High levels of PEEP may improve survival in acute respiratory distress syndrome: A meta-analysis

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Received 4 December 2008; accepted 12 February 2009
Available online 9 March 2009

KEYWORDS
Meta-analysis; Positive-pressure respiration; Respiration; Artificial; Respiratory distress syndrome; Adult

Summary
Objective: Positive end-expiratory pressure (PEEP) has been viewed as an essential component of mechanical ventilation in acute respiratory distress syndrome (ARDS) and acute lung injury (ALI). However, clinical trials have not yet convincingly demonstrated that high PEEP levels improve survival. The object of this study was to test a priori hypotheses that a small but clinically important mortality benefit of high PEEP did exist, especially in patients with greater overall severity of illness and differences in PEEP protocols might have affected the study results.
Methods: Meta-analysis of randomized controlled trials comparing high versus low PEEP in ARDS/ALI. Studies were identified by search of MEDLINE (1950–2008) and other sources.
Measurements and main results: Five studies including 2447 patients were identified. A pooled analysis showed a significant reduction in hospital mortality in favor of high PEEP (RR = 0.89; 95% CI, 0.80–0.99; p = 0.03). However, significant statistical and clinical heterogeneities such as differences in disease severity and ventilator protocols were found. The differences in PEEP protocols were not associated with differences in mortality rates. A logistic analysis suggested that the beneficial effect of high PEEP was greater in patients with higher ICU severity scores.
Conclusions: The statistical and clinical heterogeneities make proper interpretation of the results difficult. However, a small, but significant mortality benefit of high PEEP may exist. In addition, our analysis suggests the effects of high PEEP are greater in patients with higher ICU severity scores.
Published by Elsevier Ltd.

Introduction
Acute respiratory distress syndrome (ARDS) is recognized as the most severe form of acute lung injury (ALI). Despite recent advances in understanding its pathogenesis and treatment, the management of ARDS remains a challenging
Positive end-expiratory pressure (PEEP) improves gas exchange and respiratory compliance. It also reduces inflammatory mediators in plasma and bronchoalveolar lavage fluid, and ventilator-induced lung injury by preventing alveolar derecruitment which might be associated with low tidal volume mechanical ventilation.

Despite beneficial results in small randomized clinical trials favoring the combination of high PEEP and low tidal volumes, larger randomized clinical trials have not yet convincingly demonstrated that high PEEP is superior. We hypothesized that a mortality benefit of high PEEP did exist, especially in patients with greater overall severity of illness as measured by composite measures such as an APACHE II or III score, but it was so small that it could be demonstrated only in a much larger trial or a meta-analysis.

In addition, we hypothesized that differences in PEEP protocols across the clinical trials might have affected the study results. In the clinical trials which showed a significant mortality benefit, the optimal PEEP levels were determined by using static pressure-volume curves while non-beneficial trials used other methods. How to determine the “optimal” or “best” PEEP levels in ARDS/ALI is still matter of debate.

The purpose of this study was to test the above hypotheses by conducting an exploratory meta-analysis.

Methods

Identification of trials

We aimed to identify all relevant randomized controlled trials which compared the effects of high versus low PEEP levels in patients with ARDS/ALI. Two authors independently searched the National Library of Medicine’s Medline database for relevant studies in any language published from 1950 to May 2008 using the MeSH headings and keywords: Respiratory Distress Syndrome, Adult AND Positive-Pressure Respiration or PEEP, AND Survival Analysis or Survival Rate or Hospital Mortality or Treatment Outcome or Length of Stay or Ventilator Weaning AND randomized controlled trials (publication type) or controlled clinical trials or clinical trials, randomized. In addition, we searched Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, and CINAHL. Bibliographies of all selected articles and review articles that included information on PEEP in ARDS/ALI were reviewed for other relevant articles. In addition, we reviewed our personal files and contacted experts in the specialty. This search strategy was done iteratively until we did not find any new potential citations on review of the reference lists of retrieved articles.

Study selection and data extraction

To be included in the analysis trials had to be randomized clinical trials in all which all patients were admitted to a hospital with ARDS/ALI. The intervention was high versus low PEEP and trials had to have at least one of the following outcome variables: hospital mortality, ventilator weaning and length of hospital stay.

Data extraction

We independently abstracted data from all studies using standardized forms. Data were abstracted on study design, setting, and population; severity of illness; the exact methods of applying PEEP; and the outcome variables listed above. In calculating each outcome variable, we used intention to treat data (including all patients randomized). Disagreements regarding values or analysis were resolved by discussion. The methodological quality of the studies included in the meta-analysis was scored with the Jadad composite scale. This is a 5-point quality scale, with low quality studies having a score of <2 and high quality studies a score of ≥3.

Data analysis

Barotrauma and mortality were dichotomous variables, and ICU, ventilator, and organ failure-free days were continuous variables. The data analysis was performed using meta-analysis software (RevMan 4.2, Cochrane Collaboration, Oxford, and NCSS 2004, Kaysville, UT, USA and StatsDirect 2.6, StatsDirect Ltd, Sale, Cheshire, UK). The results were expressed as relative risk (RR) or odds ratio (OR) for dichotomous outcomes and weighted mean difference (WMD) for continuous outcomes, along with their 95% confidence intervals (CIs). A Z-test was performed to examine the overall effect. We tested heterogeneity between trials with $\chi^2$ tests, with $p \leq 0.05$ indicating significant heterogeneity.

A random effects model was used if significant heterogeneity was detected. A fixed effects model was used otherwise.

Results

The search strategy generated 54 studies. From these, we identified 5 randomized clinical trials, including a total of 2447 patients, which compared the effects of high versus low PEEP and met our inclusion criteria. Demographic data and overall quality ratings of the included studies are presented in Table 1a. Three studies examined the effects of high versus low PEEP levels in patients receiving low tidal volumes. The remaining 2 studies examined the combined effects of low tidal volume and high PEEP versus conventional tidal volume and low PEEP.
Table 1a  Characteristics of studies included in meta-analysis.

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Female (%)</th>
<th>Age</th>
<th>Severity score</th>
<th>PaO₂: FiO₂</th>
<th>Pulmonary ARDS (%)</th>
<th>Jadad score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amato 1998</td>
<td>High PEEP</td>
<td>29</td>
<td>NR</td>
<td>33(13)</td>
<td>28(7)³</td>
<td>112(51)</td>
<td>66</td>
</tr>
<tr>
<td></td>
<td>Low PEEP</td>
<td>24</td>
<td></td>
<td>36(14)</td>
<td>27(6)³</td>
<td>134(67)</td>
<td>46</td>
</tr>
<tr>
<td>ALVEOLI 2004</td>
<td>High PEEP</td>
<td>276</td>
<td>43</td>
<td>54(17)</td>
<td>96(33)²</td>
<td>151(67)</td>
<td>58</td>
</tr>
<tr>
<td></td>
<td>Low PEEP</td>
<td>273</td>
<td>47</td>
<td>49(17)</td>
<td>91(30)²</td>
<td>165(77)</td>
<td>53</td>
</tr>
<tr>
<td>Villar 2006</td>
<td>High PEEP</td>
<td>50</td>
<td>60</td>
<td>48</td>
<td>32(6)³</td>
<td>111</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>Low PEEP</td>
<td>45</td>
<td></td>
<td>52</td>
<td>32(6)³</td>
<td>109</td>
<td>36</td>
</tr>
<tr>
<td>EXPRESS 2008</td>
<td>High PEEP</td>
<td>385</td>
<td>32</td>
<td>60(16)</td>
<td>50(16)³</td>
<td>144 (58)</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td>Low PEEP</td>
<td>382</td>
<td>33</td>
<td>60(15)</td>
<td>49(16)³</td>
<td>143 (57)</td>
<td>75</td>
</tr>
<tr>
<td>LOV 2008</td>
<td>High PEEP</td>
<td>475</td>
<td>41</td>
<td>55(17)</td>
<td>25(8)³</td>
<td>145(48)</td>
<td>69</td>
</tr>
<tr>
<td></td>
<td>Low PEEP</td>
<td>508</td>
<td>40</td>
<td>57(17)</td>
<td>26(8)³</td>
<td>145(49)</td>
<td>76</td>
</tr>
</tbody>
</table>

Values are given as means (SDs). NR = not reported.
³ APACHE II score.
² APACHE III score.
¹ SAPS II score.

Table 1b  PEEP and tidal volumes employed in the clinical studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Set PEEP</th>
<th>Tidal volume (mL/kg*)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 1</td>
<td>Day 2—4</td>
</tr>
<tr>
<td>Amato 1998</td>
<td>High PEEP group</td>
<td>16.3 (3.8)</td>
</tr>
<tr>
<td></td>
<td>Low PEEP group</td>
<td>6.9 (3.9)</td>
</tr>
<tr>
<td></td>
<td>Difference</td>
<td>9.4²</td>
</tr>
<tr>
<td>ALVEOLI 2004</td>
<td>High PEEP group</td>
<td>14.7 (3.5)</td>
</tr>
<tr>
<td></td>
<td>Low PEEP group</td>
<td>8.9 (3.5)</td>
</tr>
<tr>
<td></td>
<td>Difference</td>
<td>5.8¹</td>
</tr>
<tr>
<td>Villar 2006</td>
<td>High PEEP group</td>
<td>14.1 (2.8)</td>
</tr>
<tr>
<td></td>
<td>Low PEEP group</td>
<td>9.0 (2.7)</td>
</tr>
<tr>
<td></td>
<td>Difference</td>
<td>5.1¹</td>
</tr>
<tr>
<td>EXPRESS 2008</td>
<td>High PEEP group</td>
<td>14.6 (3.2)</td>
</tr>
<tr>
<td></td>
<td>Low PEEP group</td>
<td>7.1 (1.8)</td>
</tr>
<tr>
<td></td>
<td>Difference</td>
<td>7.5¹</td>
</tr>
<tr>
<td>LOV 2008</td>
<td>High PEEP group</td>
<td>15.6 (3.9)</td>
</tr>
<tr>
<td></td>
<td>Low PEEP group</td>
<td>10.1 (3.0)</td>
</tr>
<tr>
<td></td>
<td>Difference</td>
<td>5.5¹</td>
</tr>
</tbody>
</table>

Values are given as means (SDs).
¹ p < 0.05.
² Predicted body weight.
³ Actual tidal volume.
hospital mortality secondary to low tidal volumes was estimated to be 13% (95% CI: −1 to 25%). This estimate was obtained by pooling data from previous randomized clinical trials. In the Amato study, the hospital mortality rate in the group treated with conventional tidal volume and low PEEP was 71%. The mortality rate for the hypothetical group treated with low tidal volume and low PEEP was estimated to be 0.71 ± 0.13 = 62% (95% CI: 53–72%). The same adjustment was made for Villar’s study before pooling the data.

A pooled analysis showed a significant reduction in hospital mortality with the use of high PEEP (RR = 0.89; 95% CI, 0.80–0.99; p = 0.03, Fig. 1). Sensitivity analyses using a random effects model, odds ratios, and risk differences did not affect the result. We conducted another sensitivity analysis by varying the RRR of hospital mortality attributed to low tidal volumes within the range of its 95% CI. Even when the highest-end of RRR (25%) was assumed (i.e., the greatest effect of low tidal volumes on mortality reduction), high PEEP strategy still marginally reduced hospital mortality (RR = 0.9; 95% CI, 0.81–1.00).

We examined the relation between treatment benefit and underlying risk. We estimated the predicted mortality rates in the included clinical trials based on reported ICU severity scores (Table 2). The predicted mortality rates in the ALVEOLI study were estimated based on the study by Cooke et al. which demonstrated a relationship between PaO2/FiO2 ratio at onset of acute lung injury and probability of hospital death. The studies which showed larger treatment effects appeared to have involved patients with greater overall severity of illness. We examined correlation, as suggested by Sharp et al., between the predicted mortality rates and RRs of hospital mortality associated with the use of high PEEP. A linear regression analysis confirmed that there was a strong negative association (correlation coefficient = −0.89, p < 0.05) between the predicted mortality and the RRs of hospital mortality—that is, higher the predicted mortality, the greater the mortality reduction associated with the use of high PEEP (Fig. 2).

We also conducted a logistic regression analysis as suggested by Thompson to examine if different PEEP strategies affected the hospital mortality rates. We hypothesized that the use of pressure–volume curves for the titration of PEEP enhanced the mortality benefits. However, the analysis failed to show a significant association between the use of pressure–volume curves and mortality rates (OR = 0.90; 95% CI: 0.57–1.44; p = 0.67).

We found a significant funnel plot asymmetry both on visual inspection and by Egger’s test (p = 0.05) and Begg-Mazumdar’s tests (p = 0.02), suggesting under-publication of negative results.

Three studies reported on 28-day mortality. The 28-day mortality rate of low PEEP strategy in Amato’s study was adjusted for the mortality reduction due to low tidal volume ventilation using the same method as described above. There was a trend toward decreased 28-day mortality (RR = 0.88; 95% CI, 0.76–1.01; p = 0.06) with the use of high PEEP (Fig. 1).

The study results revealed no statistically significant difference in ICU-free days (WMD = 0.04 days; 95% CI: −1.03 to 1.10; p = 0.94), ventilator-free days (WMD = 1.03 days; 95% CI: −1.44 to 3.51; p = 0.41), or organ failure-free days (WMD = 2.01 days; 95% CI: −1.91 to 5.93; p = 0.32) between the high and low PEEP strategies (Fig. 4). The ventilator-free days of the low PEEP strategy in Villar’s study were also adjusted for the reduction attributed to

Figure 1  Forest plot examining the effect of high versus low PEEP on hospital and 28-day mortality. RR = relative risk.
low tidal volumes using the same method described above. The incidence of barotrauma was also similar in the both strategies (OR = 1.19; 95% CI: 0.89–1.58; p = 0.25, Fig. 5).

**Discussion**

Our analysis showed high PEEP levels decreased hospital mortality when all relevant studies were combined. However, this should be interpreted with caution for the following reasons. First, the inspection of funnel plot and the statistical tests suggested a possibility of publication bias and/or small study effects. Actually, when 2 outliers were removed from the analysis, the effect of high PEEP levels on hospital mortality became no longer statistically significant (RR = 0.9; 95% CI, 0.81–1.01; p = 0.08). The small studies which showed larger treatment effects used pressure–volume curves for the titration of PEEP (Table 2). Therefore, we examined if differences in the PEEP strategies contributed to this heterogeneity. However, the use of static pressure–volume curves was not associated with the hospital mortality rates. We also found that neither the differences of PEEP levels, plateau pressures nor the static compliance between high versus low PEEP strategies were associated with the hospital mortality rates.

The method to reliably obtain optimal PEEP levels for each individual patient remains elusive despite years of extensive clinical and laboratory research and the use of FiO2–PEEP table employed in the large clinical studies has been criticized. The ARDSnet protocol lacks a solid physiologic basis and may increase the risk of alveolar overinflation. Therefore, titration of PEEP based on respiratory mechanics may be more advantageous to avoid ventilator-induced lung injury. Our finding suggests that the use of pressure–volume curve may not be the best way of finding an optimal PEEP setting as previously criticized. A practical method of identifying the “optimal” or “best” PEEP remains to be established.

On the other hand, the logistic analysis suggested that the beneficial effect of high PEEP was greater in patients with higher ICU severity scores. This finding suggests that the difference in underlying risk of death across the included trials is a significant source of heterogeneity. In other words, the difference in case mix across the included trials could explain the funnel plot asymmetry. If all the included studies had recruited patients with much higher ICU severity scores, the mortality benefit might have been easier to detect.

Second, we incorporated 2 studies which examined the combined effect of low tidal volumes and high PEEP levels. Although, hospital mortality rates from those studies were adjusted for the mortality reduction due to low tidal volumes to estimate the isolated benefit of high PEEP on hospital mortality, the accuracy of those estimates would need further validation. However, the sensitivity analyses supported the robustness of the pooled analysis.

Third, clinical heterogeneity described above raises a question if it is appropriate to estimate the effects of high PEEP from a pooled analysis. The patient characteristics among the included studies also varied widely. Predicted

| Table 2 Potential source for clinical and methodological heterogeneities. |
|---------------------------|---------------------------|---------------------------|
| Strategy used in the high PEEP group | Observed mortality % | Predicted mortality % |
|                           | (High/Low PEEP group) |   | (High/Low PEEP group) |
| Amato 1998 2 cm H2O above Pflex | 45/71 | 64/60 |
| Villar 2006 2 cm H2O above Pflex | 34/56 | 76/76 |
| ALVEOLI 2004 PEEP–FiO2 table | 25/27 | 37/36a |
| EXPRESS 2008 Titrated to Pplat of 28–30 cm H2O | 35/39 | 46/44 |
| LOV 2008 PEEP–FiO2 table | 36/40 | 53/56 |

*PEEP = lower inflection point.

**a** Estimated from PaO2/FiO2 ratios.

Figure 2 Linear regression and 95% confidence interval of relative risk of hospital mortality associated with the use of high PEEP against predicted hospital mortality. Risk of death with high PEEP relative to low PEEP decreases as predicted mortality increases. RR = relative risk.

Figure 3 Funnel plot inspection on hospital mortality.
Mortality rates ranged from 37 to 72%. The mean age ranged from 33 to 60. The proportion of pulmonary causes of acute lung injury ranged from 36 to 70% (Table 1a). Clinical heterogeneity may render pooling of the data unreliable or inappropriate but the direction of benefit is consistently in support of the high PEEP strategy. It should still be kept in mind that the magnitude of its benefit might not be generalizable because of the clinical heterogeneity.

We examined the relationship between plateau pressures and hospital mortality rates since a recent international observational study suggested that many clinicians were limiting tidal volumes only when plateau pressure was high, probably reflecting the data which showed an association between high plateau pressures and increased hospital mortality. Actually, a plot of plateau pressures versus hospital mortality including all 5 studies showed an upward inflection at lower plateau pressures (Fig. 6). The higher mortality rates associated with higher plateau pressures are likely due to conventional tidal volumes used in Amato and Villar’s studies causing overextension of the alveoli and further lung injury.

On the other hand, the higher mortality rates associated with lower plateau pressures could be attributed to the use of low PEEP levels. Conventional PEEP levels as those employed in the control groups of included trials are probably safe but lower than conventional PEEP levels may not be safe given possible increase in hospital mortality as reported by Ferguson et al.

In conclusion, although the clinical and methodological heterogeneities such as differences in disease severity and...
ventilator protocols make proper interpretation of the results difficult, a small but significant mortality benefit of high PEEP cannot be excluded. Our analysis suggests that beneficial effects of high PEEP are greater in patients with higher ICU severity scores.

Conflict of interest

None of the authors have any financial or conflict of interests that are related to this study.

Funding

None.

References


Figure 6  Polynomial regression and 95% confidence interval of hospital mortality against plateau pressure.

