Comparing the Effects of Tidal Volume, Driving Pressure, and Mechanical Power on Mortality in Trials of Lung-Protective Mechanical Ventilation

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BACKGROUND: The unifying goal of lung-protective ventilation strategies in ARDS is to minimize the strain and stress applied by mechanical ventilation to the lung to reduce ventilator-induced lung injury (VILI). The relative contributions of the magnitude and frequency of mechanical stress and the end-expiratory pressure to the development of VILI is unknown. Consequently, it is uncertain whether the risk of VILI is best quantified in terms of tidal volume (V_T), driving pressure (ΔP), or mechanical power. **METHODS:** The correlation between differences in V_T , ΔP , and mechanical power and the magnitude of mortality benefit in trials of lung-protective ventilation strategies in adult subjects with ARDS was assessed by meta-regression. Modified mechanical power was computed including PEEP ($\text{Power}_{\text{elastic}}$), excluding PEEP ($\text{Power}_{\text{dynamic}}$), and using ΔP ($\text{Power}_{\text{driving}}$). The primary analysis incorporated all included trials. A secondary subgroup analysis was restricted to trials of lower versus higher PEEP strategies. **RESULTS:** We included 9 trials involving 4,731 subjects in the analysis. Odds ratios for moderation derived from meta-regression showed that variations in V_T , ΔP , and $\text{Power}_{\text{dynamic}}$ were associated with increased mortality with odds ratios of 1.24 (95% CI 1.03–1.49), 1.31 (95% CI 1.03–1.66), and 1.37 (95% CI 1.05–1.78), respectively. In trials comparing higher versus lower PEEP strategies, $\text{Power}_{\text{elastic}}$ was increased in the higher PEEP arm (24 ± 1.7 vs 20 ± 1.5 J/min, respectively), whereas the other parameters were not affected on average by a higher PEEP ventilation strategy. **CONCLUSIONS:** In trials of lung-protective ventilation strategies, V_T , ΔP , $\text{Power}_{\text{elastic}}$, $\text{Power}_{\text{dynamic}}$, and $\text{Power}_{\text{driving}}$ exhibited similar moderation of treatment effect on mortality. In this study, modified mechanical power did not add important information on the risk of death from VILI in comparison to V_T or ΔP . *Key words:* ARDS; VILI; mechanical ventilation; mechanical power; lung-protective strategies; meta-regression. [Respir Care 2021;66(2):221–227. © 2021 Daedalus Enterprises]

Introduction

The unifying goal of lung-protective ventilation strategies in ARDS is to minimize the strain and stress applied by mechanical ventilation to the injured lung,

thereby reducing ventilator-induced lung injury (VILI).¹ Compelling evidence gathered in the last 20 years has shown that mechanical ventilation with low tidal volume (V_T) improves survival of patients with ARDS.^{2,3} Recently, driving pressure (ΔP , normalizes V_T for compliance, a surrogate of the size of the “baby lung”) has

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been shown to be a better predictor of mortality than V_T .⁴ The exact mechanism through which these parameters exert injury on the lung, however, is not clear.⁵ Although it is widely accepted that stress and strain resulting from tidal volume and applied end-expiratory pressure play a key role in the development of VILI, additional components of the mechanical breath (ie, flow and breathing frequency) also appear to contribute to tissue damage.⁶⁻⁸

Both V_T and ΔP neglect the impact of flow and breathing frequency on the development of VILI. Mechanical power has been suggested as a summary variable that incorporates all of these parameters into a single, overarching entity. Mechanical power represents the energy applied to the respiratory system to achieve a change from resting lung volume over 1 min.⁹ In other words, it characterizes the relationship between the sum of pressures applied to the respiratory system and the respective changes in lung volume they generate, accounting for the potential influences of flow and breathing frequency as well as V_T and ΔP on VILI. The association between mechanical power and VILI is not new, and it has been demonstrated in animal experiments.¹⁰ Recently, retrospective observational studies in humans have also linked mechanical power to mortality in subjects with and without ARDS.¹¹⁻¹³ However, mechanical power also carries a number of limitations, such as its lack of adjustment to the actual functional lung size and the controversial relationship between PEEP, power, and the risk of VILI.¹⁴ It is therefore uncertain whether the risk of VILI is best quantified in terms of V_T , ΔP or, mechanical power.¹⁵

We sought to explore this question by quantifying the extent to which the effect of lung-protective ventilation on mortality can be explained by its effect on each parameter in a meta-regression of clinical trials of lung-protective ventilation strategies in ARDS.

Methods

Search Strategy and Inclusion Criteria

We consulted a recent systematic review on the use of mechanical ventilation in subjects with ARDS¹⁶ and performed a comprehensive search of MEDLINE and PubMed.

Dr Goligher has disclosed relationships with Getinge and Timpel. Dr Fan has disclosed relationships with ALung Technologies and MC3 Cardiopulmonary. Dr Brochard has disclosed relationships with Medtronic|Covidien, Air Liquide, Philips, Sentec, General Electric, and Fisher & Paykel. The other authors have disclosed no conflicts of interest.

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QUICK LOOK

Current knowledge

Tidal volume (V_T) and driving pressure (ΔP) play a key role in the development of ventilator-induced lung injury (VILI), yet additional components of the mechanical breath, such as breathing frequency, may also contribute to tissue damage. Both V_T and ΔP neglect the effect of breathing frequency on the development of VILI. Mechanical power represents the energy applied to the respiratory system to achieve a change from resting lung volume, accounting for breathing frequency and flow as well as ΔP and V_T .

What this paper contributes to our knowledge

In a meta-regression of trials evaluating lung-protective ventilation strategies in subjects with ARDS, a modified version of mechanical power did not provide additional information about the risk of death from VILI in comparison to V_T or ΔP .

The search combined Medical Subject Headings and specific key words to identify trials that evaluated different lung-protective ventilation strategies (eg, lower vs higher V_T ventilation, lower vs higher PEEP ventilation, and lung recruitment maneuvers) in adult subjects with ARDS, that reported mortality as primary end point, and provided information on the variables required to compute mechanical power on day 1 after randomization. Trials of prone positioning, neuromuscular blockade, extracorporeal life support, and nonconventional modes of ventilation such as high-frequency oscillatory ventilation were excluded because we deemed it unlikely that the mechanism of benefit in these trials could be quantified in terms of V_T , ΔP , or mechanical power. This study was performed at the Interdepartmental Division of Critical Care Medicine, University of Toronto.

Data Abstraction

Two reviewers (JD, MT) independently performed the data abstraction process using a specific data-recording form. Disagreements were resolved by consulting with a third reviewer (ECG). V_T , ΔP , and Power on day 1 in both treatment and control arms were recorded.

Mechanical Power Computation

Considering that the effect of flow in the generation of VILI is unclear because most of the energy generated

by the resistive component of the respiratory system dissipates throughout the proximal airway, we excluded airway resistance from the formula proposed by Gattinoni et al⁹ to compute a modified mechanical power ($\text{Power}_{\text{elastic}}$) based purely on elastic characteristics of the respiratory system:

$$\text{Power}_{\text{elastic}} = 0.098 \times f \times \left(\Delta V^2 \times \left[\frac{1}{2} \times \text{ELrs} \right] + \Delta V \times \text{PEEP} \right)$$

where f is breathing frequency and ELrs is the elastance of the respiratory system. To test the hypothesis that static strain (ie, PEEP-derived strain) has less of an influence in the development of VILI, we also computed modified dynamic mechanical power ($\text{Power}_{\text{dynamic}}$) by considering $\text{PEEP} = 0 \text{ cm H}_2\text{O}$ in this equation:

$$\text{Power}_{\text{dynamic}} = 0.098 \times f \times \left(\Delta V^2 \times \left[\frac{1}{2} \times \text{ELrs} \right] \right)$$

Finally, driving power ($\text{Power}_{\text{driving}}$) was calculated with the formula proposed by Marini and Jaber⁵:

$$\text{Power}_{\text{driving}} = \frac{\Delta P \times f \times V_T}{10 \times C_{\text{RS}}}$$

where C_{RS} is the compliance of the respiratory system and 10 represents a predicted population averaged normal respiratory-system compliance (0.1 L/cm H₂O) suggested by Marini and Jaber⁵ to adjust for the observed “baby lung.” Of note, individual patient respiratory-system compliance would be modified by age, gender, height and other conditions.

Statistical Analysis

The effect size of these 5 potential moderators (V_T , ΔP , $\text{Power}_{\text{elastic}}$, $\text{Power}_{\text{dynamic}}$, and $\text{Power}_{\text{driving}}$) on the magnitude of the treatment effect in each trial (odds ratio for mortality at 28 d or in the ICU, whichever is the primary outcome in the individual trial) was assessed by meta-regression of the trials identified in the systematic review. The primary analysis incorporated all included trials. Because PEEP could have a different effect on the development of VILI depending on how it modifies these parameters, a secondary subgroup analysis was restricted to trials of lower versus higher PEEP strategies. Finally, we also examined the association between each variable and the risk of death across trials using generalized linear mixed-effects regression (GLMER). All statistical analyses were conducted in R 3.4.4.

Fig. 1. Flow chart.

Results

The literature search generated 2,090 titles, of which 2,072 were excluded; 18 studies were selected for full-text review. Of these, 9 met exclusion criteria or had missing data,¹⁷⁻²⁵ for a total of 9 trials^{2,3,26-32} involving 4,731 subjects for analysis (Fig. 1). Characteristics of the selected trials are described in Table 1. We observed moderate heterogeneity between the included studies ($I^2 = 55.8\%$).

In these 9 trials, the effect of the intervention on each moderator varied widely between trials (Fig. 2). Odds ratios for moderation derived from meta-regression showed that variations in V_T , ΔP , and $\text{Power}_{\text{dynamic}}$ from the trial interventions were associated with increased mortality (Table 2). Of these, $\text{Power}_{\text{dynamic}}$ exhibited the highest odds ratio, but 95% CIs overlapped substantially for all moderators. The association between treatment effect size and $\text{Power}_{\text{elastic}}$ or $\text{Power}_{\text{driving}}$ was the weakest. Similar results were observed in the GLMER analysis, although the effect of $\text{Power}_{\text{driving}}$ showed narrower confidence intervals (Table 2).

In the subset of trials comparing higher versus lower PEEP strategies, $\text{Power}_{\text{elastic}}$ was increased in the higher PEEP arm. On average, the reduction in ΔP and modified mechanical power parameters obtained from lowering V_T was much larger than that obtained by increasing PEEP (Table 3).

Discussion

In trials of lung-protective ventilation strategies, several parameters of risk for VILI (V_T , ΔP , $\text{Power}_{\text{elastic}}$, $\text{Power}_{\text{dynamic}}$, $\text{Power}_{\text{driving}}$) exhibited similar moderation of treatment effect on mortality. Our findings suggest that a modified mechanical power does not add important information about the risk of death from VILI in comparison to other commonly used static parameters such as V_T or ΔP . Unlike the other parameters, $\text{Power}_{\text{elastic}}$ did

PREDICTING MORTALITY IN LUNG-PROTECTIVE VENTILATION

Table 1. Characteristics of Included Trials

Study	Centers, no.	Intervention	Control	Subjects, <i>n</i>	Primary Outcome	Primary Finding
Amato et al ²	2	V _T 6 mL/kg PBW + LRM + PEEP per best C _{RS}	V _T 12 mL/kg PBW	53	28-d mortality	Decreased mortality in intervention arm
Brower et al ³	10	V _T 6 mL/kg PBW	V _T 12 mL/kg PBW	861	Death before discharge	Decreased mortality in intervention arm
Brower et al ²⁶	23	High PEEP/F _{IO₂} table	Low PEEP/F _{IO₂} table	549	Death before discharge	No difference in primary outcome between arms
Villar et al ²⁷	8	V _T 5–8 mL/kg PBW + PEEP per best C _{RS}	V _T 9–11 mL/kg PBW	95	ICU mortality	Decreased mortality in intervention arm
Meade et al ²⁸	30	V _T 6 mL/kg PBW + LRM + high PEEP/F _{IO₂} table	V _T 6 mL/kg PBW + low PEEP/F _{IO₂} table	983	Hospital mortality	No difference in primary outcome between arms
Mercat et al ²⁹	37	V _T 6 mL/kg PBW + high PEEP*	V _T 6 mL/kg PBW + low PEEP	767	28-d mortality	No difference in primary outcome between arms
Kacmarek et al ³⁰	20	V _T 6 mL/kg PBW + LRM + PEEP per best C _{RS}	V _T 6 mL/kg PBW + low PEEP/F _{IO₂} table	200	60-d mortality	No difference in primary outcome between arms
Cavalcanti et al ³¹	120	V _T 6 mL/kg PBW + LRM + PEEP per best C _{RS}	V _T 6 mL/kg PBW + low PEEP/F _{IO₂} table	1,010	28-d mortality	Increased mortality in intervention arm
Hodgson et al ³²	35	V _T 4–6 mL/kg PBW + daily LRM + high PEEP per S _{pO₂}	V _T 6 mL/kg PBW + low PEEP/F _{IO₂} table	113	Ventilator-free days at 28 d	No difference in mortality between arms (stopped early)

* Plateau pressure ≤ 30 cm H₂O.

V_T = tidal volume; PBW = predicted body weight; LRM = lung recruitment maneuver; C_{RS} = compliance of the respiratory system

Fig. 2. Moderating effect of tidal volume, driving pressure, mechanical power, dynamic power, and driving power on mortality effect size in trials of lung-protective ventilation strategies.

not reach statistical significance, raising the possibility that including PEEP in the computation of mechanical power degrades, rather than enhances, information about risk of VILI.

The relevance of the inspiratory flow and breathing frequency in the development of VILI has been under scrutiny for many years. Animal studies have reported that higher peak inspiratory flow could worsen gas exchange and lung

PREDICTING MORTALITY IN LUNG-PROTECTIVE VENTILATION

Table 2. Predictors of Treatment Effect and Mortality in Trials of Lung-Protective Mechanical Ventilation

Parameter	Distribution Across Trials on Day 1 After Randomization, mean $\pm$ SD	Meta-Regression		Generalized Linear Mixed-Effects Model Odds Ratio (95% CI) of Mortality for a 1-SD Increase
		Odds Ratio (95% CI) of Mortality for a 1-SD Increase in Mean Difference Between Groups	Meta-regression R^2	
V_T , mL/kg PBW	6.9 $\pm$ 2	1.24 (1.03–1.49)	0.60	1.17 (1.07–1.29)
Driving pressure, cm H ₂ O	15.5 $\pm$ 4.8	1.31 (1.03–1.66)	0.48	1.24 (1.09–1.41)
Mechanical power, J/min	22.5 $\pm$ 3.6	1.26 (.99–1.61)	0.34	1.03 (0.96–1.11)
Dynamic power, J/min	8.8 $\pm$ 3.4	1.37 (1.05–1.78)	0.60	1.24 (1.1–1.41)
Driving power, cm H ₂ O ² /min	581 $\pm$ 250	1.38 (.96–1.96)	0.22	1.27 (1.08–1.49)

V_T = tidal volume; PBW = predicted body weight

Table 3. Differences in Parameters Between Intervention and Control Arms

	Intervention	Control	Difference
V_T , mL/kg PBW			
Low versus high V_T	6.1 (1.1)	11 (0.8)	–4.8 (–6.74 to –2.92)
Low versus high PEEP	5.9 (0.5)	6.1 (0.3)	–0.16 (–0.34 to 0.01)
Driving pressure, cm H ₂ O			
Low versus high V_T	15 (1.4)	25 (2.4)	–10 (–14.42 to –5.77)
Low versus high PEEP	12 (1.1)	13 (0.9)	–1.5 (–2.22 to –0.83)
Power _{elastic} , J/min			
Low versus high V_T	19.9 (3.9)	26 (3.7)	–6 (–14.46 to 2.37)
Low versus high PEEP	24 (1.7)	20 (1.5)	5 (3.47 to 6.55)
Power _{dynamic} , J/min			
Low versus high V_T	7.5 (2.6)	15.4 (2.8)	–7.8 (–13.46 to –2.18)
Low versus high PEEP	7 (0.9)	7.9 (0.8)	–0.9 (–1.37 to –0.52)
Power _{driving} , cm H ₂ O/min			
Low versus high V_T	544 (170)	1,043 (265)	–499 (–967.05 to –31.46)
Low versus high PEEP	422 (66)	526 (79)	–103 (–156.58 to –49.70)

Data are presented as mean $\pm$ SD or mean (95% CI).

V_T = tidal volume; PBW = predicted body weight

compliance when injurious V_T is delivered.^{7,8,33} This association, however, has not been replicated in studies including humans. Most of the pressure generated by flow is spent to overcome the endotracheal tube's and the proximal airway's dependent resistance. The relevance of inspiratory flow on the development of VILI, a phenomenon that occurs at the alveolar level, is therefore doubtful.¹⁵ Admittedly, higher flows may entail a more rapid rise in alveolar stress that may be injurious, but in the absence of detailed measurements of airway and alveolar mechanics it is impossible to determine the rate of change in alveolar pressure from the flow. On the other hand, breathing frequency is one of the main components associated with mortality in a retrospective study including > 8,000 critically ill subjects.¹¹ Because mechanical power is meant to reflect the cumulative energy delivered to the respiratory system

over a period of time, breathing frequency (and not flow) appears to have a greater physiologic rationale in the development of VILI. Nevertheless, our results do not support the hypothesis that breathing frequency provides additional important information when assessing VILI risk at the bedside.

The lack of meaningful differences in effect moderation by different markers of VILI risk may be attributable to the fact that all of the relevant variation in the parameters resulted from variation in V_T (because these trials targeted lower V_T). Theoretically, the optimal lung-protective strategy should target the parameter that best quantifies the risk of VILI.³⁴ However, other mechanisms such as mechanical heterogeneity within the injured lung might also contribute to VILI³⁵ and this may not be captured by any of the aforementioned parameters.

Importantly, we also found that trials of higher versus lower PEEP did not produce meaningful between-group reductions in V_T , ΔP , $\text{Power}_{\text{elastic}}$, or $\text{Power}_{\text{dynamic}}$ (Table 3). If these parameters mediate VILI, failure to modify these parameters might explain in part why these interventions consistently failed to significantly modify mortality.^{26,28-32} Meaningful reductions in ΔP and power following increased PEEP would only be expected in subjects who exhibit substantial lung recruitment. The effect of higher versus lower PEEP on ΔP , mechanical power, and mortality require further study in this specific subgroup.

We observed moderate heterogeneity among the included studies. This enhances the relevance of selecting a meta-regression approach to analyze the data, given that a single summary measure might fail to capture the diversity among different subsets of subjects.³⁶ This is particularly true when evaluating the effect of mechanical power because its value will be more influenced by changes in V_T than by changes in PEEP or breathing frequency,⁹ as shown in our secondary analysis. The goal of meta-regression is to determine whether a given parameter (eg, modified mechanical power) can explain the observed statistical heterogeneity.

This study has several limitations. First, the number of trials is small, which limits statistical power to detect moderation of treatment effect. Individual patient data meta-analysis might provide more information. Second, we used physiological and ventilatory data collected at a single time point on the first day of the randomized trial to compute the parameters of interest, and it is unclear how accurately such data reflect overall exposure to the parameters. Moreover, we did not compute mechanical power using the original formula described by Gattinoni et al⁹ because the information needed to perform this calculation was not available in all of the reviewed studies. Although neglecting the impact of flow on the risk of VILI has a physiological rationale, the derivations presented in this study should only be considered as alternatives.

Conclusions

In summary, this analysis does not support the hypothesis that mechanical power is a more useful surrogate measure for the risk of death from VILI or for the benefit of lung-protective ventilation strategies in comparison to targeting driving pressure or tidal volume. Individual patient data meta-analysis might provide further information to confirm or refute this conclusion.

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