REVIEW | Annals of Internal Medicine

Meta-analysis: Ventilation Strategies and Outcomes of the Acute Respiratory Distress Syndrome and Acute Lung Injury

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Background: Trials have provided conflicting results regarding the effect of different ventilatory strategies on the outcomes of patients with the acute respiratory distress syndrome (ARDS) and acute lung injury.

Purpose: To determine whether ventilation with low tidal volume (V_T) and limited airway pressure or higher positive end-expiratory pressure (PEEP) improves outcomes for patients with ARDS or acute lung injury.

Data Sources: Multiple computerized databases (through March 2009), reference lists of identified articles, and queries of principal investigators. No language restrictions were applied.

Study Selection: Randomized, controlled trials (RCTs) reporting mortality and comparing lower versus higher V_T ventilation, lower versus higher PEEP, or a combination of both in adults with ARDS or acute lung injury.

Data Extraction: Using a standard protocol, 2 reviewer teams assessed trial eligibility and abstracted data on quality of study design and conduct, population characteristics, intervention, co-interventions, and confounding variables.

Data Synthesis: 4 RCTs tested lower versus higher V_T ventilation at similar PEEP in 1149 patients, 3 RCTs compared lower versus higher PEEP at low V_T ventilation in 2299 patients, and 2 RCTs compared a combination of higher V_T and lower PEEP ventilation versus lower V_T and higher PEEP ventilation in 148 patients. Lower V_T ventilation reduced hospital mortality (odds ratio, 0.75 [95% CI, 0.58 to 0.96]; $P = 0.02$) compared with higher V_T ventilation at similar PEEP. Higher PEEP did not reduce hospital mortality (odds ratio, 0.86 [CI, 0.72 to 1.02]; $P = 0.08$) compared with lower PEEP using low V_T ventilation. Higher PEEP reduced the need for rescue therapy to prevent life-threatening hypoxemia (odds ratio, 0.51 [CI, 0.36 to 0.71]; $P < 0.001$) and death (odds ratio, 0.51 [CI, 0.36 to 0.71]; $P < 0.001$) in patients receiving rescue therapies.

Limitations: Pooling according to similar ventilatory strategies resulted in few RCTs analyzed in each group. The benefit of low V_T is derived from only 1 study.

Conclusion: Available evidence from a limited number of RCTs shows better outcomes with routine use of low V_T but not high PEEP ventilation in unselected patients with ARDS or acute lung injury. High PEEP may help to prevent life-threatening hypoxemia in selected patients.

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The acute respiratory distress syndrome (ARDS) is clinically characterized by sudden onset, severe hypoxemia, radiographic evidence of bilateral pulmonary infiltration, and absence of left heart failure (1–3). Acute lung injury is a subset of ARDS with less severe impairment in oxygenation. Despite apparent improvement in management and outcome of ARDS, the mortality rate in persons with the disease remains high, ranging from 35% to 65% (4).

Although mechanical ventilation provides essential life support, it can worsen lung injury (5). Computed tomography images of patients with ARDS show nonhomogeneous distribution of pulmonary aeration. Normally aerated lung regions are relatively small but, when they receive the largest part of tidal volume (V_T) (6, 7), may be exposed to excessive alveolar wall tension and stress because of overdistention (8, 9). Atelectatic lung regions are prone to cyclic recruitment and derecruitment, leading to shear stress in adjacent aerated and nonaerated alveoli (10–12). Ventilator-induced lung injury is caused by excessive stress or strain to lung tissues that occurs during mechanical ventilation and aggravates inflammation and diffuse alveolar damage (5, 13).

Lung-protective ventilation strategies include ventilation with low V_T and limited airway pressure to reduce ventilator-induced lung injury from overdistention while allowing hypercapnia and medium to high positive end-expiratory pressure (PEEP) to keep alveoli open throughout the ventilator cycle (14). Hypercapnia and acidosis may increase intracranial pressure, induce pulmonary hypertension, depress myocardial contractility, decrease renal blood flow, and release endogenous catecholamines (15). In addition, prevention of cyclic derecruitment with higher PEEP may contribute to overdistention of normally aerated alveoli, counterbalancing the benefits from low V_T and limited airway pressure ventilation cycles (14).

The effect of different lung-protective ventilatory strategies in patients with acute lung injury or ARDS has been investigated in randomized, controlled trials (RCTs) testing higher versus lower V_T ventilation at similar PEEP (16–19), higher versus lower PEEP strategies during low V_T ventilation (20–22), and lower V_T and PEEP titrated

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greater than the lower inflection point of the individual pressure volume curve versus higher V_T and lower PEEP (23, 24). Results were partially conflicting because of differences in study design and number of enrolled patients. This may explain why most critically ill patients are still ventilated with high V_T at lower or even no PEEP (4, 25).

Our objective was to determine whether the different lung-protective ventilatory strategies improve outcome in critically ill adults with acute lung injury or ARDS.

Context

Ventilation strategies to protect the lungs of patients with the acute respiratory distress syndrome (ARDS) include low tidal volume, limited airway pressures, and medium to high positive end-expiratory pressure (PEEP), but the adoption of these strategies has been slow in some clinical settings.

Contribution

This review of randomized trial evidence for low tidal volume and high PEEP ventilation on mortality of patients with ARDS or acute lung injury found that trials were limited in number but showed mortality benefits with lower versus higher tidal volume. High PEEP did not improve mortality in unselected patients but may help patients with life-threatening hypoxemia despite other interventions.

Implication

Lower tidal volume ventilation strategies should be used for patients with ARDS or acute lung injury.

—The Editors

Methods

Data Sources and Searches

We aimed to identify all RCTs assessing the efficacy and outcomes of lower V_T ventilation, higher PEEP application, or a combination of both in adults with acute lung injury or ARDS. The electronic search strategy applied standard filters for identification of RCTs. We searched the Cochrane Central Register of Controlled Trials, MEDLINE (from inception to March 2009), and EMBASE (from inception to March 2009). Our search included the following keywords: *acute lung injury*, *ALI*, *adult respiratory distress syndrome*, *ARDS*, *protective ventilation*, *lung protective ventilation strategy*, pressure-limited ventilation, *tidal volume*, *positive end-expiratory pressure*, *PEEP*, and *random*. We did not apply language restrictions. In addition to the electronic search, we checked out cross-references from original articles and reviews.

Selection of Studies

We restricted the analysis to RCTs to guarantee control of selection bias. We did not include study designs containing inadequately adjusted planned co-interventions and quasi-randomized or crossover trials. We considered RCTs that reported mortality as a predefined end point and compared lower versus higher V_T ventilation, lower versus higher PEEP application, or a combination of these strategies in intubated and mechanically ventilated critically ill adults with acute lung injury or ARDS from any cause. Acute lung injury and ARDS had to be defined by the American-European Consensus Conference criteria (26) or by the Lung Injury Severity Score (27). Trials with a low V_T ventilation strategy had to use lower V_T, maximal inspiratory plateau pressure (P_{EI}) of 30 cm H_2O or less, or a combination, which resulted in V_T of 8 mL/kg of body weight or less, compared with conventional mechanical ventilation that used V_T ranging between 10 and 15 mL/kg. Regardless of the strategy used to deliver the lower V_T, the 2 study groups had to differ only for V_T and not for other variables associated with a low V_T ventilation strategy. Trials with high PEEP ventilation strategies had to use higher PEEP based on Fio_2–PEEP scales, titrating PEEP to greater than the lower inflection point of the individual static or quasi-static pressure volume curve at enrollment or titrating PEEP as high as possible without increasing the maximal P_{EI} to greater than 30 cm H_2O compared with conventional mechanical ventilation that used lower PEEP based on fixed Fio_2–PEEP scales or lower PEEP at higher Fio_2 to ensure adequate arterial oxygenation. We excluded studies in postoperative patients and those published only in abstract form. We contacted authors to clarify details of trials when necessary.

Outcome Measures

The primary outcome was mortality, evaluated at hospital discharge. Secondary outcomes included mortality at the end of the planned follow-up, barotrauma, use of rescue therapies owing to life-threatening hypoxemia, ventilator settings, and pulmonary function variables. Barotrauma was defined as any new pneumothorax, pneumomediastinum, subcutaneous emphysema, or pneumatocele after random assignment.

Data Extraction and Quality Assessment

Two pairs of independent reviewers performed the initial selection by screening titles and abstracts. Citations were selected for further evaluation if the studies they referred to were RCTs of lung-protective ventilatory strategies in critical ill adults or if the title or abstract did not give enough information to make an assessment. For detailed evaluation, we obtained the full text of all possibly relevant studies. Data from each study were extracted independently by the paired reviewers by using a prestandardized data abstraction form. One pair of reviewers was not informed about authors, journal, institutional affiliation, and date of publication. Data extracted from the publications were checked by another reviewer for accuracy. Quality assessment of these studies included use of randomization, reporting of allocation concealment, blinding, adequate selection and description of study population with respect to inclusion and exclusion criteria, similarity of the groups at baseline, use of a predefined treatment protocol, absence of confounders, absence of co-interventions, a priori definition of primary and secondary outcome variables, use of intention-to-treat analysis, extent of follow-up, a priori calcu-

lation of sample size, number of patients screened and included in the trial, reports on patients lost to follow-up, and planned or premature termination of the RCT. Two reviewers independently used these criteria to abstract trial quality. We resolved any disagreements by consensus in consultation with a third reviewer if needed.

Data Synthesis and Analysis

We studied the following comparisons: lower versus higher V_T ventilation using similar PEEP strategies, lower versus higher PEEP level during low V_T ventilation, and the combination of higher V_T and lower PEEP level versus lower V_T and higher PEEP level.

Qualitative Analysis

We used a narrative summary approach to describe study characteristics and variation in quality indicators among studies and to consider how these factors affect our understanding of the outcomes of the RCTs included in the Cochrane review (28, 29).

Quantitative Analysis

The meta-analysis was performed according to the Cochrane Collaboration guidelines (30). All statistical analyses were performed with Review Manager, version 4.2 (The Nordic Cochrane Center, Copenhagen, Denmark), the Cochrane Collaboration's software for preparing and maintaining Cochrane systematic reviews (30). The pooled effects estimates for binary variables were expressed as odds ratios with 95% CIs, whereas continuous variables were expressed as weighted mean differences with 95% CIs. We tested the difference in estimates of treatment effect between the treatment and control groups for each hypothesis by using a 2-sided z test with statistical significance considered at a P value of less than 0.05. We examined heterogeneity by using the Cochran Q and the I^2 test (31, 32). We predefined heterogeneity as low, moderate, and high, with I^2 statistics greater than 25%, 50%, and 75%, respectively (32). Meta-analysis with a random-effects model was applied with I^2 statistics greater than 25% (33). Otherwise, we performed meta-analysis by using a fixed-effects model. However, the possibility of a type II (false-negative) error must be considered, and we made a thorough attempt to identify clinical heterogeneity or sources of bias. We considered a 1-tailed P value less than 0.05 to be significant.

Interobserver agreement on selection of articles for inclusion and quality assessment was measured by using the Cohen (unweighted) κ statistic (34). We considered a κ value greater than 0.8 to indicate acceptable agreement.

Role of the Funding Source

We received no funding for this study.

RESULTS

Study Selection

Our initial electronic and manual search identified 1111 studies. Of these, we excluded 886 articles because they were not RCTs, did not evaluate lung-protective ventilatory strategies in patients with acute lung injury or ARDS, were duplicated references, or were not relevant. We retrieved 225 studies for more detailed analysis and excluded 216 of these (**Figure**). The 2 reviewer teams completely agreed ($\kappa = 1$) on the selection of included studies.

Study Description

Table 1 summarizes the study selection process, and **Appendix Table 1** (available at www.annals.org) summarizes the characteristics of the included RCTs. All studies were multicenter trials (16–24). We identified definition of severity of patient lung injury, V_T and P_{EI}, pH thresholds and management of acidosis, use of recruitment maneuvers, use of rescue therapies, weaning procedure, and termination of the trials as key sources of between-study variation. Qualitative analysis of key study characteristics and quality indicators revealed the following differences.

Definition of Severity of Patient Lung Injury

Acute lung injury and ARDS were defined according to the American-European Consensus Conference criteria (26) in 6 RCTs (16, 18, 20–22, 24) and according to the Lung Injury Severity Score in 2 RCTs (17, 23). Although 1 study used the definition risk for ARDS (19), all patients fulfilled the Lung Injury Severity Score criteria for ARDS. Patients with ARDS or acute lung injury were investigated in 6 RCTs (16–18, 20–22), and patients with ARDS only were investigated in 3 studies (19, 23, 24). Seven RCTs reported Acute Physiology and Chronic Health Evaluation score (16, 18–21, 23, 24), and 2 RCTs reported Simplified Acute Physiology Score II (17, 22).

V_T and P_{EI}

Four RCTs tested lower versus higher V_T ventilation at similar PEEP in 1149 patients in total (16–19), 3 RCTs compared lower versus higher PEEP values at low V_T ventilation in 2299 patients in total (20–22), and 2 RCTs compared a combination of higher V_T and lower PEEP value versus lower V_T and higher PEEP value in 148 patients in total (23, 24). Tidal volume was adjusted to actual body weight in 2 studies (17, 23), ideal body weight in 2 RCTs (18, 19), and predicted body weight in 5 RCTs (16, 20–22, 24) (**Appendix Table 2**, available at www.annals.org). Observed V_T, PEEP, respiratory rates, and P_{EI} are given in **Appendix Table 2**. All RCTs comparing lower versus higher V_T ventilation per protocol did not restrict P_{EI} of 30 cm H_2O or less in the higher V_T groups (16–19). Three RCTs demonstrating improved outcome with lower V_T ventilation observed a P_{EI} greater than 30 cm H_2O during higher V_T ventilation (16, 23, 24). Protocols for management of mechanical ventilation were used in all RCTs (16–24), thus minimizing performance bias.

pH Thresholds and Management of Acidosis

The ARDS Network strategy was to increase respiratory rate, up to 35 breaths/min, in an attempt to increase alveolar ventilation and thus keep pH greater than 7.30. Variations in V_T up to 8 mL/kg of predicted body weight and P_{EI} greater than 30 cm H_2O were allowed, and administration of sodium bicarbonate was considered when pH decreased to less than 7.15 (16, 20, 22). If pH decreased to less than a defined threshold, an increased P_{EI} greater than 30 cm H_2O was allowed in 4 RCTs (16, 19, 20, 22), and administration of sodium bicarbonate was required in 7 RCTs (16–22) (**Appendix Table 3**, available at www.annals.org). pH thresholds ranged from 7.00 to 7.30 (16–23), and were not specified in 1 RCT (24), thus leaving pH management up to the clinician. Three RCTs defined a pH of 7.3 as the threshold requiring intervention (18, 20, 22), whereas 5 studies set the threshold at 7.2 (23) or less than 7.2 (16, 17, 19, 21). The lowest pH thresholds of 7.00 (19) and 7.05 (17) were in 2 nonbeneficial RCTs, whereas the remaining 2 RCTs defined a threshold of 7.1 (21) and 7.15 (16) (**Appendix Table 3**).

Use of Recruitment Maneuvers

Recruitment maneuvers were regularly used in 2 RCTs (20, 23). In 1 RCT, only the first 80 patients randomly assigned to higher PEEP values received recruitment maneuvers (20).

Use of Rescue Therapies

Rescue therapies for refractory hypoxemia were predefined in 2 RCTs (21, 22). Rescue therapies were prone ventilation in 2 studies (21, 22), inhaled nitric oxide in 3 studies (17, 21, 22), high-frequency oscillation in 1 study (21), intravenous almitrine bismesylate in 1 study (22), and extracorporeal membrane oxygenation in 1 study (21).

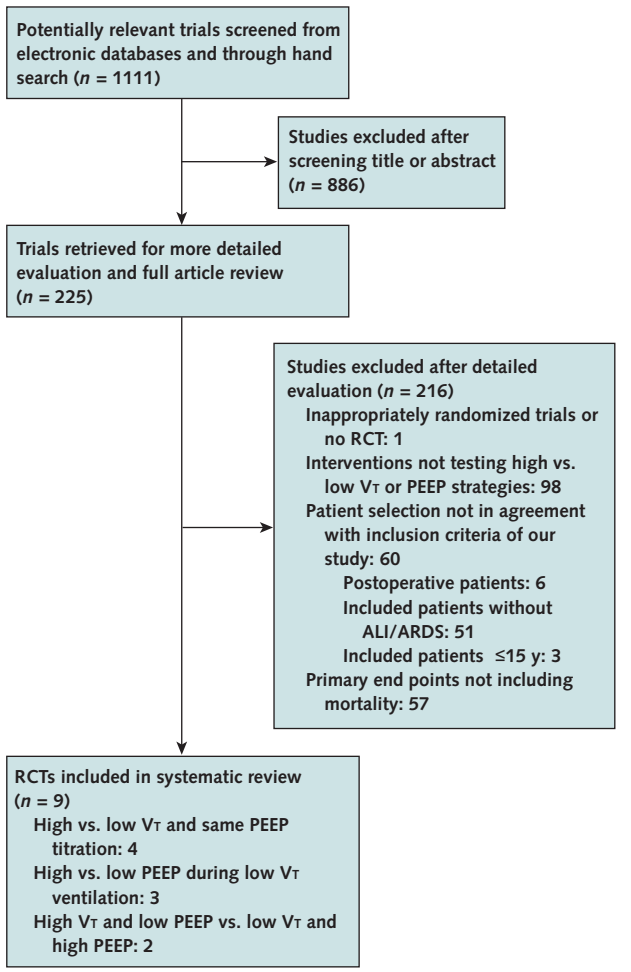
Weaning Procedure

Five studies used weaning protocols (16, 20–23).

Termination of the Trial

Only 2 RCTs were terminated after the planned estimated sample was enrolled (19, 21). Three RCTs were stopped prematurely after an interim analysis demonstrated futility (17, 20, 22). One RCT was terminated early because the center participated in another trial (18). One RCT comparing lower versus higher V_T ventilation at similar PEEP (16) and 2 RCTs comparing a higher V_T and lower PEEP ventilation strategy versus a lower V_T and higher PEEP ventilation strategy (23, 24) were stopped prematurely after interim analyses demonstrated lower mortality in the lower V_T groups. The mean duration of the individual RCTs was 33.3 months, ranging from 15 months (19) to 68 months (21). Only 3 RCTs reported on patients lost to follow-up (21, 22, 24) (**Table 1**).

Figure. **Literature search and selection.**



ALI = acute lung injury; ARDS = acute respiratory distress syndrome; PEEP = positive end-expiratory pressure; RCT = randomized, controlled trial; V_T = tidal volume.

These differences among studies partially affect the overall strength of the evidence. To minimize the effects of study variation and optimize comparisons among ventilation strategies, we grouped RCTs on the basis of lower versus higher V_T ventilation by using similar PEEP strategies, lower versus higher PEEP strategies during low V_T ventilation, and the combination of higher V_T and lower PEEP strategies versus lower V_T and higher PEEP strategies. In comparing lower versus higher V_T ventilation plus similar PEEP strategies and the combination of higher V_T and lower PEEP strategies versus lower V_T and higher PEEP strategies, the possible main confounding effect was the main goal of ventilator treatment on respiratory variables and clinical management of pH.

Evidence Synthesis

Lower Versus Higher V_T Ventilation Using Similar PEEP Values

The study characteristics that may explain differences in the benefit of lower V_T ventilation were premature ter-

Table 1. **Characteristics of the Included Studies**

Author, Year (Reference)	Random Assignment	Allocation Concealment	Blinding	Adequate Selection and Description of Study Population	Comparability of Groups (Baseline Characteristics)	Predefined Treatment Protocol
Lower vs. higher V_T at similar PEEP						
Brochard et al, 1998 (17)	Yes	Yes, by sealed envelopes	No	Yes	Yes, statistically proven for age, sex, APACHE score, SAPS II score, previous duration of MV, LISS, Pao_2–Fio_2 ratio, multiple trauma, and immunosuppression.	Yes
Brower et al, 1999 (18)	Yes	Yes, not specified	No	Yes	Yes, for age, sex, ethnic group, APACHE III score, LISS, conditions causing ARDS, and comorbid conditions. No *P* values given.	Yes
Brower et al, 2000 (16)	Yes	Yes, by computer-generated random list	No	Yes	Not for minute ventilation. Statistically proven for age, sex, ethnic group, APACHE III score, Pao_2–Fio_2 ratio, V_T, $\dot{V}_E$, number of organ failures, and cause of lung injury.	Yes
Stewart et al, 1998 (19)	Yes	Yes, by computer-generated random list	No	Yes	Not for Pao_2–Fio_2 ratio. Statistically proven for age, sex, APACHE II score, oxygen index, MODS score, and number of risk factors for ARDS.	Yes
Lower vs. higher PEEP at low V_T						
Brower et al, 2004 (20)	Yes	Yes, by computer-generated random list	No	Yes	Not for age or Pao_2–Fio_2 ratio. Statistically proven for sex, ethnic group, APACHE III score, V_T, $\dot{V}_E$, respiratory rate, number of organ failures, and cause of lung injury.	Yes
Meade et al, 2008 (21)	Yes	Yes, by computer-generated random list	No	Yes	Not for age and incidence of sepsis. Statistically proven for sex, duration of hospital stay and MV, APACHE II score, MODS score, Pao_2–Fio_2 ratio, oxygenation index, PEEP, P_{EI}, V_T, $\dot{V}_E$, respiratory rate, barotrauma, and cause of lung injury.	Yes
Mercat et al, 2008 (22)	Yes	Yes, by computer-generated random list	No	Yes	Yes, statistically proven for age, sex, SAPS II score, septic shock, number of organ failures, time since onset of ARDS, V_T, $\dot{V}_E$, respiratory rate, PEEP, P_{EI}, compliance, Pao_2–Fio_2 ratio, and cause of lung injury.	Yes
Lower V_T + higher PEEP vs. higher V_T + lower PEEP						
Amato et al, 1998 (23)	Yes	Yes, by sealed envelopes	No	Yes	Yes, statistically proven for age, duration of MV, number of organ failures, APACHE III score, critical care score, LISS, ventilator score, respiratory tract infection, sepsis, Pao_2–Fio_2 ratio, P_{FLEX}, compliance, and cause of lung injury.	Yes
Villar et al, 2006 (24)	Yes	Yes, by sealed envelopes	No	Yes	Yes, statistically proven for age, sex, APACHE II score, P_{EI}, PEEP, V_T, respiratory rate, Fio_2, Pao_2, $Paco_2$, pH, PAOP, cardiac index, LISS, duration of MV, number of organ failures, and ARDS risk factors.	Yes

APACHE = Acute Physiology and Chronic Health Evaluation; ARDS = acute respiratory distress syndrome; ECMO = extracorporeal membrane oxygenation; HFOV = high-frequency oscillatory ventilation; iNO = inhaled nitric oxide; LISS = Lung Injury Severity Score; MODS = multiple organ dysfunction score; MV = mechanical ventilation; NR = not reported; PAOP = pulmonary artery occlusion pressure; PEEP = positive end-expiratory pressure; P_{EI} = end-inspiratory pressure; P_{FLEX} = end-expiratory pressure greater than the lower inflection point on the static pressure-volume curve; RM = recruitment maneuver; SAPS = Simplified Acute Physiology Score; $\dot{V}_E$ = minute ventilation; V_T = tidal volume.

mination, differences in V_T and P_{EI}, pH thresholds and management of respiratory acidosis, and protocolized weaning. Two RCTs were stopped prematurely after an interim analysis demonstrated futility (17, 18), whereas 1 RCT (16) was stopped after 861 of 1000 planned patients were enrolled because interim analysis demonstrated benefit for lower V_T ventilation. Three nonbeneficial RCTs (17–19) showed the lowest differences of V_T and P_{EI} between groups. In the beneficial RCT (16), mean high V_T of 11.8 mL/kg of predicted body weight (SD, 0.8) resulted in the highest average P_{EI} of 33 cm H_2O (SD, 9). The lowest pH thresholds were used for lower V_T ventilation in 2 nonbeneficial RCTs (17, 19) (**Appendix Table 3**). Treatment of respiratory acidosis differed among RCTs (16–

Table 1—**Continued**

Absence of Confounders	Absence of Co-interventions	Outcome Defined A Priori	Intention-to-Treat Analysis Done	Power Analysis Done	Follow-up Duration	Patients Screened/Included in Trial, *n/n*	Reported on Patients Lost to Follow-up	End of Study (Duration of Study)
Yes	No (iNO)	Yes	Yes	Yes	60 d	NR/116	No	Terminated early because of futility (32 mo)
No (AIDS, bone marrow transplant, cancer)	Yes	Yes	Yes	Yes	28 d, successful weaning, or death	NR/52	No	Terminated early for participation in another trial (22 mo)
Yes	No (ketoconazole)	Yes	Yes	Yes	180 d or hospital discharge	NR/861	No	Terminated early because of efficacy (24 mo)
Yes	Yes	Yes	Yes	NR	Until hospital discharge	NR/120	No	As planned (15 mo)
Yes	No (RM)	Yes	Yes	Yes	90 d or hospital discharge	NR/549	No	Terminated early because of futility (17 mo)
Yes	No (iNO, HFOV, ECMO, prone positioning, RM)	Yes	Yes	Yes	Until hospital discharge	NR/983	Yes, none lost	As planned (68 mo)
Yes	No (iNO, prone positioning, RM, almitrine bismesylate)	Yes	Yes	Yes	60 d or death	3429/767	Yes, 1 patient lost	Terminated early because of futility (40 mo)
No (leptospirosis, iatrogenic death)	No (RM)	Yes	Yes	Yes	NR, 28 d	NR/53	No	Terminated early because of efficacy (56 mo)
Yes	Yes	Yes	Yes	Yes	NR, 30 d	311/95	Yes, none lost	Terminated early because of efficacy (24 mo)

19). None of the RCTs reported the number of patients requiring treatment of respiratory acidosis. A protocol for weaning was used only in the beneficial RCT (16).

Lower VT ventilation reduced the risk for hospital mortality (odds ratio, 0.75 [95% CI, 0.58 to 0.96 {$P = 0.02$}]; $I^2 = 18.3\%$ [$P = 0.29$]), but not death at the end of follow-up (odds ratio, 0.94 [CI, 0.62 to 1.41 {$P = 0.75$}]; $I^2 = 40.9\%$ [$P = 0.17$]) and barotrauma (odds ratio, 0.99 [CI, 0.68 to 1.46 {$P = 0.98$}]; $I^2 = 0\%$ [$P = 0.78$]) (**Table 2**). One study (16) that allowed higher VT ventilation, resulting in PEI greater than 30 cm H_2O, carries 86% of the weight in the pooled effect and completely accounts for the heterogeneity and positive effect of lower VT ventilation on hospital mortality. When we excluded this study from analysis, no advantage of higher VT ventilation could be demonstrated (odds ratio, 1.15 [CI, 0.63 to 2.09 {$P = 0.65$}]; $I^2 = 0\%$ [$P = 0.98$]). In the first 7 days, lower VT ventilation resulted in a lower pH at a lower PEI (**Appendix Table 4**, available at www.annals.org). Because of poorer oxygenation with lower VT ventilation, the PEEP value was higher than with high VT ventilation at day 1 (weighted mean difference, 0.71 [CI, 0.07 to 1.35 {$P = 0.03$}]; $I^2 = 45.8\%$ [$P = 0.16$]) (**Appendix Table 4**).

Table 2. **Effect of Different Lung-Protective Ventilation Strategies on Mortality and Other End Points**

Author, Year (Reference), by Study End Point	Patients, *n*	Patients With Study End Point, by Ventilation Strategy, *n/n*		Odds Ratio (95% CI)	*P* Value	I^2 Statistic	*P* Value
		Low V_T at Similar PEEP	High V_T at Similar PEEP				
Hospital mortality							
Brochard et al, 1998 (17)	116	–	–	–			
Brower et al, 1999 (18)	52	13/26	12/26	1.17 (0.39–3.47)*			
Brower et al, 2000 (16)	861	134/432	171/429	0.68 (0.51–0.90)*			
Stewart et al, 1998 (19)	120	30/60	28/60	1.14 (0.56–2.34)*			
Summary				0.75 (0.58–0.96)*	0.020	18.3	0.29
		Low PEEP at Low V_T	High PEEP at Low V_T				
Brower et al, 2004 (20)	549	69/276	75/273	0.88 (0.60–1.29)*			
Meade et al, 2008 (21)	983	173/475	205/508	0.85 (0.65–1.10)*			
Mercat et al, 2008 (22)	767	136/385	149/382	0.85 (0.64–1.15)*			
Summary				0.86 (0.72–1.02)*	0.080	0	0.99
		Low V_T + High PEEP	High V_T + Low PEEP				
Amato et al, 1998 (23)	53	13/29	17/24	0.33 (0.11–1.05)*			
Villar et al, 2006 (24)	95	17/50	25/45	0.41 (0.18–0.94)*			
Summary				0.38 (0.20–0.75)*	0.005	0	0.77
		Low V_T at Similar PEEP	High V_T at Similar PEEP				
Mortality at the end of follow-up†							
Brochard et al, 1998 (17)	116	27/58	22/58	1.43 (0.68–2.99)‡			
Brower et al, 1999 (18)	52	13/26	12/26	1.17 (0.39–3.47)‡			
Brower et al, 2000 (16)	861	134/432	171/429	0.68 (0.51–0.90)‡			
Stewart et al, 1998 (19)	120	30/60	28/60	1.14 (0.56–2.34)‡			
Summary				0.94 (0.62–1.41)‡	0.75	40.9	0.170
		Low PEEP at Low V_T	High PEEP at Low V_T				
Brower et al, 2004 (20)	549	69/276	75/273	0.88 (0.60–1.29)*			
Meade et al, 2008 (21)	983	173/475	205/508	0.85 (0.65–1.10)*			
Mercat et al, 2008 (22)	767	107/385	119/382	0.85 (0.62–1.16)*			
Summary				0.85 (0.72–1.02)*	0.080	0	0.99
		Low V_T + High PEEP	High V_T + Low PEEP				
Amato et al, 1998 (23)	53	11/29	17/24	0.25 (0.08–0.80)*			
Villar et al, 2006 (24)	95	16/50	24/45	0.41 (0.18–0.95)*			
Summary				0.35 (0.18–0.68)*	0.002	0	0.50
		Low V_T at Similar PEEP	High V_T at Similar PEEP				
Barotrauma							
Brochard et al, 1998 (17)	116	8/58	7/58	1.17 (0.39–3.46)*			
Brower et al, 1999 (18)	52	2/26	1/26	2.08 (0.18–24.51)*			
Brower et al, 2000 (16)	861	43/432	47/429	0.90 (0.58–1.39)*			
Stewart et al, 1998 (19)	120	6/60	4/60	1.56 (0.42–5.82)*			
Summary				0.99 (0.68–1.46)*	0.98	0	0.78
		Low PEEP at Low V_T	High PEEP at Low V_T				
Brower et al, 2004 (20)	549	30/276	27/273	1.11 (0.64–1.92)*			
Meade et al, 2008 (21)	983	53/475	47/508	1.23 (0.81–1.86)*			
Mercat et al, 2008 (22)	767	26/385	22/382	1.19 (0.66–2.13)*			
Summary				1.19 (0.89–1.58)*	0.25	0	0.96
		Low V_T + High PEEP	High V_T + Low PEEP				
Amato et al, 1998 (23)	53	2/29	10/24	0.10 (0.02–0.54)*			
Villar et al, 2006 (24)	95	2/50	4/45	0.43 (0.07–2.45)*			
Summary				0.20 (0.06–0.63)*	0.006	25.1	0.25

Table 2—**Continued**

Author, Year (Reference), by Study End Point	Patients, *n*	Patients With Study End Point, by Ventilation Strategy, *n/n*		Odds Ratio (95% CI)	*P* Value	I^2 Statistic	*P* Value
		Low PEEP at Low V_T	High PEEP at Low V_T				
Use of rescue therapy							
Meade et al, 2008 (21)	983	37/475	61/508	0.62 (0.40–0.95)‡			
Mercat et al, 2008 (22)	767	72/385	132/382	0.44 (0.31–0.61)‡			
Summary				0.51 (0.36–0.71)‡	<0.001	37.9	0.20
		Low PEEP at Low V_T	High PEEP at Low V_T				
Mortality in patients with rescue therapy							
Meade et al, 2008 (21)	983	20/475	45/508	0.45 (0.26–0.78)*			
Mercat et al, 2008 (22)	767	37/385	62/382	0.55 (0.36–0.85)*			
Summary				0.51 (0.36–0.71)*	<0.001	0	0.59

PEEP = positive end-expiratory pressure; V_T = tidal volume.
* Fixed odds ratio.
† Primary study end point.
‡ Random odds ratio.

Lower Versus Higher PEEP Value at Low V_T Ventilation

The relevant differences in study characteristics were premature termination, use of recruitment maneuvers, and rescue therapies. Two RCTs were stopped prematurely after interim analysis demonstrated futility (20, 22). Recruitment maneuvers were regularly used in the higher PEEP group in 1 RCT (21) and in another RCT (20), were used only in the first 80 patients assigned to higher PEEP. Two RCTs used rescue therapies more frequently for refractory hypoxemia in the lower PEEP group (21, 22).

Risk for hospital mortality (odds ratio, 0.86 [CI, 0.72 to 1.02 {$P = 0.08$}]; $I^2 = 0\%$ [$P = 0.99$]) and barotrauma (odds ratio, 1.19 [CI, 0.89 to 1.58 {$P = 0.25$}]; $I^2 = 0\%$ [$P = 0.96$]) were similar between lower and higher PEEP values at low V_T ventilation (**Table 2**). High PEEP value and lower V_T ventilation reduced requirement of rescue therapies because of life-threatening hypoxemia (odds ratio, 0.51 [CI, 0.36 to 0.71 {$P < 0.001$}]; $I^2 = 37.9\%$ [$P = 0.20$]) and decreased mortality in patients who received rescue therapy (odds ratio, 0.51 [CI, 0.36 to 0.71 {$P < 0.001$}]; $I^2 = 0\%$ [$P = 0.59$]) (**Table 2**). In the first 7 days, higher PEEP resulted in better arterial oxygenation at higher P_{EI} (**Appendix Table 4**).

Combination of Higher V_T and Lower PEEP Versus Lower V_T and Higher PEEP

Two RCTs (23, 24) had the greatest differences in V_T and P_{EI} between study groups (23, 24). One RCT (23) reported 70% mortality in the higher V_T and lower PEEP group, which may be explained by a higher incidence of leptospirosis and iatrogenic death.

The combination of lower V_T and higher PEEP reduced the risk for hospital mortality (odds ratio, 0.38 [CI, 0.20 to 0.75 {$P = 0.005$}]; $I^2 = 0\%$ [$P = 0.77$]) and barotrauma (odds ratio, 0.20 [CI, 0.06 to 0.63 {$P = 0.006$}]; $I^2 = 25.1\%$ [$P = 0.25$]) (**Table 2**). In the first 7 days, lower V_T and higher PEEP resulted in higher $PaCO_2$ at a lower P_{EI} (**Appendix Table 4**).

Discussion

Available evidence from a limited number of RCTs tends to show the following in patients with acute lung injury or ARDS: reduction in hospital mortality with lower V_T ventilation, similar hospital mortality with higher or lower PEEP strategies using lower V_T ventilation, and reduced need for rescue therapy and reduced mortality in patients receiving rescue therapies during higher PEEP ventilation with lower V_T.

Previous systematic reviews and meta-analyses did not focus strictly on the comparison between lower and higher V_T ventilation at similar PEEP; rather, they also included trials in which V_T was reduced at the same time that PEEP was markedly increased (35–37), and they did not evaluate recent RCTs comparing higher versus lower PEEP strategies with lower V_T ventilation (**Appendix Table 5**, available at www.annals.org). Our meta-analysis was performed according to the Cochrane Collaboration guidelines (30) and included 9 RCTs with a total of 3596 patients and distinguished between lower versus higher V_T ventilation using similar PEEP strategies, lower versus higher PEEP value at low V_T ventilation, and the combination of higher V_T and lower PEEP versus lower V_T and higher PEEP. Thus, our meta-analysis should better separate the effects of V_T and PEEP value on mortality.

Lower V_T ventilation using similar PEEP strategies shows a relatively consistent significant reduction in mortality. Our finding supports the hypothesis that the higher heterogeneity found in previous meta-analysis can be partially attributed to the inclusion of RCTs that simultaneously investigated lower V_T and higher PEEP strategies (38). However, from a statistical standpoint, some uncer-

tainty may still exist regarding the benefit of low VT on mortality. When the ARDS Network study (16), which carries 86% of the weight in the pooled effect and completely accounts for the heterogeneity, was excluded from analysis, no advantage of higher VT ventilation could be demonstrated.

In agreement with previous reports (35–38), we found that lower VT ventilation did not improve outcome when higher VT ventilation resulted in PEI no greater than 30 cm H_2O. However, none of our analyses demonstrated an advantage of high VT ventilation. Thus, low VT ventilation seems to be beneficial in patients with acute lung injury or ARDS for routine clinical use if potential side effects, such as hypercapnia and respiratory acidosis, are not contraindicated.

Two RCTs that did not demonstrate an advantage of lower VT ventilation accepted pH thresholds of 7.00 and 7.05 before increasing VT or administering sodium bicarbonate (17, 19). Although ventilation with lower VT was associated with lower pH and a trend toward higher $PaCO_2$, mortality was not affected. Thus, lower pH or active treatment of respiratory acidosis should not have confounded the effects of lower VT ventilation.

Although all included RCTs (16–19) tested lower versus higher VT ventilation using similar PEEP strategies, PEEP was slightly but statistically significant higher (0.8 to 1.5 cm H_2O) with lower VT ventilation on day 1. Poorer arterial oxygenation requiring higher FiO_2 to maintain the targeted oxygenation goal resulted in higher PEEP in all applied PEEP strategies (16–19). Lower VT ventilation has been demonstrated to be associated with alveolar derecruitment and hence poorer oxygenation (39), which may explain the slightly higher FiO_2 and PEEP values during lower VT ventilation on day 1. Despite the slightly higher PEEP, lower VT ventilation resulted in a significantly lower PEI. Thus, the small differences in PEEP should not have confounded the beneficial effects of lower VT ventilation.

Ventilation with lower VT and PEI was not associated with reduced risk for barotrauma. Apparently, the higher VT used in the analyzed RCTs (16–19) did not result in great enough alveolar wall tension and stress to cause alveolar rupture and gross barotrauma. However, on the basis of the definitions of barotrauma that were used, minor structural damage cannot be excluded. It is generally believed that during higher VT ventilation, even moderate alveolar wall tension and stress may induce pulmonary and systemic inflammatory response, contributing to increased morbidity and mortality (12). Because only the ARDS Network study (16) reported blood concentrations of inflammatory mediators and incidence and severity of organ dysfunction, we could not systematically analyze the importance of the ventilation-induced pulmonary and systemic inflammatory response on outcome.

Despite the different criteria used for PEEP selection, 3 RCTs (20–22) demonstrated no difference in mortality comparing lower versus higher PEEP value with lower VT ventilation. Thus, random application of either higher or lower PEEP strategy in an unselected population with acute lung injury or ARDS does not significantly improve outcome. The lack of benefit of higher PEEP strategies observed in RCTs (20–22) may be explained by inclusion of a substantial proportion of patients, in whom the extent of lung edema and collapse were modest (40). In 2 RCTs (21, 22), 7.8% to 34.6% of patients needed rescue therapies to prevent decrease in PaO_2 less than 55 mm Hg or in arterial oxygen saturation less than 88% at FiO_2 of 0.80 or greater. Requirement of rescue therapies to prevent life-threatening hypoxemia and mortality in patients who received rescue therapy were reduced in the higher PEEP groups (21, 22). Thus, our results suggest that higher PEEP strategies may be beneficial to prevent life-threatening hypoxemia in patients with severe ARDS. Despite limitation of VT, higher PEEP strategies improved arterial oxygenation and increased PEI, which may have contributed to overdistention of normally aerated alveoli, counterbalancing small possible benefits of higher PEEP in patients with less severe illness (2, 8, 40, 41). Increase in PEI during low VT ventilation was suggested be associated with a higher mortality risk (42). However, higher PEEP strategies did not result in great enough alveolar wall tension and stress to cause alveolar rupture and gross barotrauma when VT and PEI were limited. Of note, our data demonstrate that higher PEEP with PEI limited to no greater than 30 cm H_2O does not induce harm in an unselected population with acute lung injury or ARDS. To counteract possible cardiovascular depression caused by higher PEEP and PEI, frequent fluid loading associated with a positive fluid balance or vasopressors may be required, which has been shown to delay pulmonary recovery (43). Because the 3 RCTs (21, 22, 43) did not consistently report fluid and vasopressor management, we could not systematically analyze the role of these factors on outcome.

On the basis of analysis of 2 RCTs including only 148 patients, the combination of lower VT and higher PEEP reduced the risk for hospital mortality (23, 24). However, in Amato and coworkers' trial (23), mortality in the control group was 30% higher than that in similar studies. Both RCTs included patients with severe ARDS in whom higher PEEP strategies are expected to be more effective to prevent cyclic recruitment and derecruitment and hence ventilator-induced lung injury (44). Compared with ventilation with higher V_T and lower PEEP, the simultaneous reduction in VT and increase in PEEP resulted in a decrease in PEI and risk for gross barotrauma. The increase in barotrauma during ventilation with higher VT and lower PEEP may be explained by higher PEI that ranged on average between 32.6 and 34.4 cm H_2O and by increased tidal pressure amplitude. Both mechanisms could have led to excessive regional mechanical strain and stresses promoting structural parenchymal damage and clinically evident barotrauma (9).

We conducted an extensive literature search to retrieve all relevant eligible trials and to minimize the potential for publication bias. However, we could retrieve only 9 eligible RCTs that used different lung-protective ventilatory strategies, and these were not easily comparable. To minimize the degree of heterogeneity among studies, we grouped the RCTs according to the specific lung-protective ventilatory strategies used. This resulted in a relatively small number of RCTs analyzed in each group. All RCTs (16–24) reported mortality as the primary outcome, and this was evaluated at different time points after randomization. We defined hospital mortality as primary outcome; this was reported by 8 (16, 18, 19–24) of the 9 (16–24) included RCTs. Because length of mechanical ventilation, hospital stay, or intensive care stay and incidence and severity of organ dysfunction were frequently not reported or not normally distributed, we could not include them in the analysis. In addition, length of mechanical ventilation was considered difficult to interpret because 4 (17–19, 23) of the 9 RCTs did not use standardized weaning protocols.

In conclusion, on the basis of available evidence from a limited number of RCTs, routine use of low V_T tends to be beneficial in all patients with acute lung injury or ARDS because this ventilation strategy improved hospital mortality. Higher PEEP strategies during lower V_T ventilation did not improve hospital mortality and cannot be recommended in unselected patients with acute lung injury or ARDS. Higher PEEP strategies during lower V_T ventilation may prevent life-threatening hypoxemia.

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Appendix Table 1. **Characteristics of the Study Participants, Therapies, and Outcomes**

Author, Year (Reference)	Population	Intervention	Weaning Protocol	Comparison	Outcome	LOS at ICU or Hospital	Funding
Lower vs. higher V_T at similar PEEP							
Brochard et al, 1998 (17)	ARDS, by LISS	VA/VCV: V_T, 6–10 mL/kg DBW; P_{EI} <25 cm H_2O (V_T could be increased up to P_{EI} 30 cm H_2O, if Fio_2 was ≥0.9, chest wall compliance was reduced, or if pH ≤7.05); PEEP by oxygenation (<15 cm H_2O); RR, not specified; I:E, not specified. Goal: Sao_2 >92%; pH ≥7.05	Yes	VA/VCV: V_T, 10–15 mL/kg DBW; P_{EI} <60 cm H_2O, PEEP by oxygenation (<15 cm H_2O); RR to achieve $Paco_2$, 38–42 mm Hg; I:E <1. Goal: Sao_2 >92%; pH ≥7.05	Primary end point: mortality at 60 d. Secondary end points: pulmonary physiological and ventilator measurements; pulmonary complications and adverse events; incidence of intrapulmonary organ failures; duration of MV; LOS ICU; ventilator-free days at 60 d; use of rescue therapies, NMB, and sedatives.	ICU, 33.5 ± 28.7 vs. 29.7 ± 19.4 d	Local sponsor
Brower et al, 1999 (18)	ARDS	VA/VCV: V_T, 5–8 mL/kg IBW; P_{EI} <30 cm H_2O (V_T, 5 mL/kg); PEEP by Pao_2–Fio_2; RR, 6–30 breaths/min; I:E <1. Goal: Pao_2, 55–75 mm Hg; $Paco_2$, 30–45 mm Hg; Sao_2, 86%–94%; pH ≥7.2	No	VA/VCV: V_T, 10–12 mL/kg IBW; P_{EI} <45–55 cm H_2O (V_T, 5 mL/kg); PEEP by Pao_2–Fio_2; RR, 6–30 breaths/min; I:E <1. Goal: Pao_2, 55–75 mm Hg; $Paco_2$, 30–45 mm Hg; Sao_2, 86%–94%; pH ≥7.2	Primary end point: evaluation of adverse effects and potential benefits of small tidal ventilation; effects on pulmonary gas exchange, dyspnea and agitation, and circulation; time to reversal of respiratory failure, hospital mortality, pulmonary physiological and ventilator measurements (no data given); use of sedation, NMB, vasopressors; pulmonary complications and adverse events; duration of MV, hospital mortality, use of NMB.	Not reported	Not reported
Brower et al, 2000 (16)	ALI and ARDS	VA/VCV: V_T, 6 mL/kg PBW; P_{EI} <30 cm H_2O (V_T, 4 mL/kg, at least either 6 mL/kg V_T or P_{EI} 25 cm H_2O); PEEP by Pao_2–Fio_2; RR, 6–35 breaths/min; I:E, 1:1–1:3. Goal: Pao_2, 55–80 mm Hg; Sao_2, 88%–95%; pH ≥7.15	Yes	VA/VCV: V_T, 12 mL/kg PBW; P_{EI} <50 cm H_2O (V_T, 4 mL/kg, at least either 12 mL/kg V_T or P_{EI} , 45 cm H_2O); PEEP by Pao_2–Fio_2; RR, 6–35 breaths/min; I:E, 1:1–1:3. Goal: Pao_2, 55–80 mm Hg; Sao_2, 88%–95%; pH ≥7.15	Primary end point: hospital mortality. Secondary end points: pulmonary physiologic and ventilator measurements, pulmonary complications and adverse events, ventilator- and organ failure–free days at 28 d, systemic inflammatory mediators, duration of MV.	Not reported	National sponsor
Stewart et al, 1998 (19)	ALI and ARDS	PC/PLV: V_T ≤8 mL/kg IBW; PEEP by oxygenation (5–20 cm H_2O); P_{EI} <30 cm H_2O (V_T could be increased up to P_{EI} 40 cm if pH ≤7.00); RR, 5–35 breaths/min; I:E, not specified; no RM. Goal: Spo_2, 89%–93%; $Paco_2$, 35–45 mm Hg; pH >7.0	No	PC/PLV: V_T, 10–15 mL/kg IBW; PEEP by oxygenation (5–20 cm H_2O); P_{EI} <50 cm H_2O; RR, 5–35 breaths/min; I:E, not specified; no RM. Goal: Spo_2, 89%–93%; $Paco_2$, 35–45 mm Hg; pH >7.0	Primary end point: hospital mortality. Secondary end points: pulmonary physiological and ventilator measurements, pulmonary complications and adverse events, multiple organ dysfunction score, number of extrapulmonary organ failures, use of NMB, need for dialysis, duration of MV, LOS ICU and hospital.	ICU, 19.9 ± 39.1 vs. 13.7 ± 15.8 d; hospital, 33.7 ± 47.8 vs. 27.4 ± 26.5 d	National and local sponsor

Continued on following page

Appendix Table 1—**Continued**

Author, Year (Reference)	Population	Intervention	Weaning Protocol	Comparison	Outcome	LOS at ICU or Hospital	Funding
Lower vs. higher PEEP at low V_T							
Brower et al, 2004 (20)	ALI and ARDS	VA/VCV: V_T, 6 mL/kg PBW; P_{EI} <30 cm H_2O; high PEEP by Pao_2–Fio_2; RR ≤35 breaths/min; I:E, 1:1–1:3; RM in the first 80 points. Goal: Pao_2, 55–80 mm Hg; Sao_2, 88%–95%; pH ≥7.3	Yes	VA/VCV: V_T, 6 mL/kg PBW; P_{EI} <30 cm H_2O; low PEEP by Pao_2–Fio_2; RR ≤35 breaths/min; I:E, 1:1–1:3; no RM. Goal: Pao_2, 55–80 mm Hg; Sao_2, 88%–95%; pH ≥7.3	Primary end point: hospital mortality. Secondary end points: pulmonary physiologic and ventilator measurements, pulmonary complications and adverse events, ventilator- and organ failure–free days at 28 d, systemic inflammatory mediators.	Not reported	National sponsor
Meade et al, 2008 (21)	ALI and ARDS	PCV: V_T, 6 mL/kg PBW; P_{EI} <40 cm H_2O; high PEEP by Pao_2–Fio_2; RR ≤35 breaths/min; I:E, 1:1–1:3; recruitment maneuver at start of the study and after each disconnect from the ventilator. Goal: Pao_2, 55–80 mm Hg; Sao_2, 88%–93%; pH ≥7.3	Yes	VA/VCV: V_T, 6 mL/kg PBW, P_{EI} <30 cm H_2O, low PEEP by Pao_2–Fio_2, RR ≤35, I:E, 1:1–1:3; no RM. Goal: Pao_2, 55–80 mm Hg; Sao_2, 88%–93%; pH ≥7.3	Primary end point: hospital mortality, ICU mortality, 28-d mortality, and mortality rate during MV. Secondary end points: pulmonary physiologic and ventilator measurements; pulmonary complications and adverse events; use of co-interventions and rescue therapies; duration of MV; LOS ICU and hospital; need for sedatives, narcotics, NMB, dialysis, vasopressors, and corticosteroids.	Median ICU, 13 vs. 13 d; hospital, 28 vs. 29 d	Local and national sponsor
Mercat et al, 2008 (22)	ALI and ARDS	VA/VCV: V_T, 6 mL/kg PBW; P_{EI} <30 cm H_2O; PEEP as high as possible with P_{EI} 28–30 cm H_2O; RR ≤35 breaths/min; I:E, not specified; recruitment maneuver allowed but not recommended. Goal: Pao_2, 55–80 mm Hg; Sao_2, 88%–95%; pH, 7.3–7.45	Yes	VA/VCV: V_T, 6 mL/kg PBW; P_{EI} <30 cm H_2O; PEEP as low as possible, 5–9 cm H_2O; RR ≤35 breaths/min; I:E, not specified; recruitment maneuver allowed but not recommended. Goal: Pao_2, 55–80 mm Hg; Sao_2, 88%–95%; pH ≥7.3–7.45	Primary end point: mortality at 28 d. Secondary end points: hospital mortality; pulmonary physiologic and ventilator measurements; pulmonary complications and adverse events; mortality at 60 d; ventilator-free and organ failure–free days at 28 d; use of co-interventions, NMB, vasopressors, and rescue therapies.	Not reported	Local and national sponsor
Lower V_T + higher PEEP vs. higher V_T + lower PEEP							
Amato et al, 1998 (23)	ARDS by LISS	PC/PLV: V_T, ≤6 mL/kg BW; PEEP, LIP + 2 cm H_2O or 16 cm H_2O; P_{EI} <PEEP + 20; RR <30 breaths/min; I:E >1, recruitment maneuver "frequently used," especially after each disconnect from the ventilator. Goal: Pao_2, 80 mm Hg; permissive hypercapnia, pH >7.2	Yes	VA/VCV: V_T, 12 mL/kg BW; PEEP by oxygenation ≥5 cm H_2O; P_{EI}, not limited; RR, 10–24 breaths/min or $Paco_2$ >25 mm Hg; I:E, not specified; no recruitment maneuver. Goal: Pao_2, 80 mm Hg; $Paco_2$, 35–38 mm Hg	Primary end point: mortality at 28 d. Secondary end points: hospital and ICU mortality, pulmonary physiologic and ventilator measurements, pulmonary complications and adverse events, weaning rate at 28 d adjusted for APACHE score, need for dialysis and NMB.	Not reported	National and industrial sponsor

Continued on following page

Appendix Table 1—**Continued**

Author, Year (Reference)	Population	Intervention	Weaning Protocol	Comparison	Outcome	LOS at ICU or Hospital	Funding
Villar et al, 2006 (24)	ARDS	VA/VCV: V_T, 5–8 mL/kg PBW; PEEP, LIP + 2 cm H_2O or 15 cm H_2O; P_{EI}, not specified; RR by $Paco_2$; I:E, not specified; no RM. Goal: Pao_2, 70–100 mm Hg; Sao_2 >90%; $Paco_2$, 35–50 cm H_2O	No	VA/VCV: V_T, 9–11 mL/kg PBW; PEEP by oxygenation ≥5 cm H_2O; P_{EI}, not specified; RR by $Paco_2$; I:E, not specified; no RM. Goal: Pao_2, 70–100 mm Hg; Sao_2 >90%; $Paco_2$, 35–50 cm H_2O	Primary end point: ICU mortality. Secondary end points: hospital mortality, pulmonary physiologic and ventilator measurements, pulmonary complications and adverse events, ventilator-free days at 28 d, number of extrapulmonary organ failures.	Not reported	National sponsor

ALI = acute lung injury; APACHE = Acute Physiology and Chronic Health Evaluation; ARDS = acute respiratory distress syndrome; BW = body weight; DBW = dry body weight (defined as actual body weight minus estimated weight gain due to water and salt retention); IBW = ideal body weight; ICU = intensive care unit; I:E = inspiratory:expiratory time; LIP = lower inflection point; LISS = Lung Injury Severity Score; LOS = length of stay; MV = mechanical ventilation; NMB = neuromuscular blockers; PBW = predicted body weight; PC/PLV = pressure-control/pressure-limited ventilation; PCV = pressure-control ventilation; PEEP = positive end-expiratory pressure; P_{EI} = end-inspiratory pressure; RM = recruitment maneuver; RR = respiratory rate; VA/VCV = volume-assist/volume-control ventilation; V_T = tidal volume.

Appendix Table 2. Ventilator Settings and Severity Scores

Author, Year (Reference)	Intervention Group	Mean SAPS Score (SD)	Mean APACHE Score (SD)	Planned Strategy				Observed Data*			
				V_T, *mL/kg*	PEEP, *cm* H_2O	RR, *breaths/min*	P_{EI}, *cm* H_2O	V_T, *mL/kg*	PEEP, *cm* H_2O	RR, *breaths/min*	P_{EI}, *cm* H_2O
Lower vs. higher V_T at similar PEEP											
Brochard et al, 1998 (17)	Treatment	35 (12)	18 (7)	6–10 DBW	0–15 (by oxygenation)	NA	25 (−30)	7.1 (1.3)	10.7 (2.9)	NA	25.7 (5.0)
	Control	36 (13)	17 (8)	10–15 DBW	0–15 (by oxygenation)	By $Paco_2$	60	10.3 (1.7)	10.7 (2.3)	NA	31.7 (6.6)
Brower et al, 1999 (18)	Treatment	–	90.6 (26.4)†	5–8 IBW	Linear Fio_2/PEEP table	6–30 ($Paco_2$)	30	7.3 (0.1)	NA	NA	24.9 (0.8)
	Control	–	84.6 (27.1)†	10–12 IBW	Linear Fio_2/PEEP table	6–30 ($Paco_2$)	45–55	10.2 (0.1)	NA	NA	30.6 (0.8)
Brower et al, 2000 (16)	Treatment	–	81 (28)†	6 PBW	Linear Fio_2/PEEP table	6–35	30	6.2 (0.9)	9.4 (3.6)	29.0 (7.0)	25.0 (7.0)
	Control	–	84 (28)†	12 PBW	Linear Fio_2/PEEP table	6–35	50	11.8 (0.8)	8.6 (3.6)	16.0 (6.0)	33.0 (9.0)
Stewart et al, 1998 (19)	Treatment	–	22.4 (7.3)	<8 IBW	5–20 (by oxygenation)	5–35 ($Paco_2$)	30 (−40)	7.0 (0.7)	8.6 (3.0)	22.1 (6.2)	22.3 (5.4)
	Control	–	21.5 (9.5)	10–15 IBW	5–20 (by oxygenation)	5–35 ($Paco_2$)	50	10.7 (1.4)	7.2 (3.3)	15.6 (5.0)	26.8 (6.7)
Lower vs. higher PEEP at low V_T											
Brower et al, 2004 (20)	Treatment	–	96 (33)†	6 PBW	Linear Fio_2/PEEP table	6–35, by pH	30	6.0 (0.9)	14.7 (3.5)	29.0 (7.0)	27.0 (6.0)
	Control	–	91 (30)†	6 PBW	Linear Fio_2/PEEP table	6–35, by pH	30	6.1 (0.8)	8.9 (3.5)	29.0 (7.0)	24.0 (7.0)
Meade et al, 2008 (21)	Treatment	–	24.8 (7.8)	6 PBW	Linear Fio_2/PEEP table	35	40	6.8 (1.4)	15.6 (3.9)	25.2 (6.6)	30.2 (6.3)
	Control	–	25.9 (7.7)	6 PBW	Linear Fio_2/PEEP table	35	30	6.8 (1.3)	10.1 (3.0)	26.0 (6.5)	24.9 (5.1)
Mercat et al, 2008 (22)	Treatment	50 (16)	–	6 PBW	P_{EI} <28–30	35, by pH	30	6.1 (0.3)	14.6 (3.2)	28.2 (5.4)	27.5 (2.4)
	Control	49 (16)	–	6 PBW	5–9	35, by pH	30	6.1 (0.4)	7.1 (1.8)	27.8 (5.4)	21.1 (4.7)
Lower V_T + higher PEEP vs. higher V_T + lower PEEP											
Amato et al, 1998 (23)	Treatment	–	28 (7)	<6 BW	LIP + 2 or 16	30	PEEP + 20	NA	16.3 (0.7)	NA	31.8 (1.4)
	Control	–	27 (6)	12 BW	≥5 (by oxygenation)	10–24, $Paco_2$ >25	No limitation	NA	6.9 (0.8)	NA	34.4 (1.9)
Villar et al, 2006 (24)	Treatment	–	18 (7)	5–8 PBW	LIP + 2 or 15	by $Paco_2$	NA	7.3 (0.9)	14.1 (2.8)	20.6 (4.0)	30.6 (6.0)
	Control	–	18 (6)	9–11 PBW	≥5 (by oxygenation)	by $Paco_2$	NA	10.2 (1.2)	9.0 (2.7)	15.0 (3.0)	32.6 (6.2)

APACHE = Acute Physiology and Chronic Health Evaluation; BW = body weight; DBW = dry body weight (defined as actual body weight minus estimated weight gain due to water and salt retention); IBW = ideal body weight; LIP = lower inflection point; NA = not applicable; PBW = predicted body weight; PEEP = positive end-expiratory pressure; P_{EI} = end-inspiratory pressure; RR = respiratory rate; SAPS = Simplified Acute Physiology Score; V_T = tidal volume.

* Observed data are means (SDs).

† APACHE III score.

Appendix Table 3. Management of pH

Author, Year (Reference)	Study Group	pH Threshold	Planned Intervention
Lower vs. higher V_T at similar PEEP			
Brochard et al, 1998 (17)	Treatment	7.05	If pH <7.05, increase V_T until P_{EI} max is 30 cm H_2O; sodium bicarbonate (not specified); dialysis for metabolic acidosis.
	Control	Not specified	Not specified.
Brower et al, 1999 (18)	Treatment	7.30	If pH <7.3, sodium bicarbonate permissible. If pH <7.2, sodium bicarbonate (10 mEq/h) required.
	Control	7.30	If pH <7.3, sodium bicarbonate permissible. If pH <7.2, sodium bicarbonate (10 mEq/h) required.
Brower et al, 2000 (16)	Treatment	7.15	If pH <7.15 increase P_{EI} up to ≥30 cm H_2O.
	Control	7.15	If pH <7.15 increase P_{EI} up to ≥50 cm H_2O.
Stewart et al, 1998 (19)	Treatment	7.00	If pH <7.0, 2 mmol/kg sodium bicarbonate max 3 times per day, increase P_{PEAK} to max 40 cm H_2O. If refractory acidosis <7.0, withdrawal from study.
	Control	7.00	If pH <7.0, 2 mmol/kg sodium bicarbonate max 3 times per day.
Lower vs. higher PEEP at low V_T			
Brower et al, 2004 (20)	Treatment	7.30	If pH 7.15 to 7.3, increase respiratory rate to max 35 breaths/min. If respiratory rate is 35 breaths/min, give sodium bicarbonate. If pH <7.15, increase respiratory rate to max 35 breaths/min. If respiratory rate is 35 breaths/min and sodium bicarbonate has been given, increase V_T by 1 mL/kg until pH >7.1 (P_{EI} may be exceeded).
	Control	7.30	If pH 7.15 to 7.3, increase respiratory rate to max 35 breaths/min. If respiratory rate is 35 breaths/min, give sodium bicarbonate. If pH <7.15, increase respiratory rate to max 35 breaths/min. If respiratory rate is 35 breaths/min and sodium bicarbonate has been given, increase V_T by 1 mL/kg until pH >7.1 (P_{EI} may be exceeded).
Meade et al, 2008 (21)	Treatment	<7.1 for >1 h	Protocol deviation or rescue therapy, prone position, iNO, HFV, ECMO.
	Control	<7.1 for >1 h	Protocol deviation or rescue therapy, prone position, iNO, HFV, ECMO.
Mercat et al, 2008 (22)	Treatment	7.30	If pH <7.3, give sodium bicarbonate. If pH <7.15, increase V_T until max 8 mL/kg and P_{EI} max 32 cm H_2O, reduce PEEP to min 5 cm H_2O, maintain V_T min 4 mL/kg.
	Control	7.30	If pH <7.3, give sodium bicarbonate. If pH <7.15, increase V_T until max 8 mL/kg and P_{EI} max 32 cm H_2O, reduce PEEP to min 5 cm H_2O, maintain V_T min 4 mL/kg.
Lower V_T + higher PEEP vs. higher V_T + lower PEEP			
Amato et al, 1998 (23)	Treatment	7.20	If pH <7.2, sodium bicarbonate <50 mmoL/h.
	Control	Not specified	Not specified.
Villar et al, 2006 (24)	Treatment	Not specified	Management of pH up to clinician.
	Control	Not specified	Management of pH up to clinician.

ECMO = extracorporeal membrane oxygenation; HFV = high-frequency ventilation; iNO = inhaled nitric oxide; max = maximum; min = minimum; P_{PEAK} = peak inspiratory pressure; PEEP = positive end-expiratory pressure; P_{EI} = end-inspiratory pressure; V_T = tidal volume.

Appendix Table 4. Effect of Ventilation Strategies on Pulmonary Function

Strategy	Studies, *n*	Patients in Each Group, *n/n*	Weighted Mean Difference (95% CI)*	*P* Value	I^2 Statistic	*P* Value
V_T, day 1						
Lower vs. higher V_T at similar PEEP	3	550/547	−4.18 (−5.83 to −2.53)	<0.001	98.6	<0.001
Lower vs. higher PEEP at low V_T	3	1136/1163	−0.01 (−0.06 to 0.04)	0.66	0	0.43
Lower V_T + higher PEEP vs. higher V_T + lower PEEP	1	50/45	−2.90 (−3.33 to 2.47)	<0.001	NA	NA
PEEP, day 1						
Lower vs. higher V_T at similar PEEP	3	550/547	0.71 (0.07 to 1.35)	0.03	45.8	0.160
Lower vs. higher PEEP at low V_T	3	1136/1163	6.28 (4.91 to 7.64)	<0.001	96.3	<0.001
Lower V_T + higher PEEP vs. higher V_T + lower PEEP	2	79/69	7.28 (3.07 to 11.50)	<0.001	98.0	<0.001
P_{EI}, day 1						
Lower vs. higher V_T at similar PEEP	3	550/547	−6.33 (−8.52 to −4.14)	<0.001	78.2	0.010
Lower vs. higher PEEP at low V_T	3	1136/1163	4.96 (3.26 to 6.66)	<0.001	93.6	<0.001
Lower V_T + higher PEEP vs. higher V_T + lower PEEP	2	79/69	−2.53 (−3.38 to −1.67)	<0.001	0	0.65
Respiratory rate, day 1						
Lower vs. higher V_T at similar PEEP	2	492/489	9.82 (3.45 to 16.18)	0.003	97.0	<0.001
Lower vs. higher PEEP at low V_T	3	1136/1163	−0.14 (−0.91 to 0.64)	0.73	55.2	0.110
Lower V_T + higher PEEP vs. higher V_T + lower PEEP	1	50/45	5.60 (4.19 to 7.01)	<0.001	NA	NA
Pao_2, day 1						
Lower vs. higher V_T at similar PEEP	2	490/487	−1.05 (−3.83 to 1.72)	0.46	0	0.84
Lower vs. higher PEEP at low V_T	3	1136/1163	11.06 (4.50 to 17.62)	<0.001	85.1	0.001
Lower V_T + higher PEEP vs. higher V_T + lower PEEP	–	–	–	–	–	–
$Paco_2$, day 1						
Lower vs. higher V_T at similar PEEP	2	490/487	11.43 (−1.50 to 24.36)	0.080	97.0	<0.001
Lower vs. higher PEEP at low V_T	3	1136/1163	0.77 (−0.06 to 1.59)	0.070	0	0.66
Lower V_T + higher PEEP vs. higher V_T + lower PEEP	2	79/69	9.68 (−15.60 to 34.96)	0.45	99.2	<0.001
pH, day 1						
Lower vs. higher V_T at similar PEEP	1	432/429	−0.03 (−0.04 to −0.02)	<0.001	NA	NA
Lower vs. higher PEEP at low V_T	3	1136/1163	−0.01 (−0.03 to 0.00)	0.020	52.7	0.120
Lower V_T + higher PEEP vs. higher V_T + lower PEEP	2	79/69	−0.09 (−0.27 to 0.09)	0.31	99.1	<0.001
V_T, day 7						
Lower vs. higher V_T at similar PEEP	3	550/547	−3.86 (−5.09 to 2.63)	<0.001	97.2	<0.001
Lower vs. higher PEEP at low V_T	3	1136/1163	−0.03 (−0.49 to 0.44)	0.90	94.9	<0.001
Lower V_T + higher PEEP vs. higher V_T + lower PEEP	1	50/45	−2.80 (−3.23 to −2.37)	<0.001	NA	NA
PEEP, day 7						
Lower vs. higher V_T at similar PEEP	3	550/547	0.49 (−1.29 to 2.28)	0.59	90.7	<0.001
Lower vs. higher PEEP at low V_T	3	1136/1163	3.14 (1.94 to 4.34)	<0.001	92.6	<0.001
Lower V_T + higher PEEP vs. higher V_T + lower PEEP	1	50/45	−0.10 (−1.55 to 1.35)	0.89	NA	NA
P_{EI}, day 7						
Lower vs. higher V_T at similar PEEP	3	550/547	−8.77 (−11.61 to −5.92)	<0.001	84.1	0.002
Lower vs. higher PEEP at low V_T	3	1136/1163	2.35 (0.40 to 4.30)	0.02	92.6	<0.001
Lower V_T + higher PEEP vs. higher V_T + lower PEEP	1	50/45	−6.70 (−9.77 to −3.63)	<0.001	NA	NA
Respiratory rate, day 7						
Lower vs. higher V_T at similar PEEP	2	492/489	7.95 (3.74 to 12.16)	<0.001	93.0	<0.001
Lower vs. higher PEEP at low V_T	3	1136/1163	0.14 (−1.55 to 1.82)	0.87	87.5	<0.001
Lower V_T + higher PEEP vs. higher V_T + lower PEEP	1	50/45	1.90 (0.07 to 3.73)	0.040	NA	NA
Pao_2, day 7						
Lower vs. higher V_T at similar PEEP	2	490/487	−1.79 (−4.25 to 0.67)	0.150	0	0.55
Lower vs. higher PEEP at low V_T	3	1136/1163	0.02 (−1.67 to 1.70)	0.98	0	0.45
Lower V_T + higher PEEP vs. higher V_T + lower PEEP	–	–	–	–	–	–
$Paco_2$, day 7						
Lower vs. higher V_T at similar PEEP	2	490/487	9.88 (−2.35 to 22.11)	0.110	93.4	0.001
Lower vs. higher PEEP at low V_T	3	1136/1163	−1.37 (−2.31 to −0.43)	0.004	0	0.71
Lower V_T + higher PEEP vs. higher V_T + lower PEEP	1	50/45	−6.10 (−10.75 to −1.45)	0.010	NA	NA
pH, day 7						
Lower vs. higher V_T at similar PEEP	1	432/429	−0.01 (−0.02 to 0.00)	0.050	NA	NA
Lower vs. higher PEEP at low V_T	3	1136/1163	0.00 (0.00 to 0.01)	0.17	7.9	0.34
Lower V_T + higher PEEP vs. higher V_T + lower PEEP	1	50/45	0.04 (0.01 to 0.07)	0.003	NA	NA

NA = not applicable; PEEP = positive end-expiratory pressure; P_{EI} = end-inspiratory pressure; V_T = tidal volume.
* Random-effects model.

Appendix Table 5. **Characteristics, Results, and Limitations of Earlier Meta-analyses**

Meta-analysis	Studies Included	Patients in Each Group, *n/n*	Intervention	End Point	Results	Conclusions	Limitations
Eichacker et al, 2002 (38)	Amato et al, 1998 (23)	29/24	Lower V_T and higher PEEP vs. higher V_T and lower PEEP	Mortality, not differentiated	OR (95% CI), 3.97 (2.20–7.17)	The 3 nonbeneficial trials used control V_T, resulting in lower airway pressures (28–32 cm H_2O).	No summary estimate due to high statistical heterogeneity.
	Stewart et al, 1998 (19)	60/60	Lower vs. higher V_T at similar PEEP		OR (95% CI), 0.89 (0.62–1.28)	Compared with these control pressures, low V_T did not improve outcome. The 2 other trials compared low V_T ventilation with control groups with airway pressures high enough (34–37 cm H_2O) to potentially increase mortality rates.	Includes trials simultaneously reducing V_T while increasing PEEP but does not evaluate recent RCTs comparing higher versus lower PEEP strategies with lower V_T ventilation.
	Brochard et al, 1998 (17)	58/58	Lower vs. higher V_T at similar PEEP		OR (95% CI), 0.70 (0.48–1.02)		
	Brower et al, 1999 (18)	26/26	Lower vs. higher V_T at similar PEEP		OR (95% CI), 0.85 (0.49–1.48)		
	Brower et al, 2000 (16)	432/429	Lower vs. higher V_T at similar PEEP		OR (95% CI), 1.47 (1.28–1.70)		
		Total, 1202			No summary estimate	None of the trials provides a scientific basis for the use low V_T ventilation, as long as plateau pressure is maintained between 28–32 cm H_2O.	
Petrucci and Iacovelli, 2004 (36)	Amato et al, 1998 (23)	29/24	Lower V_T and higher PEEP vs. higher V_T and lower PEEP	Hospital mortality Mortality at the end of follow-up	Mortality at d 28, fixed RR (95% CI), 0.74 (0.61–0.88 [$P < 0.001$]); $I^2 = 0\%$ ($P = 0.41$)	A ventilation strategy using $V_T \leq 7$ mL/kg of measured BW and $P_{EI} \leq 31$ cm H_2O reduces mortality at d 28 and might reduce hospital and long-term mortality.	Includes trials simultaneously reducing V_T while increasing PEEP.
	Stewart et al, 1998 (19)	60/60	Lower vs. higher V_T at similar PEEP		Hospital mortality, fixed RR (95% CI), 0.82 (0.70–0.95), $I^2 = 31.8\%$ ($P = 0.22$)	When delivery of conventional V_T was associated with $P_{EI} \leq 31$ cm H_2O, no evidence existed for decreased mortality.	Does not evaluate recent RCTs comparing higher versus lower PEEP strategies with lower V_T ventilation.
	Brochard et al, 1998 (17)	58/58	Lower vs. higher V_T at similar PEEP		Mortality at the end of follow-up, fixed RR (95% CI), 0.85 (0.74–0.98 [$P = 0.030$]); $I^2 = 45.9\%$ ($P = 0.120$)		
	Brower et al, 1999 (18)	26/26	Lower vs. higher V_T at similar PEEP				
	Brower et al, 2000 (16)	432/429	Lower vs. higher V_T at similar PEEP				
		Total, 1202					
Petrucci and Iacovelli, 2007 (37)	Amato et al, 1998 (23)	29/24	Lower V_T and higher PEEP vs. higher V_T and lower PEEP	Hospital mortality Mortality at the end of follow-up	Mortality at 28 d, fixed RR (95% CI), 0.74 (0.61–0.88 [$P < 0.001$]); $I^2 = 0\%$ ($P = 0.41$)	A ventilation strategy using $V_T \leq 7$ mL/kg of measured BW and $P_{EI} \leq 31$ cm H_2O reduces mortality at d 28 and hospital mortality.	Includes trials simultaneously reducing V_T while increasing PEEP.
	Stewart et al, 1998 (19)	60/60	Lower vs. higher V_T at similar PEEP		Hospital mortality, fixed RR (95% CI), 0.80 (0.69–0.92 [$P < 0.001$]); $I^2 = 31\%$ ($P = 0.22$)	When delivery of conventional V_T was associated with $P_{EI} \leq 31$ cm H_2O, no evidence existed for decreased mortality.	Does not evaluate recent RCTs comparing higher versus lower PEEP strategies with lower V_T ventilation.

Appendix Table 5—**Continued**

Meta-analysis	Studies Included	Patients in Each Group, *n/n*	Intervention	End Point	Results	Conclusions	Limitations
	Brochard et al, 1998 (17)	58/58	Lower vs. higher V_T at similar PEEP		Mortality at the end of follow-up, fixed RR (95% CI), 0.83 (0.72–0.95 [$P < 0.001$]); $I^2 = 46\%$ ($P = 0.100$)		
	Brower et al, 1999 (18)	26/26	Lower vs. higher V_T at similar PEEP				
	Brower et al, 2000 (16)	432/429	Lower vs. higher V_T at similar PEEP				
	Villar et al, 2006 (24)	50/45	Lower V_T and higher PEEP vs. higher V_T and lower PEEP				
		Total, 1297					
Moran et al, 2005 (35)	Amato et al, 1998 (23)	29/24	Lower V_T and higher PEEP vs. higher V_T and lower PEEP	Mortality at 28 d for Brower et al, 1999 (18) Hospital mortality for Brochard et al (17)	Mortality, fixed OR (95% CI), 0.71 (0.56–0.91 [$P = 0.006$]); $I^2 = 56.8\%$ ($P = 0.060$) Meta-regression log OR <0 for V_T, 7.7 mL/kg, V_T >11.2 mL/kg, P_{EI} >29–30 cm H_2O and change in P_{EI} >5.5 cm H_2O	The pooled estimate of treatment effect favors lung-protective ventilation but did not reach statistical significance on random-effects estimation. Low V_T is not detrimental and may have advantage below threshold levels of 7.7 mL/kg PBW.	Includes trials simultaneously reducing V_T while increasing PEEP. Does not evaluate recent RCTs comparing higher versus lower PEEP strategies with lower V_T ventilation.
	Stewart et al, 1998 (19)	60/60	Lower vs. higher V_T at similar PEEP				
	Brochard et al, 1998 (17)	58/58	Lower vs. higher V_T at similar PEEP				
	Brower et al, 1999 (18)	26/26	Lower vs. higher V_T at similar PEEP				
	Brower et al, 2000 (16)	432/429	Lower vs. higher V_T at similar PEEP				
		Total, 1202					

BW = body weight; OR = odds ratio; PBW = predicted body weight; PEEP = positive end-expiratory pressure; P_{EI} = end-inspiratory pressure; RCT = randomized, controlled trial; RR = risk ratio; V_T = tidal volume.