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[Intervention Review]

High versus low positive end-expiratory pressure (PEEP) levels for mechanically ventilated adult patients with acute lung injury and acute respiratory distress syndrome

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ABSTRACT

Background

Mortality in patients with acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) remains high. These patients require mechanical ventilation, but this modality has been associated with ventilator-induced lung injury. High levels of positive end-expiratory pressure (PEEP) could reduce this condition and improve patient survival.

Objectives

To assess the benefits and harms of high versus low levels of PEEP in patients with ALI and ARDS.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*, 2013, Issue 4), MEDLINE (1950 to May 2013), EMBASE (1982 to May 2013), LILACS (1982 to May 2013) and SCI (Science Citation Index). We used the Science Citation Index to find references that have cited the identified trials. We did not specifically conduct manual searches of abstracts of conference proceedings for this review. We also searched for ongoing trials (www.trialscentral.org; www.clinicaltrial.gov and www.controlled-trials.com).

Selection criteria

We included randomized controlled trials that compared the effects of two levels of PEEP in ALI and ARDS participants who were intubated and mechanically ventilated in intensive care for at least 24 hours.

Data collection and analysis

Two review authors assessed the trial quality and extracted data independently. We contacted investigators to identify additional published and unpublished studies.

Main results

We included seven studies that compared high versus low levels of PEEP (2565 participants). In five of the studies (2417 participants), a comparison was made between high and low levels of PEEP with the same tidal volume in both groups, but in the remaining two studies

(148 participants), the tidal volume was different between high- and low-level groups. We saw evidence of risk of bias in three studies, and the remaining studies fulfilled all criteria for adequate trial quality.

In the main analysis, we assessed mortality occurring before hospital discharge only in those studies that compared high versus low PEEP with the same tidal volume in both groups. With the three studies that were included, the meta-analysis revealed no statistically significant differences between the two groups (relative risk (RR) 0.90, 95% confidence interval (CI) 0.81 to 1.01), nor was any statistically significant difference seen in the risk of barotrauma (RR 0.97, 95% CI 0.66 to 1.42). Oxygenation was improved in the high-PEEP group, although data derived from the studies showed a considerable degree of statistical heterogeneity. The number of ventilator-free days showed no significant difference between the two groups. Available data were insufficient to allow pooling of length of stay in the intensive care unit (ICU). The subgroup of participants with ARDS showed decreased mortality in the ICU, although it must be noted that in two of the three included studies, the authors used a protective ventilatory strategy involving a low tidal volume and high levels of PEEP.

Authors' conclusions

Available evidence indicates that high levels of PEEP, as compared with low levels, did not reduce mortality before hospital discharge. The data also show that high levels of PEEP produced no significant difference in the risk of barotrauma, but rather improved participants' oxygenation to the first, third, and seventh days. This review indicates that the included studies were characterized by clinical heterogeneity.

PLAIN LANGUAGE SUMMARY

High versus low levels of positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome

Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) are acute and severe conditions affecting the structure and function of the lungs that are caused by increased permeability of the alveolar-capillary barrier leading to an inflammatory injury. The mortality rate of ALI and ARDS has decreased over time and is currently reported at 43%. Patients with ALI and ARDS require mechanical ventilation, but this intervention can cause ventilator-induced lung injury. For this reason, the therapeutic target for these patients is based on lung-protective ventilation. The use of high levels of positive end-expiratory pressure (PEEP) is part of the strategy aimed at reducing ventilator-induced lung injury. PEEP is a mechanical manoeuvre that exerts a positive pressure in the lung and is used primarily to correct the hypoxaemia caused by alveolar hypoventilation. In this Cochrane review, we assess the benefits and harms of high versus low levels of PEEP in patients with ALI and ARDS. The undertaking of this review was both relevant and necessary because the optimal level of PEEP in these patients is still controversial, and available evidence indicates no difference in mortality. We included seven studies involving a total of 2565 participants and found that high levels of PEEP, as compared with low levels, did not produce a reduction in hospital mortality, although we did see a trend towards decreased mortality. We also found evidence of clinical heterogeneity among the included studies (clinical heterogeneity concerns differences in participants, interventions, and outcomes that might have an impact on results from the use of PEEP). The studies included were of moderate to good quality. We did not find a significant difference with respect to barotrauma—defined as the presence of pneumothorax on chest radiography or a chest tube insertion for known or suspected pneumothorax. We furthermore ascertained that high levels of PEEP improved participants' oxygenation up to the first, third, and seventh days. The number of ventilator-free days showed no significant difference between the two groups (the term *ventilator-free days* refers to the number of days between successful weaning from mechanical ventilation and day 28 after study enrolment), and available data were insufficient to allow pooling of lengths of stay in the intensive care unit. Additional trials will be required to determine which patients should receive high PEEP levels and the best means of applying this intervention.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. High versus low levels of PEEP for mechanically ventilated adult patients with acute lung injury and acute respiratory distress syndrome

High versus low levels of PEEP for mechanically ventilated adult patients with acute lung injury and acute respiratory distress syndrome

Patient or population: participants mechanically ventilated, adult participants with acute lung injury and acute respiratory distress syndrome.

Settings:

Intervention: high versus low levels of PEEP.

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	High versus low levels of PEEP				
Mortality before hospital discharge	Study population¹		RR 0.9 (0.81 to 1.01) ²	2299 (3 studies)	⊕⊕⊕⊕ high	
	369 per 1000	332 per 1000 (299 to 373)				
	Low¹					
	0 per 1000	0 per 1000 (0 to 0)				
	Moderate¹					
	390 per 1000	351 per 1000 (316 to 394)				
Oxygen efficiency (PaO₂/FIO₂). Day 1		The mean oxygen efficiency (PaO ₂ /FIO ₂) day 1 in the intervention groups was 41.31 higher (24.11 to 58.52 higher)		2337 (5 studies)	⊕⊕⊕⊖ moderate³	
Oxygen efficiency (PaO₂/FIO₂). Day 3		The mean oxygen efficiency (PaO ₂ /FIO ₂) day 3 in the intervention groups was 42.51 higher (25 to 60.02 higher)		2059 (5 studies)	⊕⊕⊕⊖ moderate⁴	

Oxygen efficiency (PaO ₂ /FIO ₂). Day 7	The mean oxygen efficiency (PaO ₂ /FIO ₂) day 7 in the inter-vention groups was 24.77 higher (0.92 lower to 50.45 higher)		1379 (4 studies)	⊕⊕⊕⊖ moderate ⁵
Barotrauma	Study population ⁶		RR 0.97 (0.66 to 1.42)	2504 (6 studies) ⊕⊕⊕⊕ high
	90 per 1000	87 per 1000 (59 to 127)		
	Low ⁶			
	0 per 1000	0 per 1000 (0 to 0)		
Ventilator-free days (only means)	The number of mean ventilator-free days (only means) in the intervention groups was 1.89 higher (3.58 lower to 7.36 higher)		644 (2 studies)	⊕⊕⊕⊖ moderate ⁷

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio.

GRADE Working Group grades of evidence:

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ The baseline risk is low (the risk of presenting the outcome in participants who did not receive the intervention).

² There is clinical heterogeneity in relation to subgroups of participants who receive high levels of PEEP (participants with ALI and ARDS); how to apply those high PEEP levels.

³ The quality of evidence was downgraded because of a minimal overlap among the studies. There the P value for heterogeneity was < 0,00001 and I² was 86%.

⁴ The quality of evidence was downgraded because of a minimal overlap among the studies. There the P value for heterogeneity was 0,0001 and the I² was 82%.

⁵ The quality of evidence was downgraded because of a minimal overlap among the studies. There the P value for heterogeneity was 0,0002 and the I² was 85%.

⁶ The baseline risk is low (the risk of presenting the outcome in participants who did not receive the intervention).

⁷ The quality of evidence was downgraded because of a minimal overlap among the studies. There the P value for heterogeneity was 0,005 and the I² was 87%.

BACKGROUND

Description of the condition

Acute lung injury (ALI) is caused by increased permeability of the alveolar-capillary barrier leading to an inflammatory injury to the lung with accumulation of a protein-rich pulmonary oedema, haemorrhage, a procoagulant tendency and invasion of neutrophils, macrophages and cytokines. These inflammatory damages lead to diffuse alveolar damage—the histopathologic correlate of ALI. This early, exudative phase is followed by a proliferative phase and may proceed to a fibrotic phase.

ALI is defined by the clinical features of hypoxaemia (arterial oxygen tension/fractional inspired oxygen ($\text{PaO}_2/\text{FIO}_2$) ≤ 300) regardless of the level of positive end-expiratory pressure (PEEP), bilateral pulmonary infiltrates and lack of evidence of left heart failure. Two distinct causes of ALI are known. Primary ALI can be caused by direct injury to the lung (e.g. pneumonia). Secondary ALI is caused by an indirect lung injury within the setting of a systemic process (e.g. sepsis). A more serious form of ALI is acute respiratory distress syndrome (ARDS), which has the same clinical characteristics as ALI, except that the $\text{PaO}_2/\text{FIO}_2$ in ARDS is ≤ 200 (Bernard 1994).

A new definition of ARDS was proposed last year by a panel of experts (Ranieri 2012). This new definition contains certain variations with respect to the one previously prescribed. Furthermore the authors of this recent definition found a slight improvement in predictive validity compared with the previous definition (Bernard 1994).

The incidence of ALI and ARDS is variable among studies, ranging from 5 to 86 cases per 100,000 person-years (Linko 2009; Rubenfeld 2005). The mortality rate of ALI and ARDS has decreased over time and is currently reported at 43% with high variability (Zambon 2008).

Description of the intervention

Nearly all hospitalized patients with ALI and ARDS require mechanical ventilation (MV). Among ALI and ARDS patients receiving MV, the application of a supra-atmospheric pressure at end-expiration is referred to as positive end-expiratory pressure (PEEP) (Imberger 2010). PEEP is an easily implemented intervention that is used primarily to prevent atelectasis and to correct the hypoxaemia caused by alveolar hypoventilation.

Four mechanisms have been proposed to explain the improved pulmonary function and gas exchange achieved with PEEP in MV ALI and ARDS patients. These include the following:

- An increase in functional residual capacity (FRC).
- Alveolar recruitment.
- Redistribution of extravascular lung water.
- Improved ventilation-perfusion matching (Villar 2005).

The risk-benefit profile of PEEP is unclear because this therapy may produce side effects. It may increase the physiologic dead space (Coffey 1983), decrease cardiac output (Dorinsky 1983), worsen tissue perfusion (Jedlinska 2000), promote bacterial translocation (Lachmann 2007) and increase the risk of barotrauma (Eisner 2002).

How the intervention might work

MV may induce lung injury in patients. This is usually referred to as *ventilator-induced lung injury* (VILI). Two mechanical factors may contribute to the development of VILI: volutrauma, generated by an overdistention of the aerated lung regions; and atelectrauma, that is, large shear forces produced by repetitive alveolar recruitment and derecruitment (collapse) (Mead 1970). The use of low tidal volumes and an optimal level of PEEP are important in preventing VILI. Two randomized clinical trials that used small ventilatory volumes and low plateau pressures have demonstrated reduced mortality (Amato 1998; ARDSnet 2000).

The beneficial effects of PEEP on ARDS include alveolar recruitment, which avoids cyclic airway collapse and reopening, protects lung surfactant and improves ventilation homogeneity, thus reducing VILI. Gattinoni et al demonstrated that in participants with ARDS, sequential levels of PEEP measured by computed tomographic section prevented cyclic airway collapse (Gattinoni 1993). Richard et al. found that in participants with ALI, the combination of small tidal volume ventilation and high PEEP could induce alveolar recruitment and improve oxygenation (Richard 2003). Similarly, Ranieri et al ventilated participants with low tidal volume and high PEEP and showed that this strategy reduced bronchoalveolar lavage and systemic levels of cytokines when compared with ventilation with high tidal volume and low PEEP (Ranieri 1999). Borges et al. showed that a recruitment manoeuvre with PEEP with subsequent maintenance of high levels of PEEP reversed the collapse of alveoli and improved oxygenation (Borges 2006).

Why it is important to do this review

Evidence indicates that high levels of PEEP reduce VILI in patients with ALI and ARDS. It is important to conduct this systematic review because available studies testing the effects of higher levels of PEEP were not powered sufficiently to show differences in mortality (Brower 2004; Meade 2008; Mercat 2008), and the optimal level of PEEP in patients with ALI and ARDS is still controversial. Other published Cochrane reviews have focused on this topic (Imberger 2010; Petrucci 2007), but no review has compared high versus low levels of PEEP.

A full list of terminologies used in this review will be found in [Appendix 1](#).

OBJECTIVES

We assessed the benefits and harms of high levels of PEEP compared with low levels of PEEP in adults with ALI and ARDS. We further aimed to investigate the primary outcome of mortality before hospital discharge, as well as the secondary outcomes of oxygen efficiency ($\text{PaO}_2/\text{FIO}_2$), barotrauma, ventilator-free days (VFDs) and length of stay (LOS) in the intensive care unit (ICU). We also conducted subgroup and sensitivity analyses.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomized controlled trials (RCTs) that compared the effects of two levels of PEEP in participants with ALI and ARDS who

were intubated and mechanically ventilated in intensive care for at least 24 hours.

We included studies irrespective of language and publication status.

We excluded studies that used noninvasive ventilation (NIV) as an intervention.

We excluded studies that used zero PEEP as an intervention for participants with ALI and ARDS.

We excluded prospective cohort studies, cross-over studies and quasi-randomized studies.

Types of participants

We included adults (16 years of age or older) with ALI and ARDS who were intubated and received MV using PEEP for at least 24 hours.

Types of interventions

We compared two levels of PEEP in participants with ALI and ARDS receiving MV and PEEP with or without other interventions.

Participants with higher levels of PEEP constituted the intervention group.

Types of outcome measures

Primary outcomes

- We included all trials reporting mortality before hospital discharge. If that information was absent, we considered mortality within 28 days of randomization or mortality in the ICU.

Secondary outcomes

- Oxygen efficiency ($\text{PaO}_2/\text{FIO}_2$): first, third, and seventh days.
- Barotrauma: defined as the presence of pneumothorax on chest radiograph or chest tube insertions for known or suspected spontaneous pneumothorax.
- VFDs: defined as the number of days between successful weaning from mechanical ventilation and day 28 after study enrolment (Schoenfeld 2002).
- LOS in ICU.

Search methods for identification of studies

We used the optimally sensitive search strategy developed for The Cochrane Collaboration to identify all relevant published and unpublished RCTs (Higgins 2011). We did not impose language restrictions.

Electronic searches

We searched the following databases: The Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*, Issue 4, 2013) (see Appendix 2), MEDLINE via Ovid SP (from 1950 to May 2013) (see Appendix 3), EMBASE via Ovid SP (from 1982 to May 2013) (see Appendix 4) and LILACS via the BIREME interface (from 1982 to May 2013) (see Appendix 5).

Searching other resources

We screened the reference lists of all available review articles and primary studies. We used the Science Citation Index to find references that have cited the identified trials. We contacted investigators to identify additional published and unpublished studies. We did not specifically conduct manual searches of abstracts of conference proceedings for this review.

We searched for ongoing trials at the following Websites:

- www.trialscentral.org/.
- www.clinicaltrial.gov.
- www.controlled-trials.com.

Data collection and analysis

Selection of studies

Two review authors (RSC and RN) independently screened all studies for eligibility on the basis of their titles and abstracts. We documented the reasons for excluding any studies. We resolved disagreements by consulting with a third review author (RH), who decided whether a trial would be included in our review. When the published information was insufficient, RSC contacted the first author of the relevant trial before making a decision about inclusion of the study.

We inserted a PRISMA flow chart in our review to reflect this process (Liberati 2009; Moher 2009) (Figure 1).

Figure 1. Flow diagram of the selection of trials included in the meta-analysis.

Data extraction and management

Two review authors independently (RSC and RN) extracted and collected data from the included studies on a standardized form. We resolved any discrepancies in the data by discussion. We extracted data on study design, inclusion and exclusion criteria, participant characteristics, intervention characteristics, outcomes and complications associated with intervention. One review author (RSC) entered data into Review Manager. When additional information was needed, we contacted the first author of the relevant trial.

Assessment of risk of bias in included studies

Two review authors (RSC and RN) independently judged trial quality according to the criteria outlined in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and evaluated several types of biases:

- Selection bias through evaluation of the randomization procedure and allocation concealment.
- Performance bias through evaluation of the blinding of participants and individuals administering the treatment.
- Attrition bias through evaluation of the number of participants withdrawn from the studies, reported for each group and through analysis by intention-to-treat (ITT).
- Detection bias through evaluation of the blinding of outcome assessment.
- Reporting bias through evaluation of the differences between reported and unreported findings.
- Any other sources of bias present in relevant studies.

We (RSC and RN) assessed the risk of bias. We resolved any disagreements through consultation with a third review author (RH).

We displayed the results by creating a 'Risk of bias' summary (Figure 2) and a 'Risk of bias' graph (Figure 3) using RevMan 5.1

software. We presented the risk of bias in the 'Results' section. We provided a summary assessment of the risk of bias for each outcome within and across studies.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Amato 1998	?	+	+	+	+	+	+
Brower 2004	+	+	+	+	+	-	+
Huh 2009	+	?	+	+	?	+	+
Meade 2008	+	+	+	+	+	+	+
Mercat 2008	+	+	+	+	+	+	+
Talmor 2008	+	+	+	+	+	+	+
Villar 2006	+	+	+	+	+	+	+

Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Measures of treatment effect

We presented dichotomous data as risk ratios (RRs) for relative measures and risk differences (RDs) for absolute measures. We reported continuous data as mean differences (MDs). The goals were to obtain numerical estimates of these summary statistics from each trial and then to perform a stratified analysis to combine the results.

Unit of analysis issues

We did not include studies with nonstandard designs, such as cluster-randomized trials, and studies with multiple treatment groups.

Dealing with missing data

We contacted the first authors and investigators of the studies to inquire about missing data essential for the analysis of outcomes.

Assessment of heterogeneity

We assessed statistical heterogeneity with the I^2 statistic, thereby estimating the percentage of total variance across studies that was attributable to heterogeneity rather than to chance (Higgins 2003). We considered a value of greater than 50% as definitely considerable if it was also significant. We searched for possible sources of heterogeneity including differences among participants (e.g. participants with ALI or ARDS, APACHE II (Acute Physiology and Chronic Health Evaluation II) adjusted risk of death, age, lung injury score, sepsis, number of organ failures) and the interventions used (different levels of PEEP with or without other interventions).

Clinical heterogeneity

We used clinical heterogeneity to describe differences among participants, interventions and outcomes that might have an impact on the effects of high levels of PEEP (as the study of Hodgson 2009).

Assessment of reporting biases

We examined funnel plots (a graphical display) of the size of the treatment effect for the primary outcome against trial precision ($1/\text{standard error}$) for asymmetry, to evaluate whether evidence suggested a publication bias.

Data synthesis

In the absence of significant heterogeneity ($I^2 < 20\%$), we used the fixed-effect model. At moderate levels of heterogeneity, we applied a random-effects model (I^2 statistic 20% to 50%). We interpreted an $I^2 > 50\%$ as indicating high levels of heterogeneity and then investigated its causes as follows:

- We undertook subgroup analyses, whenever possible, considering the described potential source of heterogeneity. When heterogeneity persisted, we presented the results separately and reported the reasons for heterogeneity.
- We investigated diversity in clinical and methodological aspects of the included trials.
- We performed sensitivity analyses to address the methodological quality of the trials, including and excluding trials with moderate and high risk of bias, respectively.

We used The Cochrane Collaboration's software Review Manager 5.1 (RevMan 5.1) for data organization and analysis and entered data so that the area to the left of the line of no effect indicated a favourable outcome for high positive-pressure PEEP.

Subgroup analysis and investigation of heterogeneity

We performed subgroup analyses for the following categories.

Participants

- Participants with ALI.
- Participants with ARDS.
- APACHE II-adjusted risk of death, age, lung injury score, sepsis, number of organ failures.

Intervention

Different ways of applying PEEP:

- PEEP according to the mechanical characteristics of the lung.
- PEEP according to FIO_2 and PaO_2 .

PEEP along with other interventions:

- High PEEP and low tidal volume versus low PEEP and high tidal volume.

Sensitivity analysis

We performed sensitivity analyses. We excluded trials with a high risk of bias. We compared random-effects and fixed-effect model estimates for each outcome variable. We excluded any study that appears to have a large effect size to assess its impact on the meta-analysis. We also performed sensitivity analyses because of large variations in the event rate of the control group and excluded studies with the widest variations.

Summary of findings table

We used the principles of the GRADE system (Guyatt 2008) to assess the quality of the body of evidence associated with specific outcomes in our review and used the GRADE software to construct a 'Summary of findings' (SoF) table. The GRADE approach appraises the quality of a body of evidence within a study by considering the risk of bias (methodological quality), the directness of the evidence, the heterogeneity of the data, precision effect estimates, and the risk of publication bias.

Specific outcomes included the following:

- Mortality.
- Oxygen efficiency, $\text{PaO}_2/\text{FIO}_2$ above baseline levels during the first, third, and seventh days of treatment.
- Barotrauma.
- VFDs.
- LOS in ICU.

RESULTS

Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#); [Characteristics of ongoing studies](#).

Results of the search

The electronic search resulted in 3601 studies. We excluded 3582 studies, which were clearly irrelevant or duplicates. We retrieved 19 studies for further assessment. From these 19 studies, we excluded a further 12 trials. We included only seven studies in the final analysis (Figure 1).

Included studies

We analysed the seven included studies, consisting of 2565 participants, all with ALI and ARDS. One study used lung injury severity scores (LISS) in the definition of ALI and ARDS (Amato 1998), five studies (Brower 2004; Huh 2009; Meade 2008; Mercat 2008; Talmor 2008) employed the American-European Consensus

Conference (AECC) definition and the remaining study (Villar 2006) examined participants with ARDS (likewise as defined by the AECC) who had been ventilated at the standard setting for 24 hours and persisted at a $\text{PaO}_2/\text{FIO}_2$ of ≤ 200 .

The number of participants in each study ranged from 53 (Amato 1998) to 983 (Meade 2008).

The average age at randomization was 52 years. One study (Amato 1998) included younger participants (average age 34.5 years).

One study (Meade 2008) exhibited certain differences in baseline characteristics: Participants in the control group were 2.4 years older than those in the experimental group, and their rate of sepsis at baseline was 3.7% higher. We wanted to know whether those differences were statistically significant and accordingly asked the author. Dr Meade replied that the associated P value (with a Bonferroni correction) for age was 0.03 and for sepsis was 0.24, but that these differences were minimal after the data were pooled. Furthermore, upon conducting a study in which they pooled all of the data derived from a meta-analysis of the data from individual participants, investigators found no differences between high- and low-PEEP groups with respect to age or sepsis (Briel 2010).

In one study (Talmor 2008), the data on allocation of interventions to participants, random sequence generation, and measurements of ventilator function during the first seven days of treatment were not published. The author, when contacted, answered that investigators had used a block-randomization scheme with blocks of eight. These blocks were kept in sealed envelopes that had been prepared before the study was conducted. Also, data were available to investigators for only the first 72 hours of treatment, at which point participants were turned over to their team for the usual care.

One study (Huh 2009) provided no data on allocation of interventions to participants, on exclusion criteria, and on PEEP levels and oxygenation values during the first week of treatment. We contacted the author, who sent us those missing data.

In five studies, participants were randomly assigned to receive high or low levels of PEEP with the same tidal volume in both groups (Brower 2004; Huh 2009; Meade 2008; Mercat 2008; Talmor 2008), and participants in the remaining two studies (Amato 1998; Villar 2006) received either high or low levels of PEEP with a different tidal volume in each group. Four studies included recruitment manoeuvres in the intervention group (Amato 1998; Huh 2009; Meade 2008; Talmor 2008), whereas one study included recruitment manoeuvres for only the first 80 participants (Brower 2004).

Primary and secondary outcomes varied among the included studies (Table 1). Mortality before hospital discharge was measured in five studies (Amato 1998; Brower 2004; Meade 2008; Mercat 2008; Villar 2006), mortality within 28 days in five publications (Amato 1998; Huh 2009; Meade 2008; Mercat 2008; Talmor 2008), and mortality in the ICU in four (Amato 1998; Huh 2009; Meade 2008; Villar 2006).

Five studies observed changes in oxygenation ($\text{PaO}_2/\text{FIO}_2$) on the first and third days (Brower 2004; Huh 2009; Meade 2008; Mercat 2008; Villar 2006); four studies observed changes in oxygenation ($\text{PaO}_2/\text{FIO}_2$) on the seventh day (Brower 2004; Huh 2009; Meade 2008; Mercat 2008); six reported barotrauma (Amato 1998; Brower

2004; Huh 2009; Meade 2008; Mercat 2008; Villar 2006); four indicated the number of VFDs (Brower 2004; Mercat 2008; Talmor 2008; Villar 2006); and two estimated LOS in the ICU (Huh 2009; Meade 2008).

Three studies were stopped prematurely because of a significant difference in survival between groups (Amato 1998; Mercat 2008; Villar 2006); one study was discontinued on the basis of the specified futility stopping rule (Brower 2004).

Excluded studies

We excluded 12 studies (see [Characteristics of excluded studies](#)). Six were not RCTs (Badet 2009; Burns 2001; Dellamonica 2011; Grasso 2007; Richard 2003; Toth 2007); one was a review (Kallet 2007); in three the outcomes were physiologic (Carvalho 1997; Grasso 2005; Ranieri 1999); one was the first part of a larger investigation (Amato 1995) and one did not meet our inclusion criteria because both participant groups were administered equal levels of PEEP (Oczenski 2004).

Two ongoing studies (Kacmarek 2007; Pintado 2003) were considered relevant to this review (see [Characteristics of ongoing studies](#)).

Risk of bias in included studies

The seven studies included in this review were of moderate to good quality (see [Characteristics of included studies](#)). The summary of quality assessment can be found in [Figure 2](#) and [Figure 3](#).

Allocation

In relation to the sequence generation process, one study had insufficient information (Amato 1998), five studies used blocked randomization to form the allocation for the two comparison groups (Brower 2004; Meade 2008; Mercat 2008; Talmor 2008; Villar 2006) and the last study used a random number table in the sequence generation process (Huh 2009).

In relation to concealment of the allocation sequence, in three of the studies a centralized interactive voice system was used to assign eligible participants randomly (Brower 2004; Meade 2008; Mercat 2008).

In three studies, randomization was performed through the use of sealed envelopes (Amato 1998; Villar 2006; Talmor 2008), and the last study provided insufficient information about concealment of the allocation sequence (Huh 2009).

Blinding

In relation to blinding of participants and personnel, because of the nature of the intervention, the investigators could not be blinded, but participants were unaware of their group allocation because they were critically ill and were under deep sedation. Likewise we believe that the risk of bias was low because the primary outcome is objective and all studies had a strict protocol for both treatment groups.

In relation to blinding of outcome assessment, as with blinding of participants and personnel, because of the characteristics of the primary outcome, we believe that the risk of bias was low. Likewise, in two studies the data analysis was conducted in a blinded fashion (Meade 2008; Mercat 2008).

Incomplete outcome data

Four studies performed the analysis on the basis of the ITT principle (Amato 1998; Meade 2008; Mercat 2008; Talmor 2008); one study (Amato 1998) was hampered by minor protocol violations in both groups; one study showed that seven participants who were withdrawn from the study contributed partial data for the secondary analysis (Meade 2008); one study indicated that one of the participants in the experimental group was lost on day 29 of follow-up after discharge (Mercat 2008); and the last study reported that measurements were not performed on one participant in the experimental group because the participant could not be sedated (Talmor 2008).

Three studies had incomplete outcome data (Huh 2009; Mercat 2008; Villar 2006). Mercat 2008 excluded only one participant because the family withdrew consent after randomization. Villar 2006 indicated that eight participants were lost (three in the intervention group and five in the control group) because one of the centres failed to adhere to the randomization methodology. Although no differences in outcomes were reported, these eight participants were not included in the final analysis. We believe that in these two studies (Mercat 2008; Villar 2006), the risk of bias was low because the reasons for exclusion were reported and were balanced across groups. In the remaining study (Huh 2009), the reasons for excluding participants were not reported; therefore we believe that the risk of bias was not clear.

Selective reporting

A reporting bias occurred in one study (Brower 2004) because the primary outcomes were proposed in the protocol but were performed in the study differently, and some secondary outcomes proposed in the protocol were not assessed in the study.

Other potential sources of bias

Two studies (Brower 2004; Meade 2008) reported differences in baseline characteristics between the two groups, but these differences did not change the main results.

Effects of interventions

See: [Summary of findings for the main comparison High versus low levels of PEEP for mechanically ventilated adult patients with acute lung injury and acute respiratory distress syndrome](#)

We collected data comparing the effects of high versus low levels of PEEP; five studies did so with the same tidal volume in both groups, and two studies examined high levels of PEEP with a low tidal volume versus low levels of PEEP with a higher tidal volume.

For the main analysis, we assessed mortality before hospital discharge, including those studies that compared high versus low levels of PEEP with no other interventions. We pooled three studies (Brower 2004; Meade 2008; Mercat 2008), used the fixed-effect model because the I^2 statistic was 0%, and found no statistically significant differences between the two groups (relative risk (RR) 0.90, 95% confidence interval (CI) 0.81 to 1.01) ([Analysis 1.1; Figure 4](#)).

Figure 4. Forest plot of comparison: 1 High versus low levels of PEEP, outcome: 1.1 Mortality before hospital discharge.

Five studies assessed oxygen efficiency by means of the PaO₂/FIO₂ ratio on the first and third days (Brower 2004; Huh 2009; Meade 2008; Mercat 2008; Villar 2006). An improvement in oxygenation occurred, but with heterogeneity among the included studies (Analysis 1.2; Analysis 1.3). In the analysis that assessed oxygen efficacy in this way, the random-effects model was used on the first day because the I² statistic was 86%, and a statistically significant difference between the two groups was found (mean difference 41.31, 95% CI 24.11 to 58.52; Analysis 1.2). On the third day, the random-effects model was used because the I² statistic was 82%, and a statistically significant difference between the two groups was evident (mean difference 42.51, 95% CI 25 to 60.02; Analysis 1.3). In the assessment of oxygen efficiency by means of the PaO₂/FIO₂ ratio on the seventh day, only four studies were included (Brower 2004; Huh 2009; Meade 2008; Mercat 2008) because Villar 2006 had no data on the seventh day. In this analysis, the random-effects model was used (with an I² statistic of 85%), and a statistically significant difference between the two groups was not found (mean difference 24.77, 95% CI -0.92 to 50.45; Analysis 1.4).

Among all possible sources of heterogeneity included in the protocol, we could undertake a subgroup analysis only for the participants with ARDS. Two studies assessed oxygen efficiency, as measured by the PaO₂/FIO₂ ratio, on the first and third days with these ARDS participants (Huh 2009; Villar 2006). In that analysis, on the first day the fixed-effect model was used because the I² statistic was 0%, and we saw evidence of a benefit (mean difference 17.79, 95% CI 1.37 to 34.21; Analysis 1.5). In that same analysis on the third day, the fixed-effect model was used as well (with the I² statistic likewise being 0%), and we saw evidence of a benefit (mean difference 35.30, 95% CI 14.71 to 55.90; Analysis 1.6). On the seventh day (as in Analysis 1.4), we could not perform an analysis, as Villar 2006 provided no data for the seventh day.

In six studies assessing barotrauma (Amato 1998; Brower 2004; Huh 2009; Meade 2008; Mercat 2008; Villar 2006), the random-effects model was used because the I² statistic was 40%, and a statistically significant difference between the two groups was not found (RR 0.97, 95% CI 0.66 to 1.42) (Analysis 1.7).

We assessed the number of VFDs in four studies (Brower 2004; Mercat 2008; Talmor 2008; Villar 2006). In two of those four studies, the data were expressed as medians (Mercat 2008; Talmor 2008); therefore, we treated mean and median data separately (Analysis 1.8). When we accordingly excluded both of these studies from the analysis and analysed the two studies expressing data as

mean values (Brower 2004; Villar 2006), we found no differences in the meta-analyses (RR 1.89, 95% CI -3.58 to 7.36), and we noted heterogeneity among the included studies (I² = 87%) (Analysis 1.9).

We assessed LOS in the ICU in three studies but did not pool the data for analysis for this outcome because the data were expressed differently in terms of mean and median among the three: We thus included only the data and their statistical values with those studies (Analysis 1.10). Huh 2009 used mean values and found no difference between the two groups (P = 0.6); Meade 2008 and Talmor 2008 expressed the data for this parameter as medians and likewise found no significant difference. The P value was 0.98 for the study of Meade 2008 and 0.16 for the study of Talmor 2008.

We also assessed the mortality occurring before hospital discharge, including those studies that compared high versus low levels of PEEP with or without other interventions (Amato 1998; Brower 2004; Meade 2008; Mercat 2008; Villar 2006); we used the fixed-effect model because the I² statistic was 9% and found a statistically significant difference between the two groups (RR 0.88, 95% CI 0.79 to 0.98) in the analysis (Analysis 1.11).

We pooled studies assessing mortality within 28 days of randomization. Five studies were included (Amato 1998; Huh 2009; Meade 2008; Mercat 2008; Talmor 2008); the random-effects model was used because the I² statistic was 37% and a statistically significant difference between the two groups was not found (RR 0.83, 95% CI 0.67 to 1.01; Analysis 1.12).

Subgroup analysis

We conducted subgroup analyses assessing hospital mortality. Included studies provided insufficient data for subgroup analyses evaluating the effects of sepsis, organ failure, the lung injury score, or the APACHE II-adjusted risk of death.

In subgroup analyses based on age and comprising older participants (Brower 2004; Meade 2008; Mercat 2008; Villar 2006), the fixed-effect model was used because the I² statistic was 0%, and the meta-analysis indicated a statistically significant difference between the two groups (RR 0.89, 95% CI 0.80 to 0.99) (Analysis 1.13).

In subgroup analyses based on the use of PEEP according to mechanical characteristics of the lung (Amato 1998; Mercat 2008; Villar 2006), the random-effects model was used because the I² statistic was 47% and a statistically significant difference between

the two groups was not found (RR 0.76, 95% CI 0.57 to 1.01) (Analysis 1.14).

In subgroup analyses based on the use of PEEP according to FIO_2 and PaO_2 (Brower 2004; Meade 2008), the fixed-effect model was used because the I^2 statistic was 0% and a statistically significant difference between the two groups was not found (RR 0.90, 95% CI 0.79 to 1.04) (Analysis 1.15).

In subgroup analyses based on the use of high PEEP and low tidal volume versus low PEEP and high tidal volume (Amato 1998; Villar 2006), the fixed-effect model was used because the I^2 statistic was 0% and the meta-analysis indicated a statistically significant difference between the two groups (RR 0.62, 95% CI 0.44 to 0.87) (Analysis 1.16).

We conducted subgroup analyses to assess mortality in the ICU in participants with ARDS. In the three studies included (Amato 1998; Huh 2009; Villar 2006), the random-effects model was used because the I^2 statistic was 24% and the meta-analysis indicated a statistically significant difference between the two groups (RR 0.67, 95% CI 0.48 to 0.95) (Analysis 1.17).

Sensitivity analysis

We evaluated mortality before hospital discharge in the studies of good quality (Meade 2008; Mercat 2008; Villar 2006). The random-effects model was used because the I^2 statistic was 21% and a statistically significant difference between the two groups was not found (RR 0.87, 95% CI 0.76 to 1.01) (Analysis 1.18).

We excluded the study with large effect size (Meade 2008) and used the random-effects model because the I^2 statistic was 26% and the meta-analysis indicated a statistically significant difference between the two groups (RR 0.83, 95% CI 0.69 to 0.99) (Analysis 1.19).

We did not perform sensitivity analysis to exclude studies with large variations in the control group event rate because the studies to be included are those of Analysis 1.1.

Publication bias

This assessment could not be estimated because of the small number of studies included in this review.

DISCUSSION

Summary of main results

In this meta-analysis, seven studies met the criteria for inclusion.

Of the studies selected, five assessed mortality before hospital discharge (Amato 1998; Brower 2004; Meade 2008; Mercat 2008; Villar 2006) and were of moderate to good quality.

For the main analysis, we decided to exclude studies that applied different tidal volumes between intervention and control arms (Amato 1998; Villar 2006) because lack of clarity as to whether positive results were attributable to a reduction in tidal volume, to higher levels of PEEP, or to both tactics together made conclusions difficult.

The remaining three studies (Brower 2004; Meade 2008; Mercat 2008) assessed mortality before hospital discharge; thus our primary aim was to determine whether use of higher levels of PEEP improved clinical outcome.

High levels of PEEP compared with low levels showed no statistically significant decrease in mortality before hospital discharge in participants with ALI and ARDS (Analysis 1.1; Figure 4). The forest plot, however, showed a trend towards a mortality benefit in the higher-PEEP group. Furthermore, the existence of clinical heterogeneity should be taken into account in considering that outcome because two of the studies (Brower 2004; Mercat 2008) included participants with a $\text{PaO}_2/\text{FIO}_2 \leq 300$, and Meade 2008 reported on participants with a $\text{PaO}_2/\text{FIO}_2 \leq 250$.

This outcome is similar to that obtained by Dasenbrook 2011, who found that higher levels of PEEP were not associated with significantly different 28-day mortality. That meta-analysis included four studies; three were the same as in our analysis (i.e. Brower 2004; Meade 2008; Mercat 2008), and in Talmor 2008, a ventilator strategy was used to adjust high levels of PEEP according to the oesophageal pressures of participants with ALI and ARDS. In this review, according to our analysis, clinical heterogeneity is evidenced among the included studies.

The benefit of high levels of PEEP is assessed through a reduction of the collapsed lung and is dependent on the extent of lung recruitment. Gattinoni 2006 demonstrated that use of high levels of PEEP was more beneficial in participants with lower $\text{PaO}_2/\text{FIO}_2$ ratios (ARDS rather than ALI participants) and a high percentage of potentially recruitable lung volume. Furthermore, in a later paper, Caironi 2010 analysed data from that study and provided evidence in favour of the application of high levels of PEEP, especially in participants with great lung recruitability. In addition, Hess 2011 showed that modest levels of PEEP may be more appropriate for participants with ALI (at $\text{PaO}_2/\text{FIO}_2$ ratios ≤ 300), whereas higher levels of PEEP should be used for participants with ARDS (at $\text{PaO}_2/\text{FIO}_2$ ratios ≤ 200). Therefore, the strategy of using high levels of PEEP regardless of the type of patient (i.e. those with ALI or ARDS) could be incorrect.

Of the studies involving participants with ARDS that we analysed, three had assessed mortality in the ICU (Amato 1998; Huh 2009; Villar 2006) and indicated significant differences between groups (RR 0.67, 95% CI, 0.48 to 0.95; Analysis 1.17). In assessing this result, however, we need to consider that in two of those studies (Amato 1998; Villar 2006), high levels of PEEP were part of a ventilatory strategy that also included a low tidal volume. Furthermore, in the assessment of the forest plot, these two studies proved to be of greater benefit. In addition, the meta-analysis of individual-patient data (Briel 2010) indicated that treatment effects varied with the presence or absence of ARDS, as defined by a value of $\text{PaO}_2/\text{FIO}_2$ of 200 or less, and that in participants with ARDS, higher levels of PEEP were associated with improved survival.

We need also to consider clinical heterogeneity because the trials in this analysis used different approaches to determine PEEP levels in the intervention group. Two studies (Brower 2004; Meade 2008) included recruitment manoeuvres (before the setting of PEEP) with high levels of PEEP preset according to PaO_2 and FIO_2 values. In the remaining study (Mercat 2008), the PEEP level was preset to

achieve plateau pressures between 28 and 30 cm H₂O. Despite the use of different criteria for PEEP selection, the optimal method still remains unclear. In this review, subgroup analysis that included different ways of applying PEEP (PEEP on the basis of mechanical characteristics of the lung and PEEP according to FIO₂ and PaO₂; [Analysis 1.14](#); [Analysis 1.15](#)) failed to evidence any significant difference between these two approaches.

With respect to these two issues (heterogeneous population and different ways of applying high levels of PEEP), the results of an ongoing study ([Kacmarek 2007](#)) using high levels of PEEP only in participants with ARDS, and in an individualized way, should prove to be both relevant and informative.

In the subgroup analysis, we pooled studies that assessed lung-protective ventilation (low tidal volumes and high levels of PEEP) versus conventional ventilation ([Amato 1998](#); [Villar 2006](#); [Analysis 1.16](#)) and found a decrease in mortality with the use of lung-protective ventilation (RR 0.62; 95% CI 0.44 to 0.87). For this reason, we conclude—and we must emphasize—that lung-protective ventilation was shown to be beneficial in participants with ALI and ARDS.

In participants with ALI and ARDS, the use of PEEP has been recognized as producing an improvement in oxygenation ([Borges 2006](#); [Ranieri 1991](#); [Suter 1975](#)). In this review we accordingly observed that high levels of PEEP did indeed improve oxygenation in participants up to the first, third, and seventh days of mechanical ventilation, but with heterogeneity occurring in the different analyses surveyed ([Analysis 1.2](#); [Analysis 1.3](#); [Analysis 1.4](#)). For this reason we undertook subgroup analysis of oxygen efficacy through PaO₂/FIO₂ on the first and third days in participants with ARDS, and we saw an improvement in oxygenation ([Analysis 1.5](#); [Analysis 1.6](#)), consistent with the findings of Gattinoni ([Gattinoni 2006](#)) and Grasso ([Grasso 2005](#)). Gattinoni showed that in participants with ARDS, the potential for recruitment may be greater, and the earlier physiological study of Grasso applied both lower (9 ± 2 cm H₂O) and higher (16 ± 1 cm H₂O) PEEP levels and found that participants with a high potential for recruitment had a greater increase in oxygenation (from PaO₂/FIO₂ of 150 ± 36 to PaO₂/FIO₂ 396 ± 138). By contrast, in the four studies assessing oxygenation on the seventh day ([Brower 2004](#); [Huh 2009](#); [Meade 2008](#); [Mercat 2008](#)), PEEP levels did not differ markedly between groups. Furthermore, in participants with late ARDS, improvements in oxygenation and in respiratory mechanics were less well defined, and the potential for alveolar recruitment could have been reduced ([Grasso 2002](#)). These observations could justify the marked heterogeneity that can occur in the analysis of oxygen efficiency through PaO₂/FIO₂ after seven days.

Barotrauma is a complication in mechanically ventilated patients. Two studies have examined the relationship between barotrauma and high levels of PEEP in participants with ARDS ([Weg 1998](#); [Eisner 2002](#)). [Weg 1998](#) performed an analysis of data from a prospective trial of aerosolized synthetic surfactant in participants with ARDS and found no relationship between barotrauma and a mean level of PEEP of 12 cm H₂O. [Eisner 2002](#) reported that high levels of PEEP may increase the likelihood of early barotrauma, even after control is applied for markers of acute and chronic disease severity. In the present review, six studies assessed barotrauma ([Amato 1998](#); [Brower 2004](#); [Huh 2009](#); [Meade 2008](#); [Mercat 2008](#); [Villar 2006](#)); in

accordance with [Weg 1998](#), no statistically significant difference was noted between the groups.

In conjunction with statistically significant heterogeneity, high levels of PEEP produced no significant difference between the two groups in terms of the number of VFDs. We included two studies ([Brower 2004](#); [Villar 2006](#)) that differed in two ways: First, in terms of population, [Brower 2004](#) used participants with PaO₂/FIO₂ ≤ 300, and [Villar 2006](#) reported only participants with ARDS ventilated at a standard setting for 24 hours and persisting with a PaO₂/FIO₂ ≤ 200. Second, with respect to the mode of applying high levels of PEEP, in [Brower 2004](#), PEEP levels were preset according to PaO₂ and FIO₂ values, whereas in [Villar 2006](#), those levels were preset at 2 cm H₂O above the Pflex (upward shift in the slope of the pressure-volume curve). These differences could explain the statistical heterogeneity present in the analysis of VFDs.

Data on LOS in the ICU were insufficient for an examination to be performed.

Summary of findings table

In the main analysis (mortality before hospital discharge), we do not degrade for publication bias owing to the smaller number of included studies. We downgraded the secondary outcomes of oxygen efficiency on the first, third, and seventh days, and ventilator-free days were likewise downgraded because of an inconsistency resulting from minimal overlap among the studies. Here the P value for heterogeneity was less than 0.05, and the I² was large. We did not include LOS in the ICU in the summary of findings table because we were not able to pool the data for analysis of this outcome (see [Summary of findings for the main comparison](#)).

Overall completeness and applicability of evidence

On the whole, high levels of PEEP showed no statistically significant difference in mortality before hospital discharge in participants with ALI and ARDS. This review does not present data about subgroups (ALI or ARDS) that could benefit from high levels of PEEP because clinical heterogeneity is present among the studies included for such intervention. Further studies should help to assess benefit with respect to the different ways of applying PEEP and to the advantages and disadvantages associated with different ALI and ARDS patient populations.

Quality of the evidence

The quality of evidence is good. Four studies ([Meade 2008](#); [Mercat 2008](#); [Talmor 2008](#); [Villar 2006](#)) met all criteria considered in the evaluation of risk of bias.

Potential biases in the review process

Risk of bias was noted in three of the included studies ([Amato 1998](#); [Brower 2004](#); [Huh 2009](#)). [Amato 1998](#) provided insufficient information about the sequence generation process; [Brower 2004](#) described reporting bias; and [Huh 2009](#) provided insufficient information about concealment of the allocation sequence and about exclusions.

Agreements and disagreements with other studies or reviews

To date, several reviews have examined the use of high levels of PEEP in participants with ALI and ARDS. Evidence from these reviews indicates the trend toward a decrease in mortality with the use of high levels of PEEP, especially in participants with ARDS.

[Gordo-Vidal 2007](#) evaluated four studies published from 1998 to 2006, three of which used a protective ventilatory strategy involving a low tidal volume and a high PEEP. These studies included contained statistical heterogeneity; moreover, the review failed to report a decrease in mortality (RR 0.73, 95% CI 0.49 to 1.10; $P = 0.129$). Furthermore, the sampling reported in [Gordo-Vidal 2007](#) could not take into account the studies of greatest statistical weight in this present meta-analysis (i.e. [Meade 2008](#), [Mercat 2008](#)) because those investigations had not yet been published.

Three reviews ([Oba 2009](#); [Phoenix 2009](#); [Yang 2011](#)) included the same studies as ours.

The aim of the study of [Oba 2009](#) was to test the hypothesis that in participants with ALI and ARDS, the use of high levels of PEEP resulted in lower mortality, especially in more severely ill participants. For the analysis, investigators created a hypothetical group in which participants were treated with low VT, instead of conventional tidal volumes, and low PEEP to match tidal volumes between the two groups studied in each trial. In this meta-analysis, a small but significant decrease in mortality with high PEEP may have been shown to exist (RR 0.89; 95% CI 0.80 to 0.99; $P = 0.03$). As in our review, clinical heterogeneity was present, and investigators found that the effects of high PEEP were greater in participants with higher ICU severity scores.

[Phoenix 2009](#) identified six eligible studies, of which one had evaluated mortality at day 28 ([Ranieri 1999](#)). This review furthermore included five studies ([Amato 1998](#); [Brower 2004](#); [Meade 2008](#); [Mercat 2008](#); [Villar 2006](#)) that evaluated mortality before hospital discharge. Authors in this review used a random-effects model, included no data about statistical heterogeneity, and showed a reduction in mortality (RR 0.87; 95% CI 0.78 to 0.96; $P = 0.007$). Those who performed the meta-analysis that was restricted to studies that included PEEP levels as the main variable investigated (e.g. [Brower 2004](#); [Meade 2008](#); [Mercat 2008](#)) obtained the same results as we did. Although that study argued that the evidence obtained supported the use of high levels of PEEP in unselected groups of participants with ALI or ARDS in general, or in participants with more severe disease in particular, we are not in agreement with that conclusion because we believe that a determination of which subgroup of participants (ALI or ARDS) would benefit from high levels of PEEP is necessary.

The study of [Yang 2011](#) includes the same six studies as [Phoenix 2009](#) but assesses mortality at day 28 and the rate of barotrauma. In the analysis of mortality at day 28, investigators reported a significant difference between the two groups (odds ratio (OR) 0.81, 95% CI 0.68 to 0.95; $P = 0.01$) and furthermore no significant difference in the rate of barotrauma (OR 0.91, 95% CI 0.55 to 1.51; $P = 0.72$). We assessed mortality within 28 days of randomization and found no differences between the two groups, although our analysis differs from the review of [Yang 2011](#) in the included studies.

Three reviews ([Briel 2010](#); [Dasenbrook 2011](#); [Putensen 2009](#)) as in our main analysis included randomized controlled trials of participants with a diagnosis of ALI or ARDS (as defined by the American-European Consensus Conference) that compared higher versus lower levels of PEEP at the same tidal volume in both groups (control and experimental).

[Putensen 2009](#) identified several studies in participants with ALI and ARDS that attempted to determine whether low tidal volume, high PEEP, or a combination of the two improved outcome. In a meta-analysis that included studies of high versus low PEEP with the same tidal volume, investigators found, as did we in our review, no significant decrease in mortality (OR 0.86, 95% CI 0.72 to 1.02; $P = 0.08$).

[Briel 2010](#) performed a systematic review and meta-analysis of individual-patient data from three randomized studies that compared higher versus lower PEEP levels in 2299 participants with acute lung injury. Results showed, overall, no statistically significant difference in hospital mortality between groups (RR 0.94, 95% CI 0.86 to 1.04; $P = 0.25$). However in the subgroup of participants with ARDS, higher levels of PEEP were associated with improved survival (RR 0.90, 95% CI 0.81 to 1.00; $P = 0.049$). This review included an explicit study protocol and analysis plan, along with access to trial protocols, case report forms and complete, unedited data sets and standardized outcome definitions across trials (except for rescue therapies).

The review of [Dasenbrook 2011](#) included four studies with ventilation strategies that included higher PEEP during volume and pressure limitation in participants with ALI and ARDS. This study reported that higher levels of PEEP were not associated with a significantly different mortality at day 28 (RR 0.90, 95% CI 0.79 to 1.02) or barotrauma.

None of these three reviews ([Briel 2010](#); [Dasenbrook 2011](#); [Putensen 2009](#)) demonstrated a decrease in mortality with the use of high PEEP levels. We obtained the same results in the main analysis, which included studies with similar characteristics.

AUTHORS' CONCLUSIONS

Implications for practice

In summary, the present systematic review provides evidence that the use of high levels of PEEP does not reduce mortality before hospital discharge, although the forest plot indicated a trend towards a mortality benefit in the higher-PEEP group. Moreover, in practice, we cannot recommend the routine use of high levels of PEEP in patients with ALI and ARDS because no agreement has been reached among the various studies reported here as to which group of patients should receive that specific intervention and how those high PEEP levels should be applied.

Implications for research

Further research is needed to evaluate the use of high levels of PEEP. This research should:

- Include a randomized trial of only participants with ARDS that involves the use of high compared with low levels of PEEP with the same tidal volume in both groups.
- Establish the most appropriate strategy for the application of high levels of PEEP.

Identification of these conditions will help to clarify the appropriate use of high levels of PEEP in participants with ALI and ARDS.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Amato 1998

Methods	Randomized controlled trial. Time period of study: December 1990 through July 1995.
Participants	53 participants, aged > 14 and < 70 (two centres). Included: ARDS, LISS > 2.5, Pwedge < 16 mm Hg. Conditions excluded: previous lung or neuromuscular disease, MV > 1 week, uncontrolled terminal disease, previous barotrauma, previous lung biopsy or resection, uncontrollable and progressive acidosis, signs of intracranial hypertension, and documented coronary insufficiency.
Interventions	Control (24): MV: VT: 12 mL/kg, PEEP to optimize FIO ₂ < 0.6 with adequate systemic oxygen delivery. Intervention (29): MV: VT: ≤ 6 mL/kg, recruiting manoeuvres, driving pressure < 20 cm H ₂ O, PEEP: 2 cm H ₂ O above Pflex or 16 cm H ₂ O if no Pflex.
Outcomes	Primary: mortality at day 28. Secondary: mortality before hospital discharge, barotrauma, weaning rate adjusted for APACHE II score. Other outcomes: mortality in the intensive care unit (ICU), death after weaning of MV, nosocomial pneumonia, use of paralysing agents of > 24 hours, neuropathy after extubation, dialysis required, packed red cells infused.
Notes	Discontinued during the fifth interim analysis because of a significant survival difference between the groups.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process.
Allocation concealment (selection bias)	Low risk	Opaque sealed envelopes with a 1:1 assignment scheme.

Amato 1998 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Incomplete blinding (blinding of participants but not of personnel), but outcomes not influenced.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No blinding, but outcomes not influenced.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Analysis on the basis of the intention-to-treat principle. Minor protocol violations in both groups: 4 out of 29 participants from intervention group and 1 out of 24 participants from control group.
Selective reporting (reporting bias)	Low risk	Published reports included all expected outcomes.
Other bias	Low risk	Review author believed the study to be free of other sources of bias.

Brower 2004

Methods	Randomized controlled trial. Time period of study: October 1999 through February 2002.
Participants	549 participants, aged > 13 (23 centres). Included: ALI and ARDS ($\text{PaO}_2/\text{FIO}_2 < 300$). Excluded: ≥ 36 hours had elapsed since the eligibility criteria were met, participation in other trials involving ALI within the preceding 30 days, pregnancy, increased intracranial pressure, severe neuromuscular disease, sickle cell disease, severe chronic respiratory disease, body weight greater than 1 kg per centimetre of height, burns over 40% of body-surface area, severe chronic liver disease, vasculitis with diffuse alveolar haemorrhage, a coexisting condition associated with an estimated 6-month mortality rate greater than 50%, previous bone marrow or lung transplant, refusal to be included by attending physician.
Interventions	Control (273) and intervention (276): MV: VT: 6 mL/kg PBW, respiratory rate (breaths/min) 6 to 35 to achieve arterial pH > 7.30, plateau pressure ≤ 30 cm H ₂ O, recruiting manoeuvres: in the first 80 participants (intervention group). Target ranges for oxygenation with PEEP/FIO ₂ combination: PaO ₂ between 55 and 80 mm Hg or SpO ₂ between 88% and 95%. PEEP. Control: PEEP/FIO ₂ combination: mean PEEP: 8.6 cm H ₂ O. Intervention: PEEP/FIO ₂ combination (programming with higher levels of PEEP): mean PEEP: 13.5 cm H ₂ O.
Outcomes	Primary: mortality before hospital discharge. Secondary: VFD, days not spent in ICU, days free without organ failure. Other outcomes: barotrauma, breathing without assistance by day 28.
Notes	In the first 171 participants (85 in control group, 86 in intervention group), the higher-PEEP protocol was different from the other 378 participants, but the adjusted mortality rates in both phases was small and not significant. Discontinued during the second interim analysis on the basis of the specified futility-stopping rule.

Risk of bias

Brower 2004 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants randomly allocated because authors used random permuted blocks (restricted randomization).
Allocation concealment (selection bias)	Low risk	A centralized interactive voice system used.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Incomplete blinding (blinding of participants but not personnel), but the primary outcome was not influenced.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No blinding, but the outcomes not influenced.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data.
Selective reporting (reporting bias)	High risk	Primary outcome (mortality before hospital discharge) was different from that given in the protocol (mortality at 28 days). Certain secondary outcomes in the protocol not assessed in the study.
Other bias	Low risk	Significant differences between the two groups in baseline characteristics for the mean age and the mean $\text{PaO}_2/\text{FIO}_2$, but after adjustment for differences in baseline variables, these differences did not change the main results.

Huh 2009

Methods	Randomized controlled trial. Time period of study: July 2004 through September 2006.
Participants	57 participants (one centre). Included: ARDS ($\text{PaO}_2/\text{FIO}_2 \leq 200$). Conditions excluded: elevated intracranial pressure, severe acute cardiac disease, high risk of mortality within 3 months for reasons other than ARDS (cancer patients in the terminal stage of their disease), persistent haemodynamic instability.
Interventions	Control (27) and intervention (30): MV: VT: 6 mL/kg PBW, with allowances of up to 8 mL/kg PBW if the SpO_2 were below 88%, or less than 7.2 of arterial pH by severe hypercapnoea. FIO_2 , PEEP, and respiratory rate were set to achieve an SpO_2 between 88% and 92%. PEEP. Control: PEEP/ FIO_2 combination with the goal of obtaining a lower PEEP level compatible with an oxygenation target (SpO_2 between 88% and 92%). Mean PEEP: 9 cm H_2O . Intervention: recruiting manoeuvres (extended-sigh method), next PEEP added set to 25 cm H_2O and then lowered until a decrease of greater than 2% of saturation from the previous SpO_2 and drop of static compliance.
Outcomes	Primary: improvement in oxygenation ($\text{PaO}_2/\text{FIO}_2$). Secondary: respiratory mechanics (PEEP and dynamic compliance), ICU stay, duration of sedatives and paralyzing agents, mortality at day 28, mortality at day 60, duration of MV.

Huh 2009 (Continued)

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Allocation intervention was done by random number table.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement of "low risk" or "high risk".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Incomplete blinding (blinding of participants but not personnel), but outcomes not influenced.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No blinding, but outcomes not influenced.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient reporting of exclusions. Three out of 30 participants missing from control group and 1 out of 31 participants missing from intervention group.
Selective reporting (reporting bias)	Low risk	Published reports included all expected outcomes.
Other bias	Low risk	Review author believed the study to be free of other sources of bias.

Meade 2008

Methods	Randomized controlled trial. Time period of study: August 2000 through March 2006.
Participants	983 participants (30 hospitals). Included: ALI and ARDS ($\text{PaO}_2/\text{FIO}_2 \leq 250$) during invasive MV. Excluded if: left atrial hypertension, anticipated MV < 48 hours, inability to wean from experimental strategies, severe chronic respiratory disease, neuromuscular disease, intracranial hypertension, morbid obesity, pregnancy, lack of commitment to life support, conditions with expected 6-month mortality risk > 50%, participation in a confounding trial.
Interventions	Control (508) and intervention (475): MV: ventilator mode: volume-assist control (intervention), pressure control (control). VT: ≤ 6 mL/kg PBW, plateau pressure ≤ 40 cm H ₂ O (intervention), ≤ 30 cm H ₂ O (control), respiratory rate (breaths/min) ≤ 35 , pH ≥ 7.30 . Recruiting manoeuvres: intervention group. PEEP. Control: PEEP/FIO ₂ combination: mean PEEP: 9 cm H ₂ O. Intervention: PEEP/FIO ₂ combination (programming with higher levels of PEEP): mean PEEP: 12.6 cm H ₂ O. After the first 161 participants, PEEP levels modified in intervention group for the remaining 822 participants, but mean PEEP in all participants in intervention group the same. Target ranges for oxygenation with PEEP/FIO ₂ combination: PaO ₂ between 55 and 80 mm Hg; SpO ₂ between 88% and 93%.

Meade 2008 (Continued)

Use of rescue therapies¹ (both groups) in participants with refractory hypoxaemia ($\text{PaO}_2 < 60$ mm Hg for at least 1 hour while receiving an FIO_2 of 1.0), refractory acidosis ($\text{pH} \leq 7.10$ for at least 1 hour), or refractory barotrauma (persistent pneumothorax with two chest tubes on the involved side or increasing subcutaneous or mediastinal emphysema with two chest tubes).

Outcomes	<p>Primary: all-cause hospital mortality (mortality before hospital discharge).</p> <p>Secondary: mortality during MV, mortality in ICU, mortality at day 28, barotrauma, refractory hypoxaemia, refractory acidosis, refractory barotrauma, use of rescue therapies in response to refractory hypoxaemia, refractory acidosis or refractory barotrauma, days of MV, days of ICU, days of hospitalizations.</p>
Notes	<p>After the first 161 participants, PEEP levels were modified in the intervention group for the remaining 822 participants, but these changes did not alter the outcomes.</p> <p>Rescue therapies: prone ventilation, inhaled NO, high-frequency oscillation, jet ventilation, extracorporeal membrane oxygenation.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Authors used random permuted blocks. Participants randomly allocated.
Allocation concealment (selection bias)	Low risk	Assignment performed by central computerized telephone system. A programming error occurred late that created an unexpected difference in the number of participants allocated to each group, but this problem did not alter the results.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Incomplete blinding (blinding of participants but not of personnel), but the primary outcome was not influenced.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment because one analyst was blinded to allocation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Analysis on the basis of the intention-to-treat principle. Seven participants were withdrawn from the study at various times (ranging from study days 1 to 11).
Selective reporting (reporting bias)	Low risk	Published reports included all expected outcomes.
Other bias	Low risk	A significant difference was noted between the two groups in baseline characteristics for the mean age and rate of sepsis, but these differences were minimal after the data were pooled.

Mercat 2008

Methods	Randomized controlled trial. Time period of study: September 2002 through December 2005.
Participants	767 participants, aged > 18 (37 centres). Included: ARDS. Excluded: known pregnancy, participation in another trial within 30 days, increased intracranial pressure, sickle cell disease, severe chronic respiratory disease requiring oxygen therapy or home MV, actual body weight exceeding 1 kg/cm of height, se-

Mercat 2008 (Continued)

vere burns, severe chronic liver disease, bone marrow transplant or chemotherapy-induced neutropenia, pneumothorax, expected duration of MV $\leq$ 48 hours, decision to withhold life-sustaining treatment.

Interventions	<p>Control (382) and intervention (385): MV: ventilator mode (both groups): volume-assist control, VT: 6 mL/kg PBW, plateau-pressure limit $\leq$ 30 cm H₂O, respiratory rate (breaths/min) $\leq$ 35 adjusted for a pH between 7.30 and 7.45, recruiting manoeuvres: allowed but not recommended.</p> <p>Target ranges for oxygenation: PaO₂ between 55 and 80 mm Hg; SpO₂ between 88% and 95%.</p> <p>PEEP:</p> <p>Control: Total PEEP between 5 and 9 cm H₂O.</p> <p>Intervention: PEEP level to achieve plateau pressures between 28 and 30 cm H₂O.</p> <p>Use of rescue therapies¹ (both groups) when the oxygenation goal was not met despite FIO₂ $\geq$ 0.8.</p>
Outcomes	<p>Primary: mortality at day 28.</p> <p>Secondary: mortality at day 60, mortality before hospital discharge censored on day 60, VFD, days-free without organ failure and barotrauma between day 1 and day 28.</p>
Notes	<p>1. Rescue therapies: prone ventilation, inhaled NO, almitrine bismesylate.</p> <p>Discontinued during the 18th interim analysis because of absence of 10% absolute reduction in mortality between groups.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Authors performed random allocation in permuted blocks stratified by centre.
Allocation concealment (selection bias)	Low risk	Assignment was performed by centralized-interactive telephone system.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Incomplete blinding (blinding of participants but not personnel), but outcomes not influenced
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The main analyses were conducted in a blind fashion.
Incomplete outcome data (attrition bias) All outcomes	Low risk	One participant (control) was excluded because family withdrew consent after randomization. One participant (intervention) was lost to follow-up after discharge on day 29 and was included in the analysis on the basis of the intention-to-treat principle.
Selective reporting (reporting bias)	Low risk	Published reports included all expected outcomes.
Other bias	Low risk	Review author believed the study to be free of other sources of bias.

Talmor 2008

Methods	Randomized controlled trial.
Participants	61 participants, (one centre). Included: ALI and ARDS according to the AECC. Excluded: recent injury or other pathologic condition of the oesophagus, major bronchopleural fistula and solid-organ transplantation.
Interventions	<p>In both groups, control (31) and intervention (30), the goals of MV included: a VT of 6 mL/kg PBW; a re-cruiting manoeuvre to standardize the history of lung volume, a PaO₂ between 55 and 120 mm Hg or an SpO₂ between 88% and 98%, an arterial pH of 7.30 to 7.45, and a PaCO₂ of 40 to 60 mm Hg.</p> <p>PEEP:</p> <p>Control: PEEP/FIO₂ combination.</p> <p>Intervention: Transpulmonary pressure (airway pressure minus pleural pressure) was determined, airway pressure was recorded during MV, and pleural pressure was estimated by an oesophageal balloon catheter. PEEP levels were set to achieve a transpulmonary pressure of 0 to 10 cm H₂O at end-expiration.</p> <p>All measurements were performed within 72 hours of patient inclusion.</p>
Outcomes	<p>Primary: improvement in arterial oxygenation (PaO₂/FIO₂).</p> <p>Secondary: indices of lung mechanics and gas exchange (respiratory system compliance and the ratio of physiological dead space to tidal volume), VFD, length of stay in the ICU, days not spent in ICU, mortality at day 28, mortality at day 180, days of ventilation among survivors.</p>
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients randomly allocated because authors used random allocation with the use of a block randomization scheme.
Allocation concealment (selection bias)	Low risk	Opaque sealed envelopes that were randomly ordered.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Incomplete blinding (blinding of participants but not of personnel), but the outcomes not influenced.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No blinding, but outcomes not influenced by lack of blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	In the experimental group, one participant who could not be assessed was included in the analysis on the basis of the intention-to-treat principle.
Selective reporting (reporting bias)	Low risk	Published reports included all expected outcomes.
Other bias	Low risk	Review author believed the study to be free of other sources of bias.

Villar 2006

Methods	Randomized controlled trial. Time period of study: March 1999 through March 2001.
Participants	95 participants, aged > 15. Included: persistent ARDS. Excluded: patients with acute cardiac clinical conditions, pregnancy, neuromuscular diseases, high risk of mortality within 3 months for reasons other than ARDS (severe neurologic damage, age > 80 years, and cancer patients in the terminal stage of their disease), or more than two extrapulmonary organ failures.
Interventions	Control (45) and intervention (50): MV: ventilator mode (both groups): volume-assist control, respiratory rate to maintain PaCO ₂ between 35 and 50 cm H ₂ O. Control: VT: 9 to 11 mL/kg PBW, PEEP ≥ 5 cm H ₂ O and FIO ₂ to optimize SpO ₂ > 90% and PaO ₂ between 70 and 100 mm Hg. Intervention: VT: 5 to 8 mL/kg PBW, PEEP: 2 cm H ₂ O above Pflex or 15 cm H ₂ O if no Pflex; FIO ₂ to optimize SpO ₂ > 90% and PaO ₂ between 70 and 100 mm Hg.
Outcomes	Primary: mortality in the ICU. Secondary: hospital mortality (mortality before hospital discharge), VFD, extrapulmonary organ failure, and barotrauma.
Notes	Discontinued prematurely because the absolute mortality difference between control and intervention groups satisfied the stopping rule.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Authors used blocked randomization (restricted randomization) stratified by centre.
Allocation concealment (selection bias)	Low risk	Opaque sealed envelopes that were randomly ordered.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Incomplete blinding (blinding of participants but not of personnel), but outcomes not influenced.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No blinding, but outcomes not influenced.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Three out of 53 participants missing from intervention group and five out of 50 participants missing from control group, because a centre failed to adhere to the randomization methodology. The final analysis was performed with the remaining 95 participants.
Selective reporting (reporting bias)	Low risk	Published reports included all expected outcomes.
Other bias	Low risk	Review author believed the study to be free of other sources of bias.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Amato 1995	The 28 participants in this study were included in the large study published in 1998.
Badet 2009	This study assessed the role of three ventilation strategies with recruitment manoeuvres and optimal PEEP (PEEP set to 24 cm H ₂ O and then lowered stepwise to step above which PaO ₂ decreased by ≥ 20%) in a random order in 12 participants with ALI or ARDS. Arterial blood gas values and static compliance were recorded at the end of each strategy. No control group, thus not an RCT.
Burns 2001	14 participants with ARDS were treated with each of ten tidal volume-PEEP combinations, applied in random order, to assess changes in oxygenation and respiratory compliance. No control group, thus not an RCT.
Carvalho 1997	This study was a descriptive analysis of another published study (Amato 1995) and included two groups of participants with different levels of PEEP, in which physiological variables were studied.
Dellamonica 2011	In 30 participants with ALI, two levels of PEEP were applied in a random sequence to provide a simple and accurate bedside method for assessing alveolar recruitment while monitoring strain on the lungs. We had no control group, so the trial was not an RCT.
Grasso 2005	In 19 participants with ARDS divided into two groups and with different levels of PEEP, changes in oxygenation, static lung elastance and the shape of the volume-pressure curve were assessed. Excluded because the outcomes are physiological.
Grasso 2007	In 15 participants with ARDS, two ventilatory strategies with different levels of PEEP were applied in random order. Physiological parameters and plasma inflammatory mediators were measured. No control group, thus not an RCT.
Kallet 2007	This was a review of the different ways of applying PEEP in participants with ARDS.
Oczenski 2004	This was a randomized controlled study of participants with early extrapulmonary ARDS. In this study, two groups were assigned, but both had equal levels of PEEP and differed only in the inclusion of a recruitment manoeuvre.
Ranieri 1999	This was a randomized controlled trial of participants with ARDS. Two groups were assigned with different VT and levels of PEEP. Excluded because the primary outcome is physiological (pulmonary and systemic concentrations of inflammatory mediators) and mortality is reported as a post hoc analysis.
Richard 2003	In this prospective cross-over study, 15 participants with ALI were treated with three ventilatory strategies combining different levels of PEEP and VT to investigate changes in alveolar recruitment and oxygenation. No control group, thus not an RCT.
Toth 2007	This was a study in which 18 participants with ARDS underwent recruitment manoeuvres and decremental PEEP to reach optimal PEEP (PEEP set to 26 cm H ₂ O and then lowered stepwise to step above which PaO ₂ decreased by > 10%) for assessment of respiratory and haemodynamic changes. No control group, thus not an RCT.

Characteristics of ongoing studies *[ordered by study ID]*

[Kacmarek 2007](#)

Trial name or title	ARDSnet Protocol vs Open Lung Approach in ARDS
Methods	Randomized controlled trial

Kacmarek 2007 (Continued)

Participants	Included: participants with ARDS in the first 48 hours after diagnosis, PaO ₂ /FIO ₂ must be < 200 with standard ventilator setting, no lung recruitment manoeuvres or adjunct therapy, total time on mechanical ventilation < 96 hours at time of randomization. Excluded: age < 18 years or > 80 years, weight < 35 kg PBW, body mass index > 60, intubated secondary to acute exacerbation of a chronic pulmonary disease, acute brain injury (ICP > 18 mm Hg), immunosuppression 2° to chemotherapy or radiation therapy, severe cardiac disease, pregnancy, sickle cell disease, neuromuscular disease, more than two organ failures, barotrauma, persistent haemodynamic instability, penetrating chest trauma, enrolment in another interventional study.
Interventions	Control: PEEP/FIO ₂ combination with target ranges for oxygenation: PaO ₂ between 55 and 80 mm Hg; SpO ₂ between 88% and 95%. Intervention: uses a technique with recruitment manoeuvres and optimal PEEP (the optimal PEEP level is determined by a decremental PEEP trial involving a series of pressure measurements taken after the recruitment manoeuvre).
Outcomes	<ul style="list-style-type: none"> • Mortality at day 60. • Mortality in the intensive care unit (ICU), • Mortality before hospital discharge. • Mortality at day 28, • Mortality at day 180. • Mortality at day 365. • Ventilator-free days. • Length of ICU stay. • Development of extra-pulmonary organ failures. • Duration of hospitalization. • Incidence of barotrauma. • Systemic inflammatory mediator levels. • Lung function 6 months after discharge. • Lung function 12 months after discharge. • Need for rescue therapy. • Ventilation-associated pneumonia rate.
Starting date	February 1, 2007.
Contact information	Robert Kacmarek, Massachussets General Hospital, Boston, Massachussets, United States.
Notes	

Pintado 2003

Trial name or title	Pilot study of positive end-expiratory pressure in acute respiratory distress syndrome (PEEP-HU-PA).
Methods	Randomized controlled pilot trial.
Participants	Included: participants with ARDS after 24 hours under mechanical ventilation. Excluded: age < 18 years, pregnancy, neuromuscular diseases, intracranial hypertension (head trauma), left ventricular dysfunction, mechanical ventilation for longer than 72 hours, previous barotrauma, participants with terminal stage of an illness and high risk of mortality within 90 days, participants who refused to consent to the study.

Pintado 2003 (Continued)

Interventions	<p>In both groups: MV: VT of 6 mL/kg PBW; plateau pressure $\leq$ 35 cm H₂O, respiratory rate (breaths/min) 30 to 35 to maintain a pH of 7.30 to 7.45 and FIO₂ to optimize SpO₂ between 88% and 95% or PaO₂ between 55 and 80 mm Hg.</p> <p>PEEP:</p> <p>Compliance-guided PEEP group: The PEEP level is programmed on a daily basis, according to the method described by Suter in 1978. The static compliance (Cst) is calculated at different levels of PEEP at a constant VT. The maximum value of Cst in individual patients is considered to be the best PEEP.</p> <p>FIO₂-driven-PEEP group: PEEP/FIO₂ combination.</p>
Outcomes	<p>Primary: evolution of arterial oxygenation during the 28 days after study randomization.</p> <p>Secondary: mortality at day 28, ventilator-free days.</p>
Starting date	January 2003.
Contact information	María del Consuelo Pintado, Critical Care Unit, Universitary Hospital Príncipe de Asturias, Spain.
Notes	This study has been completed.

DATA AND ANALYSES

Comparison 1. High versus low levels of PEEP

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality before hospital discharge	3	2299	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.81, 1.01]
2 Oxygen efficiency (PaO ₂ /FIO ₂). Day 1	5	2337	Mean Difference (IV, Random, 95% CI)	41.31 [24.11, 58.52]
3 Oxygen efficiency (PaO ₂ /FIO ₂). Day 3	5	2059	Mean Difference (IV, Random, 95% CI)	42.51 [25.00, 60.02]
4 Oxygen efficiency (PaO ₂ /FIO ₂). Day 7	4	1379	Mean Difference (IV, Random, 95% CI)	24.77 [-0.92, 50.45]
5 Oxygen efficiency (PaO ₂ /FIO ₂); Day 1. Patients with ARDS	2	152	Mean Difference (IV, Fixed, 95% CI)	17.79 [1.37, 34.21]
6 Oxygen efficiency (PaO ₂ /FIO ₂); Day 3. Patients with ARDS	2	151	Mean Difference (IV, Fixed, 95% CI)	35.30 [14.71, 55.90]
7 Barotrauma	6	2504	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.66, 1.42]
8 Ventilator-free days			Other data	No numeric data

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9 Ventilator-free days (only means)	2	644	Mean Difference (IV, Random, 95% CI)	1.89 [-3.58, 7.36]
10 Length of stay in the ICU			Other data	No numeric data
11 Mortality before hospital discharge (studies with or without other interventions)	5	2447	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.79, 0.98]
12 Mortality within 28 days of randomization	5	1921	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.67, 1.01]
13 Mortality before hospital discharge: older participants	4	2394	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.80, 0.99]
14 Mortality before hospital discharge. PEEP according to the mechanical characteristics of the lung	3	915	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.57, 1.01]
15 Mortality before hospital discharge. PEEP according to FIO ₂ and PaO ₂	2	1532	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.79, 1.04]
16 Mortality before hospital discharge. High PEEP and low tidal volume versus low PEEP and high tidal volume	2	148	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.44, 0.87]
17 Mortality in the Intensive Care Unit (ICU). Patients with ARDS	3	205	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.48, 0.95]
18 Mortality before hospital discharge. Sensitivity analysis. Studies of good quality	3	1845	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.76, 1.01]
19 Mortality before hospital discharge. Sensitivity analysis. Exclusion of the study with large effect size	4	1464	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.69, 0.99]

Analysis 1.1. Comparison 1 High versus low levels of PEEP, Outcome 1 Mortality before hospital discharge.

Analysis 1.2. Comparison 1 High versus low levels of PEEP, Outcome 2 Oxygen efficiency ($\text{PaO}_2/\text{FIO}_2$). Day 1.

Analysis 1.3. Comparison 1 High versus low levels of PEEP, Outcome 3 Oxygen efficiency ($\text{PaO}_2/\text{FIO}_2$). Day 3.

Analysis 1.4. Comparison 1 High versus low levels of PEEP, Outcome 4 Oxygen efficiency ($\text{PaO}_2/\text{FIO}_2$). Day 7.

Analysis 1.5. Comparison 1 High versus low levels of PEEP, Outcome 5 Oxygen efficiency (PaO₂/FIO₂); Day 1. Patients with ARDS. **Analysis 1.6. Comparison 1 High versus low levels of PEEP, Outcome 6 Oxygen efficiency (PaO₂/FIO₂); Day 3. Patients with ARDS.** **Analysis 1.7. Comparison 1 High versus low levels of PEEP, Outcome 7 Barotrauma.** **Analysis 1.8. Comparison 1 High versus low levels of PEEP, Outcome 8 Ventilator-free days.**

Study	Ventilator-free days		P Value
	High PEEP	Low PEEP	
Brower 2004	Means: 13.8	Means: 14.5	0,50

Study	Ventilator-free days		P Value
	High PEEP	Low PEEP	
Brower 2004	SD: 10.6	SD: 10.4	
Brower 2004	No. of patients: 276	No. of patients: 273	
Mercat 2008	Median: 7	Median: 3	0,04
Mercat 2008	Interquartile range: 0.0-19	Interquartile range: 0.0-17	
Mercat 2008	No. of patients: 385	No. of patients: 382	
Talmor 2008	Median: 11.5	Median: 7	0,50
Talmor 2008	Interquartile range: 0.0-20.3	Interquartile range: 0.0-17	
Talmor 2008	No. of patients: 30	No. of patients: 31	
Villar 2006	Means: 10.9	Means: 6	0,008
Villar 2006	SD: 9.4	SD: 7.9	
Villar 2006	No. of patients: 50	No. of patients: 45	

Analysis 1.9. Comparison 1 High versus low levels of PEEP, Outcome 9 Ventilator-free days (only means).

Analysis 1.10. Comparison 1 High versus low levels of PEEP, Outcome 10 Length of stay in the ICU.

Study	Length of stay in the ICU		P Value
	High PEEP	Low PEEP	
Huh 2009	Means: 25.1 days.	Means: 21.4 days	0,643
Huh 2009	SD: 5.6	SD: 5.3	
Huh 2009	No. of patients: 30	No. of patients: 27	
Meade 2008	Median: 13 days.	Median: 13 days.	0,98
Meade 2008	Interquartile range: 8-23	Interquartile range: 9-23	
Meade 2008	No. of patients: 475	No. of patients: 508	
Talmor 2008	Median: 15,5 days.	Median: 13 days.	0,16
Talmor 2008	Interquartile range: 10,8-28,5	Interquartile range: 7-22	
Talmor 2008	No. of patients: 30	No. of patients: 508	

Analysis 1.11. Comparison 1 High versus low levels of PEEP, Outcome 11 Mortality before hospital discharge (studies with or without other interventions).

Analysis 1.12. Comparison 1 High versus low levels of PEEP, Outcome 12 Mortality within 28 days of randomization.

Analysis 1.13. Comparison 1 High versus low levels of PEEP, Outcome 13 Mortality before hospital discharge: older participants.

Analysis 1.14. Comparison 1 High versus low levels of PEEP, Outcome 14 Mortality before hospital discharge. PEEP according to the mechanical characteristics of the lung.

Analysis 1.15. Comparison 1 High versus low levels of PEEP, Outcome 15 Mortality before hospital discharge. PEEP according to FIO₂ and PaO₂.

Analysis 1.16. Comparison 1 High versus low levels of PEEP, Outcome 16 Mortality before hospital discharge. High PEEP and low tidal volume versus low PEEP and high tidal volume.

Analysis 1.17. Comparison 1 High versus low levels of PEEP, Outcome 17 Mortality in the Intensive Care Unit (ICU). Patients with ARDS.

Analysis 1.18. Comparison 1 High versus low levels of PEEP, Outcome 18 Mortality before hospital discharge. Sensitivity analysis. Studies of good quality.

Analysis 1.19. Comparison 1 High versus low levels of PEEP, Outcome 19 Mortality before hospital discharge. Sensitivity analysis. Exclusion of the study with large effect size.

ADDITIONAL TABLES

Table 1. Different primary and secondary outcomes

Amato 1998	1. Mortality at day 28.	<ul style="list-style-type: none"> • Mortality before hospital discharge. • Barotrauma. • Weaning rate adjusted for APACHE II score. • Mortality in the intensive care unit (ICU). • Death after weaning of MV. • Nosocomial pneumonia. • Use of paralysing agents > 24 hours. • Neuropathy after extubation. • Dialysis required. • Packed red cells infused.
Brower 2004	1. Mortality before hospital discharge.	<ul style="list-style-type: none"> • Ventilator-free days. • Days not spent in ICU. • Days free without organ failure. • Barotrauma. • Breathing without assistance by day 28.
Huh 2009	1. Improvement in oxygenation.	<ul style="list-style-type: none"> • Respiratory mechanics (PEEP and dynamic compliance). • ICU stay. • Duration of sedatives and paralysing agents. • Mortality at day 28. • Mortality at day 60. • Duration of MV.
Meade 2008	1. Mortality all-cause hospital (mortality before hospital discharge).	<ul style="list-style-type: none"> • Mortality during MV. • Mortality in ICU. • Mortality at day 28. • Barotrauma. • Refractory hypoxaemia. • Refractory acidosis. • Refractory barotrauma. • Use of rescue therapies in response to refractory hypoxaemia, refractory acidosis or refractory barotrauma. • Days of MV. • Days of ICU. • Days of hospitalization.
Mercat 2008	1. Mortality at day 28.	<ul style="list-style-type: none"> • Mortality at day 60. • Mortality before hospital discharge censored on day 60. • Ventilator-free days. • Days free without organ failure. • Barotrauma between day 1 and day 28.
Talmor 2008	1. Improvement in oxygenation.	<ul style="list-style-type: none"> • Indexes of lung mechanics and gas exchange (respiratory system compliance and ratio of physiological dead space to tidal volume). • Ventilator-free days. • ICU stay. • Days not spent in ICU. • Mortality at day 28. • Mortality at day 180. • Days of ventilation among survivors.

Table 1. Different primary and secondary outcomes (Continued)

Villar 2006

1. Mortality in the intensive care unit (ICU).
 - Hospital mortality (mortality before hospital discharge).
 - Ventilator-free days.
 - Extrapulmonary organ failure.
 - Barotrauma.

APPENDICES

Appendix 1. Terminologies

AECC	American-European Consensus Conference definitions. ALI criteria: acute onset, $\text{PaO}_2/\text{FIO}_2 \leq 300$ (regardless of PEEP level), bilateral pulmonary infiltrates and lack of evidence of left heart failure. ARDS has the same clinical characteristics as ALI, except that the $\text{PaO}_2/\text{FIO}_2$ in ARDS is ≤ 200 (Bernard 1994).
ALI	Acute lung injury.
APACHE II	Acute Physiology and Chronic Health Evaluation II. Classification system of severity of diseases.
ARDS	Acute respiratory distress syndrome.
Days-free without organ failure	Number of days a participant was without organ failure from day 1 to day 28.
Days not spent in ICU	Number of days a participant was not in the ICU from day 1 to day 28.
Driving Pressure	Plateau pressure—PEEP.
FIO_2	Fraction of inspired oxygen.
FRC	Functional residual capacity.
ICU	Intensive care unit.
LISS	Lung injury severity score (Murray 1988). Range 0 (normal) to 4 (most severe). $\text{LISS} > 2.5 = \text{ARDS}$.
LOS	Length of stay.
MV	Mechanical ventilation.
PaCO_2	Partial pressure of arterial carbon dioxide.
PaO_2	Partial pressure of arterial oxygen.
$\text{PaO}_2/\text{FiO}_2$	Relation between partial pressure of arterial/fractional inspired oxygen.
PBW	Predicted body weights.

(Continued)

PEEP	Positive end-expiratory pressure.
Persistent ARDS	Participants with ARDS ventilated with standard setting for 24 hours who persist with $\text{PaO}_2/\text{FIO}_2 \leq 200$.
Pflex	Upward shift in the slope of the pressure-volume curve.
Pwedge	Pulmonary wedge pressure.
Recruitment manoeuvre	Manoeuvre for opening of collapsed alveoli to improve gas exchange and lung volume end-expiration and decreased VILI.
RCT	Randomized controlled trial.
SpO ₂	Arterial oxygen saturation (measured via pulse oximetry).
Static compliance (Cst)	Determined by dividing tidal volume by the difference between pressure at the end of inflation hold and PEEP.
Strain	Ratio between the amount of gas volume delivered during tidal breath and the amount of aerated lung receiving it.
VFD	Number of days between successful weaning from mechanical ventilation and day 28 after study enrolment (Schoenfeld 2002).
VILI	Ventilator-induced lung injury.
VT	Volume tidal.

Appendix 2. Search strategy for CENTRAL, *The Cochrane Library*

```
#1 MeSH descriptor Positive-Pressure Respiration explode all trees
#2 MeSH descriptor Positive-Pressure Respiration, Intrinsic explode all trees
#3 MeSH descriptor Continuous Positive Airway Pressure explode all trees
#4 MeSH descriptor Intermittent Positive-Pressure Breathing explode all trees
#5 MeSH descriptor Intermittent Positive-Pressure Ventilation explode all trees
#6 PEEP
#7 (positive airway or end?expiratory) near pressure
#8 APRV or CPAP or CPAP or PEEP* or auto?PEEP or positive?pressure
#9 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8)
#10 MeSH descriptor Acute Lung Injury explode all trees
#11 MeSH descriptor Respiratory Paralysis explode all trees
#12 MeSH descriptor Respiratory Insufficiency explode all trees
#13 MeSH descriptor Respiratory Distress Syndrome, Adult explode all trees
#14 MeSH descriptor Respiratory Distress Syndrome, Newborn explode all trees
#15 Acute near (hypox* or respiratory)
#16 respirat* near (distress or failure)
#17 lung injury or AHRF or ARDS or ALI
#18 (#10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17)
#19 (#8 AND #18)
```

Appendix 3. Search strategy for MEDLINE (Ovid SP)

```
1. exp Positive-Pressure-Respiration/ or exp Positive-Pressure-Respiration-Intrinsic/ or exp Continuous-Positive-Airway-Pressure/ or exp
Intermittent-Positive-Pressure-Breathing/ or exp Intermittent-Positive-Pressure-Ventilation/
2. (occult or auto or non?therapeutic) adj6 PEEP) or (positive pressure adj3 (respirat* or ventil*) or (positive airway or end?expiratory) adj3
pressure) or (APRV or CPAP or nCPAP or PEEP* or auto?PEEP or positive?pressure).mp.
```

3. 1 or 2
4. exp Acute Lung Injury/ or exp Respiratory-Paralysis/ or exp Respiratory-Insufficiency/ or exp Respiratory-Distress-Syndrome-Newborn/ or exp Respiratory-Distress-Syndrome-Adult/
5. ((Acute adj3 (hypox* or respiratory) or (respirat* adj3 (distress or failure) or lung injury or (AHRF or ARDS or ALI)).mp.
6. 4 or 5
7. 3 and 6
8. (randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.) not (animals not (humans and animals)).sh.
9. 7 and 8

Appendix 4. Search strategy for EMBASE (Ovid SP)

1. exp positive end expiratory pressure/ or exp intermittent positive pressure ventilation/
2. (occult or auto or non?therapeutic) adj6 PEEP) or (positive pressure adj3 (respirat* or ventil*) or (positive airway or end?expiratory) adj3 pressure) or (APRV or CPAP or nCPAP or PEEP* or auto?PEEP or positive?pressure).mp.
3. 1 or 2
4. exp acute lung injury/ or exp diaphragm paralysis/ or exp respiratory failure/ or respiratory distress/ or exp respiratory distress syndrome/ or exp adult respiratory distress syndrome/ or exp neonatal respiratory distress syndrome/
5. (Acute adj3 (hypox* or respiratory) or (respirat* adj3 (distress or failure) or lung injury or (AHRF or ARDS or ALI)).mp.
6. 4 or 5
7. 3 and 6
8. (singl* or doubl* or tripl*) adj3 blind) or crossover).ti,ab. or multicenter.ab. or placebo.sh. or controlled study.ab. or random*.ti,ab. or trial*.ti,ab.) not (animal not (human and animal)).sh.
9. 7 and 8

Appendix 5. Search strategy for LILACS (BIREME interface)

("POSITIVE-PRESSURE" or "AIRWAYPRESSURE" or "PEEP" or "positive pressure" or "presión positiva" or "pressão positiva" or "via aérea positiva" or "ruta aérea positiva" or "APRV" or "CPAP" or "nCPAP") and ("RESPIRATORYINSUFFICIENCY" or "RESPIRATORYDISTRESS" or "Lung Injury" or "Acute hypox\$" or "respirat\$ distress" or "AHRF" or "ARDS" or "ALI" or "Herida pulmonar" or "Lesão de pulmão" or "Aflição respiratória" or "Pena respiratória" or "Insuficiencia respiratoria" or "Insufficiency respiratório")

WHAT'S NEW

Date	Event	Description
17 December 2018	Amended	Editorial team changed to Cochrane Emergency and Critical Care

CONTRIBUTIONS OF AUTHORS

Conceiving the review: Roberto Santa Cruz (RSC).

Designing the review: RSC, Juan Rojas (JR), Agustin Ciapponi (AC).

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Undertaking manual searches: RSC.

Screening search results: RSC, Rolando Nervi (RN), Roberto Heredia (RH).

Organizing retrieval of articles: RSC.

Screening retrieved articles against inclusion criteria: RSC, RN, RH.

Appraising quality of articles: RSC.

Abstracting data from articles: RSC.

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Providing additional data about articles: RSC.

Obtaining and screening data on unpublished studies: RSC.

Providing data management for the review: RSC, JR, AC.

Entering data into Review Manager ([RevMan 5.1](#)): RSC, JR, AC.

Entering RevMan statistical data: RSC, JR, AC.

Performing other statistical analysis not using RevMan: RSC.

Performing double entry of data: RSC.

Interpreting data: RSC, JR, AC.

Making statistical inferences: RSC, JR, AC.

Writing the review: RSC.

Providing guidance on the review: JR, AC.

Securing funding for the review: none known.

Serving as guarantor for the review (one author): RSC.

Taking responsibility for reading and checking the review before submission: RSC.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- No sources of support, Argentina.

External sources

- No sources of support, Argentina.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The data collection and analysis sections of the review contain the following changes from corresponding sections of the protocol: In the selection of studies, Appendices 6 and 7 (present in the protocol) were excluded from the review because the data included in these appendices were developed within the text of the review.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Intensive Care Units; Length of Stay; Oxygen Consumption; Positive-Pressure Respiration [*methods] [mortality]; Randomized Controlled Trials as Topic; Respiratory Distress Syndrome, Adult [mortality] [*therapy]; Ventilator-Induced Lung Injury [mortality] [*therapy]

MeSH check words

Adult; Humans