Intensive Care Med (2022) 48:888–898
https://doi.org/10.1007/s00134-022-06724-y

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Partition of respiratory mechanics in patients with acute respiratory distress syndrome and association with outcome: a multicentre clinical study

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Abstract

Purpose: In acute respiratory distress syndrome (ARDS), physiological parameters associated with outcome may help defining targets for mechanical ventilation. This study aimed to address whether transpulmonary pressures (P_L), including transpulmonary driving pressure (DP_L), elastance-derived plateau P_L, and directly-measured end-expiratory P_L, are better associated with 60-day outcome than airway driving pressure (DP_{aw}). We also tested the combination of oxygenation and stretch index [$PaO_2/(FiO_2*DP_{aw})$].

Methods: Prospective, observational, multicentre registry of ARDS patients. Respiratory mechanics were measured early after intubation at 6 kg/ml tidal volume. We compared the predictive power of the parameters for mortality at day-60 through receiver operating characteristic (ROC) and assessed their association with 60-day mortality through unadjusted and adjusted Cox regressions. Finally, each parameter was dichotomized, and Kaplan–Meier survival curves were compared.

Results: 385 patients were enrolled 2 [1–4] days from intubation (esophageal pressure and arterial blood gases in 302 and 318 patients). As continuous variables, DP_{aw}, DP_L, and oxygenation stretch index were associated with 60-day mortality after adjustment for age and Sequential Organ Failure Assessment, whereas elastance-derived plateau P_L was not. DP_{aw} and DP_L performed equally in ROC analysis ($P=0.0835$). DP_{aw} had the best-fit Cox regression model. When dichotomizing the variables, $DP_{aw} \geq 15$, $DP_L \geq 12$, plateau $P_L \geq 24$, and oxygenation stretch index < 10 exhibited lower 60-day survival probability. Directly measured end-expiratory $P_L \geq 0$ was associated with better outcome in obese patients.

Conclusion: DP_L was equivalent predictor of outcome than DP_{aw}. Our study supports the soundness of limiting lung and airway driving pressure and maintaining positive end-expiratory P_L in obese patients.

Keywords: Acute respiratory distress syndrome, Artificial respiration, Mechanical ventilation, Positive-pressure respiration, Respiratory mechanics

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Introduction

Mechanical ventilation is lifesaving but can generate ventilator-induced lung injury (VILI) [1]. A protective ventilatory strategy which combined lower tidal volume (V_T) normalized to predicted body weight (PBW) and airway plateau pressure (Pplat) in patients with acute respiratory distress syndrome (ARDS) reduced mortality [2].

Several parameters have been suggested to monitor ventilatory strategy. Amato et al. [3] proposed that airway driving pressure (DP_{aw}) is physiologically sounder than using V_T/PBW for limiting VILI. Their retrospective analysis demonstrated that DP_{aw} was better associated with outcome than V_T/PBW or Pplat [3]. Further prospective, large observational studies also confirmed this strong association [4, 5]. DP_{aw} is thus an essential monitoring parameter and is a potential target for lung protective ventilation strategies [6].

VILI is related to the degree of lung stretch, and thus theoretically transpulmonary driving pressure (DP_L) or tidal lung stress may be a better determinant of VILI than DP_{aw} by removing the chest wall contribution to DP_{aw} [7]. Other calculated indices related to transpulmonary pressures (P_L) represent possible physiological meaning for limiting VILI. Particularly, because of the existence of pleural pressure gradient [8], P_L at dorsal lung differs from P_L at ventral lung, which may have different implications for monitoring VILI. For example, because the position of the esophagus is close to dorsal lung, the directly measured end-expiratory P_L through esophageal pressure (Pes) provides P_L at the dorsal lung, representing the degree of collapse [9–11]. On the other hand, the tidal change of pleural pressure is relatively uniform. In other words, delta Pes (i.e., delta pleural pressure at dorsal lung) is similar with the delta pleural pressure at ventral lung [10]. Thanks to this feature, the elastance-derived plateau transpulmonary pressure [12] calculated through delta Pes (see Appendix) thus represent total lung stress of ventilated "baby lung", particularly at the ventral lung, which is more susceptible to overdistension [10, 13]. All these values of transpulmonary pressure require measurement of Pes [14], which is rarely monitored in routine clinical practice. A previous study from our centre demonstrated the feasibility of embedding this technique into clinical practice [15], providing a foundation for the present study.

Our ultimate goal was to find out the most important variables that can be used as ventilatory targets for limiting the risk of VILI. However, since there is no direct, reliable approach (including biomarkers) to assess VILI at bedside, we decided to look at the associations between mechanics and mortality as an indirect approach. Certainly, mortality was not determined only by VILI but we think that, if one variable in mechanics can well represent the risk of VILI, it should be associated with mortality.

The present study describes a multicentre study to examine the relative importance on outcome of the global and partitioned respiratory mechanics in ARDS patients. Our main hypothesis was that transpulmonary driving pressure (DP_L) is a better predictor for outcome than DP_{aw}. Secondary hypothesis was that oxygenation stretch index, a composite variable using PaO_2/FiO_2 divided by DP_{aw} [15], can enhance the predictive power of DP_{aw}.

Methods

Design and settings

This was a prospective, observational, multicentre study (ClinicalTrials.gov NCT02623192). Participating centres are listed in the Supplementary file. The study was approved by research ethics boards from each centre. Informed consent was waived at the centre from Canada since mechanics measurement is a part of the standard of care in patients with moderate and severe ARDS [15]. In all remaining centres, informed consent was obtained from patient's substitute decision maker.

Patients

Inclusion criteria were the following: (1) age > 18 years; (2) ARDS per the Berlin definition [16]; (3) receiving assist/control ventilation with sedation; (4) within the first week of intubation. Exclusion criteria were the following: (1) known esophageal pathology, active upper gastrointestinal bleeding or other contraindications to gastric tube insertion; (2) severe hemodynamic instability (> 30% increase in vasopressors in the prior 6 h, or norepinephrine > 0.5 mcg/kg/min).

Measurements

Respiratory mechanics were measured in a standardized fashion as previously described [15]. Briefly, we studied patients at semi-recumbent position [17] who were not generating spontaneous breathing (no triggering and no effort during an end-expiratory occlusion) during the measurement. To achieve this, patients were receiving deep sedation with or without neuromuscular blockade (sometimes as boluses). Patients were not on extracorporeal life support and ventilated with the following settings: volume control with V_T 6 ml/kg of predicted body weight (PBW), constant inspiratory flow 50–60 L/min, 0.3-s end-inspiratory pause, and positive end-expiratory pressure (PEEP) set by the attending clinician. Pes measurements followed a standardized protocol [15], which was adapted from the procedures of EPVent study [9], in all centres. Briefly, Pes catheter was firstly passed into stomach (a depth of 60 cm and confirmed by gentle, swift compression of abdomen). The catheter was then withdrawn to a depth of 40 cm. The esophageal placement was confirmed by the presence of cardiac artifact and

the apparent difference between tidal change in Pes and airway driving pressure (to exclude misplacement in trachea). For each patient, the position of the catheter was also validated through Lanteri's modification of Baydur's occlusion test at the bedside [18, 19]. Central inspection of Pes waveforms (e.g., the presence of cardiac artifact, the absence of negative Pes swing, the validity of occlusion test) was also performed by the author L.C. Pes was only measured in patients with moderate or severe ARDS and in the absence of spontaneous breathing effort. Mechanics and arterial blood gases were measured at the clinical PEEP level and were repeated 10 min after PEEP was modified by 5 cmH_2O (increased in most cases without changing any other settings). Whether PEEP was increased (preferable option) or decreased from clinical PEEP level was decided by investigators and clinicians. The principle was to maintain Pplat $\leq$ 35 cmH_2O and keep the patient hemodynamically stable. Notice that the Pplat limit is only for the measurement safety, not for clinical practice. The measurements were repeated at a different PEEP level to observe the responses to PEEP.

Definitions in respiratory mechanics

Detailed calculations in mechanics are provided in Appendix (see supplement). We refer to global mechanics for calculations based on airway pressure, such as DP_{aw}. We calculated DP_{aw} as the difference between Pplat and total PEEP, not set PEEP. We refer to lung and chest wall mechanics when Pes and P_L were used. We partitioned DP_{aw} into $DP_{L,}$ and the chest wall driving pressure (i.e., ΔPes during a tidal breath). Since the position of the esophagus is close to dorsal lung, we further partitioned P_L specific to the ventral or dorsal lungs. Concretely, the directly measured P_L represents end-expiratory P_L across the dorsal lung, whereas the elastance-derived P_L represents end-inspiratory P_L across the ventral lung [10, 11]. We also calculated the oxygenation stretch index [$(PaO_2/(FiO_2 \times DP_{aw})$] a previously described composite index of oxygenation and mechanics [15]. Mechanical power was calculated using the formula: $0.098 \times RR \times [V_T^2 \times [0.5 \times E rs + RR \times (1 + I{:}E)/(60 \times I{:}E) \times Rrs] + V_T \times PEEP]$ [20].

Sample size estimation

The study was aimed to show that the discriminant power for predicting mortality, measured with the area under curve (AUC) of receiver operating characteristic (ROC) curve, of DP_{aw} and DP_L differed. Using Hanley and McNeils' method [21], a sample of 64 non-survivors and 160 survivors at 60 days achieve 95% power to detect a difference of 0.092 between DPaw with an AUC of 0.590 and DP_L with an AUC of 0.498, using a two-sided *z*-test at a significance level of 0.05. The correlation between the two diagnostic tests was assumed 0.834 for the survivor group and 0.870 for the non-survivor group. Assuming a dropout rate of 20%, the dropout-inflated enrollment sample size was 280 patients (200 survivors and 80 non-survivors) with Pes measured. Assumptions and data for sample size calculation was based on EPVent study [9].

Statistical analysis

All analyses were prospective unless explicitly indicated as post-hoc. For descriptive analysis, data are presented as mean ± standard derivation or median [25th–75th interquartile range (IQR)] according to skewness and normality of data checked through Shapiro–Wilk test. Characteristics and mechanics between survivors and non-survivors were compared using *t*-test or Mann–Whitney *U*-test, depending on normality, without *P*-value correction for multiple comparisons.

To compare the predictive power of mechanics, we used mortality at day-60 as a binary outcome and estimated ROC curves for mechanics as continuous variables. The AUCs were then compared by using bootstrap test for two correlated ROC curves. To test the association between outcome and mechanics, Cox proportional-hazards regression models were carried out using mechanics as continuous predictors. Association between each covariate and outcome was quantified by hazard ratio (HR) and 95% confidence interval (CI). Adjusted Cox regression models were performed to adjust the HR estimate for baseline characteristics—age and Sequential Organ Failure Assessment (SOFA) score. Proportional hazard assumption was tested for all Cox models (based on the scaled Schoenfeld residuals). Adjusted models were ranked by their Akaike information criterion (AIC). AIC addresses both goodness-of-fit and simplicity of a model. Since we compared models with the same number of independent variables for the same set of patients, the lowest AIC represented the best fit model.

Furthermore, for each mechanics parameter, we grouped patients into the lower or the higher (or equal) dichotomized group according to thresholds proposed in previous studies: 12 cmH_2O for DP_L, 15 cmH_2O for DP_{aw}, 24 cmH_2O for elastance-derived plateau P_L, 0 cmH_2O for directly measured end-expiratory P_L, and 10 mmHg/cmH_2O for oxygenation stretch index [3, 5, 14, 15]. The Kaplan–Meier approach was used to estimate survival functions in each group and unadjusted log-rank test was used to compare them.

We did not impute missing data, assuming missingness was at random; when addressing the different research questions, we used subsets with complete information.

All p-values were two-sided, with p-values < 0.05 considered statistically significant. Statistical analyses were

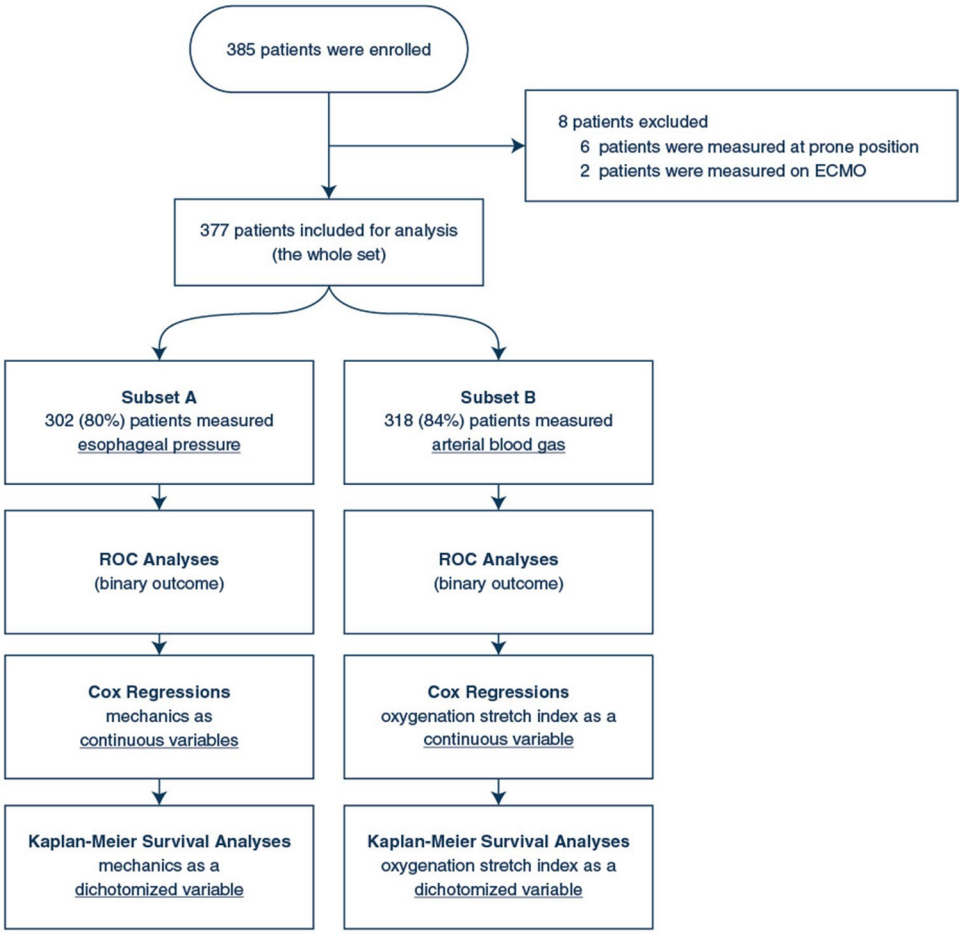

Fig. 1 Flowchart of the study

performed using R version 3.5.2 [22] with package survminer version 0.4.9.

Results

As illustrated in the flowchart (Fig. 1), 385 patients were enrolled; 8 patients were excluded from analysis since measurements were obtained in the prone position, or under extracorporeal membrane oxygenation (ECMO). The remaining 377 patients formed the study cohort.

Characteristics of the cohort are provided in Table 1. Mortality at day 60 was 37.7%. Measurements were made within 2 [IQR 1–4] days from intubation at a median clinical PEEP of 12 [IQR 10–14] cmH_2O. In univariate analysis non-survivors had higher age, APACHE II at ICU admission, higher SOFA and lower PaO_2/FiO_2 at enrollment. Respiratory mechanics are reported in Table 1. Univariate analysis suggested that non-survivors had higher Pplat, DP_{aw}, DP_L, elastance-derived plateau P_L, respiratory rate, and lower oxygenation stretch index. We did not find any statistical differences in oxygenation, blood pressure, and DP_{aw} responses to higher PEEP among survivors and non-survivors.

Mechanics and outcome

Pes was measured in 302 patients (subset A: 80% of the cohort). The median occlusion test ratio (ΔPaw/ΔPes) for validating the measured Pes was 0.91 [IQR 0.84–1.00].

AUCs of the ROC curves of DP_{aw}, DP_L, elastance-derived plateau P_L, and directly measured end-expiratory P_L for predicting mortality at day 60 were 0.62, 0.59, 0.58, and 0.53, respectively. There was no difference in AUCs between DP_{aw} and DP_L ($P = 0.0835$, Figure S1).

Unadjusted Cox regressions showed that higher DP_{aw}, higher DP_L, and higher elastance-derived plateau P_L were associated with higher HR of death (Table 2). Directly measured end-expiratory P_L was not statistically associated with 60-day mortality in this subset. DP_{aw} and DP_L remained associated with 60-day mortality after adjustment for age and SOFA (Table 2), with an attenuation of HR at low values of DP_{aw} and DP_L (Figure S2 and S3).

Table 1 General characteristics and respiratory mechanics of patients

General characteristics	Overall (*n* = 377)	Survivors (*n* = 235)	Non-survivors (*n* = 142)	*P* value*
Males—no. (%)	266 (70.6)	169 (71.9)	97 (68.3)	0.530
Age—years	60 [46, 69]	56 [43, 66]	65 [53, 76]	< 0.001
Height—cm	171 [164, 178]	171 [164, 178]	170 [163, 178]	0.980
Body Mass Index—kg/m^2	28 [24, 34]	28 [24, 33]	28 [24, 35]	0.674
APACHE II at ICU admission	24 [16, 30]	23 [16, 28]	27 [17, 32]	0.016
ICU stay prior to enrollment—days	2 [1, 5]	2 [1, 6]	2 [1, 4]	0.963
IMV days prior to enrollment—days	2 [1, 4]	2 [1, 5]	2 [1, 4]	0.350
SOFA at enrollment	11 [8, 14]	10 [7, 13]	12 [9, 16]	< 0.001
Clinical PEEP at enrollment—cmH$_2$O	12 [10, 14]	12 [10, 14]	12 [10, 14]	0.615
PaO$_2$/FiO$_2$ at enrollment—mmHg	128 [100, 162]	138 [103, 168]	115 [88, 150]	0.001
$V_{E,corr}$—L/min	12.3 [10.4, 14.5]	12.3 [10.3, 14.2]	12.3 [10.5, 14.8]	0.630
Severity of ARDS—no. (%)				0.024
Mild	38 (11.1)	28 (13.2)	10 (7.6)	
Moderate	232 (67.6)	148 (69.8)	84 (64.1)	
Severe	73 (21.3)	36 (17)	37 (28.2)	
Pulmonary ARDS—no. (%)	262 (69.5)	169 (72)	93 (65.2)	0.197
60-day mortality—no. (%)	142 (37.7)			
Global mechanics	**(*n* = 377)**	**(*n* = 235)**	**(*n* = 142)**	
PEEP—cmH$_2$O	12 [10, 15]	12 [10, 15]	12 [10, 15]	0.153
V_T/PBW—ml/kg	6.2 [5.9, 6.5]	6.1 [5.9, 6.5]	6.3 [5.9, 6.5]	0.542
Auto-PEEP—cmH$_2$O	1 [0, 1]	1 [0, 1]	1 [0, 1]	0.522
Pplat—cmH$_2$O	25 [23, 28]	25 [22, 28]	26 [24, 30]	< 0.001
DPaw—cmH$_2$O	12 [10, 14]	11 [9, 13]	13 [10, 15]	0.001
RR—cmH$_2$O	28 [24, 30]	27 [24, 30]	28 [25, 30]	0.061
Crs—ml/cmH$_2$O	35 [27, 43]	36 [29, 44]	32 [25, 41]	0.003
Rrs—cmH$_2$O/L/s	12 [9, 14]	12 [9, 14]	12 [9, 14]	0.337
Oxygenation stretch index[†]—mmHg/cmH$_2$O	11.7 [8.1, 16.2]	12.3 [9.1, 16.9]	10.8 [6.8, 14.9]	0.005
Partitioned mechanics	**(*n* = 302)**	**(*n* = 195)**	**(*n* = 107)**	
DP$_L$—cmH$_2$O	8.3 [6.3, 11]	8 [6.1, 10.6]	9.3 [6.9, 12.1]	0.010
DP$_{cw}$—cmH$_2$O	3 [2.7 4.1]	2.7 [2.7, 4.1]	3 [2.7, 4.1]	0.111
C$_L$– ml/cmH$_2$O	48 [35, 62]	50 [38, 62]	44 [30, 61]	0.009
C$_{cw}$—ml/cmH$_2$O	127 [92, 163]	130 [98, 165]	120 [85, 155]	0.180
E$_L$/Ers ratio	0.73 [0.63, 0.8]	0.73 [0.64, 0.79]	0.73 [0.63, 0.81]	0.638
Elastance-derived plateau P$_L$—cmH$_2$O	18.1 [14.5, 21.6]	17.5 [14.2, 20.8]	19.1 [15.4, 22.9]	0.012
Directly-measured end-expiratory P$_L$—cmH$_2$O	− 2.3 ± 5	− 1.9 ± 4.7	− 3 ± 5.5	0.077
Response to higher PEEP[††]	**(*n* = 311)**	**(*n* = 194)**	**(*n* = 117)**	
Higher PEEP—cmH$_2$O	15 [14, 17]	15 [14, 17]	15 [14, 17]	0.660
Lower PEEP—cmH$_2$O	10 [9, 12]	10 [9, 12]	10 [9, 12]	0.307
ΔPaO$_2$/FiO$_2$—mmHg	14 [− 3, 36]	16 [− 4, 36]	14 [− 2, 34]	0.696
ΔMAP—mmHg	− 2 [− 5, 2]	− 1 [− 5, 2]	− 2 [− 5, 1]	0.735
ΔDPaw—cmH$_2$O	1 [0, 2]	1 [0, 2]	1 [0, 2]	0.503
ΔDP$_L$—cmH$_2$O	1 [0, 2]	1 [0, 2]	1.4 [0, 3]	0.110
ΔEnd-expiratory P$_L$—cmH$_2$O	3.6 [2.6, 5]	3.6 [2.6, 5]	3.6 [2.3, 4.4]	0.276

Categorical variables are described in numbers (percentage); continuous variables are described as mean ± standard derivation or median [interquartile ranges], as appropriate

* Comparing survivors with non-survivors using t-test or Mann–Whitney U-test or chi-square, as appropriate. P values were not corrected for multiple comparisons

† Oxygenation stretch index was measured in total 318 patients, of which 194 survivors and 124 non-survivors

†† Measured variables at higher PEEP minus those at lower PEEP. For example, PaO$_2$/FiO$_2$ at high PEEP minus PaO$_2$/FiO$_2$ at lower PEEP

APACHE II Acute Physiology and Chronic Health Evaluation II score, *IMV* invasive mechanical ventilation, *SOFA* Sequential Organ Failure Assessment score, *PEEP* positive end-expiratory pressure, *PaO$_2$/FiO$_2$* the ratio of partial pressure of arterial oxygen and fraction of inspired oxygen, *$V_{E,corr}$* expired volume per minute corrected by arterial carbon dioxide, *PEEP* positive end-expiratory pressure, *V_T/PBW* tidal volume per predicted body weight, *Pplat* airway plateau pressure, *DP_{aw}* airway driving pressure which is the difference between Pplat and total PEEP, *RR* respiratory rate, *Crs* respiratory system compliance, *Rrs* respiratory system resistance, *oxygenation-stretch index* PaO$_2$/FiO$_2$ divided by DPaw, *DP_L* transpulmonary driving pressure which is the tidal change in transpulmonary pressure, *DP_{cw}* chest wall driving pressure which is the tidal change in esophageal pressure, *C_L* lung compliance, *C_{cw}* chest wall compliance, *E_L/E_{rs} ratio* lung elastance to respiratory system elastance ratio, *P_L* transpulmonary pressure, *PaO$_2$/FiO$_2$* the ratio of partial pressure of arterial oxygen and fraction of inspired oxygen, *MAP* mean arterial pressure

Table 2 Cox proportional-hazards regression models (subset A*)

Covariate	Unadjusted model		Adjusted model with DP_{aw}		Adjusted model with DP_L		Adjusted model with plateau P_L	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age	1.026 (1.013–1.039)	< 0.0001	1.025 (1.013–1.038)	< 0.0001	1.026 (1.013–1.039)	< 0.0001	1.026 (1.013–1.039)	< 0.0001
SOFA	1.157 (1.103–1.214)	< 0.0001	1.147 (1.091–1.206)	< 0.0001	1.154 (1.098–1.213)	< 0.0001	1.153 (1.097–1.212)	< 0.0001
DP_{aw}	1.116 (1.062–1.172)	< 0.0001	1.093 (1.040–1.148)	0.0004				
DP_L	1.089 (1.036–1.144)	0.0007			1.080 (1.028–1.134)	0.0023		
Plateau P_L	1.045 (1.009–1.082)	0.0140					1.034 (0.999–1.070)	0.0533
End-expiratory P_L	0.982 (0.942–1.023)	0.3900						
AIC† of adjusted model			1119		1123		1128	

* Subset A included 302 patients with measured esophageal pressure. Number of deaths was 107

† The model with lowest AIC is the one that explains the greatest amount of variation using the fewest possible independent variables. It addresses goodness of fit and simplicity of the model. Since the models presented in the Table have the same number of independent variables and the same sample, the model with lowest AIC is the best-fit model

AIC Akaike information criterion, *SOFA* Sequential Organ Failure Assessment score, DP_{aw} airway driving pressure which is the difference between Pplat and total PEEP, DP_L transpulmonary driving pressure which is the tidal change in transpulmonary pressure

Comparing adjusted Cox models, DP_{aw} had slightly better goodness-of-fit (lower AIC when the number of covariates were the same) than DP_L (Table 2). We performed post-hoc explanatory analyses to understand this result (See "Discussion") and found that chest wall driving pressure was correlated with non-pulmonary SOFA (Pearson's correlation coefficient = 0.150, $P = 0.0090$) and associated with 60-day mortality in unadjusted Cox regression (HR: 1.136, 95% CI 1.018–1.268, $P = 0.023$).

By grouping patients using thresholds used in previous studies, patients with high DP_{aw} (≥ 15 cmH_2O), high DP_L (≥ 12 cmH_2O) and high elastance-derived plateau P_L (≥ 24 cmH_2O) had lower 60-day survival probability (log-rank test, $P < 0.05$) as shown with Kaplan–Meier survival curves (Fig. 2). There was no difference in survival probability comparing positive (≥ 0 cmH_2O) with negative end-expiratory P_L (Fig. 2).

Post-hoc analyses for the obese patients

Previous study [23] showed that higher Body Mass Index correlated with higher directly measured end-expiratory P_L, supporting the hypothesis that PEEP might be particularly helpful for maintaining functional residual capacity in obese patients with more load (weight) due to fat. A recent study [24] also well demonstrated the usefulness of high airway pressure in this population. We thus conduct post-hoc analyses in patients with Pes measurement ($n = 302$) and found an interaction between directly measured end-expiratory P_L and obesity (Body Mass Index ≥ 30 kg/m^2) with regard to 60-day mortality in the adjusted Cox regression model (HR for the interaction term: 0.904, 95% CI 0.832–0.982, $P = 0.0175$). No significant interaction with obesity was found for DP_{aw}, DP_L, elastance-derived plateau P_L. There were 123 obese patients according to the abovementioned classification. Among them, obese patients with positive end-expiratory P_L had higher survival probability than those with negative end-expiratory P_L (Fig. 3, Log-rank test: 0.0042).

Oxygenation stretch index

We obtained arterial blood gases in 318 patients (subset B: 84% the cohort). Oxygenation stretch index did not present significant higher AUC for predicting mortality at day 60 (binary outcome) than DP_{aw} (0.59 vs. 0.58, $P = 0.6483$, see Figure S4).

Unadjusted Cox regression (Table S1) showed that higher oxygenation stretch index was associated with markedly lower 60-day mortality (HR: 0.959, 95% CI 0.930–0.989, $P = 0.0082$). Since both SOFA and oxygenation stretch index include PaO_2/FiO_2 as a component, multicollinearity would exist if they were added together in the multivariable Cox regression model. We thus adjusted the Cox model by age and non-pulmonary SOFA rather than SOFA. After adjustment, oxygenation stretch index remained associated with outcome (HR: 0.969, 95% CI 0.939–0.999, $P = 0.0490$).

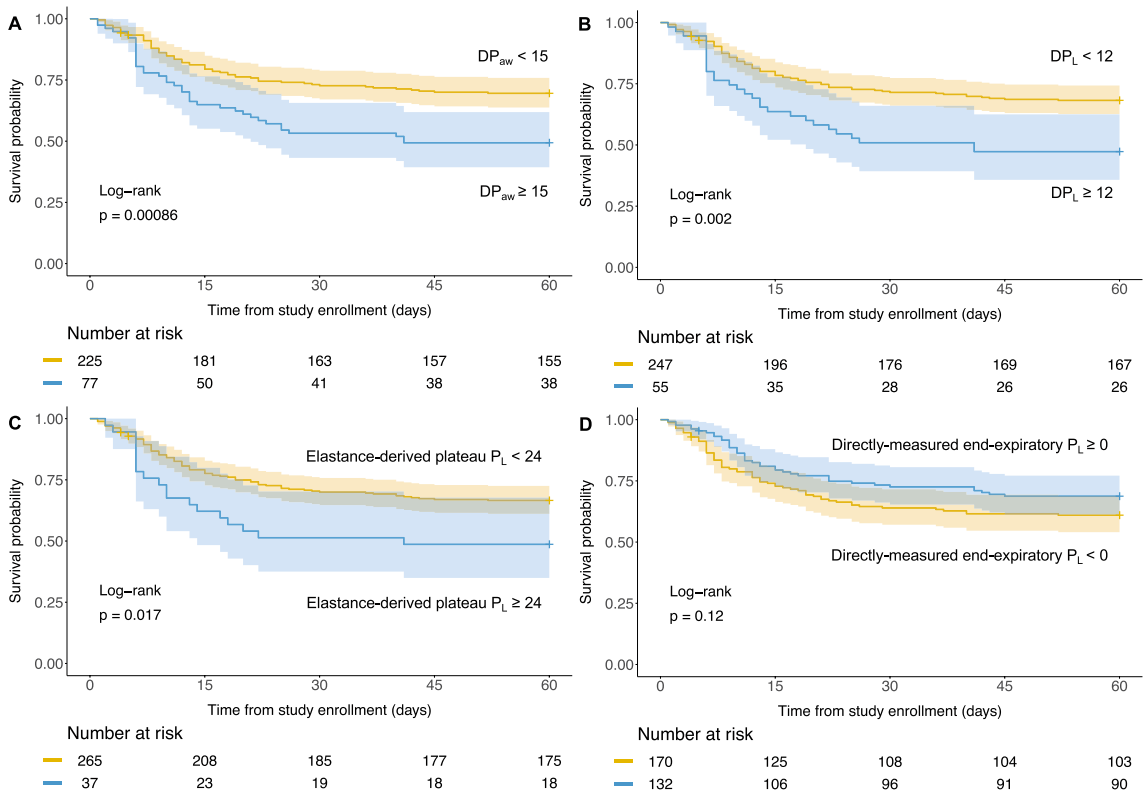

Fig. 2 Kaplan–Meier plots for patients who were measured esophageal pressure ($n = 302$). Patients were grouped by the dichotomized airway driving pressure (DP_{aw}), transpulmonary driving pressure (DP_L), elastance-derived plateau P_L, and directly-measured end-expiratory P_L, respectively

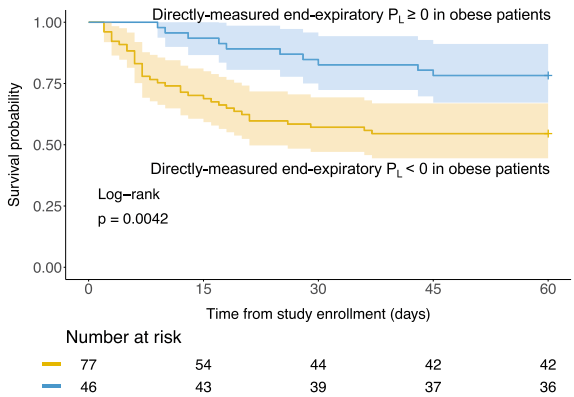

Fig. 3 Kaplan–Meier plot for obese patients who were measured esophageal pressure ($n = 123$). Obesity was defined by body mass index ≥ 30 kg/m^2, as per World Health Organization classification. Patients were grouped by the dichotomized end-expiratory PL. Notice that this is a post-hoc analysis

We repeated the modeling for DP_{aw} on the same subset of patients to compare AIC. Oxygenation stretch index did not improve AIC comparing with DP_{aw} (Table S1). To explain this result, we performed a *post-hoc* analysis to examine the association of oxygenation with outcome. Oxygenation (PaO_2/FiO_2) was not significantly associated with outcome in a Cox regression model after adjustment by DP_{aw} (Table S2. HR: 0.998, 95% CI 0.994–1.001, $P = 0.2161$).

By dichotomizing oxygenation stretch index, patients with high oxygenation stretch index (≥ 10 mmHg/cmH_2O) had higher survival probability than patients with low oxygenation stretch index (< 10 mmHg/cmH_2O) (Fig. 4, unadjusted log-rank test: $P = 0.0033$).

Post-hoc analyses on mechanical power and $DP_{aw} \times 4 + RR$

Although respiratory rate did not reach to statistically significant in univariate comparison ($P = 0.061$) and unadjusted Cox regression ($P = 0.084$), recent studies have shown the importance of respiratory rate for VILI [25]. We thus performed post-hoc analyses on mechanical power [20] and a recently proposed composite index – $DP_{aw} \times 4 + RR$ [26]. The ROC analyses showed that $DP_{aw} \times 4 + RR$ and power did not present significantly higher AUC than DP_{aw} alone for predicting the binary outcome—mortality at day 60 (Figure S5). After the adjustment for age and SOFA, the Cox regression models showed that $DPaw \times 4 + RR$ had lowest AIC (see

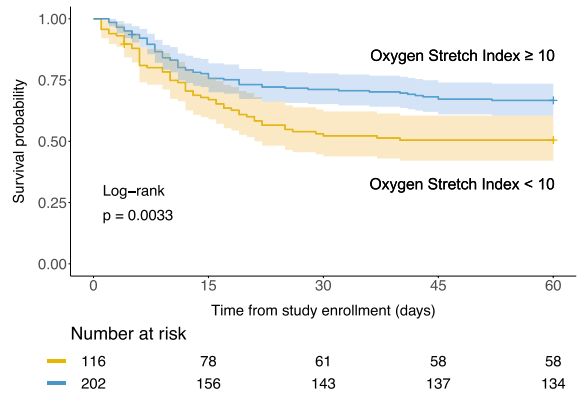

Fig. 4 Kaplan–Meier plot for patients with arterial blood gas measurement ($n = 318$), who were grouped by the dichotomized oxygenation stretch index

Table S3). Mechanical power was associated with 60-day mortality (time-dependent outcome) only when it was normalized by respiratory system compliance (Table S3).

Post-hoc sensitivity analysis for the time of measurement

To assess the possible effect of measurement time on outcome, we tested in multivariable Cox regression models the interaction term between mechanical variable of interest and a dichotomous covariate represented the time point of measurement [early (≤ 2 days); late (> 2 days)]. We chose 2 days as threshold to define early and late measurement because it represents the median value of the measurement time. There was no significant interaction between early measurement and mechanics with respect to 60-day mortality (Table S5).

Post-hoc sensitivity analysis for excluding patients who were still ventilated at day 60

We excluded 37 patients who were possibly still ventilated after 60 days (of which 17 patients missing data on ventilator weaning date) from 302 patients with Pes measured. Eventually, 265 patients were involved in this sensitivity analysis. DP_{aw}, DP_L, elastance-derived plateau P_L, remained associated with 60-day mortality after adjusted by age and SOFA. And again, the Cox regression model DP_{aw} showed lowest AIC (Table S6).

Discussion

To our knowledge, this is the largest clinical study linking data of partitioned respiratory mechanics with outcome in patients with ARDS who are already receiving 6 ml/kg PBW of V_T. Our data showed that DP_{aw} and DP_L have similar predictive power for mortality at day 60 (binary outcome) in ROC analysis. Cox regression confirmed that DP_{aw} had the highest ranked association with 60-day mortality (time-dependent outcome) after adjustment for age and SOFA (or non-pulmonary SOFA), among DP_L, elastance-derived plateau P_L, directly-measured end-expiratory P_L, and oxygenation stretch index. Our post-hoc explanatory analyses showed the following: (1) chest wall driving pressure (a component of DP_{aw}) was also associated with disease severity and survival rate; (2) positive end-expiratory P_L was associated with better outcome only in obese patients; (3) oxygenation was not significantly associated with outcome after adjustment for DP_{aw}.

Prediction versus association

It is worthy to emphasize that our ultimate goal was not the mortality prediction but to look for the most important variable that can be targeted for limiting the risk of VILI. Thus, we tested the associations between mechanics and outcomes as an indirect approach. Our main method to test the associations between the outcome and mechanics is Cox regression by treating the physiologic variables as continuous variables. We then dichotomized these variables in Kaplan–Meier survival analysis as a secondary method to test associations. Any kind of dichotomization does have limitation, but we want to see whether the previously proposed thresholds could well differentiate outcomes, and if they could potentially be used in clinical practice. Regarding the low predictive power in the ROC analyses (see the supplement), we want to stress that the predictive validity for mortality of the old American-European Consensus Conference (AECC) definition of ARDS was 0.536, whereas the Berlin definition was slightly improved but only to 0.577, in terms of AUC [16]. These definitions have several criteria, which can be considered as composite variables. Hence, the AUC of 0.62 for DP_{aw}, as a single variable, is probably a solid signal.

Lung versus respiratory system

The observation that DP_L was not better associated with outcome than DP_{aw} was unexpected [7]. We think that one explanation is the association between chest wall driving pressure, disease severity [27] and outcome. It indicates that DP_{aw} may contain information about both the risk of VILI through the best indicator of lung distension, i.e., DP_L, and also about general severity of the patient resulting in stiffer chest wall. As such, it is possible that DP_{aw} is essentially a composite index, and DP_L may remain more specific to VILI. Alternatively, the measurement of Pes changes over the low V_T used for assessing the chest wall elastance may suffer from imprecision due to the magnitude of cardiac artifact. We implemented standardized training and a specific protocol to help with Pes measurements [15]. The occlusion test ratio, an index addressing the validity of Pes, was in a valid range (0.8 to 1.2) [14, 18,

28]. Moreover, we performed the same analysis by using Pes adjusted by the occlusion test ratio, assuming a linear relation between ΔPaw and ΔPes. It slightly strengthened the adjusted Cox regression model (AIC = 1122) but did not change the conclusions.

Setting PEEP to reverse a negative end-expiratory P_L, an indicator of collapse of dorsal lung, makes physiological sense [29] and has been used in randomized clinical trials but with no impact on outcome [30]. This is in keeping with our data which demonstrated that end-expiratory P_L was not associated with outcome. We should, however, also keep in mind that the average clinical PEEP level was 12 [IQR 10–14] cmH_2O. The risk of "atelectrauma" [31] in the dorsal lung might have been already been reduced by clinical PEEP. In other words, a relatively narrow variance of PEEP levels might be insufficient to detect any significance of end-expiratory P_L.

Interestingly, the end-expiratory P_L seemed to be highly relevant in obese patients, who have a higher fat "load" than non-obese patients. This load is counter-balanced by the outward recoil force of chest wall. But when respiratory muscles are relaxed due to sedation or paralysis, a high external PEEP might be necessary to counterbalance this load and maintain end-expiratory lung volume. Hence, keeping a positive end-expiratory P_L in obese was associated with a more favorable outcome, as suggested by our data.

Oxygenation stretch index versus DP_{aw}

Our finding that oxygenation stretch index, a composite index of oxygenation and DP_{aw}, failed to strengthen the predictive power was unexpected. Interestingly, the association between oxygenation and outcome "disappeared" once it was adjusted by DP_{aw}. This was even clearer when it was adjusted by age, non-pulmonary SOFA, and DP_{aw} (Table S2. HR for oxygenation: 0.998, 95% CI 0.994–1.001, $P = 0.2161$). These results highlight the predominance of DP_{aw} over oxygenation, which is currently used to classify the severity of ARDS [16].

Limitations

Our study has several limitations. One limitation is that the measurement was performed at a single time point at the early onset of mechanical ventilation like previous studies aiming to link mechanics with outcomes [3]. Since mechanics might alter during the process of ARDS, the measurements, ideally, should be repeated daily. The repeat measurements however can be practically challenging as patients often generate spontaneous breathing effort after a few days of intubation which would greatly complicate the interpretation of measurements. Second, we used a fixed balloon volume (e.g., 1 ml for Cooper catheter), similar to other trials for simplicity [9, 30]. Our conclusions remain unchanged after adjusting Pes by the occlusion test ratio. Third, complete airway closure occurs in almost one-third of ARDS patients which can impact the accuracy of the measurement of elastance, and hence on elastance-derived plateau P_L. The present registry was done by measuring mechanics at clinical PEEP level. In our previous study [32], 15 out of 45 (33.3%) patients presented complete airway closure, which means, only 4 (8.8%) patients received a clinical PEEP below AOP. We reasoned that most of patients with airway closure should be receiving clinical PEEP higher than their airway opening pressure (AOP) in the present study, and thus, this would not substantially alter the interpretation of our results. Moreover, we also repeated the survival analysis by using mechanics measured at higher PEEP level (with the lowest likelihood of having the clinical PEEP below the AOP), and the conclusions remain unchanged except the elastance-derived plateau P_L became non-significant (see Figure S6 in the Supplement). Fourth, the time of measurement was not homogeneous among patients. Our sensitivity analysis, however, showed that the measurement time did not change the effect of the mechanics variables on the outcome. Fifth, we have missing data as indicated in Fig. 1. Handling these missing data can be difficult, and the best approach is debatable. While multivariate imputation is an alternative option with strengths and weaknesses [33], we decided to use the conventional approach—complete case analysis. Sixth, there were 54 patients affected by coronavirus disease 2019 (COVID-19) enrolled into the registry but none of these COVID-19 patients measured esophageal pressure due to infection control precautions. In other words, our results showing that transpulmonary pressures did not have stronger association with outcome than DP_{aw}, was found in non-COVID-19 patients. Last but not least, we did not collect data on key co-interventions for ARDS during the entire hospital stay, such as prone positioning, dose and duration of neuromuscular blockade, steroids, and ECMO. Particularly, prone positioning prior to the measurements might have been influenced respiratory mechanics.

Conclusion

Transpulmonary driving pressure, surprisingly, did not present a stronger association with outcome than airway driving pressure, which might partly be explained by the fact that chest wall driving pressure was associated with disease severity and outcome. Oxygenation stretch index, a composite index of oxygenation and airway driving pressure, did not outperform airway driving pressure alone.

Indeed, oxygenation was no longer associated with outcome after adjustment for airway driving pressure. Our study enhances the rationale of limiting airway but also lung driving pressure during mechanical ventilation. In addition, targeting a positive end-expiratory transpulmonary pressure seems to be relevant in obese patients. These data may help in designing new ventilatory strategies based on respiratory mechanics.

Supplementary Information
The online version contains supplementary material available at https://doi.org/10.1007/s00134-022-06724-y.

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Acknowledgements
We are grateful for Stephen Loring and Daniel Talmor's support, who kindly provide us EPVent study data for sample size estimation. We greatly appreciate the respiratory therapists in the Department of Respiratory Therapy, St Michael's Hospital (Toronto, Canada) for their persistent support and active involvement in this project, with special thanks to Orest Shklar, Pamela Greco, Hilary Every, and Thomas Piraino. We are full of gratitude to Jianing Gu and Audery Kim for their essential work on data collection and organization. This study is a part of Lu Chen's PhD program, supervised by Laurent Brochard and the Program Advisory Committee – Brian Kavanagh, John Laffey, Haibo Zhang, Arthur Slutsky, and Eddy Fan. We deeply thank their invaluable advice for improving the study.

Authors' contributions
All authors made substantial contributions to the conception or design of the study, or the acquisition or interpretation of data for the study. LC, CL, and FM conducted the statistical analysis. LC and LB drafted the manuscript. All authors revised the draft of the manuscript. All authors read and approved the final manuscript.

Funding
Dr. François Beloncle received a grant from IRSR Pays de la Loire for conducting the study in his institute. The sponsor had no role in study design, data collection, data analysis, data interpretation, or writing of the report. Dr Laurent Brochard holds the Keenan Chair in Critical Care and Acute Respiratory Failure.

Data availability
The data used in the present study are available from the corresponding author upon reasonable request.

Declarations

Conflicts of interest
All authors declared having no conflict of interest related to this work. Unrelated potential conflict are as follows: FB received research support from GE Healthcare, Medtronic and Getinge Group, consulting fees from Löwenstein Medical and travel fees from Air Liquide Medical System, which are not related to the present study. LB's laboratory received research grants from Medtronic and Draeger, equipment from Sentec, Fisher Paykel, Philips and Air Liquide, and lecture fees from Fisher Paykel.

Ethics approval
The study has been independently reviewed and approved by the local Institutional Review Board of each participated centre.

Publisher's Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Received: 2 February 2022 Accepted: 2 May 2022
Published: 7 June 2022

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