Fifty Years of Research in ARDS
Setting Positive End-expiratory Pressure in the Acute Respiratory Distress Syndrome

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Abstract:

Positive end-expiratory pressure (PEEP) has been utilized during mechanical ventilation since the first description of the acute respiratory distress syndrome (ARDS). In the subsequent decades, many different strategies for optimally titrating PEEP have been proposed. Higher PEEP can improve arterial oxygenation, reduce tidal lung stress and strain, and promote more homogenous ventilation by preventing alveolar collapse at end expiration. However, PEEP may also cause circulatory depression and contribute to ventilator-induced lung injury through alveolar overdistention. The overall effect of PEEP is primarily related to the balance between the number of alveoli that are recruited to participate in ventilation and the amount of lung that is overdistended when PEEP is applied. Techniques to assess lung recruitment from PEEP may help to direct safer and more effective PEEP titration.

Some PEEP titration strategies attempt to weigh beneficial effects on arterial oxygenation and on prevention of cyclic alveolar collapse with the harmful potential of overdistention. One method for PEEP titration is a PEEP/FiO₂ table, which prioritizes support for arterial oxygenation. Other methods set PEEP based on mechanical parameters such as the plateau pressure, respiratory system compliance, or transpulmonary pressure. No single method of PEEP titration has been shown to improve clinical outcomes compared to other approaches of setting PEEP. Future trials should focus on identifying patients who respond to higher PEEP with recruitment and on clinically important outcomes such as mortality.

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INTRODUCTION

In their landmark 1967 description of the acute respiratory distress syndrome (ARDS), Ashbaugh and colleagues noted the benefit of applying positive end-expiratory pressure (PEEP) for improving arterial oxygenation in five of their patients. (1) Two years later, they reported that continuous positive pressure breathing with PEEP levels of 7-10 cm H$_2$O improved arterial oxygenation and reduced pulmonary edema in fourteen patients with ARDS. (2) Early clinical practices were guided by this and other case reports in which PEEP was used to improve arterial oxygenation and reduce the fraction of inspired oxygen (FiO$_2$). However, intensive care physicians and physiologists soon recognized the potential adverse effects of PEEP, including barotrauma and circulatory depression. In the 50 years since the first report of ARDS, numerous approaches to setting PEEP have evolved. The recognition of ventilator-induced lung injury (VILI) and the potential role that PEEP plays in mitigating VILI shifted the goals of PEEP from improving arterial oxygenation to preventing VILI. This review examines the physiologic rationale and evidence for the various approaches to setting PEEP.

MECHANISMS OF VENTILATOR-INDUCED LUNG INJURY

Mechanical ventilation causes VILI by applying excessive force to the lung parenchyma. It was recognized in early clinical practices that high airway pressures and tidal volumes could cause gross macroscopic injury such as pneumothorax or pneumatoceles. (3) Subsequent studies in experimental models demonstrated that high inspiratory pressures and volumes could cause alveolar overdistention which result in inflammation, interstitial and alveolar edema,
hemorrhage, and hyaline membranes. (3-6) Moreover, pulmonary inflammation resulting from injurious ventilation can cause cellular damage in other organs, suggesting that VILI may contribute to multi-organ failure (“biotrauma”).(7)

VILI may also occur from ventilation at low end-expiratory lung volumes (Figure 1). At low lung volume, unstable lung units may open with inspiration and collapse with expiration. This can impair surfactant function and cause stress at points of opening and closing in small airways and alveoli.(8) Large differences in lung unit inflation (“inhomogeneities”) at the margins between aerated and atelectatic alveoli can significantly amplify lung stress. (9) Some small airways may fill with fluid or foam at low lung volumes,(10) preferentially distributing tidal ventilation to aerated lung regions resulting in regional overdistention. Moreover, liquid bridges in small airways may break under pressure during inspiration and re-form during expiration. The high surface tension forces involved with such cyclic breaking and reforming can damage the epithelium of involved airways. Lung derecruitment at low lung volumes also reduces the volume of lung available for tidal ventilation, increasing stress and strain in the ventilated “baby lung”.(11) The significance of this latter mechanism is supported by experimental and clinical observations suggesting that lung injury primarily occurs within the ventilated lung regions.(6, 12)

**BENEFICIAL EFFECTS OF PEEP**

Ashbaugh and colleagues initially hypothesized that PEEP ameliorated hypoxemia by counteracting alveolar collapse resulting from inadequate surfactant function.(1, 13) Subsequent studies confirmed that PEEP improves arterial hypoxemia primarily by recruiting
collapsed lung and thereby reducing intrapulmonary shunt. (14) Numerous studies in experimental models have demonstrated that PEEP can mitigate VILI by keeping some alveoli open that would otherwise become atelectatic or flooded at end-expiration (recruitment). (4, 8, 15, 16) This prevents possible injury resulting from cyclic lung opening and closing. (17) It additionally increases the number of aerated alveoli participating in tidal ventilation, reducing tidal lung stress and strain, which is reflected by improved lung compliance. (18, 19) Promoting more homogenous ventilation could also reduce the stress and injury at the margins between aerated and collapsed lung tissue. (9, 20)

HARMFUL EFFECTS OF PEEP

Although low levels of PEEP can improve cardiac output (21), above a certain threshold level of pressure, PEEP may reduce cardiac output. (22, 23) PEEP increases pleural pressure, elevating right atrial pressure and reducing the pressure gradient for venous return. (22, 24, 25) Diminished venous return decreases right and left ventricular preload, causing decreased cardiac output. PEEP may also increase pulmonary vascular resistance by narrowing or occluding alveolar septal vessels, which are surrounded by alveolar pressure, even when using low tidal volumes. (26) Increased pulmonary vascular resistance elevates right ventricular afterload, which may further reduce cardiac output. (27, 28) PEEP can also increase alveolar dead space by increasing the volume of lung in which alveolar pressure exceeds pulmonary capillary pressure. (21)

The hemodynamic consequences of PEEP are often overtly apparent at the bedside, whereas its adverse effects on the lung parenchyma may be more insidious. PEEP may also contribute to
VILI by increasing lung stress and strain. The application of PEEP may result in predominant alveolar recruitment, predominant alveolar overdistention, or a combination of both recruitment and overdistention. If increases in PEEP fail to adequately recruit collapsed alveoli to participate in tidal ventilation, both dynamic and end-inspiratory lung stress will increase. The resulting alveolar overdistention may propagate lung inflammation and injury, similar to the effects of excess tidal volume. The net effect of PEEP on recruitment, overdistention, and hemodynamics will depend on the level of PEEP that is applied as well as the size of the associated tidal volume. Consequently, lung recruitability is a crucial determinant of the effect of PEEP on the injured lung. (17, 29)

ASSESSING THE EFFECT OF PEEP ON LUNG RECRUITMENT

Given these mechanistic considerations, the ratio of benefit to harm from PEEP depends on the amount of lung that can be recruited by raising PEEP, which varies widely among patients with ARDS. (30) Increases in PEEP will raise total end-inspiratory lung stress in both high and low recruiters. However, in patients with greater recruitability, much of the increase in end-expiratory lung volume (EELV) with PEEP arises from opening of collapsed lung units. This reduces cyclic lung collapse and reopening. It also reduces dynamic strain in aerated lung units due to an increase in aerated volume available for tidal volume distribution. In contrast, in patients with low recruitability, PEEP causes additional distention of already aerated lung tissue, which could lead to overdistention injury, without a concomitant decrease in dynamic strain. (17) Thus, an assessment of an individual’s potential for recruitment could allow for the personalization of PEEP titration to improve the chances for benefit rather than harm. In support of this hypothesis, a secondary analysis of two trials of higher versus lower PEEP
strategies found that the oxygenation response following increases in PEEP, a marker (albeit imperfect) of lung recruitment, predicted lower mortality. Patients with greater improvements in oxygenation were less likely to die compared to patients with little or no improvement in oxygenation with PEEP. (31) This finding provides tentative clinical evidence that higher PEEP levels are of benefit when lung recruitment is achieved. Conversely, applying higher PEEP in the absence of lung recruitment was associated with worse outcomes. The lung recruitment hypothesis ultimately requires prospective confirmation in a randomized trial comparing the impact of higher versus lower PEEP in patients with and without lung recruitability. (32) Such trials, however, would require a practical and feasible means of assessing lung recruitability at the bedside.

**Techniques for Monitoring Lung Recruitment**

The volume of derecruited lung is correlated with intrapulmonary shunt, and improvements in arterial oxygenation with increased PEEP therefore often reflect lung recruitment. (30, 33-35) However, arterial oxygenation is also influenced by other factors affected by PEEP (i.e. cardiac output), so the correlation is imperfect. A seminal study of lung recruitment in ARDS patients found that a combination of physiologic variables (\(\text{PaO}_2/\text{FiO}_2 < 150\) at a PEEP of 5 cm H\(_2\)O, a decrease in dead space and an increase in respiratory system compliance (\(C_{RS}\)) with an increase in PEEP to 15 cm H\(_2\)O) predicted a higher percentage of potentially recruitable lung. (30)

Computerized tomographic scanning can define regions of lung tissue with different voxel densities, which are interpreted to indicate tissue compartments that are well-aerated, poorly aerated, and non-aerated. (30) By comparing CT images at different PEEP levels, the amount of
lung tissue that is recruited at a higher PEEP in relation to the baseline lung volume can be estimated. This approach may be a scientifically rigorous method for assessing recruitment in clinical research, but it is probably too cumbersome, costly, and risky for use in usual care.

Helium dilution or nitrogen washout techniques have been employed to measure changes in EELV at different PEEP levels. The increase in EELV from a lower to a higher PEEP level is first estimated from the product of the change in PEEP and the \( C_{RS} \) measured at the lower PEEP level. If the change in EELV measured by helium dilution or nitrogen washout exceeds the predicted change in EELV, the difference is presumed to be from recruitment. Lung recruitability can be assessed in a similar fashion using electrical impedance tomography (EIT), which permits real-time visualization of changes in the distribution of pulmonary ventilation as PEEP is adjusted. Comparison of actual and predicted increases in lung impedance following an increase in PEEP permit estimates of recruited lung volume.

A third method for assessing recruitability, which can also be conducted at the bedside, requires construction of airway pressure-volume curves during tidal ventilation at different PEEP levels. After a pressure-volume curve is established at a given PEEP level, the airway is opened to atmospheric pressure for a prolonged exhalation to functional residual capacity. Measurements of the exhaled volumes at different PEEP levels to functional residual capacity allow curves to be plotted on the same axes, with the origin at functional residual capacity and airway pressure of zero. The amount of recruitment that occurs when PEEP is raised from the lower to the higher PEEP level is assumed to be the difference in volume between the two curves at a given airway pressure (Figure 2).
Estimates of recruitability from pressure-volume curves and from helium dilution are strongly correlated with each other but both are poorly correlated with estimates of recruitability obtained from CT scanning. (40) This may be attributable to the fact that CT measures the opening of previously collapsed lung units, while techniques based on respiratory mechanics measure the volume of gas entering newly recruited lung units along with previously open units. (41) Additionally, methods that use measurements of EELV, such as CT or gas dilution, allow recruited lung volume to be calculated as a percentage of the baseline lung volume. The multiple P-V curve method does not allow for this reference, which limits the interpretation of the amount of recruited lung volume.

**APPROACHES TO SETTING PEEP AT THE BEDSIDE**

**Balancing Risks from Higher FiO$_2$ with Higher PEEP**

Earlier clinical practices were guided by the observation that, in most ARDS patients, arterial oxygenation goals could be achieved by applying PEEP levels of 5 to 12 cm H$_2$O with FiO$_2$ levels less than or equal to 0.7. (1, 2) This approach attempted to balance potential harms from alveolar overdistention and circulatory depression due to high PEEP with concerns about oxygen toxicity (42, 43), but clinicians attempted to strike this balance in many different ways. Some preferred to raise FiO$_2$ to high levels before raising PEEP above 5 cm H$_2$O, while others raised PEEP to high levels before raising FiO$_2$ above 0.50. In the National Institutes of Health ARDS Network tidal volume trial, PEEP and FiO$_2$ were adjusted in discrete steps according to a table of PEEP and FiO$_2$ combinations (Table 1A). (44) This table was developed in 1995 and represented a compromise among clinicians’ approaches at a time when there was little
consideration for the potential protective effect of PEEP against VILI. In light of growing appreciation for this important issue, the ARDS Network subsequently designed another PEEP/FiO$_2$ table employing PEEP levels on average 6 cm H$_2$O higher than those resulting from the use of the original table (Table 1B).(45) The Canadian Critical Care Clinical Trials Group also developed a similar higher PEEP/FiO$_2$ table. In two randomized clinical trials comparing the lower and higher PEEP/FiO$_2$ tables, mean arterial oxygenation increased in the higher PEEP groups, suggesting that there was greater recruitment with higher PEEPs.(45, 46) However, the oxygenation response to increased PEEP varied widely between individual patients.(31)

The use of PEEP/FiO$_2$ tables is advantageous in that they are readily implemented in routine clinical practice. However, they do not always suit clinical circumstances because some patients with severe hypoxemia have little or no improvement in oxygenation with higher PEEP. According to the table, to achieve acceptable arterial oxygenation in these patients, a higher PEEP must be applied before a higher FiO$_2$ can be used. PEEP/FiO$_2$ tables function well to increase average PEEP levels applied across patient populations, but do not necessarily guarantee optimal PEEP in individual patients.

**Opening the Lung While Avoiding Overdistention**

In another randomized clinical trial, PEEP was increased in a higher PEEP study group until inspiratory plateau pressure approached 28-30 cm H$_2$O.(47) This approach aimed to balance the potential beneficial effects of greater recruitment with the potential deleterious effects of higher PEEP on end-inspiratory lung stress and circulatory function. The higher PEEP strategy was compared to a “minimal distention” strategy that utilized PEEP levels of 5-9 cm H$_2$O. Similar
to the other large trials of higher PEEP, this study did not show a significant difference in mortality, although the higher PEEP strategy was associated with greater ventilator-free and organ failure-free days. Again, this strategy may not always arrive at optimal PEEP in individual patients. For example, a patient with mild ARDS and relatively little recruitable lung may have low baseline plateau pressures and would receive relatively high levels of PEEP, whereas a patient with more severe hypoxemia resulting from significant but potentially recruitable atelectasis will have a higher baseline plateau pressure and receive relatively lower PEEP levels.

**Optimizing Respiratory System Compliance (C\textsubscript{RS})**

Suter and colleagues originally proposed setting PEEP to maximize oxygen delivery (cardiac output multiplied by arterial oxygen content). In 15 patients with acute respiratory failure, maximum oxygen transport was attained at the PEEP associated with the highest static C\textsubscript{RS} \((21)\). Subsequent studies also suggested that PEEP titration guided by C\textsubscript{RS} was associated with improvements in organ function and oxygenation \((48, 49)\). However, these small, randomized trials were not adequately powered to assess mortality differences between groups. Additionally, cyclic opening and collapse of lung units with tidal insufflation may cause an increase in measured tidal compliance not related to the PEEP-induced end-expiratory recruitment, which may confound the assessment of the effect of changing PEEP \((34)\).

**Driving Pressure**

Driving pressure is the difference between airway inspiratory plateau pressure and PEEP. This pressure gradient is a mathematical function of the tidal volume and the C\textsubscript{RS} \((\text{driving pressure} = V_T/C_{RS})\). Because C\textsubscript{RS} is directly related to the size of the lung participating in ventilation (i.e. the
number of recruited lung units), driving pressure reflects the size of tidal volume in relation to the aerated lung volume. This may better reflect dynamic pulmonary stress and strain during mechanical ventilation. Given that PEEP ideally minimizes dynamic stress and strain by recruiting lung units to participate in ventilation, driving pressure is an attractive physiological target for PEEP titration.

A recent meta-analysis of over 3,000 patients enrolled in clinical trials of lung-protective ventilation strategies demonstrated that driving pressure was a strong predictor of mortality, with higher driving pressures associated with higher mortality. (50) Measuring driving pressure at different PEEP levels could be a practical way of assessing the balance between overdistention and opening-closing during tidal ventilation. With constant tidal volume, if PEEP is raised and driving pressure decreases, the $C_{RS}$ has decreased, suggesting that the higher PEEP caused lung recruitment. In contrast, if PEEP is raised and driving pressure increases, $C_{RS}$ has decreased, suggesting that higher PEEP caused overdistention of aerated lung. Thus, adjusting PEEP to minimize driving pressure may permit a personalized approach to minimize VILI. At a constant tidal volume, however, titrating PEEP to minimize driving pressure is equivalent to titrating PEEP to maximize $C_{RS}$. Thus this strategy may be similarly limited by observed increases in tidal compliance that are not secondary to recruitment. To obtain valid estimates of driving pressure, patients must be relaxed during pauses at end-inspiration. However, no specialized equipment is required to record and analyze airway pressure, and all modern ventilators readily permit these measurements. Prospective trials must be conducted to determine if titrating PEEP to reduce driving pressure can improve important clinical outcomes such as mortality.

**Titration Based on Pressure-Volume Curves**
Amato and colleagues constructed respiratory system pressure-volume curves in ARDS patients and set PEEP near the lower end of the middle, linear portion of the curve where the compliance is high, the so-called “inflection point”, to prevent VILI from alveolar opening and collapse at low airway pressures. (51, 52) Airway pressures above the inflection point on the pressure-volume curve are associated with a large gain in lung volume. Thus, this point was thought to indicate the pressure at which a large number of alveoli were recruited. (Figure 3)

There was a significant reduction in mortality in a lung-protective ventilation group in which PEEP was set with this approach compared to a conventional ventilation group in which PEEPs were approximately 6-8 cm H₂O lower. However, this higher PEEP strategy was combined with the use of lower tidal volumes in the lung-protective group, an intervention subsequently shown to reduce mortality apart from any effect of PEEP. (44) Therefore, it is uncertain whether the use of higher PEEP significantly contributed to the improved outcomes in that trial.

There are important limitations to using pressure-volume curves to set PEEP. Neuromuscular blockade or heavy sedation is required to avoid the effects of respiratory muscle activity. (53) The inspiratory limb of the pressure-volume curve is different from the expiratory limb, and tidal breathing probably occurs somewhere between the two curves, depending on the level of PEEP. In some patients, a lower inflection point cannot be identified. Furthermore, although substantial recruitment occurs over the lower portion of the curve, additional recruitment occurs at intermediate and even higher pressures and volumes. (34) In light of these limitations, static pressure-volume curves are rarely employed for clinical practice at present.

Stress Index
With a constant inspiratory flow (square waveform), the shape of the airway pressure-time relationship reflects changes in respiratory system compliance during inspiration. The stress index is a coefficient describing the rate of change in the slope of the pressure-time curve during tidal inspiration. If the slope of the pressure-time relationship increases during inspiration (stress index > 1), the respiratory system is becoming less compliant, perhaps from overdistention of the lungs. A decreasing slope of the pressure-time curve during inspiration suggests that the system is becoming more compliant (stress index < 1), perhaps from recruitment of alveoli that were atelectatic at end-expiration. PEEP can be adjusted to a level at which the stress index equals 1, indicating the slope of the pressure-time relationship changes minimally during inspiration. This suggests neither overdistention nor recruitment during inspiration or some balance between these two injurious forces. In 15 patients with predominantly lobar consolidation as opposed to diffuse opacifications, Grasso and colleagues compared the PEEP obtained using the ARDS Network lower PEEP/FiO₂ table with a strategy that adjusted PEEP according to stress index. In every patient, PEEP was lower when it was adjusted according to the stress index. The lower levels of PEEP based on stress index may have reflected baseline overdistention due to the patients having lobar consolidations and thus a lower likelihood of recruitment with PEEP. These lower PEEP settings were associated with higher respiratory system compliance, lower concentrations of inflammatory mediators in plasma, lower PaCO₂, and no significant change in arterial oxygenation. However, this approach requires specialized monitoring equipment to record and analyze the pressure-time relationship, limiting its adoption in clinical practice at present.

Estimating Transpulmonary Pressure
Many lung protective strategies, including the NIH ARDS Network lower tidal volume protocol, monitor airway pressures to avoid VILI. Airway pressure, however, is not always a reliable reflection of true lung stress. Conditions that increase chest wall elastance (e.g. edema, kyphoscoliosis, or abdominal hypertension) or shift the pressure-volume curve of the respiratory system or the chest wall to the right (e.g. obesity) will elevate airway pressure without an increase in lung stress (Figure 4). Consequently, clinicians may underestimate the PEEP required to achieve adequate lung recruitment because of concerns about high airway plateau pressures. Moreover, during exhalation, some lung regions, especially dependent areas, may collapse even with moderate levels of PEEP if pleural pressure is elevated. (57)

Transpulmonary pressure ($P_L$) is the pressure gradient from the airway to the pleural space. (58, 59) It more accurately reflects the stress on the lung parenchyma, independent of the chest wall. For example, if end-inspiratory $P_L$ remains within tolerable limits, it may be reasonable to consider exceeding conventional airway plateau pressure limits. Monitoring end-expiratory $P_L$ may also help to identify PEEP levels required to prevent cyclic alveolar collapse.

The major challenge to using $P_L$ to guide ventilator management is finding an accurate and practical method to estimate pleural pressure. Esophageal manometry is the most feasible means of obtaining such estimates. To measure esophageal pressure, an air- or liquid-filled catheter is positioned in the lower third of the esophagus. (58, 60) Esophageal pressure is thought to represent average pleural pressure in upright, healthy individuals. (61, 62) However, in supine, mechanically ventilated patients with ARDS, esophageal pressure rises by a variable amount because of dorsal shift of mediastinal contents and cephalad movement of the diaphragm. There is some controversy regarding the best method for utilizing esophageal
pressure to calculate $P_L$. Some investigators suggest using the absolute value of esophageal pressure (“direct measure”) with or without a correction factor to account for the weight of mediastinum and abdominal contents. (63, 64) Others investigators use the tidal change in esophageal pressure to partition lung and chest wall elastance, which can then be used to derive $P_L$ (“elastance-derived”). (65) Not surprisingly, the recommended PEEP levels obtained from the methods of estimating $P_L$ differ substantially. (66) Finally, it is not clear that a single value of esophageal pressure measured near the left lower lobe, even if it accurately reflects pleural pressure in that vicinity, can be used to represent average pleural pressure for all aspects of the lungs. (60, 67)

$P_L$ measurements have been utilized to titrate PEEP in patients with ARDS in a number of different ways. In a small study of patients with severe hypoxemia due to H1N1 influenza-associated ARDS, PEEP was increased until the maximum tolerable end-inspiratory elastance-derived $P_L$ was attained to prevent overdistention. (68) With this approach, approximately half of the patients experienced sufficient improvements in arterial oxygenation to be managed without extracorporeal membrane oxygenation, and none of these patients died. Talmor and colleagues titrated PEEP to maintain a positive end-expiratory $P_L$ (directly measured), to keep airways open at end-expiration and prevent tidal recruitment-derecruitment. In a randomized trial comparing this strategy to the ARDS Network lower PEEP/FiO$_2$ table, patients in the $P_L$-guided group had substantial improvements in arterial oxygenation. (57) The trial was not powered to compare mortality between the two groups, but there was a trend toward lower mortality in the $P_L$-guided group.

**PEEP Guided by Imaging**
An important cause of lung collapse during expiration in ARDS is from increased lung weight that compresses dependent lung regions.\(^{69, 70}\) CT scans allow regional analyses of compressive forces of lung weight at different vertical levels. The CT-derived PEEP is the sum of the superimposed pressures operating on the most dependent lung regions and the force necessary to expand the chest wall based on the chest wall elastance.\(^{71}\) Therefore, the CT-derived PEEP would hypothetically estimate the pressure necessary to keep the lung open, and it should in theory be related to the amount of recruitable lung. In a small study, however, CT scan-derived PEEP was unrelated to lung recruitability, and similar levels of PEEP were suggested in mild, moderate, and severe ARDS.\(^{71}\) Based on these results and the burdensome nature of performing serial CT scans in critically ill patients, it is unlikely that CT-derived PEEP will be useful in tailoring PEEP to individual patients in the clinical setting.

Lung ultrasound has been proposed as a practical bedside imaging alternative to CT scan to assess lung recruitment in response to PEEP. Improvement in an ultrasound re-aeration score significantly correlated with lung recruitment as measured by the pressure-volume curve method and with increases in arterial oxygenation.\(^{72}\) Ultrasound, however, cannot assess alveolar overdistention.

Electrical impedance tomography, as mentioned earlier, is an imaging technique that has been employed to titrate PEEP.\(^{73, 74}\) This technique permits concomitant monitoring of pulmonary blood flow distribution, V/Q matching, and can detect pneumothorax. While it holds promise, it has not yet been widely disseminated.

**COMPARISONS OF DIFFERENT PEEP STRATEGIES**
The three largest clinical trials of approaches to setting PEEP to date were comparisons of uniform higher versus lower PEEP strategies. None showed significant differences in mortality between the study groups.\(^{(45-47)}\) One possible reason for the lack of significant difference in mortality between study groups is that there was no attempt to identify patients who would respond to increases in PEEP with lung recruitment. Beneficial effects of higher PEEP in patients with substantial recruitability may have been counteracted by detrimental effects in patients with low recruitability, leading to an overall null result.\(^{(32)}\) This theory was supported by a subsequent individual patient data meta-analysis which found that PEEP improved survival in patients with moderate or severe ARDS ($\text{PaO}_2/\text{FiO}_2 \leq 200 \text{ mm Hg}$), who presumably have more recruitable lung.\(^{(75)}\) It also suggested that ventilation with higher PEEP might increase mortality in patients with mild ARDS.

Chiumello and colleagues tested four different bedside PEEP titration methods to identify the method that would best provide levels of PEEP in proportion to lung recruitability and severity of ARDS.\(^{(76)}\) PEEP titration strategies included the open lung approach limited by plateau pressure \(^{(47)}\), stress index \(^{(77)}\), transpulmonary pressure \(^{(57)}\), and an oxygenation strategy using a higher PEEP/\text{FiO}_2 table \(^{(46)}\). The PEEP/\text{FiO}_2 table was the only strategy that consistently provided higher PEEP levels in patients with severe ARDS and greater recruitability and provided lower PEEP levels in patients with mild ARDS and less recruitability. A secondary analysis of the data from 2 of the 3 clinical trials of higher PEEP further demonstrated that patients whose $\text{PaO}_2/\text{FiO}_2$ ratios increased with higher PEEP had lower mortality.\(^{(31)}\) This improvement in oxygenation may have represented recruitment in response to PEEP. Assessing
oxygenation response to higher PEEP may allow identification of patients more likely to benefit from a higher PEEP strategy for clinical management or recruitment in future clinical trials.

In a recent study, PEEP was set during a decremental PEEP maneuver to maximize respiratory system compliance. This was associated with significantly improved arterial oxygenation and lower driving pressures compared to patients whose PEEP was set according to the ARDS Network lower PEEP/FiO\textsubscript{2} table, but mortality was not significantly reduced.(78) Studies comparing respiratory system compliance, oxygenation strategies, and transpulmonary pressure have also demonstrated physiological benefits in titrating PEEP to maximal respiratory system compliance during a decremental PEEP trial.(48, 49) Other comparison studies have demonstrated improvements in oxygenation or lung stress with a variety of other bedside methods targeting esophageal pressure, stress index, or dead-space.(49, 57, 79) At this time, however, no trials comparing important clinical outcomes such as mortality or ventilator free days demonstrate a benefit from any of these approaches.

**CONCLUSIONS**

Since the original description of ARDS, PEEP remains a mainstay of the ventilatory management of ARDS. Yet, the optimal approach to PEEP titration has not yet been firmly established. It is plausible that customizing PEEP will not result in any improvement in clinically meaningful outcomes. From this perspective, the use of a PEEP/FiO\textsubscript{2} table or arbitrarily chosen levels of PEEP that maintain acceptable oxygenation levels may be entirely adequate. However, in our opinion, in addition to supporting arterial oxygenation, PEEP should also be applied with the goal of reducing VILI. In personal practice, based on current knowledge, PEEP is initially set
using either the higher or lower PEEP/FiO2 table. For patients with moderate-severe ARDS, PEEP is then further individually titrated to optimize compliance and minimize driving pressure. Transpulmonary pressure measurements are not routinely used to guide PEEP, although one author sometimes utilizes such measurements to confirm that the application of very high PEEP levels does not result in excess end-inspiratory lung stress (plateau transpulmonary pressure > 20 cm H\textsubscript{2}O).

Future studies are required to better understand different physiological surrogate end-points (oxygenation, lung stress, transpulmonary pressure, etc.) for PEEP titration in order to improve patient outcomes. The development of feasible and valid methods of quantifying lung recruitability and overdistention at the bedside is a high priority. Future trials must focus on selecting patients with the highest likelihood of accruing benefit from PEEP while excluding those at risk of harm. The unresolved problem of PEEP management offers important opportunities for the development of personalized mechanical ventilation.

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Figure 1.

Figure 1. Mechanisms of ventilator-induced lung injury. *Left panel* shows lung regions at end-expiration. *Right panel* shows the same lung regions at end-inspiration. (A) Patent alveoli are over-distended or stretched to injurious volumes. (B) Some tissue may be injured by excessive stress at the margins between atelectatic and aerated alveoli. (C) Small bronchioles and alveoli may be injured by mechanical forces involved in repeated opening and closing. *Reprinted from Clinics in Chest Medicine, 21(3), Roy Brower and Hank Fessler, Mechanical ventilation in acute lung injury and acute respiratory distress syndrome, 491-510, 2000, with permission from Elsevier.* (80)
Figure 2. Example of pressure-volume (P-V) curves from a representative patient at two different PEEP levels (black line = PEEP of 5 cm H$_2$O and gray line = PEEP 14 cm H$_2$O). P-V curves are plotted on the same volume axis. The *vertical solid line* indicates end-expiratory lung volume (EELV) measured using nitrogen washout/washin technique. *Dashed line* indicates volume expired from PEEP to zero end-expiratory pressure. Rec$_{mes}$ is the measured recruitment induced by the increase in PEEP from 5 to 14 cm H$_2$O. Rec$_{estim}$ is the predicted recruitment derived from the change in EELV minus the minimum predicted increase in lung volume based on compliance and the increment in PEEP. Grey inset is a schematic representation of Rec$_{estim}$.

*Reprinted from PEEP-induced changes in lung volume in acute respiratory distress syndrome. Dellamonica et al. Intensive Care Medicine 2011; 37(10), 1595-1604, with permission of Springer. (37)*
Figure 3. Sample inspiratory static pressure-volume curve of the respiratory system showing two flexion points ($P_{\text{FLEX}}$). PEEP is set above the lower inflection point to avoid alveolar collapse. Reprinted with permission of the American Thoracic Society. Copyright © 2016 American Thoracic Society. Amato et al., 1995, Beneficial Effects of the ‘Open Lung Approach’ with Low Distending Pressures in Acute Respiratory Distress Syndrome, 152(6): 1835-46. The American Journal of Respiratory and Critical Care Medicine is an official journal of the American Thoracic Society. (51)
Figure 4. Airway ($P_{aw}$), Esophageal ($P_{es}$), and Transpulmonary ($P_L$) pressure waveforms in three different clinical circumstances. The resulting $P_L$ is similar for all three patients, however the $P_{aw}$ and $P_{es}$ are different. The $P_{es}$, as an estimate of pleural pressure, varies based on the contribution of the chest wall. Reprinted with permission of the American Thoracic Society. Copyright © 2016 American Thoracic Society. Adapted from Akoumianaki et al., 2014, The Application of Esophageal Pressure Measurement in Patients with Respiratory Failure, American Journal of Respiratory and Critical Care Medicine, 189(5): 520-531. The American Journal of Respiratory and Critical Care Medicine is an official journal of the American Thoracic Society. (60)
Table 1

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<thead>
<tr>
<th>A. Lower PEEP:FiO₂ Combination</th>
</tr>
</thead>
<tbody>
<tr>
<td>FiO₂</td>
</tr>
<tr>
<td>PEEP</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B. Higher PEEP:FiO₂ Combination</th>
</tr>
</thead>
<tbody>
<tr>
<td>FiO₂</td>
</tr>
<tr>
<td>PEEP</td>
</tr>
</tbody>
</table>

Table 1. Comparison of lower (A) and higher (B) PEEP/FiO₂ combination tables. (45)