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RESEARCH ARTICLE

Mechanical and chemical power and mortality in acute respiratory distress syndrome: an exploratory analysis of six patient cohorts

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Abstract

Invasive ventilation with oxygen supplementation may inadvertently cause ventilator- and hyperoxia-induced lung injury, respectively, but their balance is fairly unaddressed. The concept of mechanical power summarizes factors of ventilation intensity associated with development of ventilator-induced lung injury. More recently, we introduced the theoretical framework for chemical power to estimate risk of hyperoxia-induced injury and allow for integration of both mechanical and chemical energy transfer per unit time. In the current study, we explored the associations of mechanical and chemical power with outcomes in mechanically ventilated patients with acute respiratory distress syndrome. In this secondary analysis of six pooled cohort studies, patients with acute

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respiratory distress syndrome per Berlin criteria and available data to calculate chemical and mechanical power on *days 1* and *2* of invasive ventilation were selected. The primary outcome was all-cause 60-day mortality. A total of 2,117 patients were included in the main analysis. Higher chemical power levels were associated with increased 60-day mortality ($P < 0.001$), regardless of the mechanical power levels. Increasing mechanical power levels combined with decreasing chemical power levels was associated with a better outcome than vice versa ($P < 0.001$). There was no interaction between both powers. In this pooled cohort study of acute respiratory distress syndrome patients receiving invasive ventilation, higher chemical power levels were associated with a higher rate of mortality, independent of mechanical power levels. These results support further experimental validation of the concept of chemical power and exploration of its balance with mechanical power to predict outcome of lung injury.

NEW & NOTEWORTHY This observational study of a combined cohort of patients with acute respiratory distress syndrome assessed the association of the novel concept of chemical power, a surrogate marker of oxygen exposure intensity, with mortality and its relative weight in this association when compared with mechanical power. Chemical power and mechanical power were independently associated with mortality. An interaction between these powers was not observed. Future experimental studies should aim to validate and optimize this novel concept.

acute respiratory distress syndrome; hyperoxia; intensive care units; mechanical ventilation; ventilator-induced lung injury

INTRODUCTION

Acute respiratory distress syndrome (ARDS) constitutes a major health burden worldwide with a high mortality (1, 2). Around one in every 10 admissions to the intensive care unit (ICU) is complicated by ARDS, with over 75% of patients requiring invasive mechanical ventilation with oxygen supplementation (1). Although undoubtedly life-saving, lung stress and strain from positive pressure ventilation may induce ventilator-induced lung injury (VILI), and high-dose oxygen therapy may inadvertently cause hyperoxia-induced lung injury (HILI; 3, 4). Previous trials have found different effects of limiting the risk of VILI or HILI (5–7). Reducing lung cellular stress and strain by protective ventilator settings has shown clear improvement in outcome (5), whereas minimizing oxygen exposure has not shown clear evidence of benefit in patients with ARDS (6, 7). The harm of VILI and HILI is generally considered separately, but preclinical evidence suggests that each of these factors may influence the potential adverse effect of the other (8–13). Theoretically, both concepts can be seen as a form of energy transfer over time, either mechanically or chemically.

Mechanical power (MP) of ventilation summarizes the total energy transferred to the lungs from the ventilator per minute (Joule/min) (14). MP has subsequently been associated with worse outcomes in patients with and without ARDS (15–17). Oxygen supplementation also causes some form of energy transfer, namely, via chemical energy. It is unclear if such chemical energy is associated with outcome and whether mechanical energy and chemical energy can be summarized as total energy transfer over time. In an attempt to address the latter, a theoretical framework of chemical power (CP), which estimates the energy released by superoxide formation from oxygen exposure over time (Joule/min), was recently introduced (18). A secondary analysis of the Re–Evaluation of the effects of high PEEP During General AnesThesia for surgery (REPEAT) study found that higher intraoperative levels of both CP and MP were associated with a higher rate of postoperative pulmonary complications (19). The association of CP with outcome, and how it is related to MP, has not yet been studied in critically ill patients.

This study conducted a secondary analysis of a composite cohort of patients with ARDS receiving invasive ventilation to investigate the associations of CP and MP with mortality. We also investigated the predictive value of summing CP and MP as total power (TP) and whether this was independent of its two individual components. The hypothesis was that CP is independently associated with mortality in patients with ARDS and that TP has predictive value.

METHODS

Study Design

Secondary analysis of a cohort composed of patients from six observational studies. This harmonized and pooled cohort, named PRactice of VENTilation in Patients with ARDS due to COVID–19 vs Pneumonia (PRoVENT-COP) was established via merging of individual data of patients included in four national, multicenter, prospective, and retrospective observational cohorts and a single-center, prospective cohort of patients with COVID-19 in Spain (20), the Netherlands (21), Argentina (22), and Brazil (23, 24); and an international, multicenter, prospective observational cohort study on critically ill patients receiving either invasive or noninvasive ventilation worldwide (1). Extensive details on the creation of the cohort have been published previously (25). The creation of the pooled database was exempted from additional IRB approval.

Study Population

Patients with a diagnosis of ARDS according to the Berlin criteria were selected from each of the included six studies (26). Patients with available ventilator data on *days 1* and *2* of invasive ventilation to calculate MP and CP were selected for the main analysis. We excluded patients who were on modes that primarily assist spontaneous breathing, such as pressure support and synchronized intermittent mandatory ventilation.

Calculation of MP, CP, and TP

MP was calculated as previously described (27) by using the simplified version of the original power equation (14), *Eq. 1*:

$$\begin{aligned}\text{MP(J/min)} = 0.098 \times \text{Tidal Volume} \times \text{Respiratory Rate} \\ \times [\text{Maximum Pressure}(P_{max}) - 0.5 \\ \times \text{Driving Pressure}(\Delta P)],\end{aligned} \quad (1)$$

where ΔP was calculated by plateau pressure (P_{plat}) minus positive end-expiratory pressure (PEEP) in patients on volume-controlled modes (VCV) or by P_{max} minus PEEP in patients on pressure-controlled ventilation modes (PCV).

CP was calculated from fraction of inspired oxygen (FI_{O_2}) using the previously proposed equation (18), *Eq. 2*:

$$\begin{aligned}\text{CP(J/min)} = 141,000 \times 1.7 \times 10^{-5} \\ + [(FI_{O_2} - 0.21) \times (1.63 \times 10^{-4})].\end{aligned} \quad (2)$$

Time-weighted averages (TWAs) of MP and CP over *days 1* and *2* of invasive ventilation were then calculated and further used in the analysis. The TWA of TP was obtained by adding the TWAs of MP and CP of each patient.

Outcomes

The primary outcome was all-cause 60-day mortality. Secondary outcomes were duration of invasive ventilation up to *day 28* and ICU length of stay up to *day 60* in all patients.

Statistical Analysis

Descriptive statistics, ventilator, and outcome data are presented as median with interquartile range [IQR] for continuous variables or as total count (N) and proportion (%) for categorical variables.

As an initial analysis, the association of CP, MP, and TP with 60-day mortality was assessed using a survival analysis. The association with endpoint mortality at *day 60* over varying levels of each variable was visualized using cubic splines. In addition, each variable was split at the median TWA to create two separate groups, and differences in survival between these groups were tested by a log-rank test.

For the main analysis, the association of CP with 60-day mortality was assessed, where patients were stratified for MP, and the association of MP with 60-day mortality was assessed while stratifying for CP. In both cases, patients were divided into quartiles, with increasing levels of the variable of interest and similar levels of the stratified variable. Cox proportional hazards models were used to estimate the hazard ratios for 60-day mortality. The model accounted for the sequential organ failure assessment (SOFA) score at *day 1* as a marker of disease severity and age, while also including a random effect per study site through a frailty term. Multicollinearity was tested by variance inflation factor. Missing SOFA scores were imputed by predictive mean matching. The possibility of effect modification between CP and MP was tested by adding an interaction term to the model and by analyzing the association of CP with outcome in patients with low and high MP separately (split at the median). The association of TP with mortality was subsequently assessed in two steps. First, the adjusted association of TP with mortality was assessed without stratification. Afterward, patients were stratified for TP and divided into quartiles of simultaneously decreasing levels of CP and increasing levels of MP in each subsequent quartile. The association with mortality among these differing compositions of similar TP was then tested. For the secondary outcomes, the main analysis was repeated, but hazard ratios were calculated using a clustered competing risk model with death as a competing risk and extubation or ICU discharge as the event of interest, while clustering for study site.

A sensitivity analysis repeating the primary analysis based on baseline (*day 1*) data was included to assess the possibility of selection bias due to loss of patients missing data on *day 2* to calculate TWAs. To assess the influence of grouping patients on PCV and VCV together, two subsets were created with only patients on PCV or VCV, and the last part of the main analysis stratifying for TP was repeated. Similarly, to assess the influence of COVID-19 and ARDS, the last part of the main analysis was repeated in two subsets with only COVID-19 or non-COVID patients.

Since multiple comparisons were made in the main analysis, namely, four, a Bonferroni correction was applied and a P value < 0.0125 was considered statistically significant. For the secondary outcomes and sensitivity analyses, a non-corrected P value < 0.05 was maintained due to their exploratory nature. Analyses were performed using R v.4.3.2 (R Foundation for Statistical Computing, Vienna, Austria) with RStudio v.1.3.1093 (RStudio, Boston, MA).

RESULTS

Descriptive Characteristics

The composite cohort consisted of 9,243 patients with ARDS. Of these patients, 5,276 (57.1%) had available data on *day 1*, and 2,117 (22.9%) had available data on both *days 1* and *2* to calculate TWAs for MP and CP while on PCV or VCV, and were therefore included in the main analysis (Fig. 1). The most common reason for exclusion was missing variables to calculate MP. An overview of the descriptive statistics of the analyzed cohort is presented in Table 1 (also see Supplemental Table SE1 and Supplemental Fig. SE1).

Outcomes

All-cause mortality at *day 60* was 36.4% ($n = 771$ patients) among the selected patients. The median [IQR] duration of invasive ventilation was 14 days [8–26] in survivors and 12 days [7–21] in nonsurvivors. At *day 28*, 1,012 patients (47.8%) had been extubated while alive. Median [IQR] length of stay in the ICU was 18 days [11–33] in survivors and 12 days [6–22] in nonsurvivors. At *day 60*, 1,247 patients (58.9%) had been discharged alive from the ICU.

Ventilator Variables

In survivors, median [IQR] TWA-CP was 10.2 J/min [7.9–13.7], TWA-MP 16.7 J/min [13.6–20.3], and TWA-TP 27.8 J/min [23.4–32.7], whereas in nonsurvivors median TWA-CP was 12.5 [9.1–16.0], TWA-MP 17.6 [13.9–21.5], and TWA-TP 30.5 [25.7–36.0]. The partial pressure of arterial oxygen (Pa_{O_2}) was similar between survivors and nonsurvivors (Table 1). Pa_{O_2} was slightly higher in patients exposed to high CP compared with low CP, whereas severe hyperoxemia was not observed (see Supplemental Table SE1).

Survival and Stratified Analyses

CP, MP, and TP were all associated with 60-day mortality in univariate analyses (Fig. 2). Variance inflation factors did not show concern of multicollinearity (see Supplemental Tables

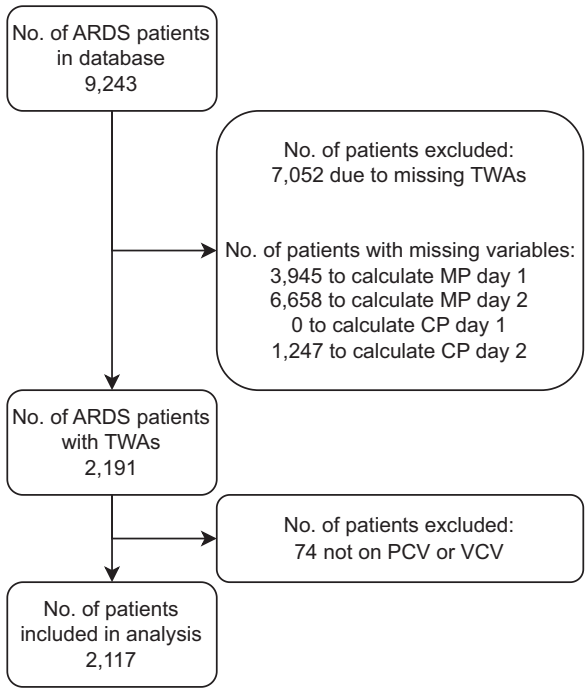

Figure 1. Patient selection for the main analysis. Patients who did not have available data on *days 1* and *2* of invasive ventilation to calculate time-weighted averages (TWAs) of mechanical power (MP) and chemical power (CP) were excluded from the primary analysis. ARDS, acute respiratory distress syndrome; PCV, pressure-controlled ventilation; VCV, volume-controlled ventilation.

SE2 and SE3). In stratified analyses, increasing CP was associated with a higher rate of mortality independent of MP and vice versa (Fig. 3). An interaction was not observed between CP and MP (see Supplemental Table SE4) and the independent association of CP with mortality was similar at low and high levels of MP (see Supplemental Fig. SE2). Increasing TP was also associated with a higher rate of mortality when adjusted for confounders (Fig. 4). As the analyzed cohort could not be adequately stratified for TP as a whole, a subset was created including only patients with TP levels within the 20–80th percentiles, after which stratification for TP resulted in similar levels of TP (see Supplemental Fig. SE3). Within this subset, the association with mortality differed among different compositions of similar TP and was thus not independent of CP and MP. TP composed by high CP and low MP was associated with a higher rate of mortality, than TP composed by high MP and low CP (Fig. 4). These results were similar for the secondary outcomes, with lower rates of extubation or ICU discharge replacing higher rates of mortality (see Supplemental Fig. SE4), except that duration of ventilation did not differ among similar levels of TP.

Sensitivity Analyses

The findings of the sensitivity analysis based on baseline data of 5,276 patients were consistent with the primary analysis using TWAs (see Supplemental Figs. SE5 and SE6). Results of the main analysis were similar in a subset of patients on VCV, whereas mortality in patients on PCV did not differ across matched TP levels (see Supplemental Fig. SE7). In patients with COVID, the findings were also consistent with the main analysis, whereas mortality in non-COVID patients did not differ between similar TP levels (see Supplemental Fig. SE8). A post hoc approximation of the altitude relative to sea level of study sites within the analyzed cohort showed that nearly all cities were located between 0 and 1,000 m (see Supplemental Table SE5).

DISCUSSION

In this exploratory secondary analysis of a large composite and mixed cohort of patients with ARDS on invasive ventilation, CP was associated with mortality, duration of invasive

Table 1. *Patient characteristics and ventilatory variables*

Patient Characteristics	Survivors (n = 1,346)		Nonsurvivors (n = 771)		P Value
	Summary	Missing	Summary	Missing	
Age, yr	61 [52–70]	0	67 [59–74]	0	<0.001
Male sex	893 (66.3)	3 (0.2)	548 (71.1)	0	0.03
Weight, kg	83 [73–95]	20 (1.5)	80 [70–92]	17 (2.2)	0.002
SOFA score *day 1*	7 [4–9]	304 (22.6)	8 [6–11]	162 (21.0)	<0.001
COVID-19	933 (69.3)	0	498 (64.6)	0	0.03
ARDS cause					
Pneumonia	1,181 (87.7)	0	659 (85.5)	0	0.14
Sepsis	69 (5.1)	0	53 (6.9)	0	0.41
Ventilatory variables (TWA)					
Tidal volume, mL	445 [395–490]	0	443 [399–495]	0	0.83
Respiratory rate, breaths/min	22 [19–24]	0	22 [19–26]	0	0.002
FI_{O_2}, %	55 [45–70]	0	65 [50–80]	0	<0.001
P_{max}, cmH_2O	25 [22–27]	0	26 [22–29]	0	<0.001
PEEP, cmH_2O	12 [10–13]	0	12 [9–14]	0	0.49
Driving pressure, cmH_2O	13 [11–15]	0	14 [11–17]	0	<0.001
Pa_{O_2}, mmHg	83 [73–99]	36 (2.7)	83 [71–101]	15 (1.9)	0.46
Pa_{O_2}/FI_{O_2}	163 [133–202]	36 (2.7)	146 [108–185]	15 (1.9)	<0.001
Pa_{O_2} > 120 mmHg	134 (10.0)	36 (2.7)	91 (11.8)	15 (1.9)	0.21
Pa_{O_2} > 250 mmHg	0	36 (2.7)	1 (0.1)	15 (1.9)	0.37

Data are presented as median with [interquartile range] or number with (%). n represents the number of patients. Ventilatory variables are time-weighted averages (TWA) over the first 2 days of invasive ventilation. Wilcoxon rank-sum test and Fisher's exact test were used. ARDS, acute respiratory distress syndrome; COVID-19, corona virus disease-19; FI_{O_2}, fraction of inspired oxygen; Pa_{O_2}, partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure; P_{max}, maximum pressure; SOFA, sequential organ failure assessment; TWA, time-weighted average.

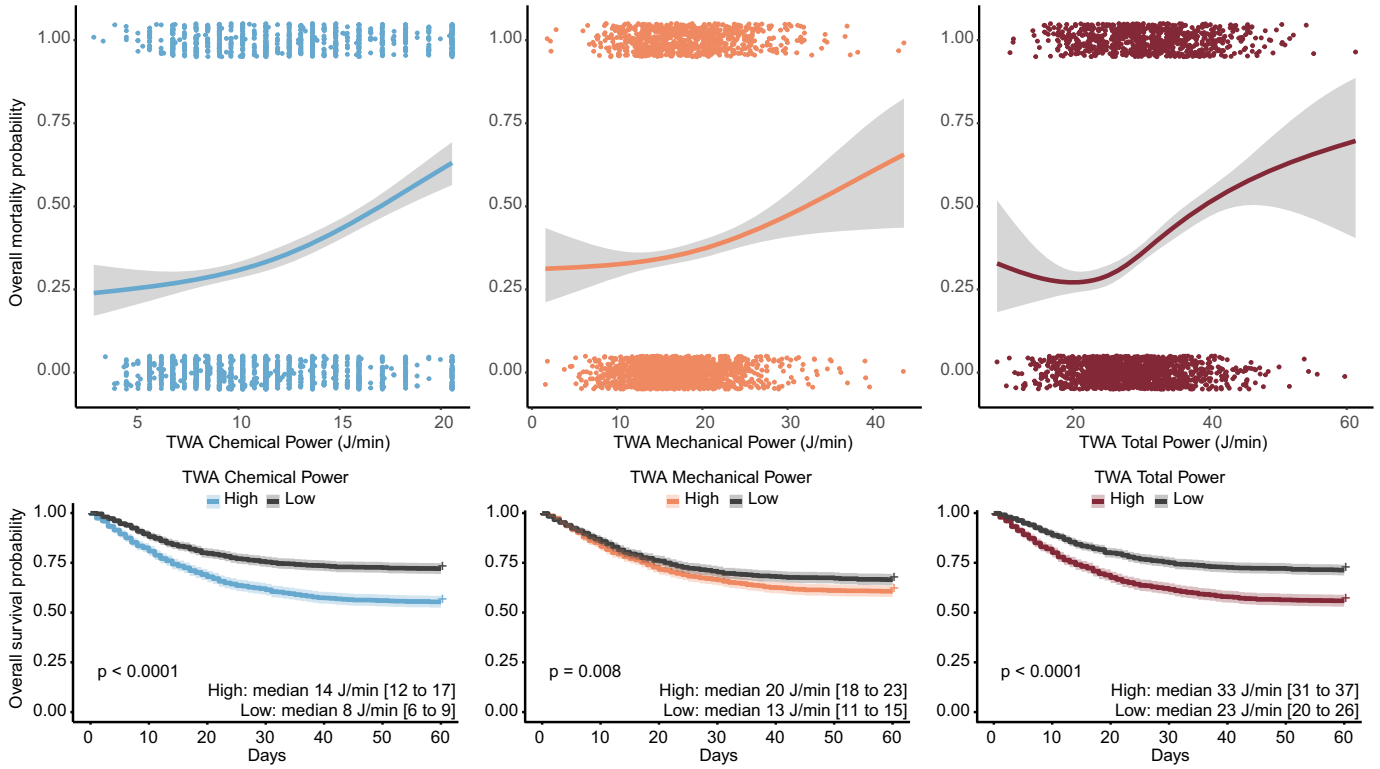

Figure 2. Visual representation of probability and Kaplan–Meier curves for 60-day mortality. *Top row*: cubic splines were used to visualize the mean probability of death over varying levels of chemical power (blue), mechanical power (orange), and total power (dark red). *Bottom row*: patients were divided into a high- and low-exposure group, split at the median time-weighted average (TWA) of each variable, and differences in survival were tested by a log-rank test.

ventilation, and ICU length of stay independent of MP. Similarly, MP was associated with outcomes independent of CP. The resulting TP was also associated with outcomes, but this was not independent of CP and MP. For similar levels of TP, a higher CP combined with lower MP was associated with worse clinical outcome.

The finding that the level of oxygen exposure, in our study estimated by CP, was strongly associated with mortality and other secondary outcomes even when adjusted for clinically important variables is in line with the findings of a similar secondary analysis of the REPEAT study (19). Other observational cohort studies which examined oxygen exposure and mortality have reported varying and contrasting findings (28–31). For example, one cohort did not observe an association of $F_{I_{O_2}}$ with mortality in univariable analysis (28), whereas in two other cohorts an initially observed association with mortality was lost after adjusting for severity of illness (29, 30). The current analysis, however, included a substantially larger sample size, aiding in statistical power. This also applied to the previously mentioned secondary analysis of the REPEAT study. In addition, previous studies mostly used single time point measurements of $F_{I_{O_2}}$ (28–30), instead the current study assessed TWA of oxygen exposure over the first 2 days. Measurement over an extended period likely better grasps the overall oxygen exposure intensity. These study characteristics strengthen the current finding that oxygen exposure was independently associated with mortality. The observed values of Pa_{O_2} were slightly higher in patients with high CP compared with patients with low CP exposure, but were not near levels that have been previously associated with mortality (32). This suggests oxygen use may have been excessive in some patients, which in theory may have led to pulmonary oxygen toxicity that could have been prevented. Still, despite correction for important covariates, it cannot be ruled out that the observed association with mortality remains partly driven by residual confounding and indication bias. Oxygen exposure will always be inherently intertwined with disease severity and clinical management decisions, which cannot be fully disentangled in observational studies. Randomized controlled trials on different oxygenation targets in critically ill adults have not yet yielded a clear answer to what extent oxygen exposure is harmful in clinical practice (32–36). One possible explanation for the lack of a clear benefit of reducing oxygen exposure in previous trials may be the "one approach fits all" design of these studies. The underlying heterogeneity that such an approach entail may mask a clinically relevant effect of specific oxygenation targets in certain patient groups or response phenotypes (37). A secondary analysis of two previous trials on oxygenation targets did indeed indicate such heterogeneity of treatment effect (38). Two other trials that analyzed strict oxygenation targets in patients with acute hypoxemic respiratory failure found no benefit to targeting a Pa_{O_2} of around 60 mmHg compared with 90 mmHg, despite reducing pulmonary oxygen exposure (6, 7). It could be that strict adherence, as is expected in a protocolized trial, to either of these targets already limits excessive oxygen use sufficiently. Another explanation here could be that the

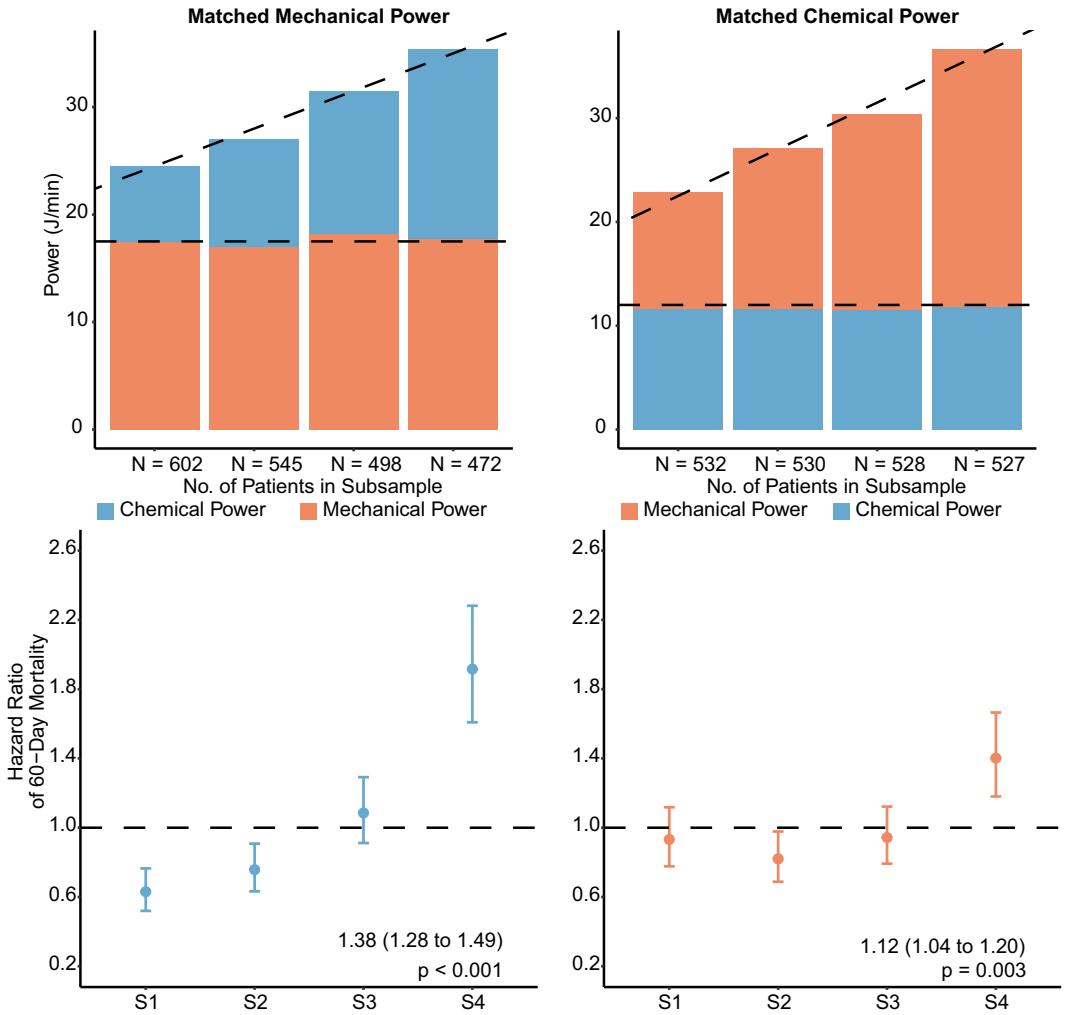

Figure 3. Stratified analysis of 60-day mortality in subsamples of patients for chemical and mechanical power. Hazard ratios were calculated using a Cox proportional hazards model for subsamples of patients with: (*left* column) increasing levels of chemical power (CP; in blue) for similar levels of mechanical power (MP; in orange; *right* column) increasing levels of MP for similar levels of CP. Each bar shows the mean level of CP and MP in a stacked manner.

benefit of further reducing oxygen exposure is offset by unintended harm from the resulting moderate hypoxemia. Again, heterogeneity in response phenotypes to such targets may be an important factor. A prospective study should investigate whether individualized oxygenation targets can translate the observed association of oxygen exposure and mortality into clinical effect.

Given the independent association of CP and that of MP with mortality, the hypothetical idea of the balance of injury between mechanically induced lung injury from excess MP (i.e., VILI) and chemically induced lung injury from excess CP (i.e., HILI) is especially intriguing (18). Evidently, the association analysis does not imply causality, but the hypothesis that the total energy over time from each component dictates injury can be generated. Estimation of the total energy exposure the lungs endured as TP was indeed clearly associated with worse outcome. However, although effect modification between CP and MP was not observed, the association of TP was not independent of its individual components, MP and CP. There seems to be no advantage yet in directly summarizing CP and MP as one (total) power, despite transformation to similar units. Both components represent crude estimations of local cellular energy dissipation, but MP can be measured more directly by feedback from the ventilator (14), whereas the estimation of CP currently remains more speculative. Pulmonary superoxide formation cannot be easily measured in clinical practice, nor are possible downstream chemical reactions included in the current concept (39). It is worth noting that with the current equation of CP, one could equally model FI_{O_2} without transformation into J/min, since the value for pulmonary oxygen consumption ($\dot{V}O_{2pulm}$) is not individually measured. However, consistent evidence exists that formation of reactive oxygen species and oxidative stress may not only increase as a result of FI_{O_2}, but also with increasing $\dot{V}O_2$, for instance with physical exercise (40–42). Our results at least support further exploration and experimental validation of the concept of CP, for example, through $\dot{V}O_{2pulm}$ measurements as a function of FI_{O_2} and energy dissipation by hyperoxia, e.g., by microcalorimetry. In theory, this could provide a better estimation for pulmonary oxygen exposure intensity than FI_{O_2} alone.

The finding that higher CP in combination with low MP was associated with worse outcome compared with the opposite was unexpected and different than we previously

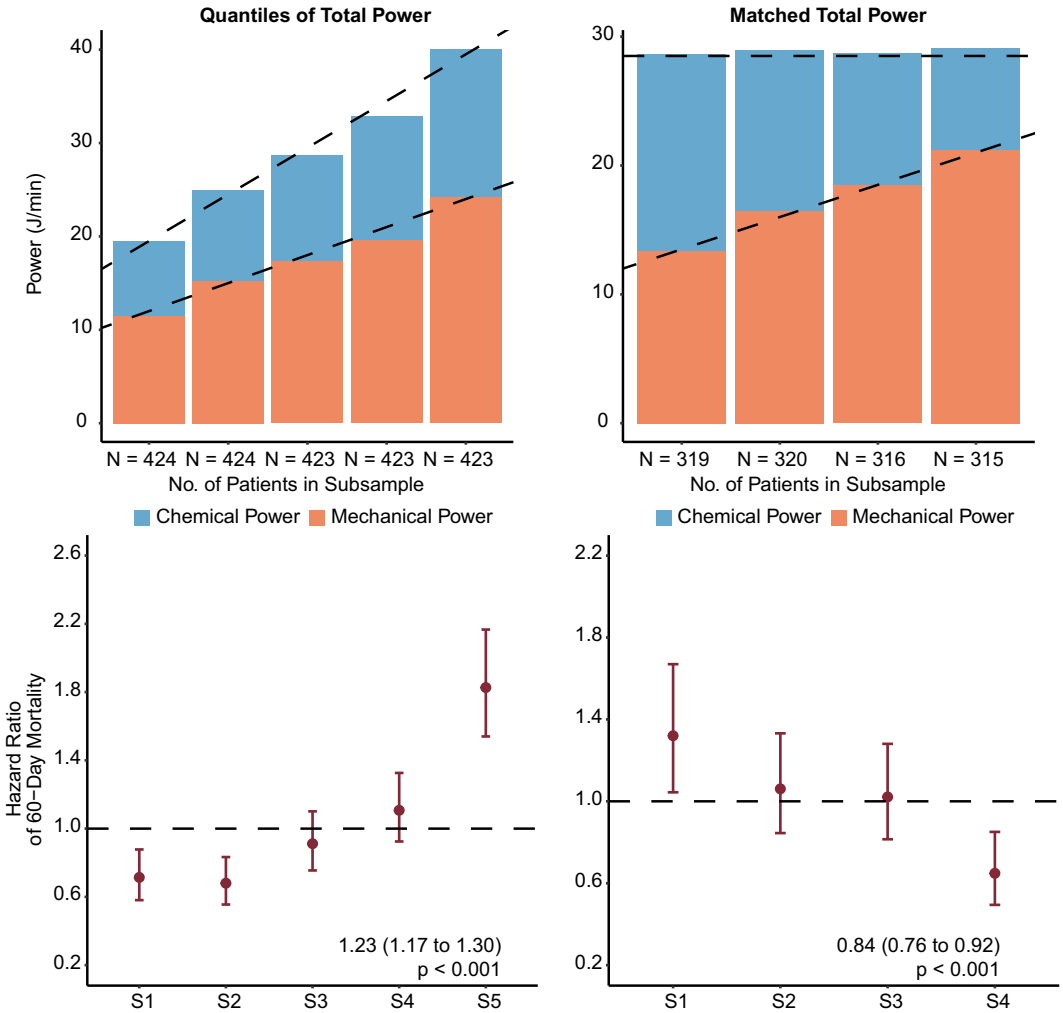

Figure 4. Stratified analysis of 60-day mortality for total power and in subsets of patients with similar total power. Hazard ratios were calculated using a Cox proportional hazards model for subsamples of patients with: (*left* column) increasing levels of total power (TP) in the overall cohort, where the composition of chemical power (CP; in blue) and mechanical power (MP; in orange; *right* column) is shown; TP values within the 20th–80th percentiles and increasing MP values at the expense of decreasing CP values for similar levels of TP. Each bar shows the mean level of CP and MP in a stacked manner.

hypothesized based on the relative contribution in terms of absolute value of transferred Joule/min (18). Although preclinical evidence suggests that oxygen toxicity is particularly harmful in the presence of other lung injury (8–13), such as positive pressure ventilation-induced injury, such an interaction was not evident in the current cohort. It remains unclear if oxygen exposure actually has more weight than lung stretch, or whether alternative explanations are relevant here. In light of this, a particularly important finding was that the greater influence of CP on outcome at similar levels of TP was not observed in non-COVID patients, whereas the finding in the overall cohort might have been driven primarily by the finding in patients with COVID. Although ARDS by SARS-CoV-2 appears to be similar to other causes of ARDS (43–45), it has been proposed that it is accompanied by more severe hypoxemia (44, 46). It could be that in patients with COVID, the $F_{I_{O_2}}$ was kept in excess, despite mild lung disease, hypothetically resulting in harmful overzealous oxygen exposure (33).

This study was strengthened by the large and broad ARDS population included, derived from various single-center and multicenter cohort studies worldwide. This limits the influence of site-specific practices on the current findings. However, certain limitations need to be addressed. First, the current work was a study of the theoretical framework of CP, meant to function as an incentive for further exploration of this novel concept. Second, as this was a secondary analysis of various observational cohorts, none of the observed associations imply causality, and the previously discussed possibility of residual confounding and indication bias remains. Third, only the first 2 days of invasive ventilation regarding oxygen exposure and ventilator settings were analyzed. Although likely a better estimate than a single baseline value, the period assessed does not capture cumulative exposure over the total duration of invasive ventilation, and changing dynamics of lung injury later during admission may have been missed (47, 48).

Conclusions

In this pooled cohort of patients with ARDS on invasive ventilation, greater oxygen exposure estimated by CP was associated with worse outcome, independent of MP.

Furthermore, greater total energy transfer to the lungs, estimated as the sum of CP and MP, was also associated with worse outcome. These results support further experimental validation and exploration of the novel concept CP and its relative role to MP.

DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author and involved parties upon reasonable request.

SUPPLEMENTAL MATERIAL

Supplemental Figs SE1–SE8 and Supplemental Tables SE1–SE5: https://doi.org/10.6084/m9.figshare.32909378.

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DISCLAIMERS

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AUTHOR CONTRIBUTIONS

T.A.L., L.D.J.B., L.M.M.-W., M.J.S., D.M.P.v.M., and R.A.B. conceived and designed research; T.A.L. performed experiments; T.A.L. analyzed data; T.A.L., L.D.J.B., L.M.M.-W., M.J.S., D.M.P.v.M., and R.A.B. interpreted results of experiments; T.A.L. prepared figures; T.A.L. and R.A.B. drafted manuscript; L.D.J.B., L.M.M.-W., P.S., S.G.B., L.C.P.A., G.B., M.B., E.E., E.F., J.C.F., H.H., J.G.L., I.M.-L., A.M., T.P., Ó.P., A.P., A.S.N., E.R., A.T., A.M.T., F.P., M.J.S., D.M.P.v.M., and R.A.B. edited and revised manuscript; T.A.L., L.D.J.B., L.M.M.-W., P.S., S.G.B., L.C.P.A., G.B., M.B., E.E., E.F., J.C.F., H.H., J.G.L., I.M.-L., A.M., T.P., Ó.P., A.P., A.S.N., E.R., A.T., A.M.T., F.P., M.J.S., D.M.P.v.M., and R.A.B. approved final version of manuscript.

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