

# Increased Driving Pressure During Assisted Ventilation for Hypoxemic Respiratory Failure Is Associated with Lower ICU Survival The ICEBERG Study

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## Abstract

**Rationale:** Driving pressure ( $\Delta P$ ) is a marker of severity and a possible target for lung protection during controlled ventilation, but its value during assisted ventilation is unknown. Inspiratory holds provide an estimate of  $\Delta P$  that is quasi-static. Expiratory holds provide an estimate of the inspiratory effort, which is useful to estimate the transpulmonary dynamic  $\Delta P$ .

**Objectives:** To assess the correlation between  $\Delta P$ s measured during assisted ventilation and ICU outcomes.

**Methods:** Multicenter prospective observational study. Patients with acute hypoxemic respiratory failure were enrolled within 48 hours of triggering the ventilator. Respiratory mechanics were measured daily, and the variables of interest were averaged over the first 3 days of partial assistance. ICU outcomes were collected until Day 90.

**Measurements and Main Results:** A total of 298 patients from 16 centers were enrolled. VT, peak airway pressure, positive end-expiratory pressure, and inspiratory effort during the first 3 days

of assisted ventilation did not differ between survivors and nonsurvivors. Quasi-static  $\Delta P$  and transpulmonary dynamic  $\Delta P$  were higher in nonsurvivors than in survivors (13 [IQR, 11–14] vs. 11 [9–13] cm H<sub>2</sub>O [ $P < 0.001$ ]; and 19 [16–23] vs. 16 [13–18] cm H<sub>2</sub>O [ $P < 0.001$ ], respectively), whereas compliance normalized to predicted body weight was lower (0.65 [0.54–0.84] vs. 0.79 [0.64–0.97] mL/cm H<sub>2</sub>O/kg;  $P < 0.001$ ). Multivariable analysis confirmed the association with outcomes. During the study days, static  $\Delta P$  significantly diverged between survivors and nonsurvivors.

**Conclusions:** During assisted ventilation,  $\Delta P$  and normalized compliance are associated with ICU outcome, despite some overlap. Although our study does not allow an estimation of whether  $\Delta P$  is a marker of severity or a cause of lung injury, it highlights the potential value of monitoring and targeting it during spontaneous assisted breathing.

**Keywords:** acute hypoxemic respiratory failure; driving pressure; assisted ventilation; protective mechanical ventilation; spontaneous breathing

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This article has a related editorial.

A data supplement for this article is available via the Supplements tab at the top of the online article.

Artificial Intelligence Disclaimer: No artificial intelligence tools were used in writing this manuscript.

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Mechanical ventilation is a lifesaving intervention for patients with acute hypoxemic respiratory failure, and overwhelming evidence shows that protective ventilation leads to better clinical outcomes (1). During the past decade, the role of driving pressure ( $\Delta P$ ) as a marker of severity (2, 3) and a potential target for protective ventilation (4, 5) has emerged.  $\Delta P$  is computed as the difference between plateau pressure ( $P_{plat}$ ), measured by performing an end-inspiratory inclusion, and positive end-expiratory pressure (PEEP). From a physiological standpoint, it represents the change in elastic pressure applied to the respiratory system during a breath. It corresponds to the ratio between  $V_T$  and compliance.

$\Delta P$  is easily measured during controlled passive mechanical ventilation, when the entire work of breathing is generated by the ventilator, often because of deep sedation and possibly neuromuscular blockade (6). The measurement of  $\Delta P$  in the presence of active spontaneous breathing is less straightforward, but possible and potentially just as relevant. Excessive lung strain may occur during spontaneous breathing as a result of the combination of the patient's muscular activity, generating negative intrathoracic pressures, and the positive pressure imposed by the ventilator (7). This interaction may be described by analogy to an iceberg, whereby a large component of

the total distending pressure is hidden to standard bedside monitoring unless an esophageal catheter is in place (8). In the absence of this gold standard, other readily applicable maneuvers have been described, allowing estimation of the total pressure applied to the respiratory system during spontaneous breathing (9).

Foti and coworkers (10) described the measurement of  $P_{plat}$ , and hence a quasi-static  $\Delta P$  ( $\Delta P_{stat}$ ) during pressure support ventilation (PSV), by performing an inspiratory hold (11). In a single-center retrospective study,  $\Delta P_{stat}$  during PSV showed a tight association with outcome, similarly to the case of controlled ventilation (12). Unfortunately,  $P_{plat}$  is not always interpretable during PSV, mainly because of the presence of concurrent muscular activity. Simple criteria have been proposed to validate this measurement (13), allowing its use for clinical practice.

An alternative approach to quantifying the change in lung stress in the presence of spontaneous breathing is to measure the negative deflection in airway pressure during an end-expiratory airway occlusion ( $\Delta P_{occ}$ ), applied for the duration of a single breath, unexpected by the patient.  $\Delta P_{occ}$  represents the pressure swing generated by the inspiratory muscles against the occluded airway. Because diaphragm activation varies minimally from breath to breath,  $\Delta P_{occ}$  can be used to infer the magnitude of the swing

in pleural pressure during nonoccluded breaths (14). Therefore,  $\Delta P_{occ}$  allows the quantification of the magnitude of inspiratory effort (muscular pressure [ $P_{mus}$ ]) and an estimated measurement of dynamic transpulmonary  $\Delta P$  ( $\Delta P_{L,dyn}$ ). This provides information about the magnitude of lung stress under dynamic inspiratory conditions.

The primary objective of this study was to prospectively verify, in a multicenter setting, the association of  $\Delta P_{stat}$  and  $\Delta P_{L,dyn}$  measured during assisted ventilation and the outcomes of patients with hypoxemic respiratory failure.

## Methods

This is a prospective, multicenter cohort study (clinicaltrials.gov identifier NCT05203536) conducted in 16 ICUs in 9 countries, led by the University of Milano-Bicocca (Monza, Italy). It was approved by the coordinating center (Fondazione Istituto di Ricovero e Cura a Carattere Scientifico San Gerardo dei Tintori, Monza, Italy) and by the relevant body of each treatment center. Informed consent was waived or obtained from patients or substitute decision-makers. A full description of the study methods is provided in the online supplement.

To ensure consistency of the maneuvers performed and the data collected, two

## At a Glance Commentary

### Scientific Knowledge on the

**Subject:** Driving pressure ( $\Delta P$ ), a surrogate of lung strain, is associated with outcomes during controlled mechanical ventilation.

### What This Study Adds to the

**Field:** The measurement of static airway  $\Delta P$  and dynamic transpulmonary  $\Delta P$  is feasible in the early transition from controlled to assisted ventilation, and these variables are independently associated with ICU survival. Clinicians should consider systematically monitoring these values to achieve safe spontaneous breathing and help prevent patient self-inflicted lung injury.

investigators from each center followed a specific training regimen that is described in detail in the online supplement.

### Patients

Adult patients were included if they were diagnosed with acute hypoxemic respiratory failure ( $\text{PaO}_2/\text{FiO}_2$  ratio  $<300$  mm Hg during the ICU stay) requiring invasive mechanical ventilation, connected to a ventilator enabling inspiratory holds during assisted modes (11) such as PSV, had evidence of spontaneous breathing activity (i.e., triggering) between 6 and 48 hours, and had no therapeutic limitations (e.g., Do Not Resuscitate orders) at the time of enrollment. Exclusion criteria are provided in the online supplement.

Patients were enrolled during the first 48 hours of assisted ventilation, after the transition from controlled ventilation. Data were collected on Days 1 (enrollment), 2, 3, 5, 7, 10, and 14 and then every 7 days until extubation or death, as well as in the 24 hours before enrollment (i.e., during controlled ventilation) (Figure 1). A complete list of data collected is provided in the online supplement. The data were collected anonymously on an online case report form developed by REDCap Cloud and provided by the leading institution.

### Data Collection

On each study day, the investigators performed three end-expiratory and three

end-inspiratory occlusions 1 minute apart and recorded the average values of Pplat and  $\Delta P_{\text{occ}}$  in the case report form. The readability of Pplat was evaluated according to standard criteria (13). When applicable, the cause of nonreadability was also recorded. The following variables were calculated as described below and in Figure 1.

- $\Delta P_{\text{stat}} = \text{Pplat} - \text{PEEP}$
- Pressure muscle index (PMI) (10) =  $\text{Pplat} - \text{peak pressure (Ppeak)}$
- $\Delta P_{\text{L,dyn}} = [(\text{Ppeak} - \text{PEEP}) - 2/3 * \Delta P_{\text{occ}}]$  (14)
- Estimated Pmus =  $(-3/4 * \Delta P_{\text{occ}})$  (14)
- Respiratory system compliance (Crs) =  $V_T / \Delta P_{\text{stat}}$
- Crs normalized to predicted body weight (Crs/PBW) = Crs/kg, as a way of normalizing compliance to an estimate of lung size. PBW was calculated using standard formulas: for male subjects,  $50 + 0.91 * (\text{height in cm} - 152.4)$ ; for female subjects,  $45.5 + 0.91 * (\text{height in cm} - 152.4)$
- Total mechanical power =  $(0.5 * \Delta P_{\text{L,dyn}} + \text{PEEP}) * V_T * \text{respiratory rate} * 0.098$  (15, 16)
- $4 * \Delta P_{\text{stat}} + \text{respiratory rate}$  (16), an alternative estimate of potential lung injury

Data about ICU and hospital mortality and duration of invasive ventilation were collected at discharge.

### Statistics

Expecting a mean  $\Delta P_{\text{stat}}$  (average of the first 3 days after enrollment) of  $10.0 \pm 2.0$  cm H<sub>2</sub>O in survivors and of  $11.6 \pm 3.1$  cm H<sub>2</sub>O in nonsurvivors and an ICU mortality rate of 25% (12), we estimated a sample size of 168 patients (with 42 foreseen deaths) to detect the expected difference with 90% power ( $1 - \beta$ ) and type I ( $\alpha$ ) error of 5%. Considering that the measurement might not be feasible in 15% of patients and an additional 5% might drop out of the study, the final sample size was set at 202 patients. Subject recruitment was continued beyond this target to allow the centers that joined the study later to also achieve enrollment.

Data are expressed as mean  $\pm$  standard deviation or median (IQR). Differences between groups were assessed by unpaired *t* test, Mann-Whitney test, or  $\chi^2$  test. Variables known to be associated with ICU mortality were *a priori* entered into multivariable logistic regression models.

Risk is reported as odds ratios with 95% confidence intervals. The goodness of fit was ranked by the Akaike information criterion. The log-rank test was used to quantify the difference in survivorship. Spearman's correlation was used to assess association between Crs measured during controlled and assisted ventilation. A longitudinal analysis was performed using a time-dependent Cox model to assess the effect of ventilation parameters on 30- and 60-day mortality. The longitudinal trajectories of respiratory variables over time were assessed in a supplementary analysis using outcome as a grouping variable. Linear mixed-effects models were fitted, incorporating natural cubic splines for time and an interaction term. A random intercept for patient identifier was included to account for within-subject repeated measurements. Finally, we assessed the association between Crs/PBW and  $\text{PaO}_2/\text{FiO}_2$  ratio using Spearman's correlation, with linear regression included for graphical representation. Statistics were performed using R statistical software.

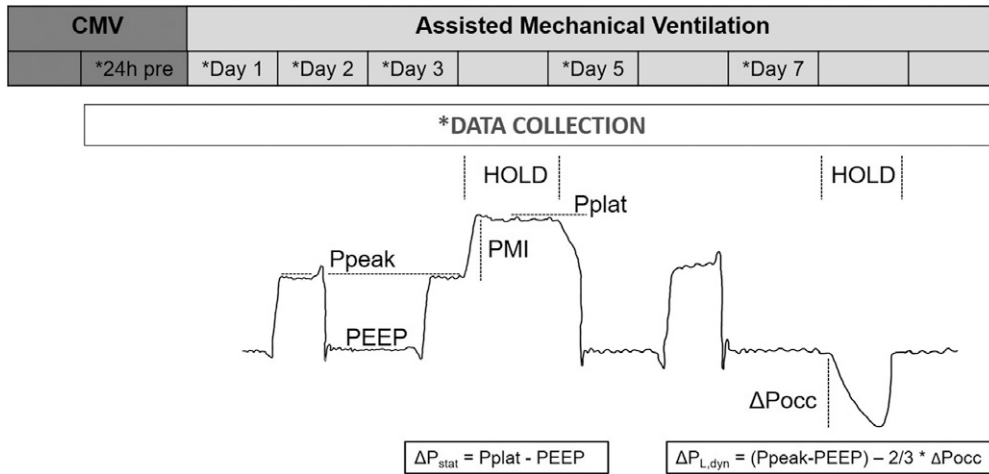
## Results

After completion of the training phase, 298 patients from 16 centers in 9 countries were enrolled (Table E1 in the online supplement). The number of patients on each study day is shown in Table E2.

### Baseline Characteristics

Baseline population characteristics and main comorbidities at ICU admission are listed in Tables 1 and E3, respectively. Sixty-seven patients (23%) died in the ICU. Nonsurvivors were significantly older, with a trend for a higher Sequential Organ Failure Assessment score at admission and more comorbidities (Tables 1 and 2). The etiology of respiratory failure was infective in most patients (Table E4). The use of neuromuscular blocking agents was significantly more frequent, but lasted for a shorter period, in survivors (Table 1).

As shown in Table E5,  $\Delta P_{\text{stat}}$  measured during the last day of controlled ventilation was significantly lower in ICU survivors, with similar  $V_T$ s, indicating greater baseline compliance in survivors. In the overall population, the degree of hypoxemia was mild, with a median  $\text{PaO}_2/\text{FiO}_2$  ratio of 205 (IQR, 161–255) mm Hg and no significant differences between survivors and nonsurvivors.



**Figure 1.** Study methods. The patients were enrolled within 48 hours of starting to trigger the ventilator (i.e., assisted mechanical ventilation). Data were collected on the last day of controlled mechanical ventilation at the indicated time points during assisted ventilation and subsequently every 7 days if ventilation was continued. Inspiratory and expiratory holds were performed on every data-collection day. The difference between plateau pressure (Pplat) and positive end-expiratory pressure (PEEP) during an inspiratory hold was used to measure the  $\Delta P_{stat}$ . PMI was calculated as the difference between Pplat and Ppeak. An estimate of  $\Delta P_{L,dyn}$  was calculated with the formula shown in the figure, whereby the  $\Delta P_{occ}$  is measured from PEEP to the nadir of airway pressure reached during an expiratory hold. \*Indicates data collection days. CMV = continuous mandatory ventilation;  $\Delta P_{L,dyn}$  = dynamic transpulmonary driving pressure;  $\Delta P_{occ}$  = occlusion pressure;  $\Delta P_{stat}$  = static driving pressure; PMI = pressure muscle index; Ppeak = peak pressure.

**Respiratory Mechanics during the First 3 Days of Assisted Ventilation**

Patients were switched to assisted ventilation after 6 (3–10) days of controlled ventilation. PSV was used in most cases (73.8% of study days), followed by pressure assist control (9.4% of study days), and the other modes accounted for the remaining 16.8% of study days. Pplat measurements during assisted ventilation were readable in 91% of study days, and at least one recording was available in the first 3 days in all patients. The main reasons reported for a nonreadable measurement were “plateau is not flat” (59%

of cases), “inspiratory muscles activity” (23%), and “expiratory muscles activity” (11%). The proportion of nonreadable measurements was higher in ICU nonsurvivors (10.5%) than in survivors (7.1%;  $P = 0.03$ ).

Figure E2 shows the tight correlation between static compliance measured on the last day of controlled ventilation and the first day of assisted ventilation ( $R = 0.731$ ;  $P < 0.001$ ).

$\Delta P_{stat}$  averaged over the first 3 days of assisted ventilation was significantly higher in nonsurvivors than in survivors ( $P < 0.001$ ;

Figure 2D), as was  $\Delta P_{L,dyn}$  ( $P < 0.001$ ; Figure 2E), albeit with a substantial overlap between survivors and nonsurvivors. When subjects were separated into two groups based on the median  $\Delta P_{stat}$  (12 cm H<sub>2</sub>O) or  $\Delta P_{L,dyn}$  (16 cm H<sub>2</sub>O) during the first 3 days of assisted ventilation, mortality was higher for the high- $\Delta P$  groups in both cases (log rank test,  $P = 0.05$  for  $\Delta P_{stat}$  [Figure 2A] and  $P = 0.01$  for  $\Delta P_{L,dyn}$  [Figure 2B]). The mortality rate (Figure 3A) increased across the quartiles of  $\Delta P_{stat}$  and  $\Delta P_{L,dyn}$  ( $P = 0.011$  and  $P < 0.001$ , respectively), and decreased with Crs/PBW ( $P = 0.019$ ), but it did not have a significant

**Table 1.** Baseline Demographic Data and Adjunctive Therapies Used before Enrollment in the Study

	All (N = 298)	Survivors (n = 231)	Nonsurvivors (n = 67)	P Value
Age, yr	63 (53–72)	61 (51–72)	68 (61–73)	0.005
BMI, kg/m <sup>2</sup>	28 (25–31)	27 (25–31)	29 (24–33)	0.144
Male sex	207 (69.7)	160 (69.6)	47 (70.1)	1.000
Nonrespiratory SOFA at ICU admission	6.0 (4.0–8.0)	6.0 (4.0–8.0)	7.0 (5.0–8.0)	0.058
No. of comorbidities	1 (0–1)	0 (0–1)	0 (0–2)	0.002
>2 comorbidities	61 (20.5)	43 (18.6)	18 (26.9)	0.168
Preenrollment treatments for acute respiratory failure				
NMBA	177 (67.8)	142 (74.7)	24 (48.0)	<0.001
NMBA duration, d	4.0 (2.0–6.0)	4.0 (2.0–6.0)	5.5 (2.8–10.0)	0.046
Prone position	67 (25.0)	53 (25.2)	14 (25.0)	1.000
ECMO	18 (6.6)	15 (7.2)	3 (5.5)	1.000

Definition of abbreviations: BMI = body mass index; ECMO = extracorporeal membrane oxygenation; NMBA = neuromuscular blocking agents; SOFA = Sequential Organ Failure Assessment. Data presented as count (percentage) median (IQR) as applicable.

**Table 2.** Patients' Outcomes

	All Patients (N = 298)	Survivors (n = 231)	Nonsurvivors (n = 67)	P Value
ICU LOS, d	19 (12–29)	18 (11–29)	20 (12–29)	0.516
Hospital LOS, d	30 (20–48)	33 (25–50)	21 (14–37)	<0.001
Tracheostomy	88 (29.5)	64 (27.7)	24 (5.8)	0.259
Controlled ventilation, d	5.0 (2.0–8.0)	5.0 (2.0–8.0)	5.0 (3.0–10.0)	0.227
Assisted ventilation, d	6.0 (3.0–13.0)	6.0 (3.0–12.5)	14.0 (5.0–19.0)	0.076

Definition of abbreviation: LOS = length of stay.

Data presented as count (percentage) median (IQR) as applicable.

association with  $P_{peak}$  ( $P = 0.129$ ) or  $\Delta P_{occ}$  ( $P = 0.314$ ). The risk of death associated with increasing values of  $\Delta P_{stat}$ ,  $\Delta P_{L,dyn}$ , and Crs/PBW is shown in Figures 3B–3D. To further support the physiological interpretation of our findings, we assessed the correlation between Crs/PBW and  $Pa_{O_2}/Fi_{O_2}$  ratio using Spearman's method, which revealed a significant positive association ( $\rho = 0.25$ ,  $P = 4.6 \times 10^{-5}$ ; Figure E3). This suggests that lower Crs/PBW is associated with worse oxygenation, likely due to reduced aerated lung volume and increased shunt.

In the longitudinal analysis performed using the time-dependent Cox model, an increase in daily  $\Delta P_{L,dyn}$  was associated with increased risks of 30-day mortality (1.07 [1.02–1.13];  $P = 0.006$ ) and 60-day mortality (1.07 [1.02–1.12];  $P = 0.003$ ), whereas daily  $\Delta P_{stat}$  showed nonsignificant associations with 30-day mortality (1.05 [0.98–1.13];  $P = 0.168$ ) and 60-day mortality (1.06 [1.00–1.13];  $P = 0.060$ ) (Tables E6 and E7). Notably, the only other ventilatory parameter associated with an increased risk of mortality was daily  $P_{peak}$ , which was significantly linked to 30-day (hazard ratio, 1.09 [95% confidence interval, 1.04–1.14];  $P < 0.001$ ) and 60-day mortality (hazard ratio, 1.09 [95% confidence interval, 1.04–1.13];  $P < 0.001$ ) (Tables E6 and E7). Figure 4 shows the longitudinal values of ventilatory parameters according to outcome over the entire study: static  $\Delta P$  significantly diverged between survivors and nonsurvivors, increasing in the latter group over time.

Other respiratory mechanical parameters averaged over the first 3 days of assisted ventilation are shown in Table 3.  $V_T$ ,  $P_{peak}$ ,  $P_{plat}$ , and PEEP did not differ between survivors and nonsurvivors, whereas Crs/PBW was significantly higher in survivors. Of note,  $V_T$  was within a safe range ( $< 8$  mL/kg) in all patients. In Figure E4, we report the effect of lower  $V_T$  values based on normalized Crs and the

corresponding risk of death (3). The  $Pa_{O_2}/Fi_{O_2}$  ratio was significantly higher in survivors than in nonsurvivors, whereas  $Pa_{CO_2}$  and pH did not differ. Lactate levels were significantly higher in nonsurvivors (Table 3).

Nonsurvivors were more deeply sedated than survivors, as indicated by the lower average Richmond Agitation Sedation Scale (RASS) in the first 3 days ( $-3.0$  [ $-4.0$  to  $-1.7$ ] vs.  $-1.5$  [ $-2.7$  to  $-0.5$ ]). In keeping with this, the percentage of days on which patients received sedatives was higher in nonsurvivors (82.2%) than in survivors (75.1%;  $P = 0.028$ ).

Table E8 shows a comparison of clinical factors and outcomes between patients with higher versus lower  $\Delta P_{stat}$  than the population median (12 cm H<sub>2</sub>O). A higher  $\Delta P_{stat}$  was associated with increased mortality and fewer ventilator-free days, a longer duration of assisted ventilation (in survivors), and a higher incidence of tracheostomy.

### Multivariable Analyses

The multivariable models included clinical predictors associated with ICU outcomes: age, RASS score,  $Pa_{O_2}/Fi_{O_2}$  ratio, and either  $\Delta P_{stat}$  or  $\Delta P_{L,dyn}$  (in two separate models, and averaged over the first 3 days of assisted ventilation; Table 3). Both models indicated that age, RASS score, and respective  $\Delta P$  were independently associated with outcome (Figure 5). Figures E5 and E6 show additional multivariable models, one including the Sequential Organ Failure Assessment score and one including Crs instead of  $\Delta P$ .

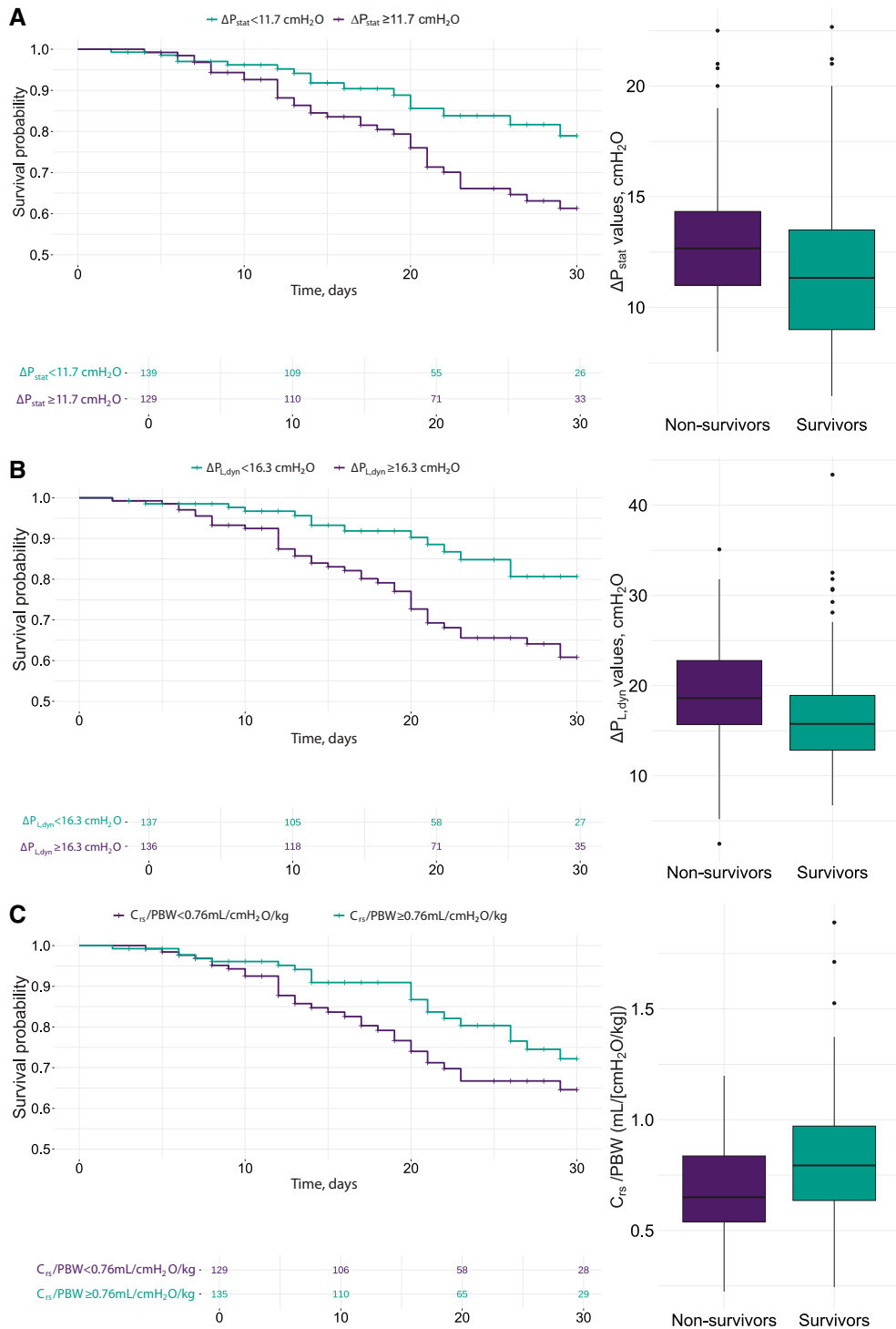
### Discussion

In this large multicenter prospective study, we report a strong association between  $\Delta P_s$  measured after the transition to assisted ventilation and patient outcomes.  $\Delta P$

measured in quasi-static (i.e., during an inspiratory hold) and dynamic (i.e., derived by the airway occlusion pressure during an expiratory hold) conditions was significantly higher in patients who did not survive their ICU stay compared with patients who were discharged alive, albeit with a substantial overlap between the groups. The population enrolled in the study included patients with acute respiratory failure of any etiology and mostly moderate severity, as reflected by a median  $Pa_{O_2}/Fi_{O_2}$  ratio of 205 mm Hg on the day before enrollment. In the multivariable analysis,  $\Delta P$  (static and dynamic) measured during assisted ventilation, RASS score, and age were significant predictors of outcome.

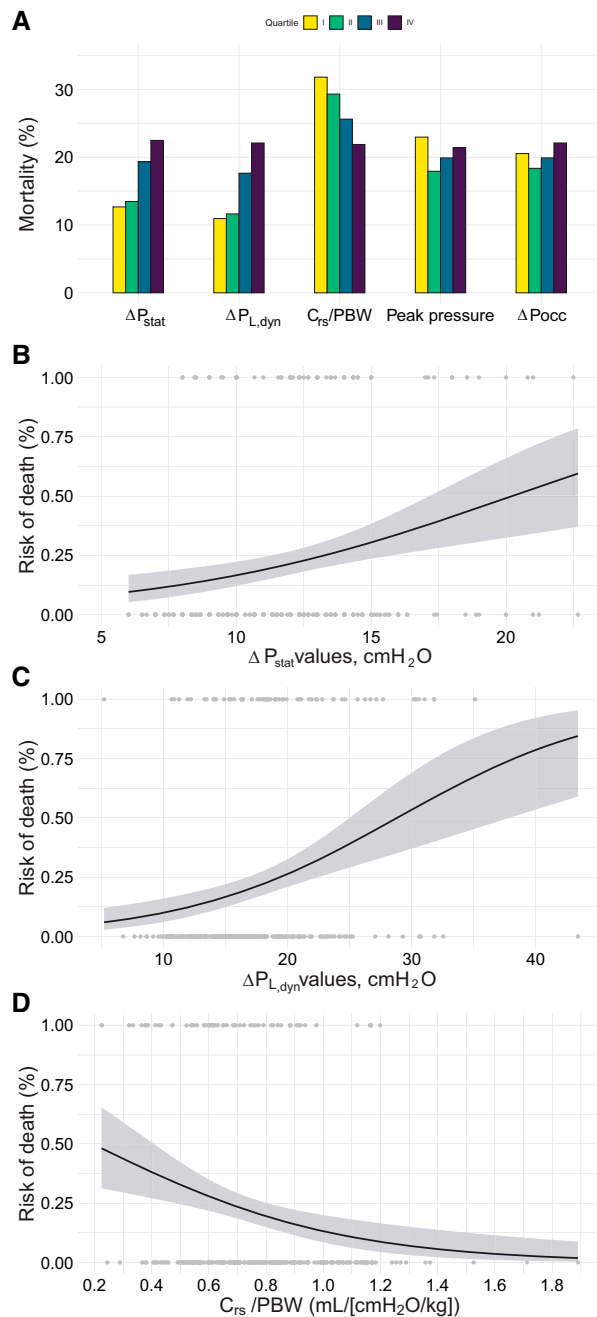
The strong association between  $\Delta P$  and outcome in patients receiving controlled ventilation is now broadly accepted despite being mainly based on observational studies (2, 17, 18). The physiological interpretation of this association is that  $\Delta P$  represents the strain applied to the respiratory system from a given  $V_T$  (19). This suggests that it is not the  $V_T$  *per se* that causes lung injury, but the amount of deformation this causes on the parenchyma, dependent on the elastic characteristics of the system ( $\Delta P = V_T / \text{compliance}$ ) (3). In our results,  $V_T$  *per se* is not associated with outcome, and all patients had a  $V_T$  within what is considered a "protective range" ( $< 8$  mL/kg), underlying how protective ventilation cannot be guaranteed by protective  $V_T$  alone.

Our study shows that normalized compliance and  $\Delta P$  are associated with the worst patient outcomes. The study is neither designed nor powered to disentangle the extent to which a higher  $\Delta P$  is a marker of lung severity versus a cause of perpetration of injury. At the same time, even if normalized compliance is low,  $\Delta P$  might be kept in a protective range if  $V_T$  is properly reduced. Zalucky and coworkers recently reported that the use of neuromuscular blockers was



**Figure 2.** Thirty-day ICU survival curves. The population was dichotomized based on the median of static (11.7 cm H<sub>2</sub>O; A) and dynamic transpulmonary (16.3 cm H<sub>2</sub>O; B) driving pressure. The log-rank test showed a significantly higher risk of mortality above the median for static ( $P=0.05$ ) and dynamic transpulmonary ( $P=0.01$ )  $\Delta P$ . The box plots of the distribution of static and dynamic transpulmonary  $\Delta P$  are shown in B, respectively, stratified by ICU survival. The population was also dichotomized according to the median value of respiratory system compliance normalized to predicted body weight (0.76 mL/[cm H<sub>2</sub>O/kg]; C). The log-rank test revealed no statistically significant difference in mortality risk above the median for this parameter ( $P=0.100$ ). The tables below each graph show the number of patients at risk at each time point.  $C_{rs}/PBW$ =respiratory system compliance normalized for predicted body weight;  $\Delta P_{L,dyn}$ =dynamic transpulmonary driving pressure;  $\Delta P_{stat}$ =static driving pressure.

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**Figure 3.** (A) Quartile distribution of  $\Delta P_{stat}$  and  $\Delta P_{L,dyn}$ , compliance of respiratory system normalized for predicted body weight, peak airway pressure, and airway  $\Delta P_{occ}$ . The y-axis represents the mortality rate, expressed as a percentage, for each quartile. (B–D) Locally weighted scatter plot smoothing curves for the risk of mortality with increasing values of static (B) and dynamic transpulmonary (C) driving pressures and compliance of the respiratory system normalized for predicted body weight (D).  $C_{rs}/PBW$  = respiratory system compliance normalized for predicted body weight;  $\Delta P_{L,dyn}$  = dynamic transpulmonary driving pressure;  $\Delta P_{occ}$  = occlusion pressure;  $\Delta P_{stat}$  = static driving pressure.

associated with a mortality benefit in patients with lower compliance (20).

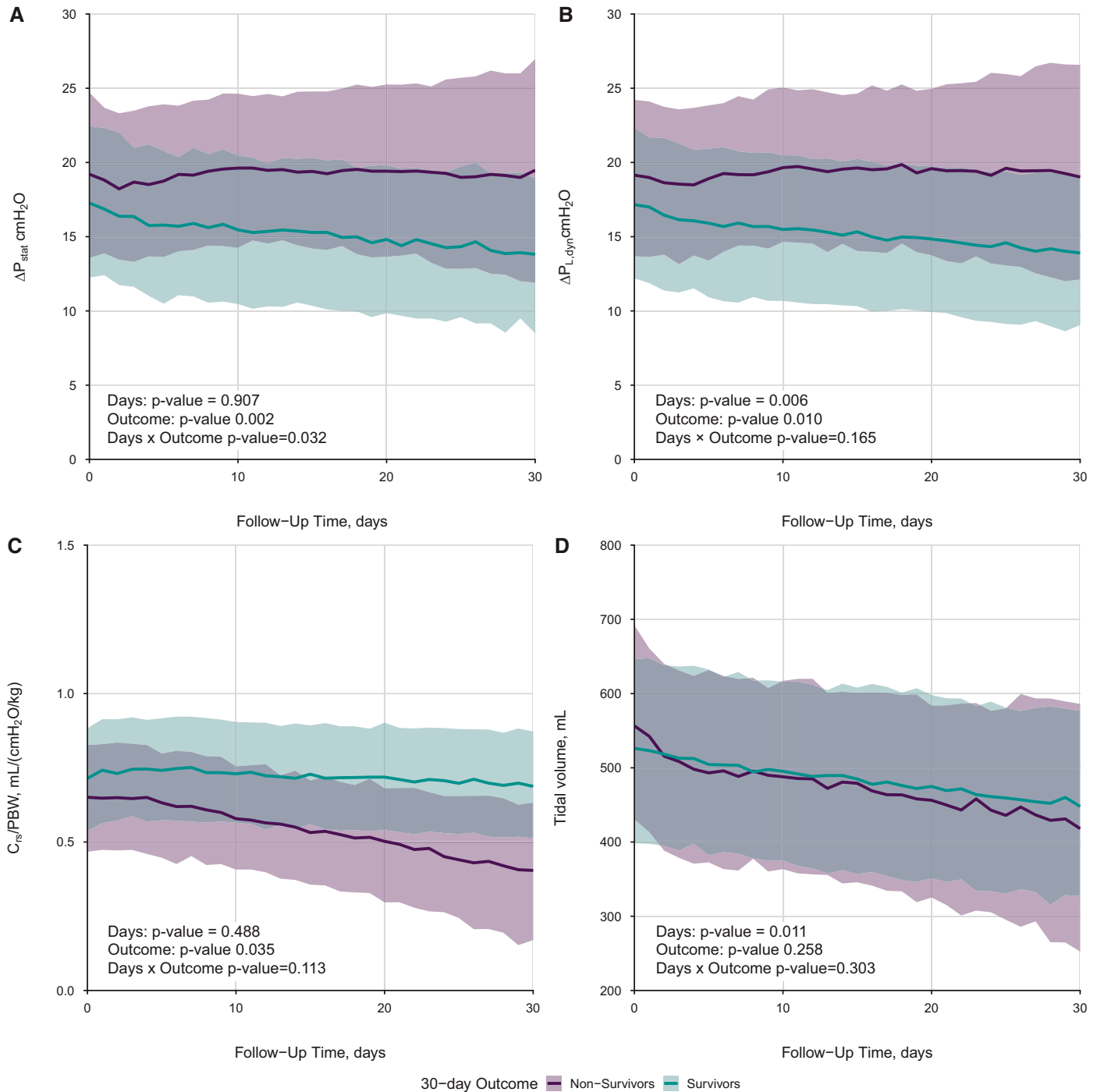
Intuitively, the same relationship between the amount of lung strain and

outcome should persist during assisted ventilation, in which the muscular inspiratory pressure contributes to lung distension and possible injury. This led to the

concept of patient self-inflicted lung injury (7) and is well described in experimental studies (21).

The use of inspiratory and expiratory holds during assisted ventilation to measure  $P_{plat}$  in PSV (11) and  $\Delta P_{occ}$  (14) has increased since it was shown that PMI (10) and  $P_{mus}$  (14), respectively derived from  $P_{plat}$  and  $\Delta P_{occ}$ , have good correlation with the esophageal pressure-derived gold-standard measurements of inspiratory effort (10, 14, 22). The same correlations have also been reported in children, in whom  $\Delta P_{occ}$  showed an excellent ability to estimate the changes in esophageal pressure (23), whereas PMI had a more variable performance (23, 24).

Performing an inspiratory hold during assisted ventilation requires the relaxation of the patient's respiratory muscles and the clinician's capability to interpret the  $P_{plat}$  correctly. Approximately 10% of the measurements are to be discarded because the  $P_{plat}$  is not flat (13), mostly because of inspiratory or expiratory muscle activity. Soundoulounaki and colleagues reported a high incidence of expiratory muscle activation (as measured by changes in gastric pressure) even in the presence of a flat plateau (25). A mechanism by which expiratory muscles reduce the end-expiratory lung volume (26) and therefore lead to the measurement of a falsely low airway static  $\Delta P$  has been recently described (27) to explain this finding. The measurement of static  $\Delta P$  includes PEEP, and, in the absence of gastric pressure measurement, it is not possible to estimate if the end-expiratory transpulmonary pressure is lower than the one PEEP would provide in a fully relaxed state. In the small population enrolled in a previous study (27), almost 50% of the patients showed a decrease of end-expiratory transpulmonary pressure associated with expiratory muscle activation. In this group, an injurious transpulmonary static  $\Delta P$  ( $>12$  cm H<sub>2</sub>O) was predicted by an airway  $\Delta P >12$  cm H<sub>2</sub>O rather than the normal cutoff of 15 cm H<sub>2</sub>O (27). In our population, a  $\Delta P >12$  cm H<sub>2</sub>O was associated with worse outcomes. The combination of these findings leads us to draw two conclusions: 1) expiratory muscle activity should be ruled out carefully by visual observation during the performance of inspiratory holds during assisted ventilation and 2) the plateau can still be flat in the presence of expiratory muscle activity and static  $\Delta P$  could be underestimated. A very cautious approach should consider only values of  $\Delta P$  well below 15 cm H<sub>2</sub>O as "protective."

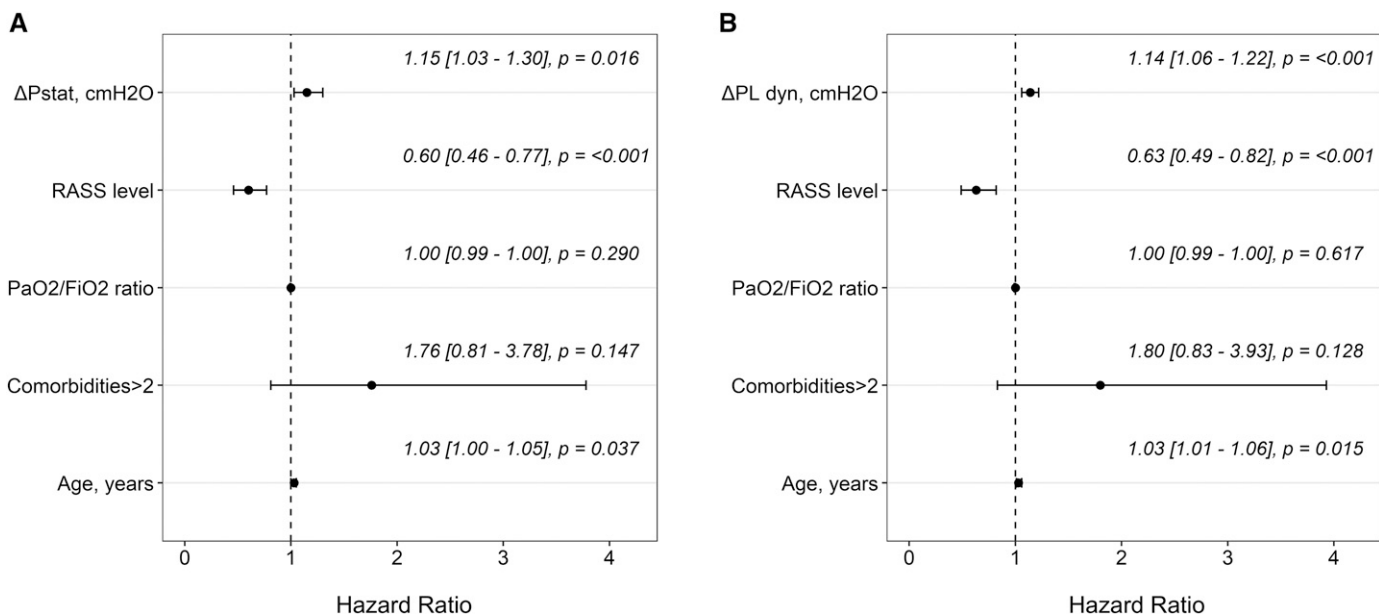


**Figure 4.** Longitudinal trajectories of respiratory variables stratified by 30-day survival status. Predicted marginal means (with 95% confidence intervals) of (A)  $\Delta P_{stat}$ , (B)  $\Delta P_{L,dyn}$ , (C)  $C_{rs}/PBW$ , and (D)  $V_T$  plotted over the first 30 days of follow-up and stratified by 30-day mortality (survivors vs. nonsurvivors). Estimates were derived from linear mixed effects models including a natural cubic spline for time (degrees of freedom = 3), an interaction term between time and 30-day mortality status, and a random intercept for patient identifier to account for repeated within-subject measures. The *P* values displayed in each panel correspond to the interaction term and indicate whether the temporal trajectory of each variable significantly differed between survivors and nonsurvivors. Color shading around the lines represents the 95% confidence intervals. All models were adjusted only for time and mortality status, with no additional covariates included.  $C_{rs}/PBW$  = respiratory system compliance normalized for predicted body weight;  $\Delta P_{L,dyn}$  = dynamic transpulmonary driving pressure;  $\Delta P_{stat}$  = static driving pressure.

**Table 3.** Respiratory Mechanics and Gas Exchanges during the First 3 Days of Assisted Mechanical Ventilation

	Total (N = 298)	Survivors (n = 231)	Nonsurvivors (n = 67)	P Value
<b>Respiratory mechanics</b>				
V <sub>T</sub> , mL	506 (428–598)	508 (424–495)	495 (443–552)	0.812
V <sub>T</sub> , mL/kg PBW	7.7 (6.6–9.2)	7.8 (6.7–9.2)	7.7 (6.6–9.2)	0.398
Pressure support value, cm H <sub>2</sub> O	8 (6–10)	8 (6–10)	9 (7–12)	0.020
RR, 1/min	19 (16–23)	19 (15–22)	20 (16–25)	0.125
PEEP, cm H <sub>2</sub> O	9 (7–12)	9 (7–12)	9 (7–12)	0.236
P <sub>peak</sub> , cm H <sub>2</sub> O	19.3 (16.3–23.3)	19.0 (16.3–23.0)	20.8 (16.1–24.7)	0.092
Plateau pressure, cm H <sub>2</sub> O	21.0 (18.0–25.0)	21.0 (18.0–25.0)	22.5 (19.0–26.0)	0.086
Static ΔP, cm H <sub>2</sub> O	11.7 (9.5–13.7)	11.3 (9.0–13.3)	12.6 (11.0–14.3)	<0.001
Dynamic ΔP <sub>L</sub> , cm H <sub>2</sub> O	16.2 (13.0–19.5)	15.7 (12.8–18.4)	18.7 (15.8–23.4)	<0.001
PMI, cm H <sub>2</sub> O	1.7 (–0.4 to 4.0)	1.7 (0.0–4.0)	1.7 (–0.5 to 3.7)	0.672
ΔP <sub>occ</sub> , cm H <sub>2</sub> O	9.8 (6.5–13.8)	9.5 (6.4–13.6)	11 (6.5–15.6)	0.133
P <sub>0.1</sub> , cm H <sub>2</sub> O	1.8 (1.2–2.9)	1.8 (1.1–2.8)	1.9 (1.4–3.3)	0.150
Compliance, mL/cm H <sub>2</sub> O	45 (35–58)	46 (37–58)	39 (31–53)	0.004
Compliance/predicted body weight, mL/(cm H <sub>2</sub> O/kg)	0.76 (0.60–0.92)	0.79 (0.64–0.97)	0.65 (0.54–0.84)	<0.001
4ΔP <sub>stat</sub> + RR	65 (56–76)	63 (55–74)	70 (65–82)	<0.001
MP <sub>tot</sub> * J/min	17 (13–22)	16 (12–22)	18 (14–24)	0.974
<b>Arterial blood gases</b>				
F <sub>IO<sub>2</sub></sub>	40 (35–48)	40 (35–47)	42 (39–50)	0.036
PaO <sub>2</sub> , mm Hg	91 (81–102)	93 (83–104)	87 (78–94)	0.002
PaCO <sub>2</sub> , mm Hg	42 (38–47)	42 (38–47)	43 (37–51)	0.424
PaO <sub>2</sub> /F <sub>IO<sub>2</sub></sub> ratio, mmHg	227 (181–274)	235 (188–281)	202 (156–250)	<0.001
pH	7.44 (7.40–7.47)	7.44 (7.42–7.47)	7.42 (7.36–7.55)	0.045
Lactate, mmol/L	1.2 (0.9–1.6)	1.2 (0.9–1.6)	1.5 (1.1–1.9)	<0.001

Definition of abbreviations: ΔP = driving pressure; ΔP<sub>L</sub> = transpulmonary driving pressure; ΔP<sub>occ</sub> = end-expiratory occlusion pressure; MP<sub>tot</sub> = total mechanical power; P<sub>0.1</sub> = airway occlusion pressure; PBW = predicted body weight; PEEP = positive end-expiratory pressure; PMI = pressure muscle index; P<sub>peak</sub> = peak pressure; RR = respiratory rate. Data presented as median (IQR). \*Calculated as 0.5 \* ΔP<sub>L,dyn</sub> + PEEP \* V<sub>T</sub> \* RR \* 0.098.



**Figure 5.** Multivariable models and odds ratios (95% confidence interval) for mortality. The models include the clinical factors known to be related to ICU outcome. The first model (A) includes the ΔP<sub>stat</sub> (n = 245, Akaike information criterion = 228), and the second model (B) includes the ΔP<sub>L,dyn</sub> (n = 252, Akaike information criterion = 223). ΔP<sub>L,dyn</sub> = dynamic transpulmonary driving pressure; ΔP<sub>stat</sub> = static driving pressure; RASS = Richmond Agitation Sedation Scale.

In our population, most patients had a protective static  $\Delta P$  ( $<14$  cm  $H_2O$  in three quarters of the population). This was likely due to the selection of the participating centers, all of which were well experienced in mechanical ventilation and applied protective settings, which probably received further attention in the setting of the study, which was focused on  $\Delta P$ . Moreover, the values of  $\Delta P$ , both static and dynamic, despite being statistically different, had a substantial overlap between survivors and nonsurvivors. Although this can be seen as a limitation of the role of  $\Delta P$  as a “prognostic” factor, it suggests that even a small reduction might have an impact on a patient’s outcome, especially in the prospective of interventional studies focused on this parameter.

Until now, only a retrospective single-center study has reported a correlation between  $\Delta P_{stat}$  measured during PSV and patient outcomes (12). Other studies support the physiological rationale of this measurement. Pérez and coworkers showed that  $\Delta P_{stat}$  in PSV correlated well with transpulmonary  $\Delta P$  measured by an esophageal catheter, and this was reproducible at three different levels of PEEP (28). In a retrospective study, Bastia and coworkers correlated compliance measured during PSV and controlled ventilation, finding good agreement between the two measurements (29). Vaporidi and coworkers measured  $\Delta P$  during proportional assisted ventilation in 62 patients for as long as 72 hours. During most of the recorded time, the patients would regulate their  $V_T$  and ventilate with a  $\Delta P <15$  cm  $H_2O$ . Most instances in which  $\Delta P$  was  $\geq 15$  cm  $H_2O$  were associated with low compliance (30).

These reports support the feasibility of measuring  $\Delta P_{stat}$  during PSV as during controlled ventilation. Our finding that  $\Delta P_{stat}$  also correlates with clinical outcomes supports the validity of these measurements. Further corroborating the robustness of this association, our study found no differences in  $V_T$  or  $P_{peak}$  between survivors and nonsurvivors, as these factors are not as directly correlated with lung strain (31).

Interestingly, the measures of respiratory effort derived from the

inspiratory and expiratory hold (PMI and  $P_{mus}$  from  $\Delta P_{occ}$ ) were not correlated with outcomes. Our population is quite homogenous in terms of effort, and the mean level of measured effort was still considered within normal limits (8). Again, this finding might imply that high respiratory effort has negative effects on outcome only when it translates into high distending pressures (which is often the case). In contrast, the presence of a presumed noninjurious effort can still lead to excessive lung strain, depending on the lung’s elastic properties. Therefore, it would be advisable to calculate the static and dynamic  $\Delta P$ s themselves and not rely solely on measurements of effort.

The measurement of  $\Delta P_{occ}$  is less dependent than  $P_{plat}$  on the clinician’s interpretation of the airway pressure waveform.  $\Delta P_{occ}$  allows for a rather simple calculation to estimate  $\Delta P_{L,dyn}$ . In our study,  $\Delta P_{L,dyn}$  had a strong relationship with patient outcomes. This association was preserved over the duration of the study and was confirmed by multivariable analysis. This is the first time that this surrogate for dynamic transpulmonary  $\Delta P$  was shown to be prospectively associated with survival. Prior reports that showed an association of dynamic airway  $\Delta P$  with outcome (18) and that a ventilatory strategy to reduce airway  $\Delta P$  (both static and dynamic) is associated with improved survival (31) were retrospective.

The significantly higher RASS suggesting, among other factors, that the patients who survived were less sedated is probably related to better gas exchanges and respiratory mechanics, which prompt the physicians to believe it is safe to reduce the sedation. However, it is possible that our findings support the evidence that a deeper level of sedation negatively affects outcomes (32, 33).

In conclusion, this is the first report of an association between respiratory mechanics ( $\Delta P$ , its trend over time, normalized compliance) measured during assisted ventilation and ICU outcomes in patients with acute hypoxemic respiratory failure in a prospective, multicenter context.

$V_T$  and respiratory effort alone did not show a correlation with survival. Despite not being able to ascertain a causal relationship, and a substantial overlap in diving pressure values between survivors and nonsurvivors, these results support the value of monitoring respiratory mechanics during assisted ventilation. Static and dynamic  $\Delta P$  might become targets for clinical trials aimed at assessing protective ventilatory strategies during assisted ventilation. ■

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