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

A Systematic Review and Meta-analysis

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

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

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

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

DESPITE a reduction in mortality rates over the past 10 years, acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) are still associated with high mortality.[1] The management of respiratory failure in this group of patients poses many challenges, and the optimal level of positive end expiratory pressure (PEEP) that is appropriate for this patient group remains controversial.[2] It is recognized that respiratory therapy itself may sometimes contribute to or aggravate preexisting lung injury[3] due to a combination of factors involving the use of excessive pressure (baro-trauma), overdistension (volu-trauma), sheer forces associated with repeated opening and collapse of diseased alveoli (atelec-trauma), and alveolar inflammation associated with positive pressure ventilation and or nosocomial infections (bio-trauma). This complex clinical condition is referred to as ventilator-induced lung injury, the prevention of which is one of the main treatment objectives whenever mechanical ventilation is instituted.[2,3] The use of low tidal volumes and the use of an optimal level of PEEP are important components of this strategy.[2] Whereas the beneficial effects of a low tidal volume strategy is largely accepted, the publication of two recent, prospective randomized clinical trials has drawn renewed attention to the optimal level of PEEP that is required in ventilating these patients.[4,5]

Both the above mentioned trials – the Lung Open Ventilation trial (LOV trial) and the expiratory pressure trial (Express trial)[4,5]–and a previous similar study by the ARDS Clinical Trials Network (ALVEOLI study)[6] have concluded that the random application of either a higher or lower level of PEEP alone had no specific mortality benefits in unselected patient groups with ALI/ARDS. However, the need for rescue therapies were significantly reduced,[4,5] and oxygenation was significantly improved[4–6] with the high PEEP strategy. Therefore, even though no mortality benefits have been demonstrated to date, it is likely that the high PEEP strategy does confer significant biologic/physiologic benefits in all patients with ARDS. Gattinoni *et al.* have argued that mortality benefits may become apparent only if future studies focus on subgroups of patients with severe lung edema, larger recruitability, and more severe lung injury.[2] While making a convincing case for functional lung imaging, Gattinoni *et al.* acknowledged that it may be necessary to adopt a pragmatic care pathway until such an approach is feasible. The strategy recommended was to set the highest level of PEEP compatible with a plateau pressure of 28–30 cm H_2O, particularly during the early and more severe stages of the disease.[2]

One of the impediments to the wider use of high PEEP is the perceived risk of baro-trauma, and current evidence is insufficient to show that the above approach[2] would not lead to a higher incidence of baro-trauma. High PEEP may also adversely affect clinical outcome by reducing venous/lymphatic drainage, which would indirectly contribute to

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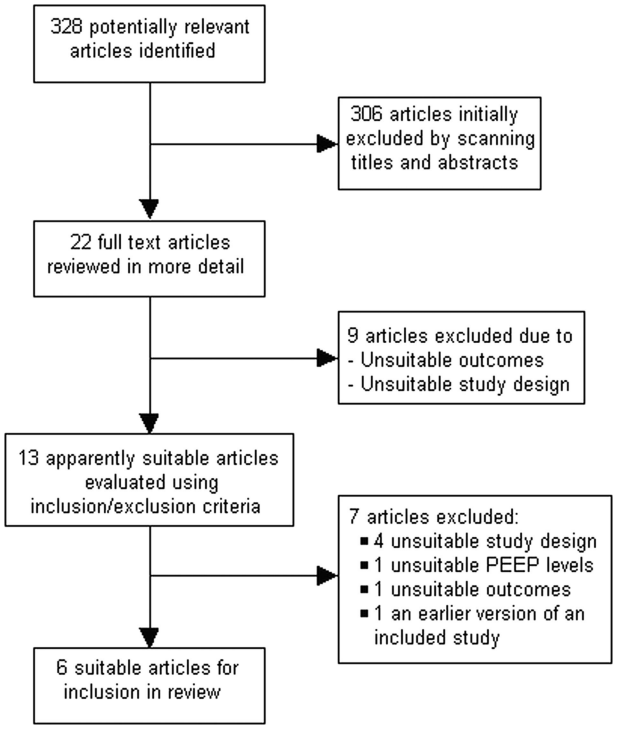

Fig. 1. Flow chart illustrating the process of identification of all the included clinical trials. PEEP = positive end expiratory pressure.

increased volume replacement therapy and generalized edema. In establishing the adverse consequences of high PEEP through the above mechanisms, however, even studies where high PEEP was used in conjunction with lower tidal volumes should provide important insights. In this context, three other relatively smaller clinical trials where high PEEP was combined with low tidal volumes are relevant.[7–9] These smaller trials also provide useful data on the effect of high PEEP on mortality that cannot be ignored when considering the current evidence on the efficacy and safety of the high PEEP strategy. The current meta-analysis was therefore undertaken with the following objectives: (1) to determine the relative risks of mortality associated with the use of high peep in patients with ALI/ARDS; (2) to determine the absolute mortality reduction associated with the high PEEP strategy; and (3) to determine the relative risk of baro-trauma associated with the high PEEP strategy.

ARDS is a very common clinical condition in the intensive care unit, and even a small reduction in absolute mortality risk is clinically relevant. The information related to absolute mortality reduction is also essential to determine whether a future definitive clinical trial is justifiable or feasible.

Materials and Methods

Identification of Trials

All relevant randomized controlled trials of adults with ALI or ARDS receiving mechanical ventilation using two levels of PEEP with or without other interventions were considered eligible for inclusion. Trials were identified by computerized searches of the Cochrane Controlled Trials Register, EMBASE (1980 to 2008 week 20), MEDLINE (1950 to May week 1 2008), and PubMed using combinations of the following terms:

- MeSH Term–Respiratory Distress Syndrome, Adult
- MeSH term–POSITIVE PRESSURE VENTILATION
- "Adult Respiratory Distress Syndrome"
- "Acute respiratory distress syndrome" or "ARDS"
- "Acute Lung Injury" or "ALI"
- "Sepsis"
- "Positive End Expiratory Pressure" or "PEEP"
- "Airway Pressure"

In addition, the references of relevant articles were read, and backward chaining of references was used to identify additional trials. Reports not including data, nonpublished studies, reports of earlier stages of studies (where the complete trial is subsequently published), nonhuman participants, and pediatric studies were excluded.

Outcome Measures and Data Extraction

The primary outcome measures sought were mortality and the incidence of baro-trauma. For all trials, other relevant data, including trial design, setting, numbers of patients, interventions, withdrawals, and patients lost to follow-up were collected.

Trial Quality Assessment

Trials were assessed for the quality of allocation concealment and methodological quality. The quality of allocation concealment was rated using the method proposed by Schulz *et al.*,[10] and methodological quality was assessed using the scoring system developed by Jadad *et al.*[11]

Data Analysis and Statistical Methods

The Mantel-Haenszel method was used to calculate the relative risks and 95% confidence intervals for mortality and the incidence of baro-trauma for each trial using StatsDirect statistical software (version 2.6.7, StatsDirect Ltd., Altrincham, UK). We tested for heterogeneity between the trials using the chi-square test ($P \leq 0.05$ indicating significant heterogeneity). $P \leq 0.10$ as suggested by Khan *et al.*[12] and the I^2 index were also used as more stringent tests for heterogeneity. $I^2 \geq 25\%$ is indicative of low heterogeneity, $I^2 \geq 50\%$ indicates moderate heterogeneity, and $I^2 \geq 75\%$ indicates high levels of heterogeneity.[13] Even though it is theoretically feasible to apply a fixed effect model as long as the statistical heterogeneity is low, it is extremely difficult in practice to interpret even the most stringent heterogeneity tests when only a small number of studies are available for analysis. We have therefore used a random effect model in the present study.[12–14] Combined odds ratios were

Table 1. Summary of All Included Trials and the Corresponding Qualitative Assessment Scores

Trial	Study Design	Total No. of Patients	Interventions		Jadad Score	Schulz Score
			High PEEP Group	Low PEEP Group		
Mercat *et al.*[5]	Multicenter randomized controlled trial in 37 intensive care units in France; conducted between September 2002 and December 2005	767	PEEP levels ≥ 10 cm H_2O Day 1 average: 15.1 ± 2.9 cm H_2O Plateau pressure: 28–30 cm H_2O Tidal volume: 6 mL/kg	PEEP levels ≤ 10 cm H_2O Day 1 average: 8.4 ± 1.9 cm H_2O Plateau pressure kept as low as possible Tidal volume: 6 mL/kg	3	A
Meade *et al.*[4]	Multicenter randomized controlled trial in 30 intensive care units in Canada, Australia, and Saudi Arabia; conducted between August 2000 and March 2006	983	PEEP levels ≥ 10 cm H_2O Day 1 average: 15.7 ± 4.0 cm H_2O Tidal volume: 6 mL/kg Plateau pressure < 40 cm H_2O Use of recruitment maneuvers at commencement of trial	PEEP levels ≤ 10 cm H_2O Day 1 average: 10.0 ± 2.9 cm H_2O Tidal volume: 6 mL/kgPlateau pressure < 30 cm H_2O	3	A
Villar *et al.*[9]	Randomized controlled trial in a network of 8 intensive care units in Spain; conducted between March 1999 and March 2001	95	PEEP levels ≥ 10 cm H_2O Day 1 average: 14.1 ± 2.8 cm H_2O Tidal volume: 5–8 mL/kg Fio_2 set to maintain arterial oxygen saturations >90% Respiratory rate set to maintain $Paco_2$ between 35 and 50 mmHg	PEEP levels ≤ 10 cm H_2O Day 1 average: 9.0 ± 2.7 cm H_2O Tidal volume: 9–11 mL/kgFio_2 set to maintain arterial oxygen saturations >90% Respiratory rate set to maintain $Paco_2$ between 35 and 50mmHg	3	A
Brower *et al.*[6]	Randomized controlled trial in 23 intensive care units in the United States; conducted between October 1999 and February 2002	549	PEEP levels ≥ 10 cm H_2O Day 1 average: 14.7 ± 3.5 cm H_2O Tidal volume: 6 mL/kg	PEEP levels ≤ 10 cm H_2O Day 1 average: 8.9 ± 3.5 cm H_2O Tidal volume of 6 mL/kg	2	A
Ranieri *et al.*[8]	Randomized controlled trial in 2 intensive care units in Italy and Switzerland; conducted between November 1995 and February 1998	37	PEEP levels ≥ 10 cm H_2O Day 1 average: 14.8 ± 2.7 cm H_2O Average tidal volume: 7.6 ± 1.1 mL/kg	PEEP levels ≤ 10 cm H_2O Day 1 average: 6.5 ± 1.7 cm H_2O Average tidal volume: 11.1 ± 1.9 mL/kg	3	A
Amato *et al.*[7]	Randomized controlled trial in 2 intensive care units in Brazil; conducted between December 1990 and July 1995)	53	PEEP levels ≥ 10 cm H_2O Day 1 average: 16.3 ± 0.7 cm H_2O Tidal volume: 6 mL/kg	PEEP levels ≤ 10 cm H_2O Day 1 average: 6.9 ± 0.8 cm H_2O Tidal volume: 12 mL/kg	3	A

PEEP = Positive end expiratory pressure.

also obtained. The role of publication and selection bias was estimated by visual inspection of the funnel plot for asymmetry. In addition, the data were formally tested for publication bias using Eggers regression approach[15] and the Begg-Mazumdar rank correlation test.[16] An Eggers P value ≤ 0.10 was considered to indicate significant asymmetry and therefore possible publication bias. For the Begg-Mazumdar rank correlation test, $P \leq 0.10$ was considered indicative of asymmetry and publication bias.[15,16]

Results

Study Identification

Database searches and backward chaining of references initially identified 328 potentially relevant articles, and the abstracts were obtained for all of these (fig. 1). After application of the inclusion and exclusion criteria, there were six randomized controlled trials[4–9] that met the inclusion criteria. The details of all the studies identified through this process are summarized in table 1.

Systematic Review and Meta-analysis

The six studies included a total of 2,484 patients (1,233 in the higher PEEP level group and 1,251 in the lower level PEEP group) obtained from 102 intensive care units in nine countries. Although the causes of lung injury varied slightly between the trials, pneumonia, sepsis, trauma, acute pancreatitis, and multiple blood transfusions accounted for the vast majority of patients. The mean ages of patients included in the trials were also largely similar and ranged from 48 to 60 yr. Patients in the lower PEEP group were significantly younger in one of the trials,[6] and the mean age in both groups was considerably lower in another trial.[7]

Methodological Quality of Studies

The methodological quality of the included studies, as assessed by the Jadad and Schulz criteria, was high. All of the trials except one had a Jadad score of 3 out of a possible 5 points (table 1). Due to the nature of the interventions, it was not possible for them to be double-blinded, which limits the total score to a maximum of 3. The lack of blinding means that it is not possible to completely eliminate detection and performance bias. The technical/practical difficulty inherent in undertaking double-blinded trials in this area should also be borne in mind in interpreting this meta-analysis. The trial that scored only 2 points on the Jadad score,[6] lost a point because no mention was made about whether any with-

Table 2. Data on Mortality from Trials Comparing the Use of High PEEP with Low PEEP

Trial	No. of Deaths		Weight (%)	Relative Risk (95% CI)
	High PEEP	Low PEEP		
Amato *et al*[7]	13/29	17/24	3.9	0.63 (0.38–1.01)
Brower *et al*[6]	69/276	75/273	15.8	0.91 (0.69–1.20)
Meade *et al*[4]	173/475	205/508	41.4	0.90 (0.77–1.06)
Mercat *et al*[5]	136/385	149/382	31.2	0.91 (0.75–1.09)
Ranieri *et al*[8]	7/18	11/19	2.2	0.67 (0.32–1.31)
Villar *et al*[9]	17/50	25/45	5.5	0.61 (0.38–0.97)
Total	415/1233	482/1251	100.0	0.87 (0.79–0.97)

PEEP = Positive end expiratory pressure.

drawals occurred during the study period. Three of the trials used intention-to-treat analysis of their data.[4,5,7] The other three trials[6,8,9] either excluded withdrawn patients from their analysis or made no mention of whether data obtained in withdrawn patients were included in the analysis. Five of the trials included a sample size power calculation in the design of the study.[4–7,9] The study by Ranieri *et al.* was not intended to assess mortality; therefore, it did not include power calculations relevant to mortality.[8] All of the included trials received a Schulz score of A, which shows that suitable randomization protocols were employed. Three studies used additional interventions besides the high and low levels of PEEP, which are likely to have affected the degree to which PEEP levels were responsible for any observed mortality benefits.[7–9] Amato *et al.*,[7] Ranieri *et al.*,[8] and Villar *et al.*[9] used lower tidal volumes in the higher PEEP groups in keeping with a protective ventilatory strategy. Therefore, we performed an additional subanalysis limited to the three larger trials[4–6] only to determine the effect of PEEP alone on observed mortality. The effect of tidal volume could be an important confounding factor, so the main conclusions drawn from the current meta-analysis are based on the latter subanalysis only. The Begg-Mazumdar rank correlation test for all six studies demonstrated significant evidence of publication bias, with a Kendalls tau value of -0.6, ($P = 0.0556$). This was verified by the Eggers regression approach, which had an intercept value of -1.71 ($P = 0.024$). Thus, both these results indicate statistical evidence of publication bias. This was confirmed by visual inspection of a funnel plot.

Meta-analysis Results

Mortality. The meta-analysis for mortality is shown in table 2 and figure 2. Five of the studies contained data on in-hospital mortality,[4–7,9] but the study by Ranieri *et al.*[8] only included data on 28-day mortality. In the current context, the two mortality figures are closely linked; therefore, we performed an initial analysis combining the two sets of mortality figures into a single meta-analysis (table 2 and fig. 2), which provides a measure of "early mortality" associated with the disease/treatment. In all trials, the early mortality was lower in the group

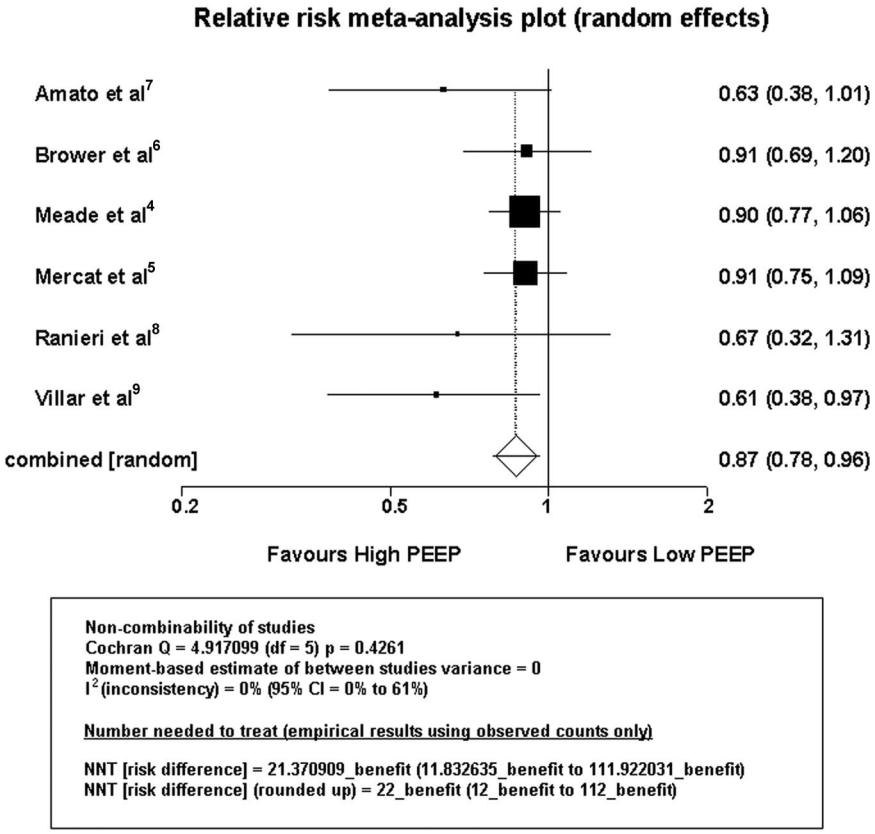

Fig. 2. Forest plot of the fixed effects model of relative risks of death associated with high positive end expiratory pressure (PEEP), as part of a protective ventilatory strategy, compared with low PEEP in acute respiratory distress syndrome (ARDS). NNT = Number needed to treat.

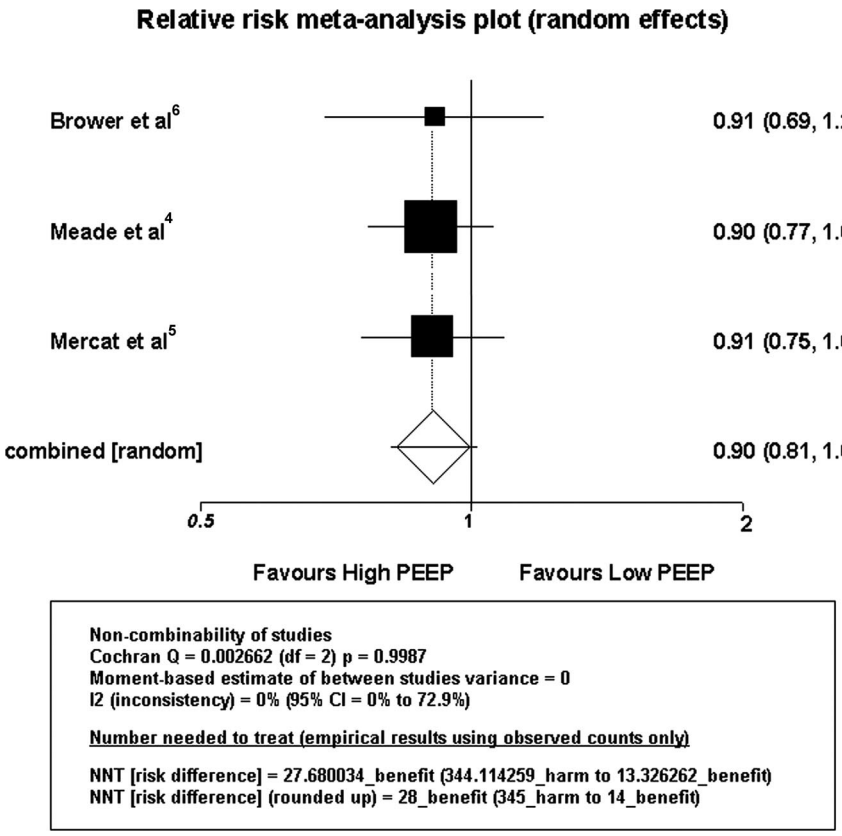

Fig. 3. Forest plot of the fixed effects model of relative risks of death associated with high positive end expiratory pressure (PEEP) use alone compared with low PEEP. NNT = Number needed to treat.

treated with higher levels of PEEP. This combined analysis of 2,484 patients with 1,233 in the higher PEEP group and 1,251 in the lower PEEP group shows that the higher PEEP group had a significantly lower early mortality than the group that received lower PEEP with a pooled relative risk of 0.87 (95% confidence interval [CI] 0.78–0.96, $P = 0.007$). The pooled odds ratio was 0.79 (95% CI 0.65–0.96, $P = 0.0199$). Exclusion of the 28-day mortality obtained from the study by Ranieri *et al.*[8] did not make any substantial difference to the findings; relative risk for in-hospital mortality was 0.87 (95% CI 0.77–0.97; $P = 0.0199$), and pooled odds ratio was 0.80 (95% CI 0.65–0.98, $P = 0.033$). This statistically significant benefit is attributable to the disproportionate effect of the three smaller trials[7–9] (where high PEEP was used in conjunction with lower tidal volumes) that collectively account for less than 12% of the weighting (table 2) and may not represent the true picture. A meta-analysis restricted to the three larger studies[4–6] that included PEEP level as the main variable investigated was therefore then undertaken, and the results are summarized in figure 3. The pooled relative risk for in-hospital mortality of these studies was 0.90 (95% CI 0.81–1.01, $P = 0.077$), with a pooled odds ratio of 0.86 (95% CI 0.72–1.02, $P = 0.077$) in favor of the higher PEEP group. Even though this difference is not statistically significant, the Forest plot (fig. 3) shows a consistent trend towards a mortality benefit, with a 3.6% reduction in absolute risk of death. Assuming that this is reproducible, one additional life may be saved for every 28 patients treated using high PEEP.

Baro-trauma. Five studies included data on the incidence of baro-traumas. (table 3 and fig. 4).[4–7,9] The pooled relative risk of baro-trauma was 0.95 (95% CI 0.62–1.45, $P = 0.81$), with a pooled odds ratio for baro-trauma of 0.91 (95% CI 0.55–1.51, $P = 0.72$). However, there was a degree of heterogeneity present between these trials (chi square = 8.28, df = 4, $P = 0.08$), with an I^2 value of 51.7%, indicating that there was a moderate level of heterogeneity present between these trials. Visual inspection of the Forest plot (fig. 4) indicates an overlap of all of the confidence intervals, except the study by Amato *et al.*[7] again confirming heterogene-

Table 3. Data on Baro-trauma Incidence from Trials Comparing the Use of High PEEP with Low PEEP

Trial	No. of Incidences of Baro-trauma		Weight (%)	Relative Risk (95% CI)
	High PEEP	Low PEEP		
Amato *et al*[7]	2/29	10/24	9.9	0.17 (0.04–0.59)
Brower *et al*[6]	30/276*	27/273*	24.9	1.10 (0.68–1.79)
Meade *et al*[4]	53/475	47/508	41.3	1.21 (0.83–1.75)
Mercat *et al*[5]	26/385	22/382	20.1	1.17 (0.68–2.02)
Villar *et al*[9]	2/50	4/45	3.8	0.45 (0.10–2.01)
Total	113/1215	110/1232	100.0	1.04 (0.81–1.33)

* The value in the table is an approximate value calculated from a percentage given in the paper by Brower *et al*[9] because the raw data were not available.
PEEP = positive end expiratory pressure.

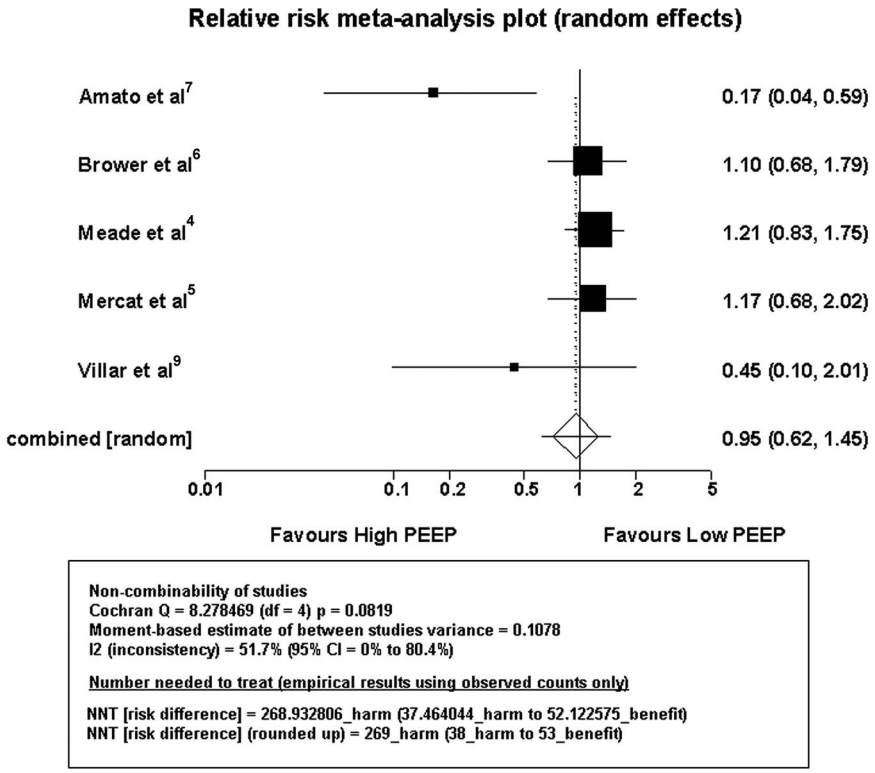

Fig. 4. Forest plot of the fixed effects model of relative risks of baro-trauma incidence associated with high positive end expiratory pressure (PEEP) compared with low PEEP in acute respiratory distress syndrome (ARDS). NNT = Number needed to treat.

ity. It was therefore necessary to exclude this study[7] and the relatively smaller study by Villar *et al.*[9] (both trials have wide confidence intervals and account for less than 15% of the weighting; table 3), and we performed a further meta-analysis that involved the three larger trials[4–6] only; the results are summarized in figure 5. Although this analysis also failed to provide statistically significant evidence of increased risk of baro-trauma (rel-

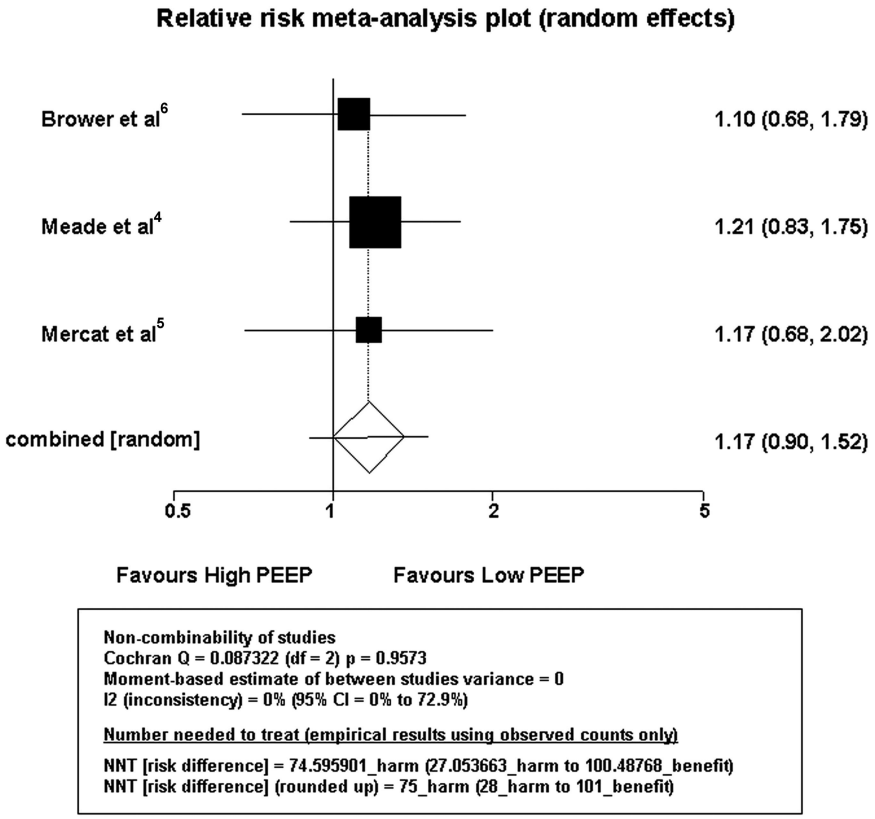

Fig. 5. Forest plot of the fixed effects model of relative risks of baro-trauma incidence associated with high positive end expiratory pressure (PEEP) use alone compared with low PEEP. NNT = Number needed to treat.

ative risk 1.17, 95% CI 0.90–1.52, $P = 0.25$), visual inspection of the Forest plot (fig. 5) indicates a possible trend towards increased risk.

Discussion

Protective ventilation strategies, which include low tidal volumes (approximately 6 ml/kg), high PEEP (>10 cm H_2O or 1–2 cm H_2O above the lower inflection point on the pressure-volume loop), and a plateau airway pressure of approximately 28–30 cm H_2O, are currently accepted as desired end points for ventilating patients with ALI/ARDS. Dissecting out the relative merits of the individual components of this combined approach, however, is fraught with difficulties. The present meta-analysis shows that the reduction in absolute mortality risk with high PEEP alone is approximately 4%; as such, one could expect to save one additional life for every 25–30 patients treated with this strategy. The absolute risk reduction is small, so any definitive study would need to recruit approximately 3,000 patients to demonstrate statistical significance. This prospect, in our view, would pose considerable financial and ethical burdens in undertaking such a study. Even though the reduction in risk of death is small, when considered in the light of high incidence and the undisputed biologic/physiologic benefits, the use of high PEEP strategy should be considered the default option in treating patients with ARDS/ALI.

Our decision to include the three clinical trials[7–9] in which higher levels of PEEP were combined with variable tidal volumes in our initial meta-analysis (fig. 2), although controversial, is useful in demonstrating the fact that similar beneficial trends have been observed in very diverse populations and geographical locations. This is crucial in addressing concerns over possible adverse consequences of a high mean intrathoracic pressure on clinical outcome. Furthermore, the mortality benefits seen in these three studies[7–9] cannot be automatically attributed to the use of low tidal volumes alone. For example, the selection of PEEP in the study by Amato *et al.*[7] was based on the lower inflection point of the pressure-volume curve. Patients who did not show an inflection point were also treated with a PEEP of approximately 15 cm H_2O when they were randomized into the treatment group, and the pooled retrospective analysis showed that mean PEEP and driving pressures (P_{Plat}-PEEP) during the first 36 h, rather than low tidal volumes, were the main independent ventilator-associated variables associated with mortality benefits.[7] In this respect, two additional studies by Stewart *et al.*[17] and Brochard *et al.*[18] require further consideration. In these two studies, involving a total of 236 patients with ALI/ARDS, a low tidal volume (approximately 7 ml/kg) did not have any beneficial effects on mortality in patients who were receiving comparable levels of PEEP.[17,18] These three trials collectively suggest that a higher level of PEEP, which minimizes cyclical opening and collapse of alveolar units and the associated atelec-trauma, is in the very least an equally important component of the protective ventilator strategy.[7,17,18] For this reason, we believe that the mortality figures from our meta-analysis of all six trials (fig. 2) is relevant despite some theoretical limitations.

Though widely considered to be a distinct clinical entity, patients with a diagnosis of ARDS/ALI represent a very heterogeneous group. It is therefore relevant to consider the subgroups that may receive maximum benefit through a high PEEP strategy. The beneficial effects of PEEP are related to the prevention of atelectasis, recruitment of already collapsed alveolar units, and avoiding the cyclical opening/collapse of alveoli.[2,3,19] These conditions are maximal in patients with a greater lung injury score and severe lung edema.[2] The maximal benefit of the high PEEP strategy in patients with more severe lung injury is best evident in the study by Villar *et al.*,[9] in which patients were recruited 24 h after meeting the ARDS criteria; as such, the study group represented a more severely ill cohort. Gattinoni *et al.*[2] have suggested that patients with a Pao_2 less than 60 mmHg for longer than 1 h while being ventilated on 100% oxygen may represent this more severe end of the spectrum.[2] Such patients are most likely to receive an independent benefit with high PEEP; in this group, it may even be necessary to set the PEEP at approximately 15 cm H_2O until the lung inflammation begins to resolve.[2] It is in this group of patients that the biologic/physiologic benefits achieved through the high PEEP strategy is likely to translate into mortality benefits.

Another important finding is the lack of significant differences in the incidence of baro-trauma between the two groups when all five trials were considered together (fig. 4). However, the three larger trials[4–6] (fig. 5) do show a nonsignificant but consistent trend towards a higher incidence. In all of the above trials, high PEEP was applied in the context of a protective ventilatory strategy, which limits the plateau airway pressure to less than 28–30 cm H_2O. The definition of the term baro-trauma was variable, and only Brower *et al.*[6] and Meade *et al.*[4] provided an adequate description of the term. Mercat *et al.*[5] only included patients suffering from pneumothorax in their data, which may account for the relatively wide confidence intervals and heterogeneity between trials. When considered together, current evidence suggests that the high PEEP strategy may, as expected, be associated with a higher incidence of baro-trauma. However, the benefits would far outweigh any potential disadvantages, particularly in patients with severe ARDS, as evidenced by the trend towards lower mortality (figs. 2 and 3).

Quality of Evidence and Limitations

The considerable overlap between the confidence intervals of the individual trials in figures 2 and 3 makes it likely that the differences is the study populations are due to chance. Although all six trials in figure 2 demonstrate a reduction in the mean mortality in the high PEEP group, the differences were statistically significant in only one trial, and it is relevant to note that this was the only trial that was restricted to patients with the more severe form of the disease.[9] Furthermore, inspection of the forest plots demonstrates that the point estimates of the relative risks of all the trials occur on the same side of the "line of no effect." This indicates that future trials are likely to show a similar effect. It is widely recognized that, despite applying stringent protocols and statistical tests, studies included in a meta-analysis of this nature will necessarily include heterogeneous groups of patients.[14] In this review, heterogeneity may have arisen from the differences in the baseline characteristics of included patients, underlying causes of lung injury, and differences in many other practices that are likely to exist between different institutions. The lack of a standard definition for the term baro-trauma across the different trials may also have contributed to the moderate heterogeneity found in the barotrauma data. Despite these differences, objective statistical tests show that these factors are unlikely to have influenced our findings.

Applicability of Evidence

The data included in this meta-analysis come from 102 different intensive care units in nine different countries. This study therefore shows that results from a variety of patients and backgrounds/practices follow a consistent pattern. In conclusion, the current meta-analysis suggests that the use of high PEEP may have an independent beneficial effect on mortality. Even though the effect size is small (less than 5%), the high incidence/prevalence of ALI/ARDS implies that this relatively simple and probably cost neutral intervention would save a large number of lives when translated globally. Any definitive study aimed at demonstrating statistical significance will require a sample size of approximately 3,000 patients; as such, it will pose considerable financial and ethical burdens. We consider that current evidence supports the use of high PEEP in unselected groups of patients with ALI/ARDS in general and those at the more severe end of the spectrum in particular in whom levels up to 15 cm H_2O may be appropriate.

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