Do the NIH ARDS Clinical Trials Network PEEP/F_{IO_2} Tables Provide the Best Evidence-Based Guide to Balancing PEEP and F_{IO_2} Settings in Adults?

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Positive end-expiratory pressure (PEEP) and inspired oxygen fraction (F_{IO_2}) are the primary means of improving P_{aO_2} during mechanical ventilation. Patients with acute respiratory distress syndrome (ARDS) typically present with a large intrapulmonary shunt, which makes even high F_{IO_2} ineffective in improving P_{aO_2}. PEEP decreases intrapulmonary shunt by recruiting collapsed alveoli, but

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PEEP is associated with important adverse effects, whereas prolonged exposure to high F_{IO_2} may cause oxidative lung injury. The improved survival found in the National Institutes of Health's ARDS Network low-tidal-volume study may suggest that their PEEP/F_{IO_2} titration tables represent the best method for adjusting these variables. Based upon an extensive literature review of PEEP and respiratory system mechanics in ARDS, we conclude that: (1) for most patients the therapeutic range of PEEP is relatively narrow, so the ARDS Network PEEP/F_{IO_2} strategy is reasonable and supported by high-level evidence, (2) how best to adjust PEEP to prevent or ameliorate ventilator-associated lung injury is unknown and still under investigation, and (3) in a small subset of patients with severe lung injury and/or abnormal chest-wall compliance, highly individualized titration of PEEP, based upon the respiratory-system pressure-volume curve, PEEP/tidal-volume titration grids, or a recruitment maneuver and a PEEP decrement trial is a reasonable alternative. *Key words: acute lung injury, acute respiratory distress syndrome, fraction of inspired oxygen, positive end-expiratory pressure, pressure-volume curve, respiratory system compliance.* [Respir Care 2007; 52(4):461–475. © 2007 Daedalus Enterprises]

Introduction

Positive end-expiratory pressure (PEEP) and inspired oxygen fraction (F_{IO_2}) are the main tools used to improve the partial pressure of arterial oxygen (P_{aO_2}) during mechanical ventilation. However, prolonged exposure to high F_{IO_2} may cause oxidative lung injury[1,2] and is ineffective in improving P_{aO_2} in the presence of a large intrapulmonary shunt,[3] which is the hallmark of acute respiratory distress syndrome (ARDS).[4,5] In contrast, PEEP is believed to recruit and stabilize collapsed small airways and alveoli, thus increasing functional residual capacity (FRC) and respiratory system compliance (C_{RS}) while reducing intrapulmonary shunt.[6–9] The subsequent rise in P_{aO_2} allows mechanical ventilation at a relatively safer F_{IO_2}.

Yet high PEEP is associated with adverse effects because transmission of positive pressure to the pleural space decreases venous return,[10,11] increases pulmonary vascular resistance,[12] and decreases left-ventricular compliance,[12,13] cardiac output, and systemic oxygen delivery.[9,12] In addition, high PEEP may cause lung overdistention, resulting in decreased C_{RS},[7,9] increased dead-space ventilation,[9] and lung rupture.[7,14,15] Paradoxical effects of high PEEP include decreased P_{aO_2} (by redistributing pulmonary blood flow to areas of low or absent ventilation),[16,17] increased alveolar epithelial permeability,[18] enhanced pulmonary edema formation,[19] and decreased reabsorption of pulmonary edema.[20]

Among individual patients both salutary and adverse effects of PEEP are difficult to predict.[7,9,21] Lung recruitment is influenced by lung and chest wall compliance[22–24] and severity of injury.[25] Adverse hemodynamic effects also are determined by lung and chest wall compliance,[26–28] as well as intravascular fluid status[29] and cardiovascular function.[30] This uncertainty has fostered divergent philosophies regarding how PEEP should be used. Some believe it should be titrated to optimize lung function (traditionally defined as maximizing pulmonary oxygen transfer efficiency[31]), while others advocate increasing PEEP just enough to ensure an adequate P_{aO_2} while minimizing adverse effects.[32] More recently, proponents of "open-lung ventilation" advocated titrating PEEP to optimize FRC, as a way to minimize ventilator-associated lung injury.[33]

This paper debates whether the National Institutes of Health ARDS Network PEEP/F_{IO_2} titration tables[34,35] represent the best evidence for clinical management of patients with ARDS and its milder form, acute lung injury (ALI). In a sense this debate is the continuation of a decades-long controversy regarding PEEP. We will present a brief orientation to evidence-based medicine, followed by a historical overview of PEEP in ARDS/ALI. Then we will present the arguments for and against use of the ARDS Network PEEP/F_{IO_2} titration tables in clinical management of ARDS/ALI.

Evidenced-Based Medicine

Traditionally, an "authority-based" model has been used to guide clinical management of patients. Generated by "expert opinion" from textbooks, committees of acknowledged experts, or highly respected clinicians,[36] this approach is vulnerable to inherent human bias and has resulted in divergent treatments and varying outcomes in patients with the same disease.[37] Thus, it may perpetuate therapies that are ineffective and sometimes harmful. This "hierarchy of authority" model gradually has been replaced by one based upon a "hierarchy of evidence."[38] Evidence-based medicine evaluates clinical studies and grades recommendations for clinical practice based upon explicit rules. In brief, the most reliable evidence for clinical practice (Level I) comes from large randomized controlled trials, where the risk for either false-positive or false-negative results is low. Moving down the hierarchy, studies conducted with less stringent observational techniques and

inadequate controls, such as nonrandomized case-control experiments and retrospective case-series reports (Levels III–V), pose an increased risk of bias toward *overestimating* therapeutic efficacy.[37] Evidence-based recommendations suggest how an "average patient" will *probably* respond to treatment, and thus may not apply to individuals with unusually severe or complicated forms of a disease.[39]

Overview: The History of PEEP

PEEP and Outcomes: Early Observational Studies

The first detailed description of ARDS appeared in 1967.[4] Patients without prior history of pulmonary disease developed acute respiratory distress characterized by diffuse hemorrhagic pulmonary edema and severe hypoxemia refractory to positive-pressure ventilation with 100% oxygen. However, treatment of intractable hypoxemia with the novel application of 7–10 cm H_2O PEEP dramatically increased P_{aO_2} and appeared to improve mortality from 71% to 29%.[3] That study had a profound impact because it occurred during the Vietnam War, when military surgeons were confronted by exceedingly high mortality rates among battle casualties with post-traumatic respiratory insufficiency.[40]

The initial impression that PEEP improved survival from ARDS was dispelled by subsequent publications in which, despite markedly improved oxygenation, mortality was 50–75%, and most patients died from multiple-organ system failure.[7,15,41–43] Only advocates of "Optimal PEEP" ($\geq$ 20 cm H_2O) claimed their approach actually reversed the pathophysiologic process of ARDS and reduced mortality to $<$ 40%.[31] However, that finding was based on a retrospective case series study.

The claim that PEEP can reverse ARDS underscored the general lack of knowledge that existed 30 years ago. Although in some animal models of lung injury PEEP appeared to reduce both histologic lesions and pulmonary edema,[44–47] others found improved oxygenation but no reduction in pulmonary edema.[48–52] Observational studies in at-risk patients suggested that early application of 8 cm H_2O PEEP reduced the incidence of ARDS.[53,54] Yet a subsequent prospective randomized trial that compared mechanical ventilation with 8 cm H_2O PEEP to no PEEP in 92 at-risk patients found no difference in the development of ARDS (25% vs 27%).[55] What was not appreciated at the time was the fact that ARDS/ALI is not simply a mechanical problem of congestive atelectasis, but rather a complex inflammatory process[56] in which improvements in oxygenation with PEEP do not reflect reversal or attenuation of the underlying disease.

Approaches to Setting PEEP: Early Recommendations

PEEP has been used in ARDS primarily to recruit and stabilize collapsed and under-ventilated alveoli so that an adequate P_{aO_2} (60–80 mm Hg) can be achieved at a relatively nontoxic F_{IO_2}.[57] What constitutes a nontoxic F_{IO_2} is uncertain, as even the seminal observational study by Nash et al[58] only tentatively implicated long-term exposure to an $F_{IO_2} \geq 0.90$ with oxygen toxicity. Subsequent studies suggested that humans are less susceptible to oxidative lung injury than other mammals, and that long-term exposure to an $F_{IO_2} \leq 0.60$ probably has minimal toxic effects.[2] Furthermore, animal studies have demonstrated that prior exposure to hypoxemia, hyperoxemia, certain pro-inflammatory mediators, and endotoxin induces tolerance to subsequent exposures to hyperoxia.[59] As patients with ARDS are exposed to most of these conditions, they may acquire additional protection from the oxygen toxicity.

In ARDS, when the circulating blood volume is adequate, PEEP set between 5–15 cm H_2O generally is well-tolerated, because low lung compliance prevents substantial transmission of positive pressure to the pleural space.[7,60] Yet reports of hemodynamic compromise, even at 10 cm H_2O,[10] and barotrauma at 13 cm H_2O,[7] probably prompted early recommendations that PEEP be limited to 10–12 cm H_2O.[32,61,62]

Optimizing Compliance

Early studies of PEEP reported that the physiologic response differed considerably between patients. Falke et al[8] and Suter et al[9] found that P_{aO_2} and C_{RS} increased with PEEP, and the magnitude of improvement was inversely related to baseline FRC. They speculated that by improving FRC and C_{RS}, PEEP moved tidal ventilation onto the steep portion of the inflation pressure-volume (P-V) curve.[8,9] In addition, these studies noted that at PEEP $>$ 10 cm H_2O, C_{RS} often decreased despite continued improvement in P_{aO_2}. These findings suggested that on a regional level, lung recruitment occurred simultaneously with overdistention, thus providing the first mechanical evidence that the distribution of lung injury in ARDS was heterogeneous.

Suter et al[9] found that for individual patients there was a "best PEEP" that produced optimal C_{RS} and the highest P_{aO_2} without compromising oxygen delivery or causing lung overdistention (Fig. 1). Subsequently, Suter et al[63] found that lung over-distention could be avoided with PEEP, by using a physiologic tidal volume (V_T) of 5–7 mL/kg. The concept of "best PEEP" was supported by Jardin et al,[43] who reported an average value of 9 ± 3 cm H_2O in ARDS. Lemaire et al[64] also affirmed the notion of "best PEEP" when they found that setting PEEP

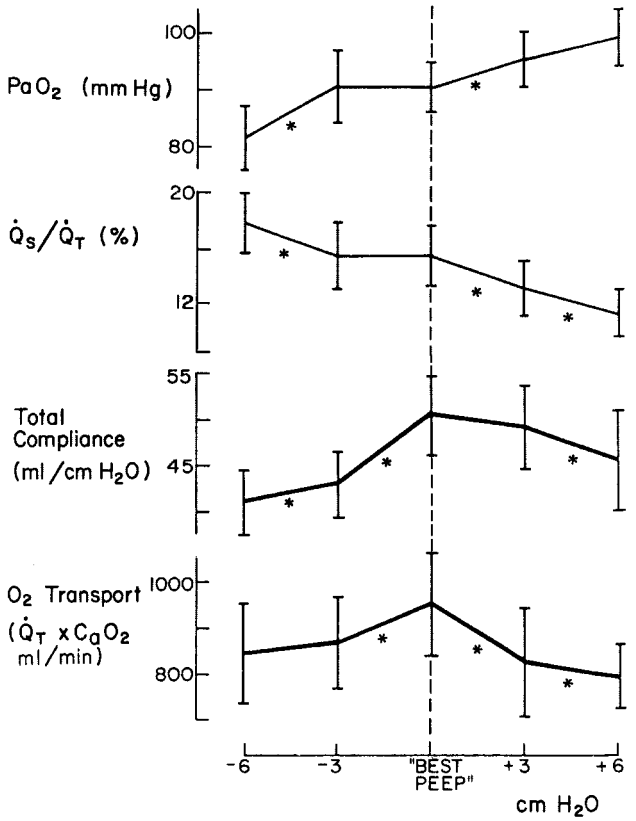

Fig. 1. The relationship of best positive end-expiratory pressure (PEEP) to partial-pressure of arterial oxygen (P_{aO_2}), intrapulmonary shunt ($\dot{Q}_S/\dot{Q}_T$), respiratory system compliance, and systemic oxygen transport in patients with acute respiratory distress syndrome. "Best PEEP" is defined as that level that produces the highest compliance and P_{aO_2} without impairing oxygen delivery to the tissues. (From Reference 9, with permission.)

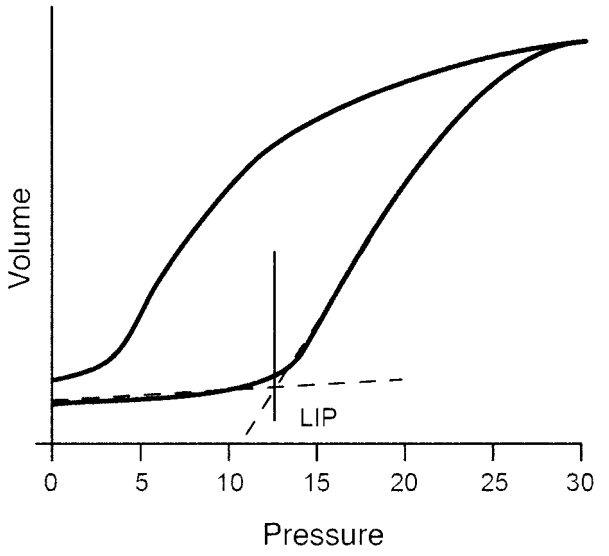

Fig. 2. Schematic of a pressure-volume curve of the respiratory system. The lower inflection point (LIP) represents the point at which lung compliance markedly increases and is believed to represent the beginning of substantial recruitment of collapsed peripheral airways and alveoli. In open-lung ventilation strategies, positive end-expiratory pressure typically is set 2 cm H_2O above the lower inflection point to prevent lung collapse at end-expiration.

3 cm H_2O above the lower inflection point on the inflation P-V curve markedly improved P_{aO_2} (Fig. 2). The average lower inflection point in these patients with ARDS was 9 ± 3.7 cm H_2O.[64] Subsequent studies supported the notion that PEEP improved FRC and altered the P-V relationship in ARDS.[65]

Minimizing Intrapulmonary Shunt

In the 1970s, "optimal PEEP" was proposed by those who believed that the hazards of PEEP were exaggerated and who rejected an arbitrarily-fixed upper limit in patients with severe hypoxemia.[31,41] Rather, they advocated titrating PEEP until the intrapulmonary shunt was reduced to 15% at an F_{IO_2} of < 0.55.[41] This approach also was called "super-PEEP," because levels between 24–44 cm H_2O often were required.[31] To counter hemodynamic compromise, hypervolemia and negative pleural pressure associated with intermittent mandatory ventilation were required.[31,66] Because continuous-flow intermittent mandatory ventilation was used, plateau pressure and C_{RS} could not be measured, thus preventing assessment of lung overdistention. Although the incidence of pneumothoraces was 14–17%,[31,41] pulmonary and subcutaneous emphysema were common.[31,66] Hemodynamic compromise was reported to be infrequent, but fluid management was not described. When Jardin et al[43] compared "best PEEP" to "optimal PEEP" of 20 cm H_2O, both fluid resuscitation and inotropic support were required to maintain systemic oxygen delivery.

Minimizing Ventilator-Associated Lung Injury

By the early 1990s, substantial evidence indicated that mechanical ventilation strategies themselves exacerbated lung injury and possibly contributed to the high mortality associated with ARDS/ALI.[67] The primary focus in ventilator-associated lung injury was stretch-related injury believed to be caused by high V_T and airway pressure. However, repetitive opening and closing of alveoli from insufficient PEEP also was believed to contribute to ventilator-associated lung injury from the resulting shear injury.

In response, open-lung ventilation focused on full lung recruitment, followed by a low-V_T and high-PEEP strategy to prevent ventilator-associated lung injury.[33] Initial lung recruitment was achieved with a brief period of pressure ventilation at 55 cm H_2O and PEEP of 16 cm H_2O.

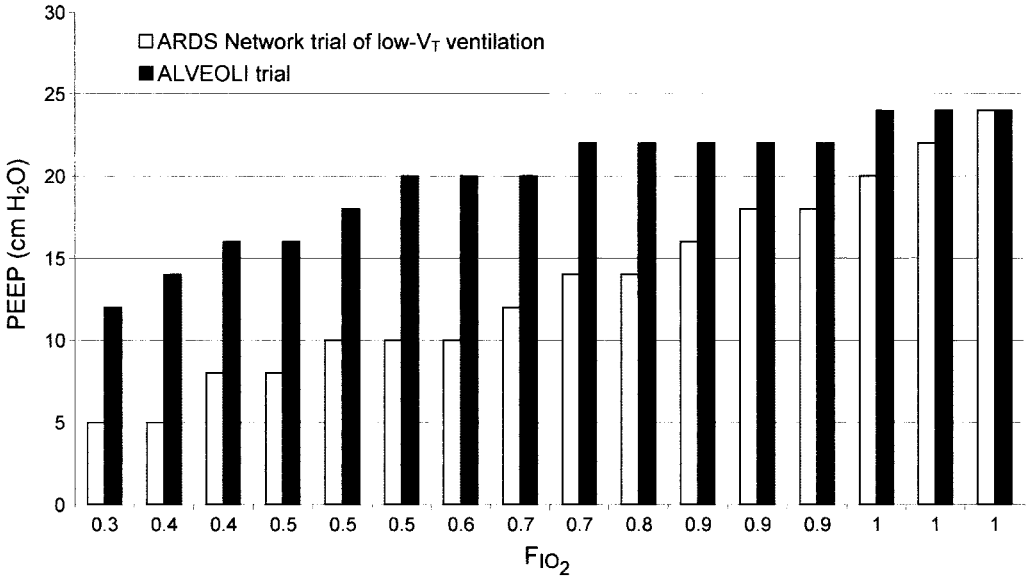

Fig. 3. Titration tables for positive end-expiratory pressure (PEEP) and inspired oxygen fraction (F_{IO_2}) from the Acute Respiratory Distress Syndrome Network's studies of low tidal volume (V_T) and high-PEEP (the ALVEOLI trial).

Tidal pressure excursions then were adjusted to $\leq$ 20 cm H_2O to prevent stretch-related injury. Shear-related injury was countered by preventing alveolar collapse with inverse-ratio ventilation titrated to an intrinsic PEEP of 16 cm H_2O. This approach has been modified so that total PEEP (applied and intrinsic) is adjusted to 2 cm H_2O above the lower inflection point on the inflation P-V curve.[68]

Countering Compressive Atelectasis

Gattinoni et al[69] proposed setting PEEP to prevent alveolar collapse, based upon findings from computed tomography (CT) studies. In ARDS, the increased densities characteristically seen in the dorsal lung are believed to represent compressive atelectasis from the weight of the overlying edematous lung. Gattinoni et al[69] proposed that a minimal PEEP of 11–14 cm H_2O might counter the superimposed hydrostatic pressure and keep the dependent lung zones open at end-expiration. This estimation is based upon the sternovertebral height of a supine adult (12–25 cm) and the average tissue density in ARDS of 0.7 g/cm^3, which produces a PEEP range of 8–18 cm H_2O.

Randomized Clinical Trials: 1998–2006

Several prospective randomized-controlled trials have compared lung-protective ventilation to a conventional-V_T approach in patients with (or at risk for) ARDS/ALI.[34,70–75] In 4 studies,[34,71–73] moderate PEEP (7–11 cm H_2O) was used to achieve adequate oxygenation at an F_{IO_2} of 0.50–0.70 in both treatment arms. In 3 studies,[70,74,75] that compared a conventional-V_T strategy to open-lung ventilation, there were marked differences in PEEP (7–9 vs 14–16 cm H_2O, respectively). Of these 7 studies, morbidity and mortality were significantly reduced in 3 trials: the low-V_T/moderate-PEEP approach of the ARDS Network,[34] and the open-lung ventilation approach of Amato et al,[70] and the ARIES (Acute Respiratory Insufficiency: Espana Study) Network.[75] Pro-inflammatory biomarkers were significantly reduced in the ARDS Network trial[34] and the study by Ranieri et al.[74] However, these studies left unanswered whether the positive results were attributable to reductions in V_T or to higher PEEP.

Subsequently, the ARDS Network compared their low-V_T/moderate-PEEP approach to a low-V_T/high-PEEP approach in a large randomized trial (Fig. 3).[35] In both treatment arms, V_T was adjusted to 4–6 mL/kg to keep plateau pressure $\leq$ 30 cm H_2O. The study was stopped early for futility, after enrolling 549 patients. Although C_{RS} and P_{aO_2}/F_{IO_2} were significantly greater in the high-PEEP arm (suggesting better lung recruitment), mortality, days of unassisted breathing, nonpulmonary-organ-failure-free days, biomarkers of inflammation, and cellular injury were not different. PEEP was significantly different between the lower and higher treatment arms (8.3 $\pm$ 3.2 cm H_2O vs 13.2 $\pm$ 3.5 cm H_2O, respectively, $p < 0.001$). Although this suggests that better lung recruitment with higher PEEP did not improve outcomes compared to a moderate PEEP strategy, the controversy on how best to adjust PEEP in ARDS/ALI is hardly settled.

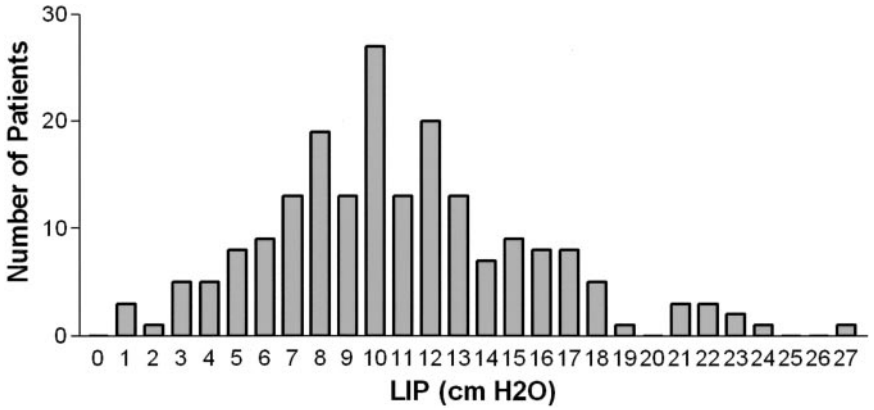

Fig. 4. Frequency distribution of 197 discrete measurements of lower inflection point (LIP) from 16 clinical studies.

Pro: The ARDS Network Tables Represent the Best Clinical Evidence to Guide Management for Titrating PEEP/F_{IO_2} During Clinical Practice.

The objective of the ARDS Network low-V_T study was to determine the effects of V_T and plateau pressure. Therefore, titration of PEEP/F_{IO_2} was based upon how these variables were adjusted in clinical practice at hospitals participating in the study (personal communications, Gordon Bernard, Vanderbilt University Medical Center, Nashville, Tennessee, and Roy Brower, Johns Hopkins Hospital, Baltimore, Maryland). Interestingly, the PEEP/F_{IO_2} titration table[34] was concordant with contemporary practices in the 1990s, as PEEP levels in ARDS generally were $\leq$ 10 cm H_2O with an F_{IO_2} of approximately 0.70.[76,77] In the study of higher versus lower PEEP,[35] it was impractical to measure P-V curves with an enrollment goal of 800 patients. Thus, the PEEP/F_{IO_2} titration table was devised to mimic the PEEP settings in the lung-protective group of the Amato study,[70] in which the initial average PEEP was 16 cm H_2O and then 13 cm H_2O from study days 3–7 (see Fig. 3).

Proposing the ARDS Network PEEP/F_{IO_2} titration tables as the best evidence-based guide in ALI/ARDS essentially is a negative argument. To begin, there is no convincing, high-level evidence that patient outcomes are improved by optimizing oxygenation, FRC, or C_{RS}. Therefore, the widely accepted goal of assuring adequate oxygenation will, for most patients, result in a relatively narrow therapeutic PEEP range. This suggests that meticulous titration of PEEP is unnecessary in most instances. Moreover, the alternative approach (open-lung ventilation) is based upon a questionable and unproven assumption that shear-related injury is an important problem in ARDS/ALI. Furthermore, PEEP is titrated by P-V curves in open-lung ventilation, which still should be considered investigational because of numerous interpretive and methodological limitations. Therefore, the ARDS Network PEEP/F_{IO_2} titration tables provide a reasonable, practical guide for clinical adjustments when the lungs are either modestly or greatly amenable to recruitment.

Historically, the recommended therapeutic range for PEEP is 5–15 cm H_2O. This narrow range has never been directly and rigorously tested in a prospective manner. The lower inflection point on the inflation P-V curve is believed to represent the beginning of substantial lung recruitment in ARDS.[78] Therefore, it may provide some insight into what PEEP range is likely to be appropriate in ARDS/ALI. Sixteen studies[78–93] have reported individual lower-inflection-point data for 197 patients with ARDS. Combining this data produces a mean lower inflection point of 10.8 $\pm$ 4.7 cm H_2O, with over 50% percent of lower-inflection-point values $\leq$ 10 cm H_2O, and 84% $\leq$ 15 cm H_2O (Fig. 4). Moreover, the 95% confidence interval estimate for the general population with ARDS is only 10.2–11.5 cm H_2O. These results are consistent with other studies, which have reported a mean lower inflection point of 8–11 cm H_2O.[64,94–98]

In the original ARDS Network PEEP/F_{IO_2} titration table,[34] PEEP of 8–14 cm H_2O was used in the F_{IO_2} range 0.40–0.80 to maintain an adequate P_{aO_2}. In the minority of patients with ARDS who exhibit profound alveolar instability, the ARDS Network higher-PEEP table[35] is a reasonable approach to maintain stable oxygenation at a relatively nontoxic F_{IO_2}. As evidence-based guidelines are focused on how the *average* patient should be treated, the ARDS Network PEEP titration strategy is congruent with the physiologic data presented above.

Lung injury in ARDS/ALI is heterogeneous: areas of normal as well as atelectatic and consolidated lung tissue are present. In areas of the lung where collapsed but recruitable alveoli are attached to aerated alveoli, opening pressures are greatly magnified across tissue junctures, so that an applied pressure of 30 cm H_2O to the terminal

airways theoretically may cause junctional tissue stresses in excess of 100 cm H_2O.[99] The rationale for setting PEEP above the lower inflection point is that low-V_T ventilation with inadequate PEEP causes cyclical recruitment/de-recruitment and produces lung injury ("atelectrauma").[100] However, "atelectrauma" created in nonperfused, saline-lavage animal models produced profound atelectasis without alveolar flooding. This may exaggerate shear stresses more than what would occur naturally in the presence of exudative alveolar edema and hemorrhage, which are the predominant pathologic features of ARDS.[4,25,101,102] In an oleic-acid-induced model of lung injury, where alveolar flooding was the primary lesion, alveolar recruitment could not be detected and the presence of a lower inflection point was probably caused by displacement of edema fluid and foam in the peripheral air spaces.[103] Thus, in the presence of alveolar flooding, when air often remains trapped behind airways blocked by foam and liquid, airway pressure is probably dissipated over a series of menisci, so local tissue stresses may be relatively small.[104] This suggests that shear-stress-related lung injury may play a smaller role in ARDS than previously thought.

Traditionally, PEEP has been titrated according to the response in P_{aO_2}, which indirectly reflects lung recruitment: FRC is essentially the alveolar volume and the primary determinant of P_{aO_2}.[105] In ARDS/ALI, because PEEP improves FRC, C_{RS}, and P_{aO_2}, improvements in P_{aO_2}/F_{IO_2} are used clinically to indicate lung recruitment. The ARDS Network PEEP/F_{IO_2} titration tables follow this approach.

The alternative method, advocated by proponents of open-lung ventilation, is to use P-V curves to set PEEP. Unfortunately, there are numerous interpretive ambiguities with P-V curves, including the influence of chest wall compliance,[81] regional lung differences in P-V curve characteristics,[106] lung volume history,[107] the occurrence of lung recruitment beyond the lower inflection point,[78,84] peripheral airway fluid movement,[103] effects of intrinsic PEEP,[88] whether the inflation or deflation limb should be used to set PEEP,[108] and interobserver variability in curve analysis.[82] Moreover, P-V curves use either a quasi-static incremental change in lung volume or a slow, continuous-flow inflation. Inevitably, these maneuvers alter the elastic and visco-elastic behavior of the lungs in a manner that may not reflect dynamic conditions during mechanical ventilation.[90,109] These ambiguities suggest that the open-lung ventilation approach to setting PEEP still is experimental and does not represent a *superior* approach, compared to titrating PEEP by oxygenation response, as in the ARDS Network approach.

Con: The ARDS Network Tables Do Not Represent the Best Clinical Evidence to Guide Management for Titrating PEEP/F_{IO_2} During Clinical Practice.

Weight of the Evidence

The results of the National Institutes of Health ARDS Network trial that found reduced mortality with low V_T (6 mL/kg predicted body weight) changed the standard of care in ARDS management.[34] This landmark trial included the use of an empirically derived PEEP/F_{IO_2} table for selecting these ventilator settings based on the current level of arterial oxygenation: in this case, a P_{aO_2} of $>$ 55 mm Hg and $<$ 80 mm Hg. While this PEEP/F_{IO_2} table is an integral part of the ARDS Network protocol, it must be clearly stated that this method for setting PEEP was not tested in the study and therefore carries no more weight of evidence than any other anecdotal experience.

Perhaps the simplest argument against the ARDS Network PEEP/F_{IO_2} table arises from the success of the low-V_T strategy. V_T is based on predicted body weight, calculated from the patient's height, the major determinant of lung volume being height, not actual weight. Just as the V_T strategy would have failed had patients not had V_T indexed to height, how could a single PEEP setting succeed without reference to respiratory mechanics and capacity for lung recruitment?

A simple example may prove more instructive. Consider the PEEP requirements of a 70-year-old with a body weight of 75 kg and a history of chronic lung disease, with bibasilar pneumonia and ARDS. Total C_{RS} is 60 mL/cm H_2O and chest wall compliance accounts for only 20% of this value. Then consider a 40-year-old, 220-kg patient with sepsis and respiratory failure following gastric bypass surgery. The patient's total C_{RS} is 20 mL/cm H_2O, with 70% of that value contributed by the chest wall. Both patients meet the definition for ARDS based on radiographic, hemodynamic, and gas-exchange criteria. Yet clearly the PEEP requirements in these 2 instances cannot be dictated by a single strategy governed by an oxygenation end point.

Is All ARDS the Same?

Evidence-based medicine relies on meta-analyses and the grading of evidence from a number of similar studies.[37–39] The success of an evidence-based review requires like methods and similar patient populations. As pointed out earlier in this article, the response to PEEP in animal models of lung injury and degree of shear-stress depends on the mechanism of lung injury. This prompts the question, is all ARDS the same?

Fauci et al[110] define a syndrome as "a group of symptoms and signs of disordered function related to one an-

Table 1. Comparison of Pulmonary and Extrapulmonary ARDS

	Pulmonary ARDS	Extrapulmonary ARDS
Etiology	Pneumonia: bacterial or viral	Multi-system trauma
	Inhalation of noxious agent	Transfusion-related acute lung injury
	Aspiration of gastric contents	Acute pancreatitis
	Isolated pulmonary contusion	Sepsis
	Fat embolus syndrome	Post-cardiopulmonary-bypass surgery
		Hemorrhagic shock
Histologic Changes		
Alveolar epithelium	Severe damage	Damage
Type I and II cells	Severe damage	Normal
Neutrophils	Prevalent with apoptosis	Uncommon
Fibrinous exudate	Common	Uncommon
Alveolar collapse	Severe	Severe
Interstitial edema	Absent	Severe
Capillary endothelium	Normal	Damaged
Mechanics		
Chest wall compliance	Normal	Reduced
Intra-abdominal pressure	Normal	Elevated
Esophageal pressure	Normal	Elevated
Lung compliance	Severely reduced	Reduced
Lower inflection point	$<$ 10 cm H_2O often absent	$>$ 10 cm H_2O usually present
Risk of overdistension	High	Low
Recruitment potential	Low	High
Computed tomography findings	Focal loss of aeration	Diffuse loss of aeration
Response to PEEP	Good (8–12 cm H_2O)	Excellent (10–20 cm H_2O)
Response to prone	Fair	Good

ARDS = acute respiratory distress syndrome
PEEP = positive end-expiratory pressure

other by means of some anatomic, physiologic, or biochemical peculiarity." Clearly ARDS meets this definition. Historically, Murray[111] suggested that the term was imprecise and suggested that ARDS might be one manifestation or many. Gattinoni et al[22] and others[112–116] have suggested that ARDS includes 2 types, based on the mechanism of injury. Pulmonary ARDS results from a direct injury to the lung, whereas extrapulmonary ARDS results from lung injury as part of an acute inflammatory response following nonpulmonary injury.

The difference between pulmonary and extrapulmonary ARDS was initially thought of simply as an etiologic distinction. However, work by both Pelosi and colleagues,[112,113] Vieira and colleagues,[114–115] and Rouby and colleagues[116] suggest that the distinction includes different physiologic manifestations and a mandate for different treatment approaches. Table 1 lists the differences between pulmonary and extrapulmonary ARDS.

Work by Rouby's group[114–116] in Paris is particularly instructive. They measured the P-V curves and performed scanographic assessments of lung morphology in 14 patients with ALI. They identified 2 groups of patients. In the first group, chest CT scans were characterized by diffuse lung hyperdensities present in the upper and lower lobes, and the P-V curves demonstrated low lung compliance and the presence of a lower inflection point. In the second group the CT scans were characterized by a distribution of lung hyperdensities, predominantly in the lower lobes (the upper lobes remained normally aerated), and there was higher lung compliance, without evidence of a lower inflection point. In both groups, PEEP induced significant alveolar recruitment. However, in the second group, recruitment was also associated with significant lung overdistention.

The findings from 2 patients in one of the Vieira et al studies[114] are shown in Figure 5. In both patients, PEEP is increased and there is a reduction in lung densities. However, in the patient with pulmonary ARDS (bottom) there is also substantial overdistention of nondependent lung regions. In this group, lower PEEP is required to reduce the untoward effects of overdistention. One might contend that these patients were the predominate patients in the ARDS Network trial, particularly that half of patients with lung compliance $>$ 0.50 mL/cm H_2O/kg predicted body weight.[34] This would explain why the mean PEEP levels are relatively low.

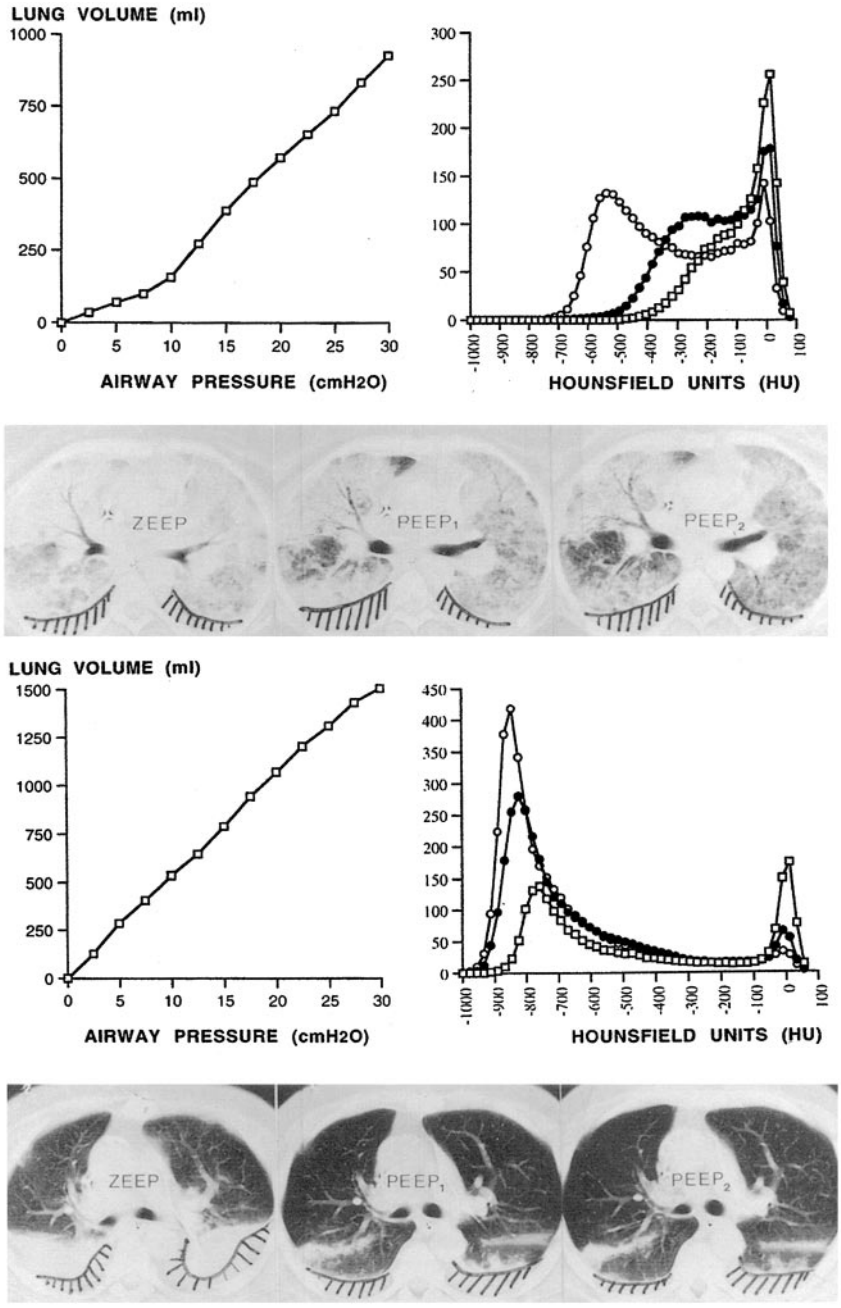

Fig. 5. Total respiratory system pressure-volume (P-V) curve (with zero end-expiratory pressure [ZEEP] conditions) and volumetric distribution of lung aeration (computed tomography [CT] attenuations in Hounsfield units [HU]) of the entire lung measured at ZEEP (open squares) and 2 positive end-expiratory pressure (PEEP) levels ($PEEP_1$ and $PEEP_2$, solid and open circles) in 2 patients with ARDS characterized by different lung morphology patterns. The dashed areas indicate pleural effusion, which was not taken into consideration for the CT analysis. In the upper part of the figure, an illustrative CT section from a patient with diffuse CT attenuations and loss of aeration is represented at ZEEP, PEEP of 12 cm H_2O ($PEEP_1$), and PEEP of 17 cm H_2O ($PEEP_2$). At ZEEP conditions, there are no normally ventilated lung regions, defined as lung areas characterized by CT attenuations ranging from −500 HU to −900 HU. After increasing levels of PEEP, nonaerated lung regions progressively decrease, whereas much of the lung parenchyma becomes normally aerated, which indicates alveolar recruitment. The threshold of overdistention (−900 HU) is never reached. In the lower part of the figure, an illustrative CT section from a patient with focal CT attenuations and loss of aeration is represented at ZEEP, PEEP of 10 cm H_2O ($PEEP_1$), and PEEP of 15 cm H_2O ($PEEP_2$). At ZEEP, the upper lobes are normally aerated, whereas the lower lobes are either poorly aerated (CT attenuations ranging from −500 HU to −100 HU) or nonaerated (CT attenuations $>$ −100 HU). With increasing PEEP, the lower lobes are recruited, as shown by a decrease in nonaerated lung volume, whereas the upper lobes are either distended or overdistended, as shown by the appearance of 250 mL of lung parenchyma characterized by CT attenuations $<$ −900 HU. (From Reference 114, with permission.)

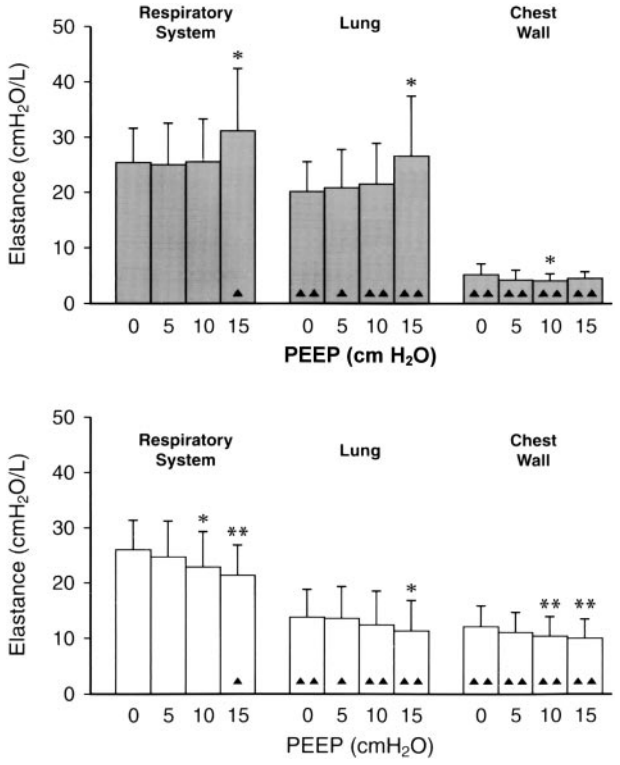

Fig. 6. Changes of static elastances of the respiratory system, lung, and chest wall as a function of positive end-expiratory pressure (PEEP) in patients with acute respiratory distress syndrome (ARDS) caused by pulmonary disease (Group 1, top panel) versus ARDS caused by extrapulmonary disease (Group 2, bottom panel). Comparison within each group: * $p < 0.05$ versus PEEP of 0 cm H_2O, ** $p < 0.01$ versus PEEP 0 cm H_2O. Comparison between the 2 groups: $p < 0.05$ versus Group 1, $p < 0.01$ versus Group 1. (From Reference 22, with permission.)

Interestingly, Gattinoni et al[22] described 2 groups of patients with pulmonary and extrapulmonary ARDS where the main differences were based on chest wall compliance. Patients with pulmonary ARDS had low lung compliance but normal chest wall compliance. In those patients, lung compliance was reduced with increasing PEEP, and chest wall compliance represented only 15% of total C_{RS}. Patients with extrapulmonary ARDS had better compliance than the patients with pulmonary ARDS, but the compliance improved with increasing PEEP. In this group, chest wall compliance was 50% of total C_{RS} (Fig. 6).

Despite apparent differences between these 2 studies, it is evident that pulmonary and extrapulmonary ARDS represent 2 distinct clinical scenarios. While both are manifest by hypoxemia and reduced pulmonary compliance, the requirement for and response to PEEP are vastly different. Under these conditions, a single PEEP/F_{IO_2} table cannot meet the needs of these critically ill patients.

The Chest Wall

Chest wall compliance represents a substantial and unpredictable effect on total C_{RS} in patients with ARDS.[22] Since the major determinant of both lung recruitment and lung injury is the transpulmonary pressure, failure to account for chest wall compliance can lead to both insufficient and excessive airway pressures.

An argument for individual application of PEEP based on estimation of chest wall compliance using esophageal pressure was presented by Talmor et al.[117] In a group of 70 medical and surgical patients with acute respiratory failure, Talmor et al found significant variations in transpulmonary pressure across the population, with a relatively high average end-expiratory pleural pressure of 17.5 cm H_2O. These authors[117] suggested that undetected variations in pleural pressure might account for inconsistent outcomes among clinical trials of ventilation strategies in ARDS. In patients with elevated pleural pressure due to abdominal distention, low PEEP and low V_T may contribute to shear-force injury from repetitive alveolar collapse at end exhalation, the end result being that the positive attributes of low-V_T ventilation might be lost due to shear injury.

Routine use of esophageal manometry in ARDS may not be warranted at this time. However, for the same level of PEEP, substantially different lung recruitment and transpulmonary pressures are generated based on esophageal and abdominal pressures. This fact alone argues against the use of a single PEEP/F_{IO_2} table for all patients with ARDS.

Pressure-Volume Curves

Earlier in this paper the discussion of P-V curves suggested that the variation and interpretation of these measurements precludes routine use. Many of these data are based on manual techniques that are in fact difficult to obtain and interpret.[78,80–84] More recently, automated P-V measurements based on a single-breath technique have been introduced on mechanical ventilators. Automation of the P-V maneuver, construction of the P-V curve (both inspiratory and expiratory), and microprocessor identification of the inflection points or point of maximum curvature greatly enhance the applicability of the P-V tool.[90–96]

While arguments abound regarding the utility of the P-V curve, whether to use the inspiratory or expiratory limb, and what the lower and upper inflection point represent, clearly microprocessor technology allows this measurement to be accomplished routinely. The use of a single breath to measure the P-V curve without reducing PEEP to 0 cm H_2O may also improve safety. The single-breath technique can be accomplished without reducing PEEP to 0 cm H_2O and in a much shorter time period. Figure 7

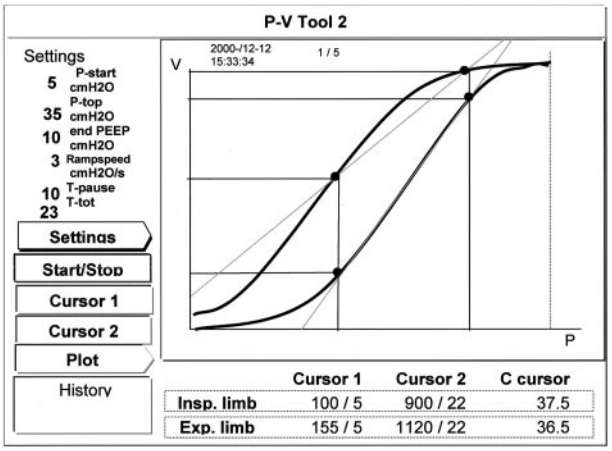

Fig. 7. Pressure-volume curve from the pressure-volume (P-V) tool of the Hamilton Galileo ventilator. The top left of the screen displays the settings. The bottom numbers depict the volume and pressure at each cursor place on the inspiratory and expiratory limb. Use of the cursors allows easy determination of the inflection points. PEEP = positive end-expiratory pressure.

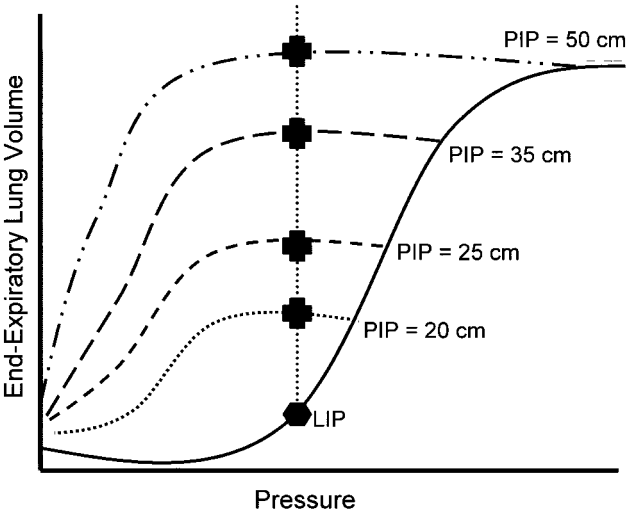

Fig. 8. Changes in end-expiratory lung volumes for a given level of positive end-expiratory pressure (PEEP) with increasing end-inspiratory pressure. PIP = peak inspiratory pressure. LIP = lower inflection point.

depicts a single-breath P-V curve that demonstrates the inspiratory and expiratory limbs. The curve was obtained with a Hamilton Galileo ventilator.

Recruitment Potential

PEEP improves arterial oxygenation by stabilizing end-expiratory lung volume and preventing alveolar collapse. The ability of PEEP to accomplish this goal depends on the lung's potential for recruitment and the inspiratory pressure. There is perhaps no greater misunderstanding surrounding PEEP than the thought that PEEP recruits the lung. PEEP is an expiratory maneuver that serves to maintain lung recruitment following a sustained inflation. This is shown nicely in Figure 8. If V_T is limited and PEEP is increased in a stepwise fashion, the amount of lung recruitment is severely limited. However, by increasing inspiratory pressure, stepwise increases in PEEP result in greater end-expiratory lung volumes.

Recruitment maneuvers and the open-lung approach are both based on the use of a sustained inflation followed by the addition of PEEP. In fact, the open-lung approach uses a PEEP decrement technique in which the airway pressure is increased and the PEEP reduced in increments while evaluating the effects on compliance.[86,87,89] By keeping the lung fully open at end-expiration, compliance improves and lung-protective ventilation is facilitated.

Recruitment potential of the lung is important, as is the appropriate selection of PEEP. In a patient with dependent atelectasis and normal-appearing lung morphology in the nondependent regions, an increase in PEEP results in a greater increase in FRC, compared to the amount of lung recruitment. In these instances the potential for overdistention is high. In the patient with an overall reduction in lung volume, an increase in PEEP results in recruitment with little overdistention. The challenge is to find a bedside technique to guide the clinician in making these assessments. One method may be the response to a sustained recruitment maneuver.

Success With Higher PEEP

Kirby et al provided the first evidence that aggressive PEEP, sometimes called super-PEEP, might have a beneficial effect on outcome in ARDS.[66] More recently, work by Amato et al[70] and Villar et al[75] also found an advantage of higher PEEP in ARDS. The question becomes, then, why did these studies find a positive effect of higher PEEP when the ALVEOLI trial[35] did not? Undoubtedly, the answer is multifactorial.

The most obvious explanation is that the individualized application of PEEP based on mechanical criteria is superior to a generic application of PEEP based on gas-exchange criteria. Using mechanical criteria allows early, aggressive application of PEEP, at a time when the lung is most amenable to recruitment. Limiting plateau pressure by selecting the appropriate V_T is the lesson from the ARDS Network trial.[34] However, when higher pressures are required (eg, for stiff chest wall or elevated intra-abdominal pressure), the use of PEEP to prevent de-recruitment may be just as important to ameliorate ventilator-associated lung injury.

Summary

Does the ARDS Network PEEP/F_{IO_2} criteria provide the best evidence for guiding the selection of PEEP and F_{IO_2} for treatment of ARDS? The answer is undoubtedly yes. If the decision is based on the best evidence, then the ARDS Network low-V_T trial and the ALVEOLI trial appear to suggest that for the routine patient with ARDS, the PEEP/F_{IO_2} table works effectively. In reality, that is what evidence-based medicine and protocols are supposed to do: provide guidance for treatment of routine patients. In more complex cases, complicated by chest wall abnormalities, refractory hypoxemia, and hemodynamic instability, a more individualized approach to PEEP and F_{IO_2} should be taken. This is where the expertise of the bedside critical care clinician has advantages over any protocol.

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Discussion

MacIntyre: In the ARDS Network PEEP-F_{IO_2} table, the P_{O_2} target range is 55–80 mm Hg. I point this out because your slide only said above 55 mm Hg. I think that's important because, by limiting it, by putting the upper limit at 80 mm Hg, it forces you to bring the PEEP down as the gas exchange gets better. That's just a minor point. Regarding a more fundamental point: there is this sort of fundamental belief that the more recruited your lung, the better your outcome. I'm not sure we have ever proved that. In the ARDS Network trial,[1] the larger-V_T strategy recruited more lung and had better compliance and better P_{O_2} than the smaller-V_T strategy, but the patients who received the larger-V_T strategy had higher mortality because of overdistention elsewhere in the lung. And again in the ALVEOLI trial,[2] the higher PEEP strategy did improve gas exchange and had much better compliance, but it made no difference in outcome. So do we really think collapsed lungs are necessarily bad? Perhaps it is the repetitive opening and closing of alveoli that really causes the problem, and that's why the low V_T is more effective, and maybe the need for PEEP is less? Maybe just leaving atelectasis alone might not be such a bad idea?

1. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. N Engl J Med 2000;342(18):1301–1308.
2. The National Heart, Blood and Lung 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.

Branson: Let me answer your first question. You are right; we don't have any proof that higher PEEP is better. The problem with the ARDS Network trials is that you are still using oxygenation as an end point. Until you agree to look at an end point of PEEP setting that has to do solely with pulmonary mechanics, you won't get the answer. There was a study on this by Amato's group[1] that looked at different PEEP levels in animals and that found that if you open the lung and recruit it, outcomes are better. This is the problem with the low-PEEP group or the high-V_T group—you increase the inspiratory volume and you've got more lung open, but you don't keep it; it keeps collapsing at end-exhalation because the PEEP is insufficient.

1. Farias LL, Faffe DS, Xisto DG, Santana MC, Lassance R, Prota LF, et al. Positive end-expiratory pressure prevents lung mechanical stress caused by recruitment/derecruitment. J Appl Physiol 2005;98(1):53–61.

MacIntyre: That's my point. I think the injury may well be from the collapse and reopening. There are 2 ways to prevent collapse and reopening. One is to keep the alveoli open with PEEP. The other, perhaps easier, is just not opening it in the first place, but instead let it stay closed so you don't get repetitive opening and closing. We are going to talk about high-frequency ventilation later on in this conference, but, conceptually, one of the reasons high-frequency ventilation might have some utility is that it avoids repetitive opening and closing of alveoli, and it's more like CPAP [continuous positive airway pressure].

Branson: I don't think leaving large volumes of atelectasis is good in terms of lung function, and it might be associated with the development of venti-

lator-associated pneumonia. High-frequency ventilation, airway pressure-release ventilation, and high PEEP with low V_T are all about getting the lung open and then moving it as little as possible. So in that case I think you are right. The question is, how do we do that, and what's the end-expiratory lung volume?

I think the study of high PEEP by Amato's group[1] showed that if you recruit the lung and use higher PEEP, you can use lower V_T and have better gas exchange, greater aeration, and lower biochemical measures of lung dysfunction. And I think that's the next study to be done in people.

1. Farias LL, Faffe DS, Xisto DG, Santana MC, Lassance R, Prota LF, et al. Positive end-expiratory pressure prevents lung mechanical stresscaused by recruitment/derecruitment. J Appl Physiol 2005;98(1):53–61.

MacIntyre: But the high-PEEP group in the ALVEOLI trial did not have lower cytokines; they were the same as the low-PEEP group.

Branson: I guess the point about both the high-PEEP and low-PEEP group in the ARDS Network study is that the problem is the end point. Just because you had *higher* PEEP does not necessarily mean that you had the *right* PEEP.

MacIntyre: But the higher PEEP clearly improved mechanics and gas exchange—*without a doubt*—but that did not translate into better outcome.

Hess: Rich, you argue that we should not be setting PEEP according to oxygenation, but rather that we should be setting it according to lung mechanics. Do we have any evidence that better lung mechanics improve outcome?

Branson: All the evidence we have is from the aforementioned Amato group study and the study by Villar et al.[1] I think we haven't done the right study yet. I don't think it matters if the patient's P_{O_2} is 80 mm Hg or 160 mm Hg, if when I set the PEEP properly, I have alveolar recruitment and I don't have loss of lung volume at end-exhalation. I don't know the answer, but that's the question, and we need to do a study to figure that out.

1. Villar J, Kacmarek RM, Perez-Mendez L, Aguirre-Jaime A. A high positive end-expiratory pressure, low-V_T ventilatory strategy improves outcome in persistent acute respiratory distress syndrome: a randomized controlled trial. Crit Care Med 2006; 34(5):1311–1318.

Steinberg: I totally agree that we have to do that study, but the question for this debate is, what is the current best evidence? I think the evidence you showed is very intriguing and hypothesis-generating, but I think that if we could get a majority of clinicians to use the ARDS Network protocol, we'd improve patient care and save lives. So I tend to think that the best evidence today supports the very practical, easy-to-use ARDS Network PEEP-F_{IO_2} scale, even if it ultimately proves not to be the very best strategy.

I'm intrigued by Neil's concept of permitting atelectasis to avoid opening and closing alveoli. I think that concept warrants more work.

Branson: My charge in this debate is to disagree and argue the other side. Clearly if the question is what's the best evidence-base, the answer is that it's the *only* evidence base. What other evidence do we have? And I agree that if you've got people who don't know what they're doing, then this is the place to start. My concept of protocols is that they allow the ICU [intensive care unit] staff to handle the "average" patient so that doctors can go handle the patients who don't fit the protocols, with their extra knowledge and skill in caring for those patients. That's what the ARDS Network PEEP-F_{IO_2} table does, in my opinion.

Hurford: I'll agree with Rich here that it sounds like this is a great thing to do, if you want to just have a one-size-fits-all strategy and you want to treat only the patients who fit the ARDS Network criteria for patient entry. But a lot of our patients don't fit those criteria, and it's hard for me to believe that I'm supposed to use the same PEEP with a 500-pound patient with severe pancreatitis—I probably can't even begin to open his lungs with a pressure less than 30 cm H_2O—as with a patient who has bilateral pneumonia after a lung-volume reduction. You're saying that we should use the same settings for both, and apply it generally across the board. I think it's fine for one particular group of patients, a standard, "garden variety" ARDS, but not for everybody.

Steinberg: I agree, but the vast majority of ARDS patients in this country are fairly routine, straightforward patients. And clinicians need guidance for those. Obviously, 5–15% of patients are exceptions to the rule; I'm not disagreeing with that. But I think the best evidence for the largest percentage of patients is the ARDS Network protocol.

Cheifetz: Taking those one step further, especially considering Bill Hurford's comment, we need to consider the world of pediatrics. We've been arguing about adult patients, but in pediatrics we do not even have a PEEP-F_{IO_2} table to argue about.

Kallet: In terms of P_{O_2} as an end point versus lung mechanics, I don't think you can divorce them that easily. If you have a low FRC [functional residual capacity], a large shunt, and a low P_{O_2}, then as you recruit the lung and FRC gets better, P_{O_2} improves, along with compliance. So I think people inevitably will tend to use P_{O_2} as a surrogate for FRC, and I think in clinical practice that is legitimate.

The other point I would make is that we have problems with the mod-

eling we're using to promote the idea of shear injury in ARDS. I think Rolph Hubmayr's work[1] is very thought-provoking. He thinks that if we have lungs that are filled with foam, and you are breaking those menisci apart with positive airway pressure, that may not result in as much shear injury as we think.

Also, remember Rimensberger's paper,[2] which suggested that if you completely recruit the lungs and get it onto the deflation limb, that you should use a PEEP below the lower inflection point? You don't need as much PEEP. That didn't turn out to be true. For the recruitment maneuvers that seem to be successful—the radical pressure control ventilation step-PEEP—you need a higher PEEP. So I think there are problems even in our modeling, that are going to require a lot more study.

1. Hubmayr RD. Perspective on lung injury and recruitment: a skeptical look at the opening and collapse story. Am J Respir Crit Care Med 2002;165(12):1647–1653.
2. Rimensberger PC, Pristine G, Mullen BM, Cox PN, Slutsky AS. Lung recruitment during small V_T ventilation allows minimal positive end-expiratory pressure without augmenting lung injury. Crit Care Med 1999;27(9):1940–1945.

Chatburn: Both P_{O_2} and compliance are surrogates for oxygen delivery, and, even though Suter's original work[1] showed that the highest oxygen delivery coincided with the highest compliance, our study[2] with pediatric patients showed that sometimes it did and sometimes it didn't, and you couldn't predict which it would be. So you can't just take on faith that good compliance and a good P_{O_2} means a good oxygen delivery.

1. Suter PM, Fairley B, Isenberg MD. Optimum end-expiratory airway pressure in patients with acute pulmonary failure. N Engl J Med 1975;292(6):284–289.
2. White MK, Galli SA, Chatburn RL, Blumer JL. Optimal positive end-expiratory pressure therapy in infants and children with acute respiratory failure. Pediatr Res 1988; 24(2):217–221.

Branson: Neil talked about pressure-controlled inverse-ratio ventilation, which always improves P_{aO_2}, but it sometimes also decreases cardiac output. We can't ignore the cardiac function, but the same is true with respect to setting PEEP. If the P-V curve says you need a PEEP of 20 cm H_2O, but at a PEEP of 16 cm H_2O your patient is hypotensive, you obviously can't go to a PEEP of 20 cm H_2O.

Ken's point is well-made, that we need a table for the average patient; but I think every patient needs a different PEEP, and it's all based on chest wall compliance and the type of ARDS. ARDS due to pneumonia is probably very different than ARDS in a trauma patient with a crushed pelvis and a grade 4 liver laceration and who has had 20 units of blood and 40 units of crystalloid and platelets and an intra-abdominal pressure already at 20 mm Hg. At PEEP of 10 or 15 cm H_2O the lungs are still airless at end-exhalation.

On looking at our ARDS patients right after the ARDS Network study was published, we said, "Boy, that's not enough PEEP." Clearly half the patients admitted to our ICU with ARDS would not have qualified for the ARDS Network trial, by the exclusion criteria. We are a surgery trauma unit, and that's different than a community hospital that usually has people with chronic lung disease who get pneumonia or people with other kinds of pneumonia. Those are different patients, and it's not just that the surgeons are "cowboys" and want to do everything, and it's not just that in the medical ICU they want to do as little as possible to avoid harming the patient.

Esteban et al[1] found that there were patients around the world (I think it was 20 percent of the patients) on no PEEP at all. I think all these patients should be on at least 5 cm H_2O. The ventilator should no longer go to zero PEEP; it should stop at 5 cm H_2O and go up from there.

1. Esteban A, Anzueto A, Frutos F, Alia I, Brochard L, Stewart TE, et al; Mechanical Ventilation International Study Group. Characteristics and outcomes in adult patients receiving mechanical ventilation: a 28-day international study. JAMA 2002; 287(3):345–355.

Hess: I think the argument for customizing PEEP and V_T, as far as that goes, in the hands of a good doctor and a good respiratory therapist (such as the people in this room) is very seductive and very convincing perhaps. But we need to remember that most ARDS patients are not taken care of by people like the people in this room. They are taken care of in community hospitals where there's not an intensivist there all day long; there may not be a respiratory therapist in the unit all day long. I'm agreeing with Ken in that we need to think about a way that we can make this useful to those clinicians and their patients.

Myers: What Rich Branson said earlier makes a lot of sense. We've had that experience with other protocols. Protocols standardize care and allow us to collect data to provide good evidence that can help those clinicians that Dean's talking about. But data sometimes give us as many questions as they do answers, and make us go back and take another look. That's the beauty of having these things. Ira made a very good point that while we're debating this PEEP-F_{IO_2} table, we don't yet have anything like it for pediatric patients, because the studies have not been done.