

Compressive Forces and Computed Tomography–derived Positive End-expiratory Pressure in Acute Respiratory Distress Syndrome

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ABSTRACT

Background: It has been suggested that higher positive end-expiratory pressure (PEEP) should be used only in patients with higher lung recruitability. In this study, the authors investigated the relationship between the recruitability and the PEEP necessary to counteract the compressive forces leading to lung collapse.

Methods: Fifty-one patients with acute respiratory distress syndrome (7 mild, 33 moderate, and 11 severe) were enrolled. Patients underwent whole-lung computed tomography (CT) scan at 5 and 45 cm H₂O. Recruitability was measured as the amount of nonaerated tissue regaining inflation from 5 to 45 cm H₂O. The compressive forces (superimposed pressure) were computed as the density times the sternum-vertebral height of the lung. CT-derived PEEP was computed as the sum of the transpulmonary pressure needed to overcome the maximal superimposed pressure and the pleural pressure needed to lift up the chest wall.

Results: Maximal superimposed pressure ranged from 6 to 18 cm H₂O, whereas CT-derived PEEP ranged from 7 to 28 cm H₂O. Median recruitability was 15% of lung parenchyma (interquartile range, 7 to 21%). Maximal superimposed pressure was weakly related with lung recruitability ($r^2 = 0.11$, $P = 0.02$), whereas CT-derived PEEP was unrelated with lung recruitability ($r^2 = 0.0003$, $P = 0.91$). The maximal superimposed pressure was 12 ± 3 , 12 ± 2 , and 13 ± 1 cm H₂O in mild, moderate, and severe acute respiratory distress syndrome, respectively, ($P = 0.0533$) with a corresponding CT-derived PEEP of 16 ± 5 , 16 ± 5 , and 18 ± 5 cm H₂O ($P = 0.48$).

Conclusions: Lung recruitability and CT scan–derived PEEP are unrelated. To overcome the compressive forces and to lift up the thoracic cage, a similar PEEP level is required in higher and lower recruiters (16.8 ± 4 vs. 16.6 ± 5.6 , $P = 1$). (ANESTHESIOLOGY 2014; 121:572-81)

SETTING positive end-expiratory pressure (PEEP) in acute respiratory distress syndrome (ARDS) remains a highly debated issue since the definition of the syndrome. This, in part, depends on the target that one wants to reach while applying the PEEP. The traditional target was the oxygenation which usually increases by increasing PEEP due to a variable combination of lung recruitment and changes in lung perfusion.¹ Actually, the highest oxygenation target has been abandoned, as possibly associated with lung hyperinflation and cardiac output depression.² In the last 2 decades, the PEEP target shifted from the optimal gas exchange to the lung protection.^{3,4} Accordingly, the optimum PEEP level should prevent the ventilator-induced lung injury by avoiding intratidal opening and closing.^{3,5} Although the higher PEEP application provided impressive positive results in experimental setting,⁶ higher or lower PEEP levels led to similar outcomes in human ARDS.⁷⁻⁹

What We Already Know about This Topic

- How much positive end-expiratory pressure to use in patients with acute respiratory distress syndrome is still controversial.

What This Article Tells Us That Is New

- Lung recruitability and computed tomography scan–derived positive end-expiratory pressure are unrelated. The positive end-expiratory pressure required in patients who had more recruitment and less recruitment was similar.

One of the possible explanations of the discrepancy between experimental and clinical findings is that PEEP may prevent ventilator-induced lung injury only in patients with higher lung recruitability. It has been shown that recruitability is largely variable in the ARDS population,¹⁰ from 0 to 70% of the lung mass. Therefore, it is possible

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that in the clinical trials, where recruitability was not considered, the positive effects of higher PEEP in patients with higher recruitability have been offset by its negative effects in patients with lower recruitability. Actually, two meta-analyses suggest that higher PEEP is of some advantage in the patients with more severe ARDS, who more frequently present higher lung recruitability.^{11,12}

In a previous study including 51 patients with ARDS, we found that the bedside PEEP-selection methods based on lung mechanics provided similar values in patients with higher and lower lung recruitability.¹³ To better understand these results, we analyzed in detail the computed tomography (CT) scans obtained in these 51 patients. The regional analysis of the CT scan allows estimation of the compressive forces acting through the lung parenchyma at different levels along the sternum-vertebral axis. Therefore, we computed in each patient the maximal compressive forces operating over the most dependent lung regions and by knowing the chest wall elastance the force necessary to expand the thoracic cage (chest wall and diaphragm). We called CT-derived PEEP the sum of these two forces and hypothesized that they could be related to lung recruitability. In fact, we previously found that the lung recruitability was greater in patients with greater severity and lung weight.¹⁰ Therefore, the aim of this study was to estimate the CT-derived PEEP, defined as the ideal pressure that would allow keeping the lung completely open by overcoming the compressive forces, and to verify whether these values are proportional to the lung recruitability.

Materials and Methods

Assumptions

Superimposed Pressure and Lung Collapse. Our approach is based on our previous observations on the pressure needed to keep the lung open in which we proposed the increased lung weight as the primary cause of regional lung collapse^{14–18} (“sponge model”). This assumption is based on the following observations: (1) in patients with ARDS, the PEEP at which the slope of the regional end-expiratory gas/tissue pressure curve changed (end-expiratory inflection point) corresponded to the superimposed pressure computed in that region¹⁹; (2) in patients with ARDS shifting the lung from supine to prone position causes the collapse of previously open ventral regions while previously closed dorsal regions regain inflation^{20,21}; (3) in normal subjects, the density gradient from sternum to vertebra estimated by CT scan corresponds to the one reported in physiological studies by using isotopes^{16,22}; and (4) in animals, the increased superimposed pressure measured by CT scan along the sternum-vertebral axis corresponds to the increase in pleural pressure directly measured by wafers.¹⁸ Therefore, although forces other than superimposed pressure are obviously involved during inspiration to overcome, as an example, the surface

tension and the tissue resistances, the bulk of data suggests that the primary force leading to lung collapse during expiration is the increased superimposed pressure. Accordingly, we assumed that the end-expiratory lung collapse could be prevented only if intraalveolar pressure greater than the superimposed pressure is applied.

Chest Wall Expansion. The airway pressure (driving pressure) is spent to expand both the lung parenchyma (transpulmonary pressure) and the chest wall.²³ At end-expiration, we assumed that the transpulmonary pressure necessary to keep the lung parenchyma open must be, at least, equal to the superimposed pressure.¹⁹ Therefore, the driving pressure necessary to keep the lung open at end-expiration (PEEP) will be the end-expiratory transpulmonary pressure equal to the maximal superimposed pressure plus the pleural pressure required to keep the chest wall expanded at the same volume. To compute the pleural pressure, we had to assume that the chest wall elastance is constant through the range of pressures we applied in this study.^{13,24} We realize that this is a simplified model of the reality as the pleural pressure is different at different lung levels for several reasons as the gravitational forces and the lung/chest wall shape mismatch.²⁵ However, no clinical means other than esophageal pressure are available to estimate the chest wall elastance,²⁶ and the esophageal pressure changes are well related to the pleural pressure changes recorded at the middle of the chest wall.^{18,27–30}

Assessment of Lung Recruitability. We assumed that the ARDS lung is fully recruited at 45 cm H₂O pressure and we defined lung recruitability as the amount of parenchyma that regain inflation at that inspiratory pressure.¹⁰ Although opening pressures greater than 45 cm H₂O up to 60 cm H₂O have been applied,^{31,32} we did not feel to use such high pressures as the 1 to 3% of further recruitability obtained at 60 cm H₂O compared with 45 cm H₂O does not justify the reported risks of fluid overload, severe respiratory acidosis due to alveolar hypoventilation,³¹ and pneumothorax.

Study Protocol

In the present report, we present the second part of the analysis of a clinical protocol (<http://www.clinicaltrials.gov> number: NCT00682942)¹³ in which four bedside PEEP-selection methods, two based on lung mechanics (ExPress—Positive End-Expiratory Pressure Setting in Adults With Acute Lung Injury and Acute Respiratory Distress Syndrome study method⁷ and Stress Index method),³³ one based on oxygenation (lung open ventilation) study method,⁹ and one based on the absolute value of esophageal pressure,³⁴ were tested in each patient, and CT scan images of the whole lung were taken at PEEP 5 cm H₂O end-expiration and 45 cm H₂O end-inspiration to measure the lung recruitability and the CT-derived PEEP. The results obtained when comparing the bedside PEEP-selection methods have been previously reported.¹³ We report here the PEEP, computed by the CT scan, necessary to counteract the compressive forces acting

through the parenchyma at end-expiration and to keep the lung mechanically open.

The study was approved by the Institutional Review Board of the two hospitals (Milan, Via Francesco Sforza 22, Milano, Italy, and Göttingen, Georg-August-Universität, Wilhelmsplatz 1 37073 Göttingen, Germany), and written consent was obtained according to the regulations applicable in each institution. In brief, 51 patients with ARDS were studied. The patients were instrumented for the measurement of the physiological variables including the esophageal pressure for partitioned lung mechanics assessment (available in 50 patients). Afterwards patients were transferred to the CT scan facility where whole-lung scans were taken at 5 and 45 cm H₂O airway pressures in static conditions after a recruitment maneuver (pressure-control mode with PEEP 5 cm H₂O, pressure above PEEP 40 cm H₂O, respiratory rate 10 breaths/min, inspiratory to expiratory time ratio 1:1, and F_{IO₂} 0.7 for 2 min).

The patient population thereafter was divided in subgroups of mild (P_{aO₂}/F_{IO₂} 200 to 300, n = 7 [14%]), moderate (P_{aO₂}/F_{IO₂} 100 to 200, n = 33 [65%]), and severe ARDS (P_{aO₂}/F_{IO₂} < 100, n = 11 [22%]) according to the Berlin classification.³⁵

CT Scan Analysis

The method have been described in details elsewhere.^{36,37} We assumed that each voxel of the lung is composed of two compartments with different density: air (with a Hounsfield unit (HU) number of -1,000) and tissue (with an HU number = 0). It follows that, knowing the HU number of each voxel, it is possible to compute the amount of gas and tissue as:

$$\text{Voxel gas volume} = (\text{HU number} / (-1,000)) \times \text{Voxel volume} \quad (1)$$

$$\text{Voxel tissue volume} = 1 - \text{Voxel gas volume} \quad (2)$$

Tissue volume includes lung tissue, blood, and edema that cannot be distinguished.

Lung tissue was classified according to its HU value in hyperinflated (HU -1,000 to -900), normally inflated (HU -900 to -500), poorly inflated (HU -500 to -100), and non-inflated lung (HU > -100) at 5 and 45 cm H₂O airway pressures. Tissue content was computed voxel by voxel applying equation 2. To compute the total amount of lung tissue, we sum the tissue content of all voxel whose HU number was in the defined range (*i.e.*, total noninflated tissue was the sum of the tissue contents of all voxels with HU > -100, poorly inflated tissue was the sum of all voxels with tissue content between -100 and -500, well-inflated tissue was the sum of tissue content of all voxels with HU between -500 and -900, and overinflated tissue was the sum of tissue content of all voxels with HU less than -900). The recruitability was defined as the fraction of noninflated tissue at 5 cm H₂O to the total lung tissue measured at 5 cm H₂O PEEP which regained inflation at 45 cm H₂O:

$$\begin{aligned} \text{Lung recruitability (fraction of lung parenchyma)} = & \\ & (\text{noninflated tissue (grams) at PEEP 5 cm H}_2\text{O} - \\ & \text{noninflated tissue (grams)} \\ & \text{at 45 cm H}_2\text{O end-inspiration}) / \\ & \text{total lung tissue (grams) at PEEP 5 cm H}_2\text{O} \end{aligned} \quad (3)$$

We defined as “consolidation” the fraction of lung parenchyma which is noninflated at 45 cm H₂O to the total lung tissue measured at 45 cm H₂O PEEP.

$$\begin{aligned} \text{Noninflated tissue (grams) at 45 cm H}_2\text{O} / \\ \text{total lung tissue (grams) at 45 cm H}_2\text{O} \end{aligned} \quad (4)$$

We defined higher and lower recruiters according to the median lung recruitability of the present population (15%). As a definite threshold of lung recruitability cannot be defined “*a priori*” we reported in Supplemental Digital Content 1, <http://links.lww.com/ALN/B65>, the same analysis using as threshold the median lung recruitability found in a previously published article (9% of total lung tissue) (Supplemental Digital Content 1, table 1, <http://links.lww.com/ALN/B65> [physiological data], table 2 [CT scan data], and table 3 [CT-derived PEEP and bedside PEEP-selection methods], and Supplemental Digital Content 1, fig. 1, <http://links.lww.com/ALN/B65> [apex-to-base distribution of consolidated, collapsed/recruitable, poorly inflated, well inflated, and overinflated tissue in higher and lower recruiters] and fig. 2 [apex-to-base distribution of superimposed pressure and CT-derived PEEP in higher and lower recruiters]).¹⁰

Computation of Compressive Forces. We divided the whole-lung CT scan taken at 5 cm H₂O PEEP in 10 sections of equal length along the longitudinal axis (apex-to-basis). In each lung, we obtained 10 sections of different height (20 per patient; see fig. 1 for details). In each section, we measured lung density (lung tissue in section [grams]/total section volume [ml]) and sternum-vertebral height (cm). Superimposed pressure was computed as:

$$\begin{aligned} \text{Lung section superimposed pressure (cm H}_2\text{O)} = & \\ & \text{Section height (cm)} \times \text{Section density} \\ & (\text{Section tissue [g]} / \text{Section volume [ml]}) \end{aligned} \quad (5)$$

In each patient, we defined the highest superimposed pressure measured in the two lungs as the maximal superimposed pressure (fig. 1).

Computation of CT-derived PEEP. We reasoned that to keep open the most dependent collapsed alveoli, a transpulmonary pressure (PL) equal at least to the maximal superimposed pressure (Sp) must be applied. In addition, to account for the chest wall mechanics, the pleural pressure (Ppl) necessary to lift up the chest wall must be added to the transpulmonary pressure to determine the CT-derived PEEP. Therefore, the CT-derived PEEP is the driving pressure to keep the lung

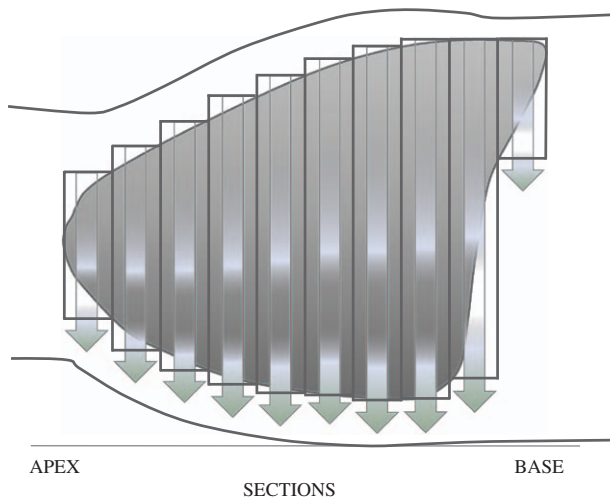


Fig. 1. Summarizes the method used to compute the maximal superimposed pressure. Each lung was first divided into 10 sections of equal length along the sternum-vertebral axis and the maximal superimposed pressure was computed in each lung section (10 values for each lung, 20 values for patient). We selected as “maximal superimposed pressure” the highest value recorded.

expanded at the end-expiration resulting from the sum of two pressures: the transpulmonary pressure (equal to the superimposed pressure) to expand the lung and the pleural pressure to expand the chest wall.

Accordingly the CT-derived PEEP was computed as follows:

$$\begin{aligned} \text{Transpulmonary pressure } (\Delta P_L) &= \text{Superimposed pressure } (Sp) \\ &= \text{PEEP} - \Delta P_{pl} \text{ (pleural pressure)} \end{aligned} \quad (6)$$

As ΔP_{pl} is equal to:

$$\Delta P_{pl} = \text{PEEP} \times E_{cw} / E_{rs} \quad (7)$$

where E_{cw} is chest wall elastance and E_{rs} is respiratory system elastance (*i.e.*, chest wall elastance [E_{cw}] plus lung elastance [E_L]).

Substituting in the equation 6:

$$Sp = \text{PEEP} - \text{PEEP} \times E_{cw} / E_{rs} \quad (8)$$

$$Sp = \text{PEEP} \times (1 - E_{cw} / E_{rs})$$

$$Sp = \text{PEEP} \times (E_{rs} - E_{cw}) / E_{rs}$$

It follows that the PEEP (CT-derived PEEP) representing the driving force to keep the lung fully open will be:

$$\text{CT-derived PEEP} = Sp \times E_{rs} / E_L \quad (9)$$

To compute the CT-derived PEEP, we always used as Sp the maximal superimposed pressure. CT-derived PEEP was available in 50 patients because the esophageal pressure data were not available in one patient.

Statistical Methods

The relationship between lung recruitability, maximal superimposed pressure, and CT-derived PEEP was assessed with linear regression. Maximal superimposed pressure and CT scan variables between higher and lower recruiters were compared with the Student *t* test or Wilcoxon test for continuously distributed variables and with chi-square test for categorical variables. Normality was tested with the Shapiro–Wilk test. The relationship between maximal superimposed pressure and CT-derived PEEP and lung section in recruiters and nonrecruiters was assessed with two-way ANOVA, and multiple comparisons were performed only between higher and lower recruiters at each level (10 multiple comparisons)

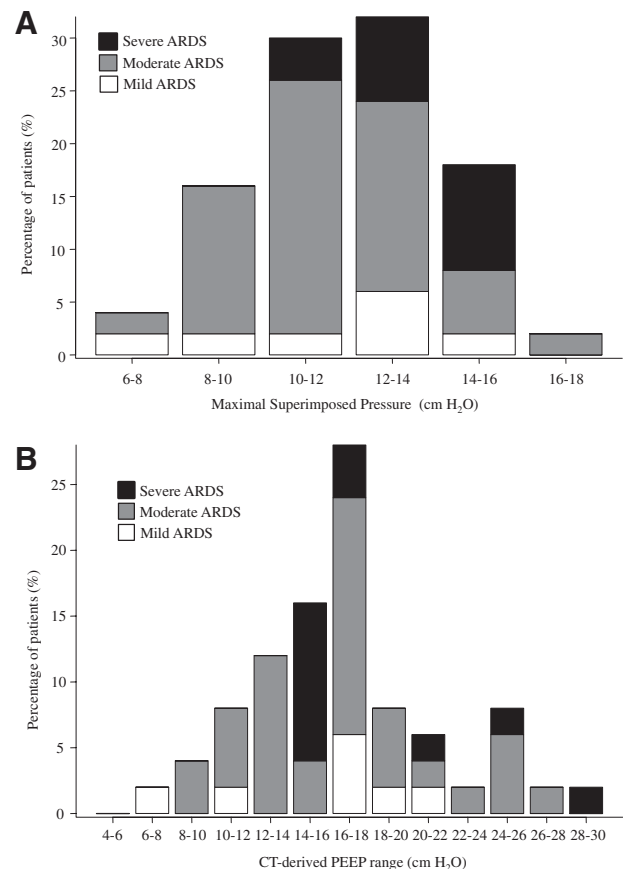


Fig. 2. Frequency distribution of maximal superimposed pressure and computed tomography (CT)-derived positive end-expiratory pressure (PEEP). (A) Presents the distribution of maximal superimposed pressure. Mild acute respiratory distress syndrome (ARDS) is shown with *white bars*, moderate ARDS with *gray bars*, and severe ARDS with *black bars*. Maximal superimposed pressure was computed dividing each lung in 10 sections along the apex-basis axis thus obtaining 20 different values of superimposed pressures and choosing the greatest one. (B) Presents the corresponding CT-derived PEEP levels (available in 50 patients). CT-derived PEEP was computed multiplying the maximal superimposed pressure times the ratio between chest wall and lung elastance. Mild ARDS is shown with *white bars*, moderate ARDS with *gray bars*, and severe ARDS with *black bars*.

with the Bonferroni correction. Significance level was set at $P = 0.05$. All tests are two tailed. The statistical analysis was performed with the R software (R Core Team [2013]. R: A language and environment for statistical computing; R Foundation for Statistical Computing, Vienna, Austria.).

Results

Maximal superimposed pressure ranged from 6 to 18 cm H₂O (fig. 2A), whereas the corresponding CT-derived PEEP levels ranged between 7 and 28 cm H₂O (fig. 2B). As shown the superimposed pressure and the CT-derived PEEP were widely distributed through the ARDS population and there was a tendency toward a small increase in superimposed pressure at the increase of ARDS severity, assessed according to Berlin definition. Actually the maximal superimposed pressure was 12 ± 3 cm H₂O in mild ARDS, 12 ± 2 cm H₂O in moderate ARDS, and 13 ± 1 cm H₂O in severe ARDS ($P = 0.0533$) resulting in similar levels of CT-derived PEEP (16 ± 5 cm H₂O in mild ARDS, 16 ± 5 cm H₂O in moderate ARDS, and 18 ± 5 cm H₂O in severe ARDS, $P = 0.48$).

Superimposed Pressure and Lung Recruitability

The relationship between the superimposed pressure and lung recruitability was weak although statistically significant (fig. 3A). In contrast, when we plotted the recruitability as a function of the CT-derived PEEP, we could not find any relationship (Spearman $\rho = -0.02$, $P = 0.90$) (fig. 3B), likely due to the variability of the ratio between respiratory system and lung elastance which, in these patients, averaged 1.38 ± 0.28 , ranging from 1.01 to 2.06.

Regional Analysis: Apex-base Sections

Figure 4A shows the regional distribution of the lung tissue compartments we defined (consolidated [not recruitable at 45 cm H₂O end-inspiratory pressure] and recruitable [openable at 45 cm H₂O end-inspiratory pressure], poorly inflated, well inflated, and overinflated) in 10 sections along the apex-base axis when patients were divided according to the median lung recruitability (15% of total lung weight). Patients with higher recruitability showed at 5 cm H₂O PEEP a greater anatomical ARDS severity presenting lower end-expiratory lung volume, a greater fraction of noninflated tissue, and lower fraction of well-inflated tissue which is reflected by greater shunt fraction and a trend toward increased dead-space fraction (tables 1 and 2). Figure 4B shows the superimposed pressure compressing each lung section and the corresponding CT-derived PEEP necessary to overcome the compression and lift up the chest wall. The difference between higher and lower recruiters, limited to 1 to 2 cm H₂O, was only statistically significant in sections 2 to 7, and these differences vanished when considering the corresponding CT-derived PEEP, due to the variability added by the chest wall elastance. See Supplemental Digital Content 1, <http://links.lww.com/ALN/B65>, for a version of figure 4

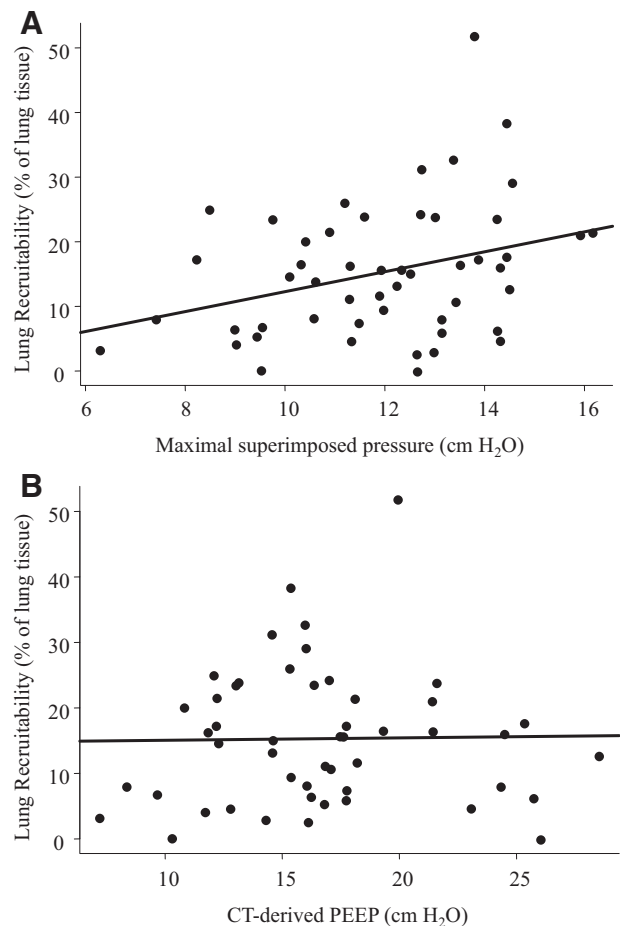


Fig. 3. Relationship between lung recruitability, maximal superimposed pressure, and computed tomography (CT)-derived positive end-expiratory pressure (PEEP). (A) Presents the relationship between lung recruitability and maximal superimposed pressure. Lung recruitability (% of total lung weight) = $-3.2 + 1.54 \times \text{Maximal superimposed pressure (cm H}_2\text{O)}$, $r^2 = 0.11$, $P = 0.02$. Lung recruitability was computed as the fraction of lung tissue which regains inflation going from PEEP 5 to 45 cm H₂O end-inspiration. (B) Presents the relationship between lung recruitability and CT-derived PEEP. Lung recruitability (% of lung weight) = $14.7 + 0.037 \times \text{CT-derived PEEP (cm H}_2\text{O)}$, $r^2 = 0.0003$, $P = 0.91$. CT-derived PEEP was available in 50 patients. As the figure presented one outlier, we tested the relationship between the two variables also with the Spearman correlation coefficient which was not statistically significant ($\rho = -0.02$, $P = 0.90$).

and table 1 using 9% recruitability threshold for defining higher and lower recruiters.

CT-derived PEEP and Bedside PEEP Methods

Computed tomography-derived PEEP was unrelated with the PEEP levels selected by the four bedside PEEP-selection methods tested. The individual regression between CT-derived PEEP and bedside PEEP-selection method is reported in Supplemental Digital Content 1, figures 2–6, <http://links.lww.com/ALN/B65>. CT-derived PEEP was on average higher than PEEP levels selected by bedside

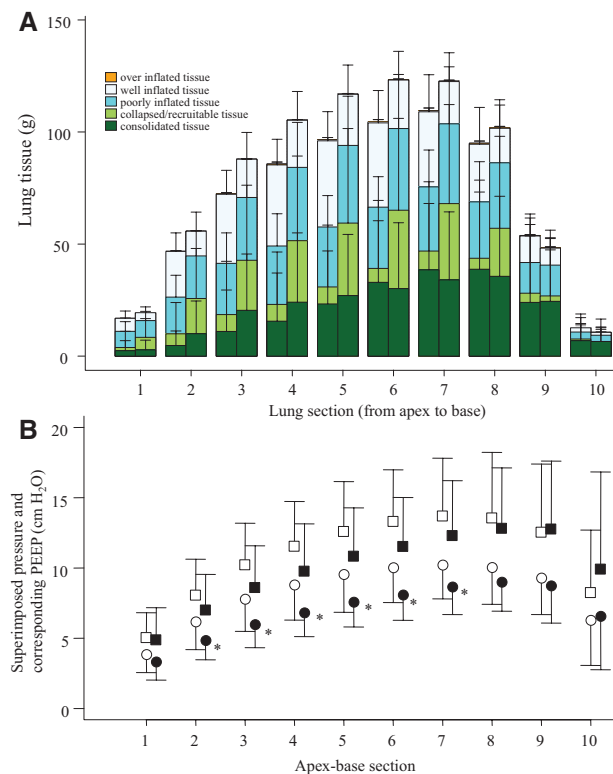


Fig. 4. Tissues distribution, superimposed pressure, and positive end-expiratory pressure (PEEP). (A) Presents the distribution of recruitable tissue (nonaerated at PEEP 5 cm H₂O and inflated at 45 cm H₂O airway pressure), consolidated tissue (not aerated both at PEEP 5 and 45 cm H₂O airway pressure), poorly inflated, well inflated, and overinflated. Each pair of bars represents a lung section; the right bars refer to higher recruiter and the left bars refer to lower recruiters. To define higher and lower recruiters, patients were divided according to the median lung recruitability (15%). Data were taken at PEEP 5 cm H₂O. (B) Presents the superimposed pressure compressing each lung section (circles) and the corresponding PEEP (squares). Black indicates lower recruiters and white higher recruiters. Data were taken at PEEP 5 cm H₂O. Values are mean and SD. We performed a two-way repeated-measures ANOVA using the maximal superimposed pressure as dependent variable and patient classification (recruiter vs. nonrecruiter) and sternum-vertebral level (from 1 to 10) as classification factors ($P < 0.0001$ for both the effect of recruiters/nonrecruiter and sternum-vertebral axis, $P = 0.07$ for interaction). *Post hoc* analysis was performed with the Bonferroni correction comparing higher and lower recruiters at each sternum-vertebral level (a total of 10 multiple comparisons were performed). A second two-way repeated-measures ANOVA was performed using as dependent variable the computed tomography-derived PEEP levels and as classification factors patient classification (recruiter vs. nonrecruiter) and sternum-vertebral level (from 1 to 10) as classification factors ANOVA ($P < 0.0001$ for both the effect of recruiters/nonrecruiter and sternum-vertebral axis, $P = 0.05$ for interaction). *Post hoc* analysis was performed with the Bonferroni correction comparing higher and lower recruiters at each sternum-vertebral level (a total of 10 multiple comparisons were performed). * $P < 0.05$ between higher and lower recruiters.

PEEP-selection methods both in higher recruiters and lower recruiters except for ExPress and Stress Index methods, which in lower recruiters, selected PEEP levels similar to the CT-derived PEEP (table 3).

Discussion

The primary finding of this study is that, in contrast with our hypothesis, the relationship between the superimposed pressure and lung recruitability was extremely weak and vanished when we considered the CT-derived PEEP instead of the superimposed pressure. Therefore, this study indicates that the average PEEP needed in patient with ARDS to keep their lung open is approximately the same (approximately 16 cm H₂O) independently on the fact that the amount of tissue to be kept open is as low as 3% or as high 50% of the total lung weight, the range of recruitability we found in the present study. The clinical issue, however, as we will discuss below, is if it is clinically advisable to use such levels of PEEP when recruitability is very low. The concept underlying the CT scan-derived PEEP is that the primary cause of lung collapse in ARDS is the superimposed pressure.^{16–19,21,38} As the superimposed pressure, in turn, is mainly determined by the lung weight¹⁶ which is also positively associated with lung recruitability,¹⁰ the lack of association between recruitability and CT-derived PEEP was unexpected. Therefore, before discussing the clinical implications of these findings, we should understand why at similar compressive forces (fig. 3B) the recruitability may be so different among the patients.

A possibility is that the computation of superimposed pressure and CT-derived PEEP is an unrealistic theoretical construction. In fact, the superimposed pressure is computed as if the lung would behave as a fluid, an approach known as “fluid-like model.” Undoubtedly, the lung is not a fluid otherwise it would collapse at a given isogravitational plane. Although this does not occur, there is consistent evidence that the gravitational forces play a role in decreasing the alveolar size in the dependent lung regions of normal subjects and in inducing the lung collapse in patients with ARDS. A gravitational gradient of lung inflation in normal subjects has been shown decades ago³⁹ and more recently by the CT scan,^{16,40} suggesting that the alveolar size may decrease according to gravity. In fact, we found that the pleural pressure gradient found reportedly in normal subjects paralleled the superimposed pressure measured by the CT scan. Moreover, the pleural pressure measured directly in experimental animals at different lung heights was coincident with the superimposed pressure computed by the CT scan at that heights.¹⁸ Finally, we found that PEEP keeps open a given lung region only when it overcomes the pressure superimposed to that region.¹⁹ This has been shown in ARDS by constructing a regional volume–pressure curve and finding that the PEEP necessary to keep open the lung region was coincident with the pressure measured at the expiratory inflection point of such curves.¹⁹ Therefore, we believe that a “sponge-like model”¹⁴ for which a wet sponge

Table 1. Main Characteristics of Patients Divided According to the Median Lung Recruitability

	Whole Population (51 Patients)	Lower Recruiters (26 Patients)	Higher Recruiters (25 Patients)	P Value
Body mass index (kg/m ²)	27 ± 6	29 ± 8	26 ± 3	0.14
Age (yr)	61 ± 16	60 ± 17	61 ± 16	0.83
Sex, number of male patients (%)	38 (75)	20 (77)	18 (72)	0.93
Days elapsed before CT scan	5 ± 7	7 ± 8	3 ± 3	<0.01
ICU survival, number (%)	21 (41)	17 (65)	13 (52)	0.40
Tidal volume (ml)/kg ideal body weight (ml/kg)	7.7 ± 1.9	7.7 ± 2.2	7.7 ± 1.6	0.41
Respiratory rate (breaths/min)	17 ± 4	18 ± 3	16 ± 3	0.03
Plateau pressure (cm H ₂ O)	18.7 ± 4.2	17.8 ± 3.8	19.6 ± 4.4	0.11
Mean airway pressure (cm H ₂ O)	10.9 ± 1.5	10.4 ± 1.1	11.3 ± 1.7	0.11
Lung elastance (cm H ₂ O/l)	20.3 ± 8.1	19.0 ± 8.7	21.5 ± 7.4	0.09
Chest wall elastance (cm H ₂ O/l)	6.8 ± 4.3	6.4 ± 3.6	7.1 ± 4.9	0.92
Intraabdominal pressure (cm H ₂ O)	9 ± 3	8 ± 3	9 ± 3	0.53
Pao ₂ /Fio ₂	144 ± 53	154 ± 46	133 ± 58	0.16
Pao ₂ (mmHg)	68 ± 13	68 ± 12	68 ± 14	0.84
Fio ₂	0.53 ± 0.19	0.47 ± 0.14	0.59 ± 0.21	0.04
Paco ₂	45 ± 7	45 ± 7	46 ± 8	0.90
Physiological dead space (%)	57 ± 14	53 ± 14	60 ± 12	0.08
Shunt (%)	41 ± 12	36 ± 10	45 ± 13	<0.01
Sao ₂ (%)	91.6 ± 3.9	92.9 ± 3.1	90.3 ± 4.2	0.03
Svo ₂ (%)	71.9 ± 7.3	72.1 ± 7.8	71.6 ± 6.8	0.78
Oxygen extraction ratio	0.22 ± 0.07	0.22 ± 0.08	0.21 ± 0.06	0.37
Cause of lung injury, number (%)				0.25
Pneumonia	26 (51)	10 (40)	16 (62)	
Sepsis	9 (18)	6 (24)	3 (12)	
Aspiration	5 (10)	2 (8)	3 (12)	
Trauma	5 (10)	3 (12)	2 (2)	
Other	6 (12)	5 (20)	1 (4)	

The table summarizes the main physiological data collected at 5 cm H₂O end-expiration. Plus-minus values are means ± SD. Because of rounding percentages may not total 100. The body mass index is the weight in kilogram divided by the square of the height in meters. Normality of variables was checked with the Shapiro-Wilk test. *P* values were obtained with Student *t* test, Wilcoxon test, chi-square test, or Fisher exact test, as appropriate. Days elapsed before CT scan were counted from ICU admission to the CT scan acquisition. Physiological dead space was available in 47 patients, 24 lower recruiters, and 23 higher recruiters. The intraabdominal pressure was measured as intrabdominal pressure injecting 100 ml of normal saline preheated at body temperature and was available in 49 patients (24 higher recruiters and 25 lower recruiters).

CT = computed tomography; Fio₂ = inspired oxygen fraction; ICU = intensive care unit; Paco₂ = arterial partial pressure of carbon dioxide; Pao₂ = arterial partial pressure of oxygen; Sao₂ = hemoglobin saturation in arterial blood; Svo₂ = saturation in venous blood sampled from a central vein.

in part collapses under its own weight reasonably reflects the ARDS lung behavior and provides a pragmatic explanation of many observations in normal and ARDS lung, including the immediate redistribution of lung collapse when shifting the patient from supine to prone position.^{21,38} The importance of superimposed pressure has been challenged by Hubmayr²⁵ who proposed different mechanisms to explain the CT scan findings, including recruitability, consolidation, and collapse. In extreme summary, Hubmayr speculated that the alveoli are not collapsed but flooded and that recruitment and inflation may occur at unknown alveolar pressure, which moves the alveolar liquid together with trapped gas, which behaves as unstable foam. Moreover, regional pleural pressure variations may occur in different lung units due to the necessity of matching the lung, considered as a gel, to the chest wall cavity at the same volume. Our “fluid-like” model and the “gel-foam” model, however, are just models with their bias and merits. We believe, however, that our model reasonably explains most of the observations done in ARDS,

in particular, the density redistribution in prone position, although we all recognize that a lung is neither a fluid nor foam or gel.

The way we computed the CT-derived PEEP may be also questioned as we assumed that the regional chest wall elastance is measured accurately by the esophageal pressure changes^{26,41} and that it is similar in the different regions of the chest wall. We are aware that it is unlikely but the esophageal pressure method is the only available method to estimate the chest wall elastance and its regional differences cannot be measured in a clinical scenario. Therefore, if the superimposed pressure, with its limitations, is the best available explanation to justify the collapse of the dependent lung regions, it follows that the CT-derived PEEP should be the best quantitative approach to compute the pressures necessary to keep the lung open at end-expiration.

The CT scan is, to date, the definitive standard for measuring the lung recruitability.¹⁰ In this study population of 51 patients, the median recruitability was 15% (interquartile

Table 2. Main CT Scan Characteristics of Patients Divided According to the Median Lung Recruitability

		Whole Population (51 Patients)	Lower Recruiters (26 Patients)	Higher Recruiters (25 Patients)	P Value
Lung recruitability (%)		15 ± 10	7 ± 4	23 ± 8	<0.0001
Lung recruitability (% of not inflated tissue)		35 ± 20	22 ± 12	49 ± 17	<0.0001
Maximal superimposed pressure (cm H ₂ O)		12 ± 2	11 ± 2	13 ± 2	0.05
CT-derived PEEP (cm H ₂ O)		17 ± 5	16 ± 6	17 ± 4	0.80
CT scan compartment	Airway pressure, cm H ₂ O				
Total tissue (g)	5	1,484 ± 487	1,388 ± 369	1,584 ± 576	0.15
	45	1,491 ± 484	1,435 ± 401	1,549 ± 559	0.29
Total gas (ml)	5	1,245 ± 588	1,533 ± 552	945 ± 468	<0.001
	45	2,910 ± 975	3,249 ± 800	2,558 ± 1,029	<0.01
Lung density (g/ml)	5	0.55 ± 0.14	0.48 ± 0.10	0.63 ± 0.13	<0.0001
	45	0.35 ± 0.11	0.31 ± 0.06	0.39 ± 0.13	0.02
Not inflated tissue (%)	5	43 ± 16	35 ± 14	50 ± 14	<0.001
	45	27 ± 13	27 ± 12	27 ± 14	0.95
Poorly inflated tissue (%)	5	29 ± 11	28 ± 9	30 ± 13	0.84
	45	26 ± 12	21 ± 6	31 ± 14	<0.01
Well-inflated tissue (%)	5	28 ± 14	36 ± 11	20 ± 11	<0.0001
	45	43 ± 14	48 ± 12	38 ± 14	<0.01
Overinflated tissue (%)	5	0 ± 1	0 ± 1	0 ± 0	0.04
	45	4 ± 4	4 ± 3	3 ± 4	0.22

The table summarizes the main CT scan data standardized at PEEP 5 cm H₂O and the CT scan data at 45 cm H₂O end-inspiration. Plus-minus values are means ± SD. Because of rounding, percentages may not total 100. Normality of variables was checked with the Shapiro-Wilk test. *P* values were obtained with Student *t* test or Wilcoxon test, as appropriate.

CT = computed tomography; PEEP = positive end expiratory pressure.

range 7 to 21%) of total lung tissue. This value is higher than the one we previously found in 68 patients with ARDS applying the same methodology of measurement and computation, likely because the overall greater severity of the present population compared with the previous one (P_{aO_2}/F_{iO_2} 144 ± 53 *vs.* 200 ± 77 mmHg [$P < 0.0001$], noninflated tissue 43 ± 16 *vs.* 37 ± 16%, $P = 0.04$). What is important to point out, however, is that in this population, as well as in the previous one, we found that lung recruitability among other factors as nature and time course of ARDS was associated to the lung weight. This is consistent with the “sponge model”: greater is the lung weight, greater the collapse will be.

Indeed, we have to discuss the relationship (or the lack of relationship) between the three variables on which we

concentrated our study: recruitability, superimposed pressure, and CT-derived PEEP. The difference in maximal superimposed pressure between higher and lower recruiters is limited to 1 to 2 cm H₂O, likely clinically irrelevant. However, we must consider that the superimposed pressure only relates to the lung density, independently on how and where the densities are generated. We may consider the consolidated tissue (pulmonary units filled with edema, cell, *etc.*) as due to the “core disease” and the recruitability (pulmonary units empty but collapsed) as due to the extent of surrounding inflammatory reaction. Accordingly, the ratio of recruitable to consolidated tissue should be somehow related to the ratio between the excess lung tissues outside the pulmonary units to inside. Let us consider two extreme

Table 3. CT-derived PEEP and Bedside PEEP Selection Methods

	Lower Recruiters (26 Patients)	Higher Recruiters (25 Patients)	P Values
CT-derived PEEP (cm H ₂ O)	16.6 ± 5.6	16.8 ± 4.0	1
ExPress method (cm H ₂ O)	15.2 ± 2.8	13.6 ± 2.7*	0.20
Stress Index method (cm H ₂ O)	14.7 ± 3.5	12.5 ± 2.5*	0.06
Absolute esophageal pressure method (cm H ₂ O)	12.4 ± 4.2*	12.7 ± 3.9*	1
LOV study method (cm H ₂ O)	10.3 ± 3.4*	12.8 ± 3.0*	0.04

Table summarizes the PEEP values selected in patients classified as lower and higher recruiters according to the median recruitability (15% of total lung tissue). We performed a two-way ANOVA for repeated measures using as dependent variable the PEEP level selected and as factors the PEEP-selection method and the patient classification (higher *vs.* lower recruiter). The effect of lung recruitability was not significant ($P = 0.76$), whereas the effects of the PEEP-selection method ($P < 0.0001$) and the interaction term were significant ($P < 0.01$). We performed *post hoc* comparisons to assess whether the PEEP levels selected were different between higher and lower recruiters and to compare the CT-derived PEEP with the PEEP values selected with bedside PEEP-selection method within lower and higher recruiters. All the *P* values of these multiple comparisons were corrected with the Bonferroni method.

* $P < 0.05$ *vs.* CT-derived PEEP.

CT = computed tomography; ExPress = Positive End-Expiratory Pressure Setting in Adults With Acute Lung Injury and Acute Respiratory Distress Syndrome; LOV = lung open ventilation; PEEP = positive end expiratory pressure.

hypothetical situations: an identical excess tissue mass totally confined outside the pulmonary units in the interstitial space or totally confined inside the pulmonary units: the superimposed pressure will be the same; however, in the first case, the whole lung is recruitable whereas in the second the recruitability is zero. These results are compatible also with the observation made by other groups^{42,43} that patients who exhibit a lobar pattern show prevalent intraalveolar distribution of edema and lower recruitability, whereas the patients with “diffuse” ARDS (and greater severity/edema) exhibit greater lung recruitability.

Therefore, we may conclude from our observations that the same PEEP is required to keep mechanically open the lung at end-expiration independently on the lung recruitability which likely depends on the nature of the disease, the time of observation, and on the extra mass distribution within the lung parenchyma (primarily intra- or extraalveolar). Interestingly, when we studied the relationship in the same patients between recruitability and the bedside PEEP-selection methods based on lung mechanics, we found that the selected PEEP was similar in patients with lower and higher recruitability.¹³

It is important to emphasize, however, that these findings do not imply that all patients with ARDS must be treated with the highest PEEP necessary to fully avoid whatever intratidal opening and closing. In fact, we may wonder whether it has any clinical sense to use PEEP values as high as 15 cm H₂O or greater, with all the clinical side effects, as hemodynamic impairment and need of volume load, to prevent the intratidal collapse when this phenomenon is limited to few grams of lung tissue, as in lower recruiters. In contrast, this level of PEEP appears reasonable if applied to prevent the intratidal opening and closing collapse of hundred grams of lung tissue, as in higher recruiters. Unfortunately, we do not know which is the threshold (if any) of intratidal opening and closing to produce ventilator-induced lung injury.

In summary, our study shows that the PEEP level necessary to keep the lung open mechanically, although variable between patients is, on average, in the range of higher PEEP (16 cm H₂O) and independent on lung recruitability. It does not provide any answer, however, on how to tailor clinically the PEEP level in a given patient, as we completely lack outcome studies, which tested higher *versus* lower levels of PEEP in an ARDS population stratified according to lung recruitability.

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Competing Interests

The authors declare no competing interests.

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