

Higher vs Lower Positive End-Expiratory Pressure in Patients With Acute Lung Injury and Acute Respiratory Distress Syndrome

Systematic Review and Meta-analysis

Matthias Briel, MD, MSc

Maureen Meade, MD, MSc

Alain Mercat, MD

Roy G. Brower, MD

Daniel Talmor, MD, MPH

Stephen D. Walter, PhD

Arthur S. Slutsky, MD

Eleanor Pullenayegum, PhD

Qi Zhou, PhD

Deborah Cook, MD, MSc

Laurent Brochard, MD

Jean-Christophe M. Richard, MD

Francois Lamontagne, MD

Neera Bhatnagar, MLIS

Thomas E. Stewart, MD

Gordon Guyatt, MD, MSc

PROTECTING LUNGS FROM VENTILATION-induced injury is an important principle in the management of patients with acute lung injury or acute respiratory distress syndrome (ARDS). Although the critical care community has generally endorsed lower tidal volumes and inspiratory pressures, the optimal level of positive end-expiratory pressure (PEEP) remains unestablished.^{1,2} Experimental data suggest that PEEP levels exceeding traditional values of 5 to 12 cm H₂O can minimize cyclical alveolar collapse and corresponding shearing injury to the lungs in patients with considerable edema and alveolar collapse.³⁻⁵ For patients with relatively mild acute lung in-

See also p 883 and Patient Page.

Context Trials comparing higher vs lower levels of positive end-expiratory pressure (PEEP) in adults with acute lung injury or acute respiratory distress syndrome (ARDS) have been underpowered to detect small but potentially important effects on mortality or to explore subgroup differences.

Objectives To evaluate the association of higher vs lower PEEP with patient-important outcomes in adults with acute lung injury or ARDS who are receiving ventilation with low tidal volumes and to investigate whether these associations differ across prespecified subgroups.

Data Sources Search of MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials (1996-January 2010) plus a hand search of conference proceedings (2004-January 2010).

Study Selection Two reviewers independently screened articles to identify studies randomly assigning adults with acute lung injury or ARDS to treatment with higher vs lower PEEP (with low tidal volume ventilation) and also reporting mortality.

Data Extraction Data from 2299 individual patients in 3 trials were analyzed using uniform outcome definitions. Prespecified effect modifiers were tested using multivariable hierarchical regression, adjusting for important prognostic factors and clustering effects.

Results There were 374 hospital deaths in 1136 patients (32.9%) assigned to treatment with higher PEEP and 409 hospital deaths in 1163 patients (35.2%) assigned to lower PEEP (adjusted relative risk [RR], 0.94; 95% confidence interval [CI], 0.86-1.04; $P=.25$). Treatment effects varied with the presence or absence of ARDS, defined by a value of 200 mm Hg or less for the ratio of partial pressure of oxygen to fraction of inspired oxygen concentration ($P=.02$ for interaction). In patients with ARDS ($n=1892$), there were 324 hospital deaths (34.1%) in the higher PEEP group and 368 (39.1%) in the lower PEEP group (adjusted RR, 0.90; 95% CI, 0.81-1.00; $P=.049$); in patients without ARDS ($n=404$), there were 50 hospital deaths (27.2%) in the higher PEEP group and 44 (19.4%) in the lower PEEP group (adjusted RR, 1.37; 95% CI, 0.98-1.92; $P=.07$). Rates of pneumothorax and vasopressor use were similar.

Conclusions Treatment with higher vs lower levels of PEEP was not associated with improved hospital survival. However, higher levels were associated with improved survival among the subgroup of patients with ARDS.

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jury, however, potential adverse consequences of higher PEEP levels, including circulatory depression⁶ or lung overdistension,⁷ may outweigh the benefits. Several multicenter, randomized trials testing the incremental effect of higher levels

Author Affiliations are listed at the end of this article.
Corresponding Author: Maureen Meade, MD, MSc, Department of Clinical Epidemiology and Biostatistics, Room 2C12, 1200 Main St W, Hamilton, ON L8N 3Z5, Canada (meadema@hhsc.ca).
Caring for the Critically Ill Patient Section Editor: Derek C. Angus, MD, MPH, Contributing Editor, *JAMA* (angusdc@upmc.edu).

of PEEP were confounded by baseline imbalances in prognostic factors and underpowered to rule in or rule out an important survival effect.⁸⁻¹⁰

Meta-analysis of individual-patient data offers important advantages over conventional meta-analysis, including standardized definitions and analyses across studies, adjustment for variations in individual patient prognosis at baseline, and more powerful investigations of subgroup effects.¹¹ In this systematic review and meta-analysis of individual-patient data, we investigated the association between higher vs lower PEEP levels and patient-important outcomes among adults with acute lung injury or ARDS who receive ventilation with low tidal volumes; we also investigated whether effects differ across prespecified patient subgroups.

METHODS

Trial Selection and Data Collection

The predefined protocol for this meta-analysis of individual-patient data is available from the authors on request. Randomized trials eligible for this review compared higher with lower levels of PEEP (mean difference of at least 3 cm H₂O between groups during first 3 days following randomization) in critically ill adults (>16 years) with a diagnosis of acute lung injury or ARDS as defined by the American-European Consensus Conference.¹² Eligible trials incorporated a target tidal volume of less than 8 mL/kg of predicted body weight in both the experimental and the control ventilation strategies and provided patient follow-up to death or for at least 20 days.

We identified eligible trials by an electronic search of MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials (all from 1996 to January 2010) using the terms *positive end-expiratory pressure**, *PEEP*, *low tidal volume**, *open lung strateg**, *acute respiratory distress*, *acute lung injur**, and *ARDS* as text words and *positive pressure respiration*, *tidal volume*, and *respiratory distress syndrome* as Medical Subject Headings. We used a sensitive filter for randomized controlled trials¹³ and imposed no lan-

guage restrictions. We hand-searched conference proceedings (from 2004 to 2010) of the American Thoracic Society, the Society of Critical Care Medicine, the American Association of Respiratory Care, the European Society of Intensive Care Medicine, the American College of Chest Physicians, and the International Symposium on Intensive Care and Emergency Medicine. We checked reference lists of identified articles, recent editorials, and related reviews and contacted experts for further eligible trials.

Two reviewers (M.B., M.M.) independently assessed trial eligibility based on titles, abstracts, full-text reports, and further information from investigators as needed. We requested the protocol, case report forms, and unedited databases from investigators of all eligible trials. Data from each trial were checked against reported results, and queries were resolved with the corresponding principal investigator, trial data manager, or statistician. Some of the outcomes in this report may differ slightly from those in published original study reports because we standardized outcome definitions and data analyses.

To identify potential sources of bias, we examined concealment of treatment allocation, blinding of clinical outcome assessments and data analyses, the proportion of patients lost to follow-up, and early stopping prior to enrollment of the target sample.¹⁴ We used the Grading of Recommendations Assessment, Development and Evaluation system to rate the overall quality of the evidence.¹⁵ In this system, randomized clinical trials provide high-quality evidence unless limited by important risk of bias, imprecision, inconsistency, indirectness, or high risk of publication bias.

Patient Outcomes and Subgroups

All investigators (with the exception of D.T., who became involved later) provided feedback and authorized the final analysis plan prior to implementation. The primary outcome was hospital mortality, measured to at least 60 days in all eligible trials. Prespecified secondary outcomes were death before discharge from the intensive care unit,

pneumothorax with need for chest tube drainage in the first 28 days, death following pneumothorax with need for chest tube drainage, time-to-unassisted breathing within the first 28 days, days with unassisted breathing between day 1 and day 28, use of rescue therapy (as defined in each trial [eTable 1, available at <http://www.jama.com>]), death following rescue therapy, and the use of neuromuscular blockers, vasopressors, and corticosteroids.

We reexamined individual-patient data on ratios of partial pressure of oxygen to fraction of inspired oxygen (FIO₂) from all included trials to classify patients as having or not having ARDS at baseline, using a threshold PaO₂:FIO₂ value of 200 mm Hg or less to define ARDS, as suggested by the American-European Consensus Conference. A priori, we hypothesized that patients with more severe lung disease as reflected in lower baseline lung compliance (estimated as tidal volume/[inspiratory plateau pressure - PEEP]), lower PaO₂:FIO₂ ratio, presence of ARDS (PaO₂:FIO₂ ratio ≤200 mm Hg), and higher oxygenation index (defined as mean airway pressure × 100/[PaO₂:FIO₂ ratio]) would have more recruitable lung units and thus derive more benefit from higher levels of PEEP.¹⁴ We hypothesized less benefit with higher PEEP in patients with higher body mass index (calculated as weight in kilograms divided by height in meters squared) because of fewer recruitable lung units.

Statistical Analysis

All patients were analyzed in the study group to which they were randomized. We used 2-sided *t* tests to compare respiratory variables during follow-up and likelihood ratio tests to compare statistical models.

For the primary analysis of hospital mortality, we calculated relative risks (RRs) and 95% confidence intervals (CIs) using log-binomial regression.¹⁶ We used a multivariable hierarchical model with baseline patient characteristics (age, presence of severe sepsis, and predicted probability of dying in hospital based on Acute Physiology and

Chronic Health Evaluation II and Simplified Acute Physiology II scores, which have similar accuracy^{17,18}) as important prognostic factors as well as a categorical “trial” variable, all as fixed effects. To account for within- and between-hospital variability, we added recruiting hospitals within trials to the model as a random effect (primary analysis model).¹¹

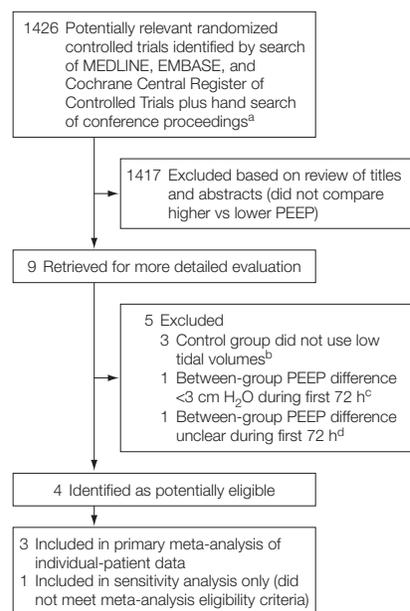
To examine lung compliance, body mass index, PaO₂:FIO₂ ratio, presence of ARDS, and oxygenation index as potential effect modifiers, we added each of these baseline variables in turn to the statistical model together with the corresponding interaction term with PEEP group, both as fixed effects.

To compare in-hospital time to death and time to unassisted breathing for the groups treated with higher and lower PEEP, we fitted Cox regression models with the same covariables. We fitted corresponding linear and log-binomial regression models for continuous and binary secondary outcomes, respectively. We explored heterogeneity in the treatment effect across trials using a likelihood ratio test that compared a more complex model that additionally included interaction terms between treat-

ment group and trial as fixed effects with a nested simpler model that excluded those interaction terms.

As prespecified sensitivity analyses, we calculated odds ratios and 95% CIs from corresponding logistic regression models; conducted a Bayesian random-effects analysis using noninformative priors¹⁹; and used multiple-imputation techniques to impute missing covariable data.²⁰ Each of these analyses generated results very similar to the ones obtained with the primary analysis model using log-binomial regression; we therefore focus this report on the results from the primary analysis model. In post hoc exploratory analyses, we examined hospital mortality by quintiles of baseline PaO₂:FIO₂ ratio and oxygenation index and investigated the stability of baseline PaO₂:FIO₂ ratios by looking at the evolution of PaO₂:FIO₂ ratios at days 1, 3, and 7 among patients with a baseline PaO₂:FIO₂ ratio greater than 200 mm Hg. We used Stata version 9.2 (StataCorp, College Station, Texas) and SAS version 11.0 (SAS Institute Inc, Cary, North Carolina) for statistical analysis, with *P* < .05 as the nominal level of statistical significance.

Figure 1. Trial Flow



PEEP indicates positive end-expiratory pressure.
^aAmerican Association of Respiratory Care, American College of Chest Physicians, American Thoracic Society, European Society of Intensive Care Medicine, International Symposium on Intensive Care and Emergency Medicine, Society of Critical Care Medicine.
^bLower PEEP groups received ventilation with traditionally high volumes (9-14 mL/kg).
^cSmall trial (N=57 patients).
^dSmall trial (N=30 patients); principal investigator did not reply to queries.

Table 1. Characteristics of Included Trials

Characteristic	Trial		
	ALVEOLI, ⁸ 2004	LOVS, ⁹ 2008	EXPRESS, ¹⁰ 2008
Inclusion criteria	Acute lung injury with PaO ₂ :FIO ₂ ≤300 ^a	Acute lung injury with PaO ₂ :FIO ₂ ≤250 ^a	Acute lung injury with PaO ₂ :FIO ₂ ≤300 ^a
Recruitment period	1999-2002	2000-2006	2002-2005
Recruiting hospitals (country)	23 (United States)	30 (Canada, Australia, Saudi Arabia)	37 (France)
Patients randomized to higher vs lower PEEP	276 vs 273	476 vs 509 ^b	385 vs 383 ^c
Validity			
Concealed allocation	Yes	Yes	Yes
Follow-up for primary outcome, %	100	100	100
Blinded data analysis	Yes	Yes	Yes
Stopped early	Stopped for perceived futility	No	Stopped for perceived futility
Experimental intervention	Higher PEEP according to FIO ₂ chart, recruitment maneuvers for first 80 patients	Higher PEEP according to FIO ₂ chart, required plateau pressures ≤40 cm H ₂ O, recruitment maneuvers	PEEP as high as possible without increasing the maximum inspiratory plateau pressure >28-30 cm H ₂ O
Control intervention	Conventional PEEP according to FIO ₂ chart, required plateau pressures ≤30 cm H ₂ O, no recruitment maneuvers	Conventional PEEP according to FIO ₂ chart, required plateau pressures ≤30 cm H ₂ O, no recruitment maneuvers	Conventional PEEP (5-9 cm H ₂ O) to meet oxygenation goals
Ventilator procedures	Target tidal volumes of 6 mL/kg of predicted body weight; plateau pressures ≤30 cm H ₂ O (with exception as above); respiratory rate ≤35/min, adjusted to achieve arterial pH 7.30-7.45; ventilator mode: volume-assist control (except higher PEEP group in LOVS required pressure control); oxygenation goals: PaO ₂ 55-80 mm Hg and SPO ₂ 88%-95%; standardized weaning		

Abbreviations: ALVEOLI, Assessment of Low Tidal Volume and Elevated End-Expiratory Pressure to Obviate Lung Injury; EXPRESS, Expiratory Pressure Study; FIO₂, fraction of inspired oxygen; LOVS, Lung Open Ventilation to Decrease Mortality in the Acute Respiratory Distress Syndrome; PEEP, positive end-expiratory pressure; SPO₂, oxygen saturation.

^aAcute lung injury defined according to the American-European Consensus Conference.¹²
^bIncludes 2 patients for whom consent was withdrawn prior to protocol initiation, without patient, family, and caregivers being aware of group assignment (ie, 983 patients analyzed).
^cIncludes 1 patient for whom consent was withdrawn prior to protocol initiation, without patient, family, and caregiver awareness of assignment (ie, 767 patients included in the analysis).

RESULTS

Three trials, including 2299 patients, met our eligibility criteria (FIGURE 1). In the Assessment of Low Tidal Volume and Elevated End-Expiratory Pressure to Obviate Lung Injury (ALVEOLI) trial (NCT00000579)⁸ and the Lung Open Ventilation to Decrease Mortality in the Acute Respiratory Distress Syndrome (LOVS) study (NCT00182195),⁹ PEEP levels were titrated to oxygenation using similar PEEP:FIO₂ charts (TABLE 1). The experimental strategy in the Expiratory Pressure Study (EXPRESS) (NCT00188058)¹⁰ titrated PEEP levels based on measurements of plateau pressure, regardless of the effect on oxygenation. Control strategies were similar in the ALVEOLI and LOVS studies, which allowed appre-

ciably higher control levels of PEEP than in the EXPRESS study. A fourth trial, the Esophageal Pressure Directed Ventilation (EPVENT) study (NCT00127491),²¹ did not explicitly aim to compare higher with lower PEEP levels and applied the allocated treatment for only 72 hours (eTables 2 and 3). In that trial, investigators titrated PEEP levels in the experimental group according to estimates of transpulmonary pressure, measured with an esophageal balloon. A sensitivity analysis including this trial did not change results appreciably (eTable 4). The methodological quality of included trials was high (Table 1). All trials concealed randomization, achieved complete follow-up for hospital mortality, and used blinded data analysis.

The higher and lower PEEP groups were similar at baseline with respect to important prognostic features (TABLE 2). Mean tidal volumes during the study were close to 6 mL/kg of predicted body weight in both groups of all 3 trials (TABLE 3). In the higher PEEP group, PEEP and plateau pressure levels were considerably higher at each point, and oxygenation was significantly better, as reflected in lower FIO₂ values.

Among the prespecified potential effect modifiers, there was a statistically significant interaction only for the presence of ARDS at baseline (P = .02). TABLE 4 therefore presents outcomes for all patients and for those with and without ARDS. Overall, the difference in hospital mortality between the higher

Table 2. Baseline Characteristics of Included Patients

Characteristic	Higher PEEP (n = 1136)	Lower PEEP (n = 1163)
Age, mean (SD), y	56 (17) [n = 1136]	56 (17) [n = 1163]
Women, No. (%)	437 (38) [n = 1136]	455 (39) [n = 1163]
Body mass index, mean (SD) ^a	27.1 (6.3) [n = 1024]	26.9 (6.6) [n = 1038]
Days in ICU prior to randomization, median (IQR), d	1 (1-3) [n = 1136]	2 (1-3) [n = 1163]
Days intubated prior to randomization, median (IQR), d	1 (1-2) [n = 1136]	1 (1-2) [n = 1163]
Probability of death from APACHE II or SAPS II scores, median (IQR)	49 (29-70) [n = 1133]	49 (29-70) [n = 1160]
No. of organ failures in addition to respiratory failure, median (IQR) ^b	1 (1-2) [n = 1123]	1 (1-2) [n = 1149]
Respiratory measures, mean (SD)		
PaO ₂ :FIO ₂ , mm Hg ^c	146 (56) [n = 1135]	148 (60) [n = 1161]
PaO ₂ :FIO ₂ ≤200 mm Hg, No. (%)	951 (84) [n = 1135]	941 (81) [n = 1161]
Oxygenation index, median (IQR) ^d	11.4 (8.2-16.8) [n = 989]	11.1 (7.7-17.0) [n = 1009]
Set PEEP, cm H ₂ O	9.9 (4.0) [n = 1135]	9.7 (3.8) [n = 1160]
Plateau pressure, cm H ₂ O	26.7 (6.4) [n = 915]	26.3 (6.6) [n = 899]
Respiratory rate, breaths/min	23.1 (6.6) [n = 1133]	23.2 (6.7) [n = 1160]
Minute ventilation, L/min	11.6 (3.2) [n = 1122]	11.7 (3.6) [n = 1151]
Tidal volume, mL/kg of predicted body weight	8.0 (1.9) [n = 1107]	8.0 (2.0) [n = 1135]
Estimated respiratory system compliance, mL/cm H ₂ O ^e	32.7 (14.9) [n = 909]	32.6 (13.7) [n = 892]
Cause of lung injury, No. (%) ^f		
Pneumonia	567 (50)	578 (50)
Aspiration	214 (19)	247 (21)
Severe sepsis, including septic shock	595 (52)	628 (54)
Multiple transfusions	71 (6.3)	74 (6.4)
Acute pancreatitis	37 (3.3)	48 (4.1)
Multiple trauma	60 (5.3)	73 (6.3)
Other ^g	146 (13)	119 (10)

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; ICU, intensive care unit; IQR, interquartile range; PEEP, positive end-expiratory pressure; SAPS II, Simplified Acute Physiology Score II.

^aCalculated as weight in kilograms divided by height in meters squared.

^bDichotomized Brussels Score as used in the Assessment of Low Tidal Volume and Elevated End-Expiratory Pressure to Obviate Lung Injury study;²² circulatory failure was defined as systolic blood pressure of 90 mm Hg or less or the need for treatment with any vasopressor; coagulation failure as platelet count of 50 000 platelets/mm³ or less; hepatic failure as serum bilirubin concentration greater than 5.9 mg/dL (100 μmol/L); renal failure as serum creatinine concentration greater than 3.4 mg/dL (300 μmol/L); and neurologic failure as Glasgow Coma Scale score of 9 or less.

^cIncludes altitude adjustment for patients from Colorado ((760/635) × PaO₂:FIO₂) and Utah ((760/642) × PaO₂:FIO₂); for 25 ALVEOLI patients with missing PaO₂:FIO₂ values at ventilation change, PaO₂:FIO₂ values from the screening form of the same day were used.

^dOxygenation index was calculated as mean airway pressure × 100/(PaO₂:FIO₂).

^eRespiratory system compliance was calculated as tidal volume/(inspiratory plateau pressure - PEEP).

^fIndividual patients could have more than 1 cause of lung injury.

^gIncludes drug overdose, prolonged shock, burn injury, inhalation injury, intra-alveolar hemorrhage, cardiopulmonary bypass, near drowning, vasculitis, and heat stroke.

and lower PEEP groups was not statistically significant (32.9% vs 35.2%; RR, 0.94; 95% CI, 0.86-1.04; $P = .25$). However, we found a statistically significant reduction of death in the intensive care unit for patients allocated to the higher PEEP group (28.5% vs 32.8%; RR, 0.87; 95% CI, 0.78-0.97; $P = .01$). Clinicians instituted rescue therapies for profound hypoxemia less frequently in patients with higher PEEP, and the rate of deaths following rescue therapy was also significantly lower. The groups did not differ significantly in rates of pneumothorax, hospital deaths following pneumothorax, use of vasopressors, or number of days with unassisted breathing during the first 28 days of study.

For patients with ARDS at baseline, those in the higher PEEP group were less likely to die in hospital (34.1% vs 39.1%; RR, 0.90; 95% CI, 0.81-1.00; $P = .049$) and more likely to achieve unassisted breathing earlier (hazard ratio, 1.16; 95% CI, 1.03-1.30; $P = .01$; proportions at 28 days, 64.3% vs 57.8%); for patients without ARDS at baseline, the RR for death in hospital with higher vs lower PEEP was 1.37 (95% CI, 0.98-1.92; $P = .07$; 27.2% vs 19.4%) and the hazard ratio for time to unassisted breathing was 0.79 (95% CI, 0.62-

0.99; $P = .04$; proportions at 28 days, 70.1% vs 80.9%) (Table 4, FIGURE 2).

Stratified results for other secondary efficacy outcomes consistently showed benefit from higher PEEP for patients with ARDS, with less benefit or even harm from higher PEEP for patients without ARDS (Table 4). A sensitivity analysis including the EPVENT trial generated RRs for hospital mortality of 0.88 (95% CI, 0.79-0.98; $P = .02$; 33.9% vs 39.0%) for patients with ARDS and 1.29 (95% CI, 0.91-1.83; $P = .14$; 26.5% vs 19.4%) for patients without ARDS.

When we explored heterogeneity in the treatment effect for hospital mortality across trials, there was no evidence for an interaction ($P = .59$ by likelihood ratio test). Analyses of hospital mortality by quintiles of baseline PaO₂:FIO₂ ratio suggest a threshold effect around a PaO₂:FIO₂ ratio of 200 mm Hg rather than a progressive increase in the effect of higher vs lower PEEP as PaO₂:FIO₂ ratio decreases (eFigure 1). This is compatible with the pattern seen for quintiles of baseline oxygenation index (eFigure 2). Exploring the stability of baseline PaO₂:FIO₂ ratios, we found that in 50% of patients with acute lung injury and not ARDS at baseline, the PaO₂:FIO₂ ratio consistently remained

above the critical threshold of 200 mm Hg at days 1, 3, and 7 after randomization.

Use of neuromuscular blockers, corticosteroids, and vasopressors was similar for the groups treated with higher and lower PEEP. About 45% of patients received neuromuscular blockers, 45% received corticosteroids, and 65% received vasopressors for a median of 3, 7, and 4 days, respectively.

COMMENT

This systematic review and meta-analysis of individual-patient data from randomized trials comparing higher with lower PEEP levels in 2299 patients with acute lung injury showed, overall, no statistically significant difference in hospital mortality. Results suggest, however, differences in the response to higher PEEP for those with ARDS vs those without ARDS at baseline. In patients with ARDS, higher levels of PEEP were associated with a relative mortality reduction of 10% (absolute difference, 4%; number needed to treat, 25). In contrast, patients with acute lung injury but without ARDS may not benefit or may actually experience harm from higher PEEP levels. The results for patients with ARDS do not exclude a small increased risk of pneumothorax (absolute risk dif-

Table 3. Respiratory Variables During First Week of Treatment

Variable	Mean (SD)								
	Day 1			Day 3			Day 7		
	Higher PEEP	Lower PEEP	<i>P</i> Value	Higher PEEP	Lower PEEP	<i>P</i> Value	Higher PEEP	Lower PEEP	<i>P</i> Value
Tidal volume, mL/kg of predicted body weight	6.3 (1.0) [n = 1051]	6.3 (0.8) [n = 1051]	.33	6.3 (1.0) [n = 793]	6.3 (1.0) [n = 852]	.47	6.5 (1.4) [n = 443]	6.4 (1.3) [n = 494]	.25
Plateau pressure, cm H ₂ O	29 (5.4) [n = 1043]	23 (5.6) [n = 991]	<.001	27 (5.6) [n = 781]	23 (5.9) [n = 825]	<.001	27 (6.2) [n = 408]	24 (6.9) [n = 443]	<.001
FIO ₂	0.51 (0.18) [n = 1053]	0.61 (0.19) [n = 1051]	<.001	0.44 (0.15) [n = 812]	0.56 (0.18) [n = 862]	<.001	0.45 (0.15) [n = 502]	0.54 (0.19) [n = 550]	<.001
PEEP, cm H ₂ O	15.3 (3.4) [n = 1053]	9.0 (3.1) [n = 1051]	<.001	13.3 (4.3) [n = 812]	8.2 (3.0) [n = 863]	<.001	10.8 (5.0) [n = 503]	7.8 (3.3) [n = 548]	<.001
Oxygenation index ^a	13.2 (8.7) [n = 949]	12.7 (7.8) [n = 944]	.16	11.2 (7.0) [n = 705]	11.6 (7.1) [n = 755]	.29	11.2 (7.1) [n = 392]	11.8 (8.4) [n = 421]	.34
PaO ₂ , mm Hg	96 (38) [n = 1024]	83 (29) [n = 1026]	<.001	87 (31) [n = 792]	82 (28) [n = 835]	<.001	84 (25) [n = 484]	83 (26) [n = 532]	.41
Paco ₂ , mm Hg	44 (11) [n = 1025]	44 (11) [n = 1026]	.42	44 (9.9) [n = 792]	44 (11) [n = 835]	.68	45 (12) [n = 485]	46 (12) [n = 532]	.06
Arterial pH	7.35 (0.09) [n = 1025]	7.36 (0.09) [n = 1026]	.02	7.38 (0.08) [n = 793]	7.38 (0.08) [n = 836]	.49	7.41 (0.08) [n = 485]	7.40 (0.08) [n = 532]	.08

Abbreviations: FIO₂, fraction of inspired oxygen; PEEP, positive end-expiratory pressure.

^aCalculated as mean airway pressure × FIO₂ × 100/PaO₂.

ference, 1.6%) with higher PEEP, but differences in fatal consequences from such barotrauma are unlikely (absolute risk difference, 0.6%; RR, 1.20; 95% CI, 0.79-1.81). Otherwise, we found no evidence suggesting serious adverse effects associated with higher PEEP in patients with ARDS.

The strengths of this review include an explicit study protocol and analysis plan; access to trial protocols, case report forms, and complete, unedited data sets; standardized outcome definitions across trials (except for rescue therapies); and analyses based on the intention-to-treat principle. To minimize the risk of overfitting and data-driven associations, we prespecified a limited number of prognostic factors and potential effect modifiers for our statistical models.²³ We calculated RRs adjusted for im-

portant prognostic factors using log-binomial models¹⁶ and allowed for potential clustering effects by using random effects for recruiting hospitals.²⁴ Our results proved robust in sensitivity analyses applying alternate statistical approaches. We followed current recommendations for subgroup analyses in meta-analysis of individual-patient data,²⁵ thereby overcoming limitations of meta-analyses using aggregated data.²⁶⁻²⁹ All included trials met high methodological quality standards (concealed randomization, explicit study protocols, and complete follow-up) and systematically collected data on important, potential adverse effects of high PEEP administration by routinely documenting deaths, pneumothorax, use of vasopressors (hemodynamic instability) and rescue therapies (refractory hypoxemia), and dura-

tion of mechanical ventilation and intensive care. An independent data and safety monitoring committee was established to monitor and protect the safety of participants in each trial. The 3 major trials included 90 multidisciplinary intensive care units with international representation; these features enhance the generalizability of our findings.

The subgroup effect for ARDS at baseline meets all criteria for a credible subgroup analysis.³⁰ We found a large and statistically significant ($P = .02$ for interaction) difference in RRs that was consistent across individual trials and efficacy outcomes. The hypothesis was generated a priori and was one of a small number tested. Exploring the effect of higher vs lower PEEP across quintiles suggests a threshold effect, rather than a progressive increase in

Table 4. Clinical Outcomes in All Patients and Stratified by Presence of ARDS at Baseline

Outcomes	All Patients				With ARDS				Without ARDS			
	No. (%)		Adjusted RR (95% CI) ^a	P Value	No. (%)		Adjusted RR (95% CI) ^a	P Value	No. (%)		Adjusted RR (95% CI) ^a	P Value
	Higher PEEP (n = 1136)	Lower PEEP (n = 1163)			Higher PEEP (n = 951)	Lower PEEP (n = 941)			Higher PEEP (n = 184)	Lower PEEP (n = 220)		
Death in hospital	374 (32.9)	409 (35.2)	0.94 (0.86 to 1.04)	.25	324 (34.1)	368 (39.1)	0.90 (0.81 to 1.00)	.049	50 (27.2)	44 (19.4)	1.37 (0.98 to 1.92)	.07
Death in ICU ^b	324 (28.5)	381 (32.8)	0.87 (0.78 to 0.97)	.01	288 (30.3)	344 (36.6)	0.85 (0.76 to 0.95)	.001	36 (19.6)	37 (16.8)	1.07 (0.74 to 1.55)	.71
Pneumothorax between day 1 and day 28 ^c	87 (7.7)	75 (6.5)	1.19 (0.89 to 1.60)	.24	80 (8.4)	64 (6.8)	1.25 (0.94 to 1.68)	.13	7 (3.8)	11 (5.0)	0.72 (0.37 to 1.39)	.33
Death after pneumothorax ^c	43 (3.8)	40 (3.5)	1.11 (0.73 to 1.69)	.63	41 (4.3)	35 (3.7)	1.20 (0.79 to 1.81)	.39	2 (1.1)	5 (2.3)	0.44 (0.08 to 2.35) ^g	.34
Days with unassisted breathing between day 1 and day 28, median (IQR) ^d	13 (0 to 22)	11 (0 to 21)	0.64 (-0.12 to 1.39) ^e	.10	12 (0-21)	7 (0-20)	1.22 (0.39 to 2.05) ^e	.004	17 (0-23)	19 (5.5-24)	-1.74 (-3.60 to 0.11) ^e	.07
Total use of rescue therapies ^f	138 (12.2)	216 (18.6)	0.64 (0.54 to 0.75)	<.001	130 (13.7)	200 (21.3)	0.63 (0.53 to 0.75)	<.001	8 (4.4)	16 (7.3)	0.60 (0.25 to 1.43) ^g	.25
Death after rescue therapy ^f	85 (7.5)	132 (11.3)	0.65 (0.52 to 0.80)	<.001	82 (8.6)	124 (13.2)	0.66 (0.52 to 0.82)	<.001	3 (1.6)	8 (3.6)	0.37 (0.10 to 1.46) ^g	.15
Use of vasopressors	722 (63.6)	759 (65.3)	0.93 (0.75 to 1.14) ^g	.49	627 (65.9)	647 (68.8)	0.90 (0.72 to 1.13) ^g	.37	95 (51.6)	111 (50.5)	0.92 (0.56 to 1.50) ^g	.72

Abbreviations: ARDS, acute respiratory distress syndrome; CI, confidence interval; ICU, intensive care unit; IQR, interquartile range; PEEP, positive end-expiratory pressure; RR, relative risk.

^aMultivariable regression with the outcome of interest as dependent variable; PEEP group, age, probability of dying in hospital derived from prognostic scores at baseline, severe sepsis at baseline, and trial as independent variables; and hospital as a random effect.

^bPatients who died before being discharged from the intensive care unit for the first time up to day 60.

^cDefined as the need for chest tube drainage.

^dMedian number of days of unassisted breathing to day 28 after randomization, assuming a patient survives and remains free of assisted breathing for at least 2 consecutive calendar days after initiation of unassisted breathing.

^eCoefficient from a corresponding linear regression model using the same independent variables and random effect as the above-described log-binomial model; for example, a coefficient of 1.22 means that patients in the group treated with higher PEEP have, on average, 1.22 days more of unassisted breathing during the first 28 days compared with patients in the group treated with lower PEEP.

^fAs defined in each trial; rescue therapies included in the Assessment of Low Tidal Volume and Elevated End-Expiratory Pressure to Obviate Lung Injury and the Lung Open Ventilation to Decrease Mortality in the Acute Respiratory Distress Syndrome studies: inhaled nitric oxide, prone ventilation, high-frequency oscillation, high-frequency jet ventilation, extracorporeal membrane oxygenation, partial liquid ventilation, and surfactant therapy. Rescue therapies included in the Expiratory Pressure Study: prone ventilation, inhaled nitric oxide, and almitrine bismesylate.

^gAdjusted odds ratio substitutes for relative risk, because the corresponding log-binomial model did not converge.

effect as PaO₂:FIO₂ ratio decreases or as the oxygenation index increases (eFigures 1 and 2). This may explain why examining PaO₂:FIO₂ ratio and oxygenation index as linear effect modifiers did not yield significant interactions.

The ARDS interaction is supported by external evidence. Earlier preclinical and clinical trials providing indirect evidence that higher PEEP strategies improve survival were restricted to animal models of ARDS^{5,31} and to patients with severe³² or persistent³³ ARDS. Moreover, a recent cohort study in patients with acute lung injury or ARDS found that the effect of PEEP on lung recruitment was closely associated with the percentage of potentially recruitable lung as determined by computed tomography.⁴ Patients with ARDS have more lung edema and thus greater recruitability than patients with acute lung injury but without ARDS.¹ In patients with ARDS, higher levels of PEEP may prevent atelectasis, recruit already collapsed alveolar units, and reduce pulmonary damage by avoiding the cyclical opening and collapse of alveoli in those patients.^{1,34,35} Patients with ARDS treated with lower PEEP levels may develop worsening lung injury, as suggested by our findings on refractory hypoxemia and use of rescue therapies.

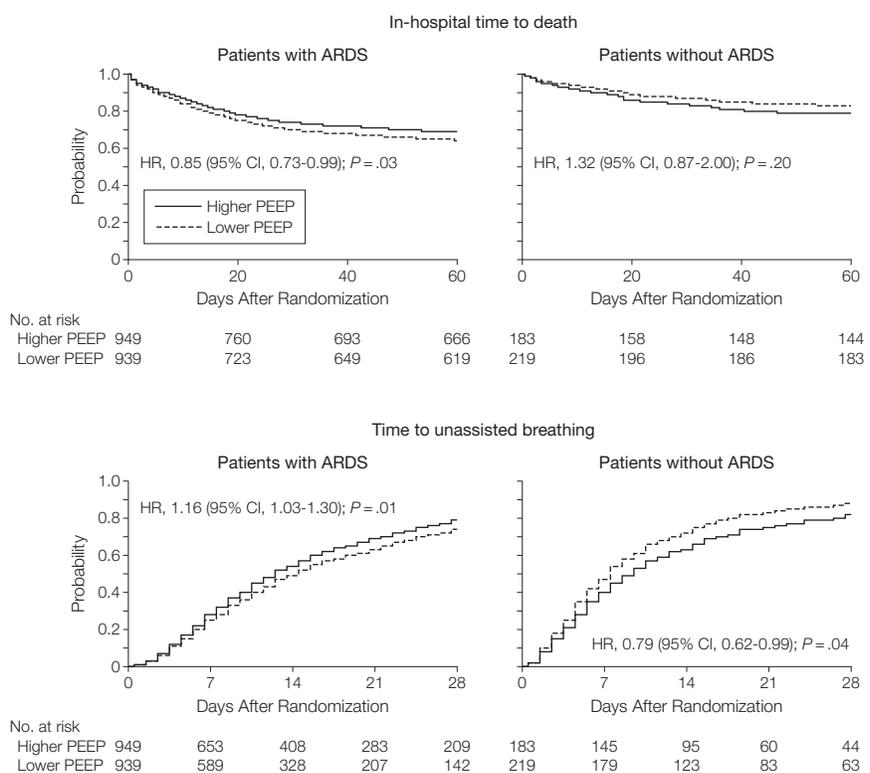
This study also has limitations. Although our subgroup finding for patients with ARDS meets common credibility criteria, we cannot rule out the possibility of a chance finding. Moreover, although we pooled the data of all eligible trials on the topic, our study had limited statistical power. In a post hoc calculation, we estimated that our primary analysis had a power of 72% to detect a 5% absolute risk reduction in hospital mortality (2-sided $\alpha = .05$). The power of our meta-analysis of individual-patient data would have been greater had none of the 3 trials stopped early for futility.

Because caregivers were not blinded to allocated PEEP strategies, differing thresholds for rescue therapy in the high and low PEEP groups could explain the lower use of rescue therapies

and mortality following rescue therapy in the higher PEEP group. Moreover, we were unable to standardize the use of rescue therapies across trials, because they depended mainly on local settings and preferences of local intensivists (eTable 1). Problems with standardization of outcomes for meta-analyses of individual-patient data could be overcome by international collaboration with coordinated protocols of individual trials. We wrote the protocol for the present study after the publication of ALVEOLI results but before the publication of those from LOVS and EXPRESS; none of the investigators knew the results from all 3 trials.

The trials in this review used different approaches to determine PEEP level. In the EXPRESS trial, PEEP levels were titrated according to bedside measurements of inspiratory plateau pressure (eAppendix). In the ALVEOLI and LOVS trials, PEEP titration was linked to oxygenation. The EPVENT trial explored a further option for PEEP titration by estimating transpulmonary pressure with the use of esophageal balloon catheters. This meta-analysis of individual-patient data is unable to provide guidance on the optimal method of titrating PEEP, since the type of PEEP titration is completely confounded with all the other

Figure 2. Time to Death in Hospital and Time to Unassisted Breathing for Higher and Lower Positive End-Expiratory Pressure (PEEP) Stratified by Presence of Acute Respiratory Distress Syndrome (ARDS) at Baseline



Cox regression models adjusting for age, probability of death in hospital derived from prognostic scores at baseline, severe sepsis at baseline, and trial. For the analysis of time to unassisted breathing, data were censored at the time of death because time to death was modeled separately and a sensitivity analysis without censoring at death yielded very similar results. Additionally including the Esophageal Pressure Directed Ventilation trial (n=61) revealed adjusted hazard ratios (HRs) for hospital mortality of 0.83 (95% confidence interval [CI], 0.71-0.96; P=.01; 33.9% vs 39.0%) for patients with ARDS (n=1941) and 1.26 (95% CI, 0.84-1.88; P=.27; 26.5% vs 19.4%) for patients without ARDS (n=416). Corresponding hazard ratios for time to unassisted breathing were 1.14 (95% CI, 1.02-1.28; P=.02; proportions at 28 days, 64.2% vs 58.0%) for patients with ARDS (n=1941) and 0.80 (95% CI, 0.64-1.01; P=.06; proportions at 28 days, 70.4% vs 79.7%) for patients without ARDS (n=416).

structural differences among the trials (eg, differences in study populations or the use of recruitment maneuvers) that are captured in the “trial effect,” which is a subject that lends itself to further research. Results of this review, however, provided no suggestion of differences in effect across the 3 major trials ($P = .59$ for interaction between trial and treatment).

Analyses involving lung compliance are limited by missing data and indirect calculations. Plateau pressures, in particular, are often difficult to measure reliably, which is reflected in a relatively high proportion of missing plateau pressures at baseline (485/2299 [21%] missing). However, sensitivity analyses using multiple imputation of missing compliance values were consistent with results from the complete case analysis. Analyses investigating body mass index as an effect modifier were limited by the systematic exclusion of patients with morbid obesity (actual body weight exceeding 1 kg/cm of height) in all 3 trials.

Current definitions for ARDS do not take into account the levels of applied PEEP; ARDS cohorts may, therefore, include patients with varying levels of lung injury.^{12,36} Moreover, $\text{PaO}_2\text{:FIO}_2$ ratios typically vary over time. Although these limitations might reduce the usefulness of our subgroup effect for a diagnosis of ARDS at baseline, further explorations supported the subgroup finding. Patients with acute lung injury but without ARDS at baseline had, in general, a better clinical prognosis throughout the first 2 months, with lung injury never evolving to ARDS in half of these patients.

Using the Grading of Recommendations Assessment, Development and Evaluation system, we have classified the evidence suggesting that higher levels of PEEP are associated with lower mortality for patients with ARDS as of high quality. Nevertheless, our confidence in this conclusion is limited by the fact that it is a subgroup result with borderline statistical significance (eTable 5). Including the EPVENT trial in a sensitivity analysis improved the

precision of this finding (individual subgroup $P = .02$). The wide CI around the estimated RR of mortality in patients without ARDS warrants a rating of moderate-quality evidence.

Without considering the subgroup analysis definitive, and while awaiting further evidence on the topic, our results may have the following clinical implications. The potentially lower hospital mortality and the absence of increased serious adverse events associated with higher PEEP levels in patients with ARDS support the safety of higher PEEP in these patients. For this purpose, clinicians could titrate PEEP as described in the 3 major trials in this review (eAppendix). For patients without ARDS, the results lack statistical power; still, the 95% CI of 0.98-1.92 for hospital mortality in patients without ARDS indicates that an RR reduction of 2% (0.4% absolute reduction) associated with higher PEEP is plausible but that larger, important risk reductions are unlikely. Clinicians should bear in mind the possible harm when considering the use of higher PEEP in patients with less severe acute lung injury.

In addition to its clinical messages, our work provides lessons for clinical trialists. Single trials, even those powered for moderate effects, will often fail to provide definitive answers. Such trials will almost invariably be unable to meaningfully address possible subgroup effects. A culture of international collaboration, ideally using coordinated trial protocols and conducting prospective meta-analysis of individual-patient data, is required to maximize the clinical information from expensive and arduous clinical trials. With a view to ultimately using individual trial data to contribute to such a larger effort, investigators should also keep this option in mind when they consider stopping trials early for futility.³⁷

In summary, this systematic review and meta-analysis of individual-patient data suggests that higher levels of PEEP may be associated with lower hospital mortality in patients meeting criteria for ARDS. Our results

further suggest that such a benefit is unlikely in patients with less severe lung injury; indeed, a strategy of treating these patients using high PEEP levels may be harmful.

Author Affiliations: Departments of Clinical Epidemiology and Biostatistics (Drs Briel, Meade, Walter, Pullenayegum, Zhou, Cook, Lamontagne, and Guyatt and Ms Bhatnagar) and Medicine (Drs Meade and Guyatt), McMaster University, Hamilton, Ontario, Canada; Basel Institute for Clinical Epidemiology, University Hospital Basel, Basel, Switzerland (Dr Briel); University Hospital Angers, Angers, France (Dr Mercat); Division of Pulmonary and Critical Care Medicine, Johns Hopkins University, Baltimore, Maryland (Dr Brower); Department of Anesthesia, Critical Care, and Pain Medicine, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, Massachusetts (Dr Talmor); University of Toronto, Toronto, Ontario, Canada (Drs Slutsky and Stewart); Medical ICU, University Hospital Albert Chenevier-Henri Mondor, INSERM Unit 955 and University Paris-Est, Créteil, France (Dr Brochard); University Hospital Charles Nicolle and UPRES EA Unit 3830, Rouen, France (Dr Richard); and University of Sherbrooke, Sherbrooke, Québec, Canada (Dr Lamontagne). **Author Contributions:** Dr Briel had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Briel, Meade, Mercat, Slutsky, Brochard, Lamontagne, Guyatt.

Acquisition of data: Briel, Meade, Mercat, Brower, Talmor, Slutsky, Brochard, Richard, Bhatnagar, Guyatt. **Analysis and interpretation of data:** Briel, Meade, Brower, Walter, Pullenayegum, Zhou, Cook, Brochard, Stewart, Guyatt.

Drafting of the manuscript: Briel, Meade, Walter, Guyatt.

Critical revision of the manuscript for important intellectual content: Meade, Mercat, Brower, Talmor, Slutsky, Pullenayegum, Zhou, Cook, Brochard, Richard, Lamontagne, Bhatnagar, Stewart.

Statistical analysis: Briel, Walter, Pullenayegum, Zhou. **Obtained funding:** Briel, Meade, Guyatt.

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