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

Eva Tejerina a,⁎, Paolo Pelosi b, Alfonso Muriel c, Oscar Peñuelas a, Yuda Sutherasan d, Fernando Frutos-Vivar a, Nicolás Nin e, Andrew R. Davies f, Fernando Rios g, Damian A. Violi h, Konstantinos Raymondis j, Javier Hurtado j, Marco González k, Bin Du l, Pravin Amin m, Salvatore M. Maggiore n, Arnaud W. Thille o, Marco Antonio Soares p, Manuel Jibaja q, Asisclio J. Villagomez r, Michael A. Kuiper s, Younsuck Koh t, Rui P. Moreno u, Amine Ali Zeggwagh v, Dimitrios Matamis w, Antonio Anzueto x, Niall D. Ferguson y, Andrés Estebana, for VENTILA group

a Hospital Universitario de Getafe & Centro de Investigación Biomédica en Red de Enfermedades Respiratorias (CIBERES), Spain
b Department of Surgical Sciences and Integrated Diagnostics, IRCCS AOU San Martino-IST, Genoa, Italy
c Unidad de Bioestadística Clínica Hospital Ramón y Cajal, Instituto Ramón y Cajal de Investigaciones Sanitarias (IRYCS) & Centro de Investigación en Red de Epidemiología y Salud Pública (CIBERESP), Spain
d Division of Pulmonary and Critical Care Medicine, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand
e Hospital Universitario de Montevideo, Uruguay
f Alfred Hospital & Monash University, Melbourne, Australia
g Hospital Nacional Alejandro Posadas, Buenos Aires, Argentina
h Hospital HIGA Guemes, Huelva, Argentina
i Medizinische Hochschule Hannover, Germany
j Hospital de Clinicas de Montevideo, Montevideo, Uruguay
k Clínica Medellín & Universidad Pontificia Bolivariana, Medellín, Colombia
l Peking Union Medical College Hospital, Beijing, People’s Republic of China
m Bombay Hospital Institute of Medical Sciences, Mumbai, India
n Policlinico “Agostino Gemelli”, Università Cattolica Del Sacro Cuore, Roma, Italy
o University Hospital of Poitiers, Poitiers, France
p Hospital Universitario San José, Belo Horizonte, Brazil
q Hospital Eugenio Espino, Quito, Ecuador
r Hospital Regional 1° de Octubre, Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado (ISSSTE), México DF, México
s Medical Center Leeuwarden (MCL), Leeuwarden, The Netherlands
t Asan Medical Center, University of Ulsan, Seoul, Republic of Korea
u Hospital de San José, Centro Hospitalar de Lisboa Central, Lisboa, Portugal
v Hôpital Ibn Sina, Rabat, Morocco
w Papageorgiou Hospital, Thessaloniki, Greece
x South Texas Veterans Health Care System and University of Texas Health Science Center, San Antonio, TX, USA
y Interdepartmental Division of Critical Care Medicine, and Departments of Medicine & Physiology, University of Toronto, Canada

A B S T R A C T

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

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 pressure).

http://dx.doi.org/10.1016/j.jcrc.2016.11.010
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 [5].

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 neurologic 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 descriptors 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/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 (inter-quartile 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

<table>
<thead>
<tr>
<th>Characteristics of patients included in the analysis.</th>
<th>Hemorrhagic stroke (N = 470)</th>
<th>Ischemic stroke (N = 214)</th>
<th>Brain trauma (N = 302)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean (SD)</td>
<td>61 (14)</td>
<td>65 (14)</td>
<td>46 (20)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>207 (44)</td>
<td>70 (33)</td>
<td>77 (25)</td>
</tr>
<tr>
<td>Body mass index, kg/m², mean (SD)</td>
<td>27 (5)</td>
<td>25 (5)</td>
<td>26 (5)</td>
</tr>
<tr>
<td>SAPS II, points, mean (SD)</td>
<td>47 (15)</td>
<td>47 (17)</td>
<td>44 (16)</td>
</tr>
<tr>
<td>Glasgow Coma Scale at admission, points, mean (SD)</td>
<td>6 (3)</td>
<td>7 (3)</td>
<td>6 (3)</td>
</tr>
<tr>
<td>Ventilator settings at day 0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mode, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volume controlleda</td>
<td>307 (65)</td>
<td>154 (72)</td>
<td>213 (71)</td>
</tr>
<tr>
<td>Pressure controlledb</td>
<td>145 (31)</td>
<td>55 (26)</td>
<td>80 (26)</td>
</tr>
<tr>
<td>Otherc</td>
<td>18 (4)</td>
<td>5 (2)</td>
<td>9 (3)</td>
</tr>
<tr>
<td>Tidal volume</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In ml, mean (SD)</td>
<td>517 (88)</td>
<td>507 (97)</td>
<td>512 (89)</td>
</tr>
<tr>
<td>In ml/kg ABW, mean (SD)</td>
<td>7.1 (1.6)</td>
<td>6.9 (1.5)</td>
<td>7.2 (1.6)</td>
</tr>
<tr>
<td>In ml/kg PBW, mean (SD)</td>
<td>8.4 (1.6)</td>
<td>8.2 (1.5)</td>
<td>8.1 (1.4)</td>
</tr>
<tr>
<td>PEEP, cmH2O, mean (SD)</td>
<td>5.2 (1.9)</td>
<td>5.4 (2.2)</td>
<td>5.5 (1.9)</td>
</tr>
<tr>
<td>Arterial blood gases at day 0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH, mean (SD)</td>
<td>7.39 (0.09)</td>
<td>7.36 (0.12)</td>
<td>7.34 (0.11)</td>
</tr>
<tr>
<td>PaCO2, mm Hg, mean (SD)</td>
<td>39 (11)</td>
<td>43 (18)</td>
<td>38 (10)</td>
</tr>
<tr>
<td>Ratio PaO2 to FiO2, mean (SD)</td>
<td>290 (105)</td>
<td>269 (105)</td>
<td>298 (105)</td>
</tr>
</tbody>
</table>

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.

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 [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 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 (biotrauma), recruitment-de-recruitment 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 Vt to predicted body weight to normalize Vt 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 VT. According to the recently published report by the group of China, this mechanical ventilation with large tidal volume is associated to ventilator-induced lung injury (VILI) related to overdistention during mechanical ventilation, and longer ICU length of stay. 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 high tidal volume 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.

References


