

Utility of driving pressure and mechanical power to guide protective ventilator settings in two cohorts of adult and pediatric patients with acute respiratory distress syndrome: A computational investigation

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ABSTRACT

Objectives: Mechanical power (MP) and driving pressure (ΔP) have been proposed as indicators, and possibly drivers, of ventilator-induced lung injury. We tested the utility of these different measures as targets to derive maximally protective ventilator settings.

Design: A high-fidelity computational simulator was matched to individual patient data and used to identify strategies that minimize ΔP , MP and a modified version of MP (MMP) that removes the direct linear, positive dependence between MP and PEEP.

Setting: Interdisciplinary Collaboration in Systems Medicine Research Network.

Subjects: Data were collected from a prospective observational cohort of pediatric ARDS from the Children's Hospital of Philadelphia (N=77) and from the low tidal volume (V_T) arm of the ARDSNetwork tidal volume trial (N=100).

Interventions: Global optimization algorithms evaluated more than 26.7 million changes to ventilator settings (approximately 150,000 per patient) to identify strategies that minimize ΔP , MP or MMP.

Measurements and Main Results: Large average reductions in ΔP (23%-Pediatric, 23%-Adult), MP (44%-Pediatric, 66%-Adult) and MMP (61%-Pediatric, 67%-Adult) were achievable in both cohorts when oxygenation and ventilation were allowed to vary within pre-specified ranges. Reductions in ΔP (12%-Pediatric, 2%-Adult), MP (24%-Pediatric, 46%-Adult) and MMP (44%-

Pediatric, 46%-Adult) were achievable even when no deterioration in gas exchange was allowed. Minimization of MP and MMP was achieved by increasing V_T and decreasing respiratory rate (RR). In the pediatric cohort, minimum ΔP was achieved by reducing V_T and increasing RR and PEEP. The ARDSNetwork dataset had limited scope for further reducing V_T , but ΔP was still significantly reduced by increasing PEEP.

Conclusions: Our analysis identified different strategies that minimized ΔP or MP consistently across pediatric and adult datasets. Minimizing standard and alternative formulations of MP led to significant increases in V_T . Targeting ΔP for minimisation resulted in ventilator settings that also reduced MP and MMP, but not vice versa.

INTRODUCTION

Mechanical power (MP) (1-3) and driving pressure (ΔP) (4) have recently been proposed as measures, and potentially drivers, of ventilator-induced lung injury (VILI) in acute respiratory distress syndrome (ARDS). MP is defined as (1):

$$MP = 0.098 \times RR \times \left\{ V_T^2 \times \left[0.5 \times EL_{rs} + RR \times \frac{(1 + I:E)}{60 \times I:E} \times R_{aw} \right] + V_T \times PEEP \right\}$$

where EL_{rs} is the elastance of the respiratory system, I:E is the inspiratory-to-expiratory time ratio, and R_{aw} is the airway resistance. ΔP is defined as the difference between plateau pressure (P_{plat}) and PEEP, and reflects the tidal volume (V_T) normalized to respiratory system compliance.

Arguments for the importance of MP focus on the injurious biophysical role of energy (stress X strain) and dynamics (rates of airway pressure change and cycling frequency) during mechanical ventilation (2), whereas arguments for the centrality of ΔP are supported by statistical and computational analyses of trial data that show strong correlations between ΔP and mortality (4, 5). However, the rationale for both MP and ΔP rely on re-analyses of adult ARDS cohorts, and while initial studies are in progress (NCT03616704 and NCT03939260), an intervention targeting either parameter has yet to be proven efficacious.

To date, there has been no randomized trial to determine the appropriate application of any type of protective ventilation in pediatric ARDS, and observational studies offer conflicting results (6-10). Ventilator management in children is often extrapolated from adults, with uncertain applicability (10). Pediatric ARDS has a distinct epidemiology, with different inciting etiologies and predictors of outcome (11, 12), relative to adults, necessitating specific investigations in children. Overall, even less evidence is available for children regarding the utility of either MP or ΔP as metrics of VILI or as modifiable ventilator parameters.

To investigate how minimizing either MP or ΔP would affect ventilator settings and gas exchange in ARDS, we employed a high-fidelity computational simulator matched to individual patient data from two separate cohorts, pediatric and adult. High-fidelity simulation holds the potential to develop, test, and directly compare ventilation strategies prior to exposing vulnerable patients to potentially damaging interventions (13). Global optimization algorithms, implemented on high-performance computing clusters, were used to evaluate more than 26.7 million different changes to the baseline ventilator settings to identify those that minimized ΔP , MP, and a modified formulation of MP (MMP) based on concerns (14) regarding the direct, positive, linear effect of positive end-expiratory pressure (PEEP) on MP in the original MP equation. Changes to ventilator settings were constrained within specified limits, and maximally protective settings optimizing ΔP , MP, and MMP were calculated for two different scenarios (a) allowing, within safe limits, some deterioration in gas exchange from baseline, and (b) without allowing any deterioration in gas exchange. The primary aim of this study was to assess the scope for achieving more protective ventilation by separately minimizing ΔP , MP, or MMP. A secondary goal of the study was to investigate to what extent protective ventilation strategies identified for the pediatric cohort were consistent with those computed for the adult cohort.

MATERIALS AND METHODS

Patient Selection

Pediatric cohort: Patients were selected from an ongoing (2011 onwards) prospective cohort (15) of intubated children meeting Berlin ARDS criteria from the Children's Hospital of Philadelphia (CHOP). The study was reviewed by the CHOP Institutional Review Board, and requirement for informed consent waived. Seventy-seven subjects between 1 month and 18 years

of age (Mean: 3.1 ± 3.3 years, 23% severe, 44% moderate and 33% mild ARDS), ventilated via cuffed endotracheal tube during neuromuscular blockade, were selected. Subjects were selected based on the initial development and validation of the pediatric algorithm. An initial development cohort of children with identically sized endotracheal tubes (5.0 mm internal diameter) under neuromuscular blockade, and two subsequent test cohorts of infants under 2 years of age and children with $V_T > 10$ mL/kg. Arterial blood gases (ABG) and ventilator changes during the first 72 hours of ARDS were recorded. All subjects were ventilated with decelerating flow in either pressure control or pressure-regulated volume control. Peak inspiratory pressure (PIP), PEEP, and exhaled V_T were collected at the ventilator for patients with $V_T \geq 100$ mL using integrated software provided by the manufacturer (Dräger, Inc., Lübeck, Germany), and using a sensor proximate to the endotracheal tube for $V_T < 100$ mL.

Adult cohort: Data were extracted from 100 adult ARDS patients randomly selected (14% severe, 66% moderate, 20% mild) from the low V_T arm of the ARMA trial (16). Data were provided in a de-identified state by the Biologic Specimen and Data Repository Information Coordinating Centre the National Heart, Lung and Blood Institute, and informed consent was not required. All patients received mechanical ventilation in assist-control ventilation mode, and we used the earliest available post-randomization data.

Simulator Calibration to Patient Data

Analyses were carried out using a simulator that includes representations of multiple interacting organ systems, incorporates a high level of physiological detail, and has been extensively validated in several previous studies of adult (17, 18) and pediatric ARDS (13) (Supplemental File, section S1-S2). The simulator was matched to individual patient data

(ventilator parameters and ABGs at single time points) using advanced global optimization algorithms, (Supplemental File, section S3). The optimal parameterisation of the simulator for each patient was used in all subsequent analyses (in the case of multiple parameterisations returning similar fits, robustness of the results was checked on the best 20).

Maximally Protective Ventilation as a Constrained Optimization Problem

After matching the model to each individual patient, the potential for achieving maximally lung-protective (but acceptably effective) ventilation was investigated by formulating and solving different optimization problems. We used advanced global optimization algorithms implemented on high-performance computing clusters to exhaustively search through more than 26.7 million different changes (approximately 150,000 per patient) to the reported ventilator settings – namely V_T , respiratory rate (RR), $F_{I}O_2$, PEEP and duty cycle (DC, inspiratory-to-total time ratio) to identify which settings produced minimum values of the following quantities:

- ΔP (difference between P_{plat}) and PEEP), with P_{plat} is calculated directly from the simulator.
- Mechanical Power, defined as (1):

$$MP = 0.098 \times RR \times \left\{ V_T^2 \times \left[0.5 \times EL_{rs} + RR \times \frac{(1 + I:E)}{60 \times I:E} \times R_{aw} \right] + V_T \times PEEP \right\} \quad (1)$$

where EL_{rs} is respiratory system elastance, I:E is inspiratory-to-expiratory ratio, and R_{aw} is the airway resistance. Note that, as shown in [1], the MP equation can also be simplified to:

$$MP = 0.098 \times RR \times V_T \times (PIP - 0.5 \times \Delta P) \quad (2)$$

- A modified version of MP, given by:

$$MMP = 0.098 \times RR \times V_T^2 \times \left[0.5 \times EL_{rs} + RR \times \frac{(1 + I:E)}{60 \times I:E} \times R_{aw} \right] \quad (3)$$

which removes the direct linear, positive dependence between MP and PEEP (14).

To ensure the relevance of these optimization problems to clinical practice, it is necessary to *constrain* the search for maximally protective settings to include only those that do not compromise oxygenation and ventilation. We did this by defining upper and lower limits for the ventilation settings themselves, and by defining allowable limits for the values of PIP, P_aO₂ and P_aCO₂ produced by the settings (Table 1). Ventilation settings that minimized ΔP , MP and MMP while keeping values of PIP, P_aO₂ and P_aCO₂ within their specified limits were computed for each patient (Approach 1). In the pediatric cohort, these limits were based on those used in the ARDSNetwork trial, adapted to match pediatric conventions (6, 8, 10, 19). As the pediatric cohort was developed using decelerating flow, as is most common in pediatrics (20), PIP was used as a constraint, rather than P_{plat}. When data indicated that a patient's initial ventilator state did not comply with one or more of the specified safety limits, changes to the settings were only made if they led to an improvement in the relevant parameters (e.g., reducing P_aCO₂ or PIP).

As an alternative strategy, we also investigated whether changes to ventilator settings could be found that minimized ΔP , MP and MMP without resulting in *any* deterioration in P_aO₂ and P_aCO₂ from baseline values (Approach 2). An upper limit of 35 cmH₂O was applied for PIP in the pediatric cohort. Due to relatively higher baseline PIP in adults, the upper limit was set to the corresponding baseline values for these patients (Supplemental File, section S6).

Statistical Analysis

Data are presented as mean \pm standard deviation (SD), or shown graphically using median, interquartile and total ranges. To avoid violation of underlying distribution assumptions, variables were compared using the signed-rank test. A two-sided p-value of < 0.05 was considered significant.

RESULTS

The Simulator Accurately Represents Individual Patient Data

The ability of the simulator to reproduce patient data was verified by comparing its responses (P_{aO_2} and P_{aCO_2}) against data on the responses of patients from both cohorts. After calibration (Supplemental File, section S3), each patient in the cohort was simulated for 30 minutes (or until reaching steady-state) under volume controlled mechanical ventilation with constant flow in the supine position. Figure 1-(A) to 1-(C) compares the outputs of the simulator with the original data, expressed as median, interquartile range and actual range for the entire cohort. Figure 1-(D) to 1-(F) shows the Bland-Altman plots for data points versus simulator output values. These results confirm the capability of the simulator to accurately replicate multiple output values of the patients included in both cohorts across a range of different ventilator settings.

Reductions in ΔP , MP, and MMP were Achieved in Both Cohorts

When ABGs were allowed to vary within pre-specified ranges (Table 1), average maximum reductions in ΔP of 3.0 ± 2.2 cmH₂O (23%) compared to baseline values in the pediatric cohort and 3.2 ± 2.1 cmH₂O (23%) in the adult cohort were achievable (Figure 2). Reductions in ΔP of over 1 cmH₂O were achieved in 95% of pediatric and 82% of adult patients. The corresponding reductions when targeting MP were 3.3 ± 2.6 J.min⁻¹ (44%) in the pediatric cohort (87% of whom had MP reduced by over 20%) and 21.0 ± 5.4 J.min⁻¹ (66%) in the adult cohort, with all patients reducing MP by over 20%. When targeting MMP, reductions were 3.7 ± 2.3 J.min⁻¹ (61%) in the pediatric cohort and 15.2 ± 4.9 J.min⁻¹ (67%) in the adult cohort

(reductions of over 20% in 95% and 99% of the pediatric and adult cohorts, respectively). Reductions were statistically significant in all groups (signed-rank test $p < 0.05$). In all the above cases, more protective ventilation was achieved with no significant deterioration in patient oxygenation (P_aO_2), although P_aCO_2 did consistently increase towards the upper limits (Supplemental File, Figure S5). In both cohorts, settings that minimized ΔP also reduced MP and MMP, whereas settings that minimized MP and MMP *increased* ΔP (largely due to the resulting increases in V_T (see below)).

When the optimizations were constrained to allow *no* deterioration in gas exchange (i.e. only changes that maintained, or improved, P_aO_2 and P_aCO_2 with respect to baseline values), reductions were achievable in ΔP of 1.6 ± 1.4 cmH₂O (12%) and 0.4 ± 1.0 cmH₂O (2%) were achievable compared to baseline values in the pediatric and adult cohorts, respectively (Figure 3). Reductions of ΔP of over 1 cmH₂O were achieved in 58% of pediatric and 16% of adult subjects. Corresponding reductions when targeting MP were 1.7 ± 1.4 J.min⁻¹ (24%) in the pediatric cohort and 14.4 ± 4.9 J.min⁻¹ (46%) in the adult cohort, with 57% of pediatric and 98% of adult patients having MP reduced by over 20%. When targeting MMP, the reductions achievable were 2.5 ± 1.5 J.min⁻¹ (44%) in the pediatric cohort (90% of whom had reductions of more than 20%) and 10.3 ± 4.4 J.min⁻¹ (46%) in the adult cohort (97% achieving reductions of more than 20%). Reductions were significant in all cases (signed-rank test $p < 0.05$).

Minimum values of ΔP and MP are Achieved by Distinct Ventilation Strategies

Minimum values of MP in both adult and pediatric cohorts were produced by *increased* V_T (Pediatric: 1.4 ± 1.8 mL.kg⁻¹ (+19%), Adult: 1.9 ± 1.1 mL.kg⁻¹ (+34%)), decreased RR (Pediatric: -8.6 ± 5.1 bpm (-34%), Adult: -15.6 ± 5.0 bpm (-56%)), DC at or close to its specified

upper limit of 0.6, and PEEP at or close to its specified lower limit of 5 cmH₂O (Figure 4). F_IO₂ increased in both pediatric and adult cohorts (Pediatric: +39%, Adult: +26%).

Similar changes in V_T, RR and DC were observed in both cohorts when targeting the MMP. As expected, minimizing MMP rather than MP resulted in higher values of PEEP in both pediatric and adult cohorts (Pediatric: 2.9 ± 4.6 cmH₂O (+39%), Adult: 3.5 ± 5.0 cmH₂O (+52%)) along with lower values of F_IO₂ in pediatric patients (-21%).

In the pediatric cohort, minimum ΔP was achieved by reducing V_T (1.3 ± 1.6 mL.kg⁻¹ (-15%)) while increasing RR and PEEP (2.3 ± 8.2 bpm (+11%) and 2.4 ± 4.5 cmH₂O (+34%) respectively). In the adult cohort, no reductions in V_T were possible, but ΔP could still be reduced by increasing PEEP (2.2 ± 3.5 cmH₂O (+32%)). No changes in DC were observed in either cohort when targeting ΔP. Patterns of changes in ventilator settings were consistent in most cases between Approach 1 (allowing some deterioration in blood gas values; Figure 4) and Approach 2 (allowing no deterioration in blood gas values; Supplemental File, Figure S7), although when minimizing ΔP in pediatric patients, Approach 2 produced higher values of F_IO₂ than Approach 1, in order to satisfy the requirement for no deterioration in oxygenation.

DISCUSSION

Our results provide several new insights into the types of ventilation strategies that are likely to promote lung protective ventilation in ARDS patients. A high degree of consistency was observed in settings that minimized ΔP, MP, and MMP across the diverse patient cohorts in both datasets, providing grounds for optimism that strategies for maximally protective ventilation could be developed that would be widely applicable in ARDS.

Perhaps the most counterintuitive result is that maximum reductions in MP and MMP are consistently achieved by *increasing* V_T , (see Figures S7 and S8), since from both the standard (Equation 1) and modified (Equation 3) formula for MP it seems obvious that lowering V_T should lower MP. Crucially, however, this ignores the impact of incorporating constraints on allowable deterioration in patient gas exchange, which would always exist in treatment strategies implemented at the bedside. These constraints, combined with the complexity of making simultaneous adjustments to multiple ventilator settings, add a host of other trade-offs that render the optimal combination of ventilator settings almost impossible to predict based on clinical intuition alone. Our results point to a complex interplay between ventilator parameters which would support the development of a closed-loop system that can incorporate direct patient inputs, thereby providing individualized safe and effective mechanical ventilation.

In the pediatric cohort, minimum values of ΔP were achieved by reducing V_T and increasing RR and PEEP. This strategy has much in common with the ARMA trial protocol, which also lowered V_T while increasing RR. Some have postulated that this combination led to increased intrinsic (and hence total) PEEP (21), which may have contributed to the mortality benefit in this trial. However, it should be noted that subsequent trials of higher versus lower PEEP have not demonstrated a mortality benefit in heterogeneous ARDS populations (22-25). Since the selected patients in the adult cohort were from the low V_T arm of the trial, no further reductions in V_T were possible without violating imposed constraints on gas exchange. However, ΔP could still be significantly reduced in this cohort by moderately increasing PEEP.

Our findings provide novel insights into the challenges of using either ΔP or MP to develop protective ventilatory strategies. In our models, targeting reductions in ΔP led to increased RR and increased PEEP. While a strong association between higher ΔP and mortality

has been demonstrated (4, 26, 27), ΔP was not a therapeutic target in these patients, and causality remains elusive. There is data suggesting that increasing RR (28) and PEEP (29) beyond safe thresholds can be deleterious in injured lungs. Furthermore, in the Alveolar Recruitment for ARDS Trial (ART) clinical trial (25), a ventilatory strategy that decreased ΔP resulted in increased mortality. The usefulness of targeting ΔP directly thus remains to be demonstrated.

These concerns also apply to strategies that target reductions in MP. While MP represents a more complete attempt to describe the contributions of multiple parameters to VILI by invoking their “energy cost,” the relative contributions of the different parameters (i.e., their relatively equal “weightings” in the formula) remains the subject of debate. An example is the controversy around how PEEP contributes to MP (14). Our results show that different formulations of the MP equation lead to different optimal strategies; specifically, higher PEEP when optimizing MMP. Our finding that strategies that minimize MP and MMP increase V_T highlights the challenges of targeting one specific parameter in designing protective ventilatory strategies. This is particularly important given the findings from recent pre-clinical animal studies that, for the same MP, strategies employing higher rather than lower V_T had increased injury (30, 31). All these findings highlight the need for prospective validation of ventilator strategies that target reduced MP. Of importance, computational modelling of the impact of targeting these parameters (or combinations of different VILI indices) may identify promising non-intuitive combinations of ventilator settings for clinical testing, and also allow more effective stratification of patient populations by revealing differences in the effects of ventilation strategies across heterogeneous patient populations. We note that current ventilators do not routinely calculate and display MP, and that the ability to do so would improve tracking of this parameter for both clinical and research purposes.

Our study has a number of limitations. The pediatric dataset was derived from a single institution, and while the severity of ARDS and outcomes were similar to other cohorts, generalizability cannot be assumed. To minimize confounding, the model was configured to represent patients who are fully sedated and/or paralyzed; therefore, autonomic reflex modules were not utilized. In both cohorts, for each patient the model was “trained” on a single dataset (i.e., ventilator settings and blood gasses recorded at a single time point) and model calculations regarding the effect of other ventilator settings on, for example, lung compliance, are predictions that assume an unchanged patient physiological state. The model also does not include the effect of inflammatory mediators, which are difficult to quantify and to isolate in clinical settings. As the model is computational in nature, it does not provide any direct physiologic, histological or biological evidence of the effects of the proposed ventilation strategies on VILI, and further animal and human studies should be performed to provide conclusive evidence of their effectiveness in achieving more protective ventilation. The model was developed to focus on ventilator settings affecting VILI; thus, we chose to set constraints on P_aCO_2 , rather than pH, which is often modified by entirely non-ventilator interventions, such as volume resuscitation or exogenous bicarbonate. Finally, models were based on ventilator settings and ABGs at single timepoints, and not on prospective data collection after planned ventilator changes. Such a study design would provide a more granular data regarding an individual patient’s response to specific ventilator adjustments.

However, our study also has several unique strengths. Over 26.7 million distinct combinations of ventilator settings were implemented and evaluated on two separate cohorts of patients with ARDS. It is difficult to imagine such a comprehensive exploration of different ventilation strategies ever being possible via animal or clinical trials. The study also allows a

direct comparison of the effects of protective ventilation strategies in adult and pediatric ARDS patients. Our results clearly demonstrate the utility of pilot studies using high-fidelity simulation to assess novel interventions targeting MP or ΔP (or any other VILI indicator), and hence to inform the design of more targeted and effective clinical trials on actual patients.

CONCLUSIONS

We identified novel ventilatory strategies that our model predicts will ΔP , MP, and MMP in datasets from adults and children with ARDS. The identified strategies were consistent within each patient group, and were similar in both adults and children, suggesting that protective ventilatory strategies derived from studies in adults may have utility in children with ARDS. Our model predicts that attempts to minimize MP could result in the use of higher V_T . Since this contradicts the current consensus on using lower V_T it raises questions regarding the use of MP as a direct target to minimize VILI, at least as currently formulated. Overall, our findings demonstrate the limitations of ventilatory strategies that target either ΔP or MP, highlighting the need to continue to refine these targets, and for ultimate validation of these strategies in clinical trials.

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Figure Legends:

Figure 1: Panels (A) to (C) compare the simulator outputs versus patient data expressed as median, interquartile ranges and actual ranges. Panels (D) to (F) show the Bland-Altman plots for simulator outputs and data. R represents the correlation coefficient of the data and the simulated values.

Figure 2: Approach 1 – Change in driving pressure, mechanical power and modified mechanical power when minimizing different targets (i.e. ΔP , MP and MMP) and allowing some deterioration in patient gas exchange. Panels (A) to (C) show results for the pediatric cohort and (D) to (F) for the adult cohort. Box plots demonstrate data as median, interquartile range and actual. Numbers on the whiskers are mean \pm SD. ΔP : Driving Pressure; MP: Mechanical Power; MMP: Modified Mechanical Power. The corresponding changes in tidal volume, respiratory rate, duty cycle, $F_{I}O_2$ and PEEP are shown in Fig. S7 and S8.

Figure 3: Approach 2 – Change in driving pressure, mechanical power and modified mechanical power when minimizing different targets (i.e. ΔP , MP and MMP) and allowing no deterioration in gas-exchange. Panels (A) to (C) show results for the pediatric cohort and (D) to (F) for the adult cohort. Box plots demonstrate data as median, interquartile range and actual. Numbers on the whiskers are mean \pm SD. ΔP : Driving Pressure; MP: Mechanical Power; MMP: Modified Mechanical Power. The corresponding changes in tidal volume, respiratory rate, duty cycle, $F_{I}O_2$ and PEEP are shown in Fig. S7 and S8.