Journal of Critical Care 38 (2017) 341–345

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.jccjournal.org

Association between ventilatory settings and development of acute respiratory distress syndrome in mechanically ventilated patients due to brain injury☆

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ARTICLE INFO

Keywords:
Acute respiratory distress syndrome
Mechanical ventilation
Neurologic disease
Driving pressure
Neurologically critically ill patients
Pulmonary complications

ABSTRACT

Purpose: In neurologically critically ill patients with mechanical ventilation (MV), the development of acute respiratory distress syndrome (ARDS) is a major contributor to morbidity and mortality, but the role of ventilatory management has been scarcely evaluated. We evaluate the association of tidal volume, level of PEEP and driving pressure with the development of ARDS in a population of patients with brain injury.
Materials and methods: We performed a secondary analysis of a prospective, observational study on mechanical ventilation.
Results: We included 986 patients mechanically ventilated due to an acute brain injury (hemorrhagic stroke, ischemic stroke or brain trauma). Incidence of ARDS in this cohort was 3%. Multivariate analysis suggested that driving pressure could be associated with the development of ARDS (odds ratio for unit increment of driving

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http://dx.doi.org/10.1016/j.jcrc.2016.11.010
0883-9441/

pressure 1.12; confidence interval for 95%: 1.01 to 1.23) whereas we did not observe association for tidal volume (in ml per kg of predicted body weight) or level of PEEP. ARDS was associated with an increase in mortality, longer duration of mechanical ventilation, and longer ICU length of stay.
Conclusions: In a cohort of brain-injured patients the development of ARDS was not common. Driving pressure was associated with the development of this disease.

1. Introduction

Pulmonary complications such as pneumonia, atelectasis, acute lung injury (ALI), and acute respiratory distress syndrome (ARDS) are commonly seen in neurologically critically ill patients with mechanical ventilation. The development of ARDS is a major contributor to mortality, and it worsens long-term neurologic outcome [1,2]. A severely and globally altered initial brain computed tomography scan and low Glasgow Coma Scale have been reported as potential risk factors for the development of ARDS in patients with acute brain injury [1-3]. More recently, it has been proposed that therapeutic strategies such as a positive fluid balance, exposure to blood products, and vasopressor dependence [4] may contribute to the development of ARDS, among major underlying ARDS risk factors (aspiration, pneumonia and lung contusion) and the severity of injury [3,5,6].

Conventional modalities of mechanical ventilation used in the management of patients with acute brain injury can often be in conflict with lung protective ventilation. Neurologically critically ill patients may be aggressively ventilated to optimize cerebral oxygenation and to maintain mild permissive hypocapnia for treatment of intracranial hypertension. This ventilatory strategy may further exacerbate the pulmonary and systemic inflammatory response and predispose to development of ARDS. Moreover, high volume ventilation has been identified as an independent predictor of early ARDS in patients with normal lungs admitted to a general intensive care unit [7,8]. Conversely, in recent systematic review and meta-analysis, ventilation with low tidal volumes has been associated with shorter duration of ventilation and lower risk of development of pulmonary complications in patients without acute respiratory distress syndrome [9,10].

However, clinical trials testing ventilation strategies designed for lung protection frequently excluded brain-injured patients, because of concerns about permissive hypercapnia while controlling intracranial pressure. As a result, different intracranial and extracranial independent predictors of ARDS have been previously identified in patients with neurological disorders, while the role of ventilatory management has been scarcely evaluated.

The objectives of the present study were to evaluate the incidence of ARDS and the effect of ventilatory settings on development of ARDS in a cohort of brain injured patients who required mechanical ventilation.

2. Materials and methods

2.1. Design

We analyzed data from a prospective, multicenter observational study of mechanically ventilated patients for at least 12 h admitted to 494 intensive care units (ICU) from 39 countries [11]. National coordinators recruited local investigators from eligible ICU. Only the investigator at each site was aware of the purpose and timing of the study in order to minimize practice changes in response to observation. The research ethics board of each participating institution approved the protocol and need for informed consent was according to local rules.

For the purpose of this analysis we included 986 patients mechanically ventilated due to an acute brain injury (hemorrhagic stroke, ischemic stroke, brain trauma).

2.2. Protocol

We collected baseline characteristics, daily ventilator settings, gas exchange, clinical management, and complication data while patients were ventilated or until day 28. Detailed descriptions of the variables collected and their definitions have been previously published [11]. Acute respiratory distress syndrome was defined according to the criteria from American European Consensus Conference (AECC) [12]: acute onset, ratio PaO2 to FiO2 < 200, bilateral infiltrate on chest radiograph and absence of heart failure. Those criteria must be met in two consecutive days to get a more consistent diagnosis.

2.3. Statistical analysis

Data are expressed as mean (standard deviation), median (interquartile range), absolute and relative frequencies as appropriate. We used Chi-square or Fisher's exact tests to compare categorical data between groups. We used the Kolmogorov-Smirnov test to assess continuous data for a normal distribution. We used two-tailed unpaired *t*-tests to compare normally distributed continuous data between two groups, and we used the Mann-Whitney *U* test for non-normally distributed continuous data comparisons.

Because each patient had repeated measurements, a multivariate generalized estimation equations model to assess for an independent association between the tidal volume and ARDS was performed. The variables entered in the model were: severity at admission estimated

Table 1
Characteristics of patients included in the analysis.

	Hemorrhagic stroke ($N = 470$)	Ischemic stroke ($N = 214$)	Brain trauma ($N = 302$)
Age, years, mean (SD)	61 (14)	65 (14)	46 (20)
Female, n (%)	207 (44)	70 (33)	77 (25)
Body mass index, kg/m^2, mean (SD)	27 (5)	25 (5)	26 (5)
SAPS II, points, mean (SD)	47 (15)	47 (17)	44 (16)
Glasgow Coma Scale at admission, points, mean (SD)	6 (3)	7 (3)	6 (3)
Ventilator settings at day 0			
Mode, n (%)			
Volume controlled[a]	307 (65)	154 (72)	213 (71)
Pressure controlled[b]	145 (31)	55 (26)	80 (26)
Other[c]	18 (4)	5 (2)	9 (3)
Tidal volume			
In ml, mean (SD)	517 (88)	507 (97)	512 (89)
In ml/kg ABW, mean (SD)	7.1 (1.6)	6.9 (1.5)	7.2 (1.6)
In ml/kg PBW, mean (SD)	8.4 (1.6)	8.2 (1.5)	8 (1.4)
PEEP, cmH_2O, mean (SD)	5.2 (1.9)	5.4 (2.2)	5.5 (1.9)
Arterial blood gases at day 0			
pH, mean (SD)	7.39 (0.09)	7.36 (0.12)	7.34(0.11)
$PaCO_2$, mm Hg, mean (SD)	39 (11)	43 (18)	38 (10)
Ratio PaO_2 to FiO_2, mean (SD)	290 (105)	269 (105)	298 (105)

[a] Includes controlled volume ventilation (CMV), and synchronized intermittent mandatory ventilation (SIMV).
[b] Includes pressure regulated volume controlled (PRVC), pressure controlled ventilation (PCV), pressure support (PS), airway pressure release ventilation/biphasic positive airway pressure (APRV/BIPAP).
[c] Includes continuous positive airway pressure (CPAP), Adaptive support ventilation (ASV), neural adjusted ventilatory assist (NAVA), proportional assist ventilation (PAV).

by SAPS II, sepsis, shock, ventilator-associated pneumonia, tidal volume (expressed in ml/kg of predicted body weight), applied PEEP and driving pressure. Analyses were performed using Stata 14.1.

3. Results

In Table 1 are showed the characteristics of patients included in the analysis.

3.1. Incidence of ARDS

Twenty-eight patients (3%) met the criteria of ARDS over the course of mechanical ventilation. To meet the criteria, median time from intubation was 2 days (interquartile range 1–7). In Table 2 is showed the comparison of baseline, management variables and complications between patients who were diagnosed of ARDS and patients without the criteria of ARDS.

Comparison in the outcome of both groups is showed in Table 3.

Table 2
Comparison of patients with acute respiratory distress syndrome and patients without acute respiratory distress syndrome.

	ARDS ($N = 28$)	No-ARDS ($N = 958$)	*P* value
Age, years, mean (SD)	55 (19)	58 (18)	0.418
Female, n (%)	9 (32)	345 (36)	0.674
Body mass index, kg/m^2, mean (SD)	27 (5)	26 (5)	0.252
SAPS II, points, mean (SD)	55 (17)	46 (16)	0.002
Glasgow Coma Scale at admission, points, mean (SD)	6 (2.5)	6 (3)	0.689
Neurologic disease, n (%)			
Hemorrhagic stroke	12 (43)	458 (48)	0.605
Ischemic stroke	5 (18)	209 (22)	0.616
Brain trauma	11 (39)	291 (30)	0.313
Arterial blood gases on first day of mechanical ventilation			
pH, mean (SD)	7.32 (0.08)	7.37 (0.11)	0.166
$PaCO_2$, mm Hg, mean (SD)	37 (9)	37 (8)	0.728
Ratio PaO_2 to FiO_2, mean (SD)	221 (117)	285 (104)	0.002
Ventilator settings on the first day of mechanical ventilation			
Mode, n (%)			0.461
Volume controlled[a]	18 (64)	656 (69)	
Pressure controlled[b]	10 (36)	270 (28)	
Other[c]	–	32 (3)	
Tidal volume			
In ml, mean (SD)	512 (70)	513 (91)	0.932
In ml/kg ABW, mean (SD)	6.5 (1.1)	7.0 (1.6)	0.154
In ml/kg PBW, mean (SD)	8.0 (1.2)	8.2 (1.7)	0.511
PEEP, cmH_2O, mean (SD)	4.8 (2.7)	5.4 (1.9)	0.217
Driving pressure, cmH_2O, mean (SD)[d]	14 (6)	12 (4)	0.067
Variables related to management[e]			
Tidal volume, ml/kg PBW, mean (SD)			
Higher	8.7 (1.8)	9.2 (2.1)	0.174
Lower	7.5 (1.8)	7.3 (1.6)	0.608
PEEP, cmH_2O, mean (SD)			
Higher	8.5 (4.3)	6.7 (2.8)	0.001
Lower	5.2 (3.2)	4.7 (1.9)	0.244
Higher driving pressure, cmH_2O, mean (SD)	19 (5)	14 (4)	<0.001
Lower ratio PaO_2 to FiO_2, mean (SD)	99 (34)	210 (90)	<0.001
Higher $PaCO_2$, mm Hg, mean (SD)	46 (11)	43 (10)	0.161
Steroids, n (%)	2 (7)	135 (14)	0.295
Cumulative fluid balance, ml, median (interquartile range)	837 (−700, 3335)	2698 (230,6592)	0.087
Events over the course of mechanical ventilation[e]			
Sepsis, n (%)	14 (50)	138 (14)	<0.001
Ventilator associated-pneumonia, n (%)	5 (18)	53 (5.5)	0.006
Shock, n (%)	23 (82)	429 (45)	<0.001

Abbreviations: ARDS: acute respiratory distress syndrome; PEEP: positive end-expiratory pressure; SD: standard deviation.

[a] Includes controlled volume ventilation (CMV), and synchronized intermittent mandatory ventilation (SIMV).

[b] Includes pressure regulated volume controlled (PRVC), pressure controlled ventilation (PCV), pressure support (PS), airway pressure release ventilation/biphasic positive airway pressure (APRV/BIPAP).

[c] Includes continuous positive airway pressure (CPAP), Adaptive support ventilation (ASV), neural adjusted ventilatory assist (NAVA), proportional assist ventilation (PAV).

[d] Driving pressure = plateau pressure minus PEEP. Data missing in 353 patients (15 in cohort of patients with ARDS and 338 in cohort of patients without ARDS).

[e] In patients with ARDS, the data are corresponding to register before diagnosis of ARDS.

Table 3
Outcome according to diagnosis of acute respiratory distress syndrome.

	ARDS ($N = 28$)	No-ARDS ($N = 958$)	*P* value
Days of ventilatory support, median (interquartile range)	12 (5, 24)	7 (4, 13)	0.016
Length of stay in the intensive care unit, median (interquartile range)	12 (5, 34)	8 (4, 18)	0.063
Length of stay in hospital, median (interquartile range)[a]	15 (6, 30)	13 (6, 56)	0.510
Mortality in the intensive care unit, n (%)	18 (64)	357 (37)	0.004
Mortality at day 28, n (%)	15 (53)	392 (41)	0.180
Mortality in the hospital, n (%)[a]	18 (69)	419 (46)	0.020

[a] Missing data in 53 patients.

3.2. Effect of tidal volume, applied PEEP and driving pressure on development of ARDS

After adjustment for severity at admission (estimated by SAPS II), known risk factors for ARDS (sepsis, shock, ventilator associated pneumonia) and variables related to ventilatory management (tidal volume, applied positive end-expiratory pressure and driving pressure) only driving pressure was associated with the diagnosis of ARDS: odds ratio per unit of increase of driving pressure 1.12; confidence interval for 95%: 1.01 to 1.23.

4. Discussion

In this prospective observational study of mechanically ventilated patients with critical neurologic illness, we found that: 1) ARDS is not a common event; 2) a high driving pressure was associated to a higher risk for ARDS; 3) ARDS was associated with a twofold increase in mortality, longer duration of mechanical ventilation, and longer ICU length of stay.

The incidence of ARDS in this cohort was lower than has been reported in other studies of brain-injured patients. In previous reports, ARDS occurs in up to 20–38% of cases of subarachnoid haemorrhage [13-15], traumatic brain injury [1,16] and spontaneous intracerebral haemorrhage [4,5,17,18], and 35% reported in a mixed cohort of neurologically ill patients [19]. Variability in ARDS incidence may reflect differences in study populations and in diagnosis approach, variable use of consensus approach. In our study, diagnostic criteria for ARDS must be met in two consecutive days to get a more consistent diagnosis. This is supported by recent reports [20,21]. In an observational study, the use of a standardized ventilatory setting at 24 h of ARDS onset allowed a more precise and clinically relevant stratification of ARDS patients [20]. And, in other large, observational study demonstrated that risk stratification of ARDS patients based on PaO2/FiO2 recorded at ARDS onset (baseline) is not clinically useful [21].

Currently, little is known about the etiology of ARDS in neurologically critically ill patients. Literature describes a “double hit model”, postulating that injurious strategies of mechanical ventilation can act as a second hit on lungs already preconditioned by the catecholamine storm and the systemic production of inflammatory mediators following brain injury [6,7]. In this context, high volume ventilation may further exacerbate the pulmonary and systemic inflammatory response in brain-injured patients with ALI/ARDS, and hyperventilation for permissive hypocapnia may be associated with more lung injury [22]. In a large-scale observational study, it was noted that neurologic patients were ventilated with mean tidal volumes approximating a 9 ml/kg of predicted body weight [23]. Higher tidal volume has also been identified as a significant and modifiable risk factor for the development of

ARDS in patients with neurological disorders [4,5]. In fact, high tidal volume ventilation has been associated to ventilator-induced lung injury (VILI) related to overdistention during mechanical ventilation (volutrauma), recruitment-derecruitment of collapsed alveoli (atelectrauma), and activation of inflammatory processes (biotrauma) [6,22,24]. So, in general ICU patients, the goals of mechanical ventilation have changed over the past 10 years from maintaining normal blood gas values, to maintaining adequate gas exchange while attempting to minimize VILI [25]. And, to minimize VILI most studies have scaled V_T to predicted body weight to normalize V_T to lung size. However, many studies suggest that tissue damage is more closely related to the unphysiological lung strain and stress generated by mechanical ventilation with large tidal volume. Thus, driving pressure is the surrogate for cycling lung strain that is most accessible and easiest to calculate, and cyclic strain predicts lung injury better than V_T. Accordingly, normalizing V_T to respiratory-system compliance would provide a better predictor of VILI than V_T alone [26]. Furthermore, a recent study also suggests that, among the respiratory variables monitored at the bedside, driving pressure was the strongest predictor of mortality [27]. So, the finding that the driving pressure is independently associated with the development of ARDS, implies that patients in whom a change in ventilator settings reduces driving pressure may have better outcome. A previous analysis [27,28] did not include neurologically critically ill patients. Thus, our results extend knowledge about protective ventilation and the potential role of the driving pressure in this population, given that brain injury may act as a preconditioning factor rendering the lung more susceptible to subsequent lung damage induced by mechanical ventilation [29].

Other therapeutic strategies, aside from ventilatory settings, could contribute to the development of ARDS in neurocritical patients. Several studies have shown ARDS to be a consequence of underlying illness and predisposing conditions such as young age, male gender, ethnicity, history of chronic arterial hypertension, diabetes, chronic obstructive pulmonary disease, development of sepsis, cardiovascular, renal and haematological dysfunctions [17,30,31]. In addition, other interventions such as exposure to blood products may potentiate pulmonary injury in a susceptible host or lead directly to transfusion-related ARDS. And, induced hypertension, frequently required for the management of cerebral perfusion pressure in patients with elevated intracranial pressure, has also been associated with an increased incidence of ARDS [3].

Among the extracranial factors, administration of vasoactive drugs and history of drug abuse have also been identified as independent predictors of ARDS in patients with traumatic brain injury [3]. However, our data suggest that the development of ARDS in neurologically mechanically ventilated patients is specifically associated with high driving pressure.

In our study, ARDS patients developed more complications during mechanical ventilation such as shock, sepsis and pneumonia associated with ventilation. ARDS was also associated with a significant increase in mortality, and it prolonged the duration of mechanical ventilation and the length of ICU stay. Similarly, in previous reports, ARDS has been identified as a major contributor to the morbidity and mortality of patients with brain injuries [2,3,5,15,17,18,30]. ARDS also worsens long-term neurologic outcome [1,2,3,32], and is associated with longer ICU and hospital length of stay [5,29]. Conversely, other studies [4,5,33] did not observe a direct association between ARDS and mortality, and the authors argued that this result may be explained by the fact that in patients with severe brain injury, the effect of ARDS is obscured by the overall mortality driven by the severity of the brain injury rather than other organ failures.

Our study has several limitations. First, this was a post-hoc analysis of previously and prospectively collected clinical data from a wide variety of ICUs, patient conditions, and clinical practices. Second, we used the traditional AECC definition of ARDS [12] as we could not apply the more recent Berlin definition [34] because the studied cohorts were prior to the Berlin conference. Otherwise, both definitions have serious limitations [20]. As the Berlin criteria, similar to the AECC criteria, did not mandate the assessment of hypoxemia under standardized ventilatory conditions, the values of PaO2/FiO2 recorded at the time of ARDS diagnosis do not provide accurate assessment of ARDS severity and outcome [21]. Even for patients with severe ARDS by the Berlin definition, only 58% demonstrated diffuse alveolar damage on autopsy [35]. Hence, one can consider that the Berlin definition also lacks specificity, and the recent LungSafe survey showed that ARDS is frequently underdiagnosed by clinicians [36]. Third, information about some important ARDS risk factors, such as massive transfusion and drug overdose was not collected as part of an international study increasing the chance for residual confounding by unmeasured variables. Fourth, we have not collected treatment variables of intracranial hypertension or specific monitoring data (intracranial pressure, cerebral perfusion pressure, etc.), but we assume that neurological patients have been treated according to the protocols and guidelines published. Fifth, we have entered the driving pressure in our analysis despite the fact that this variable has missing data (usually plateau pressure was not registered in patients ventilated with pressure controlled modes). Additionally, we were not able to collect systemic data on left ventricular filling pressures, so we determined the presence or absence of left atrial hypertension based on other available data and may have misclassified some cases of cardiogenic pulmonary edema as ARDS. Finally, this study focused on general outcomes and the details related to mechanical ventilation, thus we did not examine neurologic outcome.

In summary, the results of this study indicate that the incidence of ARDS in a mixed cohort of neurologically mechanically ventilated patients is low, and the development of ARDS is associated with the effect of a high driving pressure, a potentially modifiable risk factor. Furthermore, ARDS has a great impact on morbidity and mortality in patients suffering from brain injury and is associated with longer duration of mechanical ventilation, and longer ICU length of stay.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jcrc.2016.11.010.

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