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

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CRD summary
This review concluded that it was difficult to make definitive conclusions about high positive end-expiratory pressure (PEEP) in patients with acute respiratory distress syndrome and acute lung injury, but that the results suggested a small benefit, especially in patients with more severe disease. These conclusions are sufficiently cautious and likely to be reliable.

Authors' objectives
To determine the effects of high positive end-expiratory pressure (PEEP) on mortality in patients with acute respiratory distress syndrome (ARDS) and acute lung injury (ALI).

Searching
MEDLINE (1950 to May 2008), Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews, DARE and CINAHL were searched. Search terms were reported. Bibliographies of selected articles and relevant reviews were screened, the authors' personal files were searched and experts in the area were contacted. Published studies in any language were eligible for inclusion.

Study selection
Acute Physiology and Chronic Health Evaluation randomised controlled trials (RCTs) that compared high with low PEEP in patients admitted to hospital with ARDS or acute lung injury and that reported data on hospital mortality, ventilator weaning or length of hospital stay were eligible for inclusion.

Participants in the included studies had severity scores ranging from 25 to 32 on the Acute Physiology and Chronic Health Evaluation (APACHE) II score, from 91 to 96 on the APACHE III score and from 49 to 50 on the Simplified Acute Physiology Score (SAPS) II score. Strategies used in the high PEEP groups were 2cm H₂O above P_Flex (lower inflection point), positive end-expiratory pressure (PEEP)-FiO₂ table and titrated to Pplat of 28-30cm H₂O. Predicted mortality rates ranged from 37% to 72%. Mean age ranged from 33 to 60 years. Most studies included more men than women.

The authors did not state how papers were selected for the review.

Assessment of study quality
Studies were assessed for methodological quality using the Jadad scale to assign a score out of 5 based on the number of items fulfilled. Studies were considered low quality if they scored 2 or less and of high quality if they scored 3 or more.

The authors did not state how the validity assessment was performed.

Data extraction
Data were extracted on an intention-to-treat basis and expressed as odds ratios (OR) or relative risk (RR) for dichotomous data and as mean differences for continuous outcomes, together with their 95% confidence intervals (CI). Mortality rates from studies that examined the effects of combined low tidal volume and high PEEP with conventional tidal volume and low PEEP were adjusted for the mortality reduction due to low tidal volume. This was done by creating a hypothetical group in which patients were treated with low tidal volumes instead of conventional tidal volumes and low PEEP to match the tidal volumes between the two groups studied in each trial. Pooled data from previous RCTs were used to calculate the adjustment figure.

The authors stated that data were extracted independently; it was unclear how many reviewers were involved.
Disagreements were resolved through consensus.

**Methods of synthesis**

Pooled relative risks, odds ratios and weighted mean differences (WMD) were calculated using random-effects models where significant heterogeneity was detected and fixed-effect models where it was not. Heterogeneity was assessed using the $X^2$ test. The association between predicted mortality rates and the effects of PEEP on hospital mortality were investigated using logistic regression analysis. Publication bias was assessed using a funnel plot and the Egger and Begg-Mazumdar tests.

**Results of the review**

Five RCTs ($n=2,447$) were included. Sample size ranged from 53 to 983. One study scored the maximum of 5 points on the Jadad scale, two scored 3 and two scored 2.

High PEEP resulted in a significant reduction in hospital mortality (RR 0.89, 95% CI 0.80 to 0.99; five RCTs). There was no evidence of heterogeneity ($p=0.91$). Differences in PEEP protocols were not associated with differences in mortality rates. There was a strong negative correlation (correlation coefficient $-0.89$, $p<0.05$) between predicted mortality rates and the relative risk of hospital mortality associated with use of high PEEP; this suggested that the higher the predicted mortality the greater the mortality reduction associated with use of high PEEP. There was no association between the use of pressure-volume curves and mortality rates. There was no difference in 28-day mortality (three RCTs), intensive care unit-free days (two RCTs), ventilator-free days (four RCTs), organ failure-free days (two RCTs) or barotrauma (five RCTs) between the two treatment groups.

There was evidence of publication bias based on visual inspection of the funnel plot and using the Egger ($p=0.05$) and the Begg-Mazumdar tests ($p=0.02$), which suggested under-publication of negative results.

**Authors’ conclusions**

Statistical and clinical heterogeneity made proper interpretation of the results difficult. However, a small but significant mortality benefit of high PEEP may exist. The effects of high PEEP were greater in patients with higher intensive care unit severity scores.

**CRD commentary**

The review addressed a focused question supported by clearly defined inclusion criteria. The literature search was adequate, but it appeared that only published studies were eligible for inclusion. Publication bias was assessed in the review and found to be a potential problem. It appeared that appropriate steps were taken to minimise bias and errors in extraction of data, but it was unclear exactly how many reviewers contributed to this process and whether the same procedures were adopted during study selection and assessment of study quality. Study quality was assessed using appropriate criteria, but the results were presented only as summary quality scores instead of ratings for individual items. Therefore, the results were difficult to interpret, but suggested some potential limitations in quality of some included studies (especially given the very small size of two of the included studies). Only limited details of the included studies were reported and so it was difficult to determine the generalisability of the results. The authors acknowledged that clinical differences between studies made the evidence difficult to interpret. Despite these limitations the authors' conclusions are sufficiently cautious and likely to be reliable.

**Implications of the review for practice and research**

The authors did not state any implications for practice or research.

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