Positive end-expiratory pressure
Luciano Gattinoni\textsuperscript{a,b}, Eleonora Carlesso\textsuperscript{b}, Luca Brazzi\textsuperscript{a,b} and Pietro Caironi\textsuperscript{a,b}

\textsuperscript{a}Dipartimento di Anestesia, Rianimazione (Intensiva e Subintensiva) e Terapia del Dolor, Fondazione IRCCS – Ospedale Maggiore Policlinico Mario Negri Regina Elena \textsuperscript{b}d di Milano and \textsuperscript{b}Dipartimento di Anestesiology, Terapia Intensiva e Scienze Dermatologiche, Università degli Studi, Milan, Italy

Correspondence to Professor Luciano Gattinoni, MD, FRCP, Dipartimento di Anestesiology, Terapia Intensiva e Scienze Dermatologiche, Fondazione IRCCS – Ospedale Maggiore Policlinico, Maggiagalli, Regina Elena \textsuperscript{b}d di Milano, Via Francesco Sforza 35, 20122 Milan, Italy
Tel: +39 02 55032392; fax: +39 02 55032330; e-mail: gattinoni@policlinico.mi.it

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Purpose of review
In the last 2 years, several reports have dealt with recruitment/positive end-expiratory pressure (PEEP) selection. Most of them confirm previous results and few add new information.

Recent findings
It has been definitely confirmed that opening pressures are different throughout the acute respiratory distress syndrome lung parenchyma, ranging from 5–10 up to 30–40 cmH\textsubscript{2}O. The highest opening pressures are required to open the most dependent lung regions. It has been found that in 2 s, most of the recruitable lung regions may be open when a proper pressure is applied. The best way to assess recruitment is computed tomography scanning, whereas lung mechanics are a reasonable bedside surrogate. Impedance tomography has been increasingly tested, whereas gas exchange is the less reliable indicator of recruitment. A large outcome study showed that higher PEEP might provide survival benefit in a subgroup of more severe patients as compared with lower PEEP. To set PEEP in each individual patient, the use of the expiratory limb of the pressure–volume curve has been suggested. Setting PEEP according to transpulmonary pressure has a robust physiological background, although it requires confirmatory study.

Summary
Indiscriminate application of recruitment maneuver in unselected acute respiratory distress syndrome population does not provide benefits. However, in the most severe patients, recruitment maneuver has to be considered and higher PEEP applied. To individualize PEEP, the expiratory phase has to be considered, and the esophageal pressure measurement to compute the transpulmonary pressure should be progressively introduced in clinical practice.

Keywords
computed tomography scanning, esophageal pressure, lung recruitment, positive end-expiratory pressure, pressure–volume curve


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**Inspiratory recruitment, opening pressure, and time**

Recruitment is an inspiratory phenomenon and may be defined as the inflation of previously collapsed pulmonary units. To reopen the lung unit, a sufficient pressure must be applied. It has been shown, since several years [3], that the distribution of opening pressures throughout parenchyma of the lung is very wide (from 4–5 up to 30–40 cmH₂O or higher) and, according to computed tomography (CT) scan analysis, is Gaussian or bimodal [4].

However, Albert et al. [5*], in an interesting work on the temporal dynamics of alveolar recruitment, studied a model of induced lung injury in rats via saline lavage and visualized alveolar recruitment as a function of time for different pressures. The authors used an in-vivo microscope to measure alveolar recruitment as well as digital films to measure macroscopic gross lung recruitment. In both measurements, increasing pressure increased the percentage of lung recruitment. The authors commented that the curve was characterized by a considerable scatter, but certainly, it cannot describe the curve by a cumulative Gaussian. A wide scatter of opening pressure was also found by Grychtol et al. [6] who used, for recruitment assessment, impedance tomography in an experimental model of lung lavage. In addition, they found, as previously described [7,8], that the distribution of opening pressure likely depends on the anatomical region (lower in nondependent regions, higher in dependent ones).

For how long must a given opening pressure be applied? The issue has been studied by Albert et al. [5*] who recruited rat’s lung with 20, 30, or 40 cmH₂O for 40 s. They found that most of the gross lung recruitment occurred at 40 s after 2 s of pressure application, and developed a logical model to describe the lung opening as a function of applied pressure and time.

Therefore, the ‘physiology’ of recruitment is quite well described and depends on the presence of collapsed regions, their anatomical location, the extent of the required opening pressure, and the duration of the opening pressure application.

**Inspiratory recruitment: clinical assessment and impact**

Does the application of recruitment maneuver have any clinical impact? Before discussing the recent work on this issue, it may be worth recalling the prerequisite for lung recruitment. In fact, for the lung to be opened, it is necessary that a part of it is collapsed before the application of airway pressure. Why does the ARDS lung collapse? In general, the main reasons for lung collapse are gas re-absorption, surfactant deficit, and/or compressive forces, including gravity, for which the pulmonary units of the most dependent lung regions are compressed by the weight of the regions above. It follows that the greater is the lung edema, the greater is the weight and the regional collapse and, consequently, the greater is the lung recruitability. Indeed, the gravitational mechanism is likely the primary reason of lung collapse in human ARDS, whereas surfactant deficit and airway occlusion play a minimal role. Therefore, we may expect that recruitment maneuver is very effective when lung recruitability is high and less effective, or even nil and dangerous, when lung recruitability is low. Actually, in unselected patient population, lung recruitability is highly variable [9] and, as average, quite low. Not surprisingly, when Meade et al. [10] studied the effectiveness of recruitment maneuver in a clinical scenario, in a high percentage of patients, they found no effect or even deleterious effects.

Lung recruitment is correctly depicted as a gain of aeration of previously nonaerated lung tissue. CT scanning may easily detect and measure lung recruitability by applying, as an example, two different levels of airway pressure. However, in daily practice, CT scanning is rarely employed for clinical purposes and, even more rarely, is applied for quantification of lung recruitment. The open issue is, however, how to quantify lung recruitment at bedside. Two approaches are commonly used. The first one relies on pulmonary mechanics.

Traditionally, the pressure–volume curve has been used for this purpose, and the beginning of lung recruitment has been thought to occur at the lower inflection point, whereas the beginning of overdistension has been thought to occur at the upper inflection point. This model, however, is too simplistic, as it has been repeatedly shown by CT scan, either in humans or in animal models, that lung recruitment occurs along the entire pressure–volume curve. Jonson et al. [11] proposed to measure lung recruitment by computing the gas volume changes at the same pressure recorded by tracing two different pressure–volume curves starting from different PEEP levels. A slightly different approach implies the measurement of the hysteresis included between the inspiratory and the expiratory pressure–volume curves normalized either for predicted body weight [12] or for lung gas volume at total lung capacity [13]. Both methods concluded that pressure–volume curve hysteresis may be used to quantify lung recruitment. The problem is the identification of the gold standard method to quantify lung recruitment. Demory et al. [12] quantified it as the volume addition required to maintain 40 cmH₂O during recruitment maneuver, whereas Koefoed-Nielsen et al. [13], in a porcine model of oleic acid-induced ARDS, quantified lung recruitment as a difference of end-expiratory lung

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volumes before and after recruitment maneuver. Unfortunately, no reference to the real gold standard method (CT scanning) has been made. When we compared the pressure–volume curve hysteresis versus lung recruitment as measured by CT scanning, we could not detect any relationship [14].

A second tool largely employed to investigate the effectiveness of lung recruitment or, vice versa, the development of lung derecruitment, is by the detection of gas exchange variations. It must be pointed out, however, that variations of gas exchange are inadequate to assess lung recruitment as shown by comparing gas exchange with CT scan [15] and as anticipated decades ago by Dantzker et al. [16]. In their study, the authors clearly showed that the changes in gas exchange were primarily due to changes of cardiac output. It is in fact well known that a decrease in cardiac output (as always occurs during a recruitment maneuver) is associated with an increase in systemic arterial oxygenation (arterial partial pressure of oxygen, \( p_{aO_2} \)). Therefore, any advantage or disadvantage attributed to either lung recruitment or lung derecruitment as assessed by oxygenation changes (as frequently used in literature) must be considered with caution.

Therefore, in our opinion, lung CT scanning, to date, remains the gold standard for assessment of anatomical lung recruitment [15]. Nonetheless, other imaging technique, such as impedance tomography that has been used, in the last years, to evaluate lung volumes [17] as well as to analyze the regional distribution of alveolar ventilation and recruitment [18–23], is promising but still not applicable to clinical routine.

The assessment of lung recruitment by changes of compliance of the respiratory system or by pressure–volume curve taken at different pressures is probably the best bedside method now available, whereas oxygenation changes are inadequate to assess anatomical recruitment, being too dependent on the associated hemodynamic variations.

**Tailoring the end-expiratory pressure**

PEEP relates to the expiratory phase of the respiratory cycle, and it should keep the lung open by counteracting the compressive gravitational forces due to the lung weight. Therefore, as has been observed both in experimental models [24] and in humans [9], the response to PEEP is primarily a function of the extent of lung collapse, which, in turn, depends on the extent of lung edema. As the lung collapse is due to compressive forces along the sterno-vertebral axis in supine patients, it is obvious that in the nondependent lung regions (very close to the sternum), the lung collapse is near zero, while the compressive forces increase progressively from sternum to vertebra [7]. As a consequence, PEEP requirement is theoretically zero close to the sternum, while close to the vertebra, it has to be greater than the local compressive forces. In a normal size human, in whom the vertical height of the lung is approximately 15 cm, and the density of the lung during severe ARDS is around 0.7 g/cm³, the magnitude of the compressive forces is of the order of \( 15 \times 0.7 = 10.5 \text{cmH}_2\text{O} \). This pressure corresponds to the minimum requirement to counteract the compressive forces in the most dependent lung regions. Additional pressure must be added to lift up the thoracic cage. Therefore, if the elastics of the thoracic cage is normal, we may estimate that the PEEP applied to counteract the compressive forces of the lung and to lift up the thoracic cage in severe ARDS is around 15 cmH₂O or greater. These, at the moment, are theoretical considerations, although based on robust physiological background.

As the compressive forces and the chest wall elastics are usually not assessed in clinical practice, how should the PEEP be selected at the bedside? Over the last 30 years, several approaches have been proposed focusing first on lung mechanics (setting PEEP 2 cmH₂O greater than lower inflection point [25]), then analyzing the shape of the inspiratory pressure–time curve (linear, curvilinear, or concave, i.e., the stress index) [26], or considering the changing of the compliance of the respiratory system [27], and at the end testing the gas exchange variations, either focusing on oxygenation [4,28] or on CO₂ decrease, while maintaining unchanged total ventilation [29,30]. The three largest clinical studies on PEEP application have selected the PEEP level either focusing on gas exchange [ALVEOLI [31] and lung open ventilation (LOV) [32*]] studies or focusing on lung mechanics (ExPress Study [33*]). It is worth noting, however, that the average final PEEP found in the ‘lower’ and ‘higher’ PEEP groups resulted very similar, around 10–12 cmH₂O. These studies did not show any difference in outcome. However, in the last two studies (ExPress and LOV), it has been clearly shown that patients randomized to higher PEEP had a significantly lower rate of application of rescue therapy, finally leading to a survival benefit in the most severe ARDS [34**].

In the last few years, attention has been paid to the expiratory phase of the volume pressure curve as a tool for PEEP setting [30*,35–37]. The rationale of this approach is that, after lung opening (recruitment maneuver), the pressure to keep the lung open at a given volume is lower during the expiratory than during the inspiratory phase. However, this notion is not novel, as it has been previously called hysteresis and, more recently, closing pressure. With this approach, the PEEP value is selected according to the appearance of lung derecruitment during the expiratory phase. Unfortunately, the
pressure at which lung derecruitment is identified is the one at which the compliance decreases and/or the oxygenation/oxygen saturation decreases. Once again, both are arbitrary thresholds. Lambermont et al. [38], in a porcine oleic acid-induced ARDS model, measured the functional residual capacity (FRC) and the respiratory system compliance during a sequential PEEP ramp, changing PEEP from 20 to 0cmH\(_2\)O by 5cmH\(_2\)O stepwise reduction. They found that 20cmH\(_2\)O PEEP was associated with FRC and \(pao_2\) increase, while the maximal compliance value was obtained at 15cmH\(_2\)O, below which the compliance of the respiratory system and FRC progressively decreased. The authors discussed that the increase of FRC may indicate both lung recruitment and overdistension, and that the compliance change may discriminate between the two possibilities. Badet et al. [39] identified the best PEEP value using a decremental PEEP trial in 12 intubated and mechanically ventilated early ALI/ARDS patients. The best PEEP value was identified by a decrease in the ratio between \(pao_2\) and the inspiratory oxygen fraction (FiO\(_2\)) higher than 20% or, if there was no decrease, by the maximal \(pao_2\) value. The authors then tested three different strategies: the best PEEP alone, the optimal PEEP associated with sustained inflation, and the optimal PEEP associated with sighs ventilation (i.e., twice the basal tidal volume). They found that in the optimal PEEP associated with sighs, \(pao_2\) and compliance were significantly greater than those recorded in the other two groups. Passaro et al. [40], furthermore, investigated, in an experimental rat model of ALI, the effects of low and high levels of PEEP. They tested four different PEEP levels (1.5, 3, 4.5, and 6cmH\(_2\)O) at constant tidal volume without recruitment maneuver. They found that both lower and higher PEEP levels induced an increase in elastance and viscoelastic pressure, a worsening of systemic oxygenation, and an increase in procollagen type III (PCIII) mRNA expression. They concluded that PEEP selection titrated on the minimum elastance and the maximum oxygenation values may prevent lung injury, while deviation from these settings may be harmful.

An interesting study, although with all the limits recognized for ARDS experimental models, has been provided by Caramez et al. [30*]. They compared several methods for setting PEEP. The primary finding of the study is that dynamic tidal respiratory compliance, maximum \(pao_2\), maximum \(pao_2\) plus \(paco_2\), minimum shunt, inflation lower Pflex and point of maximal compliance increase on the inflation limb yielded similar values for open-lung PEEP. However, the open-lung PEEP values obtained using the deflation upper Pflex and the point of maximal compliance decrease on the deflation limb were significantly higher, whereas true inflection point on the deflation limb and \(paco_2\) were significantly lower than the other variables. Unfortunately, in this study, the gold standard technique to assess lung recruitment (CT scanning) has not been employed, as the authors arbitrarily chose the maximum dynamic compliance during a decremental PEEP titration as the reference.

Finally, the most innovative study that appeared on PEEP selection was provided by Talmor et al. [41**] and Sarge and Talmor [42]. They randomized 61 ARDS patients either to receive mechanical ventilation managed according to the ARDSnet trial or according to the esophageal pressure measurement. The authors hypothesized that the best PEEP to be applied was the one sufficient to maintain a positive transpulmonary pressure (i.e., esophageal pressure subtracted from airway pressure). The authors found that the \(pao_2/FiO_2\) at 72 h was 88mmHg higher in patients treated with esophageal pressure-guided mechanical ventilation as compared with the control group. Similarly, the respiratory system compliance appeared to be greater in the esophageal pressure-guided group than in the control group. Despite not finding any significantly different index of clinical outcome, they found, in a multivariate analysis corrected for Acute Physiology and Chronic Health Evaluation (APACHE) II score, a significant reduction in 28-day mortality in the esophageal pressure-guided group as compared with the control group. This study has a number of limitations and may be criticized primarily because it assumes that the esophageal pressure (with or without correction) equals the pleural pressure. We all know that this is not true, but, despite this limitation, Talmor et al. [41**] indicate a new physiological way for PEEP selection. In fact, the increased esophageal pressure observed in ARDS patients should be related to the compressive forces acting onto the lung parenchyma, which are the primary cause of collapse. Further studies are necessary to clear this issue, but the way is open.

**Conclusion**

Different opening pressures are present throughout the lung parenchyma, the highest in the most dependent lung regions. Most of the recruitable lung is open after 2 s of airway pressure application. CT scanning is still the gold standard technique for assessment of lung recruitment. However, lung mechanics is a better surrogate than gas exchange variations for assessment of lung recruitment at bedside. Promising tools, such as impedance tomography, are increasingly used and tested. The two largest outcome studies so far concluded suggested that higher PEEP should be preferred to lower PEEP in the most severe ARDS patients. Individual PEEP selection should be applied for considering the expiratory phase of the pressure–volume curve or, even better, the transpulmonary pressure.
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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

• • of special interest

• • • of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 77–78).


6 The authors studied and visualized alveolar recruitment as a function of time for different pressures. Interestingly, they found that most of the recruitable lung is open after 2 s of airway pressure application.


28 Giriš K, Hamed H, Khater Y, Kacmarek RM. A decremental PEEP trial identifies the PEEP level that maintains oxygenation after lung recruitment. Respir Care 2006; 51:1132–1139.


31 The authors compared different methods for PEEP selection at bedside analysing both respiratory and animal parameters in an animal model. The best dynamic tidal respiratory compliance was set as a ‘reference standard’. Maximum Pao2, maximum Pao2, and Pao2s min, shunt, inflation lower P0, and PmCo2 yield similar values for PEEP selection following a recruitment maneuver. Deflation upper P0 and the point of maximal compliance decrease on the deflation limb were significantly higher, and the true inflection point on the inflation limb and minimum Pao2 were significantly lower than the other variables.


34 A large, randomized clinical trial examining the effects of PEEP level in 983 ALI/ARDS patients. The control group was ventilated with target tidal volumes of 6 ml/kg IBW, plateau airway pressures not exceeding 30 cmH2O, and conventional levels of PEEP. The experimental strategy included target tidal volumes of 6 ml/kg IBW predicted body weight, plateau airway pressures not exceeding 40 cmH2O, O2 recruit- ment maneuvers, and higher PEEPs. The level of PEEP administered, either lower or higher, was selected according to an oxygenation scale conceptually similar to the one used in the previous ALVEOLI study. The authors did not find any significant difference in all-cause hospital mortality, barotrauma, and secondary outcome endpoints.


36 This is a large, randomized clinical trial on 767 ALI/ARDS patients. Patients were randomized either to a moderate PEEP strategy (minimal distension strategy) or to a level of PEEP to obtain 28–30 cmH2O airway plateau pressure (increased recruitment strategy). The authors did not find any mortality reduction in the increased recruitment strategy group. However, it improved lung function and reduced the duration of mechanical ventilation and of organ failure.


38 The authors performed an analysis of the latest large, international, randomized clinical trials on PEEP selection in ALI/ARDS patients, including subgroup analysis of the most severe patients. They concluded that random application of either higher or lower levels of PEEP in an unselected population does not significantly improve outcome. However, taking together LOT and ExPress studies, the number of patients with severe hypoxemia requiring rescue therapy in the higher PEEP level group was doubled compared with lower PEEP level group, suggesting that also the rate of pulmonary deaths was much lower. Taken together, the results suggest that the higher PEEP provides survival benefit in the most severe hypoxemic ARDS patients.


Respiratory system


The authors proposed an innovative PEEP selection method based on esophageal pressure measurement. The assumption was that esophageal pressure equals the pleural pressure. Accordingly, they hypothesized that the best PEEP to be applied was the one sufficient to maintain a positive transpulmonary pressure to avoid repeated alveolar collapse or overdistension.