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Pulmonary mechanics and mortality in mechanically ventilated patients without acute respiratory distress syndrome: a cohort study

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Abstract

Background—Driving pressure has been proposed as a major determinant of outcome in patients with acute respiratory distress syndrome (ARDS), but there is little data examining the association between pulmonary mechanics, include driving pressure, and outcomes in mechanically ventilated patients without ARDS.

Methods—Secondary analysis from 1,705 mechanically ventilated patients enrolled in a clinical study that examined outcomes associated with the use of early lung-protective mechanical ventilation. The primary outcome was mortality and the secondary outcome was the incidence of ARDS. Multivariable models were constructed to: 1) define the association between pulmonary mechanics (driving pressure, plateau pressure, and compliance) and mortality; and 2) evaluate if driving pressure contributed information beyond that provided by other pulmonary mechanics.

Results—The mortality rate for the entire cohort was 26.0%. Compared with survivors, non-survivors had significantly higher driving pressure [15.9 (5.4) vs. 14.9 (4.4), $p = 0.005$] and plateau pressure [21.4 (5.7) vs. 20.4 (4.6)], $p = 0.001$. Driving pressure was independently associated with mortality [adjusted OR, 1.04 (1.01 – 1.07)]. Models related to plateau pressure

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Conflicts of Interest

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also revealed an independent association with mortality, with similar effect size and interval estimates as driving pressure. There were 152 patients that progressed to ARDS (8.9%). Along with driving pressure and plateau pressure, mechanical power [adjusted OR, 1.03 (1.00 – 1.06)] was also independently associated with ARDS development

Conclusions—In mechanically ventilated patients, driving pressure and plateau pressure are risk factors for mortality and ARDS, and provide similar information. Mechanical power is also a risk factor for ARDS.

Keywords

driving pressure; pulmonary mechanics; mechanical ventilation; ARDS

INTRODUCTION

Lung injury during mechanical ventilation depends upon what the ventilator delivers to the lung and the characteristics of the lung itself(1). Key elements of ventilator-associated lung injury (VALI) include transalveolar pressure and lung volume, and heterogeneity in ventilation and regional overdistention(2). A lung-protective ventilation strategy aims to limit derecruitment injury while also limiting volume, inflation pressure, and end-inspiratory stretch(2). At the bedside, the basic tenets of lung-protection have involved: 1) lower tidal volume and inspiratory plateau pressure, reducing stretch and global strain; 2) setting positive end-expiratory pressure (PEEP), with or without recruitment maneuvers, to minimize derecruitment and reduce heterogeneity (regional strain reduction); and 3) to a lesser degree, manipulation of respiratory rate and flow(3, 4).

While lung-protective ventilation improves outcome in patients with acute respiratory distress syndrome (ARDS), recent data suggests that this benefit is due to decreased driving pressure (plateau pressure minus PEEP) of the respiratory system(5, 6). As compliance of the respiratory system is a surrogate for aerated lung volume, driving pressure represents tidal volume relative to aerated lung volume, and may be a more physiologically sound approach to lung-protective ventilation(7). Retrospective analyses of large randomized trials have shown that driving pressure is a key risk for death in ARDS(5, 6). However, there is limited data on driving pressure in intensive care unit (ICU) patients without ARDS. The relative importance of driving pressure, compared to other pulmonary mechanics, in this cohort of patients is also unknown.

The study objective was to examine the association between driving pressure and outcomes in mechanically ventilated ICU patients without ARDS. To compare the relative benefit of driving pressure, we also analyzed outcomes with respect to other pulmonary mechanics (i.e. plateau pressure, compliance, and mechanical power). We hypothesized that higher driving pressure would be associated with greater mortality and a higher incidence of ARDS, and driving pressure would contribute useful independent information compared with other pulmonary mechanics.

MATERIALS AND METHODS

This was a secondary analysis of all 1,705 patients enrolled in the Lung-Protective Ventilation Initiated in the Emergency Department (LOV-ED) trial(8, 9). That investigation assessed clinical outcomes associated with the implementation of early lung-protective mechanical ventilation. The primary inclusion criteria were adult ICU patients that presented to the ED and required mechanical ventilation through an endotracheal tube. ARDS was defined according to the Berlin definition and systematically adjudicated in a blinded fashion(10). The LOV-ED trial identified a reduction in the incidence of ARDS as well as mortality, and an increase in ventilator-free days, associated with the intervention. Approval was obtained from the Human Research Protection Office.

Assessments and Outcome Measures

For the present analysis, pertinent variables from the primary study were obtained from the data set. These included baseline demographics, comorbid conditions, illness severity, ventilator settings and airway pressures. For the purposes of this analysis, ventilator settings averaged over the first day are reported. Calculated ventilator variables included driving pressure (plateau pressure – PEEP), static compliance of the respiratory system [tidal volume/(plateau pressure – PEEP)]; mechanical power was expressed in joules per minute and calculated using the equation from Gattinoni et al. [$0.098 * \text{tidal volume} * \text{respiratory rate} (P_{\text{peak}} - \frac{1}{2} * \text{driving pressure})(1)$].

Patients were followed until hospital discharge or death. The primary outcome was hospital mortality. The incidence of ARDS was analyzed as a secondary outcome.

Statistical Analysis

Descriptive statistics, including counts and percentages, mean (standard deviation [SD]), and median (interquartile range [IQR]) were used to assess patient characteristics. To assess outcome predictors, categorical variables were compared using chi-square test. Continuous variables were compared using independent samples t-test or Mann-Whitney U test.

To evaluate mortality as a function of driving pressure, a backward, stepwise multivariable logistic regression model was used. Variables with clinically relevant differences that were statistically significant in univariate analysis at $P \leq 0.20$ were candidates for model inclusion. The intervention group assignment from the primary trial was *a priori* chosen to be entered into the model. Variables for model inclusion or exclusion were selected based on significance level of 0.10 for entry and removal. Model goodness of fit was assessed with the Hosmer-Lemeshow test and by examining residuals. Adjusted odds ratios (OR) and 95% confidence intervals (CI) are reported for variables in the multivariable model, adjusted for all model variables. Tests were two-tailed, and a p value <0.05 was statistically significant.

As driving pressure, plateau pressure, and compliance are mathematically and physiologically linked, statistical collinearity was expected and confirmed. To evaluate if driving pressure contributed information beyond that provided by other pulmonary mechanics, we *a priori* planned to construct and compare separate logistic regression models for each parameter, as well as for PEEP. Mechanical power was not analyzed in a

multivariable model, given a univariate statistical difference between survivors and non-survivors ($p > 0.20$). In a separate analysis to further examine if the information provided by driving pressure conferred independent predictive information on mortality, the other ventilator variables were added into the model that had driving pressure as a pre-existing covariate.

For the secondary outcome of ARDS, a similar statistical approach was used. Also, as mechanical power was significantly higher in patients developing ARDS, a multivariable model was constructed to examine the association between mechanical power and ARDS development.

RESULTS

A total of 1,705 patients were included in the study. There were 443 non-survivors, resulting in a mortality rate for the entire cohort of 26.0%. The median time to death (in days) for non-survivors was hospital day 4.5 (2.1 – 9.9). Baseline characteristics between survivors and non-survivors are presented in Table 1.

Day 1 ventilator settings are presented in Table 2. Compared with survivors, non-survivors had significantly higher driving pressure [15.9 (5.4) vs. 14.9 (4.4), $p = 0.005$] and plateau pressure [21.4 (5.7) vs. 20.4 (4.6), $p = 0.001$]. Figure 1 displays the unadjusted mortality across the tertiles of driving pressure, plateau pressure, and compliance. Though no distinct threshold was seen, mortality increased across tertiles of driving pressure and plateau pressure.

Primary analysis of mortality and independent predictive information

Table 3 displays the multivariable logistic regression model related to driving pressure. After adjusting for all identified significant confounders, driving pressure was independently associated with mortality [adjusted OR, 1.04 (1.01 – 1.07)].

Separate logistic regression models were constructed for plateau pressure, compliance, and PEEP (Supplemental Digital Content 1, Supplemental Table 1). For the model related to plateau pressure, the predictors of outcome were the same as for driving pressure. Plateau pressure was also independently associated with mortality with the same effect size and similar interval estimate as driving pressure [adjusted OR, 1.04 (1.02 – 1.07)].

Plateau pressure, compliance, and PEEP were added separately as covariates to the driving pressure model (Supplemental Digital Content 1, Supplemental Table 2)(6). In this model, plateau pressure conferred independent predictive information [adjusted OR, 1.04 (1.02 – 1.07)], while driving pressure was no longer significantly associated with mortality.

Secondary outcome

There were 152 patients that progressed to ARDS after admission (8.9%). Baseline characteristics and ventilator variables, according to ARDS status, are presented in Supplemental Digital Content 3, Supplemental Table 3. Compared to patients without ARDS, those who progressed to ARDS had significantly higher driving pressure [18.1 (5.2)

vs. 14.9 (4.6), $p < 0.001$], plateau pressure [24.9 (5.5) vs. 20.3 (4.7), $p < 0.001$], and mechanical power [17.5 (6.1) vs. 15.7 (6.0), $p = 0.001$]. Supplemental Digital Content 4, Supplemental Table 4 displays the multivariable logistic regression models for ARDS. After adjusting for all identified significant confounders, driving pressure was independently associated with ARDS development [adjusted OR, 1.08 (1.04 – 1.12)]. Separate multivariable models also revealed that plateau pressure [adjusted OR, 1.12 (1.08 – 1.17)], and mechanical power [adjusted OR, 1.03 (1.00 – 1.06)] were independently associated with ARDS development.

Figure 2 displays the unadjusted rate of ARDS across the tertiles of driving pressure, plateau pressure, compliance, and mechanical power. ARDS incidence increased across tertiles, with a steep increase between tertiles two and three.

DISCUSSION

The main components of lung-protective ventilation address tidal volume, inspiratory plateau pressure, and PEEP. Manipulation of each, along with rate and flow, can attenuate VALI(2). However, limitations exist for each element of this lung-protective bundle. Scaling tidal volume to PBW can be an imprecise estimate of the functional lung volume available for gas exchange(11). Inspiratory plateau pressure does not consider the contribution of the chest wall to respiratory system compliance, and therefore can be an inaccurate surrogate of true transalveolar stretch, especially in the setting of increased pleural pressure(2). While PEEP recruits and stabilizes alveolar units, it can also overdistend and contribute to VALI(12). Therefore, novel and more individualized approaches to lung-protection are needed and could improve outcome. Given the recent data suggesting that driving pressure is a principal determinant of mortality risk in patients with ARDS, but a lack of data in patients without ARDS, the primary hypothesis of the current analysis focused on driving pressure in a non-ARDS cohort. The results of this study expand upon the potential use of driving pressure to guide ventilator settings and prevent clinical lung injury. The primary findings were: 1) driving pressure is associated with hospital mortality and ARDS development; 2) the information provided by driving pressure and plateau pressure is largely redundant; 3) across tertiles of pulmonary mechanics, both hospital mortality and ARDS incidence increase; and 4) mechanical power is associated with the development of ARDS.

The majority of data regarding driving pressure comes from patients with established ARDS or from the operating room (5, 6, 13). In secondary analyses of randomized trials of ARDS patients, driving pressure was independently associated with mortality, and a meta-analysis of patients mechanically ventilated for general anesthesia, driving pressure was associated with the development of postoperative pulmonary complications(5, 6, 13). Our results suggest that in mechanically ventilated ICU patients without ARDS, targeting driving pressure could potentially improve outcome.

However, the increased benefit afforded by targeting driving pressure in this cohort of patients without ARDS is unclear. There is conflicting data regarding the additive prognostic benefit of driving pressure beyond other pulmonary mechanics, such as plateau pressure and compliance, in patients with established ARDS. Amato et al. concluded that driving pressure

was the ventilator variable most significantly associated with mortality and contributed independent information(5). Guerin et al. also concluded that driving pressure was associated with mortality, but contributed the same information as plateau pressure during lung-protective ventilation(6). Finally, plateau pressure was found to predict mortality better than driving pressure in a study from Villar et al(14). In this current cohort of non-ARDS patients, while the results expand upon the role of driving pressure in mechanically ventilated patients without ARDS, its relative contribution beyond inspiratory plateau pressure is open to question. Increases in mortality across tertiles were nearly identical for driving pressure and plateau pressure, and separate multivariable models produced nearly identical results. Furthermore, only plateau pressure conferred independent predictive information to the survival model when driving pressure was a pre-existing covariate. Our data suggest that the information provided by each parameter may be redundant in non-ARDS patients. The extent to which targeting driving pressure as a primary therapeutic endpoint to improve outcome needs investigated further.

ARDS was analyzed as a secondary outcome as it is in the causal pathway between VALI and mortality. An intervention that reduces VALI should theoretically reduce both ARDS incidence and mortality. The results of our ARDS analysis were consistent with the primary analysis of mortality, showing both driving pressure and plateau pressure were independently associated with ARDS incidence.

Furthermore, mechanical power was also associated with ARDS development and is an interesting finding. Mechanical power is the energy load transferred from the ventilator to the lung parenchyma, and is a composite variable determined by the ventilator-related contributors to lung injury (i.e. pressure, volume, rate, flow)(1). In an experimental model, a mechanical power of approximately 12 joules per minute was found to be a threshold above which VALI occurred (15). This threshold value was also demonstrated to be associated with mortality in a clinical study of ARDS patients receiving lung-protective ventilation(6). In our present study, those patients progressing to ARDS had a mean mechanical power of 17.5 joules per minute on day 1 of mechanical ventilation. There was also an increase in the incidence of ARDS when comparing mechanical power in tertiles 1 (below threshold value of 12 joules per minute), with that in tertiles 2 and 3 (above power threshold). Our data suggest that mechanical power could be a novel target to prevent ARDS, but needs confirmed with larger clinical trials.

Limitations

There are several important limitations to consider. This is an observational study and only describes associations. The pulmonary mechanics investigated in this study are highly correlated (mathematically, physiologically, and statistically), so any results that demonstrate a lack of additive benefit of one parameter over another should not be surprising. Prior investigations in this area have all used different statistical methodology to untangle the independent and/or additive contribution that these pulmonary mechanics may have on outcome (5, 6, 14, 16). Without a prospective, randomized trial it is impossible to say if limiting driving pressure to reduce VALI matters more than targeting other variables at the bedside. Furthermore, most patients were on a PEEP of 5 cm H₂O, which is congruent with

prior epidemiological studies of mechanically ventilated patients without ARDS (16, 17). However, it may limit the ability to detect differences in the predictive ability of driving pressure versus plateau pressure, since driving pressure equals plateau pressure minus PEEP. Our results may temper the enthusiasm for the use of driving pressure to improve outcome, but this question cannot be answered under the auspice of an observational study. Prior investigations on driving pressure excluded patients with respiratory rates that exceeded set ventilator rates. It is difficult to interpret driving pressure in the setting of active respirations; it is unknown how spontaneous respirations affected the true correlation between driving pressure and transalveolar stretch in this study. However, our results are consistent with prior investigations in ARDS patients and those in the operating room, with similar effect sizes (5, 6, 13). This study only reflects driving pressure of the respiratory system, and not driving pressure of the lung. We have no knowledge of the chest wall's contribution to our observed driving pressure, which can be substantial (18). The observed differences between pulmonary mechanics in this study were significant but clinically small. This is similar to previous work in which a mean difference of 1 cm H₂O existed between ARDS survivors and non-survivors, and a median difference of 1.5 cm H₂O existed between mechanically ventilated patients that did and did not progress to ARDS (6, 16). This fact brings into question the clinical implications with respect to adjusting ventilator settings at the bedside, and these findings are to be interpreted with caution. Finally, we did not capture the exact cause of death in these patients. While we have no reason to suspect that our cohort's deaths would be different than the most common causes of death in critically ill patients, namely multi-organ dysfunction and limitations of support, it is possible that there was imbalance in non-VALI related causes of death between survivors and non-survivors.

To conclude, in mechanically ventilated patients without ARDS, driving pressure and plateau pressure are risk factors for mortality and ARDS, and provide similar information. Mechanical power is also a risk factor for ARDS.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Unadjusted mortality across tertiles of driving pressure, plateau pressure, and compliance. The bars represent standard error. * $P < 0.05$ mortality comparison, versus the first quintile (chi-square).

Figure 2.

Unadjusted rate of ARDS across tertiles of driving pressure, plateau pressure, compliance, and mechanical power.

The bars represent standard error. * $P < 0.05$ ARDS comparison, versus the first quintile (chi-square).

Table 1

Characteristics of the study cohort according to mortality

Variables	All (n= 1,705)	Survivors (n= 1,262)	Non-survivors (n= 443)	P value
Age (yr)	58.8 (16.9)	57.2 (16.9)	63.4 (16.2)	<0.001
Male, n (%)	931 (54.6)	682 (54.0)	249 (56.2)	0.43
Race, n (%)				
Caucasian	710 (41.6)	517 (41.0)	193 (43.6)	0.34
African-American	978 (57.4)	736 (58.3)	242 (54.6)	0.18
Other	17 (1.0)	9 (0.7)	8 (1.8)	0.05
Comorbidities, n (%)				
Diabetes	593 (34.8)	442 (35.0)	151 (34.1)	0.72
Cirrhosis	125 (7.3)	84 (6.7)	41 (9.3)	0.07
CHF	404 (23.7)	304 (24.1)	100 (22.6)	0.52
Dialysis	138 (8.1)	105 (8.3)	33 (7.4)	0.56
COPD	426 (25.0)	330 (26.1)	96 (21.7)	0.06
Immunosuppression	161 (9.4)	118 (9.4)	43 (9.7)	0.83
Reason for mechanical ventilation, n (%)				
Sepsis	474 (27.8)	341 (27.0)	133 (30.0)	0.23
Medical	456 (26.7)	344 (27.3)	112 (25.3)	0.42
Trauma	392 (23.0)	276 (21.9)	116 (26.2)	0.06
Other	383 (22.5)	301 (23.9)	82 (18.5)	0.02
BMI	28.9 (10.1)	29.4 (10.6)	27.6 (8.3)	0.001
SBP	128.4 (41.3)	128.3 (39.2)	128.8 (46.8)	0.86
Lactate	2.4 (1.5 – 4.2)	2.2 (1.4 – 3.7)	3.5 (2.0 – 6.5)	<0.001
APACHE II *	15.4 (7.0)	14.9 (7.0)	16.8 (6.7)	<0.001
Sepsis, n (%)	604 (35.4)	433 (34.3)	171 (38.6)	0.10

Variables	All (n= 1,705)	Survivors (n= 1,262)	Non-survivors (n= 443)	P value
Fluid balance first week (liters)	2.8 (7.1)	1.8 (6.8)	5.8 (7.3)	<0.001
ED LPV as treatment group, n (%)	513 (30.1)	408 (32.3)	105 (23.7)	0.001

CHF: congestive heart failure; COPD: chronic obstructive pulmonary disease; BMI: body mass index; SBP: systolic blood pressure; APACHE: acute physiology and chronic health evaluation; ED: emergency department; LPV: lung-protective ventilation

Continuous variables are reported as mean (standard deviation) and median (interquartile range).

* modified score, which excludes Glasgow Coma Scale

Table 2

Ventilator variables on day 1 according to mortality

Variable	All (n= 1,705)	Survivors (n= 1,262)	Non-survivors (n= 443)	P value
Tidal volume, mL	507.2 (79.0)	506.5 (77.9)	509.3 (82.0)	0.520
Tidal volume, mL/kg PBW	8.0 (1.5)	8.0 (1.4)	8.0 (1.5)	0.721
PEEP, cm H ₂ O	5 (5 – 5)	5 (5 – 5)	5 (5 – 6)	0.059
F _I O ₂ %	44.0 (40.0 – 56.0)	42.0 (40.0 – 54.0)	48.0 (40.0 – 64.0)	<0.001
Respiratory rate	16.9 (4.3)	17.0 (4.3)	16.6 (4.2)	0.170
Peak pressure, cm H ₂ O	26.6 (6.4)	26.5 (6.1)	27.0 (7.0)	0.143
Plateau pressure, cmH ₂ O	20.7 (4.9)	20.4 (4.6)	21.4 (5.7)	0.001
Mean airway pressure, cmH ₂ O	11.3 (2.5)	11.1 (2.3)	11.9 (3.0)	0.001
Compliance respiratory system, mL/cm H ₂ O	37.8(12.4)	38.0 (12.1)	37.1 (13.3)	0.183
Driving Pressure, cm H ₂ O	15.2 (4.7)	14.9 (4.4)	15.9 (5.4)	0.005
Mechanical power, joules/min	15.9 (6.0)	15.9 (6.0)	15.8 (6.1)	0.794
pH	7.36 (0.09)	7.36 (0.08)	7.33 (0.10)	<0.001
P _a O ₂	132.4 (61.7)	140.3 (61.2)	146.4 (62.9)	0.077
P _a O ₂ :F _I O ₂	293.6 (129.6)	309.4 (127.0)	300.8 (136.5)	0.233

PBW: predicted body weight; PEEP: positive end-expiratory pressure; F_IO₂: fraction of inspired oxygen; P_aO₂: partial pressure of arterial oxygen.

Continuous variables are reported as mean (standard deviation) and median (interquartile range).

Table 3
Multivariable logistic regression analysis with hospital mortality as the dependent variable.

Variables	aOR	95% CI	P-value
Age	1.03	1.02 – 1.03	<0.001
Chronic obstructive pulmonary disease	0.74	0.54 – 0.99	0.048
Body mass index	0.99	0.97 – 1.00	0.047
Lactate	1.16	1.12 – 1.21	<0.001
APACHE II	1.02	1.00 – 1.05	0.023
Fluid balance first week	1.01	1.00 – 1.02	<0.001
ED lung-protection group	0.54	0.40 – 0.73	<0.001
Driving pressure	1.04	1.01 – 1.07	0.006

Removed from model for non-significance: cirrhosis (p = 0.51), sepsis (p= 0.41), arterial pH (0.50).
APACHE: acute physiology and chronic health evaluation; ED: emergency department