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Ventilator settings as a risk factor for acute respiratory distress syndrome in mechanically ventilated patients

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Abstract *Objective:* A single-center retrospective study initial recently identified ventilator settings as a major risk factor for the development of acute respiratory distress syndrome (ARDS) in mechanically ventilated patients who do not have ARDS from the outset. We tested this hypothesis in a larger sample of patients prospectively enrolled in a multicenter study on mechanical ventilation. *Design and setting:* From a large international mechanical ventilation study database we identified patients who required mechanical ventilation for 48 h or more but did not have ARDS at the onset of mechanical ventilation. We extracted information on demographics, initial severity of illness, ventilator settings and major underlying ARDS risk factors. Primary outcome was development of ARDS after the onset of mechanical ventilation. *Measurements and results:* Of 3,261 mechanically ventilated patients who did not have ARDS at the outset 205 (6.2%) developed ARDS 48 h or more after the onset of mechanical ventilation. Multivariate logistic regression analysis adjusted for baseline patient characteristics (age, gender, Simplified Acute Physiology Score, hypoxemia) and underlying ARDS risk factors (sepsis, trauma, pneumonia) found the development of ARDS to be associated with the initial ventilator settings: high tidal volume (odds ratio 2.6 for tidal volume >700 ml), high peak airway pressure (odds ratio 1.6 for peak airway pressure >30 cmH_2O), and high positive end-expiratory pressure (odds ratio 1.7 for end-expiratory pressure >5 cmH_2O). *Conclusions:* The association with the potentially injurious initial ventilator settings, in particular large tidal volumes, suggests that ARDS in mechanically ventilated patients is in part a preventable complication. This hypothesis needs to be tested in a prospective study.

Keywords Respiration Artificial, adverse effects · Respiratory distress syndrome, adult · Pulmonary edema, pneumonia

Introduction

Acute lung injury (ALI) and its more severe form acute respiratory distress syndrome (ARDS) present a major public health problem, with more then 150,000 affected patients each year in the United States [1, 2]. Sepsis, trauma, pneumonia, massive transfusion, and acid aspiration are well-defined risk factors for this syndrome [3, 4]. Ventilator settings, especially high tidal volumes, are known potentially to induce a syndrome that is clinically and pathologically indistinguishable from ARDS—ventilator-associated lung injury [5, 6, 7]. Indeed, lowering tidal volume is currently the only intervention shown to improve outcome in patients with established ALI/ARDS [8]. It is not known, however, whether the initial ventilator settings may cause or contribute to development of

ARDS in patients who do not have ARDS at the onset of mechanical ventilation.

An observational cohort study at the Mayo Clinic by Gajic et al. [9] recently observed a significant variability in the initial tidal volume settings (mean 10.9±2.3 ml/kg predicted body weight) in mechanically ventilated patients without ALI or ARDS. Of 332 patients ventilated for 48 h or more who did not have ALI at the onset of mechanical ventilation 80 developed ALI/ARDS (25%; 8% ALI, 17% ARDS) within 5 days of mechanical ventilation (median 2.5 days after the intubation). This single-center retrospective study identified initial large tidal volumes and blood product transfusions as major risk factors for development of ALI/ARDS regardless of underlying severity of illness and risk factors. We explored this association in a large sample of patients prospectively enrolled in a multicenter international study on mechanical ventilation [10].

Materials and methods

From the International Mechanical Ventilation Study database [10] we identified 3,261 patients who were mechanically ventilated through an endotracheal tube for 48 h or more and who did not have ARDS at the onset of mechanical ventilation. Near-complete data sets (>95%) were collected on all variables except for plateau airway pressure (approx. 35% missing in each group). We extracted data on demographics, initial (day one) ventilator settings [tidal volume, peak and plateau airway pressure, positive end-expiratory pressure (PEEP), severity of illness scores (Simplified Acute Physiology Score, SAPS)] and major underlying ARDS risk factors (sepsis, pneumonia, trauma, surgery, and aspiration). The study design and data collection procedures have been previously published in detail [10]. Our primary outcome was development of ARDS 48 h or more after the onset of mechanical ventilation as identified prospectively by the International Study investigators; ARDS was defined as per standard American European Consensus Conference Definition [11].

Static and dynamic respiratory system compliance were calculated according to following formulas: The incidence of ARDS was calculated per number of patients ventilated for at least 48 h. All data are represented as mean ±standard deviation and percentages. Continuous and categorical variables were compared using Student's t test and the χ^2 test as appropriate. To determine independently associated risk factors we created a multivariable logistic regression model. Risk factors for ALI were considered for multivariable logistic regression model if they (a) were statistically significant in bivariate analyses ($p<0.05$), (b) had high odds ratios (OR$\geq$1.5), (c) were biologically plausible, and (d) had 20% or more missing data. The variables were treated as continuous or categorical according to data distribution, the goodness of fit of the overall model, and the presence or absence of clinically meaningful threshold value. Because of the importance of the initial static respiratory system compliance in distinguishing between the potential harmful effect of the ventilator settings and the natural progression of early ARDS a separate multivariate analysis was performed on a subgroup of patients who did have plateau pressure measured and static respiratory system compliance determined. JMP statistical software (version 5, SAS Institute, Cary, N.C., USA) was used for all data analyses.

Table 1 Comparison between patients who did and did not develop ARDS after the onset of mechanical ventilation (*SAPS* Simplified Acute Physiology Score, *PEEP* positive end expiratory pressure, *Crs* respiratory system compliance, *Ppl* plateau airway pressure, *Ppk* peak airway pressure)

	ARDS (n=205)	No ARDS (n=3,056)	p
Age	55.4±17	59.7±17	<0.001
Female gender	133 (65%)	1874 (62%)	0.316
Weight (kg)	73.8±17	72.6±18	0.349
SAPS II	46.8±16	44.6±17	0.061
Postoperative	30 (15%)	470 (15%)	0.773
Aspiration	4 (2%)	86 (3%)	0.443
Sepsis	28 (14%)	302 (10%)	0.096
Pneumonia	60 (29%)	454 (15%)	<0.001
Trauma	28 (14%)	252 (8%)	0.013
PaO_2/FIO_2	175±102	230±108	<0.001
Crs dynamic (ml/cmH_2O)	26.8±14	26.9±12	0.938
Crs static (ml/cmH_2O)	39.7±19	35.8±13	0.002
Tidal Volume (ml)	670±220	620±110	<0.001
Ppk (cmH_2O)	32.7±8.4	29.2±8.0	<0.001
Ppl (cmH_2O)	22.9±6.2	21.3±4.2	<0.001
PEEP (cmH_2O)	5.1±3.8	3.5±3.1	<0.001
Hospital mortality	128 (62%)	985 (32%)	<0.001

Results

In 205 patients (6.2%) ARDS developed 48 h or more after the onset of mechanical ventilation; Table 1 summarizes clinical characteristics of mechanically ventilated patients who did and did not develop ARDS.

Patients who developed ARDS tended to be younger, were more likely to have pneumonia or trauma at the time of intubation and tended to have a lower PaO_2/FIO_2 ratio with no significant difference in dynamic respiratory system compliance (Table 1). When measured (65% of patients), the initial static respiratory system compliance was actually higher in patients who subsequently developed ARDS than in those who did not. Patients who developed ARDS were more likely to receive higher tidal volumes and higher PEEP settings with increased peak and plateau airway pressures (Table 1). Figure 1 illustrates the distribution of day 1 tidal volumes, peak airway pressures and PEEP in patients who did and did not subsequently developed ARDS. Notably, patients who developed ARDS were more likely to be ventilated with large tidal volumes (>700 ml) and higher peak airway pressures (>30 cmH_2O) then those who did not develope ARDS (Fig. 1).

Multivariate logistic regression analysis adjusted for underlying severity of illness, age, gender, weight, and ARDS risk factors found the initial ventilator settings of higher tidal volume, higher peak airway pressure, and higher PEEP to be significantly associated with the development of ARDS (Table 2). However, when the multivariate analysis was restricted to the patients whose

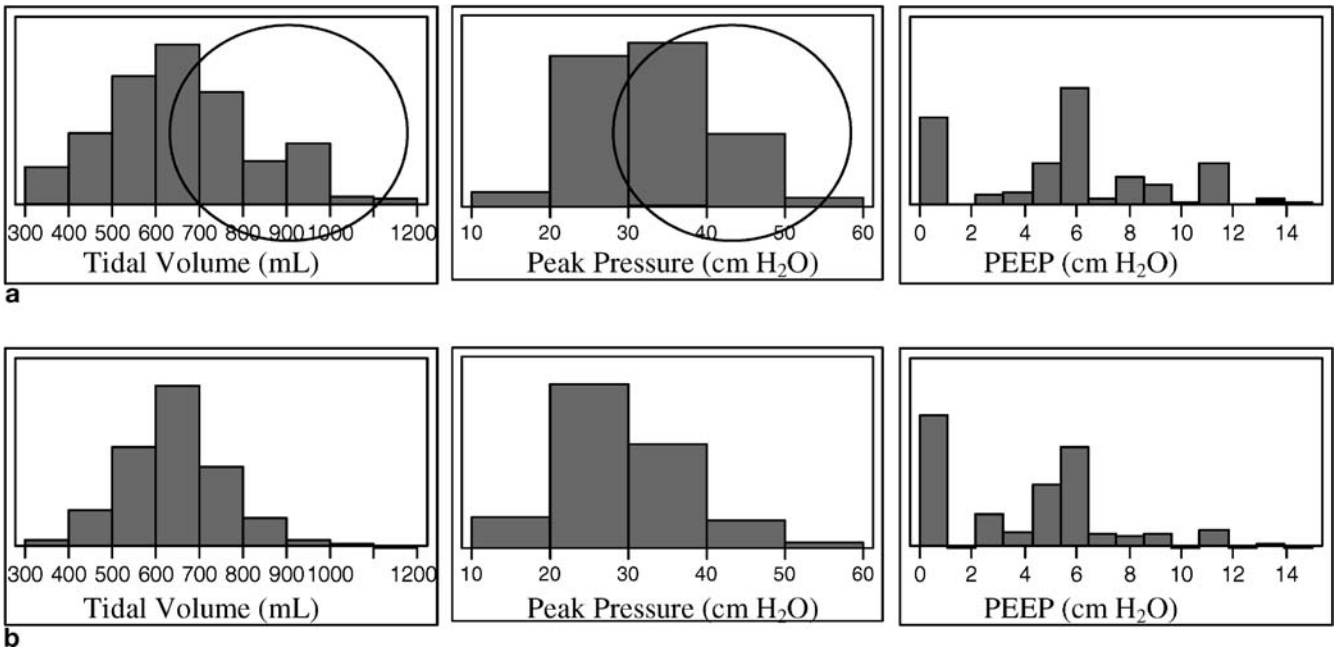

Fig. 1 Distribution of day 1 tidal volume, peak airway pressure, and PEEP among mechanically ventilated patients who did (**a**) or did not (**b**) subsequently develop ARDS

Table 2 Multivariate analysis of risk factors associated with development of ARDS: ventilator parameters (tidal volume; peak airway pressure *Ppk*, positive end-expiratory pressure, *PEEP*) were treated as continuous variables across the range of variation (model fit: R^2=0.09, p<0.001) and as discrete variables according to data distribution and clinically meaningful thresholds (model fit: R^2=0.11, p<0.001)

	Odds ratio	95% confidence interval	*p*
Continuous-variable model			
Age	0.98[a]	0.97–0.99	<0.001
SAPS II	1.01[a]	1.00–1.02	0.037
Pneumonia	2.05	1.42–2.94	<0.001
Sepsis	1.33	0.84–2.03	0.209
Trauma	1.76	1.07–2.82	0.022
PaO_2/FIO_2	0.95[a]	0.94–0.97	<0.001
Ppk (cmH_2O)	1.17[a]	1.07–1.27	<0.001
PEEP (cmH_2O)	1.08[a]	1.03–1.13	0.001
Tidal volume (ml)	1.26[a]	1.12–1.40	<0.001
Discrete-variable model			
Age[a]	0.98	0.97–0.99	<0.001
SAPS II[a]	1.01	1.00–1.02	0.013
Pneumonia	2.21	1.56–3.11	<0.001
Sepsis	1.28	0.81–1.96	0.280
Trauma	1.80	1.11–2.87	0.015
PaO_2/FIO_2[a]	0.95	0.94–0.97	<0.001
Ppk >30 cmH_2O	1.57	1.16–2.13	0.003
PEEP>5 cmH_2O	1.69	1.20–2.34	0.002
Tidal volume >700 ml	2.67	1.94–3.65	<0.001

[a] Per unit of measurement (1 cmH_2O PEEP, 5 cmH_2O Ppk; 100 ml tidal volume, 10 mmHg PaO_2/FIO_2, one unit of SAPS II score, 1 year of age)

initial static respiratory system compliance could be determined (n=2,204, 132 of whom developed ARDS), the initial large tidal volume and high peak pressure but not the PEEP settings remained significantly associated with the development of ARDS. Mechanically ventilated patients who developed ARDS had significantly worse outcome: 63% (128/205) who developed ARDS died in the hospital vs. 32% 985/3,065 (32%) of those who did not.

Discussion

In this secondary analysis of the international study database we tested the hypothesis that initial ventilator settings are associated with the subsequent development of ARDS in mechanically ventilated patients who did not have ARDS from the outset. ARDS appears to be a relatively common complication (6%) in patients on mechanical ventilation who do not have ARDS from the outset. In addition to underlying severity of illness, lower PaO_2/FIO_2, younger age, trauma, and diagnosis of pneumonia, significant risk factors for the development of ARDS were related to the initial ventilator settings, in particular high tidal volumes and high peak airway pressures.

Before we discuss the implications of our findings we need to point out a significant shortcomings of our study design. First, as many of the patients in both groups had profound baseline hypoxemia and met oxygenation cri-

Table 3 Risk factors associated with development of ARDS, multivariate analysis in patients who did have static respiratory compliance measured (n=2,204, 132 of which developed ARDS; model fit: R^2=0.12, p<0.001) (*Crs* respiratory system compliance, *Ppk* peak airway pressure, *PEEP* positive end expiratory pressure)

	Odds ratio	95% confidence interval	p
Age[a]	0.98	0.97–0.99	0.001
SAPS II[a]	1.01	1.00–1.02	0.124
Pneumonia	2.37	1.52–3.65	<0.001
Sepsis	1.14	0.63–1.95	0.644
Trauma	1.86	1.04–3.23	0.031
Crs static (ml/cmH_2O)[a]	1.09	0.96–1.21	0.157
PaO_2/FIO_2[a]	0.94	0.92–0.96	<0.001
Ppk >30 cmH_2O	1.67	1.14–2.45	0.009
PEEP>5 cmH_2O	1.08	0.66–1.73	0.758
Tidal volume >700 ml	2.55	1.67–3.89	<0.001

[a] Per unit of measurement (10 ml/cmH_2O Crs; 10 mmHg of PaO_2/FIO_2, one unit of SAPS II score, 1 year of age)

teria for ARDS, the outcome assessment was based solely on the investigator's interpretation of chest radiographs, which is known to lack sufficient precision [12]. Although study investigators at each of the centers independently reviewed the radiographs according to specified guidelines, systematic quality control was not performed. The absence of recorded height represents a major limitation preventing us from calculating tidal volumes according to lung size (predicted body weight). However, measured tidal volumes of 700 ml or more correspond to tidal volumes that are higher then 10 ml/kg predicted body weight in all but very tall men [8, 9]. Moreover, potential differences in body mass index could have influenced measurements of respiratory system compliance as well as chest radiographic readings. Actual weight, however, was similar between the groups (Table 1). Lung mechanics (peak and plateau pressures) were recorded by study investigators at multiple centers. This could have resulted in significant variability in the equipment, sedation, and paralysis and inconsistent recognition of patient-ventilator interactions and dynamic hyperinflation (auto-PEEP). Moreover, although we assume random variability in practice, we cannot exclude the possibility that higher tidal volumes were chosen purposefully to correct underlying hypoxemia, acidosis, or increased respiratory drive and minute ventilation requirement. Finally, the information about some important ARDS risk factors, such as massive transfusion and drug overdose, was not collected as the part of international study increasing the chance for residual confounding by unmeasured variables [3, 9]. As our analysis was based on single daily values of tidal volume, peak airway pressure, and PEEP, it important to emphasize that we were not able precisely to determine cumulative exposure to potentially harmful settings. However, the mean difference in day 1 vs. day 2 tidal volume was not statistically significant (666 vs. 641 ml, p=0.34).

Notwithstanding these limitations, our data suggest that the development of ARDS in mechanically ventilated patients is not only associated with underlying illness (pneumonia, trauma, SAPS, PaO_2/FIO_2) but also with interventions, specifically large tidal volume ventilator settings. While the increase in peak and plateau airway pressure at the onset of mechanical ventilation may simply represent stiffer lung ("smaller baby lung") or chest wall in a patient who is going to develop ARDS 48 h later, our data argue against this as a sole explanation. Neither static nor dynamic respiratory system compliance were initially decreased in patients who subsequently developed ARDS. Indeed, initial static respiratory system compliance was actually better in patients who subsequently developed ARDS than in those who did not. This observation and the fact that initial tidal volumes were independently associated with development of ARDS even when adjusted for the baseline hypoxemia and static respiratory system compliance suggest that ventilator settings, and large tidal volume in particular, are instrumental in the pathogenesis of this syndrome. Although no particular threshold values were apparent, the proportion of ARDS increased with the very high values of tidal volume (>700 ml) and peak airway pressure (>30 cmH_2O; Fig. 1, Table 3).

While there is a little controversy that high tidal volume is the most important risk factor for development of ventilator-induced lung injury, the importance of PEEP settings is not fully understood [5]. While many researchers routinely use higher PEEP settings to improve oxygenation and prevent atelectasis, a recent large randomized trial failed to reveal any outcome benefit [13]. The association between higher PEEP settings and development of ARDS in our study is most likely a reflection of providers' attempt to improve oxygenation in patients who were going to develop ARDS anyway. When adjusted for the initial static respiratory system compliance PEEP settings were not significantly associated with the development of ARDS.

In contrast to our single-center study, data on blood product transfusion were not collected in the international study. We can speculate that the association of trauma and late-onset ARDS reflects a large number of blood product transfusions given to these patients [3, 14]. Better prognosis of ARDS associated with trauma noted in a recent prospective study are thought in part to be due to a high incidence or transfusion-related lung injury in this patient population [15]. The association between younger age and the development of ARDS, although perhaps due to chance alone, is possible to reflect the influence of unmeasured confounding variables, such as transfusion, drug overdose, or the increased respiratory drive prompting the use of higher tidal volumes. The lower incidence (6%) of ARDS in this study than that in a single center study (17%) [9] may be related to a different as-

certainment (as the development of ARDS was not the primary outcome in the international study, some cases are likely to have been missed) and possibly to a different patient population admitted to a tertiary referral center in our single-center study.

In conclusion, ARDS is a relatively common complication in patients receiving mechanical ventilation for 48 h or more. The initial ventilator settings, in particular large tidal volume, are associated with the development of ARDS, suggesting that the way in which we ventilate our patients plays a role in the development of this syndrome. The clinical significance of this association remains to be tested in prospective studies.

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