CHEST

High vs Low PEEP in Patients With ARDS Exhibiting Intense Inspiratory Effort During Assisted Ventilation

A Randomized Crossover Trial

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BACKGROUND: Positive end-expiratory pressure (PEEP) can potentially modulate inspiratory effort (ΔPes), which is the major determinant of self-inflicted lung injury.

RESEARCH QUESTION: Does high PEEP reduce ΔPes in patients with moderate-to-severe ARDS on assisted ventilation?

STUDY DESIGN AND METHODS: Sixteen patients with $Pao_2/Fio_2 \leq 200$ mm Hg and ΔPes ≥ 10 cm H_2O underwent a randomized sequence of four ventilator settings: PEEP = 5 cm H_2O or PEEP = 15 cm H_2O + synchronous (pressure support ventilation [PSV]) or asynchronous (pressure-controlled intermittent mandatory ventilation [PC-IMV]) inspiratory assistance. ΔPes and respiratory system, lung, and chest wall mechanics were assessed with esophageal manometry and occlusions. PEEP-induced alveolar recruitment and overinflation, lung dynamic strain, and tidal volume distribution were assessed with electrical impedance tomography.

RESULTS: ΔPes was not systematically different at high vs low PEEP (pressure support ventilation: median, 20 cm H_2O; interquartile range (IQR), 15-24 cm H_2O vs median, 15 cm H_2O; IQR, 13-23 cm H_2O; $P = .24$; pressure-controlled intermittent mandatory ventilation: median, 20; IQR, 18-23 vs median, 19; IQR, 17-25; $P = .67$, respectively). Similarly, respiratory system and transpulmonary driving pressures, tidal volume, lung/chest wall mechanics, and pendelluft extent were not different between study phases. High PEEP resulted in lower or higher ΔPes, respiratory system driving pressure, and transpulmonary driving pressure according to whether this increased or decreased respiratory system compliance ($r = -0.85$, $P < .001$; $r = -0.75$, $P < .001$; $r = -0.80$, $P < .001$, respectively). PEEP-induced changes in respiratory system compliance were driven by its lung component and were dependent on the extent of PEEP-induced alveolar overinflation ($r = -0.66$, $P = .006$). High PEEP caused variable recruitment and systematic redistribution of tidal volume toward dorsal lung regions, thereby reducing dynamic strain in ventral areas (pressure support ventilation: median, 0.49; IQR, 0.37-0.83 vs median, 0.96; IQR, 0.62-1.56; $P = .003$; pressure-controlled intermittent mandatory ventilation: median, 0.65; IQR, 0.42-1.31 vs median, 1.14; IQR, 0.79-1.52; $P = .002$). All results were consistent during synchronous and asynchronous inspiratory assistance.

INTERPRETATION: The impact of high PEEP on ΔPes and lung stress is interindividually variable according to different effects on the respiratory system and lung compliance resulting from alveolar overinflation. High PEEP may help mitigate the risk of self-inflicted lung injury solely if it increases lung/respiratory system compliance.

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KEY WORDS: ARDS; artificial ventilation; inspiratory effort; PEEP; respiratory mechanics; self-inflicted lung injury; ventilator-induced lung injury

Take-home Points

Study Question: In patients with moderate-to-severe ARDS exhibiting intense inspiratory effort (ΔPes) on assisted ventilation, is high positive end-expiratory pressure (PEEP) (15 cm H_2O) capable of reducing inspiratory effort, which is the major determinant of self-inflicted lung injury?

Results: In 16 patients with ARDS, the impact of high PEEP on ΔPes and tidal lung stress was critically dependent on its effect on respiratory system compliance. Higher PEEP resulted in either decreases or increases in ΔPes, respiratory system driving pressure, and transpulmonary driving pressure according to whether this improved or worsened respiratory system compliance, respectively.

Interpretation: In patients with ARDS with intense ΔPes, high PEEP may mitigate the risk of self-inflicted lung injury solely if it improves respiratory system compliance.

Spontaneous breathing is often maintained during mechanical ventilation in patients with ARDS.[1-3] Compared with fully controlled ventilation, benefits of spontaneous breathing include gas exchange and hemodynamics improvement,[1] better ventilation-perfusion matching,[4] and decreased ventilator-induced diaphragmatic dysfunction.[5] However, vigorous spontaneous effort can worsen lung injury through several mechanisms including global and local overdistension, increased lung perfusion, and negative-pressure pulmonary edema due to increases in transmural vascular pressure.[6-9] Moreover, although muscle pressure is uniformly distributed in healthy lungs,[10-12] diaphragmatic contraction may be transmitted heterogeneously in injured lungs: this causes a shift of gas from nondependent to dependent lung regions (pendelluft phenomenon), which generates local overstretch aggravating lung injury.[13-16] Finally, intense inspiratory effort (ΔPes) causes diaphragm injury through sarcomeric disruption and contractile fatigue: this is associated with prolonged duration of mechanical ventilation and poor clinical outcome.[17,18]

There is now great interest in identifying strategies to modulateΔPes and facilitate lung-protective ventilation in patients who preserve spontaneous breathing during mechanical ventilation.[9,19,20] High positive end-expiratory pressure (PEEP) (10-15 cm H_2O) has been proposed to modulate ΔPes and prevent injurious inflation patterns in animal models and few clinical studies,[7,8,15,19] but its effects have not been systematically investigated in humans.

We conducted a prospective physiologic study to comprehensively evaluate the effects of high PEEP in patients with ARDS exhibiting intense ΔPes (estimated by esophageal pressure swing) during assisted ventilation. Our hypothesis was that high PEEP could reduce ΔPes in these patients.

Study Design and Methods

This prospective physiologic study was conducted in the 20-bed general ICU of a tertiary care university hospital in Italy (Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome) between May 2021 and June 2022. The study was approved by a local ethics committee (No. 0009985/20), and all enrolled patients or next of kin provided written informed consent to participate in the study and data analysis. Study protocol was registered on ClinicalTrials.gov prior to enrollment start (NCT04241874).

ABBREVIATIONS: ΔP_{CW} = chest wall driving pressure; ΔPes = inspiratory effort; ΔP_L = transpulmonary driving pressure; ΔP_{RS} = respiratory system driving pressure; C_{RS} = respiratory system compliance; EELI = end-expiratory lung impedance; EIT = electrical impedance tomography; IQR = interquartile range; Paw = airway pressure; PBW = predicted body weight; PC-IMV = pressure-controlled intermittent mandatory ventilation; Pdi = transdiaphragmatic pressure; PEEP = positive end-expiratory pressure; Pes = esophageal pressure; $Pes_{end-exp}$ = end-expiratory esophageal pressure; $Pes_{end-insp}$ = end-inspiratory esophageal pressure; P_L = transpulmonary pressure; Pmus = total muscle inspiratory pressure; Pplat = airway plateau pressure; PS = pressure support; PSV = pressure support ventilation; ROI = region of interest; TidalΔZ = estimate of tidal volume; V_T = tidal volume

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Patients

Adult intubated patients with ARDS were screened for eligibility. ARDS was defined according to current guidelines.[21] Patients on assisted ventilation per clinical decision were enrolled if the following criteria were met: (1) moderate-to-severe hypoxemia ($Pa_{O_2}/F_{I_{O_2}} \leq 200$ mm Hg) and (2) intense ΔPes, defined as a negative deflection in the airway pressure (Paw) ≥ 13 cm H_2O in the first breath recorded during an end-expiratory hold (this corresponds to tidal ΔPes ≥ 10 cm H_2O).[22] Exclusion criteria were pregnancy, pneumothorax or pneumomediastinum, contraindication to electrical impedance tomography (EIT) monitoring (eg, presence of pacemaker or automatic implantable cardioverter defibrillator), impossibility to place the EIT belt in the proper position (eg, presence of surgical wounds dressing), and any contraindication to the insertion of a nasogastric tube (eg, recent upper GI surgery, esophageal varices).

Study Protocol

All patients were connected to a mechanical ventilator (Carescape R860; GE Healthcare) through a bitube circuit. Patients were placed in the semirecumbent position (45°) during all study phases. Pressure support (PS) was set by the attending physician to target a predefined tidal volume (V_T) range of approximately 6 to 8 mL/kg of predicted body weight (PBW).

For each patient, four different ventilator settings were tested in a randomized order (e-Fig 1). Synchronous inspiratory assistance was delivered with pressure support ventilation (PSV). Asynchronous inspiratory assistance was delivered with pressure-controlled intermittent mandatory ventilation (PC-IMV) (Fig 1). Each step lasted 30 min. The ventilator was set as follows: (1) PEEP = 5 cm H_2O + PS, (2) PEEP = 15 cm H_2O + PS, (3) PEEP = 5 cm H_2O + PC-IMV (asynchronous inspiratory assistance 15 cycles/min, inspiratory time = 1 s, inspiratory pressure = PS), and (4) PEEP = 15 cm H_2O + PC-IMV (asynchronous inspiratory assistance 15 cycles/min, inspiratory time = 1 s, inspiratory pressure = PS). For the comparison between low and high PEEP, we selected a high PEEP value capable of mitigating ΔPes in the animal model and some human observations.[8]

Measurements

Patient demographics and most relevant clinical characteristics were collected. Sex, age, PBW, BMI, Simplified Acute Physiology Score II values, Sequential Organ Failure Assessment score, ARDS etiology, and days spent on mechanical ventilation were recorded at enrollment. For each phase, the initial 25 min were devoted to ensuring the patient's full adaptation to the mode, and the signal acquisition was done during the following 5 min.

During the study, patients underwent standard monitoring, including heart rate, invasive BP, and peripherical oxygen saturation. A nasogastric tube with an esophageal balloon catheter (Nutrivent; Sidam) was inserted to measure esophageal pressure (Pes). Correct catheter position and adequate balloon inflation were confirmed by the end-expiratory occlusion maneuver.[23]

A pneumotachograph (FluxMed) measured flow and Paw. These, together with Pes and gastric pressure, were recorded on a dedicated laptop. An EIT-dedicated belt, containing 16 equally spaced electrodes (LuMon; Sentec) was placed at the fifth to sixth intercostal space and connected to the same device (FluxMed). All signals were acquired in phase with an analog digital converter at a sample rate of 40 Hz.

At the end of each study phase, once a stable breathing pattern was obtained, arterial blood gases were analyzed, hemodynamic parameters were collected, and EIT, flow, airway, Pes, and gastric pressure were recorded in phase. The amplitude of ΔPes was derived from the analyses of Pes tracings and measured as the pressure developed between the start of the pressure deflection and the maximal negative value of the esophageal waveform. Values of ΔPes obtained from all respiratory cycles in the 5-min recording were averaged for each study step. The 1-s inspiratory and 5-s expiratory holds were performed at the end of the 5-min recording to monitor static pressures of the respiratory system. Recorded waveforms were reviewed afterward to measure respiratory mechanics and breathing effort (e-Appendix 1). V_T was measured as digital integration of the inspiratory flow. Transpulmonary pressure (P_L) was calculated as Paw minus Pes.

The following parameters were measured: average ΔPes (surrogate of ΔPes); airway plateau pressure (Pplat); end-inspiratory esophageal pressure ($Pes_{end\text{-}insp}$); end-expiratory esophageal pressure ($Pes_{end\text{-}exp}$); respiratory system driving pressure (ΔP_{RS} = Pplat − PEEP); chest wall driving pressure (ΔP_{CW} = $Pes_{end\text{-}insp}$ − $Pes_{end\text{-}exp}$); transpulmonary driving pressure (ΔP_L = [Pplat − $Pes_{end\text{-}insp}$] − [PEEP−$Pes_{end\text{-}exp}$]); respiratory system compliance (C_{RS} = V_T/ΔPaw); chest wall compliance ($V_T/\Delta P_{CW}$); lung compliance ($V_T/\Delta P_L$); end-expiratory transpulmonary pressure (PEEP−$Pes_{end\text{-}exp}$); esophageal pressure-time product (calculated as the area subtended by Pes and chest wall static recoil pressure during inspiration); transdiaphragmatic pressure (Pdi) change during inspiration (Pdi = gastric pressure − Pes); total respiratory muscle pressure (Pmus), defined as ΔP_{CW} + ΔPes; and the patient's total respiratory rate.

EIT data quantifying the amplitude of impedance changes within pixels were expressed in arbitrary units. Raw EIT data were analyzed offline according to a previously described methodology.[24,25] EIT was used to assess estimate of tidal volume (TidalΔZ) (and expressed in arbitrary units) and its distribution in four lung regions of interest (ROIs) (ventral, midventral, middorsal, dorsal), pendelluft extent, aerated lung size, PEEP-induced alveolar recruitment, and overinflation. Aerated lung size (expressed in arbitrary units) at low PEEP was derived from TidalΔZ and the relationship between lung stress and strain. PEEP-induced recruitment and overinflation assessment was based on a simplified method based on multiple pressure-volume curves and the change in end-expiratory lung impedance (EELI). Aerated lung size at high PEEP was then calculated as aerated lung size at low PEEP plus PEEP-induced alveolar recruitment. Lung dynamic strain was calculated as the ratio of TidalΔZ to aerated lung size. Detailed description of the methodology and assumptions used for these calculations is provided in e-Appendix 1: these are consistent with previous investigations.[25-32]

Study End Points

The primary end point of this study was the change in ΔPes at high vs low PEEP.

Secondary end points, evaluated at high PEEP vs low PEEP, were ΔP_L (used as surrogate for lung distension) and regional distribution of tidal ventilation as assessed by EIT: V_T size and distribution in the four ROIs of the lung (ventral, midventral, middorsal, and dorsal); amount of pendelluft, expressed in terms of % of V_T[24]; global and regional EELI, derived from the impedance signal and lung strain definition; and global and regional dynamic lung strain, computed as the ratio of V_T to EELI.

Sample Size Calculation

To our knowledge, until now, no study has systematically investigated the effects of different PEEP levels on the ΔPes in mechanically ventilated patients with ARDS. Thus, consistent with similar investigations on the topic[8,25,33] and adopting a conservative

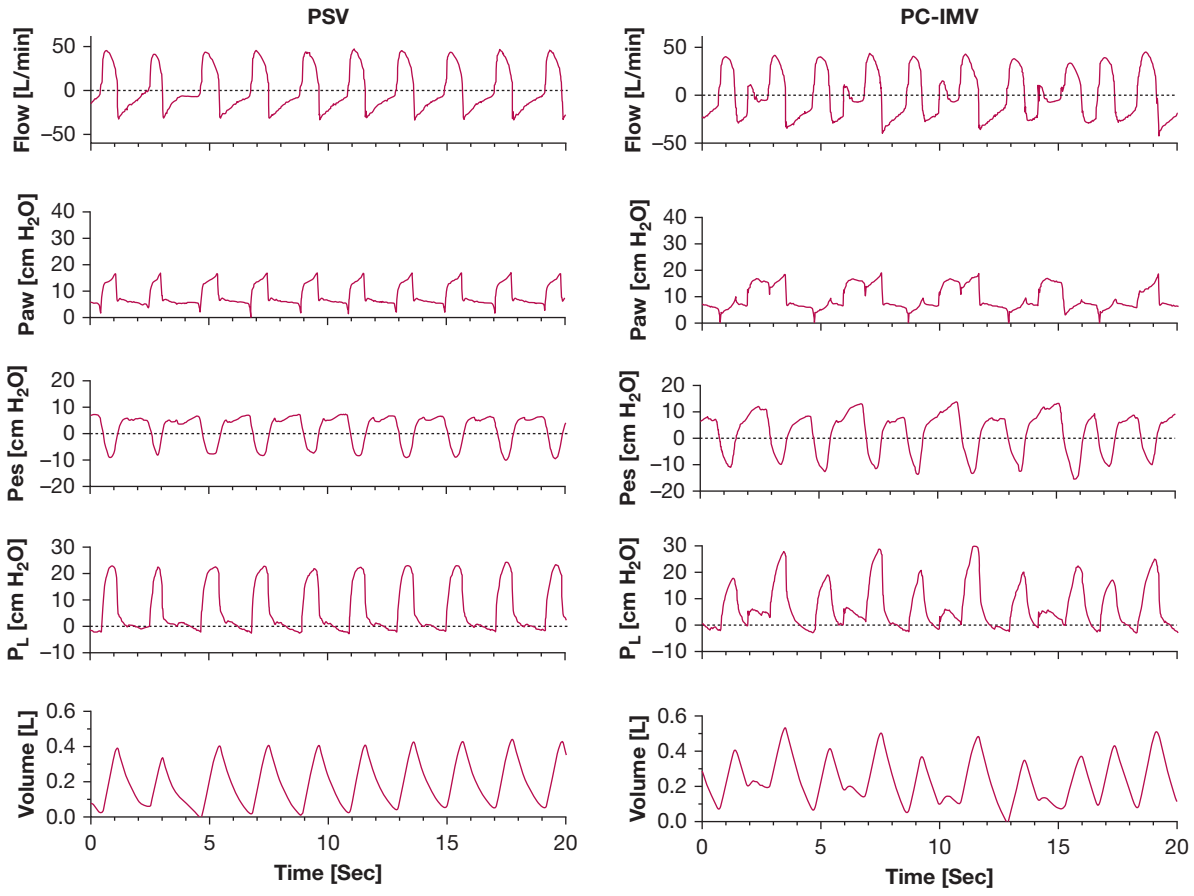

Figure 1 – *Respiratory tracings of airflow, airway pressure, esophageal pressure, transpulmonary pressure, and tidal volume during synchronized and nonsynchronized ventilation modes. Respiratory tracings were obtained from one of the study patients. During nonsynchronized ventilation mode (PC-IMV), the patient can breathe spontaneously without mechanical assistance and no synchronization based on inspiratory/expiratory triggers is provided. Paw = airway pressure; PC-IMV = pressure-controlled intermittent mandatory ventilation; Pes = esophageal pressure; P_L = transpulmonary pressure; PSV = pressure support ventilation.*

approach, we planned to enroll 16 patients, which represent an adequate sample to draw conclusions on our specific end points.

Statistical Analysis

Data distribution was assessed with the Kolmogorov-Smirnov test. Continuous variables with normal distributions were expressed as mean ± SD, whereas those with nonnormal distributions were expressed as median and interquartile range. Paired comparisons for continuous variables were assessed by the Wilcoxon test. Categoric variables were presented as count and proportions. Multivariate analysis (stepwise linear regression) was used to identify patients' demographic or clinical characteristics that affected PEEP-induced changes in ΔPes. Correlations between continuous variables were assessed with Pearson correlation: r (95% CI) and P values were reported. Agreement between PEEP-induced changes in ΔPes and changes in Pmus and Pdi was assessed using the Bland-Altman approach (e-Appendix 1). All results with a two-tailed $P \leq .05$ were considered statistically significant. Statistical analysis was performed with MedCalc Statistical Software version 14.12.0 (MedCalc Software bvba) and GraphPad Prism V 8.0.2 (PRISM).

Results

Demographics and clinical characteristics of the enrolled patients are displayed in Table 1. Median value of inspiratory occlusion pressure at study inclusion was 22 cm H_2O (interquartile range [IQR], 18-25). Some patients received norepinephrine, but in all cases at doses < 0.2 μg/kg/min. Dosage remained unchanged throughout the study in all patients. With constant F_{IO_2}, Pa_{O_2} (and consequently Pa_{O_2}/F_{IO_2}) increased with high PEEP in both PSV and PC-IMV modes (Table 2). Representative tracing records illustrating the differences between PSV and PC-IMV are provided in Figure 1.

Inspiratory Effort

ΔPes was not different at high PEEP compared with low PEEP (in the PSV mode: low PEEP ΔPes = 15 cm H_2O [IQR, 13-23]; high PEEP ΔPes = 20 cm H_2O [IQR,

TABLE 1] Demographics and Baseline Characteristics of Enrolled Patients

Characteristic	Population (N = 16)
Female sex	6 (38)
Age, y	75 (69-78)
BMI, kg/m^2	26 (24-27)
SAPS II	57 (45-65)
SOFA[a]	9 (6-10)
Cause of ARDS	
Bacterial pneumonia	8 (50)
Extrapulmonary sepsis	4 (25)
COVID-19	4 (25)
Duration of invasive MV,[a] d	5 (3.75-10.25)
Duration of assisted MV,[a] d	3 (1-4.25)
pH[a]	7.46 (7.43-7.50)
Pao_2/Fio_2,[a] mm Hg	133 (120-146)
$Paco_2$[a], mm Hg	44 (40-45)
Fio_2[a]	0.5 (0.50-0.60)
Length of ICU stay[a]	10 (6-14)
ICU mortality	11 (69)
ΔPocc, cm H_2O	22 (18-25)
$P0_1$, cm H_2O	5.5 (3.8-8.2)
Heart rate, beats/min	79 (71-91)
Arterial pressure	
Systolic, mm Hg	126 (118-158)
Diastolic, mm Hg	70 (52-70)
Mean, mm Hg	87 (80-95)

Data are expressed as median (25th-75th percentile) or No. (%). ΔPocc = occlusion pressure; MV = mechanical ventilation; SAPS = Simplified Acute Physiology Score II; SOFA = Sequential Organ Failure Assessment.
[a]At study inclusion.

15-24]; $P = .24$; in the PC-IMV mode: low PEEP ΔPes = 19 cm H_2O [IQR, 17-25]; high PEEP ΔPes = 20 cm H_2O [IQR, 18-23]; $P = .67$) (Table 2). However, changes in ΔPes due to PEEP were highly interindividually variable (Fig 2). During PSV, PEEP-induced changes in ΔPes were inversely proportional to the change in C_{RS}: at higher PEEP (r −= 0.85; 95% CI, −0.87 to −0.24; $P < .001$), ΔPes increased in patients whose C_{RS} decreased, whereas ΔPes decreased when C_{RS} increased (Figs 3, 4). These results were confirmed by multivariate analysis; details are provided in e-Appendix 1. Similar results were found during PC-IMV (e-Fig 2).

The correlation between PEEP-induced changes in ΔPes and C_{RS} resulted almost exclusively from changes in the lung component of C_{RS} (e-Fig 3).

To rule out the possible interference of expiratory muscles recruitment, we assessed the relationship between PEEP-induced changes in Pdi and changes in C_{RS}, which confirmed the inverse relationship ($r = -0.76$; 95% CI, −0.90 to −0.43; $P = .006$ during PSV; $r = -0.59$; 95% CI, −0.84 to −0.13 during PC-IMV). To further validate the use of ΔPes to measure ΔPes, we confirmed that PEEP-induced changes in ΔPes were a reliable estimate of PEEP-induced changes in Pdi and Pmus (results in e-Appendix 1 and e-Fig 4).

Driving Pressure-Tidal Lung Stress

In the overall cohort, respiratory system driving pressure (ΔP_{RS}) and ΔP_L were not different at high PEEP compared with low PEEP, both during PSV and PC-IMV (Table 2). However, PEEP-induced changes in ΔP_{RS} and ΔP_L were highly interindividually variable (Fig 2). During PSV, PEEP-induced changes in ΔP_{RS} and ΔP_L were inversely proportional to the change in C_{RS} ($r = -0.75$; 95% CI, −0.91 to −0.41; $P < .001$ and $r = -0.80$; 95% CI, −0.93 to −0.49; $P < .001$, respectively): ΔP_{RS} and ΔP_L increased in patients who showed PEEP-induced decreases in C_{RS}, whereas ΔP_{RS} and ΔP_L decreased in patients who showed PEEP-induced increases in C_{RS} (Figs 3, 4); similar results were found during PC-IMV (e-Fig 2).

EIT-Derived Indexes

EIT-derived results are displayed in Table 2.

Aerated lung size (equivalent of functional residual capacity) significantly increased at higher PEEP levels in both the PSV and PC-IMV modes ($P < .01$). From the analysis of ROIs, the increase in aerated lung size appeared to be more prevalent in the middle and dorsal regions of the lung.

High PEEP produced a variable amount of alveolar recruitment.

During PSV, PEEP-induced changes in C_{RS} were independent from the variable extent of alveolar recruitment ($r = 0.14$; 95% CI, −0.38 to 0.60; $P = .60$), and inversely related to the amount of alveolar overinflation ($r = -0.66$; 95% CI, −0.87 to −0.24; $P = .006$) (Fig 3). Results were similar during PC-IMV (e-Fig 2).

TidalΔZ (equivalent of V_T) decreased at higher PEEP in the ventral and midventral lung regions and increased in the middorsal and dorsal areas during both study ventilation modes.

The median amount of pendelluft, expressed as % of V_T , was not different at high vs low PEEP, either in PSV (high PEEP: 24%; low PEEP: 20%, $P = .23$) or PC-IMV

TABLE 2] Main Results of the Study

Parameter	PSV + PEEP 5 cm H_2O (N = 16)	PSV + PEEP 15 cm H_2O (N = 16)	*P* Value	PC-IMV + PEEP 5 cm H_2O (N = 16)	PC-IMV + PEEP 15 cm H_2O (N = 16)	*P* Value
Respiratory mechanics and breathing pattern						
Inspiratory pressure, cm H_2O	10 (9 to 11)	10 (9 to 11)	N/A	10 (9 to 11)	10 (9 to 11)	N/A
Pplat, cm H_2O	19 (18 to 23)	30 (27 to 34)	< .0001	20 (17 to 25)	29 (26 to 33)	< .0001
ΔP_{RS}, cm H_2O	14 (12 to 17)	15 (12 to 19)	.86	15 (12 to 19)	13 (11 to 18)	.32
V_T, mL	420 (370 to 448)	380 (353 to 406)	.23	400 (364 to 450)	369 (298 to 395)	.03
V_T, mL/kg	5 (5 to 6)	5 (5 to 6)	.23	6 (5 to 6)	5 (4 to 5)	.03
Pes, end-expiratory, cm H_2O	6 (5 to 8)	11 (8 to 14)	.0008	7 (5 to 9)	12 (9 to 13)	.001
Pes, end-inspiratory, cm H_2O	9 (7 to 12)	14 (10 to 16)	.0004	11 (9 to 12)	14 (13 to 17)	.0004
ΔPes, cm H_2O	15 (13 to 23)	20 (15 to 24)	.24	19 (17 to 25)	20 (18 to 23)	.67
Pga, cm H_2O	11 (9 to 16)	12 (9 to 14.9)	.39	11 (8 to 16)	12 (8 to 15)	.32
Pdi, cm H_2O	31 (23 to 35)	31 (27 to 37)	.23	34 (27 to 39)	32 (27 to 38)	.43
Static ΔP_L, cm H_2O	11 (10 to 15)	13 (10 to 15)	.45	12 (10 to 15)	10 (9 to 14)	.25
Dynamic ΔP_L, cm H_2O	26 (7 to 24)	28 (7 to 27)	.13	24 (6 to 25)	26 (8 to 26)	.09
Transpulmonary pressure, end-expiratory, cm H_2O	−1 (−3 to 0)	4 (2 to 8)	< .0001	−2 (−4 to 0)	3 (3 to 6)	.0002
Pmus, cm H_2O	18 (16 to 24)	22 (16 to 25)	.36	22 (20 to 26)	22 (20 to 29)	.64
Respiratory system compliance, mL/cm H_2O	30 (24 to 33)	24 (20 to 34)	.38	27 (24 to 33)	24 (21 to 31)	.35
Lung compliance, mL/cm H_2O	37 (29 to 43)	27 (23 to 46)	.40	33 (28 to 41)	31 (28 to 41)	.60
Chest wall compliance, mL/cm H_2O	158 (116 to 212)	171 (134 to 206)	.19	154 (108 to 206)	113 (90 to 177)	.25
Respiratory rate, breaths/min	26 (21 to 28)	24 (20 to 28)	.43	26 (24 to 28)	25 (23 to 27)	.52
Muscular inspiratory time, s	0.8 (0.7 to 1.1)	0.8 (0.7 to 1)	.92	0.8 (0.6 to 0.9)	0.9 (0.7 to 1.1)	.64
Muscular expiratory time, s	1.4 (1.2 to 1.9)	1.9 (1.6 to 2.1)	.07	1.4 (1.1 to 1.8)	1.5 (1.2 to 1.9)	.15
Pes pressure-time product per min, cm H_2O/s/min	312 (215 to 356)	235 (178 to 337)	.09	283 (264 to 379)	236 (211 to 348)	.23
Gas exchange						
F_{IO_2}, mm Hg	0.5 (0.5 to 0.6)	0.5 (0.5 to 0.6)	N/A	0.5 (0.5 to 0.6)	0.5 (0.5 to 0.6)	N/A
Pa_{O_2}, mm Hg	73 (65 to 78)	77 (67 to 93)	.09	75 (65 to 79)	84 (76 to 101)	.016
Pa_{O_2}/F_{IO_2}, mm Hg	132 (120 to 149)	144 (115 to 162)	.08	137 (110 to 148)	151 (138 to 163)	.016
Sp_{O_2}, %	93 (91 to 94)	95 (93 to 96)	.19	94 (92 to 95)	95 (92 to 95)	.95
Pa_{CO_2}, mm Hg	44 (40 to 46)	48 (45 to 51)	.04	45 (42 to 47)	47 (46 to 51)	.03
pH	7.46 (7.44 to 7.52)	7.47 (7.39 to 7.49)	.23	7.46 (7.44 to 7.51)	7.44 (7.40 to 7.49)	.04

(Continued)

TABLE 2] *(Continued)*

Parameter	PSV + PEEP 5 cm H_2O (N = 16)	PSV + PEEP 15 cm H_2O (N = 16)	*P* Value	PC-IMV + PEEP 5 cm H_2O (N = 16)	PC-IMV + PEEP 15 cm H_2O (N = 16)	*P* Value
Electrical impedance tomography-derived measures						
TidalΔZ derived from each pixel analysis, arbitrary units	2,901 (2,021 to 3,718)	2,680 (1,761 to 3,066)	.09	2,840 (1,797 to 3,352)	2,584 (2,012 to 2,794)	.06
Ventral ROI	45 (31 to 83)	40 (26 to 72)	.05	44 (31 to 84)	36 (28 to 58)	.04
Midventral ROI	310 (174 to 405)	272 (191 to 382)	.86	272 (185 to 343)	253 (193 to 387)	.86
Middorsal ROI	645 (384 to 800)	724 (589 to 833)	.07	573 (414 to 698)	673 (496 to 829)	.13
Dorsal ROI	190 (133 to 292)	249 (210 to 305)	.06	173 (107 to 264)	245 (183 to 312)	.09
Ventral + midventral ROI	378 (208 to 479)	273 (191 to 382)	.02	334 (223 to 417)	292 (223 to 447)	.52
Dorsal + middorsal ROI	828 (516 to 1,017)	997 (802 to 1,085)	.07	783 (544 to 913)	949 (664 to 1,157)	.10
TidalΔZ derived from global impedance curve, arbitrary units	1,177 (764 to 1,537)	1,201 (9,823 to 1,474)	.23	998 (548 to 1,351)	1,131 (976 to 1,451)	.18
Pendelluft, % TidalΔZ	24 (18 to 36)	20 (14 to 31)	.23	25 (22 to 36)	19 (15 to 34)	.06
Aerated lung size, arbitrary units	1,174 (903 to 1,806)	1,344 (1,006 to 2,364)	.01	1,004 (629 to 1,566)	1,272 (1,098 to 1,928)	.0002
Ventral ROI	70 (54 to 108)	62 (35 to 81)	.46	37 (29 to 57)	46 (33 to 97)	.01
Midventral ROI	336 (277 to 518)	425 (314 to 670)	.0004	302 (193 to 467)	384 (298 to 625)	.003
Middorsal ROI	578 (408 to 1,000)	612 (497 to 1,260)	.005	498 (289 to 742)	713 (514 to 917)	.001
Dorsal ROI	169 (123 to 306)	201 (150 to 422)	.12	150 (92 to 236)	217 (159 to 309)	.002
Dynamic strain	0.82 (0.75 to 1.06)	0.87 (0.53 to 1.07)	.78	0.9 (0.7 to 1.1)	0.74 (0.45 to 1.09)	.50
Ventral ROI	0.96 (0.62 to 1.56)	0.49 (0.37 to 0.83)	.003	1.14 (0.79 to 1.52)	0.65 (0.42 to 1.31)	.002
Midventral ROI	0.93 (0.69 to 1)	0.74 (0.43 to 0.95)	.09	1 (0.58 to 1.05)	0.71 (0.47 to 0.91)	.09
Middorsal ROI	0.88 (0.8 to 1)	0.96 (0.76 to 1.38)	.9	0.95 (0.76 to 1.38)	0.84 (0.51 to 1.18)	.82
Dorsal ROI	0.92 (0.7 to 1.01)	1.06 (0.62 to 1.28)	.56	0.89 (0.6 to 1.4)	1.36 (0.85 to 1.77)	.05
Hemodynamics						
Heart rate, beats/min	80 (68 to 95)	80 (67 to 89)	.53	83 (64 to 88)	77 (67 to 93)	.82
Arterial pressure						
Systolic	129 (114 to 157)	128 (117 to 160)	.85	133 (115 to 154)	140 (120 to 160)	.12
Diastolic	53 (50 to 70)	57 (50 to 70)	.86	56 (52 to 60)	55 (52 to 69)	.42
Mean	81 (70 to 100)	84 (74 to 92)	.98	82 (74 to 92)	85 (75 to 96)	.19

Data are expressed as median (25th-75th percentile) or as otherwise indicated. ΔPes = inspiratory effort; ΔP_L = transpulmonary driving pressure; ΔP_{RS} = static respiratory system driving pressure; N/A = not applicable; PC-IMV = pressure controlled-intermittent mandatory ventilation; Pdi = transdiaphragmatic pressure; PEEP = positive end-expiratory pressure; Pes = esophageal pressure; Pga = gastric pressure; Pplat = plateau pressure; Pmus = total respiratory muscle pressure; PSV = pressure support ventilation; ROI = region of interest; Spo_2 = peripheral oxygen saturation; TidalΔZ = tidal impedance variation; V_T = tidal volume.

mode (high PEEP: 25%; low PEEP: 19%, $P = .06$). Pendelluft involving > 10% of V_T was detected in all patients during all study phases.

Lung dynamic strain diminished high PEEP compared with low PEEP in both study ventilation modes (PSV: 0.49 [IQR, 0.37-0.83] vs 0.96 [IQR, 0.62-1.56]; $P = .003$; PC-IMV: 0.65 [IQR, 0.42-1.31] vs 1.14 [IQR, 0.79-1.52]; $P = .002$), respectively. From the analysis of ROIs, dynamic strain showed a significant decrease at high PEEP in the ventral lung regions, whereas it remained almost unchanged in the other lung areas (Fig 5, Table 2).

Discussion

To our knowledge, this is the first study providing a systematic evaluation of the physiologic effects of high PEEP in patients with ARDS who show high ΔPes on assisted ventilation. Our results can be summarized as follows:

- The impact of high PEEP on ΔPes and tidal lung stress critically depends on its effect on respiratory system compliance. Higher PEEP can result in either decreases or increases in ΔPes, ΔP_{RS}, and transpulmonary driving pressure according to whether this generates improved or worsened respiratory system compliance, respectively.
- PEEP-induced changes respiratory system compliance reflect almost exclusively changes in lung compliance: these are mostly a consequence of lung overinflation and are not related to the variable extent of alveolar recruitment.
- High PEEP promotes a shift of tidal ventilation toward dorsal lung regions, yielding reduced lung dynamic strain in ventral areas.
- High PEEP does not primarily affect V_T size and pendelluft extent.
- The physiologic effects of high PEEP are similar during fully synchronous or asynchronous inspiratory support.

Maintenance of spontaneous breathing during ARDS has several advantages: it helps protect diaphragm function, enhances recruitment of collapsed lung areas, decreases atelectrauma, and improves ventilation-perfusion matching.[34] Additionally, it optimizes patient comfort and reduces sedation needs, potentially shortening the duration of mechanical ventilation and promoting earlier weaning.[6] However, when the ΔPes is high, spontaneous breathing can itself aggravate lung damage, especially in patients with severe lung injury.[15] Strong ΔPes causes increased P_L swings, high tidal volumes, increased transvascular pressure yielding lung edema, local overstretch due to the pendelluft phenomenon, and diaphragm injury.[7,14-17] All these mechanisms lead to self-inflicted lung injury. The intensity of ΔPes, rather than the extent of P_L swings, is the major determinant of self-inflicted lung injury.[35] Therefore, there is great interest in identifying techniques to modulate ΔPes in patients exhibiting high ΔPes during assisted ventilation.

Several strategies have been suggested for this purpose.[9,19,20] First, common factors increasing respiratory drive (ie, fever, metabolic acidosis, pain) should be corrected. Then, sedative drugs or partial neuromuscular blockade may be considered.[36]

The use of higher PEEP levels has been hypothesized as a strategy to mitigate ΔPes and prevent injurious inflation patterns when spontaneous breathing is maintained. Güldner et al[37] suggested that PEEP may play a key role in enhancing lung protection during spontaneous breathing: in subsequent experimental studies, use of PEEP was found to reduce lung damage and inflammatory markers,[38,39] with highest PEEP levels (15 cm H_2O) capable of modulating ΔPes, improving ventilation homogeneity, and preventing pendelluft. All these mechanisms mitigate self-inflicted lung injury.[8,16]

Possible mechanisms of PEEP-induced ΔPes reduction include the following: diaphragmatic electromechanical uncoupling due to muscle flattening and change in the force-length relationship of its fibers,[40,41] lower efficiency of the ribs in the generation of negative pleural pressures caused by the horizontal angling of the ribs relative to the spine,[40,41] vagus-mediated respiratory drive inhibition by pulmonary stretch receptor activity,[42,43] and reduction of respiratory drive due to oxygenation improvement.[44,45] However, the physiologic effects of high PEEP compared with low PEEP have never been investigated in humans with ARDS exhibiting high ΔPes during assisted ventilation.

The results of this study partially support the idea that 15-cm H_2O PEEP may help modulate ΔPes, but indicate that response to PEEP is interindividually variable according to PEEP-induced changes in the respiratory system and lung compliance. The patients showed PEEP-induced decreases in ΔPes solely when high PEEP yielded increased lung compliance; otherwise, if PEEP decreased lung compliance, ΔPes increased. These results are consistent with clinical findings in similar settings.[19] Results on ΔP_{RS} and transpulmonary driving

pressure showed a similar behavior, indicating that PEEP can reduce tidal lung stress solely if it ameliorates lung mechanics. With unchanged airway resistance, lung/respiratory system compliance and inspiratory assistance (as it is in our study), ΔP_{RS}, and transpulmonary driving pressure change consistently with ΔPes. In our study, high PEEP did not systematically affect pendelluft extent or global VT size. With constant inspiratory assistance, pendelluft extent and VT size are a direct consequence of ΔPes. Interventions that do not modulate ΔPes can hardly modify these parameters.[24,25]

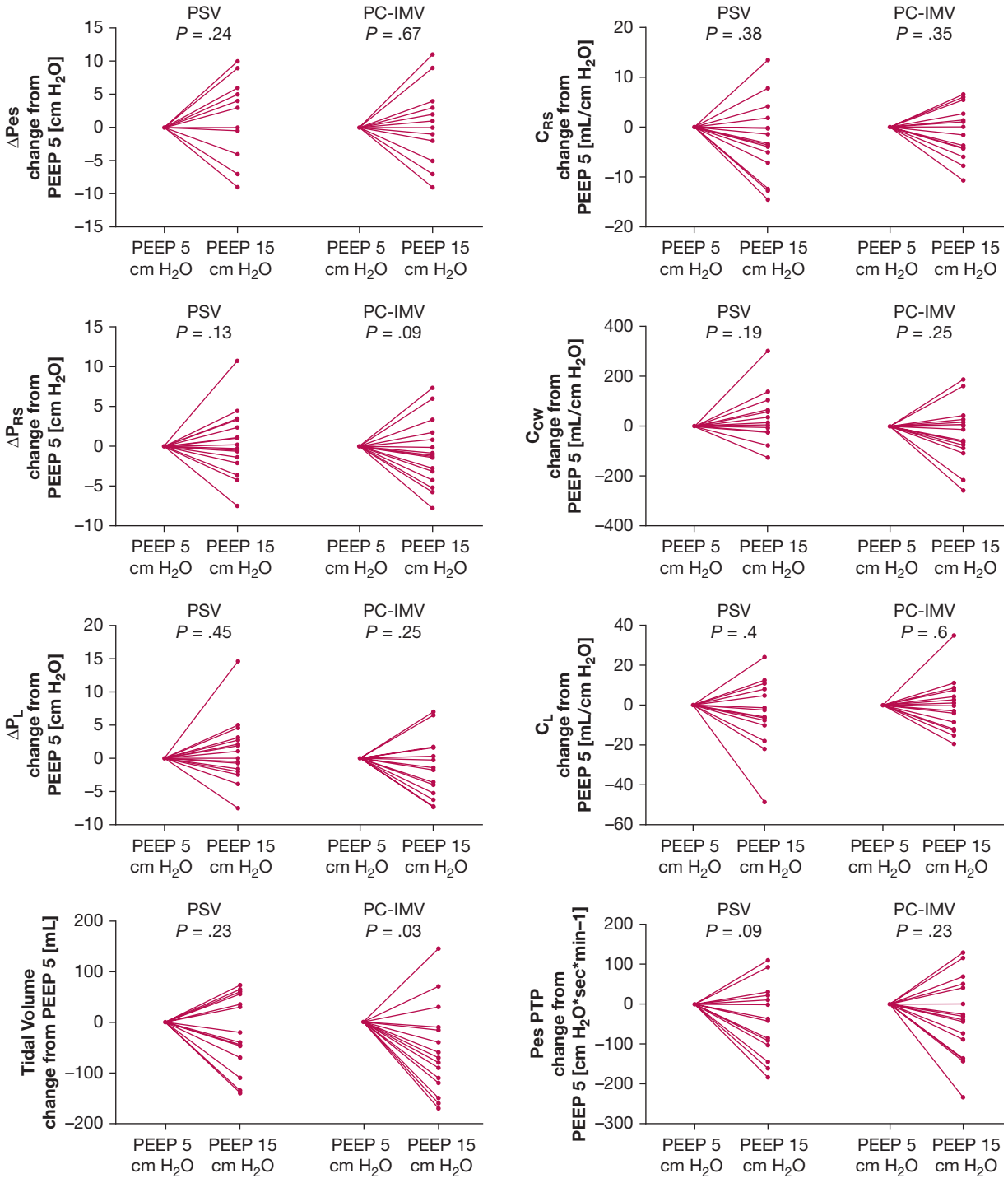

Figure 2 – *Respiratory mechanics at two levels of PEEP. Results are expressed as absolute changes from low PEEP. ΔPes = inspiratory effort; ΔP_L = transpulmonary driving pressure; ΔP_{RS} = respiratory system driving pressure; C_{CW} = chest wall compliance; C_L = lung compliance; C_{RS} = respiratory system compliance; PC-IMV = pressure-controlled intermittent mandatory ventilation; PEEP = positive end-expiratory pressure; PesPTP = esophageal pressure pressure-time product; PSV = pressure support ventilation.*

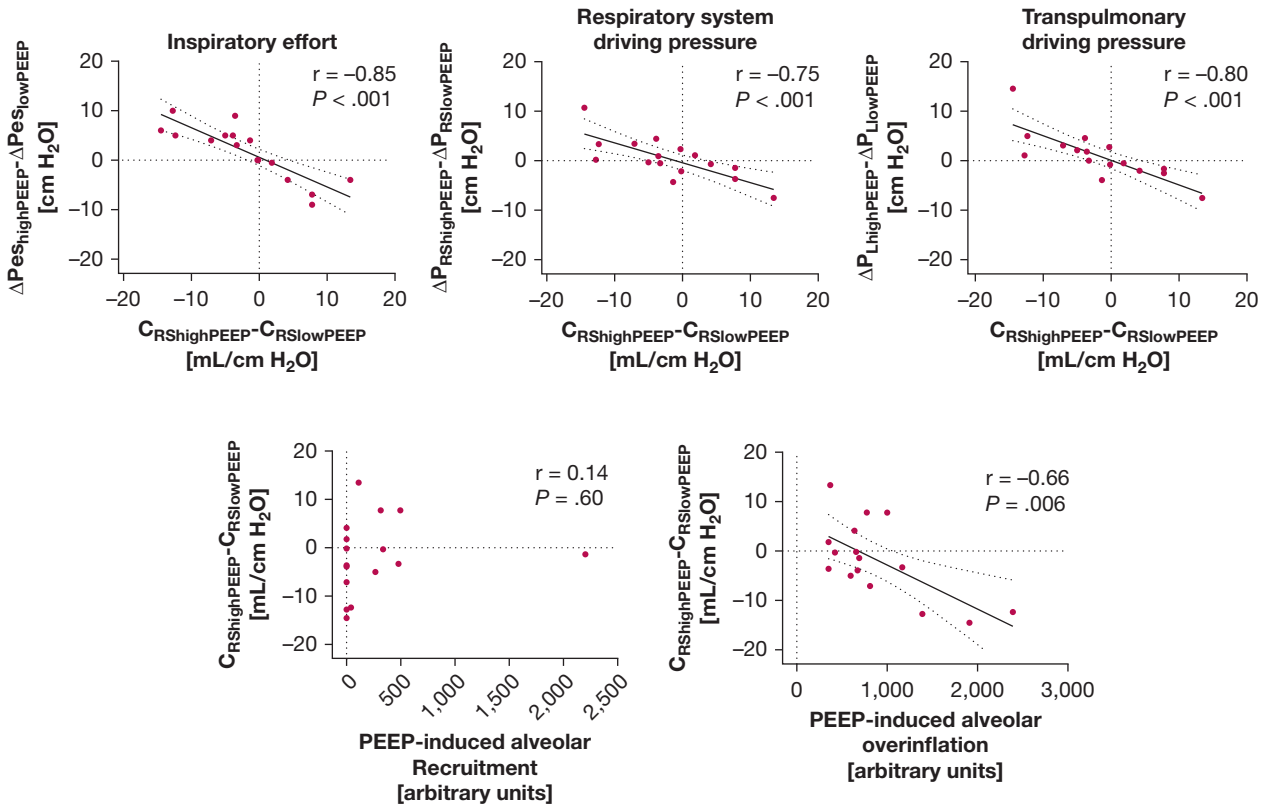

Figure 3 – *A-E, Correlation between changes in ΔPes and changes in the compliance of the respiratory system (pressure support ventilation). A-C, The graphs describe PEEP-induced changes in ΔPes; ΔP_{RS} and ΔP_L are dependent on PEEP-induced change in C_{RS}. D, E, PEEP-induced changes in C_{RS} were related to the extent of lung overinflation, but not to the amount of alveolar recruitment. Alveolar recruitment and overinflation were assessed with electrical impedance tomography and a simplified technique based on the pressure-volume curve concept. Results for pressure-controlled intermittent mandatory ventilation are provided in e-Fig 2. ΔPes = inspiratory effort; ΔP_L = transpulmonary driving pressure; ΔP_{RS} = respiratory system driving pressure; C_{RS} = respiratory system compliance; PEEP = positive end-expiratory pressure.*

In our study, the change in lung compliance produced by PEEP was mostly a consequence of lung overinflation, which here is intended as the minimal PEEP-induced increase in lung volume estimated from pressure-volume curves and EIT.[26,28,29,46] Lung compliance change was not affected by the extent of lung recruitment; this is consistent with data indicating that PEEP-induced changes in compliance do not reflect the extent of alveolar recruitment.[28,47-49] It is well acknowledged that high PEEP may worsen lung compliance because of alveolar overinflation, especially if the upper inflection point of the pressure-volume curve is reached with tidal ventilation.[50,51] The upper inflection point can be reached at relatively low lung volumes in patients with low respiratory system compliance. The patients showed a median compliance of 30 cm H_2O, which is relatively low.[52]

The linear relationship observed between PEEP-induced changes in respiratory system compliance and ΔPes is physiologically sound. First, the strength of ΔPes is affected by the intensity of the patient's respiratory neural output activity, which is mostly determined by the ventilatory demand (ie, the need to achieve blood gas and ventilation targets). Accordingly, ΔPes was increased or decreased according to whether the elastic workload was higher or lower, respectively. Second, commonly accepted mechanisms to explain PEEP-induced decreases in ΔPes in animal ARDS models involve the diaphragm flattening and changes in the inclination angle of the ribs.[40,41] We cannot exclude that an increased stiffness of the respiratory system after increasing PEEP may hinder the expected changes in the thoracic cage conformation and consequently affect ΔPes.

The heterogeneous response to PEEP observed in our study is partially different from that observed in experimental ARDS in the animal model, in which high PEEP systematically reduces ΔPes and lung stress.[8,16,34] In the animal model, recruitability was relatively high, and high PEEP mostly generated increases in respiratory

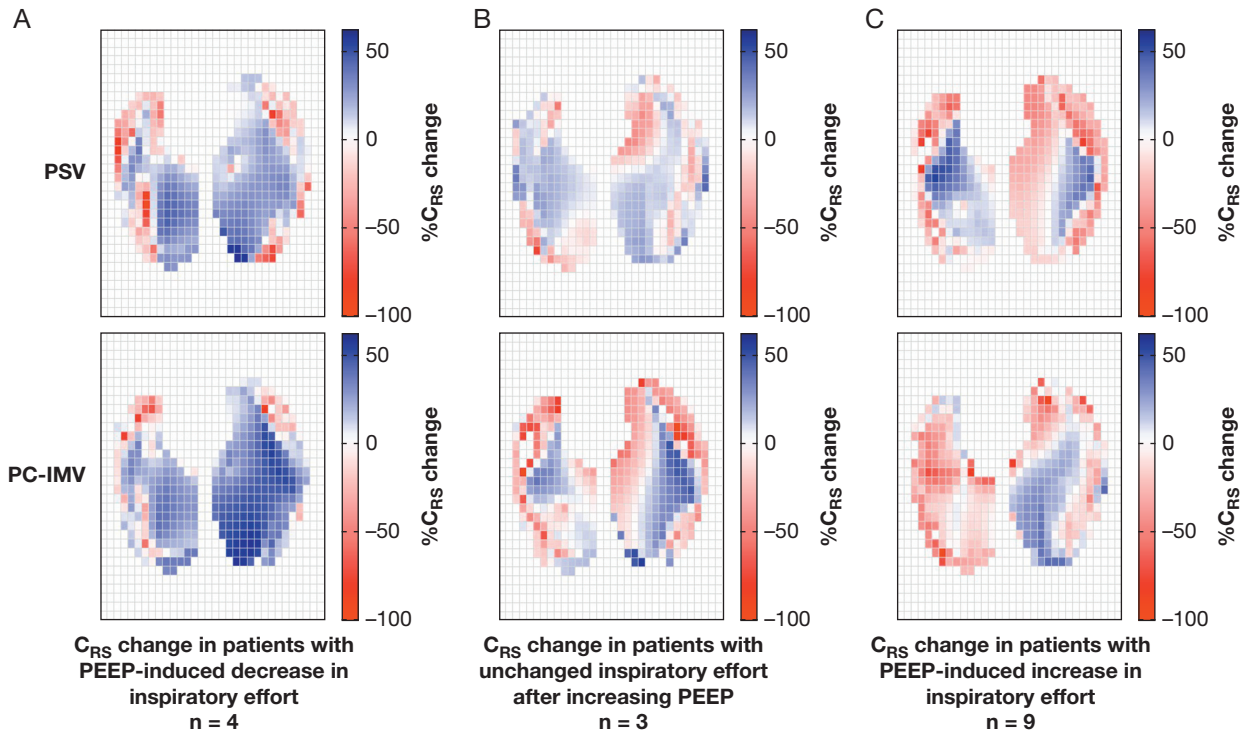

Figure 4 – *A-C, Regional changes of compliance of the respiratory system between high PEEP and low PEEP. Illustrations depict the average values of the changes in respiratory system compliance within each lung pixel. Blue pixels represent those with increased compliance, whereas red pixels are those with decreased compliance. Color intensity displays the percentage of the change in compliance. A, Patients with decreased inspiratory effort at high PEEP were those in whom compliance increased (n = 4). B, Patients with almost unchanged inspiratory effort (esophageal pressure variation ≤ 1 cm H_2O) showed similar compliance at the two levels of PEEP (n = 3). C, Patients with increased inspiratory effort at high PEEP were those in whom compliance decreased (n = 9). C_{RS} = respiratory system compliance; PC-IMV = pressure-controlled intermittent mandatory ventilation; PEEP = positive end-expiratory pressure; PSV = pressure support ventilation.*

system compliance, which was not the case in the patients in our study.[53] Moreover, in the animal model, experiments are usually conducted within 24 h from ARDS onset, whereas patients in our study had undergone mechanical ventilation for a median time of 5 days before enrollment. Response to PEEP tends to be lower after some days of mechanical ventilation.

Tidal volume was redistributed toward dorsal lung regions, and dynamic strain was lower in the ventral areas with high vs low PEEP. This is consistent with PEEP mechanism of action in patients with ARDS, and may help protect ventral areas from ventilator-induced lung injury.[53-56]

Our results were consistent during both synchronous and asynchronous inspiratory assistance: this is relevant because inspiratory desynchronization has also been suggested to prevent excessive increases in tidal lung stress. Nonsynchronized modes may lower P_L swings and V_T,[57] but may cause increases in patient effort.[58] Our data indicate that PEEP effects on ΔPes and transpulmonary driving pressure vary among individuals both in synchronous or asynchronous ventilatory modes, and critically depend on the changes in compliance.

This study has potentially relevant clinical implications. It demonstrates that, in intubated patients with moderate-to-severe ARDS who are spontaneously breathing, intense ΔPes and tidal lung stress can be attenuated by PEEP only if this increases lung and respiratory system compliance. Use of high PEEP in patients who do not respond to the intervention may be mostly detrimental because it may cause diaphragm injury and increases in driving pressures.[59] Our findings may guide physicians in selecting appropriate levels of PEEP if an intense ΔPes is exhibited, with the final aim of maintaining lung and diaphragm-protective ventilation without restoring muscle paralysis. Our findings suggest that treatment individualization may be considered in these patients. ΔPes can be reduced by higher PEEP when this is associated with improved lung compliance. Further increases in ΔPes should be expected with PEEP if this is associated with worsened lung compliance. Importantly, both ΔPes and respiratory system compliance can be

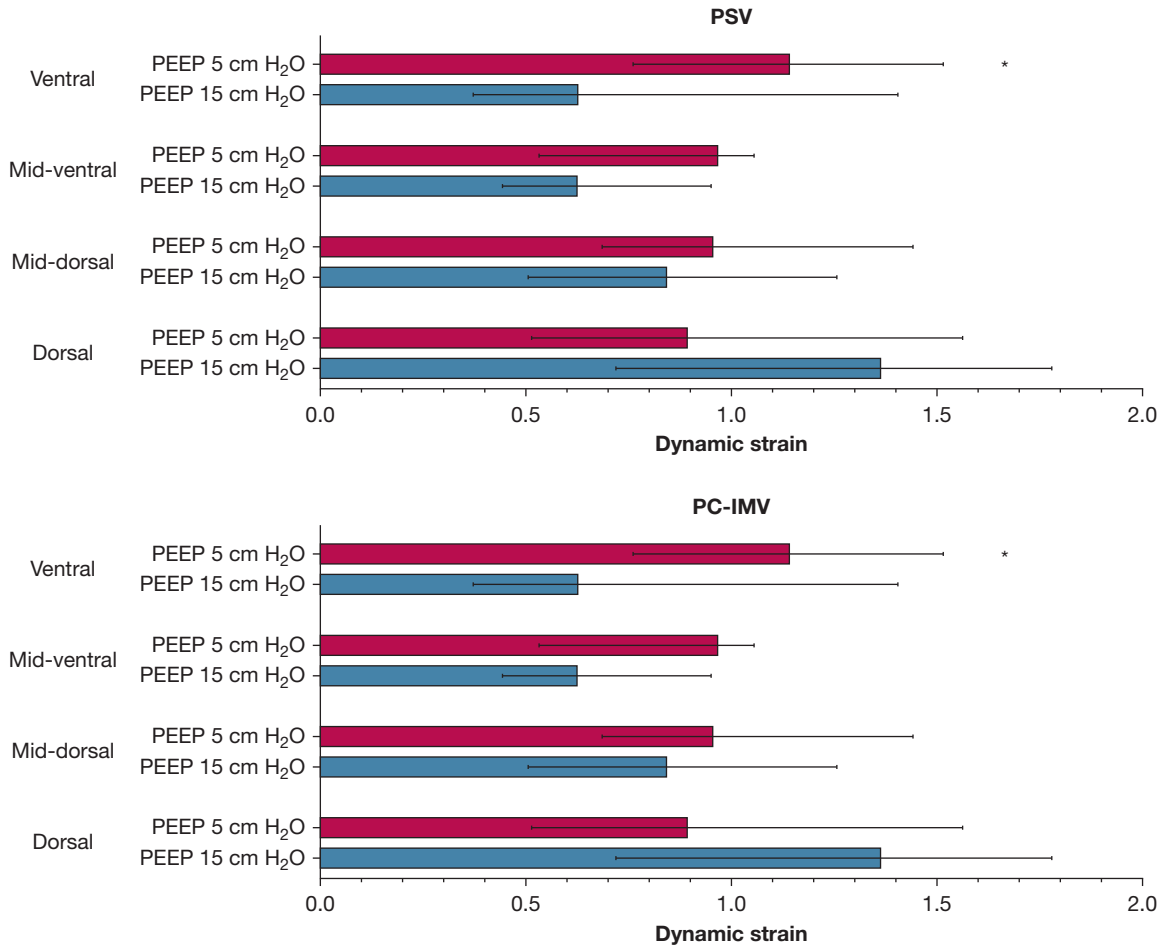

Figure 5 – *Regional dynamic strain at two levels of PEEP. High PEEP induced a redistribution of tidal ventilation toward dorsal lung regions with a significant reduction in lung dynamic strain in ventral areas. PC-IMV = pressure-controlled intermittent mandatory ventilation; PEEP = positive end-expiratory pressure; PSV = pressure support ventilation.* *P ≤ .05.

easily measured at the bedside without additional equipment.[6,60-62] We also showed that high PEEP, despite not systematically affecting ΔPes, P_L swings, and pendelluft extent, reduces dynamic strain in ventral areas (ie, baby lung). Dynamic strain is the main determinant of ventilator-induced lung injury, which mostly injures ventral, nondependent lung areas. ΔPes is the major determinant of self-inflicted lung injury that mostly occurs in the dorsal, dependent zones. The relative effects of these two mechanisms in determining the safety of respiratory support has yet to be identified.[8,63-65]

Our study has limitations. First, we used surrogate parameters to estimate aerated lung size. This was not the absolute EELI measured by EIT (which involves the global impedance of the thorax and not only the lung), but was derived from the relationship between stress and strain, as previously suggested.[25] This approach is based on a well-established physiologic concept; however, our approximation was that no recruitment occurred between 0 and 5 cm H_2O. We deem this may be an acceptable approximation. Also, dynamic strain calculation is a direct consequence of this. Therefore, absolute values should be interpreted cautiously. Second, we did not measure neural respiratory drive, which might have helped in clarifying the response of spontaneous ΔPes in patients with different lung mechanical properties. Third, only two PEEP levels were studied, and we cannot rule out that an intermediate PEEP level could represent the optimal setting for these patients.[66]

Interpretation

In patients with ARDS with preserved spontaneous breathing undergoing assisted ventilation and exhibiting intense ΔPes, the effect of high PEEP on ΔPes and lung stress varies depending on changes in respiratory system

compliance (mostly its lung component). ΔPes and driving pressure decrease if higher PEEP yields increased compliance, whereas ΔPes and driving pressure increase if compliance decreases. Consistent with classical physiology, PEEP-induced changes in lung compliance mostly depend on the extent of alveolar overinflation.

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Author contributions: D. L. G. takes responsibility for (is the guarantor of) the content of the manuscript, including the data and analysis. G. B., V. G., and D. L. G. designed the study. All authors contributed to data collection. L. D. C., T. R., and L. S. M. analyzed the data. G. B. and V. G. drafted the manuscript. L. B., R. R. D. S. S., and M. A. critically revised the first draft of the manuscript. All authors approved the final version of the manuscript and agreed on submitting it to *CHEST*.

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Additional information: The e-Appendix and e-Figures are available online under "Supplementary Data."

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