47

Figure 12 Regional oxygen saturation in ARDS patients with and without early hypercapnia

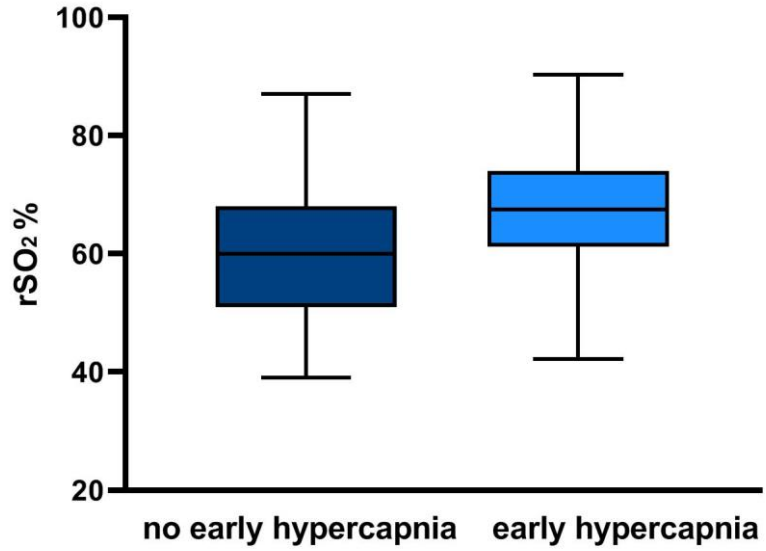

Figure 12 Regional oxygen saturation (rSO_2) in ARDS patients with and without early hypercapnia. rSO_2 was the mean value during each measurement. The figure shows that patients with early hypercapnia had a significantly higher rSO_2 than patients without early hypercapnia (67.32 ± 10.20 vs. 59.81 ± 12.03, $p<0.001$). Data are shown as median (boxes) with Tukey whiskers.

5. 5 Mixed linear model

The mixed linear model showed no significant association of early hypercapnia with impaired CVA (Table 8). Hypocapnia during measurement was associated with impaired CVA (Table 8, Figure 13). No significant association was observed between impaired CVA and other variables included in the model (sedation mode, ARDS severity, age, ARDS etiology), as demonstrated in Table 8.

Table 8 Mixed linear model - estimates of fixed effects

Parameter	Estimate	95% CI - Low	95% CI - Up	*p*
Intercept	0.177	-0.059	0.414	0.139
No early hypercapnia (vs. early hypercapnia = $PaCO_2$ ≥ 50mmHg)	0.023	-0.054	0.100	0.556
Sedation				
Mixed Sedation (vs. no sedation)	-0.042	-0.217	0.133	0.635
Intravenous sedation (vs. no sedation)	-0.074	-0.235	0.087	0.363
Inhalational sedation (vs. no sedation)	-0.076	-0.260	0.107	0.410
ARDS severity				
Mild (vs. severe)	0.032	-0.062	0.126	0.498
Moderate (vs. severe)	-0.018	-0.102	0.065	0.663
Age (per year increase)	0.001	-0.001	0.004	0.275
Hypocapnia during the measurement period[a]	0.155	0.014	0.296	0.032
ARDS etiology (community-acquired vs. hospital-acquired)[b]	0.047	-0.027	0.122	0.208

Table 8 Linear mixed model - estimates of fixed effects. The variables position (prone vs. supine), inhaled nitric oxide, extracorporeal membrane oxygenation, and the sequential organ failure assessment score during measurement were included in the initial model and eliminated during the stepwise-backwards reduction. ARDS acute respiratory distress syndrome. [a] Vs. Normo- and hypercapnia. [b] ARDS etiology was categorized as 'community-acquired' and 'hospital-acquired' for the linear mixed model.

From Kahl, U., Yu, Y., Nierhaus, A., Frings, D., Sensen, B., Daubmann, A., Kluge, S., Fischer, M., 2021. Cerebrovascular autoregulation and arterial carbon dioxide in patients with acute respiratory distress syndrome: a prospective observational cohort study. Ann. Intensive Care 11, 47.

Figure 13 Cerebrovascular autoregulation impairment and carbon dioxide during measurement

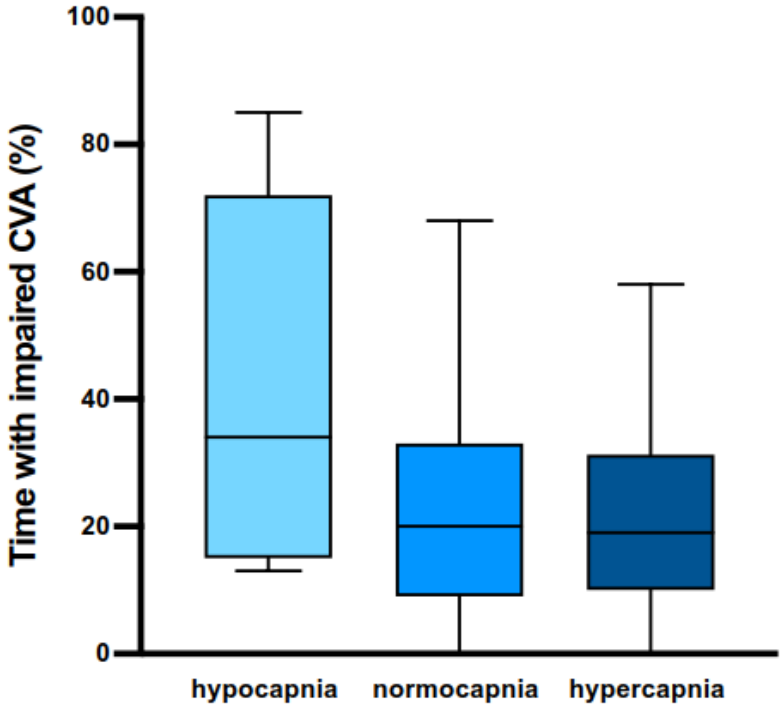

Figure 13 Cerebrovascular autoregulation impairment and carbon dioxide during measurement. Percentage of time with impaired cerebrovascular autoregulation (CVA) (in % of the total monitoring time) is presented for patients with hypocapnia ($PaCO_2$ < 35 mmHg), normocapnia ($PaCO_2$ 35–50 mmHg) and hypercapnia ($PaCO_2$ > 50 mmHg) during the CVA measurement. Data are shown as median (boxes) with Tukey whiskers.

According to Kahl, U., Yu, Y., Nierhaus, A., Frings, D., Sensen, B., Daubmann, A., Kluge, S., Fischer, M., 2021. Cerebrovascular autoregulation and arterial carbon dioxide in patients with acute respiratory distress syndrome: a prospective observational cohort study. Ann. Intensive Care 11, 47

5. 6 Subgroup analysis in patients with or without veno-venous extracorporeal membrane oxygenation

Of all patients included, 19 (28.8%) patients required vv-ECMO, and a total of 31 CVA measurements were performed during extracorporeal organ support with vv-ECMO. The percentage of time with impaired CVA did not differ between measurements with and without ECMO treatment (Table 9). Compared with measurements without ECMO support, PaO_2/FiO_2 ratios were significantly lower in patients with ECMO (p < 0.001).

Table 9 Cerebrovascular hemodynamic variables and parameters from blood gas analyses during cerebrovascular autoregulation measurements in patients with and without veno-venous extracorporeal membrane oxygenation

	No ECMO (n=47) Measurement periods=86	**ECMO (n=19)** Measurement periods=31
Cerebrovascular autoregulation		
Time with impaired CVA, %	25.84 ± 17.94	21.76 ± 20.7
Cerebral oxygenation index COx	0.10 ± 0.14	0.01 ± 0.22
rSO_2, %	63.21 ± 11.6	67.32 ± 10.96
Hemodynamic parameters		
Heart rate, bpm	85.2 ± 20.1	91.2 ± 16.9
Mean arterial pressure, mmHg	75.53 ± 10.27	75.23 ± 8.66
Pulse pressure, mmHg	71.2 ± 18.9	70.0 ± 15.7
Arterial blood gas analyses		
pH	7.40 ± 0.08	7.41 ± 0.10
$PaCO_2$, mmHg	47.1 ± 11.3	45.7 ± 6.3
PaO_2 mmHg	85.4 ± 20.0	79.2 ± 14.9
PaO_2/FiO_2 ratio	176.8 ± 62.5	82.6 ± 15.7
HCO_3^-, mmHg	27.3 ± 5.1	28.8 ± 5.7
Lactate, mmol/l	1.8 ± 1.5	2.6 ± 3.0
Hemoglobin, g/dl	9.4 ± 1.7	10 ± 0.9
△[a] pH	0.01 ± 0.02	0.01 ± 0.03
△[a] $PaCO_2$	1.36 ± 2.64	2.2 ± 2.9
△[a] PaO_2/FiO_2 ratio	10.5 ± 19.5	5.5 ± 7.3

Table 9 Hemodynamic parameters and selected results from blood gas analyses and cerebrovascular autoregulation (CVA) parameters in patients with and without veno-venous extracorporeal membrane oxygenation (vv-ECMO). Data are given by mean ± SD. Mean values are from the first and second CVA measurement stratified by the requirement of vv-ECMO. [a] Δvalues refer to the mean difference between the first and the second CVA measurement in one study participant. rSO_2 regional oxygen saturation, $PaCO_2$ arterial partial pressure of carbon dioxide, PaO_2 arterial partial pressure of oxygen, HCO_3^- Bicarbonate.

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A total of seven patients had repeated CVA measurements with and without ECMO support. The percentage of time with impaired CVA did not differ between measurements with and without ECMO (29.93 ± 31.90 vs. 31.97 ± 16.27, p = 0.886). The percentage of time with impaired CVA for patients with and without ECMO treatment during CVA measurement is presented in Figure 14.

Figure 14 The percentage of time with impaired cerebrovascular autoregulation in patients with and without extracorporeal membrane oxygenation

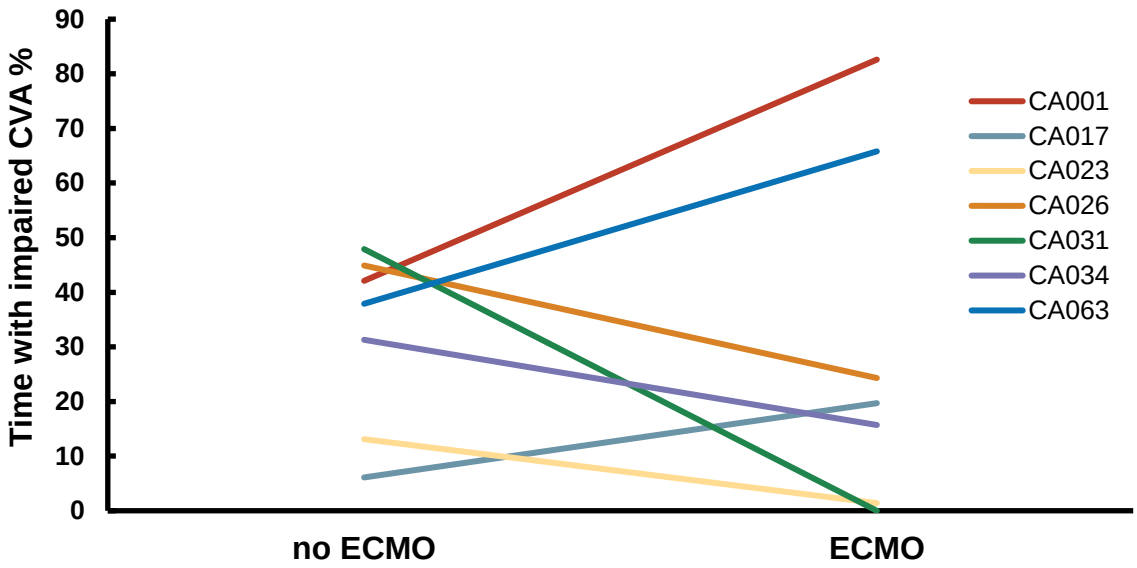

Figure 14 The percentage of time with impaired cerebrovascular autoregulation (CVA) in patients with repeated assessments with and without extracorporeal membrane oxygenation (ECMO). Each patient is indicated by a different color. This figure is from the supplementary information of our publication (Kahl et al., 2021).

According to Kahl, U., Yu, Y., Nierhaus, A., Frings, D., Sensen, B., Daubmann, A., Kluge, S., Fischer, M., 2021. Cerebrovascular autoregulation and arterial carbon dioxide in patients with acute respiratory distress syndrome: a prospective observational cohort study. Ann. Intensive Care 11, 47

5. 7 Sensitivity analyses

We performed two sensitivity analyses.

For the first sensitivity analysis, we used a different cut-off value with $PaCO_2 \geq 60$ mmHg and pH < 7.35 to define early hypercapnia (Table 10). We obtained similar results in this sensitivity analysis compared with early hypercapnia defined as $PaCO_2 \geq 50$ mmHg with pH < 7.35. Early hypercapnia was not associated with impaired CVA. Compared with normocapnia and hypercapnia, hypocapnia during CVA measurement was significantly associated with impaired CVA (Table 10). Other variables in the model that included age and ARDS etiology, were not associated with impaired CVA.

For the second sensitivity analysis, we used delta $PaCO_2$ as the independent variable of primary interest (Table 11). Delta $PaCO_2$ was defined as the difference in $PaCO_2$ between ARDS diagnosis and CVA measurement. No association between delta $PaCO_2$ and impaired CVA was found. By contrast, hypocapnia during CVA measurement was associated with impaired CVA (Table 11).

Table 10 Sensitivity analysis with a different definition of early hypercapnia ($PaCO_2$ ≥ 60 mmHg and pH < 7.35)

Parameter	Estimate	95% CI - Low	95% CI - Up	*p*
Intercept	0.117	-0.020	0.255	0.093
No early hypercapnia (vs. early hypercapnia = $PaCO_2$ ≥ 60mmHg)	0.045	-0.024	0.114	0.196
Age (per year increase)	0.001	-0.001	0.003	0.352
Hypocapnia during the measurement period[a]	0.186	0.072	0.300	0.002
ARDS etiology (community-acquired vs. hospital-acquired)[b]	0.049	-0.021	0.120	0.166

Table 10 Sensitivity analysis with a different definition of early hypercapnia ($PaCO_2$ ≥ 60 mmHg and pH < 7.35). Linear mixed model - estimates of fixed effects. The variables ARDS severity (mild / moderate / severe) and sedation (none / intravenous / inhalational / mixed), position (prone vs. supine), inhaled nitric oxide, extracorporeal membrane oxygenation, and the sequential organ failure assessment score during measurement were included in the initial model and eliminated during the stepwise-backwards reduction. ARDS acute respiratory distress syndrome. [a] Vs. Normocapnia and hypercapnia. [b] ARDS etiology was categorized as 'community-acquired' and 'hospital-acquired' for the linear mixed model.

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Table 11 Sensitivity analysis with the difference in $PaCO_2$ between acute respiratory distress syndrome diagnosis and cerebrovascular autoregulation measurement

Parameter	Estimate	95% CI - Low	95% CI - Up	*p*
Intercept	0.1921	0.0497	0.3344	0.009
Delta $PaCO_2$ (per mmHg increase)[a]	-0.0004	-0.0018	0.0009	0.507
No ECMO (vs. ECMO during measurement)[b]	-0.0125	-0.1059	0.0809	0.791
Age (per year increase)	0.0010	-0.0014	0.0033	0.403
Hypocapnia during the measurement period[c]	0.1815	0.0664	0.2967	0.002

Table 11 Sensitivity analysis with delta $PaCO_2$. Linear mixed model - estimates of fixed effects. The variables position (prone vs. supine), sedation, ARDS severity, inhaled nitric oxide, ARDS etiology (community-acquired vs. hospital-acquired) and the sequential organ failure assessment score during measurement were included in the initial model and eliminated during the stepwise-backwards reduction-process. [a] Difference in $PaCO_2$ between ARDS onset and CVA assessment. [b] ECMO Extracorporeal membrane oxygenation. [c] Vs. Normo- and hypercapnia

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5. 8 Neurocognitive outcomes in patients with acute respiratory distress syndrome

Thirty-three patients were examined with cerebral CT during their ICU stay, which revealed that 10 patients had acute brain injury (Table 12). Among them, four patients were diagnosed with intracranial hemorrhage and two patients had cerebral ischemia. Six patients had new neurological disorders, including encephalopathy and seizure. The percentage of time with impaired CVA in these patients are listed in Table 12.

Table 12 Acute brain injury and new central nervous disorders during intensive care unit stay

	n (%)	Time with impaired CVA%
Acute brain injury during ICU stay		
No cerebral CT scan	33 (50)	21.9 ± 16.9
Cerebral CT without new ABI	23 (34.8)	28.1 ± 13.7
Intracranial hemorrhage	4 (6.1)	25.8 ± 11.6
Cerebral ischemia	2 (3)	22.8 ± 7.1
Other[a]	4 (6.1)	23.2 ± 7.9
New central nervous system disorder		
No focal neurological symptoms	29 (43.9)	25.4 ± 19
Encephalopathy	3 (4.5)	21.4 ± 0.4
Seizure	3 (4.5)	31.2 ± 3.9
Non-survivor[b]	31 (47)	23 ± 11.7

Table 12 Acute brain injury and new central nervous disorders during intensive care unit (ICU) stay Data are shown in n (%) or mean ± SD. Mean percentage of time with impaired cerebrovascular autoregulation (CVA), stratified by acute brain injury on neuroimaging and new central nervous system disorders with clinical manifestation. [a] Other findings include hygroma (n=2), right and left parietal lesions indicative for cerebral aspergillosis (n=1), global brain edema (n=1). [b] Patients who were died in the ICU. This table is from the supplementary information of our publication (Kahl et al., 2021).

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Of 35 (53%) ICU survivors, two patients died within three months after they were discharged from ICU. Two patients lost to follow-up and we obtained 3-month follow-up in 31 ARDS survivors. There was no difference when comparing impaired CVA in ARDS survivors and non-survivors with a Mann-Whitney U test (26.4 ± 18.4 vs. 22.9 ± 11.3; $p = 0.577$).

Telephone interviews for functional outcomes were performed in 31 (47%) patients with the patient or next of kin or caregiver. 21/31 (67.7%) of these patients had moderate or severe functional disability. The functional outcomes and percentage of time with impaired CVA in different functional outcomes are presented in Table 13.

Table 13 Functional outcome at three months after patients were discharged from intensive care unit

Functional outcome	n (%)	Time with impaired CVA (%)
Full recovery or mild disability	10 (15.2)	23.6 ± 17.5
Moderate disability, independence in activities of daily living	12 (18.2)	35.2 ± 21.1
Severe disability, dependent in activities of daily living	9 (13.6)	17.7 ± 9.7
Coma or persistent vegetative state	0 (0.0)	---
Dead	33 (50.0)	22.9 ± 11.3

Table 13 Functional outcome at three months after patients were discharged from intensive care unit. Data are shown in n (%) or mean ± SD. CVA cerebrovascular autoregulation. This table is from the supplementary information of our publication (Kahl et al., 2021).

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Table 14 Cognitive function and health-related quality of life three months after patients were discharged from the intensive care unit

	score
Cognitive questionnaires failure (CFQ)	29.73 ± 19.81
Physical component sum score (PCS)	33.15 ± 11.9
Mental component sum score (MCS)	45.37 ± 10.6
SF-36 Subscale scores	
Physical functioning	39.47 ± 34.15
Role-physical	25 ± 40.18
Bodily pain	54.2 ± 29.26
General health	49.25 ± 21.6
Vitality	42.6 ± 19.53
Social functioning	59 ± 32.78
Role-emotional	42.67 ± 45.67
Mental health	66.88 ± 20.87

Table 14 Cognitive function and health-related quality of life three months after patients were discharged from the intensive care unit

Self-reported outcomes were obtained from 22 (33%) patients (CFQ for cognitive function) and 25 (37.8 %) patients (SF-36 for HRQL). The mental component sum score was higher than the physical component sum score in ARDS survivors. In the SF-36 subscales scores, role physical was the lowest, while mental health was the highest. The detailed scores are listed in Table 14. No correction was observed between CFQ score, physical component sum score, mental component sum score and impaired CVA (Table 15).

Table 15 Correlation between impaired cerebrovascular autoregulation and cognitive failures questionnaire score, physical component sum score and mental component sum score

	Time with impaired CVA%		Mean COx	
	Correlation coefficient[a]	*p*	Correlation coefficient[a]	*p*
CFQ	-0.258	0.246	-0.1	0.659
PCS	0.128	0.54	0.09	0.67
MCS	0.326	0.112	0.117	0.577

Table 15 Correlation between cognitive failures questionnaire (CFQ) score, physical component sum score (PCS) and mental component sum score (MCS) with impaired cerebrovascular autoregulation (CVA). [a]spearman correlation was used in the analysis.

6. Discussion

6. 1 Interpretation

6. 1. 1. Summary

In the present prospective observational cohort study, we compared CVA between ARDS patients with and without early hypercapnia. We did not find an association between early hypercapnia and impaired CVA during the acute phase of ARDS. However, hypocapnia during the CVA measurement was significantly associated with impaired CVA. The subgroup analysis showed that the CVA function did not differ between patients with and without ECMO treatment. There was no correlation between impaired CVA, self-assessed cognitive failures, and HRQL.

6. 1. 2. Cerebrovascular autoregulation in patients with acute respiratory distress syndrome

CVA describes the ability of intracranial blood vessels to minimize fluctuations in CBF during changes in CPP or ABP, which is essential to maintain relatively stable cerebral perfusion (Aaslid et al., 1989). However, CVA may be affected by various factors, such as hypoxemia, dyscapnia, vasoactive substances, and sedatives. These conditions are commonly seen in ARDS patients, which leads to the assumption that CVA may be impaired in these patients. In addition, ARDS survivors frequently suffer from cognitive and psychological disorders, and causes of the neurological disorders are not fully understood (Mart and Ware, 2020). We hypothesized that impaired CVA may be involved. However, little is known about CVA in ARDS patients. To date, there have been two studies on CVA function in adult ARDS patients (Schramm et al., 2013; Yang et al., 2014). Both studies aimed to explore the influence of PEEP on CVA in ARDS patients. Schramm et al. conducted TCD-based CVA measurements in 20 mechanically ventilated adult ARDS patients (Schramm et al., 2013). In this study, impaired CVA was defined as a moving correlation coefficient between CBF and ABP above 0.3, and 55% of the patients presented with impaired CVA. Similarly, Yang et al. assessed CVA with TCD in adult patients with moderate and severe ARDS and found that approximately 50% of the patients presented with impaired CVA (Yang et al., 2014). Both studies found that an increasing PEEP did not further impair CVA, which was independent of pre-existing CVA impairment.

6. 1. 3 Comparison of effects of hypocapnia and hypercapnia on cerebrovascular autoregulation in our study with other studies

In the present study, we investigated the influence of dyscapnia on CVA, since CO_2 is known to be one of the key influence factors on CVA (Meng and Gelb, 2015). We found that early hypercapnia was not associated with impaired CVA.

To date, no studies have investigated the effect of CO_2 on CVA in adult patients with ARDS. In one study, including very low birth weight infants requiring mechanical ventilation for respiratory distress syndrome, $PaCO_2$ > 45 mmHg indicated CVA impairment (Kaiser et al., 2005). This result contrasts the findings of our study.

Studies investigating the association between hypercapnia and impaired CVA in patients other than ARDS, found comparable results as we did in the present study. In children treated with ECMO, Joram et al. demonstrated that hypercapnia was not associated with impaired CVA under normotensive or hypertensive conditions (Joram et al., 2021).

Contrary to our finding, impaired CVA was demonstrated in patients with hypercapnia in previous studies (Kaiser et al., 2005; Panerai et al., 1999; McCulloch et al., 2000). In eight healthy subjects during general anesthesia, McCulloch et al. showed that $PaCO_2$ between 50 to 66 mmHg was associated with impaired CVA (McCulloch et al., 2000). In 15 normal healthy subjects, impaired CVA was also observed in hypercapnia which was caused by breathing 5% mixture of CO_2 in the air (Perry et al., 2014).

One study including ARDS patients with subarachnoid hemorrhage, investigating the association between hypercapnia and ICP, found no harmful effects of hypercapnia (Petridis et al., 2010). In this study, $PaCO_2$ was 50–60 mmHg in ARDS patients due to lung-protective ventilation strategies, and hypercapnia did not increase ICP and did not decrease CPP, indicating that hypercapnia might not further impair CVA in ARDS patients with subarachnoid hemorrhage.

In the present study, we found that in ARDS patients, hypocapnia during the CVA measurement was associated with impaired CVA. Previous studies including patients other than ARDS patients had similar results. CVA was measured during ABP fluctuations caused by angiotensin infusion in patients with severe head injury, and CVA was lost when $PaCO_2$ decreased to mean value of 23.1 mmHg (Cold et al., 1981). In healthy subjects, CVA was evaluated through TCD based CBF velocity and ABP, and a significant short-term decrease in CVA efficiency was observed in hypocapnia caused by hyperventilation (Dineen et al., 2010). Contrary to our study, some studies have reported that hypocapnia might be beneficial to CVA function in normal subjects and patients with TBI (McCulloch et al., 2005; Zhang et

al., 2016). In patients undergoing elective surgery with isoflurane anesthesia, McCulloch et al. found that hypocapnia reduced isoflurane-induced CVA impairment (McCulloch et al., 2005). In patients with TBI, hypocapnia allowed the return of impaired CVA to normal levels (Zhang et al., 2016).

The influence of hypocapnia is not limited to the impaired CVA, further effects of hypocapnia on the cerebral vasculature have been described. First, in healthy volunteers, an approximate 30% decrease in CBF was observed, when $PaCO_2$ decreased from normocapnia to hypocapnia (Fortune et al., 1995). Decreased CBF due to hypocapnia may lead to inadequate cerebral perfusion, as decreased CBF is associated with reduced oxygen supply (Zhong Zhang et al., 2019). Second, systemic hypocapnia can result in cerebrospinal fluid alkalosis, which decreases CBF and cerebral blood volume (Laffey and Kavanagh, 2002). Third, as described by Zhang et al., hypocapnia induced respiratory alkalosis may result in a leftward shift of the oxygen-hemoglobin dissociation curve, reducing oxygen delivery to the brain (Zhong Zhang et al., 2019). Additionally, hypocapnia increased both neuronal excitability and excitatory synaptic transmission, which led to increased oxygen consumption (Gerard Curley et al., 2010). Therefore, hypocapnia could result in an imbalance between oxygen supply and demand. Thus, hypocapnia is likely to cause damage to CVA function.

Furthermore, previous studies report that patients with hypocapnia have a higher rate of neurological complications and even mortality. Hypocapnia was more likely to have an association with neurologic events, such as cerebral hemorrhage, cerebral infraction, seizures (Cashen et al., 2018). In patients younger than 19 years treated with ECMO, neurological events occurred in half of patients with $PaCO_2$ below 30 mmHg within 48 hours of ECMO initiation (Cashen et al., 2018).Furthermore, in an international multicenter study, including patients with mild and moderate ARDS, $PaCO_2$ below 35 mmHg within the first two days of ARDS diagnosis was associated with increased ICU mortality (Madotto et al., 2020).

When comparing the present study with previous research, several differences must be considered.

First, study participants were adult ARDS patients in the present study. By contrast, previous studies that investigated the effect of CO_2 levels on CVA and that are discussed above, study subjects were healthy adults, infants or patients with other diseases (Kaiser et al., 2005; Panerai et al., 1999; Taccone et al., 2010). Patients with ARDS are different from other study populations. In these patients, hypoxemia and dyscapnia are caused by pulmonary dysfunction. Therefore, ARDS patients may be exposed to hypercapnia or hypocapnia for hours or even days. On the contrary, in previous studies, hypercapnia and hypocapnia were

induced by short periods of inhalation of high concentrations of CO_2 or short periods of hyperventilation (Panerai et al., 1999; Perry et al., 2014).

Second, an important issue that deserves attention is the definition of hypercapnia, which varies from study to study. The different definitions of hypercapnia undoubtedly affect the results. We investigated early hypercapnia according to highest $PaCO_2$ in the first 24 hours after ARDS diagnosis. According to Nin et al., the threshold for hypercapnia was 50 mmHg (Nin et al., 2017). Other studies defined hypercapnia as a $PaCO_2$ of 40 mmHg to 50 mmHg (Panerai et al., 1999; Taccone et al., 2010).

Third, the method of CVA measurement differs across studies. In the present study, we used continuous rSO_2 based on NIRS. ICM+ software was used to calculate the correlation coefficient between ABP and rSO_2. Although this method is now being applied in an increasing number of studies, many previous studies used different approaches to evaluate CVA, such as monitoring CVA using a TCD-based approach (Berg and Plovsing, 2016; Taccone et al., 2010).

Fourth, the definition of impaired CVA varies in different studies. We used the percentage of measuring time with COx above threshold as primary endpoint. The same approach has been used by Lee et al (Lee et al., 2019). Other studies have used the mean NIRS based COx above threshold or the mean TCD based mean velocity index above threshold (M. Ono et al., 2012; Schramm et al., 2012). Therefore, in studies with different populations and CVA measurement methods, the association between $PaCO_2$ and impaired CVA might be not consistent.

6. 1. 4 Carbon dioxide fluctuations on cerebrovascular autoregulation

Our study did not observe an association between impaired CVA and fluctuations in $PaCO_2$ in the sensitivity analysis. However, previous studies have described the association of CO_2 fluctuations with impaired CVA and poor neurological outcomes. In a study with subjects under general anesthesia, CO_2 levels were regulated by ventilation (McCulloch et al., 2000). The impairment of CVA increased with gradual CO_2 changes (McCulloch et al., 2000). Similar studies observed the effects of rapid changes of CO_2 on neurological outcomes. These studies were mostly conducted in patients treated with ECMO, as ECMO initiation could cause an obvious fluctuation of CO_2. In a multicenter retrospective cohort study, an increased incidence of neurological complications was observed in patients who experienced a significant decrease in $PaCO_2$ within 24 hours of ECMO initiation (Diehl et al., 2020). As described by Diehl et al., a reduction in arterial CO_2 > 20 mmHg from the initiation of ECMO was associated with neurologic complications (Diehl et al., 2020). Moreover, in a retrospective observational study with pediatric patients, the magnitude of $PaCO_2$ change

(≥25 mmHg) after ECMO initiation was associated with mortality (Bembea et al., 2013). There are some differences between these studies and our study. A key point was that in these studies, fluctuations in CO_2 were achieved by human intervention, either by adjusting ventilation or ECMO settings in a relatively short time. By contrast, the majority of patients enrolled in our study were not treated with ECMO, and $PaCO_2$ fluctuations were attributable to respiratory failure and lung-protective ventilation. Furthermore, the mean time interval between ARDS diagnosis and CVA measurements was 2–8 days, which was longer than in other studies on the effects of CO_2 fluctuations. Continuous CVA monitoring during ARDS acute phase is needed to further explain the impact of CO_2 fluctuations on CVA in ARDS patients.

6. 1. 5 The incidence of early hypercapnia and prognosis in the present study

We observed early hypercapnia in 59.1% of ARDS patients, which was higher than reported in previous studies (Nin et al., 2017). There are some possible reasons. First, hypercapnia was defined as the highest $PaCO_2$ value higher than 50 mmHg within 24 hours of ARDS diagnosis in the present study. Nin et al. defined the maximum $PaCO_2$ values above 50 mmHg within the first 48 hours of mechanical ventilation in ARDS patients (Nin et al., 2017). Second, according to Nin et al., ARDS patients with hypercapnia were shown with a significantly lower PaO_2/FiO_2 than patients without hypercapnia (Nin et al., 2017). Thus, ARDS patients with low PaO_2/FiO_2 are likely to develop hypercapnia. In the present study, 84.8% of patients had moderate or severe ARDS. The proportion of severe ARDS was higher than previous studies (Bellani et al., 2016; Nin et al., 2017). Third, another notable factor is the tidal volume during mechanical ventilation, as low tidal volumes are more likely to cause CO_2 retention. The mean tidal volume was 5.6 ml/ideal body weight for patients with early hypercapnia and 6.3 ml/ideal body weight for patients without early hypercapnia in our study. By comparison, in the study of Nin et al., most of ARDS patients had higher tidal volumes with 6–8 ml/actual body weight (Nin et al., 2017).

Furthermore, ICU mortality was 41% for ARDS patients with early hypercapnia and 56% for patients without early hypercapnia in our study. Nin et al. showed that severe hypercapnia was independently associated with increased ICU mortality, with a 62.8% ICU mortality for severe hypercapnia in ARDS patients compared to 49.6% mortality in patients without hypercapnia (Nin et al., 2017). The difference in ICU mortality between studies might be due to the different period ARDS treatment strategies. Nin et al. included ARDS patients in 1998, 2004, and 2010. Since then, therapeutic measures of ARDS have significantly improved, which could explain why our patients had a lower ICU mortality than ARDS patients included in the study of Nin et al. In a more recent international study, ICU mortality was lower than in

our study (Bellani et al., 2016). Compared to Bellani and colleagues' study, the relative higher ICU mortality of ARDS patients in our study was probably due to the different severity of ARDS patients. In our study, 42.4% of patients were diagnosed with severe ARDS, compared to 23.4% in their study. Moreover, compared to previously mentioned studies, our study included a relatively small number of ARDS patients in a single center tertiary hospital. Thus, considering the severity, current treatment level, and relatively small sample of ARDS patients in our study, the ICU mortality is explainable comparing to other studies.

6. 1. 6 Effects of extracorporeal membrane oxygenation on cerebrovascular autoregulation

We did not observe a difference in percentage of time with impaired CVA between measurements with and without ECMO treatment. Extracorporeal life support is increasingly applied to patients with refractory cardiac and/or respiratory failure (Sanaiha et al., 2019). Hypoxia, hypotension and dyscapnia may impair CVA and occur frequently in patients prior to ECMO treatment. These conditions leave the brain vulnerable to fluctuations in blood pressure (Short, 2005). The treatment of ECMO appears to be associated with impaired CVA and poor neurological outcome. In newborn lambs model receiving vv-ECMO, CBF decreased when CPP was below 25 mmHg, indicating impaired CVA, and in controls without vv-ECMO support, CVA remained intact and CBF kept constant during any change in CPP (Walker et al., 1996). A previous study showed that the first 24 hours following ECMO initiation represented the most critical period for CVA (Joram et al., 2020). In pediatric patients, a higher COx was seen during the first day of vv-ECMO or va-ECMO treatment compared to the second day, which suggested that CVA impairment occurred more likely during the initial period of ECMO (Joram et al., 2020). Moreover, patients who experienced acute neurological events had worse CVA compared to those without acute neurological events under ECMO treatment (Joram et al., 2020; Tian et al., 2017).

No association between ECMO and CVA impairment was observed in our study, which was probably because there were only 19 ECMO patients in the subgroup analysis. Besides, we did not monitor CVA during the ECMO initiation, but when patients were relatively hemodynamically stable several hours after ECMO initiation. Further research is needed on the effect of ECMO treatment on CVA, and strategies to reduce neurological complications after ECMO treatment by detecting CVA.

6. 1. 7 Cerebrovascular autoregulation and neurological outcome

In our study, survivors of ARDS had poor HRQL and cognitive function three months after discharge from the ICU. Similar to our results, poorer physical function and cognitive function

were observed in ARDS survivors compared to healthy or non-ARDS critically ill patients (Davidson et al., 1999; Mikkelsen et al., 2009). Many factors which frequently occur in ARDS patients can induce cognitive impairment, such as mechanical ventilation, sedatives, sepsis, and environmental factors (Sasannejad et al., 2019). Our study did not observe an association between CVA impairment and neurocognitive outcomes in ARDS patients. This may be due to the limited number of patients who completed the follow-up and our study was not powered to detect an association between impaired CVA and neurocognitive outcome. To date, there are no previous studies on CVA impairment and neurocognitive outcome in ARDS patients. However, there are many studies focusing on CVA in critically ill patients as well as in patients undergoing cardiac surgery and its relationship with neurocognitive outcomes.

Contrary to our study, CVA impairment was associated with neurological outcomes in critically ill patients. In patients with mechanical ventilation or shock, the time with cumulative duration of CVA dysfunction within the first three days of ICU was significantly associated with the subsequent development of delirium (Lee et al., 2019). Among critically ill patients, most studies addressed septic patients. Crippa et al conducted a study including patients within 48 hours of sepsis diagnosis (Crippa et al., 2018). CVA was assessed through mean flow index, which is the correlation coefficient between ABP and TCD-based CBF velocity. In this study, patients with sepsis-associated brain dysfunction had a significantly worse CVA than those without brain dysfunction, and impaired CVA was demonstrated as an independent predictor of sepsis-associated brain dysfunction in logistic regression analysis (Crippa et al., 2018). Similarly, in a study from Schramm et al, within the first 48 hours of sepsis, CVA was impaired in approximately 60% of patients with severe sepsis or septic shock. Sepsis patients with delirium had a higher rate of impaired CVA than those without delirium (Schramm et al., 2012). There are some differences between these studies and our study. First, unlike ARDS patients, patients with sepsis have a high chance of septic encephalopathy due to systemic inflammation, which may directly impair neurocognitive function (Mazeraud et al., 2020). Additionally, we obtained self-assessed cognitive status and HRQL from ARDS survivors by questionnaires three months after they were discharged from the ICU, whereas the aforementioned studies accessed delirium or sepsis-associated brain dysfunction in the ICU (Crippa et al., 2018; Schramm et al., 2012).

In patients undergoing cardiac surgery, an association between impaired CVA and postoperative neurological outcomes has also been reported. In a prospective, observational study by Chan and Aneman that included patients undergoing cardiac surgery, postoperative impaired CVA was associated with the onset of delirium following cardiac surgery (Chan and Aneman, 2019). Similarly, Kumpaitiene et al. reported that the duration of the single longest

CVA impairment during cardiac surgery was associated with postoperative cognitive dysfunction (Kumpaitiene et al., 2019). Moreover, Caldas et al. found that CVA impairment was more severe on the first day after surgery compared to before surgery or 7 days after surgery (Caldas et al., 2019).

Additionally, an interesting approach is the use of CVA measurement to guide hemodynamic management. Brown et al. demonstrated that patients with CVA-guided MAP above the lower limit of CVA during cardiopulmonary bypass surgery had a lower incidence of postoperative delirium than those with a targeted MAP above 60 mmHg (Brown et al., 2019).

However, comparability with the present study is limited, since unlike ARDS patients, patients undergoing cardiac surgery have more risk factors for cognitive impairment, such as on-pump surgery, surgical stress, intraoperative hypotension, intraoperative bleeding, and intraoperative altered homeostasis (Kapoor, 2020). More studies on CVA function and neurological outcomes in ARDS patients are warranted in the future.

6. 2 Implications for clinical practice

To date, the subject of permissive hypercapnia in ARDS patients remains controversial. The lung-protective ventilation strategies is recommended for ARDS patients (Fan et al., 2017). Patients receive low tidal volume and limited pressure to avoid VILI while increasing the incidence of hypercapnia (Fan et al., 2017). Previous studies have demonstrated that lung-protective ventilation was beneficial and reduced mortality in ARDS patients (Hickling et al., 1994). However, in a large sample study with mechanically ventilated patients, Tiruvoipati et al. demonstrated that patients with hypercapnia had higher hospital mortality compared with those with normocapnia after adjusting for severity of illness (Tiruvoipati et al., 2017). Results of our study indicated that neither early hypercapnia, nor hypercapnia during CVA measurement was associated with impaired CVA during ARDS. Additionally, no difference was found in mortality between patients with and without early hypercapnia. Thus, we may deduct that in ARDS patients, hypercapnia is acceptable within certain limits when considering the effect on CVA. However, we cannot make assumptions about the association of early hypercapnia and mortality in ARDS patients, since our study was not designed to detect such an association.

Our study also found that ARDS patients with hypocapnia during CVA measurement had a significantly higher percentage of time with CVA impairment. This suggests a negative effect of hypocapnia on CVA in patients with ARDS. Interestingly, further negative effects of hypocapnia in ARDS patients have been described in previous studies. In a multicenter study, the effect of $PaCO_2$ on patients within the 48 hours of ARDS diagnosis was examined,

and 9.3% of ARDS patients demonstrated hypocapnia with $PaCO_2$ below 35 mmHg (Madotto et al., 2020). In the propensity score matched analysis of this study, mild to moderate ARDS patients with hypocapnia showed a significantly higher ICU mortality than patients with normocapnia (Madotto et al., 2020). Considering the finding together with our results, we suggest that in clinical management of ARDS patients, hypocapnia should be avoided.

Finally, NIRS-based CVA measurement provides us with a non-invasive and bedside method to evaluate CVA. To date, it is mainly used in the fields of neonatology, cardiac surgery, and neurocritical care, yet its application in critically ill patients with ARDS is rare (Moerman and De Hert, 2017). Considering the high incidence of CVA impairment, it might be beneficial to include NIRS-based CVA measurement into standard care for ARDS patients. Identifying individual MAP target according to CVA measurement in clinical management is a potential application in critically ill patients (Goodson et al., 2018). In ARDS patients treated with ECMO, CVA measurements may be useful due to the hemodynamic instability caused by relatively frequent fluctuations in oxygen, CO_2, and ABP (Kazmi et al., 2018). More studies and efforts are still needed, especially in making CVA monitoring more accurate, easier and affordable for bedside use.

6. 3 Limitations

First, this was an observational study, and ARDS patients received individualized treatment based on their underlying diseases, the severity of ARDS, and comorbidities. In the mixed linear model, we included clinical factors that may have influenced CVA, such as SOFA score, ARDS etiology, ARDS severity and ARDS treatment strategies. However, we cannot guarantee that we have accounted for all confounding factors contributing to this highly heterogeneous patient cohort.

In our study cohort, patients who breathed spontaneously without sedation were more likely to develop hypocapnia. We tried to account for this fact by including the type of sedation as a possible confounder into the mixed linear model and no association was observed with impaired CVA.

Second, comparability between our study and previous research is limited, since the definition of hypercapnia varies across studies (Madotto et al., 2020; Nin et al., 2017). Thus, we performed a sensitivity analysis defining $PaCO_2 \geq 60$ mmHg and $PH < 7.35$ as hypercapnia. We obtained similar results to the original definition of hypercapnia ($PaCO_2 \geq 50$ mmHg and $PH < 7.35$), which confirmed the robustness of our model.

Third, although the NIRS based method is being used more and more widely for CVA monitoring, the substitution of rSO_2 for CBF is subject to some assumptions. As described

previously, fluctuations in rSO_2 can be attributed to changes in CBF when other determinants are assumed to remain constant (Bush et al., 2019). For this reason, we kept the ventilator parameters unchanged 30 minutes before and during the CVA measurement to ensure the correctness of the measurement.

Furthermore, rSO_2 was monitored on one side of the forehead in our study. It provided rSO_2 in the area of the frontal cortex (Steppan and Hogue, 2014). In our study, patients with neurological disorders prior to ICU admission were excluded, allowing prefrontal cerebral oxygenation to be more representative. We took 60–90 minutes for each measurement, but continuous CVA monitoring throughout the whole acute stage of ARDS would be better to observe the effect of CO_2 fluctuations on CVA. The threshold of COx for CVA impairment was 0.3 in the study. Although 0.3 has been used most often in previous studies, there is no uniform standard for CVA impairment to date (K. M. Brady et al., 2010; Masahiro Ono et al., 2012).

Additionally, ARDS patients with early hypercapnia demonstrated with a significant higher rSO_2 than patients without early hypercapnia in our study. Similarly, in a randomised controlled trial, mild hypercapnia (45–55 mmHg) was associated with a stable increase in rSO_2 in patients undergoing major surgery (Wong et al., 2020). A low cerebral oxygenation has been described to affect neurological outcomes in critically ill patients with mechanical ventilation, and/or vasopressor support (Wood et al., 2017). However, our study was not designed for comparing the association between rSO_2 and neurological outcomes in ARDS patients. Further study is needed about whether cerebral oxygenation in ARDS patients is associated with neurological outcome.

Finally, this thesis presents the finding of a single-center observational study, and more research is needed to confirm our results. Hypothesis 2 regarding the relationship between CVA impairment and neurocognitive outcome was exploratory. Thus, this topic requires further research. Further studies might investigate other factors influencing CVA in ARDS patients, as well as how to protect CVA function in ARDS patients, and therapeutic measures for brain protection in ARDS patients.

7. Conclusion

In this prospective observational study, no association was observed between CVA impairment and early hypercapnia in ARDS patients. Thus, mild to moderate hypercapnia may be safe in terms of CVA function and may be tolerated to a certain extent to ensure lung-protective ventilation during the acute phase of ARDS. In contrast, hypocapnia during CVA measurement was associated with impaired CVA. Therefore, hypocapnia may impair CVA function and should be avoided in ARDS patients.

Patients with ARDS had a poor neurocognitive outcome three months after discharge from ICU. No correlation between impaired CVA and self-assessed cognitive failures, as well as HRQL was found three months after discharged from ICU. Considering the high incidence of impaired CVA as well as the poor neurocognitive outcomes in ARDS patients, it may be beneficial to apply CVA measurement into the standard of care for ARDS patients.

8. References

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9. Abstract

Background: Acute respiratory distress syndrome (ARDS) is a life-threatening form of respiratory failure. The average hospital mortality for ARDS patients is 40%, and it is higher in patients with hypercapnia. Cerebrovascular autoregulation (CVA) is a protective control mechanism that maintains relatively constant cerebral blood flow despite changes of arterial blood pressure. Carbon dioxide is one of the key influence factors on CVA. The aim of this study was to compare CVA function in ARDS patients with and without early hypercapnia, as well as the association between CVA impairment and neurocognitive outcomes.

Methods: Between December 2018 and November 2019, we conducted a prospective observational cohort study during the acute stage of ARDS. Patients with pre-existing neurological diseases and chronic hypercapnia were excluded. CVA was assessed using the cerebral oxygenation index, which is the correlation coefficient between regional oxygen saturation measured with near-infrared spectroscopy and arterial blood pressure. CVA was measured twice with each measurement lasting 60–90 minutes. The primary endpoint was the percentage of monitoring time with impaired CVA. Patients were divided into two groups based on arterial partial pressure of carbon dioxide ($PaCO_2$) and pH level at ARDS onset: 1) early hypercapnia ($PaCO_2 \geq 50$mmHg, pH < 7.35) and 2) no early hypercapnia ($PaCO_2 <$ 50mmHg). Functional, neurocognitive, and health outcomes were assessed three months after discharge from the intensive care unit (ICU) with the Cerebral Performance Category, the Cognitive Failures Questionnaire, and the 36-item Short-Form Health Survey.

Results: We included 66 ARDS patients and performed 117 CVA assessments. Early hypercapnia was not associated with the percentage of time above a pathologic COx threshold (B=0.023 [95%CI: -0.054; 0.100], p=0.556). Hypocapnia during measurement was associated with impaired CVA (B=0.155 [95%CI: 0.014; 0.296], p=0.032). 21/31 (67.7%) patients who completed follow-up three months after discharge from the ICU had moderate or severe functional disability. The average self-assessed cognitive failure score was 29.73 ± 19.81. In health-related quality of life assessment, physical sum score was 33.2 ± 11.9, and mental sum score was 45.4 ±10.6. No correlation between impaired CVA, cognitive, and health outcomes were observed.

Conclusion: Our results show that hypercapnia during the acute stage of ARDS is not associated with CVA impairment and may be tolerated to a certain extent to achieve lung protective ventilation. However, hypocapnia may compromise CVA function. The potential association between impaired CVA, cognitive, and health outcomes warrants investigation in future studies.

10. Zusammenfassung

Hintergrund: Das akute Atemnotsyndrom (ARDS) ist eine lebensbedrohliche Form der Ateminsuffizienz. Die durchschnittliche Krankenhaussterblichkeit von Patienten mit ARDS beträgt etwa 40 % und ist bei Patienten mit früher Hyperkapnie sogar noch höher. Zerebrovaskuläre Autoregulation (CVA) ist ein schützender Kontrollmechanismus, der den zerebralen Blutfluss konstant hält, unabhängig von Schwankungen des systemischen arteriellen Mitteldrucks. Der arteriell Kohlenstoffdioxidpartialdruck hat einen großen Einfluss auf die CVA. Ziel dieser Studie war es, zu untersuchen ob die CVA bei ARDS-Patienten mit früher Hyperkapnie stärker eingeschränkt ist, als bei Patienten ohne frühe Hyperkapnie. Des weiteren sollte untersucht werden, ob eine Einschränkung der CVA während der akuten Phase des ARDS mit einem schlechtem neurokognitivem Outcome assoziiert ist.

Methoden: Zwischen Dezember 2018 und November 2019 führten wir eine prospektive Beobachtungs-Kohortenstudie durch. Eingeschlossen wurden Patienten im akuten Stadium des ARDS. Patienten mit vorbestehenden neurologischen Erkrankungen und chronischer Hyperkapnie wurden ausgeschlossen. Die CVA wurde unter Verwendung des cerebralen Oxygenierungsindex gemessen, der der Korrelationskoeffizient zwischen der regionalen Sauerstoffsättigung, gemessen mit (Nah-Infrarot-Spektroskopie) und dem mittleren arteriellen Druck. Die CVA wurde zweimal gemessen, wobei jede Messung 60–90 Minuten dauerte. Der primäre Endpunkt war der prozentuale Anteil der Messzeit, während der die CVA beeinträchtigt war. Die Patienten wurden basierend auf dem arteriellen Kohlenstoffdioxidpartialdruckes ($PaCO_2$) und dem pH-Wert zu Beginn des ARDS in zwei Gruppen eingeteilt: 1) die Gruppe mit früher Hyperkapnie ($PaCO_2 \geq 50$ mmHg, pH < 7,35) und 2) Gruppe ohne frühe Hyperkapnie ($PaCO_2 < 50$ mmHg). Das funktionelle, neurokognitive und gesundheitliche Outcome wurde 3 Monate nach der Entlassung von der Intensivstation (ICU) mit der Cerebral Performance Category, dem Cognitive Failures Questionnaire und der 36-Item-Short-Form Health Survey bewertet.

Ergebnisse: Wir schlossen 66 ARDS-Patienten ein und führten 117 CVA-Beurteilungen durch. Eine frühe Hyperkapnie war nicht mit einer Beeinträchtigung der CVA assoziiert (B = 0,023 [95 % KI: -0,054; 0,100], p = 0,556). Eine Hypokapnie während der Messung war mit einer Beeinträchtigung der CVA assoziiert (B=0,155 [95 % KI: 0,014; 0,296], p=0,032). 21/31 (67,7%) Patienten, welche drei Monate nach der Entlassung von der Intensivstation im Rahmen des Follow-Ups untersucht wurden, litten unter mittelschweren bis schweren Einschränkungen. Der durchschnittliche Score für die Selbstbeurteilung von kognitiven fehlern betrug 29,73 ± 19,81. Für die Selbsteinschätzung der gesundheitsbezogenen

Lebensqualität betrug der körperliche Summenscore 33,2 ± 11,9 und der psychische Summenscore 45,4 ± 10,6. Es wurde keine Korrelation zwischen einer Beeinträchtigung der CVA und funktionellem, neurokognitivem oder gesundheitlichem Outcome beobachtet.

Schlussfolgerung: Unsere Ergebnisse zeigen, dass eine Hyperkapnie im akuten Stadium des ARDS nicht mit einer Beeinträchtigung der CVA assoziiert ist. Eine Hyperkapnie kann bis zu einem gewissen Grad toleriert werden, um eine lungenprotektive Beatmung zu ermöglichen. Eine Hypokapnie kann die CVA beeinträchtigen. Der potenzielle Zusammenhang zwischen Beeinträchtigung der CVA, kognitiven und funktionellem, neurokognitivem oder gesundheitlichem Outcome sollte in zukünftigen Studien untersucht werden.

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12. Curriculum Vitae

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Publications

Kahl, Ursula, **Yuanyuan Yu**, Axel Nierhaus, Daniel Frings, Barbara Sensen, Anne Daubmann, Stefan Kluge, and Marlene Fischer. 2021. ‘Cerebrovascular Autoregulation and Arterial Carbon Dioxide in Patients with Acute Respiratory Distress Syndrome: A Prospective Observational Cohort Study’. Annals of Intensive Care 11(1):47. doi: 10.1186/s13613-021-00831-7.

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13. Eidesstattliche Erklärung

Ich versichere ausdrücklich, dass ich die Arbeit selbständig und ohne fremde Hilfe verfasst, andere als die von mir angegebenen Quellen und Hilfsmittel nicht benutzt und die aus den benutzten Werken wörtlich oder inhaltlich entnommenen Stellen einzeln nach Ausgabe (Auflage und Jahr des Erscheinens), Band und Seite des benutzten Werkes kenntlich gemacht habe.

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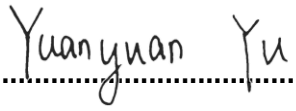
Unterschrift:.....  .....