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# Outcome of Adults Acute Lung Injury in High vs Low Positive End-Expiratory Pressure: Systematic Review

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**Review Article**

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**Abstract** – ***Background:*** Studies contrasting higher and lower PEEP in individuals with ALI have not been sufficiently powered to examine differences or identify subtle but potentially significant impacts on mortality. Our objective was to evaluate the association between high versus low PEEP and patient-important outcomes in individuals with ALI receiving low TVs ventilation. ***Method:*** The PRISMA statement was followed in the course of this systematic review investigation. Randomized trials that qualified for this review examined higher and lower PEEP levels in critically ill patients diagnosed with ALI. To locate relevant trials, we performed an electronic search of MEDLINE, Cochrane, and EMBASE (all from 2000 to 2011). We only included English-language randomized controlled trials. ***Results:*** Four trials yielded 2394 patients met our eligibility criteria. In the Assessment of Low TV and Elevated End-Expiratory Pressure to ALI and the Lung Open Ventilation to Reduce Mortality in the ARDS, PEEP levels were titrated to oxygenation using equivalent PEEP to FIO2 charts. The Expiratory Pressure Study's experimental strategy titrated PEEP levels based on plateau pressure data, regardless of the effect on oxygenation. ***Conclusion:*** Higher PEEP levels associated with a lower hospital death rate in patients with ARDS. Additionally, our findings suggest that this is unlikely to be beneficial for patients with less severe lung injuries; in fact, treating these patients with high PEEP levels may be harmful.

**Keywords** – Acute lung injury, Positive End-Expiratory Pressure, Tidal volume, acute respiratory distress syndrome.

## INTRODUCTION

An important part of treating acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) is PEEP, or positive end-expiratory pressure (1). PEEP is titrated in clinical practice based on its ability to improve hypoxemia and reduce intrapulmonary shunting (2). In numerous models of ventilation-induced lung injury, PEEP shielded the lung, according to experimental research (3). The mechanisms underlying this protective effect remain unclear, but one possibility is that PEEP-induced alveolar recruitment plays a role. This recruitment maintains lung surfactant, prevents cyclic airway collapse and reopening, and enhances ventilation homogeneity. Despite the frequent correlation between oxygenation and alveolar recruitment, oxygenation is not a reliable indicator of recruitment since it is impacted by numerous other parameters, such as hemodynamics. Alveolar recruitment occurs throughout the respiratory system's volume-pressure connection and is dependent on the airway pressure reached, according to analysis of this relationship (4–8). Additionally, for a given maximal airway pressure, a combination of high PEEP and modest tidal volume (TV) was more successful in encouraging recruitment than the reverse (9).

The understanding that tissue stress contributes to lung injury brought on by ventilators was a significant development in the treatment of ALI and ARDS patients (10). It has been discovered that utilizing low TVs and keeping the plateau pressure of these patients at no more than 30 cm H2O increase survival (10). Although there is ongoing debate on the optimal clinical strategy, preventing hyperinflation has emerged as a key goal when choosing ventilator settings. A balance between PEEP-induced alveolar recruitment and hyperinflation must be achieved because greater PEEP levels may exacerbate hyperinflation.

In people with ALI getting low TVs ventilation, our goal was to assess the relationship between high versus low PEEP and patient-important outcomes.

## METHOD

This systematic review study was conducted according to Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement (11). Higher and lower levels of PEEP were compared in critically sick persons with ALI diagnosis in randomized studies that were eligible for this review. Trials that met certain criteria included patient follow-up until death or for a minimum of 15 days, with a goal tidal volume of less than 8 mL/kg of estimated body weight in both the experimental and control breathing techniques.

Using the terms "positive end-expiratory pressure," "PEEP," "open lung strategy," "low tidal volume," "acute lung injury," "acute respiratory distress," and "ARDS" as text words and "positive pressure respiration," "respiratory distress syndrome," and "tidal volume" as medical subject headings, we conducted an electronic search of MEDLINE, Cochrane, and EMBASE (all from 2000 to 2011) to find eligible trials. Only randomized controlled studies that were written in English were included. We looked through recognized papers' reference lists, current editorials, and relevant reviews, and we got in touch with specialists to find further studies that would qualify.

Four writers independently assessed trial eligibility based on titles, abstracts, full-text reports, and extra information from investigators when required. Data was extracted by all authors using (Google sheet and Google form) in a predesigned table which include (study citation, publication year, population characteristics, study duration, interventional group, control group, study aim, and main findings)

**RESULT**

2394 patients from four trials (Fig 1) satisfied our eligibility requirements. PEEP levels were titrated to oxygenation using comparable PEEP to FIO2 charts in the Assessment of Low Tidal Volume and Elevated End-Expiratory Pressure to ALI (2) and the Lung Open Ventilation to Reduce Mortality in the ARDS (12). Regardless of the impact on oxygenation, the experimental approach used in the Expiratory Pressure Study (13) titrated PEEP levels based on plateau pressure readings.

Comparable control procedures were employed in the Brower et al.(2) and Meade et al. (12) experiments, resulting in significantly greater PEEP control levels than in the Mercat et al. study. Every trial used blinded data analysis, accomplished complete follow-up for hospital mortality, and hid randomization.

According to Villar et al., 2006 (14) study, After randomization, there was a higher mean difference in the number of subsequent organ failures in the control group, when compared to a strategy with a greater TV and relatively low PEEP, a mechanical ventilation approach with a low TV and a PEEP level set on day 1 above Pflex had a beneficial effect on outcome in patients with severe and chronic ARDS (Table 1).

In Brower et al., 2004 (2) study, from the initial day to day 28, the lower-PEEP group's mean duration of independent breathing was 14.5 days, while the higher-PEEP group's mean was 13.8 days. When patients with ALI are placed on mechanical ventilation and given a TV aim of 6 ml per kilogram of projected body weight and an end-inspiratory plateau-pressure limit of 30 cm of water, the clinical outcomes are the same regardless of the PEEP levels employed. In Meade et al., 2008 (12) study, a comprehensive protocolized ventilation strategy targeted at lung recruitment and opening did not significantly change all-cause mortality for patients with ALI and ARDS when compared to an existing low TV protocolized ventilation strategy. This "open-lung" technique seems to promote the use of rescue medicines and secondary end goals related to hypoxemia. In Mercat et al., 2008 (13) study, mortality did not significantly decrease with PEEP settings that reduced hyperinflation and maximized alveolar recruitment. On the other hand, it improved lung function and reduced the amount of time required for mechanical ventilation and organ failure.

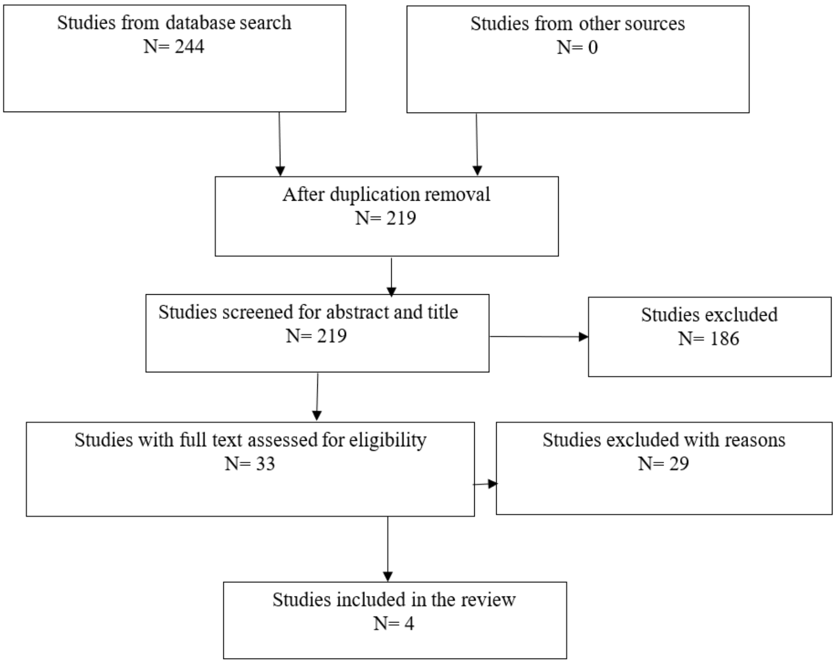


**Figure 1: PRISMA Consort Chart of Selection Process**

**Table 1: Characteristics of the Include Studies**

| Citation | Study aim | Study period | Intervention | Control | Main findings |
|---|---|---|---|---|---|
| Villar et al., 2006 (14) | The authors postulated that patients with severe and persistent ARDS would fare better if their ventilatory strategy relied on positive end expiratory pressure (PEEP) above the lower inflection point of the respiratory system's pressure volume curve (Pflex), which was set on day 1 with a low TV. | 2 years | On day 1, PEEP was set at Pflex = 2 cm H2O, and the TV was 5–8 mL/kg PBW. The respiratory rate was changed to keep PaCO2 between 35 and 50 mm Hg, while FIO2 was controlled to maintain arterial oxygen saturation >90% and PaO2 70–100 mm Hg in both groups. | The predicted body weight (PBW) was 9–11 mL/kg, and the PEEP was greater than 5 cm H2O. | The primary outcome indicators included nonpulmonary organ failure, ventilator-free days, and mortality in the ICU and hospital. Pflex/LTV was preferred in terms of ICU mortality, hospital mortality, and ventilator-free days (VFD) at day 28. The control group experienced a greater mean difference in the number of subsequent organ failures following randomization. In patients with severe and chronic ARDS, a mechanical ventilation approach with a low TV and a PEEP level set on day 1 above Pflex had a positive effect on outcome when compared to a strategy with a higher TV and relatively low PEEP. |
| Brower et al., 2004 (2) | To contrast the impact of varying PEEP levels on these patients' clinical outcomes | 3 years | Increased PEEP based on the FIO2 chart and recruitment strategies for the initial 80 patients | Conventional PEEP necessitated plateau pressures of less than 30 cm H2O and no recruitment procedures, per the FIO2 chart. | On days 1 through 4, the lower PEEP group's mean PEEP value was 8.3 cm of water, while the higher PEEP group's mean value was 13.2 cm of water. Prior to hospital release, the death rates were 24.9 percent and 27.5 percent, respectively. Breathing was done without assistance for a mean of 14.5 days in the lower-PEEP group and 13.8 days in the higher-PEEP group from the first day to day 28. Whether lower or higher PEEP levels are used, the clinical results are the same in patients with ALI receiving mechanical ventilation with a TV objective of 6 ml per kilogram of projected body weight and an end-inspiratory plateau-pressure limit of 30 cm of water. |

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|---|---|---|---|---|---|
| Meade et al., 2008 (12) | To contrast a tried-and-true low-TV breathing strategy with an experimental plan that combined high PEEP, lung recruitment techniques, and low TV. | 6 years | Increased PEEP based on the FIO2 chart, plateau pressures less than 40 cm H2O, and recruitment techniques. | Conventional PEEP necessitated plateau pressures of less than 30 cm H2O and no recruitment procedures, as per the FIO2 chart. | Upon recruitment, 85% of the 983 trial participants satisfied ARDS criteria. The two groups' TVs stayed almost the same, and after the first 72 hours, the experimental group's mean PEEP was 14.6 cm H2O, while the controls' was 9.8 cm H2O. Hospital death rates for all causes were 36.4% and 40.4%, respectively. 11.2% and 9.1% of patients had barotrauma. Refractory hypoxemia, refractory hypoxemia-related deaths, and previously specified eligible use of rescue treatments were all less common in the experimental group. When compared to an established low TV protocolized ventilation strategy, a multifaceted protocolized ventilation strategy aimed at recruiting and opening the lung did not significantly alter all-cause mortality for patients with ALI and ARDS. The usage of rescue therapies and secondary end objectives connected to hypoxemia seemed to be improved by this "open-lung" approach. |
| Mercat et al., 2008 (13) | To examine the impact on outcome between a hyperinflation strategy limited to avoiding alveolar distension in ALI patients and a PEEP strategy targeted at enhancing alveolar recruitment. | 3 years | Without raising the maximal inspiratory pressure of 28 to 30 cm H2O, PEEP should be as high as feasible. | Standard PEEP (5 to 9 cm H2O) to achieve desired oxygenation levels | In the limited distension group, the mortality rate at 28 days was 31.2%, while in the higher recruitment group, it was 27.8%. In the limited distension group, the hospital death rate was 39.0%, while in the increased recruitment group, it was 35.4%. There was a greater median number of VFDs in the increased recruitment group as compared to the limited distension group. Additionally, there was a correlation shown between this method and increased fluid requirements, better oxygenation, lower utilization of adjunctive medicines, and higher compliance levels.<br>PEEP settings that maximized alveolar recruitment while reducing hyperinflation did not result in a discernible decrease in mortality. It did, however, enhance lung function and shorten the time needed for both organ failure and mechanical ventilation. |

**DISCUSSION**

Overall, we did not observed significant difference in hospital mortality among the 2394 patients with ALI who were the subjects of this systematic evaluation of patient-level data from randomized trials comparing greater with lower PEEP levels. Greater PEEP levels were linked to the reduction in relative mortality in ARDS patients.

In contrast, increased PEEP levels might not help individuals with ALI who do not have ARDS, or they might even be detrimental to them. Results for ARDS patients do not rule out a little increase in pneumothorax risk with higher PEEP; nevertheless, variations in the likelihood of fatal outcomes from this type of barotrauma seem improbable. Otherwise, we could not discover information indicating that individuals with ARDS may experience significant side effects from increased PEEP.

There is outside evidence to support the ARDS connection. Preclinical and clinical investigations that offered oblique data suggesting increased PEEP techniques enhance survival were limited to ARDS animal models (15,16) and patients with severe or persistent (14) ARDS. Furthermore, the effect of PEEP on lung recruitment was found to be closely correlated with the percentage of potentially recruitable lung as measured by computed tomography in a recent cohort study of patients with ALI or ARDS (17). Individuals with ALI but not ARDS are less recruitable since they have less lung edema.1. Higher PEEP levels in ARDS patients can minimize lung damage by recruiting already collapsed alveolar units, preventing atelectasis, and preventing the cyclical opening and collapsing of alveoli (18–20). Our findings on refractory hypoxemia and the utilization of rescue medications show that patients with ARDS treated with decreased PEEP levels may experience increasing lung damage.

Several methods were employed by the trials in this study to ascertain PEEP level. PEEP levels were titrated in Mercat et al. (13) trial based on bedside inspiratory pressure measurements. The PEEP titration was associated with oxygenation in Roy et al. and Meade et al trials (2,12). Since the type of PEEP titration is completely confounded with all the other structural differences among the trials that are captured in this study of individual-patient data is unable to provide guidance on the optimal method of titrating PEEP. This is a topic that warrants further investigation. However, the review's findings offered no indication of variations in the three large trials' respective effects.

However, in the Mercat et al. trial, a higher degree of PEEP strategy did not result with worse hemodynamics, regardless of the number of cardiovascular failure free days or the need for vasopressors. Only patients who have a strong potential for alveolar recruitment may benefit from higher PEEP levels (17). Patients' potential for PEEP-induced recruitment varies greatly, and it is correlated with the severity of lung injury, particularly oxygenation impairment (21). The results based on oxygenation impairment at Mercat et al. study enrollment and analysis of ALI patients without ARDS indicate that, in contrast to ARDS, lung injury may be associated with fewer benefits and more negative effects from high doses of PEEP.

The studies by Villar et al. and Brower et al. differ in that the latter study included individuals with less severe lung injuries. When ARDS was defined by the American-European Consensus Conference and all patients were on conventional ventilator settings, Villar et al. made sure that all of the patients in their study had developed and persistent ARDS 24 hours later. Greater PEEP is safe for ARDS patients since it may reduce hospital mortality and there are no more major adverse events linked to greater PEEP levels in these patients. When evaluating the use of increased PEEP in patients with less severe ALI, clinicians should assess the potential risk.

## CONCLUSION

According to this systematic evaluation of randomized controlled trials, patients with ARDS may have reduced hospital death rates when their PEEP levels are higher. Our findings also imply that patients with less severe lung injuries are unlikely to benefit from this; in fact, treating these patients with high PEEP levels may be detrimental.

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