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ORIGINAL

Personalized positive end-expiratory pressure in spontaneously breathing patients with acute respiratory distress syndrome by simultaneous electrical impedance tomography and transpulmonary pressure monitoring: a randomized crossover trial

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Abstract

Purpose: Personalized positive end-expiratory pressure (PEEP) might foster lung and diaphragm protection in patients with acute respiratory distress syndrome (ARDS) who are undergoing pressure support ventilation (PSV). We aimed to compare the physiologic effects of personalized PEEP set according to synchronized electrical impedance tomography (EIT) and driving transpulmonary pressure (ΔPL) monitoring against a classical lower PEEP/FiO_2 table in intubated ARDS patients undergoing PSV.

Methods: A cross-over randomized multicenter study was conducted in 30 ARDS patients with simultaneous recording of the airway, esophageal and transpulmonary pressure, together with EIT during PSV. Following a decremental PEEP trial (18 cmH_2O to 4 cmH_2O), $PEEP_{EIT\text{-}\Delta PL}$ was identified as the level with the smallest difference between lung overdistension and collapse. A low PEEP/FiO_2 table was used to select $PEEP_{TABLE}$. Each PEEP strategy was applied for 20 min, and physiologic data were collected at the end of each step.

Results: The PEEP trial was well tolerated. Median $PEEP_{EIT\text{-}\Delta PL}$ was higher than $PEEP_{TABLE}$ (10 [8–12] vs. 8 [5–10] cmH_2O; $P=0.021$) and, at the individual patient level, $PEEP_{EIT\text{-}\Delta PL}$ level differed from $PEEP_{TABLE}$ in all patients. Overall, $PEEP_{EIT\text{-}\Delta PL}$ was associated with lower dynamic ΔPL ($P<0.001$) and pressure–time product ($P<0.001$), but there was variability among patients. $PEEP_{EIT\text{-}\Delta PL}$ also decreased respiratory drive and effort ($P<0.001$), improved regional lung mechanics ($P<0.05$) and reversed lung collapse ($P=0.007$) without increasing overdistension ($P=0.695$).

Conclusion: Personalized PEEP selected using synchronized EIT and transpulmonary pressure monitoring could be associated with reduced dynamic lung stress and metabolic work of breathing in ARDS patients undergoing PSV.

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Introduction

Acute respiratory distress syndrome (ARDS) requiring mechanical ventilation represents one of the main reasons for admission to the intensive care unit (ICU) [1]. Personalization of mechanical ventilation settings requires a balance between competing goals: restoring adequate gas exchange, limiting ventilation-induced lung injury (VILI), avoiding respiratory muscle disuse, and minimizing hemodynamic impairment [2].

During controlled mechanical ventilation, the appropriate method to set positive end-expiratory pressure (PEEP) remains a matter of debate [3]. Several titration strategies have been described but, in most centers, PEEP is still selected based on the ARDSNet lower $PEEP/FiO_2$ table and/or the best respiratory system compliance [1, 4]. However, physiologic and clinical evidence have already highlighted the limits of these approaches, which might even be harmful in unselected ARDS patients [5]. More recently, electrical impedance tomography (EIT) has emerged as a non-invasive lung imaging technique that provides real-time information regarding regional tidal ventilation and lung mechanics. EIT is a promising tool to guide PEEP selection based on minimizing lung collapse and overdistension (i.e., two key determinants of VILI) [6].

Transitioning ARDS patients from controlled ventilation to pressure support ventilation (PSV), is associated with multiple benefits if respiratory drive remains within physiological limits [7]. However, in patients undergoing PSV, multiple factors influence oxygenation (e.g., improved hemodynamics vs. increased oxygen consumption) and obtaining accurate measures of the respiratory system mechanics is challenging [8, 9]. Thus, selecting PEEP using an oxygenation or respiratory system compliance target might be even more inappropriate during PSV. EIT-based PEEP selection could also present challenges (as it has traditionally been based on static measures of airway driving pressure) but we recently developed a novel approach coupling EIT and transpulmonary pressure (PL) monitoring to identify the PEEP associated with an optimal compromise between lung collapse and overdistension during PSV [10].

In the present study, we hypothesized that personalized PEEP selected by synchronized EIT and PL monitoring during PSV would be associated with physiological benefits for the lung and diaphragm, compared to the classical lower $PEEP/FiO_2$ table.

Take-home message

In patients with acute respiratory distress syndrome undergoing pressure support ventilation, a personalised positive end-expiratory pressure strategy based on the best compromise between lung overdistension and collapse assessed using electrical impedance tomography and transpulmonary pressure monitoring, decreases lung stress and work of breathing. Underlying mechanisms include reduced respiratory drive and improved neuro-ventilatory efficiency.

Methods

This was a prospective, cross-over, randomized physiological study performed in the general ICUs of the Maggiore Policlinico Hospital (Milan, Italy), Policlinico Universitario A. Gemelli Hospital (Rome, Italy), and Sant'Anna Hospital (Ferrara, Italy). The study was approved by the Ethical Committee of each participating center (ref. no. 19_2023bis, 48_2023 and 823_2022, respectively) and informed consent was obtained from all patients following local regulations.

Study population

The study was performed between December 2022 and December 2023 and included intubated patients with ARDS and a Richmond Agitation Sedation Scale (RASS) between −2 and 0, who were undergoing PSV. Exclusion criteria included clinical $FiO_2 > 0.8$, age < 18 years-old, hemodynamic instability, pneumothorax, history of severe chronic obstructive pulmonary disease, inability to correctly position the EIT belt (e.g., due to chest drains, rib fractures), contraindications to EIT monitoring (e.g. pacemaker, unstable spinal injuries) or to esophageal catheter insertion (e.g. uncontrolled coagulopathy, esophageal varices).

Data collection

At enrollment, the following variables were collected: demographic information, comorbidities, simplified acute physiology score II (SAPS II) upon admission to the ICU, sequential organ failure assessment (SOFA) score, days of intubation, days since the switch to PSV, etiology of ARDS, focal vs. diffuse radiological pattern [11], doses of sedation and analgesia, ventilator settings, and blood gas analyses. Ventilator-free days at day 28

and in-hospital mortality were collected as follow-up outcomes.

Physiologic monitoring

An esophageal catheter (Adult Esophageal Balloon Catheter Set, Cooper Surgical, CT, USA or Nutrivent, Sidam, Italy) was inserted through the nostril to the lower third of the esophagus and inflated. Correct positioning was confirmed by the presence of cardiac oscillations and by an end-expiratory occlusion test [12]. Airway and esophageal pressure (Paw and Pes) were continuously monitored by a dedicated system (PulmoVista 500, Dräger, Lübeck, Germany) and PL was calculated as the difference between Paw and Pes. Dynamic driving PL (ΔPLdyn) was calculated as the difference between the maximal inspiratory and end-expiratory PL.

A dedicated EIT belt with 16 electrodes was placed around the patient's chest at the fifth or sixth intercostal space and connected to the same EIT monitor (PulmoVista® 500, Dräger, Lübeck, Germany). EIT data were synchronized with the PL waveform, acquired at a frame rate of 50 Hz and stored for offline analysis.

Study protocol

The pressure support level, FiO_2, and infusion rates of sedation and analgesia medication were unchanged during all study phases. Presence of leaks in the respiratory circuit was excluded and cuff pressure was checked before each study step.

First, all patients were placed in a supine semi-recumbent position (30–45°) and underwent a decremental PEEP trial from 18 cmH_2O to 4 cmH_2O, with 2-cmH_2O steps lasting 2 min each. End-expiratory occlusions were performed at each step of the trial to measure P0.1 and end-expiratory occlusion (ΔPocc) (see below). Then, EIT and PL tracings from the PEEP trial were promptly downloaded and analyzed by a previously published custom-made software (MATLAB R2021, MatWorks, MA, USA) [10]. Briefly, dynamic lung compliance for each pixel (CLpx) was calculated as:

$$\mathrm{CLpx} = \Delta\mathrm{Zpx} / \Delta\mathrm{PLdyn},$$

Where ΔZpx is the pixel-level inspiratory change in impedance.

For each PEEP level, 5–10 breaths towards the end of the step were selected and the resulting CLpx were averaged to obtain a pixel-level lung compliance map. At each PEEP level, CLpx was compared to the highest CLpx measured during the trial and the pixel was categorized as collapsed (lower CLpx at lower PEEP), overdistended (lower CLpx at higher PEEP) or normal. Finally, the % of overdistension and collapse at each PEEP step was computed as previously described. $PEEP_{EIT\text{-}\Delta PL}$ was defined as the PEEP which yielded the smallest difference between the percentage of collapse and overdistension [10, 13]. During the offline calculation of $PEEP_{EIT\text{-}\Delta PL}$ patients were switched back to the previous clinical PEEP setting for approximately 5 min.

Then, $PEEP_{EIT\text{-}\Delta PL}$ was compared with $PEEP_{TABLE}$, which was selected according to the classical ARDSnet lower $PEEP/FiO_2$ table, targeting a SpO_2 between 88% and 95% [3]. After identification of the two PEEP levels, patients were ventilated with each PEEP for 20 min in a random computer-generated order (R software). Randomization was performed centrally, and participating centres were notified of the result by telephone. The second study step was started immediately following the first step, with no delay or washout period. Based on previous studies, we considered that the measured physiological effects could be entirely attributed to the selected PEEP after 20 min [14, 15]. The randomized cross-over design was chosen to decrease the probability of observing the effects of transitioning from a lower to a higher PEEP level (or vice versa) and to isolate the independent impact of each individual PEEP level.

Study measures

Towards the end of each 20-min study step ($PEEP_{EIT\text{-}\Delta PL}$ and $PEEP_{TABLE}$), the following data were collected:

- Respiratory mechanics:
  1. Tidal volume (VT)
  2. Respiratory rate
  3. Minute ventilation
  4. Dynamic lung stress, as assessed by ΔPLdyn
  5. Dynamic lung compliance (CL dynamic), calculated as VT / ΔPLdyn
  6. End-expiratory transpulmonary pressure ($PL_{End\text{-}EXP}$)
- Respiratory drive and effort:
  1. Inspiratory muscular pressure (Pmus)
  2. Pressure-time product (PTPmus) of the respiratory muscles, per breath and per minute
  3. Airway occlusion pressure during the first 100 ms of inspiration (P0.1)
  4. Maximal deflection in airway pressure measured during a ΔPocc [16]
- EIT data:
  1. Percentage of lung collapse and overdistension [13]

(2) Percentage of pixels recruited (i.e., pixels that increase their CLpx) compared to a PEEP 4 cmH_2O [17]
(3) Regional pendelluft (ventral and dorsal) [18]
(4) Regional dynamic lung compliance (ventral and dorsal), calculated as regional VT divided by ΔPLdyn
(5) Lung recruitability, calculated as the difference between the percentage of lung collapse at PEEP 4 cmH_2O minus collapse at PEEP 18 cmH_2O during the decremental PEEP trial [6, 13]

- Gas exchange:

(1) Arterial PCO_2 and pH
(2) PaO_2/FiO_2 ratio
(3) Central venous oxygen saturation

- Hemodynamics:

(1) Heart rate
(2) Systolic arterial blood pressure
(3) Diastolic blood pressure
(4) Mean blood pressure

More detailed description of the variables of interest can be found in the electronic supplementary material (ESM).

Sample size

Based on previous studies [19, 20], we hypothesized that the application of $PEEP_{EIT\text{-}\Delta PL}$ would result in a reduction of ΔPLdyn of 2.0 ± 3.5 cmH_2O, as compared to $PEEP_{TABLE}$. Accordingly, we calculated that enrolling a sample size of at least 27 patients would result in a power of 0.80 with a probability of type I error of 0.05 (pwrss R package) [21]. Three patients were added to account for potential drop-outs.

Statistical analysis

Data are expressed as mean ± standard deviation or median [1^{st}–3^{rd} quartile], according to the Shapiro–Wilk test. Categorical data are expressed as number of cases (percentage). The comparison between physiological variables measured at $PEEP_{EIT\text{-}\Delta PL}$ vs. $PEEP_{TABLE}$ was performed using the paired t-test or Wilcoxon signed rank test, as appropriate.

To investigate the potential causes and detrimental consequences of increased respiratory drive, data from both study steps were pooled together and bivariate associations between P0.1 and other physiological measures were tested through linear mixed-effects models, considering each patient as a random intercept and slope to account for repeated measures. When model's assumptions were not reached, the dependent variable was log transformed. In these cases, regression lines were constructed and plotted based on the output of the model after predicted coefficients were inverse transformed (exponential function). The corresponding beta coefficients with 95% confidence intervals (CIs) of the original models and conditional R^2 were reported [22].

The interaction between patient's characteristics (2 groups based on the median value) and the effects of PEEP on lung stress and work of breathing were tested by 2-way repeated measures ANOVA. Linear mixed effects models used ΔPLdyn and PTPmus as dependent variables, patients as random slope and intercept, and the PEEP strategy and grouping characteristic as fixed interacting effects. The same approach was implemented to test the relevance of any carryover effect. In cases where a positive interaction was observed ($P \leq 0.05$), a post-hoc Bonferroni correction was performed.

Correlations between non-repeated variables, instead, were analyzed with Spearman or Pearson coefficients, as appropriate.

A two-tailed P-value ≤ 0.05 was considered statistically significant. The analysis of data was performed with R software version 4.2.2 (R Foundation for Statistical Computing, Wien, Austria).

Results

Study population

269 intubated patients with ARDS were screened, 239 were excluded according to exclusion criteria and thirty were enrolled from the 3 study centers (ESM, Figure E1). Patients were intubated for 6 [3–9] days and had been switched to PSV for 3 [1–5] days prior to study enrollment. The pressure support level was 8 ± 2 cmH_2O with a PEEP of 9 ± 3 cmH_2O; with these settings, average PaO_2/FiO_2 was 205 ± 54 mmHg with 18 patients (60%) having mild, 11 (37%) moderate, 1 (3%) severe ARDS; arterial PCO_2 was 45 ± 6 mmHg; pH 7.43 ± 0.03; respiratory rate 19 ± 7 bpm. Twenty-two patients (73%) had an infectious etiology for ARDS. The baseline characteristics of the study population are reported in Table 1.

PEEP assigned by the two personalized methods

All patients tolerated the decremental PEEP trial without additional sedation, adverse events or need to interrupt for safety reasons. The order of PEEP strategies was well balanced: 16 (53%) subjects were assigned to $PEEP_{EIT\text{-}\Delta PL}$ as the first study step (ESM, Figure E1).

The optimal PEEP level balancing overdistension and collapse identified by EIT and PL during the decremental PEEP trial was 10 [8–12] cmH_2O, while the $PEEP/FiO_2$ table assigned a lower level of 8 [5–10] cmH_2O (P=0.021). More interestingly, no correlation was observed between

the two methods (rho = −0.32; P = 0.087) and, at the individual patient level, none of the enrolled subjects were assigned to the same PEEP during the 2 study steps (ESM, Figure E2A). Differences between the assigned $PEEP_{EIT\text{-}\Delta PL}$ and $PEEP_{TABLE}$ ranged between −4 cmH_2O and +7 cmH_2O (ESM, Figure E2B). One illustrative patient who had a different PEEP level assigned by each method is shown in ESM, Figure E3.

Physiologic effects of $PEEP_{EIT\text{-}\Delta PL}$

During the two randomised study steps, the level of pressure support was kept constant at 8 ± 2 cmH_2O with a FiO_2 of 0.45 ± 0.1. $PEEP_{EIT\text{-}\Delta PL}$ was associated with lower dynamic lung stress (mean difference in ΔPLdyn (−1.7 [95% CI: −2.64 to −0.73] cmH_2O; P < 0.001) (Fig. 1A, B) and decreased metabolic work of breathing (mean difference in PTPmus −35.2 [95% CI: −50.7 to −19.7] cmH_2O·s/min; P < 0.001) (Fig. 1C, D), as compared to $PEEP_{TABLE}$ (ESM, Table E1). At the individual patient level, ΔPLdyn decreased in 22 (73%) subjects during $PEEP_{EIT\text{-}\Delta PL}$; in these cases, the mean difference of ΔPLdyn between $PEEP_{EIT\text{-}\Delta PL}$ and $PEEP_{TABLE}$ was −2.44 [95% CI: −3.59 to −1.3] cmH_2O, while it was + 0.39 [95% CI: + 0.01 to + 0.76] cmH_2O for those in whom no decrease was observed. Similarly, PTPmus decreased in 25 (83%) patients during $PEEP_{EIT\text{-}\Delta PL}$; the mean difference between the 2 PEEP strategies was −45 [95% CI: −60.7 to −29.4] cmH_2O·s/min in patients who exhibited a decrease and + 16.3 [95% CI: + 5.8 to + 26.7] cmH_2O·s/min among those in whom it did not decrease. The order in which the 2 PEEP strategies were provided did not affect the results (interaction PEEP strategy x order of PEEP strategy: P = 0.932 for ΔPLdyn and P = 0.845 for PTPmusc per minute), suggesting the absence of any carryover effect.

Advanced analysis of EIT data recorded towards the end of the 2 study steps demonstrated that $PEEP_{EIT\text{-}\Delta PL}$ induced greater recruitment of alveolar units as compared to $PEEP_{TABLE}$ (mean difference between the two steps + 4.1 [95% CI: −0.02 to + 8.6] %; P = 0.060) (ESM, Figure E4A and Table E1) leading to less alveolar collapse (mean difference between the two steps −8.5 [95% CI: −14.4 to −2.5] %; P = 0.007) (ESM, Figure E4B and Table E1). Despite being on average higher, $PEEP_{EIT\text{-}\Delta PL}$ did not increase the risk of alveolar overdistension (OD) (P = 0.695) (ESM, Figure E4C and Table E1) in comparison to $PEEP_{TABLE}$. We analyzed the reduction of ΔPLdyn and PTPmus according to whether patients experienced more (2.9 [95% CI, 1.1–4.6%; n = 19) or less OD (−4.1 [95% CI, −6.5–1.6%; n = 11) at $PEEP_{EIT\text{-}\Delta PL}$. We observed no interaction between the amount of OD and the effects of each PEEP strategy on ΔPLdyn (interaction PEEP method x group—P = 0.142) and PTPmus (interaction PEEP method x group—P = 0.177), probably because the increase in OD was small.

Table 1 Study population

ARDS patients on PSV, n = 30	
Demographics	
Age (years), mean ± SD	63.6 ± 14.2
Gender (M/F), *n* (%)	23 (76.7) / 7 (23.3)
BMI (Kg/m^2), mean ± SD	27.7 ± 4.9
SAPS II score at admission, median [IQR]	41 [34–47]
SOFA (points), median [IQR]	5 [3–7.3]
Co-morbidities, *n* (%)	
Arterial hypertension	14 (46.6)
Chronic heart disease	5 (16.7)
Mild chronic pulmonary disease	3 (1)
Diabetes mellitus	3 (1)
Other	5 (16.6)
Characteristics of ARDS	
Days since intubation, median [IQR]	6 [3–9]
Days since switch to PSV, median [IQR]	3 [1–5]
Infectious etiology, *n* (%)	22 (73.3)
Primary ARDS, *n* (%)	22 (73.3)
Focal / Non-focal ARDS, *n* (%)	13 (43) / 17 (57)
Arterial pH, mean ± SD	7.43 ± 0.05
$PaCO_2$ (mmHg), mean ± SD	45 ± 6
PaO_2/FiO_2 (mmHg), mean ± SD	205 ± 54
ARDS category (mild/moderate/severe), *n* (%)	18 (60) / 11 (36.7) / 1 (3.3)
Sedation and analgesia during the study	
RASS score, median [IQR]	−2 [−2– −1]
Propofol, *n* (%)	21 (70)
Propofol infusion rate (mg/kg/h), median [IQR]	2.33 [1.87–2.74]
Fentanyl, *n* (%)	23 76.6)
Fentanyl infusion rate (μg/kg/h), median [IQR]	0.42 (0.09–0.82)
Outcomes	
28-d VFDs, median (IQR)	15 [2–20]
Hospital mortality, *n* (%)	6 (20)

ARDS acute respiratory distress syndrome, *PSV* pressure support ventilation, *BMI* body mass index, *SAPS* simplified acute physiology score, *SOFA* sequential organ failure assessment, $PaCO_2$ arterial concentration of carbon dioxide, PaO_2 arterial concentration of oxygen, FiO_2 fraction of inspired oxygen, *RASS* Richmond Agitation-Sedation Scale, *VFDs* ventilator-free days, *IQR* interquartile range, *SD* standard deviation

Oxygenation was similar at $PEEP_{EIT\text{-}\Delta PL}$ compared to $PEEP_{TABLE}$ (ESM, Table E1), and $PaCO_2$ and pH were nearly identical (ESM, Table E1). Respiratory rate, tidal volume and minute ventilation were not different between $PEEP_{EIT\text{-}\Delta PL}$ and $PEEP_{TABLE}$ steps (ESM, Table E1). The two PEEP levels also had similar effects on hemodynamics (ESM, Table E1). Central venous oxygen saturation was not collected in 4 (13%) patients

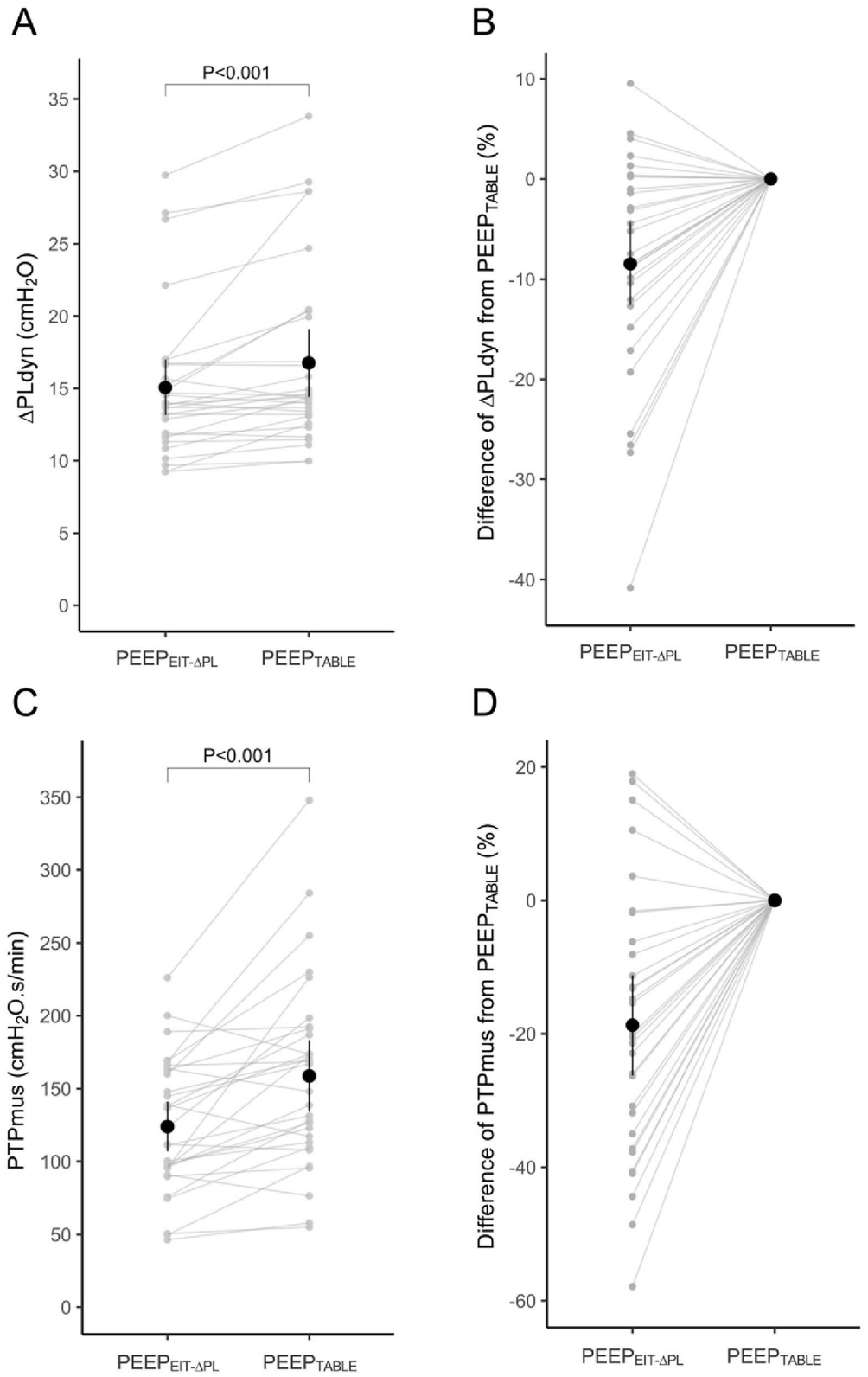

Fig. 1 Effects of $PEEP_{EIT\text{-}\Delta PL}$ on dynamic lung stress (**A**, **B**) and inspiratory work of breathing (**C**, **D**) compared to $PEEP_{TABLE}$. *ΔPLdyn* dynamic transpulmonary driving pressure, *PTPmus* pressure–time product, *EIT* electrical impedance tomography

for technical reasons, representing the only missing data. All the remaining variables were available for comparison between the 2 study steps.

Physiologic mechanisms underlying the reduction in lung stress and work of breathing by $PEEP_{EIT\text{-}\Delta PL}$

The decrease in ΔPLdyn and PTPmus induced by $PEEP_{EIT\text{-}\Delta PL}$ was caused by a reduction in inspiratory drive and effort, as assessed, respectively, by P0.1 (mean difference between the two steps −0.81 [95% CI: −1.12 to −0.5] cmH_2O; $P<0.001$), Pmus (−2.17 [95% CI: −3.31 to −1.04] cmH_2O; $P<0.001$) and PTPmus per breath (−1.33 [95% CI: −2 to −0.67] $cmH_2O{\cdot}s$; $P<0.001$) (Fig. 2A–C). Inspiratory drive and effort likely decreased during $PEEP_{EIT\text{-}\Delta PL}$ due to better global and regional lung mechanics (Fig. 3A–C).

Causes and consequences of increased respiratory drive

When data from both study steps were pooled together, factors measured at each PEEP level that correlated with higher respiratory drive (P0.1) were: more lung collapse (β: 0.016 [95% CI: 0.009 to 0.024]; $P=0.002$), lower $PL_{End\text{-}EXP}$ (β: −0.050 [95% CI: −0.079 to −0.019]; $P=0.003$) and lower dynamic lung compliance (β: −0.019 [95% CI: −0.027 to −0.010, 95% CI]; $P<0.001$) (Fig. 4A–C). These could be regarded as causes of increased respiratory drive that were improved by the application of $PEEP_{EIT\text{-}\Delta PL}$.

As expected, higher respiratory drive (P0.1) led to stronger inspiratory effort (Pmus and PTPmus) (β: 2.76 [95% CI: 1.98 to 3.56]; $P<0.001$ and β: 37.9 [95% CI: 26.6 to 49.5]; $P<0.001$, respectively) and to higher dynamic lung stress (ΔPLdyn) (β: 2.45 [95% CI: 1.43 to 3.09]; $P<0.001$) (Fig. 5A–C).

Patient characteristics associated with greater physiologic benefits at $PEEP_{EIT\text{-}\Delta PL}$

The decrease in dynamic lung stress and metabolic work of breathing was correlated with higher baseline recruitability (rho = −0.38; $P=0.041$ and rho = −0.43; $P=0.018$, respectively) (ESM, Figure E5A-B). Higher PaO_2/FiO_2 measured at enrolment was associated with a larger reduction of dynamic lung stress (rho = −0.39; $P=0.041$) but not with the decrease in work of breathing (rho = −0.087; $P=0.649$) (ESM, Figure E5C-D). We also divided patients into "higher" and "lower" recruitability based on the median value (17.3%). We observed differential effects of the PEEP strategy depending on the degree of recruitability (interaction PEEP method x recruitability—$P=0.016$ for ΔPLdyn and $P=0.005$ for PTPmus). $PEEP_{EIT\text{-}\Delta PL}$ led to greater benefits specifically in the subgroup of patients with higher recruitability ($P<0.001$ for both ΔPLdyn and PTPmus) (ESM, Figure E6). In addition, improved ΔPLdyn during $PEEP_{EIT\text{-}\Delta PL}$ was observed only in patients with a

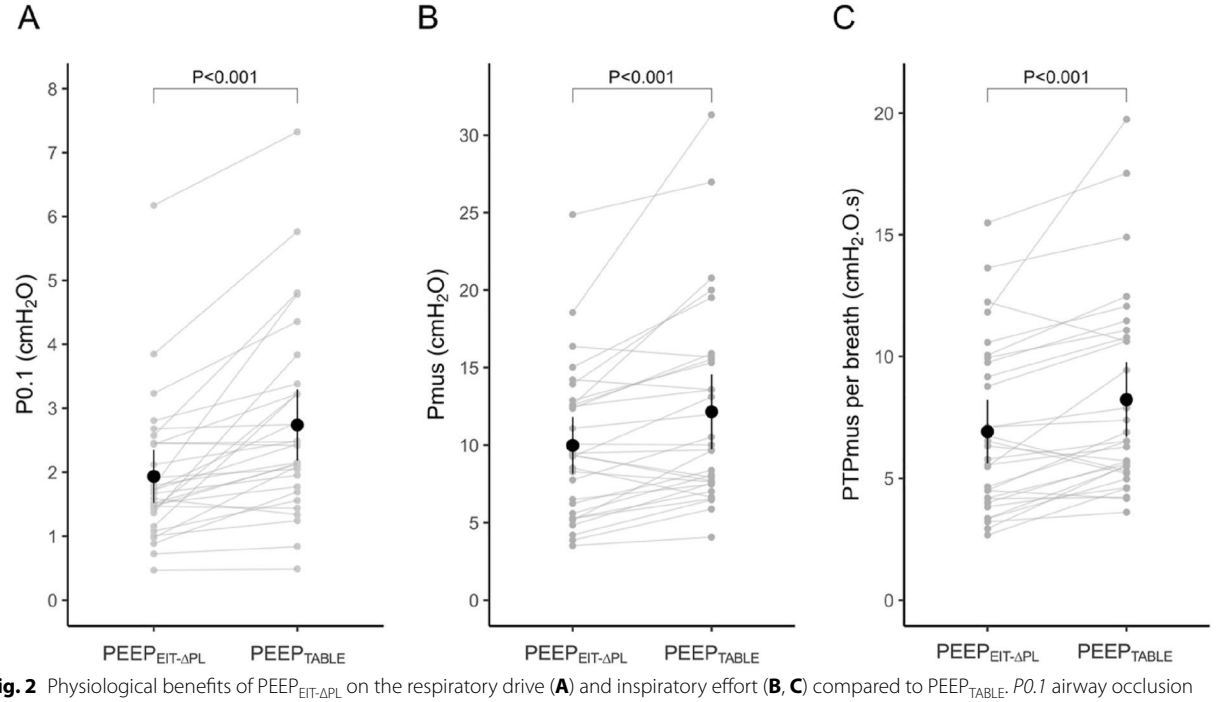

Fig. 2 Physiological benefits of $PEEP_{EIT\text{-}\Delta PL}$ on the respiratory drive (**A**) and inspiratory effort (**B**, **C**) compared to $PEEP_{TABLE}$. *P0.1* airway occlusion pressure during the first 100 ms, *Pmus* inspiratory muscular pressure, *PTPmus* pressure–time product, *EIT* electrical impedance tomography, *PL* transpulmonary pressure

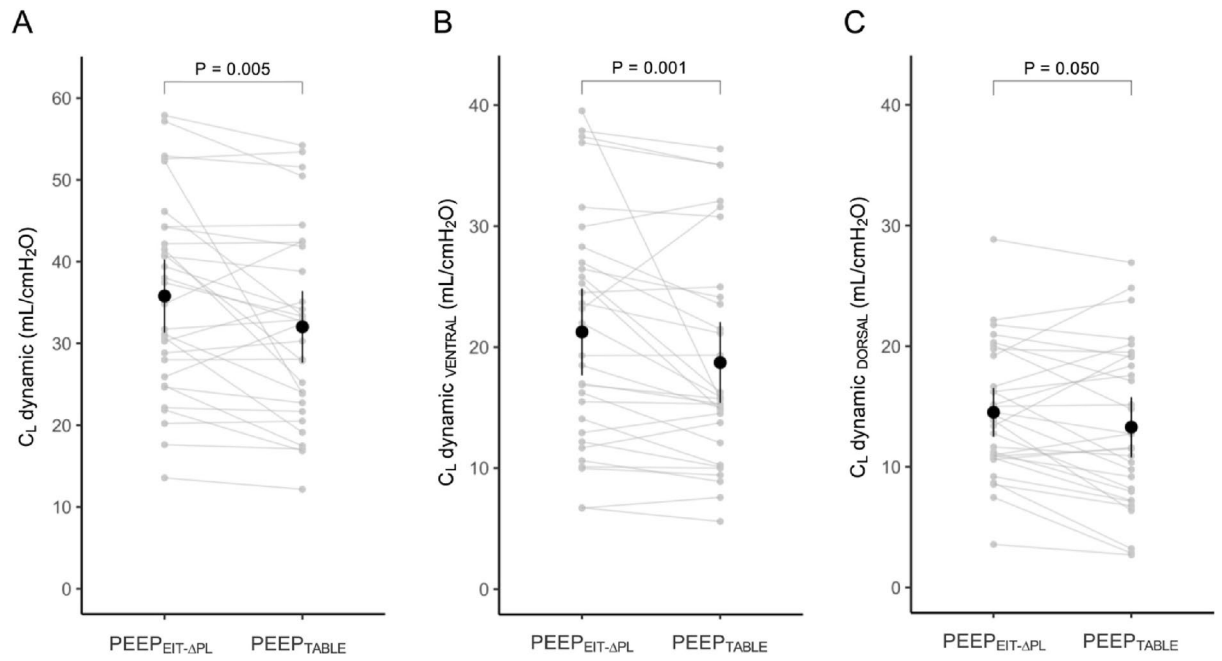

Fig. 3 Impact of PEEP$_{EIT-\Delta PL}$ on global (**A**) and regional (**B**, **C**) lung mechanics compared to PEEP$_{TABLE}$. *VT* tidal volume, *P0.1* airway occlusion pressure during the first 100 ms, *PTPmus* pressure–time product, C_L *dynamic* dynamic lung compliance, *EIT* electrical impedance tomography, *PL* transpulmonary pressure

baseline $PaO_2/FiO_2 > 200$ mmHg ($P < 0.001$), but not in those with $PaO_2/FiO_2 < 200$ mmHg ($P > 0.999$) (ESM, Figure E7). Interestingly, baseline recruitability and oxygenation were not correlated (rho = 0.022; $P = 0.908$) (ESM, Figure E8), likely indicating physiologic improvement of the ventilated lung despite some persistent alveolar collapse.

We found no association between the morphological pattern of ARDS (focal vs non-focal) and PEEP (interaction morphological pattern x PEEP strategy: $P = 0.709$ for ΔPLdyn and $P = 0.832$ for PTPmus). Finally, the body mass index (BMI) was not associated with the effect of the two PEEP strategies on lung stress (interaction body mass index (BMI) group x PEEP strategy: $P = 0.428$) or metabolic work of breathing (interaction BMI group x PEEP strategy: $P = 0.995$).

Alternative bedside methods to select personalized PEEP without EIT and esophageal pressure

The level of PEEP selected by the lowest P0.1 and lowest ΔPocc measured during the decremental PEEP trial was 10 [8–12] cmH$_2$O and 10 [6.5–15.5] cmH$_2$O, respectively. Although there was a weak correlation between PEEP$_{EIT-\Delta PL}$ and PEEP selected by these two simplified methods (Fig. 6A–B), there was variability at the individual-patient level: P0.1-based PEEP differed from PEEP$_{EIT-\Delta PL}$ in 47% of patients ($n = 14$) (Fig. 6C), while the ΔPocc-based PEEP differed in 80% of the patients ($n = 24$) (Fig. 6D).

Discussion

The main findings of this study are that in ARDS patients switched to PSV, EIT-based PEEP was slightly higher than the classical lower PEEP/FiO$_2$ table and, at the individual patient level, the PEEP levels selected by each method were not correlated. Personalized PEEP$_{EIT-\Delta PL}$ resulted in lower dynamic lung stress and work of breathing, without significant changes in oxygenation, CO_2 clearance, respiratory rate, tidal volume, or hemodynamics. Physiologic effects of PEEP$_{EIT-\Delta PL}$ were achieved by a reduction in respiratory drive, improved lung mechanics, less alveolar collapse and marginal additional overinflation. PEEP$_{EIT-\Delta PL}$ showed more benefits for patients with higher baseline alveolar recruitability and PaO_2/FiO_2 values. Finally, simple bedside alternatives to EIT, such as P0.1- and ΔPocc-based PEEP selection, yielded PEEP values that were more similar to EIT as compared to the lower PEEP/FiO$_2$ table, but with significant variability at the patient level.

Setting PEEP in ARDS is challenging [23], and the complexity of PEEP titration may increase when respiratory muscles contribute to tidal breathing [24]. The goal of PEEP titration is both lung and diaphragm protection in spontaneously breathing ARDS patients [25], which could

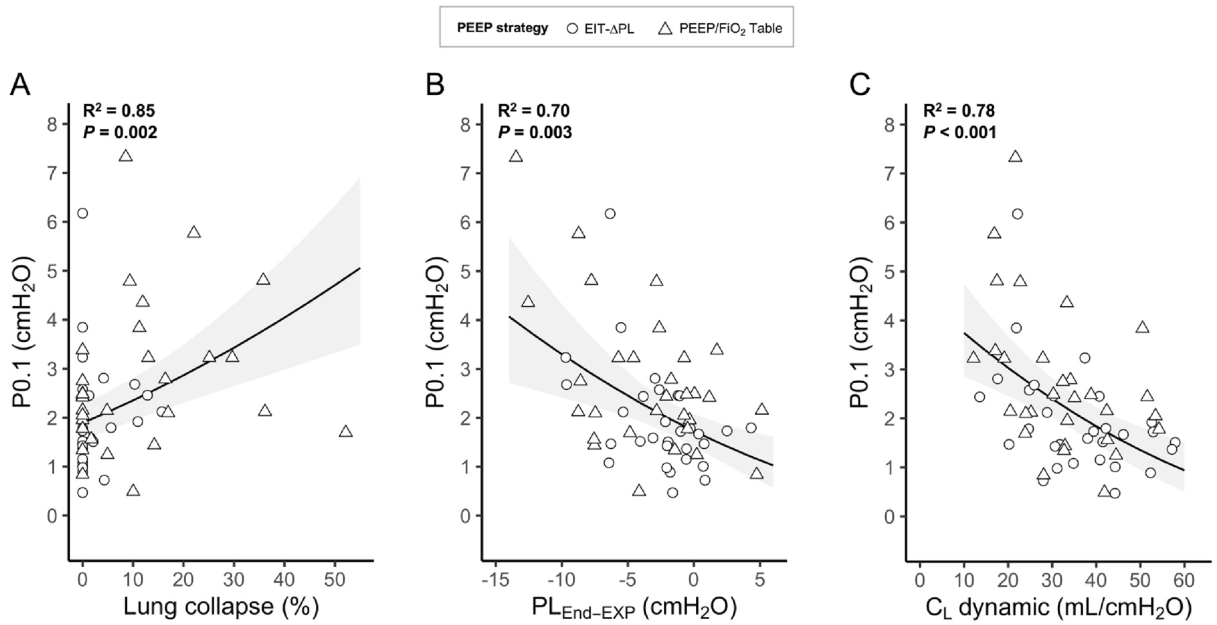

Fig. 4 Potential pathophysiological mechanisms mediating increased respiratory drive (P0.1). *P0.1* airway occlusion pressure during the first 100 ms, $PL_{End\text{-}EXP}$ transpulmonary pressure at the end of expiration, C_L *dynamic* dynamic lung compliance

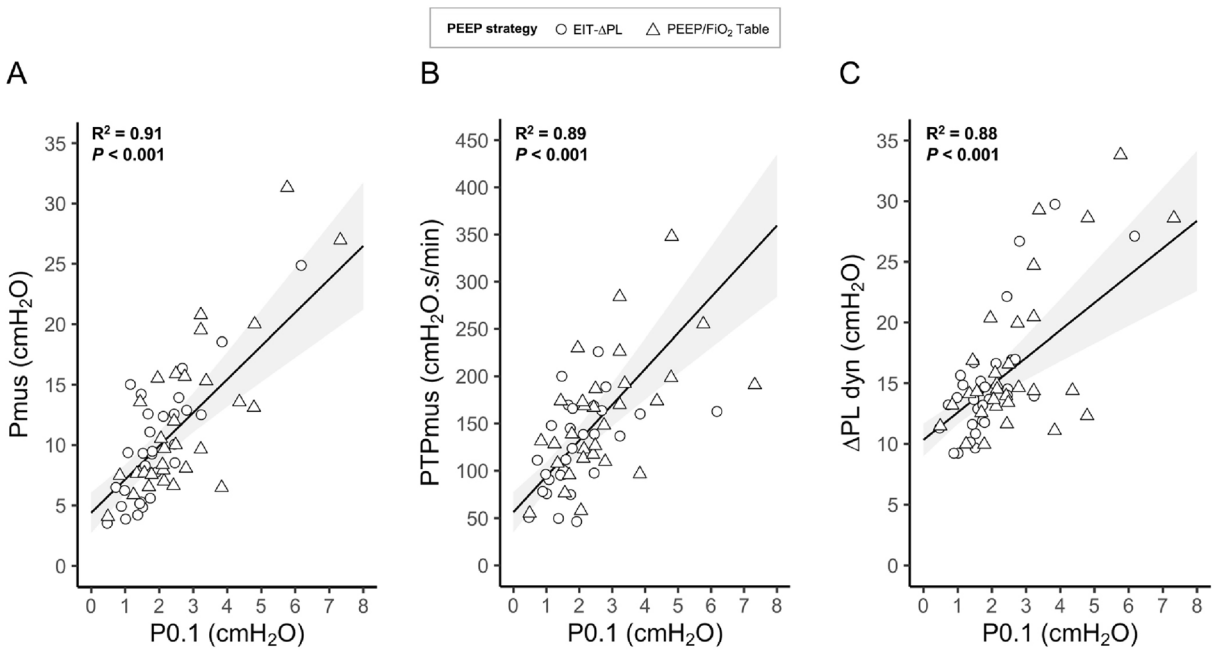

Fig. 5 Consequences of increased respiratory drive (P0.1) on inspiratory effort (Pmus and PTPmus) and dynamic lung stress (ΔPLdyn). *P0.1* airway occlusion pressure during the first 100 ms, *Pmus* inspiratory muscular pressure, *PTPmus* pressure–time product, *ΔPLdyn* dynamic transpulmonary driving pressure

theoretically be achieved through control of respiratory drive. Recent studies have shown that, although respiratory drive seems to decrease at higher PEEP levels [26], there is significant variability at the individual patient level. Improved respiratory system compliance could be the mechanism for the reduction of drive at higher PEEP

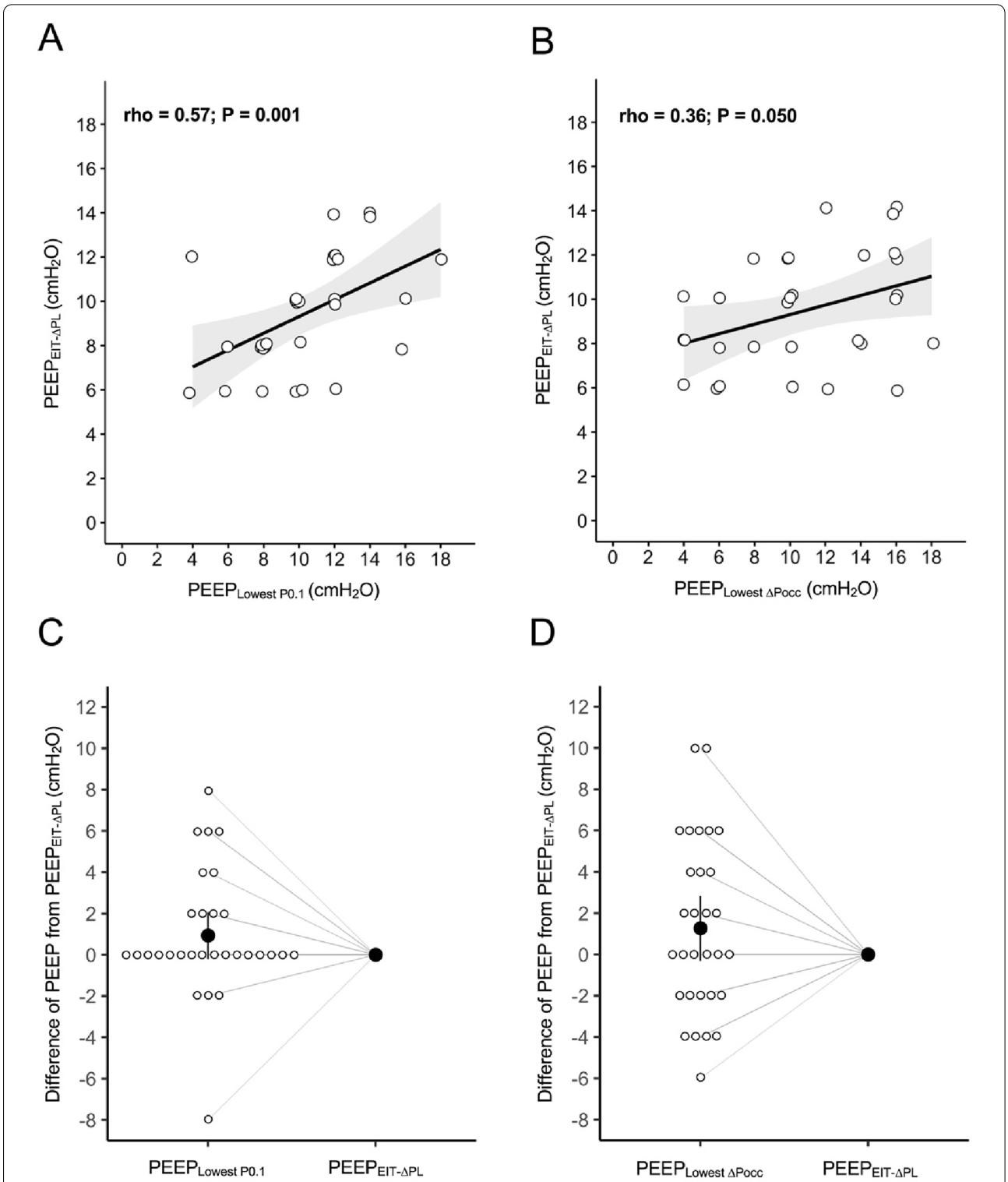

Fig. 6 Correlation between $PEEP_{EIT-\Delta PL}$ and PEEP selected by the lowest P0.1 (**A**) and lowest ΔPocc (**B**), and differences of assigned PEEP levels between $PEEP_{EIT-\Delta PL}$ and these two non-invasive approaches (**C**, **D**). *P0.1* airway occlusion pressure during the first 100 ms, *ΔPocc* occlusion pressure, *EIT* electrical impedance tomography, *PL* transpulmonary pressure

[19, 20, 27, 28]. However, at higher PEEP levels, compliance is affected both by alveolar recruitment and overdistension, and advanced respiratory monitoring could be crucial for fine-tuning the setting of PEEP [4, 29, 30]. We previously described a novel PEEP titration method that combines a dynamic lung stress assessment with measurements of the regional distribution of tidal volume by EIT [10], potentially representing an ideal bedside guide for PEEP selection in spontaneously breathing patients.

In this study, we compared this novel EIT-ΔPL method with a classical and widely used oxygenation-based method, the lower PEEP/FiO_2 ARDSnet table [3]. The novel approach led to PEEP values that were higher and were associated with lower dynamic lung stress without an increase in overdistension. These results suggest that oxygenation improves during PSV not only due to recruitment but also to alternative mechanisms, such as improved hemodynamics or a larger fraction of tidal volume distributed to the well-perfused dorsal lung regions. Setting PEEP using the lower ARDSnet table may, therefore, lead to an underestimation of the level of PEEP required to maintain optimal lung recruitment [8, 31]. $PEEP_{EIT\text{-}\Delta PL}$ instead, provided similar oxygenation and improved regional dynamic lung compliances, decreasing respiratory drive and the risk of elevated regional stretch. Of note, lung protection and improved oxygenation do not always co-exist, and aiming for higher oxygenation targets may expose the lung and diaphragm to non-protective conditions [32]. Indeed, subgroup analysis showed that patients with more potentially recruitable lungs and, paradoxically, higher baseline oxygenation obtained greater benefits from $PEEP_{EIT\text{-}\Delta PL.}$

During $PEEP_{EIT\text{-}\Delta PL}$, dynamic lung stress decreased by almost 10% and metabolic work of breathing by 20%. These values could be associated with substantial clinical benefits by lowering the work of breathing in patients with increased effort, potentially avoiding worsening lung and diaphragm injury and/or the need to restore controlled ventilation. In addition, this study was performed in the semi-recumbent position, which sometimes can worsen compliance. Thus, results may differ in patients lying flat or prone. While the supine position is uncommon and not recommended, the awake prone position is increasingly used to improve gas exchange: in the prone position, overdistension is attenuated and recruitability increases, thus $PEEP_{EIT\text{-}\Delta PL}$ could be associated with pronounced benefits in this patient population.

In spontaneously breathing ARDS patients, PEEP titration can also affect the diaphragm function [33, 34]. Mechanical properties and efficiency of the respiratory muscles will change because of the impact of PEEP on diaphragmatic position and geometry. We found that $PEEP_{EIT\text{-}\Delta PL}$ decreased muscular inspiratory pressure and the pressure–time product, thereby reducing the metabolic work of breathing and the risk of diaphragm injury. Even though the main underlying mechanisms were reduced alveolar collapse and improvement of lungs mechanics with $PEEP_{EIT\text{-}\Delta PL}$, we cannot exclude that higher PEEP levels may have affected diaphragmatic geometry, altering muscular efficiency, resulting in lower pressure–time product but unchanged energy consumption [35].

We compared the optimal $PEEP_{EIT\text{-}\Delta PL}$ level with the one selected by alternative methods that are related to respiratory drive (P0.1) and effort (ΔPocc) but do not require additional monitoring [16, 36]. We found some agreement, especially for the lowest P0.1 measured during the decremental PEEP trial, which provided an identical PEEP suggestion in 53% of patients and a PEEP level that differed by < 4 cmH_2O in 80% of patients. This could be explained by the correlations described between P0.1 and mechanical properties of the lung, like collapse, end-expiratory transpulmonary pressure, lung compliance and dynamic stress, making it a valid clinical alternative to more advanced and expensive monitoring systems, for example in developing countries or during pandemics.

Our study has some limitations. First, we assessed the short-term physiologic benefits of $PEEP_{EIT\text{-}\Delta PL}$ but the impact on long-term clinical outcomes remains to be verified. Second, as the main outcome involved analysis of airway pressure waveforms, blinding the assessors to study interventions was not feasible. Third, esophageal pressure measurements represent a single average value of pleural pressure that, in reality, differs regionally, and this adds some imprecision to the calculation of pixel-level compliances. Fourth, EIT only visualizes a portion of the lungs and therefore yields only a partial assessment of tidal changes across patients with highly heterogeneous sub-phenotypes of ARDS. Fifth, the lower PEEP/FiO_2 table has been chosen because it corresponds more closely to PEEP levels set by clinicians in the real world [1]. However, given higher average values for $PEEP_{EIT\text{-}\Delta PL}$, it could be interesting to compare its effects also with the higher PEEP/FiO_2 table. Sixth, even though $PEEP_{EIT\text{-}\Delta PL}$ provided, on average, physiological benefits, it is important to note that some patients did not benefit from an improvement in lung and diaphragm protection. In these patients, inappropriate application of higher PEEP could lead to worsening lung injury and a positive fluid balance. This result further underlies the need for personalization through advanced respiratory monitoring and to select patients who could benefit most from the proposed approach. Seventh, we enrolled mostly ARDS patients with mild hypoxemia [37]. However, oxygenation may not be a reliable marker of the severity of lung injury in these patients and, in fact, the range of recruitability in

our population was like previous studies that included more severe patients undergoing controlled ventilation [6, 38]. Finally, a cross-over design was chosen to minimise the risk of observing the effects of sequential application of PEEP strategies, rather than the isolated effects of each individual PEEP. However, given the personalised nature of each strategy, with $PEEP_{EIT\text{-}\Delta PL}$ unpredictably being lower or higher than $PEEP_{TABLE}$, this may have been an unnecessary methodological step.

Conclusions

Among ARDS patients undergoing PSV, coupling EIT with transpulmonary pressure monitoring identifies a personalized PEEP that differs from the classical lower $PEEP/FiO_2$ table and is associated with several physiologic changes that may enhance lung and diaphragm protection. However, the observed variability among patients underscores the need to identify those with the greatest likelihood of deriving a benefit. The PEEP level associated with the lowest P0.1 obtained during a decremental trial could be investigated in future studies as a simple alternative to select personalized PEEP.

Supplementary Information
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Substantial contributions to the conception or design of the work: TM, DLG, SS, ES, ML, GG. Acquisition, analysis, or interpretation of data for the work: all authors. Drafting the work or revising it critically for important intellectual content: all authors. Final approval of the version submitted for publication: all authors. Accountability for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: all authors.

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Data availability
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest
GG, personal fees from Getinge (payment for lectures). TM, personal fees for speaking at sponsored symposia by Drager, Fisher and Paykel. All other authors, none.

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