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Original Article

# Association of ventilation volumes, pressures and rates with the mechanical power of ventilation in patients without acute respiratory distress syndrome: exploring the impact of rate reduction

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## Summary

**Introduction** High mechanical power is associated with mortality in patients who are critically ill and require invasive ventilation. It remains uncertain which components of mechanical power – volume, pressure or rate – increase mechanical power the most.

**Methods** We conducted a post hoc analysis of a database containing individual patient data from three randomised clinical trials of ventilation in patients without acute respiratory distress syndrome. The primary endpoint was mechanical power. We used linear regression; double stratification to create subgroups of participants; and mediation analysis to assess the impact of changes in volumes, pressures and rates on mechanical power.

**Results** A total of 1732 patients were included and analysed. The median (IQR [range]) mechanical power was 12.3 (9.3–17.1 [3.7–50.1]) $J.min^{-1}$. In linear regression, respiratory rate (36%) and peak pressure (51%) explained most of the increase in mechanical power. Increasing quintiles of peak pressure stratified on constant levels of respiratory rate resulted in higher risks of high mechanical power (relative risk 2.2 (95%CI 1.8–2.6), $p < 0.01$), while decreasing quintiles of respiratory rate stratified on constant levels of peak pressure resulted in lower risks of high mechanical power (relative risk 0.2 (95%CI 0.2–0.3), $p < 0.01$). Mediation analysis showed that a reduction in respiratory rate, with the increase in tidal volume, partially mediates an effect of reduction in mechanical power (average causal mediation effect -0.10, 95%CI -0.12 to -0.09, $p < 0.01$), but still with a direct effect of tidal volume on mechanical power (average direct effect 0.15, 95%CI 0.11–0.19, $p < 0.01$).

**Discussion** In this cohort of patients without acute respiratory distress syndrome, pressure and respiratory rate were the most important determinants of mechanical power. The respiratory rate may be the most attractive ventilator setting to adjust when targeting a lower mechanical power.

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‡Protective Ventilation in Patients Without ARDS (PReVENT).
§Restricted versus Liberal Positive End-expiratory Pressure in Patients Without ARDS (RELAx).
*Collaborative authors are detailed in online Supporting Information Appendix S1.

## Introduction

High mechanical power of ventilation is associated with mortality and morbidity in patients who are critically ill and receiving invasive ventilation [1–4]. Even brief periods of high mechanical power have been shown to have a detrimental impact on outcome [1]. Mechanical power represents the overall energy transferred from the ventilator to the respiratory system and is derived from three components: tidal volumes; pressures; and rates [5].

It remains uncertain how specific components of mechanical power should be titrated to minimise harm to patients. Altering one component may affect another in ways that have contrasting effects on mechanical power. For example, reducing tidal volume ($V_T$) could lead to a decrease in peak and driving pressure (Ppeak and ΔP) [6], but an accompanying increase in respiratory rate might nullify (or even amplify) the reduction in mechanical power. Furthermore, other ventilator settings may impact mechanical power through uncertain effects on the other components. For instance, higher positive end-expiratory pressure (PEEP) might reduce mechanical power, but only in patients for whom higher PEEP decreases ΔP [7].

In this pooled individual patient data analysis of three ventilation studies in patients who were critically ill and receiving invasive ventilation, we examined the relative effects of the components of mechanical power using linear regression; double stratification; and mediation analysis. Our objective was to explore the impact of rate reduction on mechanical power. We hypothesised that the individual components have diverse effects on mechanical power and that respiratory rate reduction is the optimal way to reduce overall mechanical power.

## Methods

The three randomised clinical trials included in this analysis were approved by the Institutional Review Board of the Academic Medical Centre, Amsterdam, the Netherlands [8–10]. Written informed consent was obtained from patients or their legal representatives. Alignment between research methodology, design, inclusion and exclusion criteria and data collection procedures enabled the merging of individual participant data for this analysis. Data were pooled to include baseline characteristics; ventilator parameters after 1 h and at a fixed time-point in the morning in the first three full calendar days; and outcomes (online Supporting Information Appendices S2 and S3).

The primary endpoint for this study was mechanical power. Secondary endpoints include 28-day mortality; ICU mortality; ICU duration of stay; and duration of mechanical ventilation. The number of complete datasets in the pooled database served as the sample size. A detailed statistical analysis plan is provided in online Supporting Information Appendix S4. Proportions were compared using $X^2$ or Fisher's exact tests, and continuous variables using paired t-tests or Wilcoxon signed-rank tests. Missing data were < 0.5% (online Supporting Information Table S1). A p value < 0.05 was considered significant. Analyses were performed with R version 4.0.3 (R Foundation, Vienna, Austria).

To assess the continuous relationship between the components of mechanical power, a linear regression analysis was performed with mechanical power as a continuous variable. Patients were grouped by an upper quartile cut-point of 17 $J.min^{-1}$ [1, 3]. Four subgroups each for $V_T$ and respiratory rate, and for Ppeak and respiratory rate were created. Mechanical power levels were visualised using cumulative distribution graphs for each subgroup. To assess the impact of the ventilator variables respiratory rate and Ppeak on mechanical power, we used a double stratification approach creating quintiles based on these variables. Relative risk for high mechanical power (≥ 17 $J.min^{-1}$ [1, 3]) and 28-day mortality was calculated for

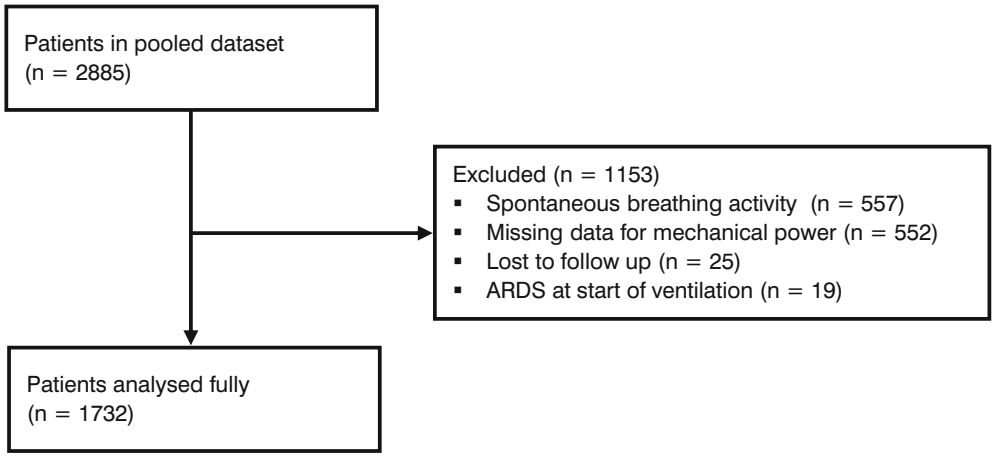


**Figure 1** Study flowchart of patients included in this analysis. ARDS, acute respiratory distress syndrome.

each quintile, with results displayed in stacked-bar plots with error bars. Analyses were repeated using a median mechanical power cut-off (≥ 12.3 J.min$^{-1}$) and including ΔP as a variable.

We performed a mediation analysis to explore how variables interact through a third variable, the mediator. This approach helps determine whether the effect of the first variable on the second is direct or occurs through the mediator. In our study, we assessed the impact of changes in Ppeak and respiratory rate as potential mediators, according to pre-specified $V_T$ groups, on the amount of mechanical power. We adjusted for confounders based on clinical relevance, including compliance of the respiratory system; bicarbonate; ventilatory ratio; and ratio of arterial oxygen partial pressure to fractional inspired oxygen ($PaO_2/F_IO_2$). In the primary analysis, mechanical power was dichotomised (cut-off 17 J.min$^{-1}$) and in a sensitivity analyses it was a continuous variable. We estimated the total effect (of $V_T$ on mechanical power), the average causal mediation effect (how much of the effect of $V_T$ on mechanical power is explained by the mediator) and the average direct effect (how much of the effect of $V_T$ on mechanical power is still explained by $V_T$ after considering the effect of the mediator). Missing data were addressed via multiple imputations with predictive mean matching [11]. Centres were included as random effects to adjust for this potential confounder.

## Results

Of 2871 patients randomised in NEBULAE, PReVENT or RELAx [8–10], 1732 (60%) were included in this analysis (Fig. 1). Those patients who were receiving invasive ventilation with a spontaneous ventilation mode at the first calendar day or had missing data to calculate mechanical power were not included. Patients with high mechanical power were more often male and receiving invasive ventilation for respiratory failure (Table 1 and online Supporting Information Table S2).

In the entire cohort, median (IQR [range]) mechanical power was 12.3 (9.3–17.1 [3.7–50.1]) J.min$^{-1}$ (Table 2). Participants with mechanical power ≥ 17 J.min$^{-1}$ received invasive ventilation with higher median $V_T$, respiratory rate, median Ppeak, ΔP and median PEEP. Creating groups using the median mechanical power level of 12.3 J.min$^{-1}$ did not change these findings (online Supporting Information Table S3).

Mechanical power increased progressively across the following patient groups receiving mechanical ventilation: low $V_T$ and low respiratory rate; high $V_T$ and low respiratory rate; low $V_T$ and high respiratory rate; and high $V_T$ and high respiratory rate (Fig. 2 and online Supporting Information Table S4). Likewise, mechanical power increased progressively across the following patient group receiving invasive ventilation: low Ppeak and low respiratory rate; low Ppeak and high respiratory rate; high Ppeak and low respiratory rate; and high Ppeak and high respiratory rate (Fig. 2 and online Supporting Information Table S5).

Tidal volume explained 3% of the increase in the amount of mechanical power; respiratory rate explained 36%; ΔP explained 24%; and Ppeak explained 51% (online Supporting Information Table S6). In the four subgroups of low and high $V_T$ and low and high respiratory rate, Ppeak and respiratory rate were also found to explain most of the variance in mechanical power, except in the group with low $V_T$ and low respiratory rate (online Supporting Information Table S7).

**Table 1** Patient characteristics and clinical outcomes with a mechanical power cut-off of 17 J.min$^{-1}$. Values are number (proportion) or median (IQR [range]).

| | All participants n = 1732 | Patients with high mechanical power n = 440 | Patients with low mechanical power n = 1292 | p value |
|---|---|---|---|---|
| Sex; male | 1102 (64%) | 322 (73%) | 779 (60%) | 0.042 |
| Age; y | 67 (57–75 [18–98]) | 65 (57–73 [19–88]) | 67 (57–75 [18–98]) | 0.061 |
| Weight; kg | 80 (70–90 [33–200]) | 84 (71–95 [38–140]) | 79 (69–89 [33–200]) | < 0.001 |
| Predicted bodyweight; kg | 70 (61–75 [30–98]) | 71 (63–79 [30–96]) | 68 (60–75 [32–98]) | < 0.001 |
| BMI; kg.m$^{-2}$ | 26 (23–29 [14–58]) | 26 (24–30 [14–49] | 26 (23–29 [14–58]) | < 0.001 |
| APACHE 2 score | 23 (18–29 [0–71]) | 25 (18–31 [0–71]) | 23 (18–29 [0–71]) | 0.030 |
| Reason for ICU admission | | | | < 0.001 |
| Medical | 1334 (77%) | 375 (85%) | 959 (74%) | |
| Surgical | 398 (23%) | 65 (15%) | 333 (26%) | |
| Reason for tracheal intubation | | | | < 0.001 |
| Respiratory failure | 675 (39%) | 219 (49%) | 456 (35%) | |
| Cardiac arrest | 466 (27%) | 73 (17%) | 393 (30%) | |
| Decreased consciousness | 217 (13%) | 69 (16%) | 148 (11%) | |
| After surgery | 262 (15%) | 48 (11%) | 214 (1%7) | |
| Other | 112 (6%) | 31 (7%) | 91 (7%) | |
| Duration of ventilation; days | 3 (1–8 [0–34]) | 4 (1–9 [0–28]) | 3 (1–7 [0–34]) | 0.030 |
| ICU duration of stay; days | 5 (3–10 [0–158]) | 6 (3–12 [0–73]) | 5 (3–10 [0–158]) | 0.022 |
| ICU mortality | 507 (29%) | 164 (37%) | 343 (27%) | < 0.001 |
| 28-day mortality | 579 (33%) | 183 (42%) | 396 (31%) | < 0.001 |
| 90-day mortality | 648 (38%) | 198 (45%) | 450 (35%) | < 0.001 |

**Table 2** Ventilatory variables with a mechanical power cut-off of 17 J.min$^{-1}$. Values are median (IQR [range]).

| | All patients n = 1732 | Patients with high mechanical power n = 440 | Patients with low mechanical power n = 1292 | p value |
|---|---|---|---|---|
| Mechanical power; J.min$^{-1}$ | 12.3 (9.3–17.1 [3.7–50.1]) | 20.9 (18.7–24.4 [17.0–50.1]) | 10.7 (8.4–13.2 [1.7–17.0]) | < 0.001 |
| $V_T$; ml | 493 (422–574 [153–1285]) | 514 (460–601 [295–1285]) | 483 (413–564 [153–1111]) | < 0.001 |
| $V_T$; ml.kg predicted bodyweight$^{-1}$ | 7.2 (6.3–8.7 [4.0–21.5]) | 7.4 (6.4–8.9 [4.6–18.1]) | 7.1 (6.2–8.6 [4.0–21.5]) | 0.010 |
| Respiratory rate; breaths.min$^{-1}$ | 19 (16–23 [6–46]) | 24 (20–28 [11–46]) | 18 (15–20 [6–37]) | < 0.001 |
| Minute volume; l.min$^{-1}$ | 9.3 (7.8–11.3 [2.2–25.7]) | 12.3 (10.9–14.3 [7.6–25.7]) | 8.6 (7.3–9.9 [2.2–19.5]) | < 0.001 |
| Ppeak; cm$H_2O^{-1}$ | 20 (17–24 [5–46]) | 26 (23–30 [5–46]) | 19 (16–22 [5–44]) | < 0.001 |
| PEEP; cm$H_2O^{-1}$ | 8 (5–8 [0–25]) | 10 (8–12 [0–25]) | 7 (5–8 [0–20]) | < 0.001 |
| ΔP; cm$H_2O^{-1}$ | 13 (10–16 [4–38]) | 16 (13–20 [4–36]) | 12 (9–15 [4–38]) | < 0.001 |
| $C_{RS}$; l.cm$H_2O^{-1}$ | 38.4 (28.7–53.3 [5.7–244.1]) | 31.8 (24.0–42.3 [9.0–214]) | 41.0 (30.8–56.8 [5.7–244.1]) | < 0.001 |
| $F_IO_2$; % | 40 (35–55 [21–100]) | 50 (40–65 [21–100]) | 40 (30–50 [21–100]) | < 0.001 |
| pH | 7.36 (7.27–7.42 [7.06–7.67] | 7.35 (7.26–7.43 [7.06–7.57]) | 7.36 (7.28–7.41 [7.09–7.67] | 0.960 |
| $PaCO_2$; kPa | 4.9 (4.1–5.6 [1.8–9.5]) | 4.8 (3.9–5.5 [2.0–9.4]) | 4.9 (4.2–5.6 [1.8–9.5] | 0.470 |
| $PaO_2/F_IO_2$; kPa | 32.3 (20.4–48.0 [3.1–114.4] | 25.3 (17.3–35.6 [3.1–93.1] | 35.4 (35.5–50.8 [4.0–114.4] | < 0.001 |

$V_T$, tidal volume; Ppeak, peak pressure; PEEP, positive end-expiratory pressure; ΔP, driving pressure; $C_{RS}$, respiratory system compliance; $F_IO_2$, fraction of inspired oxygen; pH, arterial pH; $PaCO_2$, partial arterial pressure of carbon dioxide; $PaO_2$, partial arterial pressure of oxygen.

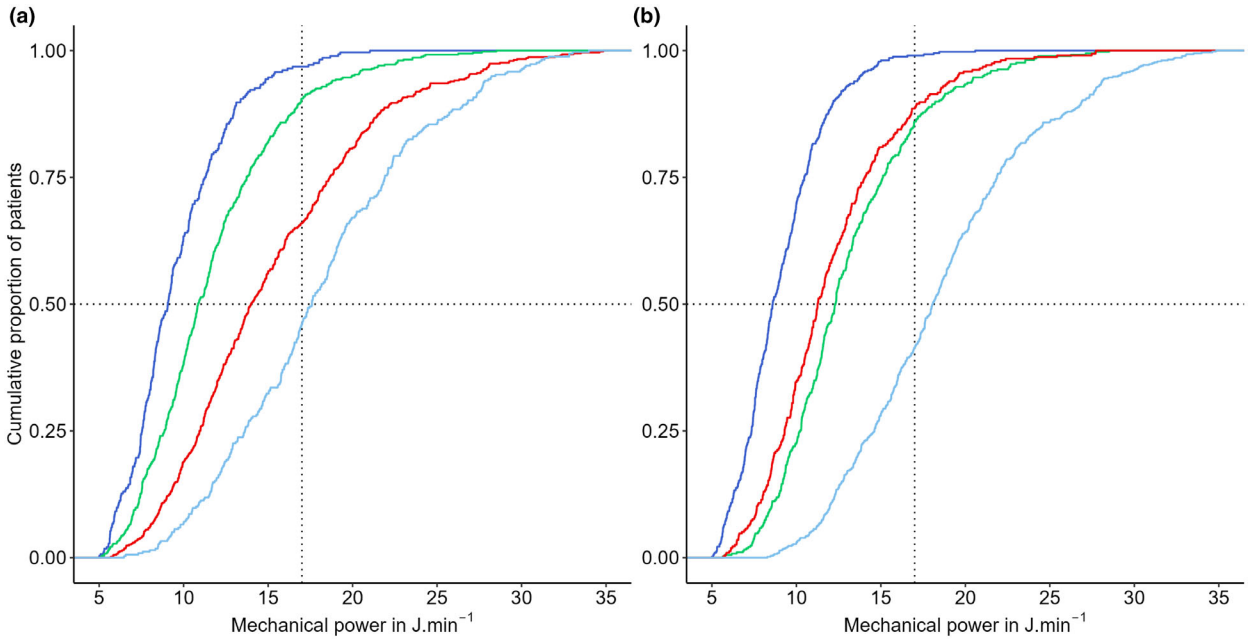


**Figure 2** Cumulative distribution plots of mechanical power in four groups. (a) Dark blue, low tidal volume ($V_T$) and low respiratory rate; green, high $V_T$ and low respiratory rate; red, low $V_T$ and high respiratory rate; light blue, high $V_T$ and high respiratory rate. (b) Dark blue, low peak pressure (Ppeak) and low respiratory rate; red, low Ppeak and high respiratory rate; green, high Ppeak and low respiratory rate; light blue, high Ppeak and high respiratory rate. Vertical dotted lines represent a broadly accepted safety cut-off for mechanical power of 17 J.min$^{-1}$ and horizontal dotted lines show the median proportion of patients reaching this cut-off.

Double stratification led to quintiles with differences in patient and baseline characteristics (online Supporting Information Tables S8–S10) and differences in ventilation characteristics (online Supporting Information Tables S11–S13). An increasing Ppeak and matched respiratory rate increased the relative risk for mechanical power ≥ 17 J.min$^{-1}$ (relative risk 2.2, 95%CI 1.8–2.6, $p < 0.01$) (Fig. 3). An increasing Ppeak and decreasing respiratory rate did not increase the relative risk for mechanical power ≥ 17 J.min$^{-1}$. A matched Ppeak and decreasing respiratory rate decreased the relative risk of mechanical power ≥ 17 J.min$^{-1}$ (relative risk 0.2, 95%CI 0.2–0.3, $p < 0.01$). Replacing Ppeak by ΔP did not change these findings (online Supporting Information Figure S1). Findings were similar when a cut-off for mechanical power of 12.3 J.min$^{-1}$ was used (online Supporting Information Figure S2). A reduction in respiratory rate with the increase in $V_T$, partially mediated a reduction in mechanical power, but the direct effect of $V_T$ was larger. A reduction in Ppeak, with increased $V_T$ mediated increased mechanical power but the direct effect of increasing $V_T$ on mechanical power was not significant (Table 3, online Supporting Information Figures S3 and S4). Replacing Ppeak for ΔP (online Supporting Information Table S14 and Figure S5) and using mechanical power as a continuous variable (online Supporting Information Table S15 and Figures S6 and S7) did not change these findings.

Ppeak matched with increasing respiratory rate increased the relative risk for 28-day mortality (relative risk 1.2, 95%CI 1.0–1.4, $p < 0.01$). However, Ppeak matched with decreasing respiratory rate decreased the relative risk for 28-day mortality (relative risk 0.8, 95%CI 0.7–0.9, $p < 0.01$) (Fig. 3). Patients with a mechanical power level ≥ 17 J.min$^{-1}$ had higher 28 day and ICU mortality, longer ICU duration of stay and longer duration of ventilation (Table 1). This effect was similar using the median (IQR [range]) mechanical power of 12.3 (9.3–17.1 [3.7–50.1]) J.min$^{-1}$ (online Supporting Information Table S2) and in the double stratification groups (online Supporting Information Tables S8–S10).

## Discussion

In this post hoc pooled individual patient level analysis of three randomised clinical trials in patients who were critically ill without ARDS, we found that a rise in mechanical power was best explained by increased Ppeak and respiratory rate. This is important, because respiratory rate is underexplored as a potentially attractive variable to adjust when targeting a lower

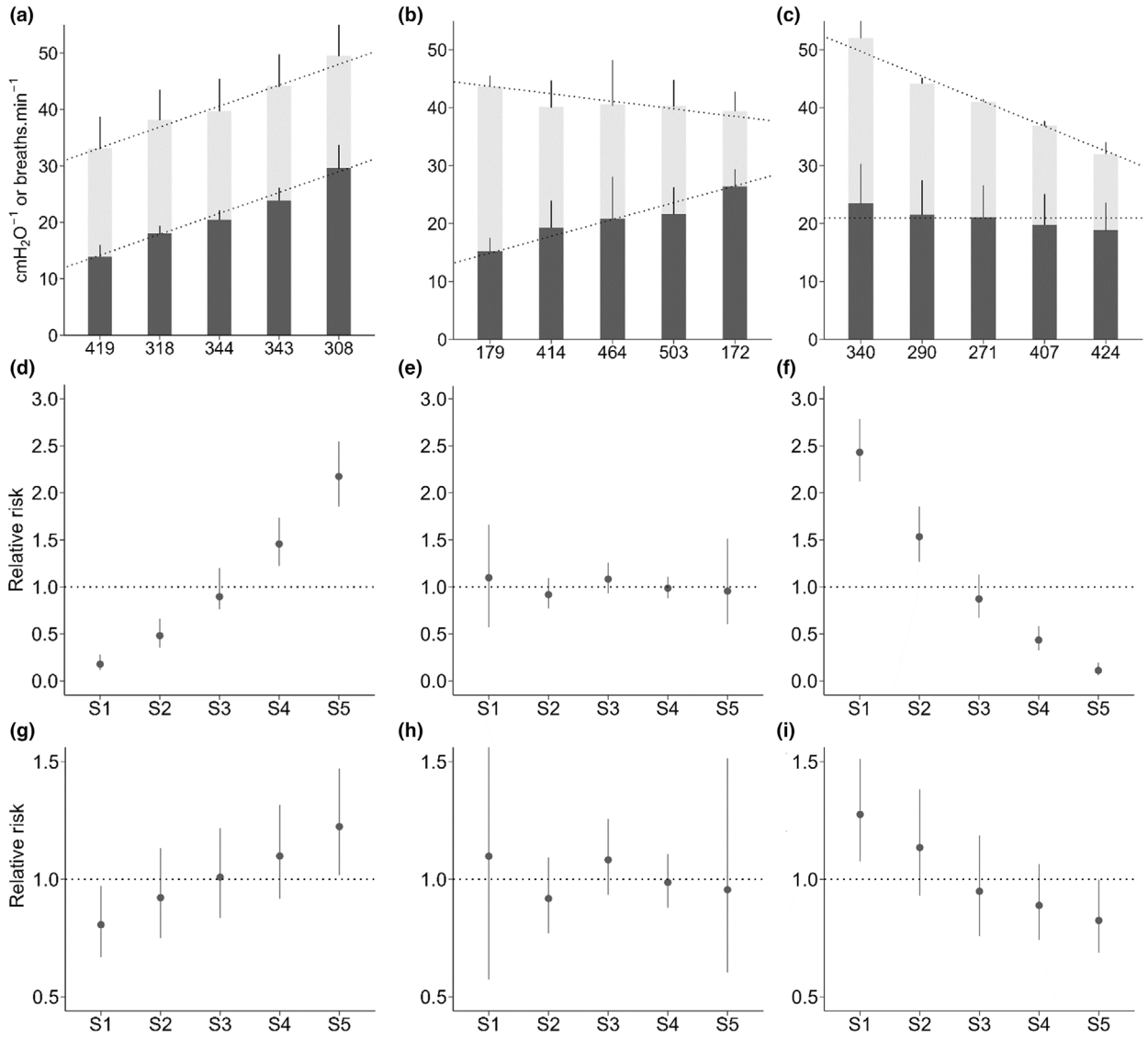


**Figure 3** Top panels: – stacked bar plots of stratified and resampled peak pressure (Ppeak) (dark grey) and respiratory rate (light grey); middle panels: – error bars of relative risk of mechanical power ≥ 17 J.min$^{-1}$; and bottom panels: – error bars of relative risk of 28-day mortality; each resampling produced subsamples (S1 to S5) with similar mean values for one ventilator variable but different values for the other variable; top panels show double stratification for (a) increasing Ppeak and matched respiratory rate; (b) increasing Ppeak and decreasing respiratory rate; and (c) matched Ppeak and decreasing respiratory rate. Lines at the top of the bars represent the standard deviation of the corresponding value of the subsamples. Middle panels, corresponding relative risks of high mechanical power ≥ 17 J.min$^{-1}$ are shown, calculated for each subsample; error bars represent the 95%CI for (d) increasing Ppeak and matched respiratory rate; (e) increasing Ppeak and decreasing respiratory rate; and (f) matched Ppeak and decreasing respiratory rate. Bottom panels: corresponding relative risks of 28-day mortality are shown, calculated for each subsample; error bars represent the 95%CI for (g) increasing Ppeak and matched respiratory rate; (h) increasing Ppeak and decreasing respiratory rate; and (i) matched Ppeak and decreasing respiratory rate.

mechanical power. Further work is required to move beyond these observed associations to an interventional randomised trial to test if lower respiratory rate strategies can reduce mechanical power and the subsequent risk of lung injury in patients who require mechanical ventilation.

We have shown that an increase in any of the constituent ventilatory variables is associated with an overall increase in mechanical power; however, an increase in mechanical power was better explained by an increase in respiratory rate or Ppeak than an increase in $V_T$ or $\Delta P$. We

**Table 3** Mediation analysis results using respiratory rate and peak pressure as mediator.

| | Estimate effect (95%CI) | p value |
|---|---|---|
| **Respiratory rate** | | |
| Total effect of tidal volume | 0.05 (0.01–0.09) | 0.020 |
| Average causal mediation effect of respiratory rate | -0.10 (-0.12 to -0.09) | < 0.001 |
| Average direct effect of increase of tidal volume | 0.15 (0.11–0.19) | < 0.001 |
| **Peak pressure** | | |
| Total effect of tidal volume | 0.05 (-0.01–0.09) | 0.280 |
| Average causal mediation effect of peak pressure | 0.08 (0.05–0.10) | < 0.001 |
| Average direct effect of increase of tidal volume | -0.03 (-0.07–0.01) | 0.140 |

further explored that mechanical power was highest in subgroups of patients receiving ventilation with higher respiratory rate. In addition, a reduction in mechanical power was partially mediated by lower respiratory rate, but a higher $V_T$ led to a higher mechanical power. Outcomes were worse in patients with high mechanical power, and in the subgroups with higher respiratory rate. This pattern was seen for all clinical endpoints.

This analysis focused on the question of which ventilator variable is most attractive to adjust when striving to achieve reduced mechanical power levels. In the existing literature, one study showed that a protocolised decrease of the respiratory rate resulted in lower mechanical power compared with a higher respiratory rate [12]. Another retrospective study found that during surgery a higher respiratory rate was associated with a greater risk of postoperative pulmonary complications [13]. While we used real-life data collected prospectively from three studies, other investigations have used a computational simulator to evaluate the effects of changes in ventilator settings [14] or studied time-varying data of ventilation strategies using specific combinations of the four components [15]. The findings of our study increase the understanding of which of the four components to prioritise when low mechanical power levels are targeted.

One salient finding of the double stratification analysis was that reducing respiratory rate, with matched or increasing Ppeak, lowered minute volume without raising $PaCO_2$. Additionally, lowering respiratory rate with matched Ppeak increased $V_T$ but reduced ΔP in two studies of automated ventilation; a lower respiratory rate resulted in an anticipated decrease in minute volume [16, 17] without affecting gas exchange, suggesting wasted ventilation with higher respiratory rate [18]. Recent studies found that lowering respiratory rate is feasible and can effectively reduce mechanical power by following a guideline that keeps $PaCO_2$ and pH within safe thresholds [12, and Damiani, unpublished observations]. However, those studies only included patients with COVID-19, in whom the disease primarily affects the lungs and may not fully apply conditions such as sepsis-related ARDS with metabolic acidosis and increased dead space that make respiratory rate reductions less safe.

In the mediation analysis, we included confounders that might contribute to an increased respiratory rate, such as respiratory system compliance and the ventilatory ratio. The findings suggest that in this cohort of patients without ARDS, a reduction in respiratory rate together with an increase in $V_T$ leads to a lower mechanical power. Therefore, it could be feasible to increase $V_T$ within safe limits, to reduce respiratory rate and to lower mechanical power. Patients who are critically ill often have a respiratory system compliance where a strictly low $V_T$ does not always need to be pursued or has benefits [2, 19]. In the mediation analysis, an increase in $V_T$, together with a decrease in Ppeak, does not lead to a lower mechanical power. This analysis suggests that adjusting respiratory rate is the most appropriate and feasible approach to lower mechanical power, especially in the current era of low $V_T$ ventilation.

In this analysis, we used a simplified mechanical power calculation to maintain clinical relevance. Mechanical power is a complex concept with an unclear contribution from each variable. Changing one ventilatory setting has knock on influences on the multiple components that influence mechanical power. Reducing $V_T$ generally lowers ΔP and Ppeak, but further lowering $V_T$ often has limited benefits and can be harmful [2, 19]. Higher PEEP can lower ΔP by alveolar recruitment, but risks overdistension if set too high. Lung stress and strain increase with higher respiratory rate [20] and increase the risk of lung injury [21–23]. Lowering respiratory rate in volume-controlled ventilation reduces pressure by longer inspiration time but can prolong high pressure in pressure-controlled ventilation. Ppeak and ΔP are more reflective of underlying pulmonary disease and

are harder to reduce than the respiratory rate. This interplay of ventilator settings shows the difficulty in optimisation mechanical power.

We showed an association with respiratory rate and mortality and with Ppeak. While previous studies [24, 25] highlighted a strong link between ΔP and mortality, our analysis showed a stronger connection with Ppeak. The reason for this could be that most studies focused on patients with ARDS who had more severe lung disease. The patients in the datasets used were likely to have had higher compliance, where less PEEP was needed, resulting in lower and less harmful ΔP. Increasing respiratory rate is often used as a strategy to maintain $V_T$ and minimise Ppeak. While knowledge of possible harm of high respiratory rate is growing [13, 26, 27], it remains underexplored in lung-protective ventilation strategies aimed at improving outcomes.

This analysis has strengths and limitations. We used data from three robust multicentre randomised clinical studies in patients who were critically ill and receiving invasive ventilation in the ICU, meaning that ventilator data were captured prospectively and meticulously. The three studies were performed in academic and non-academic centres, increasing the generalisability of the findings. We did not include patients who were breathing spontaneously, as current equations for mechanical power were designed for use in mandatory ventilation modes. We did not include patients with ARDS, who tend to have stiffer lungs thus impacting on mechanical power. We did not include patients who required pronation, so our findings are not generalisable in this cohort. We used a simplified equation for mechanical power equations because of its convenience and wide use, but this is one of many approaches proposed in the literature [28–30]. This was a secondary analysis of three studies testing other interventions, with two of them randomising patients to lower or higher $V_T$ or PEEP, and one requiring lung-protective ventilation. Protocols were strict and may not represent wider practice. Finally, our analysis shows associations, not causality.

In summary, we found that, in patients who are critically ill but without ARDS, a rise in mechanical power was best explained by increased Ppeak and respiratory rate. We recommend that, given the current use of low $V_T$ ventilation, the respiratory rate may be a more favourable variable to adjust when aiming to reduce mechanical power and potentially lower mortality. However, this hypothesis requires confirmation through a clinical trial in which patients are allocated randomly to ventilatory strategies using lower or higher respiratory rates to understand if this can reduce the risk of iatrogenic lung injury and improve clinical outcomes.

## Acknowledgements

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## References

1. Serpa Neto A, Deliberato RO, Johnson AEW, et al. Mechanical power of ventilation is associated with mortality in critically ill patients: an analysis of patients in two observational cohorts. *Intensive Care Med* 2018; **44**: 1914–22. https://doi.org/10.1007/s00134-018-5375-6.
2. Costa ELV, Slutsky AS, Brochard LJ, et al. Ventilatory variables and mechanical power in patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2021; **204**: 303–11. https://doi.org/10.1164/rccm.202009-3467OC.
3. Urner M, Jüni P, Hansen B, Wettstein MS, Ferguson ND, Fan E. Time-varying intensity of mechanical ventilation and mortality in patients with acute respiratory failure: a registry-based, prospective cohort study. *Lancet Respir Med* 2020; **8**: 905–13. https://doi.org/10.1016/S2213-2600(20)30325-8.
4. Coppola S, Caccioppola A, Froio S, et al. Effect of mechanical power on intensive care mortality in ARDS patients. *Crit Care* 2020; **24**: 246. https://doi.org/10.1186/s13054-020-02963-x.
5. Gattinoni L, Tonetti T, Cressoni M, et al. Ventilator-related causes of lung injury: the mechanical power. *Intensive Care Med* 2016; **42**: 1567–75. https://doi.org/10.1007/s00134-016-4505-2.

6. Brower RG, Matthay MA, Morris A, Schoenfeld D, Thompson BT, Wheeler A. 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**: 1301–8. https://doi.org/10.1056/NEJM200005043421801.
7. Amato MB, Meade MO, Slutsky AS, et al. Driving pressure and survival in the acute respiratory distress syndrome. *N Engl J Med* 2015; **372**: 747–55. https://doi.org/10.1056/NEJMe1414218.
8. van Meenen DMP, van der Hoeven SM, Binnekade JM, et al. Effect of on-demand vs routine nebulization of acetylcysteine with salbutamol on ventilator-free days in intensive care unit patients receiving invasive ventilation: a randomized clinical trial. *JAMA* 2018; **319**: 993–1001. https://doi.org/10.1001/jama.2018.0949.
9. Simonis FD, Serpa Neto A, Binnekade JM, et al. Effect of a low vs intermediate tidal volume strategy on ventilator-free days in intensive care unit patients without ARDS: a randomized clinical trial. *JAMA* 2018; **320**: 1872–80. https://doi.org/10.1001/jama.2018.14280.
10. Algera AG, Pisani L, Serpa Neto A, et al. Effect of a lower vs higher positive end-expiratory pressure strategy on ventilator-free days in ICU patients without ARDS: a randomized clinical trial. *JAMA* 2020; **324**: 2509–20. https://doi.org/10.1001/jama.2020.23517.
11. van Buuren S. *Flexible Imputation of Missing Data*, 2nd edn. New York: Chapman and Hall/CRC, 2018.
12. Damiani LF, Oviedo V, Alegria L, et al. Reduction of respiratory rate in COVID-19-associated ARDS. *Respir Care* 2022; **67**: 1173–6. https://doi.org/10.4187/respcare.09938.
13. Santer P, Zheng S, Hammer M, et al. Ventilatory frequency during intraoperative mechanical ventilation and postoperative pulmonary complications: a hospital registry study. *Br J Anaesth* 2020; **125**: e130–9. https://doi.org/10.1016/j.bja.2020.02.018.
14. Saffaran S, Das A, Laffey JG, Hardman JG, Yehya N, Bates DG. 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. *Crit Care Med* 2020; **48**: 1001–8. https://doi.org/10.1097/CCM.0000000000004372.
15. Kassis EB, Hu S, Lu M, et al. Titration of ventilator settings to target driving pressure and mechanical power. *Respir Care* 2022; **68**: 199–207. https://doi.org/10.4187/respcare.10258.
16. Buiteman-Kruizinga LA, Mkadmi HE, Serpa Neto A, et al. Effect of INTELLiVENT-ASV versus conventional ventilation on ventilation intensity in patients with COVID-19 ARDS – an observational study. *J Clin Med* 2021; **10**: 10. https://doi.org/10.3390/jcm10225409.
17. Buiteman-Kruizinga LA, van Meenen DMP, Bos LDJ, van der Heiden PLJ, Paulus F, Schultz MJ. A closed-loop ventilation mode that targets the lowest work and force of breathing reduces the transpulmonary driving pressure in patients with moderate-to-severe ARDS. *Intensive Care Med Exp* 2023; **11**: 42. https://doi.org/10.1186/s40635-023-00527-1.
18. Robertson HT. Dead space: the physiology of wasted ventilation. *Eur Respir J* 2015; **45**: 1704–16. https://doi.org/10.1183/09031936.50137614.
19. Goligher EC, Costa ELV, Yarnell CJ, et al. Effect of lowering Vt on mortality in acute respiratory distress syndrome varies with respiratory system elastance. *Am J Respir Crit Care Med* 2021; **203**: 1378–85. https://doi.org/10.1164/rccm.202009-3536OC.
20. Rezoagli E, Laffey JG, Bellani G. Monitoring lung injury severity and ventilation intensity during mechanical ventilation. *Semin Respir Crit Care Med* 2022; **43**: 346–68. https://doi.org/10.1055/s-0042-1748917.
21. Hotchkiss JR Jr, Blanch L, Murias G, et al. Effects of decreased respiratory frequency on ventilator-induced lung injury. *Am J Respir Crit Care Med* 2000; **161**: 463–8. https://doi.org/10.1164/ajrccm.161.2.9811008.
22. Protti A, Maraffi T, Milesi M, et al. Role of strain rate in the pathogenesis of ventilator-induced lung edema. *Crit Care Med* 2016; **44**: e838–45. https://doi.org/10.1097/CCM.0000000000001718.
23. Akoumianaki E, Vaporidi K, Georgopoulos D. The injurious effects of elevated or nonelevated respiratory rate during mechanical ventilation. *Am J Respir Crit Care Med* 2019; **199**: 149–57. https://doi.org/10.1164/rccm.201804-0726CI.
24. Tonna JE, Peltan I, Brown SM, Herrick JS, Keenan HT. Mechanical power and driving pressure as predictors of mortality among patients with ARDS. *Intensive Care Med* 2020; **46**: 1941–3. https://doi.org/10.1007/s00134-020-06130-2.
25. Wu HP, Leu SW, Lin SW, et al. Role of changes in driving pressure and mechanical power in predicting mortality in patients with acute respiratory distress syndrome. *Diagnostics (Basel)* 2023; **13**: 13. https://doi.org/10.3390/diagnostics13071226.
26. Kregenow DA, Rubenfeld GD, Hudson LD, Swenson ER. Hypercapnic acidosis and mortality in acute lung injury. *Crit Care Med* 2006; **34**: 1–7. https://doi.org/10.1097/01.ccm.0000194533.75481.03.
27. Laffey JG, Bellani G, Pham T, et al. Potentially modifiable factors contributing to outcome from acute respiratory distress syndrome: the LUNG SAFE study. *Intensive Care Med* 2016; **42**: 1865–76. https://doi.org/10.1007/s00134-016-4571-5.
28. Trinkle CA, Broaddus RN, Sturgill JL, Waters CM, Morris PE. Simple, accurate calculation of mechanical power in pressure controlled ventilation (PCV). *y* 2022; **10**: 22. https://doi.org/10.1186/s40635-022-00448-5.
29. Zheng H, Xu Z, Zhou J, et al. The accuracy of simplified calculation of mechanical power: a simulation study. *J Thorac Dis* 2023; **15**: 3237–44. https://doi.org/10.21037/jtd-22-1409.
30. Jo YY, Chang YJ, Lee D, Kim YB, Jung J, Kwak HJ. Comparisons of mechanical power and respiratory mechanics in pressure-controlled ventilation and volume-controlled ventilation during laparoscopic cholecystectomy in elderly patients. *J Pers Med* 2023; **13**: 13. https://doi.org/10.3390/jpm13020201.


## Supporting Information

Additional supporting information may be found online via the journal website.

**Appendix S1.** Collaborative investigators.

**Appendix S2.** Details about the pooled database.

**Appendix S3.** Data and equations used in the analysis.

**Appendix S4.** Detailed statistical analysis plan.

**Figure S1.** Bar plots of stratified and resampled ΔP and respiratory rate, and error bars of relative risk of mechanical power ≥ 17 J.min$^{-1}$ and of 28-day mortality.

**Figure S2.** Bar plots of stratified and resampled Ppeak and respiratory rate, and error bars of relative risk of mechanical power ≥ 12.3 J.min$^{-1}$ and of 28-day mortality.

**Figure S3.** Mediation analysis with respiratory rate as mediator and mechanical power as dichotomous variable with a cut off of 17 J.min$^{-1}$.

**Figure S4.** Mediation analysis with peak pressure as mediator and mechanical power as dichotomous variable with a cut off of 17 $J.min^{-1}$.

**Figure S5.** Mediation analysis with driving pressure as mediator and mechanical power as dichotomous variable with a cut off of $J.min^{-1}$.

**Figure S6.** Mediation analysis with respiratory rate as mediator and mechanical power as continuous variable.

**Figure S7.** Mediation analysis with peak pressure as mediator and mechanical power as continuous variable.

**Table S1.** Missing data.

**Table S2.** Patient characteristics and clinical outcomes using a mechanical power cut off of 12.3 $J.min^{-1}$.

**Table S3.** Ventilatory variables using a mechanical power cut off of 12.3 $J.min^{-1}$.

**Table S4.** Combinations of $V_T$ and respiratory rate and the effect on mechanical power.

**Table S5.** Combinations of Ppeak and respiratory rate and the effect on mechanical power.

**Table S6.** Linear regression results in all patients.

**Table S7.** Linear regression results in four groups of $V_T$ and respiratory rate.

**Table S8.** Patient characteristics and clinical outcomes of increasing Ppeak and matched respiratory rate.

**Table S9.** Patient characteristics and clinical outcomes of increasing Ppeak and decreasing respiratory rate.

**Table S10.** Patient characteristics and clinical outcomes of matched Ppeak and decreasing respiratory rate.

**Table S11.** Ventilatory variables of increasing Ppeak and matched respiratory rate.

**Table S12.** Ventilatory variables of increasing Ppeak and decreasing respiratory rate.

**Table S13.** Ventilatory variables of matched Ppeak and decreasing respiratory rate.

**Table S14.** Mediation analysis with $\Delta P$ as mediator.

**Table S15.** Mediation analysis with mechanical power as continuous outcome.