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

Sina Saffaran, MSc[1]; Anup Das, PhD[1]; John G. Laffey, MD[2]; Jonathan G. Hardman, PhD[3]; Nadir Yehya, MD[4]; Declan G. Bates, PhD[1]

Objectives: Mechanical power and driving pressure 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 driving pressure, mechanical power, and a modified mechanical power that removes the direct linear, positive dependence between mechanical power and positive end-expiratory pressure.

Setting: Interdisciplinary Collaboration in Systems Medicine Research Network.

Subjects: Data were collected from a prospective observational cohort of pediatric acute respiratory distress syndrome from the Children's Hospital of Philadelphia ($n = 77$) and from the low tidal volume arm of the Acute Respiratory Distress Syndrome Network 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 driving pressure, mechanical power, or modified mechanical power.

Measurements and Main Results: Large average reductions in driving pressure (pediatric: 23%, adult: 23%), mechanical power (pediatric: 44%, adult: 66%), and modified mechanical power (pediatric: 61%, adult: 67%) were achievable in both cohorts when oxygenation and ventilation were allowed to vary within prespecified ranges. Reductions in driving pressure (pediatric: 12%, adult: 2%), mechanical power (pediatric: 24%, adult: 46%), and modified mechanical power (pediatric: 44%, adult: 46%) were achievable even when no deterioration in gas exchange was allowed. Minimization of mechanical power and modified mechanical power was achieved by increasing tidal volume and decreasing respiratory rate. In the pediatric cohort, minimum driving pressure was achieved by reducing tidal volume and increasing respiratory rate and positive end-expiratory pressure. The Acute Respiratory Distress Syndrome Network dataset had limited scope for further reducing tidal volume, but driving pressure was still significantly reduced by increasing positive end-expiratory pressure.

Conclusions: Our analysis identified different strategies that minimized driving pressure or mechanical power consistently across pediatric and adult datasets. Minimizing standard and alternative formulations of mechanical power led to significant increases in tidal volume. Targeting driving pressure for minimization resulted in ventilator settings that also reduced mechanical power and modified mechanical power, but not vice versa. (*Crit Care Med* 2020; XX:00–00)

Key Words: adult acute respiratory distress syndrome; computer simulation; mechanical ventilation; pediatric acute respiratory distress syndrome; protective ventilation; ventilator-induced lung injury

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):

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

[1]School of Engineering, University of Warwick, Coventry, United Kingdom.
[2]Anaesthesia and Intensive Care Medicine, School of Medicine, NUI Galway, Galway, Ireland.
[3]Anaesthesia & Critical Care, Division of Clinical Neuroscience, School of Medicine, University of Nottingham, Nottingham, United Kingdom.
[4]Department of Anaesthesiology and Critical Care Medicine, Children's Hospital of Philadelphia, University of Pennsylvania, Philadelphia, PA.

Copyright © 2020 by the Society of Critical Care Medicine and Wolters Kluwer Health, Inc. All Rights Reserved.

DOI: 10.1097/CCM.0000000000004372

Copyright © 2020 by the Society of Critical Care Medicine and Wolters Kluwer Health, Inc. All Rights Reserved.

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 positive end-expiratory pressure (PEEP) and reflects the tidal volume (Vt) 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 reanalyzes of adult ARDS cohorts, and while initial studies are in progress (NCT03616704 and NCT03939260), an intervention targeting either variable 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 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 variables.

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 mechanical power (MMP) based on concerns (14) regarding the direct, positive, linear effect of 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 1) allowing, within safe limits, some deterioration in gas exchange from baseline and 2) 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 old (mean: 3.1 ± 3.3 yr, 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 old and children with Vt greater than 10 mL/kg. Arterial blood gases (ABGs) 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 Vt were collected at the ventilator for patients with Vt greater than or equal to 100 mL using integrated software provided by the manufacturer (Dräger, Lübeck, Germany) and using a sensor proximate to the endotracheal tube for Vt less than 100 mL.

Adult Cohort. Data were extracted from 100 adult ARDS patients randomly selected (14% severe, 66% moderate, 20% mild) from the low Vt arm of the Ventilation with Lower Tidal Volumes as Compared with Traditional Tidal Volumes for Acute Lung Injury and the Acute Respiratory Distress Syndrome (ARMA) trial (16). Data were provided in a de-identified state by the Biologic Specimen and Data Repository Information Coordinating Center 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 postrandomization 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 physiologic detail, and has been extensively validated in several previous studies of adult (17, 18) and pediatric ARDS (13) (**Supplemental File**, **section S1–S2**, Supplemental Digital Content 1, http://links.lww.com/CCM/F483). The simulator was matched to individual patient data (ventilator variables and ABGs at single time points) using advanced global optimization algorithms (**Supplemental File**, **section S3**, Supplemental Digital Content 1, http://links.lww.com/CCM/F483). The optimal parameterization (**Supplemental File, section S4**, Supplemental Digital Content 1, http://links.lww.com/CCM/F483) of the simulator for each patient was used in all subsequent analyses (in the case of multiple parameterizations 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

Copyright © 2020 by the Society of Critical Care Medicine and Wolters Kluwer Health, Inc. All Rights Reserved.

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_{IO_2}, PEEP, and duty cycle (DC, inspiratory-to-total time ratio) to identify which settings produced minimum values of the following quantities:

1) ΔP (difference between P_{plat}) and PEEP), with P_{plat} is calculated directly from the simulator.
2) MP, 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:

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

3) 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, Pao_2, and $Paco_2$ produced by the settings (**Table 1**). Ventilation settings that minimized ΔP, MP, and MMP while keeping values of PIP, Pao_2, and $Paco_2$ 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 variables (e.g., reducing $Paco_2$ 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 Pao_2 and $Paco_2$ from baseline values (Approach 2). An upper limit of 35 cm H_2O 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**, Supplemental Digital Content 1, http://links.lww.com/CCM/F483).

Statistical Analysis

Data are presented as mean ± 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 less than 0.05 was considered significant.

TABLE 1. Allowable Ranges of Variation for Ventilator Variables (Approach 1 and 2) and Predefined Safety Constraints (Approach 1)

	Pediatric		Adult	
Variable	**Lower Limit**	**Upper Limit**	**Lower Limit**	**Upper Limit**
Allowable ranges for ventilator variables				
Positive end-expiratory pressure (cm H_2O)	5	18	5	20
Respiratory rate (breaths/min)	10	40	10	40
Tidal volume (mL·kg^{-1})	3	12	3	10
Duty cycle	0.3	0.6	0.2	0.8
F_{IO_2}	0.21	1	0.21	1
Predefined safety constraints				
Pao_2 (mm Hg)	60	120	55	100
$Paco_2$ (mm Hg)	–	60	–	60
Peak inspiratory pressure (cm H_2O)	–	35	–	35

Dashes indicate lower limit was not set.

Copyright © 2020 by the Society of Critical Care Medicine and Wolters Kluwer Health, Inc. All Rights Reserved.

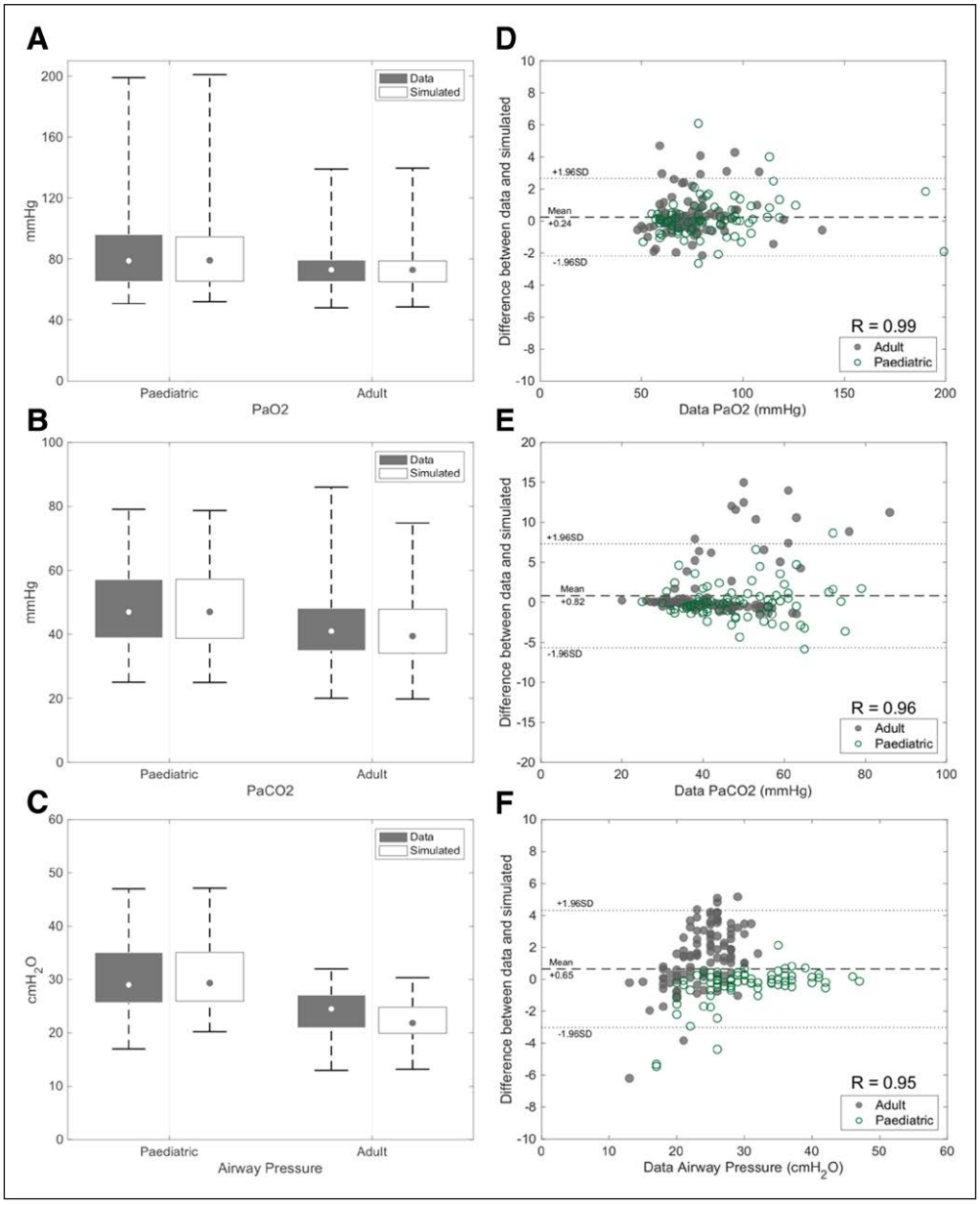

Figure 1. The simulator reliably reproduces clinical data. **A–C**, Compare the simulator outputs versus patient data expressed as median, interquartile ranges, and actual ranges. **D–F**, The Bland-Altman plots for simulator outputs and data. *R* represents the correlation coefficient of the data and the simulated values.

RESULTS

The Simulator Accurately Represents Individual Patient Data

The ability of the simulator to reproduce patient data was verified by comparing its responses (Pao_2 and $Paco_2$) against data on the responses of patients from both cohorts. After calibration (Supplemental File, section S3, Supplemental Digital Content 1, http://links.lww.com/CCM/F483), 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–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–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 prespecified ranges (Table 1), average maximum reductions in ΔP of 3.0 ± 2.2 cm H_2O (23%) compared with baseline values in the pediatric cohort and 3.2 ± 2.1 cm H_2O (23%) in the adult cohort were achievable (**Fig. 2**). Reductions in ΔP of over 1 cm H_2O were achieved in 95% of pediatric and 82% of adult patients. The corresponding reductions when targeting MP were 3.3 ± 2.6 $J \cdot min^{-1}$ (44%) in the pediatric cohort (87% of whom had MP reduced by over 20%) and 21.0 ± 5.4 $J \cdot min^{-1}$ (66%) in the adult cohort, with all patients reducing MP by over 20%. When targeting MMP, reductions were 3.7 ± 2.3 $J \cdot min^{-1}$ (61%) in the pediatric cohort and 15.2 ± 4.9 $J \cdot min^{-1}$ (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 (Pao_2), although $Paco_2$ did consistently increased toward the upper limits (**Supplemental File**, **Fig. S5**, Supplemental Digital Content 1, http://links.lww.com/CCM/F483). 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, Pao_2 and $Paco_2$ with respect to baseline values), reductions were achievable in ΔP of 1.6 ± 1.4 cm

Copyright © 2020 by the Society of Critical Care Medicine and Wolters Kluwer Health, Inc. All Rights Reserved.

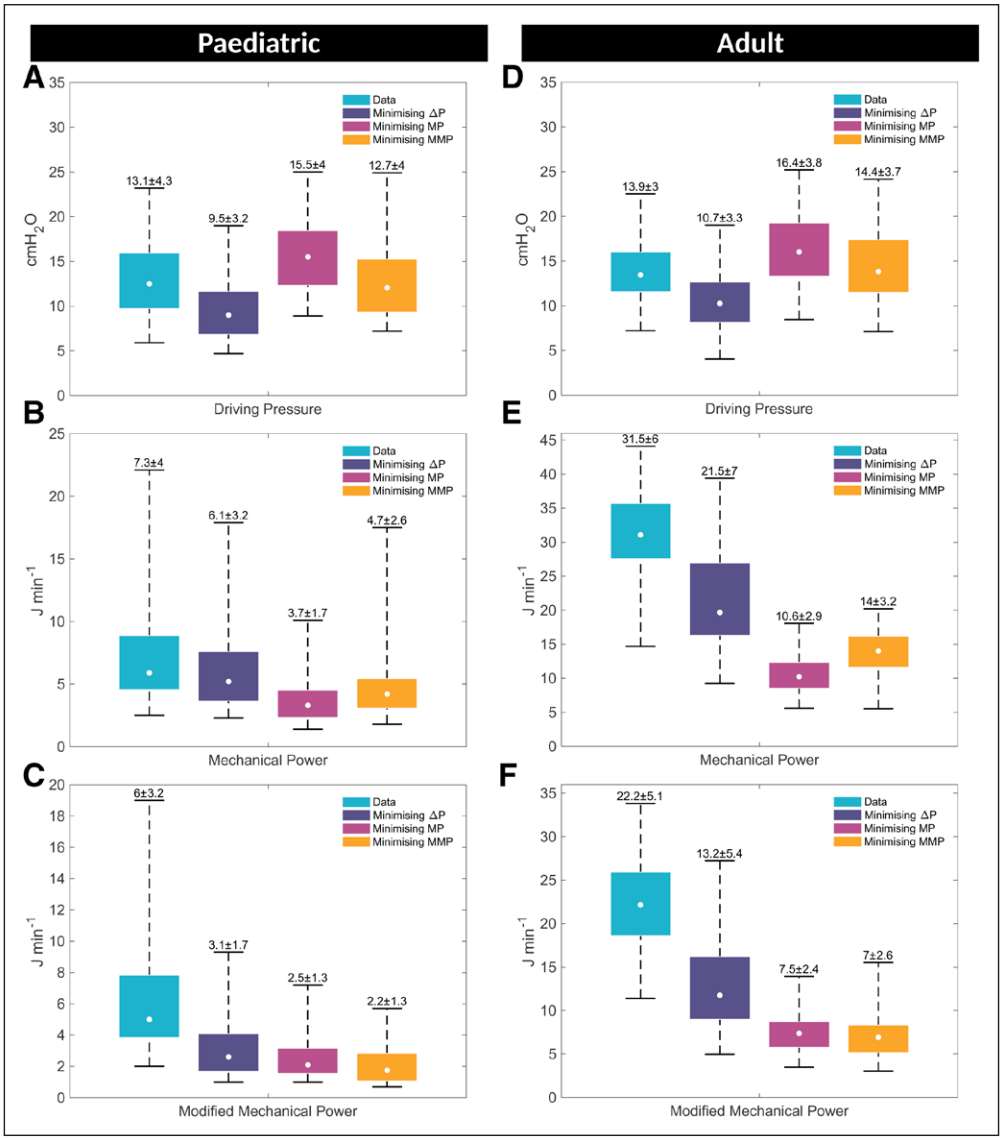

Figure 2. Approach 1—Change in driving pressure (ΔP), mechanical power (MP), and modified mechanical power (MMP) when minimizing different targets and allowing some deterioration in patient gas exchange. **A–C**, Results for the pediatric cohort and (**D–F**) for the adult cohort. *Box plots* demonstrate data as median, interquartile range, and actual. Numbers on the *whiskers* are mean ± SD. The corresponding changes in tidal volume, respiratory rate, duty cycle, F_{IO_2}, and positive end-expiratory pressure are shown in Figures S7 and S8 (Supplemental Digital Content 1, http://links.lww.com/CCM/F483).

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 breaths/min [–34%], adult: –15.6 ± 5.0 breaths/min [–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 cm H_2O **Supplemental File, Fig. S7**, Supplemental Digital Content 1, http://links.lww.com/CCM/F483). F_{IO_2} 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 cm H_2O [+39%], adult: 3.5 ± 5.0 cm H_2O [+52%]) along with lower values of F_{IO_2} 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 breaths/min [+11%] and 2.4 ± 4.5 cm H_2O [+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 cm H_2O [+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; Supplemental File, Fig. S7, http://links.lww.com/CCM/F483) and Approach 2 (allowing no deterioration in blood gas values; **Supplemental File, Fig. S8**, Supplemental Digital Content 1, http://links.lww.com/CCM/F483), although when minimizing ΔP in pediatric patients, Approach 2 produced higher values of F_{IO_2} than Approach 1, in order to satisfy the requirement for no deterioration in oxygenation.

H_2O (12%) and 0.4 ± 1.0 cm H_2O (2%) were achievable compared with baseline values in the pediatric and adult cohorts, respectively (**Fig. 3**). Reductions of ΔP of over 1 cm H_2O 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 $p < 0.05$).

Copyright © 2020 by the Society of Critical Care Medicine and Wolters Kluwer Health, Inc. All Rights Reserved.

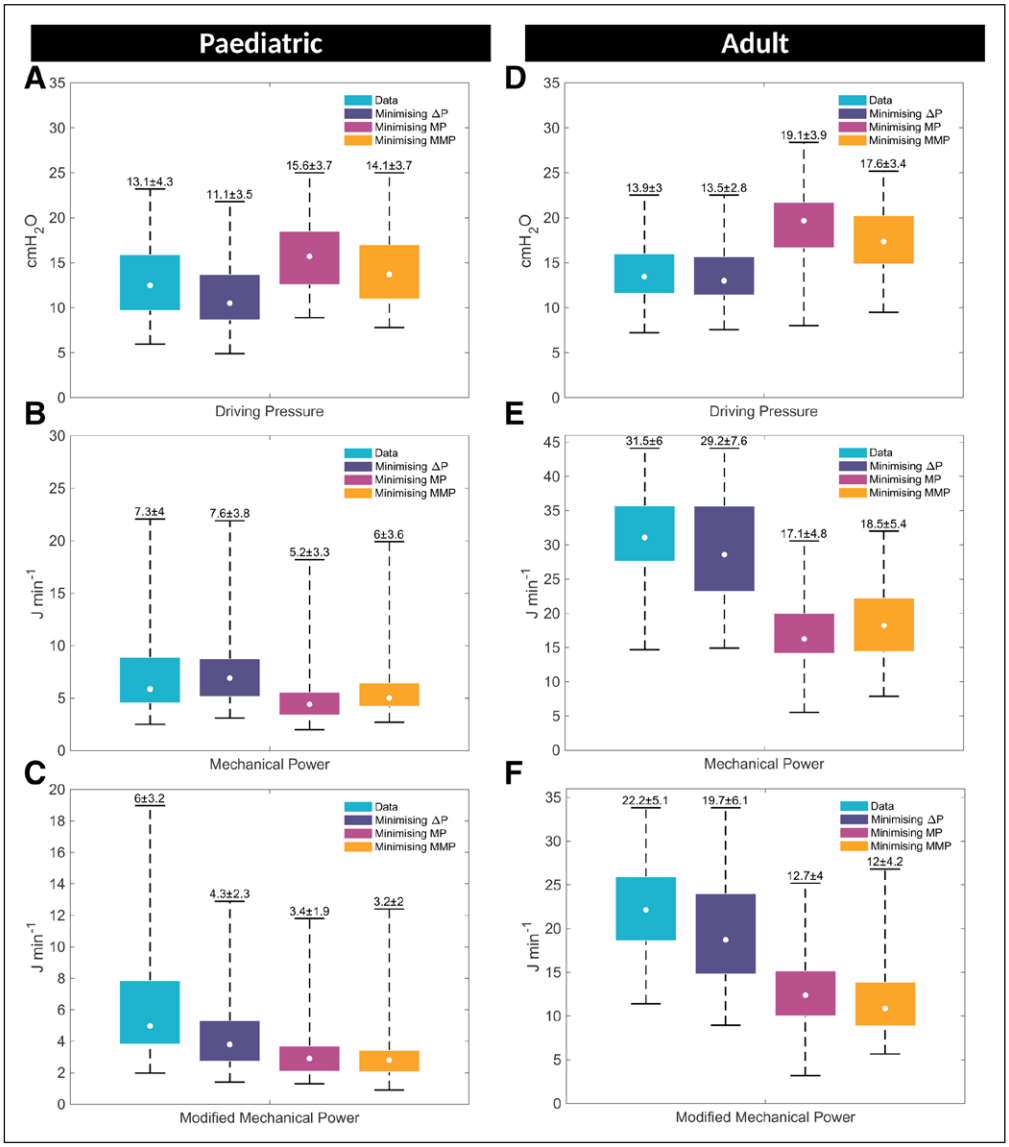

Figure 3. Approach 2—Change in driving pressure (ΔP), mechanical power (MP), and modified mechanical power (MMP) when minimizing different targets and allowing no deterioration in gas exchange. **A–C**, Results for the pediatric cohort and (**D–F**) for the adult cohort. *Box plots* demonstrate data as median, interquartile range, and actual. Numbers on the *whiskers* are mean ± SD. The corresponding changes in tidal volume, respiratory rate, duty cycle, FIO_2, and positive end-expiratory pressure are shown in Figures S7 and S8 (Supplemental Digital Content 1, http://links.lww.com/CCM/F483).

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" VT (**Figs.** S7 and **S8**, Supplemental Digital Content 1, http://links.lww.com/CCM/F483), since from both the standard (Equation 1) and modified (Equation 3) formula for MP it seems obvious that lowering VT 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 variables, 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 VT and increasing RR and PEEP. This strategy has much in common with the ARMA trial protocol, which also lowered VT 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 VT arm of the trial, no further reductions in VT 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. Although 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

Copyright © 2020 by the Society of Critical Care Medicine and Wolters Kluwer Health, Inc. All Rights Reserved.

in injured lungs. Furthermore, in the Alveolar Recruitment for ARDS Trial 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. Although MP represents a more complete attempt to describe the contributions of multiple variables to VILI by invoking their "energy cost," the relative contributions of the different variables (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 Vt highlights the challenges of targeting one specific variable in designing protective ventilatory strategies. This is particularly important given the findings from recent preclinical animal studies that, for the same MP, strategies employing higher rather than lower Vt had increased injury (30, 31). All these findings highlight the need for prospective validation of ventilator strategies that target reduced MP. Of importance, computational modeling of the impact of targeting these variables (or combinations of different VILI indices) may identify promising nonintuitive 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 variable 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 used. 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 physiologic 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 $Paco_2$, rather than pH, which is often modified by entirely nonventilator 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 Vt. Since this contradicts the current consensus on using lower Vt 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.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (http://journals.lww.com/ccmjournal).

Drs. Das, Hardman, and Bates received support for article research from the Research Councils UK (RCUK). Drs. Hardman's and Bates's institution received funding from Engineering and Physical Sciences RCUK (Grant Number EP/P023444/1). Dr. Yehya's institution received funding from the National Heart, Lung, and Blood Institute and he received support for article research from the National Institutes of Health (NIH) (Grant Number NIH K23 HL-136688). The remaining authors have disclosed that they do not have any potential conflicts of interest.

Clinical data were collected at the Children's Hospital of Philadelphia and the study was performed at The University of Warwick.

For information regarding this article, E-mail: yehyan@email.chop.edu; D.Bates@warwick.ac.uk

---

REFERENCES

1. Gattinoni L, Tonetti T, Cressoni M, et al: Ventilator-related causes of lung injury: The mechanical power. *Intensive Care Med* 2016; 42:1567–1575
2. Vasques F, Duscio E, Pasticci I, et al: Is the mechanical power the final word on ventilator-induced lung injury?—we are not sure. *Ann Transl Med* 2018; 6:395
3. Serpa Neto A, Deliberato RO, Johnson AEW, et al; PROVE Network Investigators: Mechanical power of ventilation is associated with mor-

Copyright © 2020 by the Society of Critical Care Medicine and Wolters Kluwer Health, Inc. All Rights Reserved.

tality in critically ill patients: An analysis of patients in two observational cohorts. *Intensive Care Med* 2018; 44:1914–1922

4. Amato MB, Meade MO, Slutsky AS, et al: Driving pressure and survival in the acute respiratory distress syndrome. *N Engl J Med* 2015; 372:747–755
5. Das A, Camporota L, Hardman JG, et al: What links ventilator driving pressure with survival in the acute respiratory distress syndrome? A computational study. *Respir Res* 2019; 20:29
6. Erickson S, Schibler A, Numa A, et al; Paediatric Study Group; Australian and New Zealand Intensive Care Society: Acute lung injury in pediatric intensive care in Australia and New Zealand: A prospective, multicenter, observational study. *Pediatr Crit Care Med* 2007; 8:317–323
7. Albuali WH, Singh RN, Fraser DD, et al: Have changes in ventilation practice improved outcome in children with acute lung injury? *Pediatr Crit Care Med* 2007; 8:324–330
8. Khemani RG, Conti D, Alonzo TA, et al: Effect of tidal volume in children with acute hypoxemic respiratory failure. *Intensive Care Med* 2009; 35:1428–1437
9. de Jager P, Burgerhof JG, van Heerde M, et al: Tidal volume and mortality in mechanically ventilated children: A systematic review and meta-analysis of observational studies*. *Crit Care Med* 2014; 42:2461–2472
10. Yehya N, Thomas NJ: Disassociating lung mechanics and oxygenation in pediatric acute respiratory distress syndrome. *Crit Care Med* 2017; 45:1232–1239
11. Yehya N, Keim G, Thomas NJ: Subtypes of pediatric acute respiratory distress syndrome have different predictors of mortality. *Intensive Care Med* 2018; 44:1230–1239
12. Khemani RG, Smith L, Lopez-Fernandez YM, et al; Pediatric Acute Respiratory Distress syndrome Incidence and Epidemiology (PARDIE) Investigators; Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network: Paediatric acute respiratory distress syndrome incidence and epidemiology (PARDIE): An international, observational study. *Lancet Respir Med* 2019; 7:115–128
13. Saffaran S, Das A, Hardman JG, et al: High-fidelity computational simulation to refine strategies for lung-protective ventilation in paediatric acute respiratory distress syndrome. *Intensive Care Med* 2019; 45:1055–1057
14. Huhle R, Serpa Neto A, Schultz MJ, et al: Is mechanical power the final word on ventilator-induced lung injury?-no. *Ann Transl Med* 2018; 6:394
15. Yehya N, Thomas NJ, Khemani RG: Risk stratification using oxygenation in the first 24 hours of pediatric acute respiratory distress syndrome. *Crit Care Med* 2018; 46:619–624
16. Brower RG, Matthay MA, Morris A, et al; Acute Respiratory Distress Syndrome Network: Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000; 342:1301–1308
17. Das A, Cole O, Chikhani M, et al: Evaluation of lung recruitment maneuvers in acute respiratory distress syndrome using computer simulation. *Crit Care* 2015; 19:8
18. Chikhani M, Das A, Haque M, et al: High PEEP in acute respiratory distress syndrome: Quantitative evaluation between improved arterial oxygenation and decreased oxygen delivery. *Br J Anaesth* 2016; 117:650–658
19. Khemani RG, Markovitz BP, Curley MAQ: Characteristics of children intubated and mechanically ventilated in 16 PICUs. *Chest* 2009; 136:765–771
20. Santschi M, Jouvet P, Leclerc F, et al; PALIVE Investigators; Pediatric Acute Lung Injury and Sepsis Investigators Network (PALISI); European Society of Pediatric and Neonatal Intensive Care (ESPNIC): Acute lung injury in children: Therapeutic practice and feasibility of international clinical trials. *Pediatr Crit Care Med* 2010; 11:681–689
21. de Durante G, del Turco M, Rustichini L, et al: ARDSNet lower tidal volume ventilatory strategy may generate intrinsic positive end-expiratory pressure in patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2002; 165:1271–1274
22. Brower RG, Lanken PN, MacIntyre N, et al; National Heart, Lung, and Blood Institute ARDS Clinical Trials Network: Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. *N Engl J Med* 2004; 351:327–336
23. Mercat A, Richard JC, Vielle B, et al; Expiratory Pressure (Express) Study Group: Positive end-expiratory pressure setting in adults with acute lung injury and acute respiratory distress syndrome: A randomized controlled trial. *JAMA* 2008; 299:646–655
24. Meade MO, Cook DJ, Guyatt GH, et al; Lung Open Ventilation Study Investigators: Ventilation strategy using low tidal volumes, recruitment maneuvers, and high positive end-expiratory pressure for acute lung injury and acute respiratory distress syndrome: A randomized controlled trial. *JAMA* 2008; 299:637–645
25. Cavalcanti AB, Suzumura ÉA, Laranjeira LN, et al; Writing Group for the Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial (ART) Investigators: Effect of lung recruitment and titrated positive end-expiratory pressure (PEEP) vs low PEEP on mortality in patients with acute respiratory distress syndrome: A randomized clinical trial. *JAMA* 2017; 318:1335–1345
26. Bellani G, Laffey JG, Pham T, et al; LUNG SAFE Investigators; ESICM Trials Group: Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. *JAMA* 2016; 315:788–800
27. Laffey JG, Bellani G, Pham T, et al; LUNG SAFE Investigators and the ESICM Trials Group: Potentially modifiable factors contributing to outcome from acute respiratory distress syndrome: The LUNG SAFE study. *Intensive Care Med* 2016; 42:1865–1876
28. Retamal J, Borges JB, Bruhn A, et al: High respiratory rate is associated with early reduction of lung edema clearance in an experimental model of ARDS. *Acta Anaesthesiol Scand* 2016; 60:79–92
29. Retamal J, Bugedo G, Larsson A, et al: High PEEP levels are associated with overdistension and tidal recruitment/derecruitment in ARDS patients. *Acta Anaesthesiol Scand* 2015; 59:1161–1169
30. Moraes L, Silva PL, Thompson A, et al: Impact of different tidal volume levels at low mechanical power on ventilator-induced lung injury in rats. *Front Physiol* 2018; 9:318
31. Santos RS, Maia LA, Oliveira MV, et al: Biologic impact of mechanical power at high and low tidal volumes in experimental mild acute respiratory distress syndrome. *Anesthesiology* 2018; 128:1193–1206

Copyright © 2020 by the Society of Critical Care Medicine and Wolters Kluwer Health, Inc. All Rights Reserved.