FIFTY YEARS OF RESEARCH IN ARDS

Setting Positive End-Expiratory Pressure in Acute Respiratory Distress Syndrome

Sarina K. Sahetya¹, Ewan C. Goligher^{2,3}, and Roy G. Brower¹

¹Division of Pulmonary and Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland; ²Interdepartmental Division of Critical Care Medicine, University of Toronto, Toronto, Ontario, Canada; and ³Department of Medicine, Division of Respiriology, University Health Network and Mount Sinai Hospital, Toronto, Canada

Abstract

Positive end-expiratory pressure (PEEP) has been used during mechanical ventilation since the first description of 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 that 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 with other approaches of setting PEEP. Future trials should focus on identifying individuals who respond to higher PEEP with recruitment and on clinically important outcomes (e.g., mortality).

Keywords: acute respiratory distress syndrome (ARDS); positive end-expiratory pressure (PEEP); mechanical ventilation

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 H₂O improved arterial oxygenation and reduced pulmonary edema in 14 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 FiO₂. 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 VILI

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 pneumatocoeles (3). Subsequent studies in

(Received in original form October 11, 2016; accepted in final form February 1, 2017)

Supported by the NHLBI of the National Institutes of Health under Award Number T32HL007534 and by a Post-Doctoral Fellowship from the Canadian Institutes of Health Research. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Author Contributions: S.K.S., E.C.G., and R.G.B. contributed to manuscript preparation.

Correspondence and requests for reprints should be addressed to Sarina K. Sahetya, M.D., Division of Pulmonary and Critical Care Medicine, Johns Hopkins University School of Medicine, 1830 Building, 5th Floor – Pulmonary, Baltimore, MD 21287. E-mail: ssahetya1@jhmi.edu

CME will be available for this article at www.atsjournals.org

Am J Respir Crit Care Med Vol 195, Iss 11, pp 1429–1438, Jun 1, 2017

Copyright © 2017 by the American Thoracic Society

Originally Published in Press as DOI: 10.1164/rccm.201610-2035CI on February 1, 2017

Internet address: www.atsjournals.org

experimental models demonstrated that high inspiratory pressures and volumes could cause alveolar overdistention, which results 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 multiorgan 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 and resulting in regional overdistention. Moreover, liquid bridges in small airways may break under pressure during inspiration and reform 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, which increases stress and strain in the ventilated “baby lung.” (11) The significance of this latter mechanism is supported by experimental and clinical observations that suggest 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 lungs 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 also 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 homogeneous 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

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 overdistended 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 with permission from Reference 80.

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 and 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

Importance of Lung Recruitment

Because of 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 PEEP strategies versus lower PEEP strategies found that the oxygenation response after 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 with patients with little or no improvement in oxygenation with PEEP (31). This finding provided 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 PEEP versus lower PEEP in patients with and without lung recruitability (32). However, such trials 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 patients with ARDS found that a combination of physiologic variables ($\text{PaO}_2/\text{FiO}_2 < 150$ at a PEEP of 5 cm H₂O, a decrease in dead space, and an increase in respiratory system compliance [C_{RS}] with an increase in PEEP to 15 cm H₂O) predicted a higher percentage of potentially recruitable lung (30).

Computed tomographic (CT) 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 nonaerated (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 used to measure changes in EELV at different PEEP levels (36–38). 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, 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 after an increase in PEEP permit estimates of recruited lung volume (39).

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 FRC. Measurements of the exhaled volumes at different PEEP levels to FRC allow curves to be plotted on the same axes, with the origin at FRC and an 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) (37, 40).

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, whereas techniques based on respiratory mechanics measure the volume of gas entering newly recruited lung units together with previously open units (41). In addition, 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 pressure–volume 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 individuals with ARDS, arterial oxygenation goals could be achieved by applying PEEP levels of 5 to 12 cm H₂O with FiO_2 levels ≤ 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 H₂O, whereas others raised PEEP to high levels before raising FiO_2 above 0.50.

Figure 2. Example of pressure–volume (P–V) curves from a representative patient at two different positive end-expiratory pressure (PEEP) levels (dark blue line, PEEP of 5 cm H₂O and pink line, PEEP 14 cm H₂O). P–V curves are plotted on the same volume axis. The vertical solid line indicates end-expiratory lung volume (EELV) measured using a nitrogen washout/washin technique. The dashed lines indicate volume expired from PEEP to zero end-expiratory pressure (PEEP-vol 1 and PEEP-vol 2). Rec_{mes} is the measured recruitment induced by the increase in PEEP from 5 to 14 cm H₂O. 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. Gray inset is a representation of Rec_{estim}. Reprinted with permission from Reference 37.

In the National Institutes of Health ARDS Network tidal volume trial, PEEP and F_IO₂ were adjusted in discrete steps according to a table of PEEP and F_IO₂ combinations (Table 1) (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/F_IO₂ table that used PEEP levels an average

of 6 cm H₂O higher than those that resulted from the use of the original table (Table 1) (45). The Canadian Critical Care Clinical Trials Group also developed a similar higher PEEP/F_IO₂ table. In two randomized clinical trials that compared the lower and higher PEEP/F_IO₂ tables, mean arterial oxygenation increased in the higher PEEP groups, which suggested that there was greater recruitment with higher PEEPs (45, 46). However, the oxygenation response to increased PEEP varied widely between individual patients (31).

Table 1. Comparison of Lower and Higher PEEP/F_IO₂ Combination Tables

Lower PEEP/F _I O ₂ Combination*													
F _I O ₂	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.7	0.7	0.8	0.9	0.9	1.0
PEEP, cm H ₂ O	5	5	8	8	10	10	10	12	14	14	14	16	18–24
Higher PEEP/F _I O ₂ Combination†													
F _I O ₂	0.3	0.3	0.4	0.4	0.5	0.5	0.5	0.6	0.7	0.8	0.8	0.9	1.0
PEEP, cm H ₂ O	12	14	14	16	16	18	20	20	20	20	22	22	22–24

Definition of abbreviation: PEEP = positive end-expiratory pressure.

*Reference 44.

†Reference 45.

The use of PEEP/F_IO₂ 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 F_IO₂ can be used. PEEP/F_IO₂ 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 the inspiratory plateau pressure approached 28–30 cm H₂O (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 with a “minimal distention” strategy that used PEEP levels of 5–9 cm H₂O. 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 Compliance

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_{RS} (21). Subsequent studies also suggested that PEEP titration guided by C_{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. In addition, cyclic opening and collapse of lung units with tidal insufflation might cause an increase in measured tidal compliance not related to the PEEP-induced end-expiratory recruitment, which might 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_{RS} (driving pressure = V_T/C_{RS}). Because C_{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. Because 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 more than 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 the aerated lung. Thus, adjusting PEEP to minimize driving pressure may permit a personalized approach to minimize VILI. However, at a constant tidal volume, 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 patients with ARDS 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 believed 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 with 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 not used for clinical practice at present.

Stress Index

With a constant inspiratory flow (square waveform), the shape of the airway

Figure 3. Sample inspiratory static pressure–volume curve of the respiratory system showing two inflection points (P_{FLEX}). Positive end-expiratory pressure (PEEP) is set above the lower inflection point to avoid alveolar collapse. *Smaller black triangles* represent static inflation pressure points measured from a representative patient. *Small gray shaded triangle* represents the calculated compliance with a small tidal volume. *Larger gray shaded triangle* represents the calculated compliance with a high tidal volume. Reprinted with permission from Reference 51.

pressure–time relationship reflects changes in C_{RS} during inspiration. The stress index is a coefficient that describes the rate of change in the slope of the pressure–time curve during tidal inspiration (54). If the slope of the pressure–time relationship increases during inspiration (stress index >1), the respiratory system becomes 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 that 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 (55). 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/ FiO_2 table with a strategy that adjusted PEEP according to the stress index (56). In every patient, PEEP was lower when it was adjusted according to the stress index. The lower levels of PEEP based on the stress index might 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 C_{RS} , lower concentrations of inflammatory mediators in plasma, lower $PaCO_2$, and no significant change in arterial oxygenation. However, this approach requires specialized monitoring equipment to record and analyze the pressure–time relationship, which limits its adoption in clinical practice at present.

Estimating Transpulmonary Pressure

Many lung protective strategies, including the National Institutes of Health ARDS Network lower tidal volume protocol, monitor airway pressures to avoid VILI. However, airway pressure 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 believed to represent average pleural pressure in upright, healthy individuals (61, 62). However, in supine, mechanically ventilated patients with ARDS, esophageal pressure rises by a

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 from Reference 60. ARDS = acute respiratory distress syndrome.

variable amount because of dorsal shift of mediastinal contents and cephalad movement of the diaphragm. There is some controversy regarding the best method for using 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 used 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 that compared 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 will hypothetically estimate the pressure necessary to keep the lung open, and it should in theory be related to the amount of recruitable lung. However, in a small study, 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 used to titrate PEEP (73, 74). This technique permits concomitant monitoring of pulmonary blood flow distribution, ventilation–perfusion matching, and can detect pneumothorax. Although 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 PEEP strategies 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 was 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 might 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 that found that PEEP improved survival in patients with moderate or severe ARDS ($PaO_2/FiO_2 \leq 200$ mm Hg),

who presumably had 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), P_L (57), and an oxygenation strategy using a higher PEEP/ FiO_2 table (46). The PEEP/ 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 two of the three clinical trials of higher PEEP further demonstrated that patients whose PaO_2/FiO_2 ratios increased with higher PEEP had lower mortality (31). This improvement in oxygenation might have represented recruitment in response to PEEP. Assessing oxygenation response to higher PEEP might 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 C_{RS} . This was associated with significantly improved arterial oxygenation and lower driving pressures compared with patients whose PEEP was set according to the ARDS Network lower PEEP/ FiO_2 table, but mortality was not significantly reduced (78). Studies comparing C_{RS} compliance, oxygenation strategies, and P_L also demonstrated physiological benefits in titrating PEEP to maximal C_{RS} during a decremental PEEP trial (48, 49). Other comparison studies demonstrated improvements in oxygenation or lung stress with a variety of other bedside methods that targeted esophageal pressure, the 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, have demonstrated 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/FiO₂ 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 (45, 46). For patients with moderate to severe ARDS, PEEP is then further individually titrated to optimize compliance and minimize driving pressure. P_L measurements are not routinely used to guide PEEP, although one author sometimes uses such measurements to confirm that the application of high PEEP levels does not result in excess end-inspiratory lung stress (plateau P_L > 20 cm H₂O).

Future studies are required to better understand different physiological surrogate endpoints (oxygenation, lung stress, P_L, etc.) for PEEP titration 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. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

References

- Ashbaugh DG, Bigelow DB, Petty TL, Levine BE. Acute respiratory distress in adults. *Lancet* 1967;2:319–323.
- Ashbaugh DG, Petty TL, Bigelow DB, Harris TM. Continuous positive-pressure breathing (CPPB) in adult respiratory distress syndrome. *J Thorac Cardiovasc Surg* 1969;57:31–41.
- Dreyfuss D, Saumon G. Ventilator-induced lung injury: lessons from experimental studies. *Am J Respir Crit Care Med* 1998;157:294–323.
- Webb HH, Tierney DF. Experimental pulmonary edema due to intermittent positive pressure ventilation with high inflation pressures. Protection by positive end-expiratory pressure. *Am Rev Respir Dis* 1974;110:556–565.
- Dreyfuss D, Soler P, Basset G, Saumon G. High inflation pressure pulmonary edema. Respective effects of high airway pressure, high tidal volume, and positive end-expiratory pressure. *Am Rev Respir Dis* 1988;137:1159–1164.
- Bellani G, Guerra L, Musch G, Zanella A, Patroniti N, Mauri T, Messa C, Pesenti A. Lung regional metabolic activity and gas volume changes induced by tidal ventilation in patients with acute lung injury. *Am J Respir Crit Care Med* 2011;183:1193–1199.
- Dos Santos CC, Slutsky AS. Invited review: mechanisms of ventilator-induced lung injury: a perspective. *J Appl Physiol* (1985) 2000;89:1645–1655.
- Muscledere JG, Mullen JB, Gan K, Slutsky AS. Tidal ventilation at low airway pressures can augment lung injury. *Am J Respir Crit Care Med* 1994;149:1327–1334.
- Mead J, Takishima T, Leith D. Stress distribution in lungs: a model of pulmonary elasticity. *J Appl Physiol* 1970;28:596–608.
- Martynowicz MA, Walters BJ, Hubmayr RD. Mechanisms of recruitment in oleic acid-injured lungs. *J Appl Physiol* (1985) 2001;90:1744–1753.
- Cereda M, Emami K, Xin Y, Kadlecsek S, Kuzma NN, Mongkolwisetwara P, Profka H, Pickup S, Ishii M, Kavanagh BP, et al. Imaging the interaction of atelectasis and overdistension in surfactant-depleted lungs. *Crit Care Med* 2013;41:527–535.
- Tsuchida S, Engelberts D, Peltekova V, Hopkins N, Frndova H, Babyn P, McKelvie C, Post M, McLoughlin P, Kavanagh BP. Atelectasis causes alveolar injury in nonatelectatic lung regions. *Am J Respir Crit Care Med* 2006;174:279–289.
- Faridy EE, Permutt S, Riley RL. Effect of ventilation on surface forces in excised dogs' lungs. *J Appl Physiol* 1966;21:1453–1462.
- Mélot C. Contribution of multiple inert gas elimination technique to pulmonary medicine. 5. Ventilation-perfusion relationships in acute respiratory failure. *Thorax* 1994;49:1251–1258.
- Tremblay L, Valenza F, Ribeiro SP, Li J, Slutsky AS. Injurious ventilatory strategies increase cytokines and c-fos m-RNA expression in an isolated rat lung model. *J Clin Invest* 1997;99:944–952.
- Corbridge TC, Wood LDH, Crawford GP, Chudoba MJ, Yanos J, Sznajder JL. Adverse effects of large tidal volume and low PEEP in canine acid aspiration. *Am Rev Respir Dis* 1990;142:311–315.
- Caironi P, Cressoni M, Chiumello D, Ranieri M, Quintel M, Russo SG, Cornejo R, Bugedo G, Carlesso E, Russo R, et al. Lung opening and closing during ventilation of acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2010;181:578–586.
- Protti A, Andreis DT, Monti M, Santini A, Sparacino CC, Langer T, Votta E, Gatti S, Lombardi L, Leopardi O, et al. Lung stress and strain during mechanical ventilation: any difference between statics and dynamics? *Crit Care Med* 2013;41:1046–1055.
- Di Marco F, Devaquet J, Lyazidi A, Galia F, da Costa NP, Fumagalli R, Brochard L. Positive end-expiratory pressure-induced functional recruitment in patients with acute respiratory distress syndrome. *Crit Care Med* 2010;38:127–132.
- Cressoni M, Cadringer P, Chirurazzi C, Amini M, Gallazzi E, Marino A, Brioni M, Carlesso E, Chiumello D, Quintel M, et al. Lung inhomogeneity in patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2014;189:149–158.
- Suter PM, Fairley B, Isenberg MD. Optimum end-expiratory airway pressure in patients with acute pulmonary failure. *N Engl J Med* 1975;292:284–289.
- Barach AL, Eckman M, Ginsburg E, Rumsey C, Korr I, Eckman I, Besson G. Studies on positive pressure respiration: general aspects and types of pressure breathing; effects on respiration and circulation at sea level. *J Aviat Med* 1946;17:290–32.
- Motley HL, Courmand A, Eckman M, Richards J. Physiological studies on man with the pneumatic balance resuscitator, Burns model. *J Aviat Med* 1946;17:431–461.
- Courmand A, Motley HL, Werko L, Richards D. Physiological studies of the effects of intermittent positive pressure breathing on cardiac output in man. *Am J Physiol* 1948;152:162–174.
- Dhainaut JF, Devaux JY, Monsallier JF, Brunet F, Villemant D, Huyghebaert MF. Mechanisms of decreased left ventricular preload during continuous positive pressure ventilation in ARDS. *Chest* 1986;90:74–80.
- Fougères E, Teboul JL, Richard C, Osman D, Chemla D, Monnet X. Hemodynamic impact of a positive end-expiratory pressure setting in acute respiratory distress syndrome: importance of the volume status. *Crit Care Med* 2010;38:802–807.
- Jardin F, Delorme G, Hardy A, Auvert B, Beauchet A, Bourdarias JP. Reevaluation of hemodynamic consequences of positive pressure ventilation: emphasis on cyclic right ventricular afterloading by mechanical lung inflation. *Anesthesiology* 1990;72:966–970.
- Mekontso Dessap A, Boissier F, Charron C, Bégot E, Repessé X, Legras A, Brun-Buisson C, Vignon P, Vieillard-Baron A. Acute cor pulmonale during protective ventilation for acute respiratory distress syndrome: prevalence, predictors, and clinical impact. *Intensive Care Med* 2016;42:862–870.

29. Puybasset L, Gusman P, Muller JC, Cluzel P, Coriat P, Rouby JJ. Regional distribution of gas and tissue in acute respiratory distress syndrome. III. Consequences for the effects of positive end-expiratory pressure. CT Scan ARDS Study Group. Adult Respiratory Distress Syndrome. *Intensive Care Med* 2000;26:1215-1227.
30. Gattinoni L, Caironi P, Cressoni M, Chiumello D, Ranieri VM, Quintel M, Russo S, Patroniti N, Cornejo R, Bugeo G. Lung recruitment in patients with the acute respiratory distress syndrome. *N Engl J Med* 2006;354:1775-1786.
31. Goligher EC, Kavanagh BP, Rubenfeld GD, Adhikari NK, Pinto R, Fan E, Brochard LJ, Granton JT, Mercat A, Marie Richard JC, et al. Oxygenation response to positive end-expiratory pressure predicts mortality in acute respiratory distress syndrome. A secondary analysis of the LOVS and ExPress trials. *Am J Respir Crit Care Med* 2014;190:70-76.
32. Goligher EC, Kavanagh BP, Rubenfeld GD, Ferguson ND. Physiologic responsiveness should guide entry into randomized controlled trials. *Am J Respir Crit Care Med* 2015;192:1416-1419.
33. Grasso S, Fanelli V, Cafarelli A, Anaclerio R, Amabile M, Ancona G, Fiore T. Effects of high versus low positive end-expiratory pressures in acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2005;171:1002-1008.
34. Maggiore SM, Jonson B, Richard J-C, Jaber S, Lemaire F, Brochard L. Alveolar derecruitment at decremental positive end-expiratory pressure levels in acute lung injury: comparison with the lower inflection point, oxygenation, and compliance. *Am J Respir Crit Care Med* 2001;164:795-801.
35. Reske AW, Costa EL, Reske AP, Rau A, Borges JB, Beraldo MA, Gottschaldt U, Seiwerts M, Schreiter D, Petroff D, et al. Bedside estimation of nonaerated lung tissue using blood gas analysis. *Crit Care Med* 2013;41:732-743.
36. Chiumello D, Cressoni M, Chierichetti M, Tallarini F, Botticelli M, Berto V, Mietto C, Gattinoni L. Nitrogen washout/washin, helium dilution and computed tomography in the assessment of end expiratory lung volume. *Crit Care* 2008;12:R150.
37. Dellamonica J, Lerolle N, Sargentini C, Beduneau G, Di Marco F, Mercat A, Richard JCM, Diehl JL, Mancebo J, Rouby JJ, et al. PEEP-induced changes in lung volume in acute respiratory distress syndrome. Two methods to estimate alveolar recruitment. *Intensive Care Med* 2011;37:1595-1604.
38. Dellamonica J, Lerolle N, Sargentini C, Beduneau G, Di Marco F, Mercat A, Richard J-CM, Diehl J-L, Mancebo J, Rouby J-J, et al. Accuracy and precision of end-expiratory lung-volume measurements by automated nitrogen washout/washin technique in patients with acute respiratory distress syndrome. *Crit Care* 2011;15:R294.
39. Mauri T, Eronia N, Turrini C, Battistini M, Grasselli G, Rona R, Volta CA, Bellani G, Pesenti A. Bedside assessment of the effects of positive end-expiratory pressure on lung inflation and recruitment by the helium dilution technique and electrical impedance tomography. *Intensive Care Med* 2016;42:1576-1587.
40. Chiumello D, Marino A, Brioni M, Cigada I, Menga F, Colombo A, Crimella F, Algieri I, Cressoni M, Carlesso E, et al. Lung recruitment assessed by respiratory mechanics and computed tomography in patients with acute respiratory distress syndrome. What is the relationship? *Am J Respir Crit Care Med* 2016;193:1254-1263.
41. Amato MB, Santiago RR. The recruitability paradox. *Am J Respir Crit Care Med* 2016;193:1192-1195.
42. Comroe JH, Dripps RD, Dumke PR, Deming M. Oxygen toxicity. *JAMA* 1945;128:710-717.
43. Nash G, Blennerhassett JB, Pontoppidan H. Pulmonary lesions associated with oxygen therapy and artificial ventilation. *N Engl J Med* 1967;276:368-374.
44. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000;342:1301-1308.
45. Brower RG, Lanken PN, MacIntyre N, Matthay MA, Morris A, Ancukiewicz M, Schoenfeld D, Thompson BT; National Heart, Lung, and Blood Institute ARDS Clinical Trials Network. Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. *N Engl J Med* 2004;351:327-336.
46. Meade MO, Cook DJ, Guyatt GH, Slutsky AS, Arabi YM, Cooper DJ, Davies AR, Hand LE, Zhou Q, Thabane L, et al.; Lung Open Ventilation Study Investigators. Ventilation strategy using low tidal volumes, recruitment maneuvers, and high positive end-expiratory pressure for acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. *JAMA* 2008;299:637-645.
47. Mercat A, Richard JC, Vielle B, Jaber S, Osman D, Diehl JL, Lefrant JY, Prat G, Richecoeur J, Nieszkowska A, et al.; Expiratory Pressure (Express) Study Group. Positive end-expiratory pressure setting in adults with acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. *JAMA* 2008;299:646-655.
48. Pintado M-C, de Pablo R, Trascasa M, Milicua J-M, Rogero S, Daguerre M, Cambroner J-A, Arribas I, Sánchez-García M. Individualized PEEP setting in subjects with ARDS: a randomized controlled pilot study. *Respir Care* 2013;58:1416-1423.
49. Rodriguez PO, Bonelli I, Setten M, Attie S, Madorno M, Maskin LP, Valentini R. Transpulmonary pressure and gas exchange during decremental PEEP titration in pulmonary ARDS patients. *Respir Care* 2013;58:754-763.
50. Amato MB, Meade MO, Slutsky AS, Brochard L, Costa EL, Schoenfeld DA, Stewart TE, Briel M, Talmor D, Mercat A, et al. Driving pressure and survival in the acute respiratory distress syndrome. *N Engl J Med* 2015;372:747-755.
51. Amato MB, Barbas CS, Medeiros DM, Schettino GdeP, Lorenzi Filho G, Kairalla RA, Deheinzelin D, Morais C, Fernandes Ede O, Takagaki TY, et al. Beneficial effects of the "open lung approach" with low distending pressures in acute respiratory distress syndrome. A prospective randomized study on mechanical ventilation. *Am J Respir Crit Care Med* 1995;152:1835-1846.
52. Amato MBP, Barbas CSV, Medeiros DM, Magaldi RB, Schettino GP, Lorenzi-Filho G, Kairalla RA, Deheinzelin D, Munoz C, Oliveira R, et al. Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. *N Engl J Med* 1998;338:347-354.
53. Decalliot F, Demoule A, Maggiore SM, Jonson B, Duvaldestin P, Brochard L. Pressure-volume curves with and without muscle paralysis in acute respiratory distress syndrome. *Intensive Care Med* 2006;32:1322-1328.
54. Grasso S, Terragni P, Mascia L, Fanelli V, Quintel M, Herrmann P, Hedenstierna G, Slutsky AS, Ranieri VM. Airway pressure-time curve profile (stress index) detects tidal recruitment/hyperinflation in experimental acute lung injury. *Crit Care Med* 2004;32:1018-1027.
55. Ranieri VM, Giuliani R, Fiore T, Dambrosio M, Milic-Emili J. Volume-pressure curve of the respiratory system predicts effects of PEEP in ARDS: "occlusion" versus "constant flow" technique. *Am J Respir Crit Care Med* 1994;149:27-27.
56. Grasso S, Stripoli T, De Michele M, Bruno F, Moschetta M, Angelelli G, Munno I, Ruggiero V, Anaclerio R, Cafarelli A, et al. ARDSnet ventilatory protocol and alveolar hyperinflation: role of positive end-expiratory pressure. *Am J Respir Crit Care Med* 2007;176:761-767.
57. Talmor D, Sarge T, Malhotra A, O'Donnell CR, Ritz R, Lisbon A, Novack V, Loring SH. Mechanical ventilation guided by esophageal pressure in acute lung injury. *N Engl J Med* 2008;359:2095-2104.
58. Mauri T, Yoshida T, Bellani G, Goligher EC, Carteaux G, Rittayamai N, Mojoli F, Chiumello D, Piquilloud L, Grasso S, et al.; PLeUral pressure working Group (PLUG—Acute Respiratory Failure section of the European Society of Intensive Care Medicine). Esophageal and transpulmonary pressure in the clinical setting: meaning, usefulness and perspectives. *Intensive Care Med* 2016;42:1360-1373.
59. Loring SH, Topulos GP, Hubmayr RD. Transpulmonary pressure: the importance of precise definitions and limiting assumptions. *Am J Respir Crit Care Med* 2016;194:1452-1457.
60. Akoumianaki E, Maggiore SM, Valenza F, Bellani G, Jubran A, Loring SH, Pelosi P, Talmor D, Grasso S, Chiumello D, et al.; PLUG Working Group (Acute Respiratory Failure Section of the European Society of Intensive Care Medicine). The application of esophageal pressure measurement in patients with respiratory failure. *Am J Respir Crit Care Med* 2014;189:520-531.

61. Milic-Emili J, Mead J, Turner JM, Glauser EM. Improved technique for estimating pleural pressure from esophageal balloons. *J Appl Physiol* 1964;19:207–211.
62. Mead J, Gaensler EA. Esophageal and pleural pressures in man, upright and supine. *J Appl Physiol* 1959;14:81–83.
63. Washko GR, O'Donnell CR, Loring SH. Volume-related and volume-independent effects of posture on esophageal and transpulmonary pressures in healthy subjects. *J Appl Physiol* (1985) 2006;100:753–758.
64. Talmor D, Sarge T, O'Donnell CR, Ritz R, Malhotra A, Lisbon A, Loring SH. Esophageal and transpulmonary pressures in acute respiratory failure. *Crit Care Med* 2006;34:1389–1394.
65. Gattinoni L, Chiumello D, Carlesso E, Valenza F. Bench-to-bedside review: chest wall elastance in acute lung injury/acute respiratory distress syndrome patients. *Crit Care* 2004;8:350–355.
66. Gulati G, Novero A, Loring SH, Talmor D. Pleural pressure and optimal positive end-expiratory pressure based on esophageal pressure versus chest wall elastance: incompatible results*. *Crit Care Med* 2013;41:1951–1957.
67. Sahetya SK, Brower RG. The promises and problems of transpulmonary pressure measurements in acute respiratory distress syndrome. *Curr Opin Crit Care* 2016;22:7–13.
68. Grasso S, Terragni P, Birocco A, Urbino R, Del Sorbo L, Filippini C, Mascia L, Pesenti A, Zangrillo A, Gattinoni L, et al. ECMO criteria for influenza A (H1N1)-associated ARDS: role of transpulmonary pressure. *Intensive Care Med* 2012;38:395–403.
69. Pelosi P, Goldner M, McKibben A, Adams A, Eccher G, Caironi P, Losappio S, Gattinoni L, Marini JJ. Recruitment and derecruitment during acute respiratory failure: an experimental study. *Am J Respir Crit Care Med* 2001;164:122–130.
70. Gattinoni L, Pelosi P, Crotti S, Valenza F. Effects of positive end-expiratory pressure on regional distribution of tidal volume and recruitment in adult respiratory distress syndrome. *Am J Respir Crit Care Med* 1995;151:1807–1814.
71. Cressoni M, Chiumello D, Carlesso E, Chiurazzi C, Amini M, Brioni M, Cadringer P, Quintel M, Gattinoni L. Compressive forces and computed tomography-derived positive end-expiratory pressure in acute respiratory distress syndrome. *Anesthesiology* 2014;121:572–581.
72. Bouhemed B, Brisson H, Le-Guen M, Arbelot C, Lu Q, Rouby J-J. Bedside ultrasound assessment of positive end-expiratory pressure-induced lung recruitment. *Am J Respir Crit Care Med* 2011;183:341–347.
73. Costa ELV, Borges JB, Melo A, Suarez-Sipmann F, Toufen C Jr, Bohm SH, Amato MBP. Bedside estimation of recruitable alveolar collapse and hyperdistension by electrical impedance tomography. *Intensive Care Med* 2009;35:1132–1137.
74. Kobylanski J, Murray A, Brace D, Goligher E, Fan E. Electrical impedance tomography in adult patients undergoing mechanical ventilation: a systematic review. *J Crit Care* 2016;35:33–50.
75. Briel M, Meade M, Mercat A, Brower RG, Talmor D, Walter SD, Slutsky AS, Pullenayegum E, Zhou Q, Cook D, et al. Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: systematic review and meta-analysis. *JAMA* 2010;303:865–873.
76. Chiumello D, Cressoni M, Carlesso E, Caspani ML, Marino A, Gallazzi E, Caironi P, Lazzerini M, Moerer O, Quintel M, et al. Bedside selection of positive end-expiratory pressure in mild, moderate, and severe acute respiratory distress syndrome. *Crit Care Med* 2014;42:252–264.
77. Ranieri VM, Zhang H, Mascia L, Aubin M, Lin CY, Mullen JB, Grasso S, Binnie M, Volgyesi GA, Eng P, et al. Pressure-time curve predicts minimally injurious ventilatory strategy in an isolated rat lung model. *Anesthesiology* 2000;93:1320–1328.
78. Kacmarek RM, Villar J, Sulemanji D, Montiel R, Ferrando C, Blanco J, Koh Y, Soler JA, Martínez D, Hernández M, et al.; Open Lung Approach Network. Open lung approach for the acute respiratory distress syndrome: a pilot, randomized controlled trial. *Crit Care Med* 2016;44:32–42.
79. Terragni PP, Filippini C, Slutsky AS, Birocco A, Tenaglia T, Grasso S, Stripoli T, Pasero D, Urbino R, Fanelli V, et al. Accuracy of plateau pressure and stress index to identify injurious ventilation in patients with acute respiratory distress syndrome. *Anesthesiology* 2013;119:880–889.
80. Brower RG, Fessler HE. Mechanical ventilation in acute lung injury and acute respiratory distress syndrome. *Clin Chest Med* 2000;21:491–510, viii.