How Much PEEP? Do We Need Another Meta-Analysis?

That ventilator-induced lung injury can result from inappropriate ventilator settings is now well accepted. Tidal volume limitation (6 mL/kg ideal body weight) and inspiratory pressure limitation (plateau pressure less than 30 cm H_2O) are now standards of care to avoid over-distention injury for patients with acute lung injury (ALI) and the acute respiratory distress syndrome (ARDS).[1] It is also accepted that cyclical alveolar opening and closing throughout the respiratory cycle is injurious.[2] Thus, PEEP sufficient to maintain alveolar recruitment is also important. There should be no argument that no PEEP (zero) causes harm in patients with ALI/ARDS. However, unlike tidal volume and plateau pressure limitation, the level of PEEP that should be used is controversial.

To date, 6 clinical trials have assessed the application of lower versus higher levels of PEEP in patients with ALI/ARDS (Table 1).[3-8] Of these, only two have reported a significant reduction in mortality with the use of higher levels of PEEP.[3,7] In both of these studies, only patients with ARDS were enrolled and the level of PEEP was determined from the respiratory system pressure-volume curve. However, 2 interventions were applied in both of these studies. That is, a higher level of PEEP was combined with a lower tidal volume. Therefore, it is unknown whether the mortality benefit was related to the higher PEEP level, lower tidal volume, or combined effect of the 2 interventions.

There have been 3 clinical trials in which tidal volume was held constant at 6 mL/kg ideal body weight, but in which patients were randomly assigned to receive either a higher level of PEEP or a lower level of PEEP.[4-6] Each of these studies enrolled patients with both ALI and ARDS. In the groups of patients receiving higher levels of PEEP, there were benefits such as higher P_{aO_2}/F_{IO_2}, higher respiratory-system compliance, less frequent use of rescue therapies for refractory hypoxemia, and a greater number of ventilator-free days. But, perhaps disappointing for many, there was no significant reduction in mortality for patients receiving higher PEEP. A more recent study used esophageal pressure measurements to set PEEP according to transpulmonary pressure. Although this resulted in a higher P_{aO_2}/F_{IO_2}, compared to patients receiving a more conservative level of PEEP, the trial was not designed to demonstrate a mortality benefit.[8]

Within the critical care community there has been intense debate surrounding the likely reasons for the negative results of the clinical trials comparing PEEP levels. Perhaps PEEP was applied using the wrong strategies. Perhaps the groups receiving higher and lower PEEP were contaminated, in that each contained patients who received benefit and harm—thus no difference when the groups were compared against one another (selection bias). Or, perhaps each study, although relatively large, was underpowered to detect a small, but clinically important, difference.

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The value of a meta-analysis is that, by pooling data from several studies, statistical power is improved. Thus, results from smaller negative studies might prove positive when combined in a meta-analysis. In this issue of RESPIRATORY CARE is reported a meta-analysis of studies evaluating higher versus lower levels of PEEP in patients with ALI/ARDS.[9] But the meta-analysis by Dasenbrook is not the first, and a fair question might be, do we need another meta-analysis on this subject? There have been 4 previous meta-analyses published on the topic of higher versus lower PEEP in patients with ALI/ARDS (Table 2).[10-13] But each of these used slightly different methodology than Dasenbrook and none of the others include the paper by Talmor.[8] So publishing the meta-analysis by Dasenbrook is easy to defend.

If alveolar recruitment potential is low, an increase in PEEP will have a marginal effect on shunt and P_{aO_2}, and it may contribute to over-distention of already open alveoli. This results in decreased respiratory-system compliance, increased dead space, and redistribution of pulmonary blood flow to unventilated alveoli. However, when the potential for recruitment is high, the benefit of higher levels of PEEP may outweigh the potential for harm due to over-distention.[14] When the P_{aO_2}/F_{IO_2} is lower (ARDS rather than ALI), the potential for recruitment may be greater[15] and higher PEEP may lead to lower mortality.[10] The potential for recruitment may also be greater when chest wall compliance is reduced.[8,16] Alveolar recruitment can be identified in an individual patient by a trial of increased PEEP. Alveolar recruitment has likely occurred if an increase in PEEP results in an increase in P_{aO_2}, a decrease in P_{aCO_2}, and improved respiratory-system compliance.[2,15]

The best technique to select PEEP is unclear. There is heterogeneity in each of the meta-analyses, because each

Table 1. Studies That Have Compared Higher Versus Lower Levels of PEEP In Patients With Acute Lung Injury and the Acute Respiratory Distress Syndrome

First Author	Patients (n)	Intervention Group (higher PEEP)	Control Group (lower PEEP)	Average PEEP Difference (cm H_2O, %)	Major Finding
Amato[3]	53	V_T 6 mL/kg, PEEP 16.4 ± 0.4 cm H_2O	V_T 12 mL/kg, PEEP 8.7 ± 0.4 cm H_2O	7.7 (46)	Mortality reduced from 71% to 38% with intervention
Brower[4]	549	V_T 6 mL/kg, PEEP 13.2 ± 3.5 cm H_2O	V_T 6 mL/kg, PEEP 8.3 ± 3.2 cm H_2O	4.9 (37)	Similar mortality, higher P_{aO_2}/F_{IO_2}, and higher compliance with higher PEEP
Villar[7]	103	V_T 7.3 ± 0.9 mL/kg, PEEP 14.1 ± 2.8 cm H_2O	V_T 10.2 ± 1.2 mL/kg, PEEP 7.3 ± 0.9 cm H_2O	6.8 (48)	Mortality reduced from 53% to 32% with intervention
Mercat[6]	767	V_T 6 mL/kg, PEEP set to reach a plateau pressure of 28–30 cm H_2O (14.6 ± 3.2 cm H_2O)	V_T 6 mL/kg, moderate PEEP strategy of 5–9 cm H_2O (7.1 ± 1.8 cm H_2O)	7.5 (51)	Similar mortality, higher-PEEP group had more ventilator-free days, higher compliance, better oxygenation, and less use of adjunctive therapies
Meade[5]	983	V_T 6 mL/kg, PEEP 14.6 ± 3.4 cm H_2O	V_T 6 mL/kg, PEEP 9.8 ± 2.7 cm H_2O	4.8 (32)	Similar mortality, higher-PEEP group had lower rate of refractory hypoxemia, death with refractory hypoxemia, and use of rescue therapies
Talmor[8]	61	Esophageal pressure guided PEEP (V_T 7.1 ± 1.3 mL/kg and PEEP 17 ± 6 cm H_2O)	ARDS Network low-PEEP table (V_T 6.8 ± 1 mL/kg and PEEP 10 ± 4 cm H_2O)	7.6 (43)	No significant difference in mortality, higher-PEEP group had higher P_{aO_2}/F_{IO_2}

Table 2. Meta-Analyses of Studies That Have Compared Higher Versus Lower PEEP

First Author	Studies Included	Principal Finding	Comments
Oba[11]	Amato[3] Brower[4] Meade[5] Mercat[6] Villar[7]	Reduction in hospital mortality in favor of high PEEP (RR 0.89, 95% CI 0.80–0.99, P = .03).	Analysis included studies that used 2 simultaneous interventions (higher PEEP with lower V_T vs lower PEEP with higher V_T).
Putensen[13]	Brower[4] Meade[5] Mercat[6]	Higher PEEP did not reduce hospital mortality (OR 0.86, 95% CI 0.72–1.02, P = .08)	Also reported that lower V_T reduced hospital mortality (OR 0.75, 95% CI 0.58–0.96, P = .02) compared with higher V_T at similar PEEP.
Phoenix[12]	Brower[4] Meade[5] Mercat[6]	Higher PEEP did not reduce hospital mortality in the 3 trials in which 2 levels of PEEP were used, but V_T was held constant (RR 0.90, 95% CI 0.72–1.02, P = .077)	Concluded that high PEEP may have a clinically relevant mortality benefit.
Briel[10]	Brower[4] Meade[5] Mercat[6]	In patients with ARDS, benefit from higher PEEP (RR 0.90, 95% CI 0.81–1.00, P = .049), in patients without ARDS, no benefit from higher PEEP (RR 1.37, 95% CI 0.98–1.92, P = .07).	Used patient-level data rather than pooled results.
Dasenbrook[9]	Brower[4] Meade[5] Mercat[6] Talmor[8]	No significant difference in 28-day mortality for higher versus lower PEEP (RR 0.90, 95% CI 0.79–1.02) or in hospital mortality for higher versus lower PEEP (RR 0.94, 95% CI 0.84–1.05)	Pneumothorax rate *not* increased with higher PEEP.

RR = risk ratio
OR = odds ratio

primary study used a different method to select PEEP. Indeed, a variety of techniques for PEEP selection have been described (Table 3) and it is unclear whether any one is superior to the others. We published 2 case reports recently, in the same issue of RESPIRATORY CARE, in which one described the use of esophageal manometry to set PEEP[19] and the other used pressure-volume curves to set PEEP.[20] Some have suggested a decremental, rather than an incremental, PEEP trial.[21,22] Using this approach, PEEP is set ≥ 20 cm H_2O and then decreased to identify the level that produces the best compliance. However, a recent study was unable to show differences in patient outcomes

Table 3. Methods for Selecting PEEP

Oxygenation	Use of a table of F_{IO_2} and PEEP combinations to achieve P_{aO_2} or S_{pO_2} within a targeted range.[1,4,5]
Compliance	Use of PEEP that results in the highest respiratory-system compliance.[17]
Stress index	The pressure-time curve is observed during constant-flow inhalation for signs of tidal recruitment and over-distention.[18]
Esophageal pressure	Estimate the intra-pleural pressure via esophageal balloon measurement to determine the optimal level of PEEP required.[8]
Pressure-volume curve	PEEP is set slightly greater than the lower inflection point.[3,7]

when setting PEEP by a table was compared to a method using recruitment maneuvers and decremental PEEP.[23]

Use of higher levels of PEEP, when compared to use of moderate levels of PEEP, does not lead to lower mortality in groups of unselected patients with ALI/ARDS. It is becoming increasingly recognized that different PEEP strategies may be needed for different types of ARDS—for example, when the lungs are highly recruitable versus poorly recruitable. Unfortunately, given the complexity of conducting clinical trials in patients with ALI/ARDS, it is unlikely that high-level studies of higher versus lower levels of PEEP will be conducted in patients selected based on alveolar recruitment potential.

So where does this leave us at the bedside? First, PEEP is good for patients with ALI/ARDS. The debate is not whether PEEP should be used, but rather how much PEEP should be used. Second, the available evidence suggests that modest levels of PEEP may be more appropriate for ALI ($P_{aO_2}/F_{IO_2} > 200$ mm Hg), whereas higher levels of PEEP should be used for ARDS ($P_{aO_2}/F_{IO_2} \leq 200$ mm Hg). Higher levels of PEEP should be reserved for patients in whom alveolar recruitment can be demonstrated. Increasing PEEP while driving up the plateau pressure to harmful levels makes no sense. Finally, appropriately powered randomized controlled studies are needed to determine whether there is a best method to set PEEP.

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