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Positive End-Expiratory Pressure and Respiratory Rate Modify the Association of Mechanical Power and Driving Pressure With Mortality Among Patients With Acute Respiratory Distress Syndrome

IMPORTANCE: Mechanical power and driving pressure have known associations with survival for patients with acute respiratory distress syndrome.

OBJECTIVES: To further understand the relative importance of mechanical power and driving pressure as clinical targets for ventilator management.

DESIGN: Secondary observational analysis of randomized clinical trial data.

SETTING AND PARTICIPANTS: Patients with the acute respiratory distress syndrome from three Acute Respiratory Distress Syndrome Network trials.

MAIN OUTCOMES AND MEASURES: After adjusting for patient severity in a multivariate Cox proportional hazards model, we examined the relative association of driving pressure and mechanical power with hospital mortality. Among 2,410 patients, the relationship between driving pressure and mechanical power with mortality was modified by respiratory rate, positive end-expiratory pressure, and flow.

RESULTS: Among patients with low respiratory rate (< 26), only power was significantly associated with mortality (power [hazard ratio, 1.82; 95% CI, 1.41–2.35; $p < 0.001$] vs driving pressure [hazard ratio, 1.01; 95% CI, 0.84–1.21; $p = 0.95$]), while among patients with high respiratory rate, neither was associated with mortality. Both power and driving pressure were associated with mortality at high airway flow (power [hazard ratio, 1.28; 95% CI, 1.15–1.43; $p < 0.001$] vs driving pressure [hazard ratio, 1.15; 95% CI, 1.01–1.30; $p = 0.041$]) and neither at low flow. At low positive end-expiratory pressure, neither was associated with mortality, whereas at high positive end-expiratory pressure (≥ 10 cm H₂O), only power was significantly associated with mortality (power [hazard ratio, 1.22; 95% CI, 1.09–1.37; $p < 0.001$] vs driving pressure [hazard ratio, 1.16; 95% CI, 0.99–1.35; $p = 0.059$]).

CONCLUSIONS AND RELEVANCE: The relationship between mechanical power and driving pressure with mortality differed within severity subgroups defined by positive end-expiratory pressure, respiratory rate, and airway flow.

KEY WORDS: acute respiratory distress syndrome; driving pressure; mechanical power; mechanical ventilation; ventilator-induced lung injury

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Mechanical power and driving pressure (ΔP) have been shown in observational studies to be independently associated with hospital mortality (1–3), but the way in which mechanical power and ΔP should inform the design of prospective trials is not known. It is not known 1) which clinically modifiable elements of power are most important or 2) under what clinical conditions mechanical power may be a more useful measure of

risk. Positive end-expiratory pressure (PEEP) (4, 5) and respiratory rate (RR) (6) are two potentially modifiable individual ventilator settings that have each been associated with mortality in previous studies. If the strength of the relationship between ΔP or mechanical power with mortality is modified at different values of PEEP or RR, it would suggest that prospective trials should consider these additional parameters in trials of ΔP or mechanical power (7).

To understand the relative importance of these two measures of risk (ΔP and mechanical power) under different clinical conditions, we examined the relationship of power and ΔP with mortality at different RRs, airway flow, and PEEP using pooled patients from three randomized controlled trials of acute respiratory distress syndrome (ARDS). Additionally, we asked which of the clinically modifiable variables within the power equation—that is, variables amenable to adjustment in a clinical trial—were most highly associated with mortality.

METHODS

Our analysis is reported according to the Strengthening of Reporting of Observational Studies in Epidemiology guidelines (**Online Data Supplement**, <http://links.lww.com/CCX/A854>) (8).

Data Source

Data and approval were obtained from the Biologic Specimen and Data Repository Information Coordinating Center of the National Heart, Lung, and Blood Institute (NHLBI) on March 8, 2018. This study was approved by the University of Utah Institutional Review Board (IRB) under IRB Number 00093669 on July 12, 2016.

Study Population

This observational cohort study included the 2,452 patients enrolled within three randomized clinical trials (RCTs) from NHLBI ARDS Network: Lower versus higher tidal volume (ARMA), ketoconazole treatment, and lisofylline treatment (9); Assessment of Low tidal Volume and elevated End-expiratory volume to Obviate Lung Injury (ALVEOLI) (4); and Fluid and Catheter Treatment Trial (FACTT) which enrolled patients from March 1996 to October 2005. Per our previous analysis, 1) we excluded patients who died or were weaned from mechanical

ventilation prior to 24 hours after randomization, received pressure support ventilation during the period of analysis, or had RRs higher than the ventilator settings or inconsistent data and 2) performed these analyses only within retained patients who were not making respiratory efforts (**Fig. E1**, <http://links.lww.com/CCX/A854>). As power includes RR, the association with mortality may be influenced by active respiratory efforts. We pooled patients from all three trials to increase sample size.

Study Variables and Outcomes

The primary outcome was 60-day hospital survival. The primary predictors were ΔP and respiratory system mechanical power at study day 1. We transformed the distributions of ΔP and mechanical power to mean 2.46 and SD 1, to compare the predictive values of ΔP and mechanical power. Standardizing to a mean of 2.46 rather than 0 (which is typical) ensured that all values were positive. To facilitate comparisons with previous publications (1, 2), data from patients who were discharged before day 60 were censored at day 60 as were the patients considered to be alive at day 60. Patient-level data for analysis across all studies included the variables age, sex, PaO_2/FiO_2 ratio, arterial pH, ventilator settings, the Acute Physiology and Chronic Health Evaluation (APACHE) III score, and an indicator variable for the trial in which the patient had been enrolled. The APACHE III score was either available within the dataset or calculated for analysis. ΔP (in cm H_2O) was calculated as (Plateau pressure (P_{PLAT})–PEEP) (2). Mechanical power applied to the respiratory system (in joules/min) was calculated using the simplified formula originally published by Gattinoni et al (10) that is mathematically equivalent to the extended formula (Online Data Supplement, <http://links.lww.com/CCX/A853>): $Power = (0.098 \times RR \times V_T \times [Peak\ pressure\ (P_{PEAK}) - (\frac{1}{2} \times P_{PLAT} - PEEP)])$. As a correlate of lung size, power was normalized to respiratory system compliance (10–12). Airway flow was calculated for the purposes of analysis as (tidal volume [V_T]/inspiratory time), resulting in average airway flow over the entire inspiratory phase, rather than peak flow. We previously assessed for variable correlation and multicollinearity (1). All continuous variables were transformed to standard normal distributions (mean 0 and variance 1), to interpret their effect on mortality in SD units.

Statistical Analysis

Our primary analysis was conducted on the three ARDS trials combined to maximize statistical power. We examined the relative performance of ΔP and mechanical power for predicting mortality within different levels (strata) of RR, airway flow, and PEEP. Strata were defined based on the median value of each variable, which was used to stratify values into “high” and “low” groups (strata). We repeated the multivariable model with these subgroups and assessed for interactions. We repeated the model three times, once for RR, flow, and PEEP. The RR model included interactions between all predictors in the multivariable model with high ($\geq 26/\text{min}$) and low strata RR. Patient strata were split on the median value of the variable. We similarly repeated this modeling framework including interactions with high ($\geq 20.4\text{ L}/\text{min}$) and low strata of airway flow and high ($\text{PEEP} \geq 10\text{ cm H}_2\text{O}$) and low strata of PEEP. Hazard ratios (HRs), 95% CIs, and p values were reported for each subgroup, along with the p value for the interaction of each variable with the subgroup indicator.

As a secondary analysis, to examine whether the independent relationship of mechanical power with mortality, despite adjustment for ΔP , was due to the inclusion of additional variables, we analyzed a model in which we added these additional individual component variables to ΔP . Comparing the equations for ΔP and the original formula for mechanical power, these variables were: RR, flow, PEEP, and V_T squared. We compared four different competing prediction models. We calculated the time-dependent receiver operating characteristic (ROC) curve of these models at day 60. In order to compare the predictive accuracy of our four models, we calculated both the area under the ROC curve (AUC) and concordance statistic (C -statistic) to assess the discrimination ability of our various models. Similar to the AUC, the C -statistic is a way to quantify the predictive accuracy of the model. Further details are listed in the Supplement.

We considered p values of less than 0.05 to be statistically significant. All analysis were performed using SAS software, Version 9.4 (SAS Institute, Cary, NC).

RESULTS

After excluding ineligible patients, there were 2,410 patients for analysis among all trials (ARMA: 861;

ALVEOLI: 549; FACTT: 1,000) (Fig. E1, <http://links.lww.com/CCX/A854>). Characteristics of patients after stratification are listed in **Tables E1–E4** (<http://links.lww.com/CCX/A854>).

Respiratory Rate

Separating patients into high and low strata of RR (median RR value, 26 breaths per minute), in a model combining mechanical power and ΔP , among patients with lower RR ($\text{RR} < 26/\text{min}$) only mechanical power was associated with mortality (power [HR, 1.82; 95% CI, 1.41–2.35; $p < 0.001$] vs ΔP [HR, 1.01; 95% CI, 0.84–1.21; $p = 0.95$]), whereas among patients with higher RRs ($\text{RR} \geq 26/\text{min}$) neither was associated with mortality (ΔP [HR, 1.24; 95% CI, 1.00–1.55; $p = 0.052$] vs power [HR, 1.10; 95% CI, 0.93–1.30; $p = 0.26$]) (**Table 1**).

Airway Flow Averaged Over the Entire Cycle

After stratification on average inspiratory airway flow (median flow value: 20.4 L/min), both mechanical power and ΔP were associated with mortality at high flow ($\geq 20.4\text{ L}/\text{min}$) (power [HR, 1.28; 95% CI, 1.15–1.43; $p < 0.001$] vs ΔP [HR, 1.15; 95% CI, 1.01–1.30; $p = 0.041$]) (**Table 2**). At low flow ($< 20.4\text{ L}/\text{min}$), neither variable retained a significant relationship with mortality (power [HR, 1.18; 95% CI, 0.95–1.47; $p = 0.13$] vs ΔP [HR, 1.12; 95% CI, 0.83–1.51; $p = 0.46$]).

Positive End-Expiratory Pressure

After stratification on PEEP (median PEEP value: 10 cm H₂O), at low PEEP, neither variable was associated with mortality (ΔP [HR, 1.18; 95% CI, 0.99–1.41; $p = 0.061$] vs power [HR, 1.13; 95% CI, 0.94–1.35; $p = 0.19$]) (**Table 3**). At high PEEP ($\text{PEEP} \geq 10$), mechanical power was significantly associated with mortality (power [HR, 1.22; 95% CI, 1.09–1.37; $p < 0.001$] vs ΔP [HR, 1.16; 95% CI, 0.99–1.35; $p = 0.059$]).

Model Performance

In a secondary analysis, to test the hypothesis whether the improved performance of a multivariate Cox model with mechanical power + ΔP could be explained by the simple addition of the individual ventilatory variables bundled within the power calculation (compared with

TABLE 1.
Cox Proportional Hazard Results for the Interaction of Respiratory Rate With Driving Pressure and Mechanical Power

Variable	Low (RR < 26/min) (n = 989)		High (RR ≥ 26/min) (n = 1,005)		Interaction
	HR for Mortality (95% CI)	p	HR for Mortality (95% CI)	p	p
Age	1.52 (1.33–1.74)	< 0.001	1.54 (1.35–1.75)	< 0.001	0.90
Trial					
Lower vs higher tidal volume	Reference	–	Reference	–	–
Assessment of Low tidal Volume and elevated End-expiratory volume to Obviate Lung Injury	0.44 (0.28–0.70)	< 0.001	0.59 (0.43–0.81)	< 0.001	0.30
Fluid and Catheter Treatment Trial	0.43 (0.29–0.62)	< 0.001	0.41 (0.31–0.55)	< 0.001	0.88
Acute Physiology and Chronic Health Evaluation III	1.65 (1.42–1.91)	< 0.001	1.45 (1.28–1.65)	< 0.001	0.21
Arterial pH at entry	1.12 (0.94–1.34)	0.20	0.92 (0.81–1.05)	0.22	0.079
PaO ₂ :FiO ₂ at entry	1.04 (0.92–1.19)	0.53	0.83 (0.72–0.96)	0.015	0.023
Driving pressure	1.01 (0.84–1.21)	0.95	1.24 (1.00–1.55)	0.052	0.15
Mechanical power	1.82 (1.41–2.35)	< 0.001	1.10 (0.93–1.30)	0.26	0.001

HR = hazard ratio, RR/min = respiratory rate per minute.

TABLE 2.
Cox Proportional Hazard Results for the Interaction of Average Airway Flow With Driving Pressure and Mechanical Power

Variable	Low (< 20.4 L/min) (n = 943)		High (≥ 20.4 L/min) (n = 918)		Interaction
	HR for Mortality (95% CI)	p	HR for Mortality (95% CI)	p	p
Age	1.34 (1.15–1.56)	< 0.001	1.62 (1.44–1.83)	< 0.001	0.057
Trial					
Lower vs higher tidal volume	Reference	–	Reference	–	–
Assessment of Low tidal Volume and elevated End-expiratory volume to Obviate Lung Injury	0.71 (0.20–2.52)	0.60	0.60 (0.39–0.92)	0.019	0.81
Fluid and Catheter Treatment Trial	0.56 (0.16–1.95)	0.37	0.48 (0.33–0.71)	< 0.001	0.80
Acute Physiology and Chronic Health Evaluation III	2.00 (1.70–2.34)	< 0.001	1.33 (1.17–1.51)	< 0.001	< 0.001
Arterial pH at entry	1.04 (0.88–1.22)	0.68	0.94 (0.82–1.08)	0.39	0.39
PaO ₂ :FiO ₂ at entry	1.04 (0.89–1.21)	0.64	0.81 (0.71–0.93)	0.003	0.021
Driving pressure	1.12 (0.83–1.51)	0.46	1.15 (1.01–1.30)	0.041	0.90
Mechanical power	1.18 (0.95–1.47)	0.13	1.28 (1.15–1.43)	< 0.001	0.51

HR = hazard ratio, L/min = liters per minute.

TABLE 3.**Cox Proportional Hazard Results for the Interaction of Positive End-Expiratory Pressure With Driving Pressure and Mechanical Power**

Variable	Low (< 10 cm H ₂ O) (n = 879)		High (≥ 10 cm H ₂ O) (n = 1,115)		Interaction
	HR for Mortality (95% CI)	p	HR for Mortality (95% CI)	p	p
Age	1.52 (1.29–1.78)	< 0.001	1.51 (1.35–1.70)	< 0.001	0.98
Trial					
Lower vs higher tidal volume	Reference	–	Reference	–	–
Assessment of Low tidal Volume and elevated End-expiratory volume to Obviate Lung Injury	0.53 (0.31–0.91)	0.021	0.52 (0.39–0.70)	< 0.001	0.97
Fluid and Catheter Treatment Trial	0.48 (0.34–0.70)	< 0.001	0.40 (0.30–0.53)	< 0.001	0.41
Acute Physiology and Chronic Health Evaluation III	1.50 (1.28–1.76)	< 0.001	1.57 (1.39–1.77)	< 0.001	0.67
Arterial pH at entry	0.86 (0.72–1.02)	0.086	1.07 (0.94–1.21)	0.32	0.051
Pao ₂ :Fio ₂ at entry	1.07 (0.92–1.23)	0.38	0.93 (0.80–1.08)	0.34	0.19
Driving pressure	1.18 (0.99–1.41)	0.061	1.16 (0.99–1.35)	0.059	0.85
Mechanical power	1.13 (0.94–1.35)	0.19	1.22 (1.09–1.37)	< 0.001	0.46

HR = hazard ratio.

the calculation of ΔP), we examined a model with ΔP alone, and then manually added the individual components of RR, flow, PEEP, and $(V_T)^{\text{quared}}$ to this model. This combined model performed significantly better than ΔP alone (*C*-difference = 0.0135; *SE* = 0.0063; *p* = 0.032) (Tables 4 and 5), but there was minimal difference against a model of mechanical power + ΔP (*C*-difference = 0.0061; *SE* = 0.049; *p* = 0.21), confirming the hypothesis.

DISCUSSION

We found that mechanical power and ΔP have different strengths of association with mortality across different strata of RR, flow, and PEEP, for mechanically ventilated patients with ARDS. Our findings suggest that ΔP and mechanical power are differently important among different patient severity subgroups. We specifically found that below a RR of 26, or above a

TABLE 4.**Area Under the Receiver Operating Characteristic Curves and Concordance Statistics (Predictive Ability) for the Four Competing Prediction Models**

Model	Area Under the Receiver Operating Characteristic Curve	Concordance Statistic
Driving pressure + mechanical power	0.7015	0.7301
Driving pressure	0.7175	0.7228
Mechanical power	0.7090	0.7316
Driving pressure + respiratory rate + flow + positive end-expiratory pressure + (tidal volume) ²	0.7253	0.7363

Note: All models are adjusted for the base covariates of age, trial, Acute Physiology and Chronic Health Evaluation III score, arterial pH at baseline, and Pao₂:Fio₂ at baseline.

TABLE 5.
Comparison of Pairwise Differences in the Concordance Statistics for Selected Models

Model 1	Model 2	C-Difference (SE)	p
Driving pressure + respiratory rate + flow + PEEP + (tidal volume) ²	Driving pressure + mechanical power	0.0061 (0.0049)	0.21
Driving pressure + respiratory rate + flow + PEEP + (tidal volume) ²	Driving pressure	0.0135 (0.0063)	0.032
Driving pressure + mechanical power	Driving pressure	0.0074 (0.0037)	0.047

PEEP = positive end-expiratory pressure.

Note: All models are adjusted for the base covariates of age, trial, Acute Physiology and Chronic Health Evaluation III score, arterial pH at baseline, and $\text{PaO}_2/\text{FiO}_2$ at baseline.

PEEP of 10, mechanical power has a stronger relationship with mortality than does ΔP .

Our data point to patient subgroups in which minimizing ventilator power may be more important than minimizing ΔP . It has been previously shown among patients with extracorporeal support, for instance, that RR reductions are associated with less lung injury (6, 13), and that rising RRs temporally associate with decreasing $\text{PaO}_2/\text{FiO}_2$ (14). While we recognize that, without extracorporeal support, ventilator settings such as PEEP and RR often reflect the severity of ARDS, it may be clinically relevant to widen the current standards of lung-protective ventilation to include further relevant variables, such as RR and PEEP, in the broader context of the mechanical power (15). Trials could usefully compare standard ventilator management strategies to strategies differentially emphasizing power versus ΔP optimization in the subgroups of patients with higher RR or lower PEEP.

Our findings also support the observation that mechanical power's statistically significant relationship with mortality, despite adjusting for ΔP (1), may be due to the fact that mechanical power includes all of the components of ΔP plus adds clinically modifiable parameters associated with ventilator-induced lung injury (VILI), such as flow and RR (16–19). Illustrating this, we found that by including the individual variables that mathematically distinguish the mechanical power and ΔP equations (i.e., RR, PEEP, flow, and the square of V_T) into a multivariate model with ΔP , the model had improved discriminatory power for mortality compared with the model with ΔP alone but not the model with mechanical power alone. Together, our finding that the relationship of mechanical power and mortality was modified by RR adds further data that just as large V_T are injurious, increased frequency of

those V_T may also be injurious (20). Importantly, our findings apply only to patients who were not making respiratory efforts and, as the traditional assessment of mechanical power is only valid without respiratory efforts (14, 21), these conclusions should not be applied to spontaneously breathing patients.

Strengths of the study include its comparative analysis of power and ΔP with multivariable models within a large, generalizable cohort of ARDS, as modified by patient severity subgroups. Limitations of the study include secondary data analysis, and that we had no data on transpulmonary ΔP and mechanical power applied to the lung, which may be the most important determinant of VILI in ARDS.

CONCLUSIONS

The strong association of mechanical power with mortality in comparison to ΔP can be mathematically approximated by the addition of additional individual potentially modifiable ventilatory variables in a model with ΔP . Mechanical power's relationship with mortality is modified by RR, and is stronger than ΔP at RRs less than 26, or PEEP greater than 10, suggesting that prospective trials should consider examining ventilator strategies focused on minimizing mechanical power among patients with these settings.

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Dr. Tonna had full access to all the data in the study, takes responsibility for the integrity of the data, the accuracy of the data analysis, and the integrity of the submission as a whole, from inception to published article. Drs. Tonna, Peltan, Brown, Presson, and Keenan conceived study design; Drs. Tonna, Peltan, Brown, Presson, Herrick, and Keenan contributed to conduct of the study; Drs. Tonna, Peltan, Presson, and Herrick contributed to data acquisition and analysis; Drs. Tonna, Presson, Herrick, and Keenan drafted the work; all authors revised the article for important intellectual content, had final approval of the work to be published, and agree to be accountable for all aspects of the work.

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