



Different ventilation intensities among various categories of patients ventilated for reasons other than ARDS—A pooled analysis of 4 observational studies

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ABSTRACT

Purpose: We investigated driving pressure (ΔP) and mechanical power (MP) and associations with clinical outcomes in critically ill patients ventilated for reasons other than ARDS.

Materials and methods: Individual patient data analysis of a pooled database that included patients from four observational studies of ventilation. ΔP and MP were compared among invasively ventilated non-ARDS patients with sepsis, with pneumonia, and not having sepsis or pneumonia. The primary endpoint was ΔP ; secondary endpoints included MP, ICU mortality and length of stay, and duration of ventilation.

Results: This analysis included 372 (11%) sepsis patients, 944 (28%) pneumonia patients, and 2040 (61%) patients ventilated for any other reason. On day 1, median ΔP was higher in sepsis (14 [11–18] cmH₂O) and pneumonia patients (14 [11–18] cmH₂O), as compared to patients not having sepsis or pneumonia (13 [10–16]

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cmH₂O) ($P < 0.001$). Median MP was also higher in sepsis and pneumonia patients. ΔP , as opposed to MP, was associated with ICU mortality in sepsis and pneumonia patients.

Conclusions: The intensity of ventilation differed between patients with sepsis or pneumonia and patients receiving ventilation for any other reason; ΔP was associated with higher mortality in sepsis and pneumonia patients.

Registration: This post hoc analysis was not registered; the individual studies that were merged into the used database were registered at clinicaltrials.gov: NCT01268410 (ERICC), NCT02010073 (LUNG SAFE), NCT01868321 (PROVENT), and NCT03188770 (PROVENT-iMiC).

1. Introduction

Interest in the intensity of ventilation, reflected by driving pressure (ΔP) [1] and mechanical power of ventilation (MP) [2,3], is growing as intensity of ventilation has been shown to have independent associations with outcome. As such, ΔP and MP could be attractive targets in ventilation management [4,5]. ΔP and MP have mainly been investigated in patients with acute respiratory distress syndrome (ARDS) [1,3,6]. The majority of invasively ventilated critically ill patients, however, do not have ARDS [7,8], and these patients likely receive ventilation with lower ΔP and less MP. It is also uncertain whether measures of intensity of ventilation have independent associations with outcome in non-ARDS patients.

Ventilation management may differ between sepsis and pneumonia patients and patients receiving ventilation for other reasons, potentially leading to differences in ΔP and MP. Sepsis patients often have or develop metabolic acidosis [9], triggering the use of a higher respiratory rate (RR), and maybe even the use of higher tidal volumes (V_T). Sepsis patients may also need larger volumes of intravenous fluids to correct hypotension and hypoperfusion [10], which could potentially result in pulmonary edema and subsequent reduction in pulmonary compliance, even if a recent study showed that the occurrence of pulmonary edema due to aggressive intravenous fluid treatment in sepsis patients may be less extensive than previously believed [11]. Pneumonia patients can have a lower respiratory system compliance, which may trigger the use of lower V_T and a higher RR.

We calculated and compared ΔP and MP in no-ARDS patients with sepsis or pneumonia, and patients not having sepsis or pneumonia. For this, we used a pooled dataset of four observational studies of ventilation. We hypothesized that ΔP and MP would be different between sepsis and pneumonia patients and patients not having sepsis or pneumonia. Furthermore, we studied associations of ΔP and MP with mortality in the three patient groups.

2. Methods

2.1. Study design and ethics

This is an individual patient data analysis of a pooled dataset of 4 prospective, observational studies of ventilation in critically ill patients conducted between 2011 and 2018, named ‘Epidemiology of Respiratory Insufficiency in Critical Care’ (ERICC) [12], ‘Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure’ (LUNG SAFE) [6], ‘Practice of VENTilation in critically ill patients without ARDS’ (PROVENT) [13], and ‘Practice of VENTilation in critically ill patients in Middle-income Countries’ (PROVENT-iMiC) [14]. These studies were chosen because they employed a consistent data collection approach.

The study protocols of each study underwent initial approval by a central Institutional Review Board, followed by subsequent approval by a national or local ethics committee where necessary. Informed consent was obtained when it was deemed necessary according to national legislation. The four studies were registered at clinicaltrials.gov (NCT01268410, NCT02010073, NCT01868321, and NCT03188770). The databases of the 4 studies were standardized, using the case report

forms and data dictionaries, and thereafter merged into the pooled database. The creation of the pooled database, including our specific modifications for patient’s categorization, did not need additional ethical approval. This post hoc analysis was not registered. Further information regarding the used database, named ‘PROVENT, PROVENT-iMiC, ERICC and LUNG SAFE’ (PROPERLy) has been published elsewhere [15].

2.2. Patients

The studies shared a common set of inclusion criteria, specifically, admission to an ICU for individuals aged 18 years or older (or 16 for LUNG SAFE), along with receiving ventilation within defined time frames. Exclusion criteria varied slightly among the studies, detailed in **Supplementary file eTable 1**.

For the current analyses we excluded patients with ARDS on admission, and patients that could not be labelled as having either sepsis or pneumonia, or neither of these two conditions. We also excluded patients who did not receive invasive ventilation, and patients with an incomplete follow-up.

Patient labeling

1. Patients admitted for sepsis, not caused by pneumonia: those patients who exhibited a positive risk factor for sepsis exclusively were placed within the ‘sepsis’ group.
2. Patients admitted for pneumonia, including patients with pneumo-sepsis: patients who displayed risk factors for both sepsis and pneumonia, or just for pneumonia, were thoughtfully classified into the ‘pneumonia’ group. This was undertaken to prevent any inadvertent misclassification and to safeguard against the inclusion of patients who could potentially have sepsis-related pulmonary complications or lung damage that might affect ventilation.
3. Patients not having sepsis or pneumonia or pneumo-sepsis: those patients whose admission factors did not align with sepsis or pneumonia risk were grouped as patients admitted for another reason. This category included patients admitted for reasons that were neither related to sepsis nor pneumonia.

2.3. Endpoints

The primary endpoint was ΔP . Secondary endpoints included MP, ICU mortality and length of stay (LOS), and duration of ventilation.

Definitions and calculations.

We defined ‘day 1’ as the first full calendar day of ventilation; the following days were named ‘day 2’ and ‘day 3’.

The MP was calculated using eq. 1, wherein ΔP was calculated using eqs. 2 and 3 for patients under volume-controlled ventilation, and for patients under pressure-controlled ventilation [16], respectively:

$$MP [J/min] = 0.098 * V_T [mL]^* RR^* (P_{max} [cmH_2O] - 0.5 * \Delta P [cmH_2O]) \quad (1)$$

$$\Delta P [cmH_2O] = P_{plat} [cmH_2O] - PEEP [cmH_2O] \quad (2)$$

$$\Delta P [cmH_2O] = P_{max} [cmH_2O] - PEEP [cmH_2O] \quad (3)$$

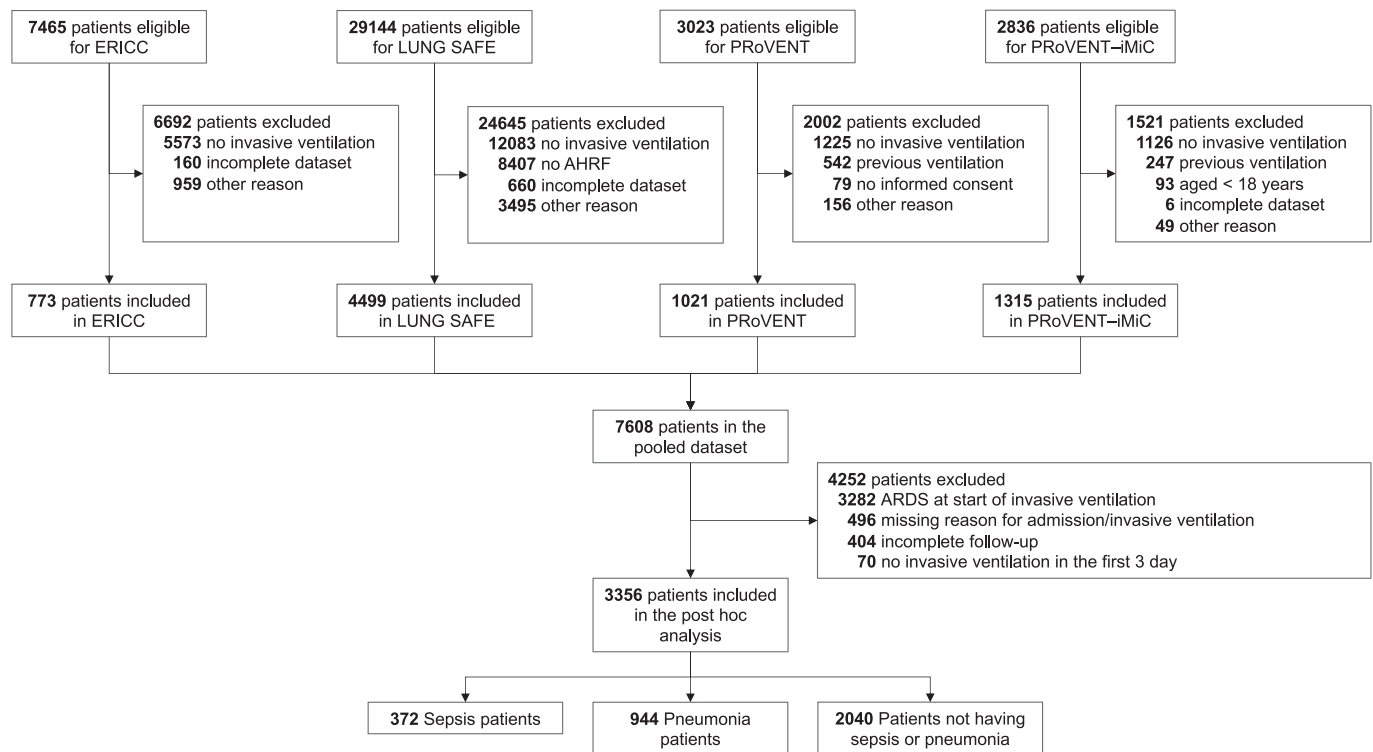


Fig. 1. Flow of patients.

Abbreviations: AHRF, Acute Hypoxemic Respiratory Failure; ARDS, Acute Respiratory Distress Syndrome; ERICC, Epidemiology of Respiratory Insufficiency in Critical Care; LUNG SAFE, Large observational study to Understand the Global impact of Severe Acute respiratory Failure; PROVENT Practice of VENTilation in critically ill patients without ARDS study; PROVENT-iMiC, Practice of VENTilation in critically ill patients in middle income countries study.

Respiratory system compliance (C_{RS}) was calculated using eq. 4:

$$C_{RS} [\text{mL}/\text{cmH}_2\text{O}] = V_T [\text{mL}]/\Delta P [\text{cmH}_2\text{O}] \quad (4)$$

Predicted Body Weight (PBW) was calculated using eqs. 5 and 6, for males and females, respectively:

$$\text{PBW} [\text{kg}] = 50 + 0.91^* (\text{height} [\text{cm}] - 152.4 [\text{cm}]) \quad (5)$$

$$\text{PBW} [\text{kg}] = 45.5 + 0.91^* (\text{height} [\text{cm}] - 152.4 [\text{cm}]) \quad (6)$$

Ventilatory Ratio (VR) is calculated using eq. 7, wherein 'ideal PaCO_2 ' is set at 5 kPa for all patients [17].

$$\text{VR} = (\text{measured minute ventilation} [\text{mL}/\text{min}]^* \text{measured } \text{PaCO}_2 [\text{kPa}]) / (\text{predicted minute ventilation} [\text{mL}/\text{min}]^* \text{ideal } \text{PaCO}_2 [\text{kPa}]) \quad (7)$$

ICU mortality was defined as any death that happened in the ICU. Duration of ventilation was measured as the time a patient received mechanical ventilation support during their ICU stay. ICU-LOS referred to how long a patient stayed in the ICU, starting from admission until they left the ICU or passed away there.

2.4. Sample size

We did not perform a formal sample size calculation; the number of available patients in the merged database served as the sample size.

2.5. Statistical analysis

Categorical variables were presented as counts and percentages, while continuous data as medians with interquartile range. Numbers of missing data are reported in Supplementary file eTable 2, and we did not use imputation.

Differences in ΔP and MP, and key ventilatory settings and parameters between the three groups were compared using a Kruskal Wallis test for continuous variables and a chi-square test for categorical variables. If a significant difference was found a Wilcoxon rank sum test was used to specify between which of the groups differed with respect to the median ΔP and MP. We applied Bonferroni correction, to correct for multiple testing, setting the significance level to 0.016.

We used cumulative distribution plots to visualize ΔP , MP, and other key ventilatory settings and parameters, on day 1, 2 and 3. Herein, vertical dotted lines indicate the median of the overall population for each day.

The association of ΔP and MP with ICU mortality on day 1 was examined by calculating odds ratios (ORs) using a univariate logistic regression model. To adjust for baseline disease severity, we used a multivariate logistic regression model. Covariates with a known or suspected effect on outcome were entered in the model: arterial pH, baseline SOFA score, presence of active cancer, type of admission, and age. Additionally, duration of ventilation and ICU-LOS were assessed through linear regression models. Effect estimates for duration of ventilation and ICU-LOS were expressed as exponential beta coefficients with 95% confidence interval to enhance interpretability. These models were adjusted for the same baseline characteristics.

We performed a sensitivity analysis excluded patients with evidence of spontaneous breathing activity, defined as total RR exceeding set RR by >2 breaths per minute were excluded [18].

We performed two posthoc analyses. In one additional analysis, we investigated the association of ΔP and MP with two additional end-points, hospital mortality and hospital lengths of stay. In a second posthoc analysis, we adjusted for the comorbidities COPD, diabetes, chronic renal failure, chronic heart failure, immunosuppression, chronic liver failure in a multivariate logistic regression model.

All statistical analyses were performed using R version 4.0.3 (www.r-project.org). A P-value < 0.05 was considered statistically significant.

Table 1
Demographic and Clinical Characteristics.

	Sepsis patients (N = 372)	Pneumonia patients (N = 944)	Patients not having sepsis or pneumonia (N = 2040)	P
Age, year	62 [49–71]	65 [51–77]	60 [45–71]	< 0.001
Sex, male	222/372 (60)	606/944 (64)	1265/2038 (62)	0.277
Height, cm	165 [159–172]	168 [160–175]	167 [160–175]	0.025
Weight, kg	80 [69–89]	70 [60–80]	75 [65–88]	< 0.001
PBW, kg	61.5 [52.4–67.8]	61.6 [53.3–69.7]	61.5 (52.4–70.6)	0.038
BMI, kg/m ²	26.7 [24.3–30.0]	24.8 [22.1–28.1]	25.7 [23.1–29.4]	< 0.001
Admission type				< 0.001
Medical	242/371 (65.2)	785/944 (83.2)	947/2037 (46.5)	
Surgical elective	17/371 (4.6)	50/944 (5.3)	586/2037 (28.8)	
Surgical urgency	108/371 (29.1)	86/944 (9.1)	344/2037 (16.9)	
Trauma	4/371 (1.1)	23/944 (2.4)	160/2037 (7.9)	
Disease severity				
SOFA score	9 [6–12]	8 [5–10]	7 [4–9]	< 0.001
Comorbidities				
Diabetes	109/372 (29.3)	238/944 (25.2)	468/2036 (23.0)	0.025
Chronic renal failure	59/372 (15.9)	122/944 (12.9)	202/2037 (9.9)	0.001
CHF	28/372 (7.5)	96/944 (10.2)	250/2034 (12.3)	0.014
COPD	27/372 (7.3)	226/944 (23.9)	205/2028 (10.1)	< 0.001
Immunosuppression	12/172 (7.0)	69/751 (9.2)	79/1202 (6.6)	0.099
Chronic liver failure	24/372 (6.5)	35/944 (3.7)	79/2036 (3.9)	0.054
Hematologic neoplasia	9/338 (2.7)	31/842 (3.7)	9/1278 (0.7)	< 0.001
Specific risk factor				
Non-cardiogenic shock	107/372 (28.8)	88/944 (9.3)	224/2040 (11.0)	< 0.001
Pancreatitis	6/138 (4.3)	3/487 (0.6)	10/444 (2.3)	0.008
Gastric aspiration	14/372 (3.8)	91/944 (9.6)	198/2040 (9.7)	0.001
Transfusion related acute lung injury	4/138 (2.9)	6/487 (1.2)	24/444 (5.4)	0.001
Inhalation	3/372 (0.8)	10/781 (1.3)	44/2040 (2.2)	0.092
Pulmonary contusion	1/372 (0.3)	8/781 (1.0)	72/2040 (3.5)	< 0.001
Burn	0/138 (0.0)	0/487 (0.0)	6/444 (1.4)	0.014
Pulmonary vasculitis	1/138 (0.7)	4/487 (0.8)	3/444 (0.7)	0.967
Near-drowning	0/372 (0.0)	0/781 (0.0)	4/2040 (0.2)	0.322
Drug overdose	1/138 (0.7)	9/487 (1.8)	17/444 (3.8)	0.055

Data, inherent to day 1, are expressed as median with [IQR] or numbers n/N (proportions) where appropriate. ‘N’ in n/N may not always represent the total number of individuals within the group due to the existence of missing values, reported in the supplement: Appendix II.
Abbreviations: ARDS, Acute Respiratory Distress Syndrome; BMI, Body Mass Index; IQR, interquartile range; PBW, predicted body weight; SOFA, Sequential Organ Failure Assessment; CHF, Chronic Heart Failure; COPD, Chronic Obstructive Pulmonary Disease.

Where appropriate, statistical uncertainty was expressed by 95% confidence intervals (CI).

3. Results

3.1. Patients

Out of 7608 patients in the pooled dataset, 4252 were excluded (Fig. 1). Main reasons for exclusion were the presence of ARDS at start of invasive ventilation or missing data for patient labeling.
Out of the remaining 3356 patients, 372 (11%) had sepsis and 944 (28%) had pneumonia. Patients groups were different with respect to median age, median body weight and the body mass index, and the medical history (Table 1). Sepsis patients and pneumonia patients had higher median SOFA scores than patients not having sepsis or pneumonia. Ventilation characteristics are shown in Table 2 and Supplementary file eFigure 1.

3.2. Ventilation intensity

On day 1, median ΔP was higher in sepsis patients and pneumonia patients (14 [11–18] and 14 [11–18] cm H₂O) compared to patients not having sepsis or pneumonia (13 [10–16] cm H₂O) (P < 0.001) (Fig. 2 and Table 2). Differences in ΔP became smaller on the following two days, but remained statistically significant.
On day 1, median MP was higher in sepsis patients and pneumonia patients (13.3 [9.7–18.6], 13.6 [10.1–19.5] J/min) compared to patients not having sepsis or pneumonia (11.2 [8.3–15.4] J/min) (P < 0.001). The differences in MP became smaller on the following two days

as well, but differences remained statistically significant.

3.3. Associations with outcomes

Findings of the univariate analysis are presented in Supplementary eTable 3. In the multivariable analysis, we observed that both ΔP and MP exhibited odds ratios >1 for ICU mortality, duration of ventilation, and ICU-LOS (Table 3). A higher ΔP was linked to higher ICU mortality in sepsis and pneumonia patients.

3.4. Sensitivity analysis

An analysis excluding patients with evidence of spontaneously breathing did not change the findings (Supplementary file eFigure 2 and eTable 4).

3.5. Posthoc analyses

The posthoc analysis of associations of ΔP and MP with hospital mortality and hospital LOS (Supplementary eTable 5), and the model adjusted for the comorbidities (Supplementary eTable 6) mirrored the findings of the original analyses.

4. Discussion

The main findings of this individual patient data analysis of a pooled dataset of 4 studies of ventilation in critically ill patients can be summarized as follows: (1) ΔP and MP are higher in sepsis and pneumonia patients as compared to patients not having sepsis or pneumonia; (2) ΔP

Table 2

Ventilatory variables and gas exchanges of the patients according to the type of illness.

	Sepsis patients (N = 372)	Pneumonia patients (N = 944)	Patients not having sepsis or pneumonia (N = 2040)	P
Mode of Ventilation				< 0.001
VAC	125/371 (33.7)	274/935 (29.3)	596/2000 (29.8)	
PC/BIPAP/APRV	101/371 (27.2)	325/935 (34.8)	562/2000 (28.1)	
SIMV	87/371 (23.5)	139/935 (14.9)	549/2000 (27.5)	
PSV	27/371 (7.3)	102/935 (10.9)	165/2000 (8.2)	
PRVC	22/371 (5.9)	56/935 (6.0)	80/2000 (4.0)	
CPAP	3/371 (0.8)	15/935 (1.6)	12/2000 (0.6)	
NAVA	1/371 (0.3)	0/935 (0.0)	2/2000 (0.1)	
other modes	5/371 (1.3)	24/935 (2.6)	34/2000 (1.7)	
V _T , mL PBW	7.92 [6.97–9.14]	7.48 [6.43–8.76]	7.90 [6.82–9.09]	< 0.001
PEEP, cmH ₂ O	5 [5–8]	7 [5–8]	5 [5–8]	< 0.001
P _{max} , cmH ₂ O	22 [19–27]	24 [20–29]	21 [17–25]	< 0.001
P _{plat} , cmH ₂ O	18 [16–23]	20 [16–24]	17 [14–20]	< 0.001
RR tot, bpm	18 [16–22]	18 [15–23]	16 [14–20]	< 0.001
VR	1.49 [1.07–1.78]	1.64 [1.23–2.11]	1.31 [1.05–1.70]	< 0.001
C _{RS} (mL/cmH ₂ O)	33 [26–45]	33 [25–45]	38 [28–51]	< 0.001
PaO ₂ /FiO ₂	231 [170–300]	185 [127–246]	253 [172–351]	< 0.001
FiO ₂	0.50 [0.40–0.60]	0.50 [0.40–0.70]	0.50 [0.40–0.60]	< 0.001
pH	7.35 [7.26–7.41]	7.36 [7.27–7.43]	7.36 [7.30–7.42]	0.006
PaCO ₂ , mmHg	36.0 [30.0–43.3]	41.0 [34.0–50.6]	38.0 [33.0–45.0]	< 0.001

Data, inherent to day 1, are expressed as median with [IQR] or numbers n/N (proportions) where appropriate. 'N' in n/N may not always represent the total number of individuals within the group due to the existence of missing values, reported in Appendix II.

Abbreviations: ABW, Actual Body Weight; ARDS, Acute Respiratory Distress Syndrome; APRV, Airway Pressure Release Ventilation; Bi-PAP, Bi-level Positive Airway Pressure; C-PAP, Continuous-Positive Airway Pressure; CRS, Compliance respiratory system; FiO₂, Fraction of inspired Oxygen; IQR, interquartile range; NAVA, Neurally Adjusted Ventilatory Assist; PaCO₂, Partial pressure of carbon dioxide; PaO₂, Partial pressure of Oxygen; PEEP, Positive End Expiratory Pressure; PBW, Predicted Body Weight; PC, Pressure Control; P_{max}, peak inspiratory pressure; P_{plat}, plateau pressure; PRVC, Pressure Regulated Volume Controlled; PSV, Pressure Support Ventilation; RR, Respiratory Rate; SIMV Synchronized Intermittent Mandatory Ventilation; VT, Tidal volume; Vent, Ventilation; VAC, Ventilation Assist Control; VR, Ventilatory Ratio. *values are given only for patients under volumetric controlled mode ventilation.

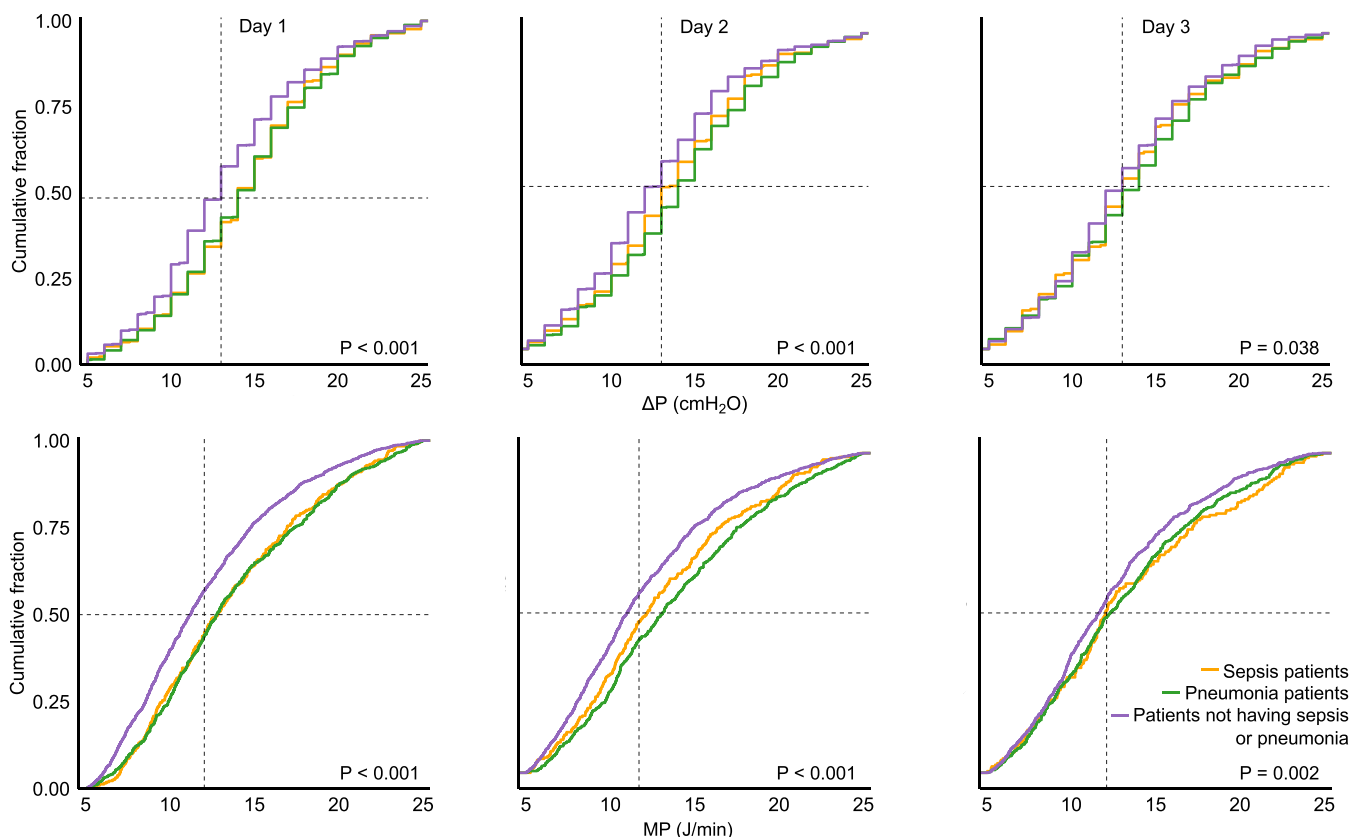


Fig. 2. Driving pressure and mechanical power of ventilation on day 1, 2, and 3 in sepsis patients, pneumonia patients, and patients receiving ventilation for any other reason.

Vertical dotted lines indicate the median of the overall population for each day; horizontal dotted lines always represent the proportion of 0.5.

Abbreviations: ΔP, driving pressure; MP, mechanical power of ventilation.

Table 3
Association of ΔP and MP with clinical outcomes.

	Sepsis patients (N = 372)	P	Pneumonia patients (N = 944)	P	Patients not having sepsis or pneumonia (N = 2040)	P
ICU mortality, odds ratio (95% CI)						
ΔP	1.06 (1.02–1.11)	0.005	1.03 (1.01–1.06)	0.014	1.02 (0.99–1.04)	0.149
MP	1.03 (1.00–1.07)	0.075	1.00 (0.98–1.02)	0.886	1.02 (1.00–1.04)	0.121
Duration of ventilation, exponential beta coefficient (95% CI)						
ΔP	1.13 (0.95–1.35)	0.155	1.11 (0.97–1.28)	0.132	1.19 (1.09–1.29)	< 0.001
MP	1.11 (0.93–1.31)	0.247	1.03 (0.92–1.14)	0.644	1.10 (1.02–1.20)	0.015
Length of stay in ICU, exponential beta coefficient (95% CI)						
ΔP	1.08 (0.86–1.37)	0.504	1.02 (0.87–1.19)	0.829	1.10 (1.00–1.21)	0.048
MP	1.24 (1.00–1.56)	0.056	1.03 (0.92–1.16)	0.572	1.13 (1.03–1.24)	0.009

Data, inherent to day 1, are expressed using logistic or multiple linear regression models as appropriate (95% Confidence Interval). Results were summarized as Odd Ratio (OR) for ICU mortality and exponential beta coefficient for duration of ventilation and length of stay in ICU. Covariates entered in the model are: arterial pH, baseline SOFA score, presence of active cancer, type of admission, and age.
Abbreviations: ΔP, driving pressure; MP, mechanical power of ventilation; ICU, intensive care unit.

and MP remain different during the first 3 days of invasive ventilation; and (3) ΔP, but not MP, has association with ICU mortality in sepsis and pneumonia patients, and not in patients not having sepsis or pneumonia. Our analysis has strengths. We used the individual patient data of multicenter studies of ventilation, meaning that we could use prospectively collected ventilation data to calculate ΔP and MP. The sample size was large with patients originating from over 500 ICUs in both university-affiliated and non-university hospitals, improving the generalizability of the findings. We had a predefined analysis plan, wherein we excluded patients with ARDS on admission to create homogeneous groups of patients. The analysis plan, including a sensitivity analysis with only patients in whom we could reliably calculate ΔP and MP, was strictly followed. Our findings contribute significantly to our comprehension of ΔP levels within a highly constrained cohort of invasive ventilated patient not having ARDS. Interestingly, median ΔP levels in our cohort, especially among sepsis and pneumonia patients, closely resemble the levels documented in studies involving patients with ARDS [19–22]. Furthermore, we observed a slight elevation in median ΔP levels from patients not having sepsis or pneumonia to sepsis patients and pneumonia patients, almost aligning with the ΔP levels in patients with mild, moderate and severe ARDS as reported previously [23]. It is worth noting that also range of ΔP values is nearly identical to that of ARDS patients [6,24], and even patients with ARDS related to COVID–19 [18,23,25,26], suggesting that the lungs of sepsis and pneumonia patients not having ARDS are equally stiff as the lungs of patients with ARDS. Diminished lung compliance is a significant factor in increasing ΔP, yet other elements may also contribute to ΔP. In non-ARDS patients higher V_T could be more accepted, thereby elevating ΔP. Similarly, the less frequent use of high PEEP in non-ARDS patients, coupled with higher V_T , can also raise ΔP. Additionally, factors such as airway resistance in COPD, prevalent in the pneumonia patient group, may further contribute to a higher ΔP [27]. Opposite to what we found in respect to ΔP, median MP levels in our cohort are remarkably lower compared to those reported in previous studies involving ARDS patients originating from before the COVID–19

pandemic [5,22], as well as those in the numerous reports on studies in patients with ARDS related to COVID–19 [18,25,26,28–30]. The reason for the discrepancy in median MP levels between our patients and those with ARDS in other reports, despite similarities in ΔP, remains speculative. One plausible explanation could be the higher deadspace fraction in ARDS patients, which would require higher RR. The RR is a critical component in calculating MP [31,32], and is essential in this context. The results of our analysis align with those of previous studies regarding the associations of ΔP with various outcomes. A seminal individual patient data meta-analysis, encompassing nine randomized clinical trials of invasive ventilation in ARDS patients [1], demonstrated that ΔP emerged as the most significant variable for stratifying mortality risk, regardless of V_T , PEEP and plateau pressures. Subsequent studies in ARDS patients [5,33,34], in patients not having ARDS [35], and in mixed ICU cohorts [2,29] have consistently reaffirmed this finding. Our study not only confirms the relationship between ΔP and ICU mortality in sepsis and pneumonia patients, but also establishes associations of ΔP with ICU length of stay and duration of ventilation. It is worth noting that in some of our subgroups, the sample size might have been insufficient to confidently confirm associations with outcomes. Using ΔP and MP as ventilation targets is an appealing approach. ΔP and MP, however, may be differently affected by various factors. Important to notice, is that both ΔP and MP may be inherently elevated due to underlying lung pathology. Yet, other elements may also contribute to ΔP [27]. In non-ARDS patients, higher V_T could be more accepted, thereby elevating ΔP. While is uncertain whether a high PEEP strategy always should be preferred over a low PEEP strategy in patients with ARDS [21,36,37] and those without ARDS [8], ΔP is also tied to the effects of PEEP on lung recruitment and overdistension. Additionally, factors such as airway resistance in COPD, prevalent in the pneumonia patient group, may further contribute to a higher ΔP. Next, MP is influenced by the RR, and it remains uncertain if a lower V_T strategy should be pursued at the cost of a higher RR [24]. The crucial and probably deleterious role of RR is not understood properly yet. Further research is imperative to elucidate the ideal strategies for targeting these parameters and their potential effects on clinical outcomes. This analysis has limitations. The studies we used for this analysis did not specifically focus on ΔP and MP, and some studies were performed well before interest in these parameters emerged. In none of the studies, inspiratory and expiratory holds were used, which could affect the reliability of the reported ΔP and MP. However, we were able to calculate ΔP and MP at all time points for all patients as all their elements were collected simultaneously. In the presence of spontaneous breathing, calculating ΔP and MP could result in too low levels. Nevertheless, the sensitivity analysis that excluded patients with spontaneous breathing activity revealed comparable findings. We used a simplified equation for calculating MP, which might lack accuracy. While this equation has been validated before [32] and was used in previous studies [3,16,24], MP is ideally calculated from continuous recordings of airway pressure and volume to achieve maximal granularity and accuracy [38]. As with other analyses that pool data from large observational studies, residual confounding cannot be excluded. There was also a large number of missings with regard to the endpoints used in one of the posthoc analyses, related to study design of the original investigations. We made a deliberate decision to categorize patients, and findings might have been slightly different if we had categorized patients differently. The pooled studies included patients who required ventilation for a period exceeding 24 h. This restricts the generalizability. While we excluded patients with ARDS on admission to create homogeneous groups of patients, we had to rely on the accuracy of the original studies with regard to this diagnosis. Last, it is important to note that the associations found do not confirm causal relationships.

5. Conclusion

In this cohort of non-ARDS patients, the intensity of ventilation was

higher in sepsis and pneumonia patients as compared to patients not having sepsis or pneumonia. ΔP was associated with higher mortality in sepsis and pneumonia patients, but not in patients not having sepsis or pneumonia.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jccr.2024.154531>.

References

- [1] Amato MBP, Meade MO, Slutsky AS, Brochard L, Costa ELV, Schoenfeld DA, et al. Driving pressure and survival in the acute respiratory distress syndrome. *N. Engl. J. Med.* 2015;372:747–55.
- [2] 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.
- [3] for the PROVE Network Investigators, Serpa Neto A, Deliberato RO, AEW Johnson, Bos LD, Amorim P, 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.
- [4] Tonetti T, Vasques F, Rapetti F, Maiolo G, Collino F, Romitti F, et al. Driving pressure and mechanical power: new targets for VILI prevention. *Ann Transl Med* 2017;5:286.
- [5] Saffran 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.
- [6] Bellani G, Laffey JG, Pham T, Fan E, Brochard L, Esteban A, et al. Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. *JAMA.* 2016;315:788.
 - [7] Simonis FD, Binnekade JM, Braber A, Gelissen HP, Heidt J, Horn J, et al. PRoVENT - protective ventilation in patients without ARDS at start of ventilation: study protocol for a randomized controlled trial. *Trials.* 2015;16:226.
 - [8] for the RELAx Investigators and the PROVE Network Investigators, Algera AG, Pisani L, DCJ Bergmans, den Boer S, CAJ de Borgie, et al. RELAx – REstricted versus Liberal positive end-expiratory pressure in patients without ARDS: protocol for a randomized controlled trial. *Trials.* 2018;19:272.
 - [9] Suetrong B, Walley KR. Lactic acidosis in Sepsis: It's not all anaerobic. *Chest.* 2016; 149:252–61.
 - [10] Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. *Intensive Care Med.* 2021;47:1181–247.
 - [11] The National Heart, Lung, and Blood Institute prevention and early treatment of acute lung injury clinical trials network. Early restrictive or Liberal fluid Management for Sepsis-Induced Hypotension. *N. Engl. J. Med.* 2023;388:499–510.
 - [12] The ERICC. (epidemiology of respiratory insufficiency in critical care) investigators, Azevedo LC, park M, Salluh JI, Rea-Neto a, Souza-Dantas VC, et al. clinical outcomes of patients requiring ventilatory support in Brazilian intensive care units: a multicenter, prospective, cohort study. *Crit. Care* 2013;17:R63.
 - [13] Neto AS, Barbas CSV, Simonis FD, Artigas-Raventós A, Canet J, Determann RM, et al. Epidemiological characteristics, practice of ventilation, and clinical outcome in patients at risk of acute respiratory distress syndrome in intensive care units from 16 countries (PRoVENT): an international, multicentre, prospective study. *Lancet Respir. Med.* 2016;4:882–93.
 - [14] Pisani L, Algera AG, Serpa Neto A, Ahsan A, Beane A, Chittawatanarat K, et al. Epidemiological characteristics, ventilator management, and clinical outcome in patients receiving invasive ventilation in intensive care units from 10 Asian middle-income countries (PRoVENT-IMIC): an international, multicenter, prospective study. *Am J Trop Med Hyg [Internet]* 2021. <https://doi.org/10.4269/ajtmh.20-1177> [cited 2023 Nov 7]; Available from:.
 - [15] Pisani L, Algera AG, Neto AS, Azevedo L, Pham T, Paulus F, et al. Geoeconomic variations in epidemiology, ventilation management, and outcomes in invasively ventilated intensive care unit patients without acute respiratory distress syndrome: a pooled analysis of four observational studies. *Lancet Glob. Health* 2022;10: e227–35.
 - [16] Van Meenen DMP, Algera AG, Schuijt MTU, Simonis FD, Van Der Hoeven SM, Neto AS, et al. Effect of mechanical power on mortality in invasively ventilated ICU patients without the acute respiratory distress syndrome: an analysis of three randomised clinical trials. *Eur. J. Anaesthesiol.* 2023;40:21–8.
 - [17] Sinha P, Calfee CS, Beitler JR, Soni N, Ho K, Matthay MA, et al. Physiologic analysis and clinical performance of the Ventilatory ratio in acute respiratory distress syndrome. *Am. J. Respir. Crit. Care Med.* 2019;199:333–41.
 - [18] Schuijt MTU, Schultz MJ, Paulus F, Serpa Neto A. For the PRoVENT-COVID collaborative group, Van Akkeren JP, et al. association of intensity of ventilation with 28-day mortality in COVID-19 patients with acute respiratory failure: insights from the PRoVENT-COVID study. *Crit. Care* 2021;25:283.
 - [19] Chiumello D, Carlesso E, Brioni M, Cressoni M. Airway driving pressure and lung stress in ARDS patients. *Crit. Care* 2016;20:276.
 - [20] Bellani G, Grassi A, Sosio S, Gatti S, Kavanagh BP, Pesenti A, et al. Driving pressure is associated with outcome during assisted ventilation in acute respiratory distress syndrome. *Anesthesiology.* 2019;131:594–604.
 - [21] Writing Group for the Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial (ART) Investigators, Cavalcanti AB, Suzumura ÉA, Laranjeira LN, DDM Paisani, Damiani LP, et al. Effect of Lung Recruitment and Titrated Positive End-Expiratory Pressure (PEEP) vs Low PEEP on Mortality in Patients With Acute Respiratory Distress Syndrome: A Randomized Clinical Trial. *JAMA* 2017;318: 1335.
 - [22] 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* 2023;11:42.
 - [23] Bos LDJ, Sijding M, Sinha P, Bhavani SV, Lyons PG, Bewley AF, et al. Longitudinal respiratory subphenotypes in patients with COVID-19-related acute respiratory distress syndrome: results from three observational cohorts. *Lancet Respir. Med.* 2021;9:1377–86.
 - [24] Costa ELV, Slutsky AS, Brochard LJ, Brower R, Serpa-Neto A, Cavalcanti AB, et al. Ventilatory variables and mechanical power in patients with acute respiratory distress syndrome. *Am. J. Respir. Crit. Care Med.* 2021;204:303–11.
 - [25] Botta M, Tsonas AM, Pillay J, Boers LS, Algera AG, Bos LDJ, et al. Ventilation management and clinical outcomes in invasively ventilated patients with COVID-19 (PRoVENT-COVID): a national, multicentre, observational cohort study. *Lancet Respir. Med.* 2021;9:139–48.
 - [26] Richard J-C, Terzi N, Yonis H, Chorfa F, Wallet F, Dupuis C, et al. Ultra-low tidal volume ventilation for COVID-19-related ARDS in France (VT4COVID): a multicentre, open-label, parallel-group, randomised trial. *Lancet. Respir. Med.* 2023;11:901–1002.
 - [27] Beitler JR, Malhotra A, Thompson BT. Ventilator-induced lung injury. *Clin. Chest Med.* 2016;37:633–46.
 - [28] Stalla Alves Da Fonseca R, Martins Correa Boniatti V, Carneiro Teixeira M, Preisig Werlang A, Martins F, Henrique Rigotti Soares P, et al. In: Tisherman SA, editor. Mechanical Power in Prone Position Intubated Patients with COVID-19-Related ARDS: A Cohort Study. 2023. *Crit Care Res Pract.*; 2023. p. 1–6.
 - [29] Azizi BA, Munoz-Acuna R, Suleiman A, Ahrens E, Redaelli S, Tartler TM, et al. Mechanical power and 30-day mortality in mechanically ventilated, critically ill patients with and without coronavirus Disease-2019: a hospital registry study. *J. Intensive Care* 2023;11:14.
 - [30] Buiteman-Kruizinga LA, Mkadmi HE, Serpa Neto A, Kruizinga MD, Botta M, Schultz MJ, 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;10:5409.
 - [31] Silva PL, Ball L, Rocco PRM, Pelosi P. Power to mechanical power to minimize ventilator-induced lung injury? *Intensive Care Med* 2019;7:38.
 - [32] Chiumello D, Gotti M, Guanziroli M, Formenti P, Umbrello M, Pasticci I, et al. Bedside calculation of mechanical power during volume- and pressure-controlled mechanical ventilation. *Crit. Care* 2020;24:417.
 - [33] Villar J, Martín-Rodríguez C, Domínguez-Berrot AM, Fernández L, Ferrando C, Soler JA, et al. A quantile analysis of plateau and driving pressures: effects on mortality in patients with acute respiratory distress syndrome receiving lung-protective ventilation*. *Crit. Care Med.* 2017;45:843–50.
 - [34] Parhar KKS, Zjadewicz K, Soo A, Sutton A, Zjadewicz M, Doig L, et al. Epidemiology, mechanical power, and 3-year outcomes in acute respiratory distress syndrome patients using standardized screening. An observational cohort study. *Ann Am Thorac Soc* 2019;16:1263–72.
 - [35] Wu H-P, Hu H-C, Chu C-M, Kao K-C. The association between higher driving pressure and higher mortality in patients with pneumonia without acute respiratory distress syndrome. *J. Formos. Med. Assoc.* 2021;120:204–11.
 - [36] Neto AS, Tomlinson G, Sahetya SK, Ball L, Nichol AD, Hodgson C, et al. Higher PEEP for acute respiratory distress syndrome: a Bayesian meta-analysis of randomised clinical trials. *Crit Care Resusc* 2021;23:171–82.
 - [37] Constantin J-M, Jabaudon M, Lefrant J-Y, Jaber S, Quenot J-P, Langeron O, et al. Personalised mechanical ventilation tailored to lung morphology versus low positive end-expiratory pressure for patients with acute respiratory distress syndrome in France (the LIVE study): a multicentre, single-blind, randomised controlled trial. *Lancet Respir. Med.* 2019;7:870–80.
 - [38] Schaefer MS, Loring SH, Talmor D, Baedorf-Kassiss EN. Comparison of mechanical power estimations in mechanically ventilated patients with ARDS: a secondary data analysis from the EPVent study. *Intensive Care Med.* 2021;47:130–2.