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, MSc1; Anup Das, PhD1; John G. Laffey, MD2; Jonathan G. Hardman, PhD3; Nadir Yehya, MD4; Declan G. Bates, PhD1

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.


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 (∆P) (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):

\[
MP = 0.098 \times RR \times \left( V_{T}^{0.5} \times \left[ 0.5 \times EL_{rs} \right] + RR \times \left( \frac{1+I:E}{60 \times I:E} \times R_{res} \right) + V_{T} \times PEEP \right)
\]
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 positive end-expiratory pressure (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 PEEP 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 reanalyses of adult ARDS cohorts, and while initial studies are in progress (NCT03616704 and NCT03939260), an intervention 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 V$_t$ 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 V$_t$ were collected at the ventilator for patients with V$_t$ 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 V$_t$ 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 V$_t$ 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](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](http://links.lww.com/CCM/F483)). The optimal parameterization ([Supplemental File, section S4, Supplemental Digital Content 1, http://links.lww.com/CCM/F483](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
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), \( Fio_2 \), PEEP, and duty cycle (DC, inspiratory-to-total time ratio) to identify which settings produced minimum values of the following quantities:

1) \( \Delta P \) (difference between \( P_{plat} \) and PEEP), with \( P_{plat} \) is calculated directly from the simulator.

2) \( MP \), defined as (1):

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

(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:

\[
MP = 0.098 \times RR \times V_t \times \left( PIP \times 0.5 \times \Delta P \right)
\]

(2)

3) A modified version of \( MP \), given by:

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

(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 \( \Delta P \), 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 \( \Delta P \), 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\(_2\)O 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>
<thead>
<tr>
<th>TABLE 1. Allowable Ranges of Variation for Ventilator Variables (Approach 1 and 2) and Predefined Safety Constraints (Approach 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Variable</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Allowable ranges for ventilator variables</td>
</tr>
<tr>
<td>Positive end-expiratory pressure (cm H(_2)O)</td>
</tr>
<tr>
<td>Respiratory rate (breaths/min)</td>
</tr>
<tr>
<td>Tidal volume (mL·kg(^{-1}))</td>
</tr>
<tr>
<td>Duty cycle</td>
</tr>
<tr>
<td>( Fio_2 )</td>
</tr>
<tr>
<td>Predefined safety constraints</td>
</tr>
<tr>
<td>( Pao_2 ) (mm Hg)</td>
</tr>
<tr>
<td>( Paco_2 ) (mm Hg)</td>
</tr>
<tr>
<td>Peak inspiratory pressure (cm H(_2)O)</td>
</tr>
</tbody>
</table>

Dashes indicate lower limit was not set.
RESULTS

The Simulator Accurately Represents Individual Patient Data

The ability of the simulator to reproduce patient data was verified by comparing its responses (Pao2 and Paco2) 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 ∆P, MP, and MMP Were Achieved in Both Cohorts

When ABGs were allowed to vary within prespecified ranges (Table 1), average maximum reductions in ∆P of 3.0 ± 2.2 cm H2O (23%) compared with baseline values in the pediatric cohort and 3.2 ± 2.1 cm H2O (23%) in the adult cohort were achievable (Fig. 2). Reductions in ∆P of over 1 cm H2O 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 (Pao2), although Paco2 did consistently increase toward the upper limits (Supplemental File, Fig. S5, Supplemental Digital Content 1, http://links.lww.com/CCM/F483). In both cohorts, settings that minimized ∆P also reduced MP and MMP whereas settings that minimized MP and MMP “increased” ∆P (largely due to the resulting increases in Vt (see below).

When the optimizations were constrained to allow “no” deterioration in gas exchange (i.e., only changes that maintained, or improved, Pao2 and Paco2 with respect to baseline values), reductions were achievable in ∆P of 1.6 ± 1.4 cm

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.
H₂O (12%) and 0.4 ± 1.0 cm H₂O (2%) were achievable compared with baseline values in the pediatric and adult cohorts, respectively (Fig. 3). Reductions of ∆P of over 1 cm H₂O 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 ∆P and MP Are Achieved by Distinct Ventilation Strategies

Minimum values of MP in both adult and pediatric cohorts were produced by “increased” Vt (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 H₂O Supp. File, Fig. S7, Supplemental Digital Content 1, http://links.lww.com/CCM/F483). Fio₂ increased in both pediatric and adult cohorts (pediatric: +39%, adult: +26%).

Similar changes in Vt, 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 H₂O [+39%], adult: 3.5 ± 5.0 cm H₂O [+52%]) along with lower values of Fio₂ in pediatric patients (–21%).

In the pediatric cohort, minimum ∆P was achieved by reducing Vt (1.3 ± 1.6 mL·kg⁻¹ [–15%]) while increasing RR and PEEP (2.2 ± 3.5 cm H₂O [+32%]). No changes in DC were observed in either cohort when targeting ∆P. Patterns of changes in ventilator settings were consistent in most cases between Approach 1 (allowing some deterioration in patient gas exchange) and Approach 2 (allowing no deterioration in blood gas values; Supp. File, Fig. S7, http://links.lww.com/CCM/F483) and Approach 2 (allowing no deterioration in blood gas values; Supp. File, Fig. S8, Supplemental Digital Content 1, http://links.lww.com/CCM/F483), although when minimizing ∆P in pediatric patients, Approach 2 produced higher values of Fio₂ 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 $\Delta P$, 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" $V_t$ (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 $V_t$ 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 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 $\Delta P$ 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, $\Delta P$ could still be significantly reduced in this cohort by moderately increasing PEEP.

Our findings provide novel insights into the challenges of using either $\Delta P$ or MP to develop protective ventilatory strategies. In our models, targeting reductions in $\Delta P$ led to increased RR and increased PEEP. Although a strong association between higher $\Delta P$ and mortality has been demonstrated (4, 26, 27), $\Delta P$ 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 clinical trial (25), a ventilatory strategy that decreased $\Delta P$ resulted in increased mortality. The usefulness of targeting $\Delta P$ 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 $V_t$ 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 $V_t$ had increased injury (30, 31). All these findings highlight the need for prospective validation of ventilator strategies that target reduced MP. Of importance, computational 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 gases 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 $\text{PaCO}_2$, 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 $\Delta P$ (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 $\Delta P$, 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 $\Delta P$ 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

3. Serpa Neto A, Deliberato RO, Johnson AEW, et al; PROVE Network Investigators: Mechanical power of ventilation is associated with mor-
Saffaran et al


