CRITICAL CARE MEDICINE

ANESTHESIOLOGY

# Lung Recruitment in Obese Patients with Acute Respiratory Distress Syndrome

Jacopo Fumagalli, M.D., Roberta R. S. Santiago, M.D., Ph.D., Maddalena Teggia Droghi, M.D., Changsheng Zhang, M.D., Ph.D., Florian J. Fintelmann, M.D., Fabian M. Troschel, Cand. Med., Caio C. A. Morais, R.R.T., Ph.D., Marcelo B. P. Amato, M.D., Ph.D., Robert M. Kacmarek, R.R.T., Ph.D., Lorenzo Berra, M.D., on behalf of the Lung Rescue Team Investigators*

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## ABSTRACT

**Background:** Obese patients are characterized by normal chest-wall elastance and high pleural pressure and have been excluded from trials assessing best strategies to set positive end-expiratory pressure (PEEP) in acute respiratory distress syndrome (ARDS). The authors hypothesized that severely obese patients with ARDS present with a high degree of lung collapse, reversible by titrated PEEP preceded by a lung recruitment maneuver.

**Methods:** Severely obese ARDS patients were enrolled in a physiologic crossover study evaluating the effects of three PEEP titration strategies applied in the following order: (1) $\text{PEEP}_{\text{ARDSNET}}$: the low PEEP/$\text{FIO}_2$ ARDSnet table; (2) $\text{PEEP}_{\text{INCREMENTAL}}$: PEEP levels set to determine a positive end-expiratory transpulmonary pressure; and (3) $\text{PEEP}_{\text{DECREMENTAL}}$: PEEP levels set to determine the lowest respiratory system elastance during a decremental PEEP trial following a recruitment maneuver on respiratory mechanics, regional lung collapse, and overdistension according to electrical impedance tomography and gas exchange.

**Results:** Fourteen patients underwent the study procedures. At $\text{PEEP}_{\text{ARDSNET}}$ (13 ± 1 cm $H_2O$) end-expiratory transpulmonary pressure was negative (−5 ± 5 cm $H_2O$), lung elastance was 27 ± 12 cm $H_2O$/L, and $\text{PaO}_2/\text{FIO}_2$ was 194 ± 111 mmHg. Compared to $\text{PEEP}_{\text{ARDSNET,}}$ at $\text{PEEP}_{\text{INCREMENTAL}}$ level (22 ± 3 cm $H_2O$) lung volume increased (977 ± 708 ml), lung elastance decreased (23 ± 7 cm $H_2O$/l), lung collapse decreased (18 ± 10%), and ventilation homogeneity increased thus rising oxygenation (251 ± 105 mmHg), despite higher overdistension levels (16 ± 12%), all values $P < 0.05$ *versus* $\text{PEEP}_{\text{ARDSnet}}$. Setting PEEP according to a $\text{PEEP}_{\text{DECREMENTAL}}$ trial after a recruitment maneuver (21 ± 4 cm $H_2O$, $P = 0.99$ *vs.* $\text{PEEP}_{\text{INCREMENTAL}}$) further lowered lung elastance (19 ± 6 cm $H_2O$/l) and increased oxygenation (329 ± 82 mmHg) while reducing lung collapse (9 ± 2%) and overdistension (11 ± 2%), all values $P < 0.05$ *versus* $\text{PEEP}_{\text{ARDSnet}}$ and $\text{PEEP}_{\text{INCREMENTAL}}$. All patients were maintained on titrated PEEP levels up to 24 h without hemodynamic or ventilation related complications.

**Conclusions:** Among the PEEP titration strategies tested, setting PEEP according to a $\text{PEEP}_{\text{DECREMENTAL}}$ trial preceded by a recruitment maneuver obtained the best lung function by decreasing lung overdistension and collapse, restoring lung elastance, and oxygenation suggesting lung tissue recruitment.

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## EDITOR'S PERSPECTIVE

### What We Already Know about This Topic

- Obesity increases the propensity to atelectasis in acute respiratory distress syndrome, but the optimal approach to reversing this atelectasis is uncertain

### What This Article Tells Us That Is New

- A clinical crossover study comparing three approaches to titrate positive end-expiratory pressure (PEEP; according to a fixed table, according to end-expiratory esophageal pressure, and targeting the best compliance during a decremental PEEP trial) found that a recruitment maneuver followed by decremental PEEP minimized atelectasis and overdistension, and best restored compliance and oxygenation without causing hemodynamic impairment

ACUTE respiratory distress syndrome (ARDS) is associated with high morbidity and mortality.[1] The introduction of lung protective ventilation with a low tidal volume and low airway pressure in patients with ARDS has been shown to improve patient survival.[2] Strategies aimed at minimizing alveolar collapse by transiently increasing airway pressure with a recruitment maneuver and titration of positive end-expiratory pressure (PEEP) to optimal respiratory system compliance have failed to provide consistent results.[3,4] The use of recruitment maneuvers and high PEEP levels (open lung approach) have been advocated to reestablish lung volume and prevent cyclic opening and closing of small airways while avoiding increases in lung strain.[5–8] However, all ARDS patients may not have recruitable lungs,[9] making it difficult to predict those patients that benefit most from an open lung approach.

In intubated and mechanically ventilated morbidly obese patients, the chest-wall elastance is not altered.[10,11] However, due to the "mass loading" effect of the mass of the thoracoabdominal structures pleural pressure is increased and the chest-wall pressure–volume curve is right-shifted leading to decreased transpulmonary pressure, reduced functional residual capacity, high lung elastance, and formation of atelectasis.[10,12] However, the slope of the pressure–volume curve remains essentially unchanged.[10] Recent physiologic studies showed that a negative end-expiratory transpulmonary pressure is responsible for alveolar collapse in obese patients.[13] In non-ARDS obese patients, setting PEEP to establish a positive end-expiratory transpulmonary pressure is not by itself sufficient to restore lung volume and lung mechanics.

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However, lung volume and lung mechanics can be optimized by applying lung recruitment maneuvers and then setting PEEP by decremental PEEP trial at the best respiratory system elastance.[11]

A body mass index exceeding 35 kg/m$^2$ is a common exclusion criterion in large clinical trials evaluating PEEP in ARDS.[14–16] Although a *post hoc* analysis of the ALVEOLI study demonstrated that obese patients with a body mass index between 30 and 35 kg/m$^2$ assigned to a high PEEP experienced lower mortality compared with those assigned to a low PEEP (18% *vs.* 32%; $P = 0.04$), however, severely obese patients (body mass index greater than 35 kg/m$^2$) were not studied.[17] The absence of physiologic studies and clinical trials to guide optimal ventilation management in this subset of ARDS patients is particularly worrisome considering that, recently, obesity has become a major health care concern in the United States. Nationally, nearly 38% of adults are obese and 8% have a body mass index greater than 40 kg/m$^2$.[18] Large observational studies reported that, among ventilated patients admitted to the intensive care unit, obese patients are much more likely to develop ARDS than nonobese patients.[19,20]

We hypothesized that lungs of severely obese patients with ARDS are highly recruitable and that a recruitment maneuver would improve lung mechanics, distribution of ventilation, dead space fraction and oxygenation while avoiding lung overdistention. To test our hypothesis, we designed a clinical crossover physiologic study in severely obese patients (body mass index greater than 35 kg/m$^2$) with ARDS. PEEP strategies evaluated included the low PEEP/$F_{IO_2}$ ARDSnet table,[2] PEEP titration to positive end-expiratory transpulmonary pressure without lung recruitment,[21] and PEEP titration to the best respiratory system elastance after a recruitment maneuver.[22]

## Materials and Methods

The study was approved by the Massachusetts General Hospital Institutional Review Board (Boston, Massachusetts; IRB No. 2015P001515) and registered on Clinical Trials (NCT02503241).

### Study Population

From April 1, 2016 to July 30, 2017 severely obese adult patients (body mass index greater than 35 kg/m$^2$) admitted to the Medical or Surgical intensive care units of the Massachusetts General Hospital (Boston, Massachusetts) entered the study after written informed consent was obtained. Among patients enrolled in the study, those meeting the Berlin criteria for ARDS[23] were included in the present analysis.

### Study Procedures

After assessing proper sedation level patients were paralyzed by administration of 0.2 mg/kg of cisatracurium besylate. Patients were ventilated in volume-controlled ventilation at 6 ml/kg of predicted body weight, $F_{IO_2}$ and respiratory rate were maintained as set per clinical management to maintain $S_{PO_2}$ = 88 to 95% and $P_{ACO_2}$ less than 50 mmHg, inspiratory to expiratory ratio was set at 1:2 with 0.3 s of inspiratory pause time.

The study protocol had three phases, always performed in the following order (fig. 1):

1. *PEEP titrated according to the low PEEP/$F_{IO_2}$ ARDSnet table*[2]*: (PEEP$_{ARDSnet}$).*
2. *Pleural pressure targeted-incremental PEEP (PEEP$_{INCREMENTAL}$):* PEEP progressively increased by 2 cm $H_2O$ every 60 s until the end-expiratory transpulmonary pressure equaled 0 to 2 cm $H_2O$ representing the optimal incremental PEEP.[21]
3. *Optimal Decremental PEEP (PEEP$_{DECREMENTAL}$):* A recruitment maneuver was performed in pressure control ventilation, driving pressure of 10 cm $H_2O$, by stepwise increase in PEEP 5 cm $H_2O$ every 30 s targeting a maximum plateau pressure of 50 cm $H_2O$ held for 1 min (see Supplemental Digital Content 1, http://links.lww.com/ALN/B878, for details). Following the recruitment maneuver, a PEEP$_{DECREMENTAL}$ trial was performed in volume-controlled ventilation starting at a PEEP level that maintained the plateau pressure less than 50 cm $H_2O$ and by decreasing PEEP by 2 cm $H_2O$ every 60 s. The PEEP level resulting in the lowest respiratory system elastance identified the optimal PEEP$_{DECREMENTAL}$.[22]

***Measurements.*** All measurements during PEEP$_{ARDSnet}$, PEEP$_{INCREMENTAL}$, and PEEP$_{DECREMENTAL}$ were performed at steady state after 10 to 15 min on stable ventilatory settings.[24]

**Respiratory Mechanics.** A nasogastric tube with esophageal balloon was inserted (AVEA Ventilator Nasogastric Pressure Monitoring Tube Set; CareFusion, USA), and balloon positioning and inflation volume were verified[25,26] (see Supplemental Digital Content 1, http://links.lww.com/ALN/B878, and Supplemental Digital Content 2, figure E1, http://links.lww.com/ALN/B879, for details). Airway pressure, flow, esophageal pressure, and capnogram were continuously recorded. To measure the changes in

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This article is featured in "This Month in Anesthesiology," page 1A. Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org). Preliminary data from this study was presented as an abstract presentation and oral communication at the 38th International Symposium on Intensive Care and Emergency Medicine, March 20–23, 2018, Square Brussels Meeting Center, Mont des Arts, Brussels, Belgium. J.F. and R.R.S.S. contributed equally to this article.

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*Members of Massachusetts General Hospital Lung Rescue Team Investigators are listed in the appendix.

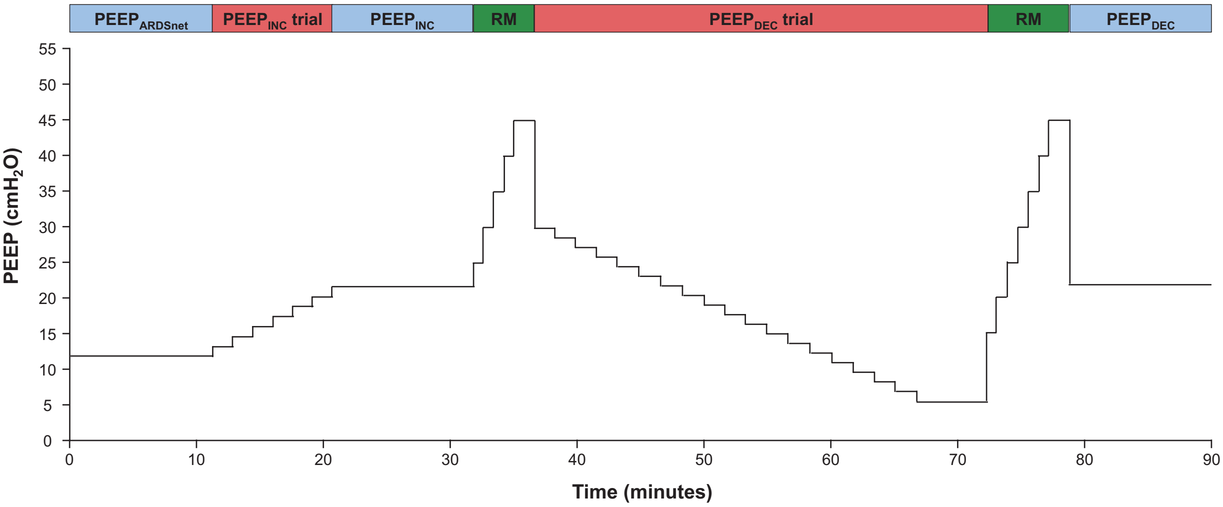

**Fig. 1.** Study protocol maneuvers. The image illustrates the positive end-expiratory pressure (PEEP) levels applied over time during the study protocol. After measurements were obtained at the PEEP level, determined according to the low PEEP/high $F\text{IO}_2$ table ($\text{PEEP}_{\text{ARDSnet}}$), stepwise increases in PEEP by 2 cm $H_2O$ every 60 s were performed during the $\text{PEEP}_{\text{INCREMENTAL}}$ trial in order to reach +2 cm $H_2O$ end expiratory transpulmonary pressure ([$P_L$E] ($\text{PEEP}_{\text{INCREMENTAL}}$). After a recruitment maneuver a $\text{PEEP}_{\text{DECREMENTAL}}$ trial was performed by stepwise decrease in PEEP by 2 cm $H_2O$ every 60 s. After the second recruitment maneuver, PEEP was set at the level determining the lowest respiratory system elastance during the $\text{PEEP}_{\text{DECREMENTAL}}$ trial ($\text{PEEP}_{\text{DECREMENTAL}}$). All study procedures were performed in volume-controlled ventilation (tidal volume = 6 ml/kg predicted body weight), recruitment maneuvers were performed in pressure-controlled ventilation (driving pressure = 10 cm $H_2O$).

intrathoracic pressures and lung volumes within a breathing cycle a resampling and interpolation process was used and a single "average" respiratory cycle was obtained for each patient at different ventilatory settings. Airway and esophageal pressures at end-inspiration and at end-expiration were obtained at zero flow. Tidal volume was calculated as the integral of the expiratory flow-time waveform.

To describe lung mechanics at different ventilatory settings, absolute esophageal pressure at end-inspiration and end-expiration (after optimizing balloon volume) were recorded and used to calculate lung and chest-wall elastance. As recently reported[27] we used the difference between airway opening pressure ($P_{AW}$) and esophageal pressure ($P_{ES}$) at end expiration to calculate end-expiratory transpulmonary pressure ($P_L$E), reflecting transpulmonary pressure ($P_L$) in the middle to dependent regions of the lung:

$$P_L E = \text{PEEP} - \text{end-expiratory } P_{ES}$$

To determine alveolar tidal stretch at each breath, driving $P_L$ was computed as:

$$\Delta P_L = \left(\text{Plateau pressure} - \text{end-inspiratory } P_{ES}\right) - \left(\text{PEEP} - \text{end-expiratory } P_{ES}\right)$$

To describe the contribution of resistive forces on lung mechanics at decreasing lung volumes, airways resistance was calculated by quasi static measurement at the three PEEP study steps while the least square fitting method[28] was used throughout the $\text{PEEP}_{\text{DECREMENTAL}}$ trial to minimize interference with electrical impedance tomography acquisition measurements. Intraabdominal hypertension was excluded by measuring bladder pressure less than 12 cm $H_2O$ before initiation of study procedures.[29]

**Gas Exchange.** Blood gas samples were obtained after ventilating patients for 10 to 15 min at 100% $F\text{IO}_2$ with $\text{PEEP}_{\text{ARDSnet}}$, $\text{PEEP}_{\text{INCREMENTAL}}$ and $\text{PEEP}_{\text{DECREMENTAL}}$. To measure the effects of PEEP on dead space, volumetric capnography was continuously recorded (Respironics NM3; Philips, USA).[30] Physiologic dead space was calculated by applying the Enghoff modification of the Bohr equation. Anatomic and alveolar dead-space volumes were determined by calculating the expired gas volume until the inflection point of phase II was reached in the volumetric capnogram.[31]

**Electrical Impedance Tomography Lung Imaging.** Electrical impedance tomography (Enlight 1800; Timpel SA, Brazil) is a noninvasive, radiation-free, real-time imaging method that measures global and regional changes in lung volumes.[32] Lung collapse and overdistension percentages were determined by comparing each electrical impedance tomography pixel-compliance during $\text{PEEP}_{\text{ARDSnet}}$, $\text{PEEP}_{\text{INCREMENTAL}}$, and $\text{PEEP}_{\text{DECREMENTAL}}$ ventilation.[33] Each pixel-compliance was determined by dividing tidal impedance change by the variation in pressure during the respiratory cycle. Therefore, overdistension was identified when, for a given pixel, aeration increased and compliance worsened. On the other hand, reversal of collapse was identified if aeration increased and compliance improved. To compare lung morphology between the PEEP levels obtained during the $PEEP_{INCREMENTAL}$ and $PEEP_{DECREMENTAL}$ titration, all measurement were referenced to the best pixel-compliance obtained during the $PEEP_{DECREMENTAL}$ trial after the recruitment maneuver since the recruitment maneuver allows the measurement of ventilation distribution in all the recruitable pixels. The lung images were divided in four regions, each covering 25% of the ventrodorsal lung area (Supplement Digital Content 2, figure E2, http://links.lww.com/ALN/B879). Homogeneity of ventilation was expressed as percentage of tidal ventilation directed to each region. Changes in end-expiratory lung volume were calculated from changes in end-expiratory lung impedance after linear transformation to volume, expressed in milliliters.[34]

**Radiologic Imaging.** Routine portable chest radiographs performed within 24 h before and 24 h after the study protocol were reviewed by a board-certified fellowship-trained thoracic radiologist (F.J.F.) blinded to the order of image acquisition. The radiologist evaluated difference in lung volumes based on the number of visible posterior ribs, overinflation defined as flattening of the hemidiaphragms, and presence of atelectasis. The presence of barotrauma (pneumothorax, pneumomediastinum) was also assessed.

## Statistical Analysis

We anticipated enrolling 14 patients in this two-treatment crossover study based on an expected decrease in lung elastance of 1.7 ± 1.8 cm $H_2O/l$[11] at $PEEP_{DECREMENTAL}$ *versus* $PEEP_{INCREMENTAL}$, with a power of 90% and a two-sided 0.05 significance level.

The Shapiro–Wilk test was used to assess normality of continuous variables. Data are expressed as mean ± SD or median [interquartile range] as appropriate. Categorical variables are expressed as count (n) and proportion (%). Continuous variables were compared by one-way ANOVA for repeated measure, and whenever a difference between groups was detected, intergroup comparison was performed with paired Student's *t* tests. For nonnormally distributed variables, one-way ANOVA for repeated measure on ranks was performed. *Post hoc* Bonferroni correction was applied for multiple comparisons. Statistical significance was defined as $P < 0.05$ (two-tailed). Statistical analysis was performed by using SigmaPlot 11.0 software (Systat Software Inc, USA).

Please refer to online Supplemental Digital Content 1, http://links.lww.com/ALN/B878, and Supplemental Digital Content 2, http://links.lww.com/ALN/B879, for details about: inclusion and exclusion criteria, procedures, and data analysis.

## Results

Among patients admitted to the participating intensive care units during the study period and requiring mechanical ventilation lasting longer than 24 h (N = 1,053), 117 patients had a body mass index greater than 35 kg/m². Among the latter cohort, 30 patients met the inclusion criteria, 28 patients were approached to obtain consent (2 patients excluded for logistical reasons), and 24 patients were enrolled and completed the study procedures. Fourteen severely obese patients (body mass index = 58.6 ± 11.0 kg/m²) matched the Berlin definition criteria for ARDS diagnosis. The population characteristics are summarized in table 1 (see Supplemental Digital Content 2, table E1, http://links.lww.com/ALN/B879, for additional details).

At screening, within 6 h after the start of mechanical ventilation, patients were hypoxemic ($PaO_2/FiO_2$ = 150 ± 81) on a PEEP greater than or equal to 5 cm $H_2O$ and met the Berlin criteria for ARDS. The intensive care unit team treated the patients according to the ARDSnet lung protective ventilation strategy: volume-controlled ventilation with tidal volume 6 ± 1 ml/kg predicted body weight. Selected $PEEP_{ARDSnet}$ (13 ± 1 cm $H_2O$) improved $PaO_2/FiO_2$ to 194 ± 111 from screening while maintaining plateau pressure less than 28 cm $H_2O$ (table 2). A respiratory rate of 26 ± 5 breaths per minute was necessary to maintain normocapnia. In 7 out of 14 patients, ARDS second line therapies were instituted to treat either patients' uncontrolled respiratory drive or refractory hypoxemia (table 1). Prone positioning was never attempted because it was considered unsafe due to patients' body habitus and hemodynamic instability. In four patients, extracorporeal membrane oxygenation support was discussed as rescue therapy by the intensive care unit team but initiation of extracorporeal

**Table 1.** Characteristics of the Patients

| | |
|---|---|
| Population (n) | 14 |
| Age, years | 52 ± 15 |
| Female, n (%) | 8 (57) |
| BMI, kg/m² | 58.6 ± 11.0 |
| Actual weight, kg | 167.4 ± 34.8 |
| Predicted body weight, kg | 62.7 ± 11.0 |
| APACHE II score | 21.8 ± 8.8 |
| Reason for ICU admission | |
| Medical, n (%) | 6 (43) |
| Surgical, n (%) | 8 (57) |
| Hypotension requiring vasopressors, n (%) | 12 (86) |
| $PaO_2/FiO_2$, mmHg* | 150 ± 81 |
| MV prior the study, days | 1 [0 - 4] |
| Rescue therapies, n (%) | 7 (50) |
| Pulmonary vasodilators, n (%) | 3 (21) |
| NMBA continuous infusion, n (%) | 7 (50) |

Data are expressed as mean ± SD or number (%) as appropriate. APACHE, Acute Physiology and Chronic Health Evaluation; BMI, body mass index; ICU, intensive care unit; MV, mechanical ventilation; NMBA, neuromuscular blocking agents; $PaO_2/FiO_2$, arterial partial pressure of oxygen to inspired fraction of oxygen ratio.
*At the time of screening, N = 13.

**Table 2.** Ventilator Settings, Respiratory Mechanics, Hemodynamic, Gas Exchange

| | $PEEP_{ARDSnet}$ | $PEEP_{INCREMENTAL}$ | $PEEP_{DECREMENTAL}$ | ∆Mean $PEEP_{INC}$-$PEEP_{ARDSnet}$ [95% CI] | ∆Mean $PEEP_{DEC}$- $PEEP_{ARDSnet}$ [95% CI] | ∆Mean $PEEP_{DEC}$- $PEEP_{INC}$ [95% CI] |
|---|---|---|---|---|---|---|
| PEEP, cm $H_2O$ | 13 ± 1 | 22 ± 3* | 21 ± 4* | 9 [7;11] | 9 [7;11] | –1 [–2;1] |
| P-plat, cm $H_2O$ | 26 ± 4 | 33 ± 4* | 31 ± 4* | 7 [5;9] | 5 [3;7] | –2 [–4;0] |
| Driving pressure, cm $H_2O$ | 13 ± 4 | 11 ± 2* | 10 ± 2*§ | –2 [–3;–1] | –3 [–5;–2] | –1 [–2;0] |
| $P_L$E, cm $H_2O$ | –5 ± 5 | 1 ± 4* | 1 ± 4* | 6 [4;8] | 6 [4;8] | 0 [–2;1] |
| Driving $P_{L,}$ cm $H_2O$ | 10 ± 4 | 9 ± 3* | 7 ± 4*§ | –1 [–2;0] | –3 [–4;-1] | –2 [–2;0] |
| $Elastance_{RS}$, cm $H_2O$/l | 34 ± 13 | 29 ± 8* | 25 ± 6*§ | –6 [–9;–2] | –10 [–14;–5] | –4 [–7;–2] |
| $Elastance_L$, cm $H_2O$/l | 27 ± 12 | 23 ± 7* | 19 ± 6*§ | –4 [–7;–1] | –7 [–11;–3] | –4 [–6;-1] |
| $Elastance_{CW}$, cm $H_2O$/l | 8 ± 5 | 6 ± 4* | 6 ± 3* | –2 [–3;0] | –2 [–4;0] | 0 [–1;0] |
| $R_{AW}$, cm $H_2O \cdot l^{-1} \cdot sec^{-1}$ | 14 ± 2 | 12 ± 2* | 12 ± 2* | –2 [–3;–1] | –2 [–3;–1] | 0 [–1;0] |
| EELV, ml‡ | – | 977 ± 708* | 1064 ± 813* | 978 [569;1386] | 1065 [596;1535] | 88 [–283;459] |
| HR, bpm | 89 ± 22 | 85 ± 20 | 87 ± 20 | –4 [–9;1] | –2 [–9;4] | 1 [–2;5] |
| MAP, mmHg | 83 ± 11 | 77 ± 7 | 82 ± 9§ | –6 [–11;–1] | –1 [–8;6] | 5 [1;9] |
| pH | 7.35 ± 0.06 | 7.34 ± 0.07 | 7.32 ± 0.07*§ | –0.00 [–0.02;0.01] | –0.03 [–0.05;–0.01] | –0.02 [–0.03;–0.01] |
| $PaO_2/FiO_2$ | 194 ± 111 | 251 ± 105* | 329 ± 82*§ | 57 [13;101] | 134 [70;199] | 77 [36;119] |
| $PaCO_2$, mmHg | 45 ± 10 | 46 ± 9 | 49 ± 10*§ | 1 [–1;2] | 3 [1;6] | 3 [1;5] |
| $V_D/V_T$† | | | | | | |
| Physiologic, % | 49 ± 11 | 47 ± 11 | 47 ± 12 | –2 [–4;1] | –1 [–5;2] | 0 [–2;2] |
| Airways, % | 30 ± 5 | 33 ± 6* | 31 ± 7 | 3 [1;5] | 1 [–2;4] | –2 [–5;1] |
| Alveolar, % | 19 ± 9 | 15 ± 8* | 16 ± 9 | –4 [-8;–1] | –3 [–7;2] | 2 [–1;5] |

Data from 14 patients. Data are expressed as mean ± SD. $Elastance_{CW}$, elastance of the chest wall; $Elastance_L$, elastance of the lung; $Elastance_{RS}$, elastance of the respiratory system; EELV, end-expiratory lung volume; HR, heart rate; IBW, ideal body weight; MAP, mean arterial pressure; $PaCO_2$, arterial partial pressure of carbon dioxide; $PaO_2/FiO_2$, arterial partial pressure of oxygen to inspired fraction of oxygen ratio; PEEP, positive end-expiratory pressure; $P_L$E, end-expiratory transpulmonary pressure; P-Plat, plateau pressure; $R_{AW}$, airway resistance; RR, respiratory rate; $V_D/V_T$, dead space; Vt=tidal volume.

*$P < 0.05$ compared to $PEEP_{ARDSnet}$ ($P < 0.05$); †N = 11; ‡EELV is expressed as volume increment from the $PEEP_{ARDSnet}$ level; §$P < 0.05$ compared to $PEEP_{INCREMENTAL}$.

membrane oxygenation was declined due to severe obesity and difficulties associated with cannula placement.

Computed tomography scans of the chest were performed in three patients before the study procedures to rule out pulmonary embolism. Representative images are displayed in Supplement Digital Content 2, figure E3, http://links.lww.com/ALN/B879, showing bilateral parenchymal ground-glass and consolidative opacities with an antero-posterior density gradient characteristic of ARDS.

After consent was obtained, study procedures were started on average 1 [range 0 - 4] day after the initiation of mechanical ventilation. No data was missing on any patient unless specifically reported.

### Both PEEP Titration Techniques ($PEEP_{INCREMENTAL}$ *vs.* $PEEP_{DECREMENTAL}$) Identified Similar Optimal PEEP Levels, Higher than the $PEEP_{ARDSnet}$

The PEEP titration technique did not affect the measured value of end-expiratory transpulmonary pressure (Supplement Digital Content 2, fig. E4, http://links.lww.com/ALN/B879). There was no difference in the titrated PEEP levels obtained: 22 ± 3 cm $H_2O$ and 21 ± 4 cm $H_2O$ ($PEEP_{INCREMENTAL}$ *vs.* $PEEP_{DECREMENTAL}$ respectively), determining an end-expiratory transpulmonary pressure 1 ± 4 cm $H_2O$ and 1 ± 4 cm $H_2O$ ($PEEP_{INCREMENTAL}$ *vs.* $PEEP_{DECREMENTAL}$ respectively). At $PEEP_{ARDSnet}$ level, the end-expiratory transpulmonary pressure was −5 ± 5 cm $H_2O$ (table 2).

### Compared to $PEEP_{ARDSnet}$, Titrated PEEP Levels Improved Lung Mechanics by Lowering Driving Pressure, and Increasing End-expiratory Lung Volume and Oxygenation

At $PEEP_{ARDSnet}$, study patients had increased respiratory system elastance, lung elastance and poor oxygenation. Compared to $PEEP_{ARDSnet}$ level, lung elastance decreased at $PEEP_{INCREMENTAL}$ level and further decreased after a recruitment maneuver and a $PEEP_{DECREMENTAL}$ trial. At $PEEP_{DECREMENTAL}$ level after a recruitment maneuver, the improvement in respiratory mechanics was mainly attributable to a decrease in lung elastance (fig. 2; table 2). Accordingly, setting PEEP at optimal $PEEP_{DECREMENTAL}$ after a recruitment maneuver resulted in the lowest airways and transpulmonary driving pressure (table 2; fig. 3).

Compared to $PEEP_{ARDSnet}$ lung volume increased similarly at $PEEP_{INREMENTAL}$ and $PEEP_{DECREMENTAL}$ levels (table 2).

Arterial oxygenation increased at titrated $PEEP_{INCREMENTAL}$ and further improved at titrated $PEEP_{DECREMENTAL}$ after a recruitment maneuver (fig. 3). Dead space fraction was not affected by either titrated PEEP method (table 2).

During the $\text{PEEP}_{\text{DECREMENTAL}}$ trial, airway resistance increased as PEEP decreased (fig. 4).

### Titrated PEEP Levels Improved Homogeneity of Ventilation Compared to $\text{PEEP}_{\text{ARDSnet}}$ by Minimizing Alveolar Collapse and Overdistension

Compared to $\text{PEEP}_{\text{ARDSnet}}$, titrated PEEP levels decreased the amount of lung collapse as measured by electrical impedance tomography, with $\text{PEEP}_{\text{DECREMENTAL}}$ after a recruitment maneuver more beneficial than the $\text{PEEP}_{\text{INCREMENTAL}}$ strategy (fig. 5A). Conversely the percentage of lung overdistension increased at titrated $\text{PEEP}_{\text{INCREMENTAL}}$ levels while remaining unchanged at titrated $\text{PEEP}_{\text{DECREMENTAL}}$ levels after a recruitment maneuver when compared to $\text{PEEP}_{\text{ARDSnet}}$ (fig. 5B). Titrated PEEP levels diverted tidal ventilation to the most dorsal regions of the lung (fig. 5C).

During the $\text{PEEP}_{\text{DECREMENTAL}}$ trial after a recruitment maneuver lung collapse started at approximately 4 ± 3 cm $H_2O$ end-expiratory transpulmonary pressure and increased the more end-expiratory transpulmonary pressure decreased (fig. 6). The crossing of the lines in figure 5 represents the PEEP level during the $\text{PEEP}_{\text{DECREMENTAL}}$ trial where collapse and overdistension were essentially equal. This occurred at an end-expiratory transpulmonary pressure of about +1 cm $H_2O$.

On chest radiograph, low lung volumes were present in 10 out of 14 patients prior to intervention and lung volumes increased in all cases after the intervention by 0.7 [0.2; 1.1] intercostal spaces on average. One postintervention chest radiograph demonstrated mild overinflation (Supplement Digital Content 2, table E2 and fig. E5, http://links.lww.com/ALN/B879).

### Titrated PEEP Levels Were Hemodynamically Well Tolerated and Did Not Cause Any Adverse Events

All patients completed the entire study procedures and were ventilated at titrated $\text{PEEP}_{\text{DECREMENTAL}}$ level for at least 24 h after the study procedures.

At the time of the study procedures nine patients were on vasopressors. Despite the increased level of intrathoracic pressure at titrated PEEP (about 9 cm $H_2O$ on average), none of the nine patients required increased vasopressors infusion within 24 h after the study. The remaining five patients remained hemodynamically stable without any requirement of vasopressor drugs neither at the time of the study procedures nor in the following 24 h.

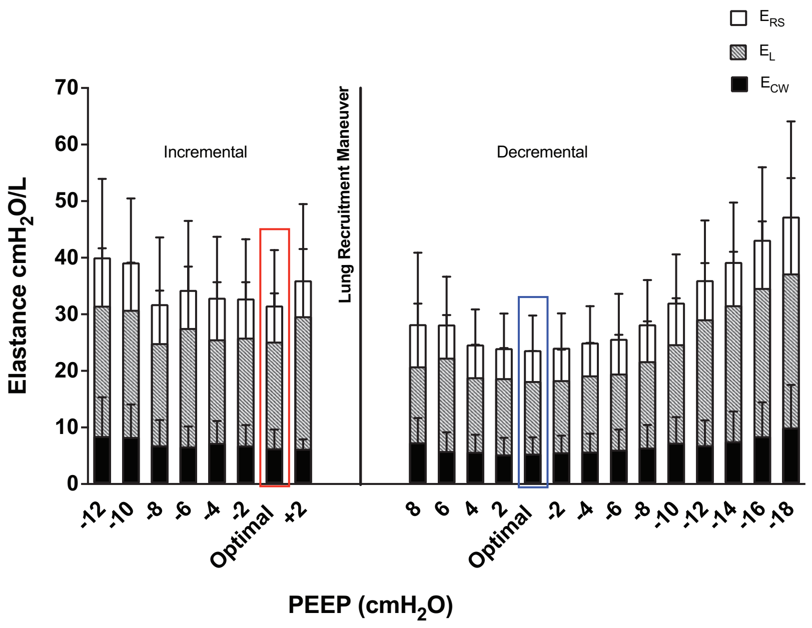

**Fig. 2.** Lung mechanics during a positive end-expiratory pressure $(\text{PEEP})_{\text{INCREMENTAL}}$ and a $\text{PEEP}_{\text{DECREMENTAL}}$ trial. Elastance of the respiratory system ($E_{RS}$), lung ($E_L$), and chest-wall ($E_{CW}$) through at stepwise increase in PEEP ($\text{PEEP}_{\text{INCREMENTAL}}$ trial) and stepwise decrease in PEEP after a recruitment maneuver ($\text{PEEP}_{\text{DECREMENTAL}}$ trial). $\text{PEEP}_{\text{INCREMENTAL}}$ trial is represented on the left side of the figure while the $\text{PEEP}_{\text{DECREMENTAL}}$ trial is represented on the right side of the figure. During both the incremental and decremental trial, PEEP settings began on the left and proceeded to the right of each figure. The PEEP levels during the $\text{PEEP}_{\text{INCREMENTAL}}$ trial are expressed as relative value to the PEEP level at which each patient reached an end-expiratory transpulmonary pressure between 0 and 2 cm $H_2O$ ($\text{PEEP}_{\text{INCREMENTAL}}$). The PEEP levels during the $\text{PEEP}_{\text{DECREMENTAL}}$ trial are expressed as relative value to the PEEP level at which each patient reached the lowest $E_{RS}$ ($\text{PEEP}_{\text{DECREMENTAL}}$). Data are expressed as mean ± SD.

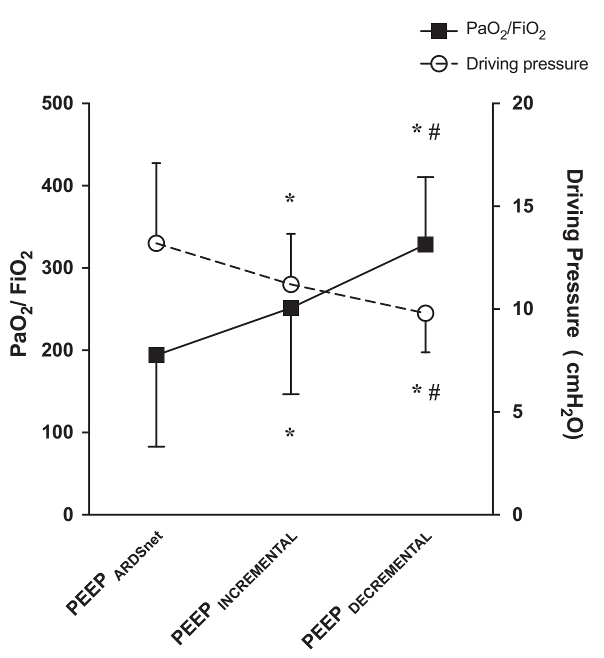

**Fig. 3.** Oxygenation and driving pressure. Oxygenation (arterial partial pressure of oxygen to inspired fraction of oxygen ratio) and respiratory system stress as airway driving pressure are represented at the three time-points of the study protocol. The stepwise increase in oxygenation together with the decrease in driving pressure are indicative of progressive lung recruitment. Setting positive end-expiratory pressure (PEEP) according to a $\text{PEEP}_{\text{DECREMENTAL}}$ trial after a recruitment maneuver obtains the highest oxygenation and represents the most protective lung ventilation strategy. $^{*}P < 0.05$ *vs.* $\text{PEEP}_{\text{ARDSnet}}$; $\#P < 0.05$ *vs.* $\text{PEEP}_{\text{INCREMENTAL}}$. Data are expressed as mean ± SD.

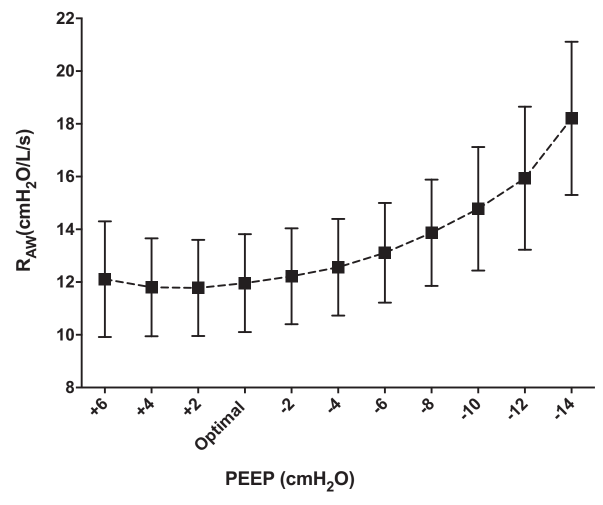

**Fig. 4.** Airways resistance. Airways resistance ($R_{AW}$) throughout a positive end-expiratory pressure $(\text{PEEP})_{\text{DECREMENTAL}}$ trial preceded by a recruitment maneuver: $R_{AW}$ increase as the lung volume decreases due to the decreasing levels of PEEP. The PEEP levels during the $\text{PEEP}_{\text{DECREMENTAL}}$ trial are expressed as relative value to the PEEP level at which each patient reached the lowest lung elastence ($E_L$) ($\text{PEEP}_{\text{DECREMENTAL}}$). Data are expressed as mean ± SD.

The 24-h fluid balance after the end of the study procedures was negative (less than −1,000 ml) in four patients, even (between −1,000 and +1,000 ml) in seven patients and positive (greater than +1,000 ml) in three patients. During this time period, only one patient received fluid boluses (*i.e.,* 500 ml crystalloids or 250 ml 5% albumin). The fluid boluses were administered for new onset atrial fibrillation (total 24-h fluid balance: +1,300 ml). The arrhythmia resolved within 10 h after amiodarone infusion. For the remaining two patients, the positive fluid balance was secondary to anuria which developed before the study procedures.

Chest radiograph performed within 24 h after the study procedures did not show barotrauma.

## Discussion

The main findings of this study are that in severely obese patients with an early diagnosis of ARDS: (1) titration of PEEP according to the low PEEP/$\text{F}\text{IO}_2$ ARDSnet table is associated with low $\text{Pa}\text{O}_2$/$\text{F}\text{IO}_2$ levels, lung atelectasis, and nonhomogeneous ventilation; (2) reversible lung collapse contributes substantially to respiratory failure in morbidly obese patients; (3) lung recruitment maneuvers are required to reverse alveolar collapse, despite the use of sufficient PEEP to establish a positive end-expiratory transpulmonary pressure; and (4) setting PEEP by a $\text{PEEP}_{\text{DECREMENTAL}}$ trial after a recruitment maneuver improves lung mechanics, lung volumes, and oxygenation, minimizing reversible lung collapse and overdistension more than the same PEEP level without lung recruitment.

Since its introduction, the ARDSnet table became synonymous with lung protective ventilation. However, an improved understanding of driving pressure and regional lung ventilation has resulted in an appreciation of the complexity of lung protective ventilation in ARDS, leading us to question a “one-size-fits-all” approach (PEEP/$\text{F}\text{IO}_2$ table). In the present physiologic study, PEEP levels of obese patients with ARDS were all initially titrated according to the ARDSnet low PEEP/$\text{F}\text{IO}_2$ table, which resulted in severely low $\text{Pa}\text{O}_2$/$\text{F}\text{IO}_2$ levels, impaired lung elastance, and nonhomogeneous distribution of ventilation directed mostly to the nondependent regions of the lung, and elevated driving pressure. All study patients met the ARDS Berlin definition. Due to severe refractory hypoxemia and elevated driving pressure, second line therapies were initiated in 7 of the 14 patients, including paralysis and inhaled pulmonary

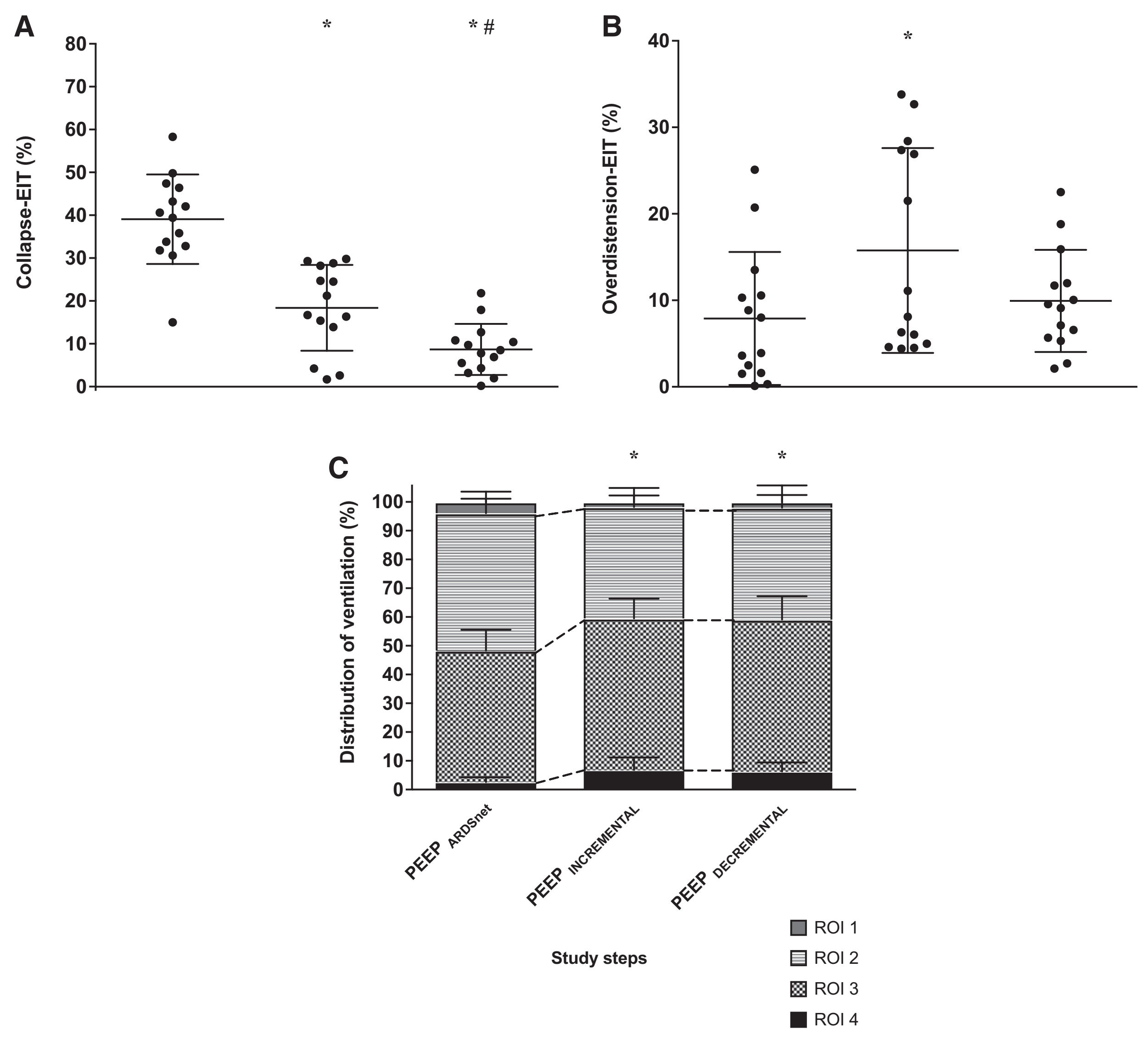

**Fig. 5.** Lung collapse, overdistension, and distribution of ventilation measured by the electrical impedance tomography technique at the three time-points of the study protocol. Lung collapse decreases at positive end-expiratory pressure (PEEP)$_{\text{INCREMENTAL}}$ levels compared to PEEP$_{\text{ARDSnet}}$ levels and further decreases at PEEP$_{\text{DECREMENTAL}}$ levels after a recruitment maneuver. Lung overdistension increases at PEEP$_{\text{INCREMENTAL}}$ levels compared to PEEP$_{\text{ARDSnet,}}$ while it is unaltered at PEEP$_{\text{DECREMENTAL}}$ levels after a recruitment maneuver. Distribution of ventilation is represented as percentage of the tidal volume distributed to four lung regions of interest (ROI), each one covering 25% of total lung volume (ROI 1 to 4 corresponds to the most nondependent to the most dependent areas of the lung). Both PEEP$_{\text{INCREMENTAL}}$ and PEEP$_{\text{DECREMENTAL}}$ levels redistribute tidal ventilation to the most dependent areas of the lung. $^*P < 0.05$ *vs.* PEEP$_{\text{ARDSnet}}$; # means $P < 0.05$ *vs.* PEEP$_{\text{INCREMENTAL.}}$ Data are expressed as single values from each patient (lung collapse and overdistension) and mean ± SD.

vasodilators. Extracorporeal life support was declined by the cardiac surgery consult team in four patients for technical reasons.

By using the absolute pressure information from an esophageal balloon, we increased PEEP to 9 cmH$_2$O above PEEP$_{\text{ARDSnet}}$, targeting an end-expiratory transpulmonary pressure in between 0 and 2 cm H$_2$O (PEEP$_{\text{INCREMENTAL}}$). This maneuver quickly improved oxygenation, respiratory mechanics and reduced driving pressures, confirming the benefits of this strategy, as previously reported by Talmor *et al.*[21] Finally, we demonstrated that a recruitment maneuver followed by a PEEP$_{\text{DECREMENTAL}}$ trial based on best respiratory system elastance (*i.e.,* not using esophageal pressure) resulted in equivalent levels of "optimum" PEEP as the PEEP$_{\text{INCREMENTAL}}$ approach, but further benefited oxygenation and lung mechanics. When comparing

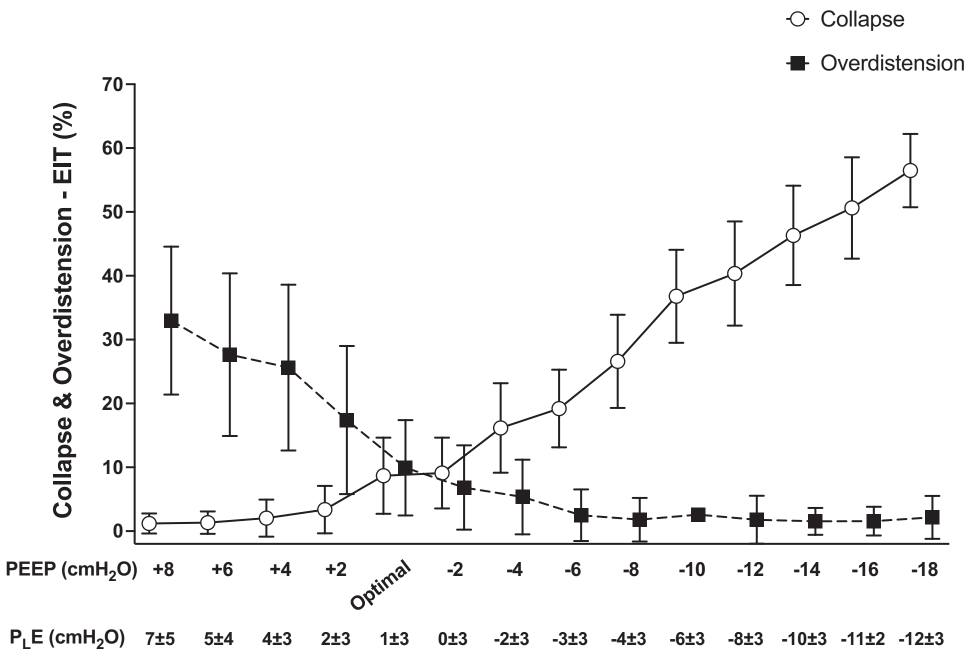

**Fig. 6.** Transpulmonary pressure and lung morphology. Percentage of lung collapse (*empty circles*) and overdistension (*squares*) during the positive end-expiratory pressure $(\text{PEEP})_{\text{DECREMENTAL}}$ trials. End-expiratory transpulmonary pressure ($P_L$E) at each PEEP step is represented at the bottom of the graph. Lung collapse starts at ≈ 3.6 ± 0.9 $\text{cmH}_2\text{O}$ $P_L$E. The PEEP levels during the $\text{PEEP}_{\text{DECREMENTAL}}$ trial are expressed as relative value to the PEEP level at which each patient reached the lowest respiratory system elastance ($\text{PEEP}_{\text{DECREMENTAL}}$). Data are expressed as mean ± SD.

$\text{PEEP}_{\text{INCREMENTAL}}$ *versus* $\text{PEEP}_{\text{DECREMENTAL}}$, we observed additional recruitment of dependent lung collapse, associated with a further reduction in overdistension of nondependent lung, and both contributing to a further reduction in driving pressures (for the same tidal volume), which likely resulted in less injurious mechanical ventilation.[35] The observed benefit of $\text{PEEP}_{\text{DECREMENTAL}}$ over $\text{PEEP}_{\text{INCREMENTAL}}$ both on lung mechanics and oxygenation suggests that lungs of obese ARDS patients are highly recruitable. As a consequence, driving airway and transpulmonary pressure progressively decreased at $\text{PEEP}_{\text{INCREMENTAL}}$ levels and was further lowered at $\text{PEEP}_{\text{DECREMENTAL}}$ levels, implying a more protective ventilator strategy.

When comparing the present results of ARDS obese patients with findings from our previous study in obese patients with acute respiratory failure without ARDS,[11] we found intriguing similarities. First, the level of PEEP necessary to counterbalance the increased pleural pressure determining a positive end-expiratory transpulmonary pressure[21] corresponds to the PEEP level determining the lowest respiratory system elastance according to a $\text{PEEP}_{\text{DECREMENTAL}}$ trial following a recruitment maneuver. In the current study, we could also show that this level of PEEP resulted in an optimum compromise between overdistension and lung collapse. Second, severely obese paralyzed and mechanically ventilated patients—with or without ARDS—show similar optimal levels of PEEP. Third, increased respiratory elastance in obesity—with and without ARDS—is attributable exclusively to an increased lung elastance, while chest-wall elastance is unaltered. Consistent with these findings, titration of PEEP by a $\text{PEEP}_{\text{DECREMENTAL}}$ trial after a recruitment maneuver resulted in a remarkable improvement in lung elastance. All these findings suggest that the lungs of obese patients show a high proportion of recruitable lung collapse, more than the general population of ARDS patients. The high PEEP required in obese patients is mostly needed to counterbalance the increased levels of pleural pressure.

Our physiologic findings are different from what was shown recently in the Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial.[3] In the latter study, conducted in a non-obese population, patients underwent randomization to the decremental PEEP titration and recruitment maneuver arm without thorough assessment for lung tissue recruitability. Furthermore, the recruitment maneuver procedure, which was associated with cardiac arrest in three patients in the Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial required a much longer period to perform at higher airway pressures than used in our study. Our recruitment procedure, does not seem to impair hemodynamics in obese patients, possibly due to their high pleural pressures.

Setting PEEP at $\text{PEEP}_{\text{INCREMENTAL}}$ and $\text{PEEP}_{\text{DECREMENTAL}}$ levels raised intrathoracic volume by 977 ± 708 ml and

1,064 ± 813 ml, respectively, corresponding to an increase in end-expiratory esophageal pressure of only 3 ± 2 cm $H_2O$ and 3 ± 2 cm $H_2O$, respectively. Accordingly chest wall elastance would have been 4 ± 4 and 3 ± 5 cm $H_2O$/l, values significantly lower than the ones measured according to the standard formula derived form esophageal pressure changes during tidal ventilation. This observation is in line with the hypothesis of a time dependent behavior of the chest-wall[36]: higher chest-wall elastance is detected when intrathoracic volume is quickly changed (tidal stretch) while lower values are measured if slow deformation is applied (PEEP related stretch).

As recently shown, when measuring lung tissue recruitment as an increase in end expiratory lung volume promoted by PEEP, the vertical shift of the respiratory system pressure-volume curve above the predicted inflation volume due to PEEP does not allow precise quantification of lung recruitment.[37] In the current study, however, the increase in lung volume and aeration of dependent lung regions (electrical impedance tomography data) was followed by an improvement in regional respiratory system elastance, together with a decrease in shunt fraction. Altogether, these findings are indicative of lung tissue recruitment.[38] The electrical impedance tomography estimates of lung collapse have been validated against computed tomography[33]; however, these electrical impedance tomography estimates are based on regional compliance, and not on lung density. Thus, they may be theoretically affected by small airways collapse, a potential scenario in obese patients with pleural pressures exceeding airway pressures.[39] This phenomenon, if present, might mislead the measurement of regional lung compliance and thus of lung recruitment and collapse by electrical impedance tomography. Airway collapse is sensed as a silent electrical impedance tomographic zone, causing a decrease in the estimates of regional compliance. If airway collapse is not followed by distal alveolar collapse, this phenomenon might cause some overestimation of lung collapse—but not of overdistension. Thus, it is possible that the estimates of lung collapse were slightly overestimated, especially at the $PEEP_{ARDSnet}$, when negative end-expiratory transpulmonary pressure were common. However, they would not cause any bias in the comparison between $PEEP_{INCREMENTAL}$ *versus* $PEEP_{DECREMENTAL}$, since both reached a positive end-expiratory transpulmonary pressure and both resulted in similar applied PEEP. At the same ventilator PEEP level, we must expect a similar degree of airway closure.[39] Although differentiation between the contribution of alveolar collapse and airways closure to the development of respiratory failure was beyond the purpose of this study, our electrical impedance tomography observations, in conjunction with the low oxygenation levels, and computerized tomography showing massive alveolar collapse, suggest that lung collapse plays a major role in this patient population. We further demonstrated that in obese patients reducing PEEP during the $PEEP_{DECREMENTAL}$ trial below end-expiratory transpulmonary pressure level causes a decrease in lung volume large enough to increase airways resistances.[40]

## Limitations of the Study

There are methodologic limitations to this study. The order of the study procedures was not randomized. Our aim was to differentiate between the effects of titrated PEEP levels alone *versus* titrated PEEP levels after a recruitment maneuver. Since the high airway pressure reached during the recruitment maneuver may have had a carry-over effect on the values measured at $PEEP_{INCREMENTAL}$, the order of study procedures was fixed.

## Conclusion

In critically-ill obese patients with ARDS, titration of PEEP according to the low PEEP/$F_{IO_2}$ ARDSnet table is associated with low $P_{AO_2}/F_{IO_2}$ levels, lung atelectasis and negative transpulmonary pressures. Among the two PEEP titration strategies tested, performing a recruitment maneuver and then applying PEEP according to a $PEEP_{DECREMENTAL}$ trial obtained the best lung function by decreasing lung overdistension and collapse, minimizing driving pressure, and restoring lung elastance and oxygenation, suggesting that lungs of obese patients with ARDS are highly recruitable. The PEEP level required to obtain a positive end-expiratory transpulmonary pressure corresponds to the PEEP level identifying the lowest respiratory system elastance according to a $PEEP_{DECREMENTAL}$ trial after a recruitment maneuver. According to electrical impedance tomography data, $PEEP_{DECREMENTAL}$ levels coincided with the minimum level of both lung collapse and lung overdistension. Further investigation is required to determine if the proposed approach can improve outcomes in this patient population.

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## Competing Interests

Dr. Amato reports that his research laboratory has received grants in the last 5 yr from the Covidien/Medtronics

(Minneapolis, Minnesota; research on mechanical ventilation), Orange Med (Irvine, California; mechanical ventilation), and Timpel S.A. (São Paulo, Brazil; electrical impedance tomography). Dr. Kacmarek is a consultant for Medtronic and Orange Med, and has received research grants from Medtronic and Venner Medical (Dänischenhagen, Germany). Dr. Berra received research grants from Venner Medical and the National Institutes of Health/National Heart, Lung, and Blood Institute (Bethesda, Maryland) grant No. 1 K23 HL128882-01A1 for the project titled "Hemolysis and Nitric Oxide." The other authors declare no competing interests.

## Correspondence

Address correspondence to Dr. Berra: Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, Harvard Medical School, 55 Fruit Street, 02114, Boston, Massachusetts. lberra@mgh.harvard.edu. This article may be accessed for personal use at no charge through the Journal Web site, www.anesthesiology.org.

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## Appendix

Collaborators:

Sophia Palma, B.Sc., Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, Boston, Massachusetts

Grant M. Larson, E.M.T-B., Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, Boston, Massachusetts

Shigeru W. Kaneki, B.A., Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, Boston, Massachusetts

Daniel Fisher, R.R.T., Respiratory Care Department, Massachusetts General Hospital, Boston, Massachusetts

Emanuele Rezoagli, M.D., Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, Boston, Massachusetts

Massimiliano Pirrone, M.D., Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, Boston, Massachusetts

Francesco Marrazzo M.D., Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, Boston, Massachusetts

Hui Zhang, M.D., Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, Boston, Massachusetts

Jing Zhao, M.D., Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, Boston, Massachusetts