Point: Should Positive End-Expiratory Pressure in Patients With ARDS Be Set on Oxygenation? Yes

Abbreviations: ALI = acute lung injury; LIP = lower inflection point; PEEP = positive end-expiratory pressure; Pflex = inflection point; PV = pressure-volume

Positive end-expiratory pressure (PEEP) is externally applied through the ventilator circuit during mechanical ventilation. In injured regions with airless alveoli capable of being opened (recruitable alveoli), PEEP may diminish ventilator-induced lung injury by decreasing cyclic collapse and reopening. Alveolar recruitment may improve ventilation-perfusion matching and reduce exposure to oxygen (a cellular toxin). In less injured or healthy lung regions, PEEP may cause overdistention injury. Balancing recruitment and overdistention effects of PEEP is an important clinical challenge. We know little about the interactions between PEEP and FIO_2 , between circulatory status and PEEP/ FIO_2 used to increase arterial oxygenation, and between PEEP and lung injury etiology. Thus, the best strategy for adjusting PEEP remains uncertain. Two strategies are common: (1) titration of PEEP based on static or dynamic respiratory system pressure-volume (PV) relationships and (2) pairing of PEEP and FIO_2 into a PEEP/ FIO_2 table.

PV RELATIONSHIPS TO GUIDE PEEP

This approach evaluates respiratory system compliance. Patients commonly are heavily sedated or paralyzed to minimize voluntary or involuntary muscle contractions, including coughing and bronchoconstriction, respectively. Muscle contraction and coughing alter respiratory system PV curves and hinder reproducibility. Both regional variability of lung injury and nonreproducibility of bedside PV data have likely contributed to mixed clinical results.

A single-compartment lung model analyzing the PV curve between functional residual capacity and total lung capacity associates the lower inflection point

(LIP) with the recruitment pressure threshold and the upper inflection point with the overdistention pressure threshold (Fig 1). However, the regional variability (nonuniformity) of lung injury makes applicability questionable. Alveolar recruitment and overdistention overlap, and no clear separation can be found in most patients.¹ Some lung regions will not recruit.² Indeed, several studies have found only a weak relationship between the LIP and alveolar recruitment.³⁻⁶ Recruitment occurs both below and above the LIP, and, thus, alveoli could be opening and closing during tidal ventilation, even after application of PEEP up to 15 cm H_2O .^{4,6,7} Further, the LIP often is not discernible or may be lower than commonly applied PEEP levels.⁶

Two trials of PEEP determined from PV curve analysis strategies yielded different effects on mortality despite similar beneficial effects on duration of ventilation.^{8,9} Importantly, clinical outcomes in these studies cannot be attributed to alteration of PEEP alone because both trials also compared lower tidal volumes to larger tidal volumes. A strategy to remove chest wall effects on respiratory system PV curves by

FIGURE 1. The inspiratory limb of the pressure (x-axis)-volume (y-axis) curve is characteristically sigmoid. Along the continuum of increasing pressure and volume (a-c), alveoli (represented by ovals and circles) progressively distend. Below the lower inflection point (a), increased pressure may recruit airless alveoli. Between the lower and upper inflection points (b), open alveoli distend with increased pressure. Above the upper inflection point (c), alveoli may overdistend with increased pressure and become injured (indicated by the dashed line).

estimating transpulmonary pressure with esophageal manometry looks promising. The $\text{PaO}_2/\text{FIO}_2$ ratio was 88 mm Hg higher in the esophageal manometry group ($P = .002$) at 72 h, and 28-day mortality was lower in the experimental group ($P = .055$).¹⁰ However, esophageal manometry may not yet be practical in routine ICU care.

A simple assessment of PV relationships is the stress index: the analysis of pressure change over the tidal breath with constant inspiratory flow. The stress index may be useful in recognizing alveolar recruitment and alveolar hyperinflation during the tidal breath.^{9,10} One study compared the stress index titration of PEEP in 15 subjects¹¹ with the use of the PEEP/ FIO_2 table from the ARDS Network low tidal volume ventilation trial.¹² The authors found that the stress index titration group had lower PEEP, higher respiratory system compliance, and lower inflammatory plasma cytokines.¹¹ These results are limited by subject selection, surrogate outcome use,¹³ sedation requirement, and potential confounding of chest wall PV relationships.³

In summary, bedside PV relationship approaches to setting PEEP are oversimplified, yield noisy signals, are difficult to obtain and reproduce without heavy sedation or paralysis, and have not produced important clinical outcomes. Use of PV relationships to set PEEP in current clinical practice thus remains limited.

PAIRING PEEP AND FIO_2

Clinical investigations of smaller tidal volumes with restriction of plateau pressure in humans appeared in the late 1990s and in 2000 with mixed results.^{8,14-16} Most of the larger studies used a PEEP/ FIO_2 table (Table 1) because it was logical, required no sedation or paralysis, and was user friendly. PEEP/ FIO_2 tables usually incorporate an upper pressure limit and a reasonable (but not necessarily maximal) arterial oxygenation target, and they attempt to balance concerns of overdistention lung injury and oxygen toxicity.

Although PEEP/ FIO_2 tables are crude and may not balance perfectly the risks and benefits of PEEP and FIO_2 ,¹¹ they provide a reasonable bedside strategy in acute lung injury (ALI)/ARDS. Three clinical trials have explored different PEEP/ FIO_2 combinations with $\leq 6\text{-mL/kg}$ predicted body weight tidal volumes. In two of these trials, investigators compared higher PEEP with lower PEEP using different PEEP/ FIO_2 tables for each group and a target PaO_2 of 55 to 80 mm Hg.^{13,17} The groups in both trials had similar hospital mortality. In a third large clinical trial, investigators compared subjects with ARDS treated with PEEP 5 to 9 cm H_2O with subjects treated with PEEP titrated upward until the plateau

Table 1—Paired FIO_2 and PEEP

FIO_2	PEEP, cm H_2O
0.3	5
0.4	5
0.4	8
0.5	8
0.5	10
0.6	10
0.7	10
0.7	12
0.7	14
0.8	14
0.9	14
0.9	16
0.9	18
1.0	18
1.0	20
1.0	22
1.0	24

Adapted from the ARDS Network.¹² PEEP = positive end-expiratory pressure.

pressure was maximally 28 to 30 cm H_2O .¹⁸ Hospital mortality did not differ ($P = .30$) between the groups. However, ventilator-free days were higher in the high-PEEP group, and surrogate outcomes of oxygenation improved. Mercat et al¹⁸ did not evaluate the performance of PEEP/ FIO_2 tables in either group. Their methodologic approach is feasible in the clinical environment, but it is unclear how this approach compares to the simple use of paired PEEP/ FIO_2 tables.

Two recent meta-analyses including all three trials confirmed that higher PEEP was not associated with decreased mortality.^{19,20} However, in one of these meta-analyses,²⁰ the subgroup of subjects with more severe lung injury (ie, those with $\text{PaO}_2/\text{FIO}_2 < 200$) benefited from a high PEEP strategy, raising the question of tailoring management according to the admission $\text{PaO}_2/\text{FIO}_2$. For example, the PEEP/ FIO_2 table might differ according to the degree of potentially recruitable lung.²¹ Future PEEP/ FIO_2 tables might incorporate (1) different tables for different admission $\text{PaO}_2/\text{FIO}_2$ or different chest radiographic infiltrate distributions, (2) different PEEP/ FIO_2 combinations based on responsiveness to PEEP,¹¹ and (3) chest CT scan²¹ or electrical impedance tomography²² information. Finally, better understanding of appropriate arterial oxygen targets would also influence design of future PEEP/ FIO_2 tables and of further studies. Of note, patients with ALI/ARDS may have greater alveolar recruitment potential than patients with other etiologies of lung failure.²¹ These approaches build on the putative wisdom of tailoring interventions to individual patient physiology with the standardization and facile implementation of a PEEP/ FIO_2 table.

Current best evidence for the management of patients with ALI/ARDS includes a simple PEEP/FiO₂ table as an integral component of the 6-mL/kg predicted body weight tidal volume strategy. It is part of a reproducible experimental method used in trials prior to and since publication of the original ARDS Network strategy. Experienced intensivists have judged the PEEP/FiO₂ table useful, and no other practical, evidence-based approach appears superior. The PEEP/FiO₂ table, although not perfect, is, thus, a reasonable mechanical ventilation strategy component that should be used in patients with ALI. The PEEP/FiO₂ table is a method that can translate research results into clinical practice more easily than more complex management strategies.

SUMMARY

Complex techniques of managing PEEP, such as with analysis of PV relationships, suffer from several important limitations. Inflection points on the PV curve are not tightly linked to alveolar recruitment. Moreover, these PV strategies are time consuming, difficult to interpret, and have yet to affect clinical outcomes. In contrast, PEEP/FiO₂ tables provide a reasonable treatment strategy, are clinically easy to use, and are amenable to widespread application. We conclude that best current ventilator practice in patients with ALI/ARDS includes a PEEP/FiO₂ table as part of a low tidal volume strategy (≤ 6 mL/kg predicted body weight). Although imperfect, PEEP/FiO₂ tables are a reasonable approach.

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Counterpoint: Should Positive End-Expiratory Pressure in Patients With ARDS Be Set Based on Oxygenation? No

Nearly 40 years ago, novel animal studies laid the foundation for lung-protective ventilation. Both lung overdistention and the absence of positive end-expiratory pressure (PEEP) were linked to gross and histologic lung injury.¹ Tidal volume was shown subsequently to be clinically important: 6 mL/kg compared with 12 mL/kg predicted body weight reduced absolute mortality by 9% in patients with acute lung injury (ALI) or ARDS.² PEEP is biologically relevant, too: Limiting tidal recruitment and derecruitment reduces lung inflammation.^{3,4,5,6} Yet PEEP may provoke deleterious effects, so that choosing the appropriate level requires balancing benefits and costs. In addition, PEEP should be individualized—in the right amount, to those most likely to benefit.

In most patients with ALI and ARDS, the clinician chooses a level of PEEP based on oxygenation. Typically, low oxygen saturation leads to an increase in PEEP, whereas elevated saturations prompt a reduced PEEP. One widely used approach is that devised by the ARDS Network, in which PEEP and FIO_2 combinations are chosen from a table to achieve oxygenation goals.² Basing the dose of PEEP on arterial oxygenation has multiple, serious drawbacks, however. First, the degree to which PEEP recruits lung varies dramatically from patient to patient. For example, extrapulmonary ARDS tends to respond to PEEP with higher compliance and CT scan evidence of recruitment, whereas pulmonary ARDS does not.⁷ Similarly, those with ARDS harbor more potential for recruitment than those with ALI, but, overall, the amount of recruitable lung is modest (13%).⁸ To the extent that PEEP is valuable because it prevents cyclic recruitment and derecruitment, a rational approach should base the level of PEEP on the degree of recruitability, rather than assuming all lungs behave identically.

In patients with ALI and ARDS, lung units collapse largely because of compressive forces, especially in dependent lung zones. One would anticipate PEEP to be effective in keeping the lung open when it produces a positive transpulmonary pressure. Surprisingly, when patients are managed according to the ARDS Network standard of care recommendations, transpulmonary pressure is most often negative, despite PEEP.⁹ The reasons that pleural pressure is often so high include the weight of edematous lung, raised abdominal pressure,⁷ and expiratory muscle contraction.¹⁰ Thus, even when lung is recruitable,