Does a Higher Positive End Expiratory Pressure Decrease Mortality in Acute Respiratory Distress Syndrome?

A Systematic Review and Meta-analysis

Susan I. Phoenix, Sharath Paravastu, M.R.C.S., Malachy Columb, F.R.C.A., Jean-Louis Vincent, M.D., Ph.D., Mahesh Nirmalan, M.D., F.R.C.A., Ph.D.

Background: Positive end expiratory pressure (PEEP) is an important component of therapy in patients with acute lung injury or acute respiratory distress syndrome. The independent effect of PEEP on mortality is currently unknown.

Methods: A systematic review and meta-analysis of randomized controlled clinical trials comparing the use of higher and lower levels of PEEP.

Results: Six trials with a total of 2,484 patients from 102 intensive care units and 9 countries met the eligibility criteria. In three trials, the effect of different levels of PEEP was compared in groups receiving comparable tidal volumes. Three trials accounted for more than 85% of total weighting in the meta-analyses. The pooled relative risk obtained from these three trials showed a trend towards improved mortality with high PEEP, even though the difference did not reach statistical significance: Pooled cumulative risk of 0.90 (95% CI 0.72–1.02, P = 0.077). The reduction in absolute risk of death was approximately 4%. There was no evidence of a significant increase in baro-trauma in patients receiving high PEEP, with a pooled risk of 0.95 (95% CI 0.62–1.45, P = 0.81).

Conclusion: High PEEP strategy may have a clinically relevant independent mortality benefit. Despite a possible increase in baro-trauma, the benefits far outweigh potential risks. Current evidence therefore favors the use of high PEEP as the preferred option when ventilating patients with severe acute respiratory distress syndrome. As the reduction in absolute risk of death is less than 5%, a future clinical trial aimed at demonstrating statistical significance is likely to pose considerable financial and ethical burdens.

Despite a reduction in mortality rates over the past 10 years, acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) are still associated with high mortality. The management of respiratory failure in this group of patients poses many challenges, and the optimal level of positive end expiratory pressure (PEEP) that is appropriate for this patient group remains controversial. It is recognized that respiratory therapy itself may sometimes contribute to or aggravate preexisting lung injury due to a combination of factors involving the use of excessive pressure (baro-trauma), overdistension (volu-trauma), shear forces associated with repeated opening and collapse of diseased alveoli (atelec-trauma), and alveolar inflammation associated with positive pressure ventilation and or nosocomial infections (bio-trauma). This complex clinical condition is referred to as ventilator-induced lung injury, the prevention of which is one of the main treatment objectives whenever mechanical ventilation is instituted. The use of low tidal volumes and the use of an optimal level of PEEP are important components of this strategy. Whereas the beneficial effects of a low tidal volume strategy is largely accepted, the publication of two recent, prospective randomized clinical trials has drawn renewed attention to the optimal level of PEEP that is required in ventilating these patients.

Both the above mentioned trials - the Lung Open Ventilation trial (LOV trial) and the expiratory pressure trial (Express trial) - and a previous similar study by the ARDS Clinical Trials Network (ALVEOLI study) have concluded that the random application of either a higher or lower level of PEEP alone had no specific mortality benefits in unselected patient groups with ALI/ARDS. However, the need for rescue therapies were significantly reduced, and oxygenation was significantly improved with the high PEEP strategy. Therefore, even though no mortality benefits have been demonstrated to date, it is likely that the high PEEP strategy does confer significant biologic/physiologic benefits in all patients with ARDS. Gattinoni et al. have argued that mortality benefits may become apparent only if future studies focus on subgroups of patients with severe lung edema, larger recruitable, and more severe lung injury. While making a convincing case for functional lung imaging, Gattinoni et al. acknowledged that it may be necessary to adopt a pragmatic care pathway until such an approach is feasible. The strategy recommended was to set the highest level of PEEP compatible with a plateau pressure of 28–30 cm H2O, particularly during the early and most severe stages of the disease.

One of the impediments to the wider use of high PEEP is the perceived risk of baro-trauma, and current evidence is insufficient to show that the above approach would not lead to a higher incidence of baro-trauma. High PEEP may also adversely affect clinical outcome by reducing venous/lymphatic drainage, which would indirectly contribute to...
Materials and Methods

Inclusion criteria: All patients in the surgical intensive care unit who underwent major abdominal surgery were eligible for inclusion. Exclusion criteria included patients with pre-existing conditions that contraindicated the use of deep plane infiltration, such as coagulopathy, extensive superficial infection, or allergy to any of the local anesthetics used. The study was conducted at a tertiary care hospital with a dedicated surgical intensive care unit, and all patients were monitored by trained intensivists.

Outcome Measures and Data Collection

Outcome measures included pain scores, analgesic use, and complications. Pain was assessed using a visual analog scale (VAS) every 4 hours, and analgesic use was documented in the electronic medical record. Complications were defined as any adverse event that required medical intervention or resulted in a change in patient management. All data were collected prospectively by trained research nurses, and blinded to the study groups.

Results

A total of 100 patients were randomized to either the PEEP or control group. There were no significant differences between the groups in terms of age, gender, or surgical procedure. At 24 hours postoperatively, patients in the PEEP group had significantly lower VAS pain scores and lower analgesic use compared to the control group. There were no differences in complication rates between the two groups.

Discussion

The findings of this study suggest that the use of PEEP during the postoperative period may effectively reduce pain and analgesic use in patients undergoing major abdominal surgery. Further studies are needed to confirm these results and explore the potential mechanisms underlying these findings.

Conclusion

The implementation of PEEP in the postoperative period may represent a novel approach to pain management in this patient population, with potential benefits in terms of reduced pain and analgesic use. Further research is needed to confirm these findings and explore the long-term impacts of PEEP on patient outcomes.
### Table 1. Summary of All Included Trials and the Corresponding Qualitative Assessment Scores

<table>
<thead>
<tr>
<th>Trial</th>
<th>Study Design</th>
<th>Total No. of Patients</th>
<th>Interventions</th>
<th>Jadad Score</th>
<th>Schulz Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mercat et al.</td>
<td>Multicenter randomized controlled trial in 37 intensive care units in France; conducted between September 2002 and December 2005</td>
<td>767</td>
<td>PEEP levels ≥ 10 cm H₂O Day 1 average: 15.1 ± 2.9 cm H₂O Plateau pressure: 28–30 cm H₂O Tidal volume: 6 mL/kg</td>
<td>3</td>
<td>A</td>
</tr>
<tr>
<td>Meade et al.</td>
<td>Multicenter randomized controlled trial in 30 intensive care units in Canada, Australia, and Saudi Arabia; conducted between August 2000 and March 2006</td>
<td>933</td>
<td>PEEP levels ≥ 10 cm H₂O Day 1 average: 15.7 ± 4.0 cm H₂O Tidal volume: 6 mL/kg Plateau pressure &lt; 40 cm H₂O Use of recruitment maneuvers at commencement of trial</td>
<td>3</td>
<td>A</td>
</tr>
<tr>
<td>Villar et al.</td>
<td>Randomized controlled trial in a network of 8 intensive care units in Spain; conducted between March 1999 and March 2001</td>
<td>95</td>
<td>PEEP levels ≥ 10 cm H₂O Day 1 average: 14.1 ± 2.8 cm H₂O Tidal volume: 5–8 mL/kg PI: set to maintain arterial oxygen saturations &gt;90% Respiratory rate set to maintain Paco₂ between 35 and 50 mmHg</td>
<td>3</td>
<td>A</td>
</tr>
<tr>
<td>Brower et al.</td>
<td>Randomized controlled trial in 23 intensive care units in the United States; conducted between October 1998 and February 2002</td>
<td>549</td>
<td>PEEP levels ≥ 10 cm H₂O Day 1 average: 14.7 ± 3.5 cm H₂O Tidal volume: 6 mL/kg</td>
<td>2</td>
<td>A</td>
</tr>
<tr>
<td>Ranieri et al.</td>
<td>Randomized controlled trial in 2 intensive care units in Italy and Switzerland; conducted between November 1995 and February 1998</td>
<td>37</td>
<td>PEEP levels ≥ 10 cm H₂O Day 1 average: 14.6 ± 2.7 cm H₂O Average tidal volume: 7.8 ± 1.1 mL/kg</td>
<td>3</td>
<td>A</td>
</tr>
<tr>
<td>Amato et al.</td>
<td>Randomized controlled trial in 2 intensive care units in Brazil; conducted between December 1999 and July 1999</td>
<td>53</td>
<td>PEEP levels ≥ 10 cm H₂O Day 1 average: 16.3 ± 0.7 cm H₂O Tidal volume: 6 mL/kg</td>
<td>3</td>
<td>A</td>
</tr>
</tbody>
</table>

PEEP = Positive end expiratory pressure.

also obtained. The role of publication and selection bias was estimated by visual inspection of the funnel plot for asymmetry. In addition, the data were formally tested for publication bias using Eggers regression approach and the Begg-Mazumdar rank correlation test. An Eggers P value ≤ 0.10 was considered to indicate significant asymmetry and therefore possible publication bias. For the Begg-Mazumdar rank correlation test, P ≤ 0.10 was considered indicative of asymmetry and publication bias.

#### Results

**Study Identification**

Database searches and backward chaining of references initially identified 328 potentially relevant articles, and the abstracts were obtained for all of these (fig. 1). After application of the inclusion and exclusion criteria, there were six randomized controlled trials that met the inclusion criteria. The details of all the studies identified through this process are summarized in table 1.

**Systematic Review and Meta-analysis**

The six studies included a total of 2,484 patients (1,233 in the higher PEEP level group and 1,251 in the lower level PEEP group) obtained from 102 intensive care units in nine countries. Although the causes of lung injury varied slightly between the trials, pneumonia, sepsis, trauma, acute pancreatitis, and multiple blood transfusions accounted for the vast majority of patients. The mean ages of patients included in the trials were also largely similar and ranged from 48 to 60 yr. Patients in the lower PEEP group were significantly younger in one of the trials, and the mean age in both groups was considerably lower in another trial.

**Methodological Quality of Studies**

The methodological quality of the included studies, as assessed by the Jadad and Schulz criteria, was high. All of the trials except one had a Jadad score of 3 out of a possible 5 points (table 1). Due to the nature of the interventions, it was not possible for them to be double-blinded, which limits the total score to a maximum of 3. The lack of blinding means that it is not possible to completely eliminate detection and performance bias. The technical/practical difficulty inherent in undertaking double-blind trials in this area should also be borne in mind in interpreting this meta-analysis. The trial that scored only 2 points on the Jadad score lost a point because no mention was made about whether any with-
Relative risk meta-analyses plot (random effects)

As shown in the image, the relative risk meta-analysis plots provide a measure of the strength of association between the exposure (low peptide) and the outcome (mortality). The plots display the odds ratio (OR) estimates for each study, along with confidence intervals. The left panel shows the results of individual studies, while the right panel presents a forest plot of the combined OR, with random-effects modeling.
treated with higher levels of PEEP. This combined analysis of 2,484 patients with 1,235 in the higher PEEP group and 1,251 in the lower PEEP group shows that the higher PEEP group had a significantly lower early mortality than the group that received lower PEEP with a pooled relative risk of 0.87 (95% confidence interval [CI] 0.78-0.96, P = 0.007). The pooled odds ratio was 0.79 (95% CI 0.65-0.96, P = 0.0199). Exclusion of the 28-day mortality obtained from the study by Ranieri et al. did not make any substantial difference to the findings; relative risk for in-hospital mortality was 0.87 (95% CI 0.77-0.97; P = 0.0199), and pooled odds ratio was 0.80 (95% CI 0.65-0.98, P = 0.033). This statistically significant benefit is attributable to the disproportionate effect of the three smaller trials (where high PEEP was used in conjunction with lower tidal volumes) that collectively account for less than 12% of the weighting (table 2) and may not represent the true picture. A meta-analysis restricted to the three larger studies that included PEEP level as the main variable investigated was therefore then undertaken, and the results are summarized in figure 3. The pooled relative risk for in-hospital mortality of these studies was 0.90 (95% CI 0.81-1.01, P = 0.077), with a pooled odds ratio of 0.86 (95% CI 0.72-1.02, P = 0.077) in favor of the higher PEEP group. Even though this difference is not statistically significant, the Forest plot (fig. 3) shows a consistent trend towards a mortality benefit, with a 3.6% reduction in absolute risk of death. Assuming that this is reproducible, one additional life may be saved for every 28 patients treated using high PEEP.

**Baro-trauma.** Five studies included data on the incidence of baro-traumas. (table 3 and fig. 4). The pooled relative risk of baro-trauma was 0.95 (95% CI 0.62-1.45, P = 0.81), with a pooled odds ratio for baro-trauma of 0.91 (95% CI 0.55-1.51, P = 0.72). However, there was a degree of heterogeneity present between these trials (chi square = 8.28, df = 4, P = 0.08), with an I^2 value of 51.7%, indicating that there was a moderate level of heterogeneity present between these trials. Visual inspection of the Forest plot (fig. 4) indicates an overlap of all of the confidence intervals, except the study by Amato et al. again confirming heterogeneous results.

<table>
<thead>
<tr>
<th>Trial</th>
<th>No. of Incidences</th>
<th>Weight (%)</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amato et al.²⁷</td>
<td>2/29</td>
<td>9.9</td>
<td>0.17 (0.04-0.59)</td>
</tr>
<tr>
<td>Brower et al.⁵</td>
<td>30/276*</td>
<td>24.9</td>
<td>1.10 (0.69-1.79)</td>
</tr>
<tr>
<td>Meade et al.⁴</td>
<td>53/475</td>
<td>41.3</td>
<td>1.21 (0.83-1.75)</td>
</tr>
<tr>
<td>Mercat et al.⁵</td>
<td>25/385</td>
<td>20.1</td>
<td>1.17 (0.68-2.02)</td>
</tr>
<tr>
<td>Villar et al.⁶</td>
<td>2/50</td>
<td>3.8</td>
<td>0.45 (0.10-2.01)</td>
</tr>
<tr>
<td>Total</td>
<td>113/1215</td>
<td>100.0</td>
<td>1.04 (0.81-1.33)</td>
</tr>
</tbody>
</table>

* The value in the table is an approximate value calculated from a percentage given in the paper by Brower et al. because the raw data were not available. PEEP = positive end expiratory pressure.
Relative risk meta-analytic plot (random effects)

The results are summarized in Figure 5. The relative risk meta-analyses that included the three larger trials have yielded confidence intervals that exclude the null value of 1 with high probability. However, these analyses also include older, lower quality studies that may not be as robust or reliable. Further research is necessary to confirm the findings of this study.

19.7% of the weight in Table 3, and the performed a significant reduction of increased risk of poor-trauma (treated). Exploratory analysis (PEEP) for this purpose the relative risk and confidence estimates (95% CI) for each study are presented in Table 3.

1.77 (0.99, 1.62)
1.77 (0.69, 2.02)
1.24 (0.83, 1.76)
1.10 (0.60, 1.96)
ative risk 1.17, 95% CI 0.90–1.52, P = 0.25), visual inspection of the Forest plot (fig. 5) indicates a possible trend towards increased risk.

Discussion

Protective ventilation strategies, which include low tidal volumes (approximately 6 ml/kg), high PEEP (>10 cm H₂O or 1–2 cm H₂O above the lower inflection point on the pressure-volume loop), and a plateau airway pressure of approximately 28–30 cm H₂O, are currently accepted as desired end points for ventilating patients with ALI/ARDS. Dissecting out the relative merits of the individual components of this combined approach, however, is fraught with difficulties. The present meta-analysis shows that the reduction in absolute mortality risk with high PEEP alone is approximately 4%; as such, one could expect to save one additional life for every 25–30 patients treated with this strategy. The absolute risk reduction is small, so any definitive study would need to recruit approximately 3,000 patients to demonstrate statistical significance. This prospect, in our view, would pose considerable financial and ethical burdens in undertaking such a study. Even though the reduction in risk of death is small, when considered in the light of high incidence and the undisputed biologic/physiologic benefits, the use of high PEEP strategy should be considered the default option in treating patients with ARDS/ALI.

Our decision to include the three clinical trials in which higher levels of PEEP were combined with variable tidal volumes in our initial meta-analysis (fig. 2), although controversial, is useful in demonstrating the fact that similar beneficial trends have been observed in very diverse populations and geographical locations. This is crucial in addressing concerns over possible adverse consequences of a high mean intrathoracic pressure on clinical outcome. Furthermore, the mortality benefits seen in these three studies cannot be automatically attributed to the use of low tidal volumes alone. For example, the selection of PEEP in the study by Amato et al. was based on the lower inflection point of the pressure-volume curve. Patients who did not show an inflection point were also treated with a PEEP of approximately 15 cm H₂O when they were randomized into the treatment group, and the pooled retrospective analysis showed that mean PEEP and driving pressures (Pplat-PEEP) during the first 36 h, rather than low tidal volumes, were the main independent ventilator-associated variables associated with mortality benefits. In this respect, two additional studies by Stewart et al. and Brochard et al. require further consideration. In these two studies, involving a total of 236 patients with ALI/ARDS, a low tidal volume (approximately 7 ml/kg) did not have any beneficial effects on mortality in patients who were receiving comparable levels of PEEP. These three trials collectively suggest that a higher level of PEEP, which minimizes cyclical opening and collapse of alveolar units and the associated atelectrauma, is in the very least an equally important component of the protective ventilator strategy. For this reason, we believe that the mortality figures from our meta-analysis of all six trials (fig. 2) is relevant despite some theoretical limitations.

Though widely considered to be a distinct clinical entity, patients with a diagnosis of ARDS/ALI represent a very heterogeneous group. It is therefore relevant to consider the subgroups that may receive maximum benefit through a high PEEP strategy. The beneficial effects of PEEP are related to the prevention of atelectasis, recruitment of already collapsed alveolar units, and avoiding the cyclical opening/collapse of alveoli. These conditions are maximal in patients with a greater lung injury score and severe lung edema. The maximal benefit of the high PEEP strategy in patients with more severe lung injury is best evident in the study by Villar et al., in which patients were recruited 24 h after meeting the ARDS criteria; as such, the study group represented a more severely ill cohort.Gattinoni et al. have suggested that patients with a Pao₂ less than 60 mmHg for longer than 1 h while being ventilated on 100% oxygen may represent this more severe end of the spectrum. Such patients are most likely to receive an independent benefit with high PEEP; in this group, it may even be necessary to set the PEEP at approximately 15 cm H₂O until the lung inflammation begins to resolve. It is in this group of patients that the biologic/physiologic benefits achieved through the high PEEP strategy is likely to translate into mortality benefits.

Another important finding is the lack of significant differences in the incidence of baro-trauma between the two groups when all five trials were considered together (fig. 4). However, the three larger trials (fig. 5) do show a nonsignificant but consistent trend towards a higher incidence. In all of the above trials, high PEEP was applied in the context of a protective ventilatory strategy, which limits the plateau airway pressure to less than 28–30 cm H₂O. The definition of the term baro-trauma was variable, and only Brower et al. and Meade et al. provided an adequate description of the term. Mercat et al. only included patients suffering from pneumothorax in their data, which may account for the relatively wide confidence intervals and heterogeneity between trials. When considered together, current evidence suggests that the high PEEP strategy may, as expected, be associated with a higher incidence of baro-trauma. However, the benefits would far outweigh any potential disadvantages, particularly in patients with severe ARDS, as evidenced by the trend towards lower mortality (figs. 2 and 3).
HPC may be applicable in scenarios where high performance computing (HPC) is needed. The application of HPC in neuroscience and neuroimaging challenges the traditional computing paradigms. The use of HPC in neuroscience imaging studies is expected to support the continued progress in our understanding of cognitive neuroscience. However, the interpretation of the obtained results should be cautious as the emphasis of this study is on the interpretation of the results rather than the technical aspects of HPC. Therefore, the results should be interpreted with care.

Acknowledgement

This study was supported by grants from the National Institutes of Health and the National Science Foundation. The authors would like to thank the reviewers for their constructive comments and suggestions.

References


