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Higher versus Lower Positive End-Expiratory Pressures in Patients with the Acute Respiratory Distress Syndrome

The National Heart, Lung, and Blood Institute ARDS Clinical Trials Network*

ABSTRACT

BACKGROUND

Most patients requiring mechanical ventilation for acute lung injury and the acute respiratory distress syndrome (ARDS) receive positive end-expiratory pressure (PEEP) of 5 to 12 cm of water. Higher PEEP levels may improve oxygenation and reduce ventilator-induced lung injury but may also cause circulatory depression and lung injury from overdistention. We conducted this trial to compare the effects of higher and lower PEEP levels on clinical outcomes in these patients.

METHODS

We randomly assigned 549 patients with acute lung injury and ARDS to receive mechanical ventilation with either lower or higher PEEP levels, which were set according to different tables of predetermined combinations of PEEP and fraction of inspired oxygen.

RESULTS

Mean (±SD) PEEP values on days 1 through 4 were 8.3±3.2 cm of water in the lower-PEEP group and 13.2±3.5 cm of water in the higher-PEEP group (P<0.001). The rates of death before hospital discharge were 24.9 percent and 27.5 percent, respectively (P=0.48; 95 percent confidence interval for the difference between groups, −10.0 to 4.7 percent). From day 1 to day 28, breathing was unassisted for a mean of 14.5±10.4 days in the lower-PEEP group and 13.8±10.6 days in the higher-PEEP group (P=0.50).

CONCLUSIONS

These results suggest that in patients with acute lung injury and ARDS who receive mechanical ventilation with a tidal-volume goal of 6 ml per kilogram of predicted body weight and an end-inspiratory plateau-pressure limit of 30 cm of water, clinical outcomes are similar whether lower or higher PEEP levels are used.

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Mechanical ventilation is critical for the survival of most patients with acute lung injury and the acute respiratory distress syndrome (ARDS). However, some approaches to mechanical ventilation may cause additional lung injury,[1,2] which could delay or prevent resolution of respiratory failure. Ventilator-induced lung injury may be caused by overdistention of aerated lung regions, especially when large tidal volumes are used.[3-5] Ventilator-induced lung injury may also occur if a substantial portion of the lung is not aerated at end-expiration because of atelectasis, flooding, and consolidation. This may cause excessive mechanical forces in aerated lung regions,[6] between aerated and nonaerated lung regions,[7] or in bronchioles and alveoli that open and close with each breath.[8]

The proportion of nonaerated lung may be reduced by applying positive end-expiratory pressure (PEEP).[9,10] This therapy usually improves arterial oxygenation, but it may cause circulatory depression[11] and increase pulmonary edema.[12,13] Moreover, PEEP may increase airway pressures and lung volumes, which could contribute to ventilator-induced lung injury from overdistention. Most patients with acute lung injury and ARDS have been treated with PEEP values of 5 to 12 cm of water,[14-16] a range that presumably reflects physicians' attempts to balance the beneficial effects of PEEP on arterial oxygenation with these adverse effects.

PEEP levels that exceed these traditional levels may decrease ventilator-induced lung injury by further reducing the proportion of nonaerated lung.[8,17] Moreover, higher PEEP levels may allow arterial-oxygenation goals to be met with the use of a lower fraction of inspired oxygen (FiO_2), which could reduce the adverse pulmonary effects of oxygen.[18] In recent studies of patients with acute lung injury and ARDS, ventilation strategies that included higher PEEP levels were associated with better survival and lower levels of inflammatory mediators in plasma and bronchoalveolar-lavage fluid.[19,20] However, the patients who received higher PEEP levels also received lower tidal volumes and inspiratory airway pressures. Therefore, it is not clear whether the better survival and lower levels of inflammatory mediators resulted from the higher PEEP levels, the lower tidal volumes and airway pressures, or both. In another trial,[21] mortality was lower in a study group that received lower tidal volumes and inspiratory pressures and PEEP levels that were similar to those used by most clinicians.[14-16] We conducted the present trial to determine whether the use of higher PEEP levels would improve clinical outcomes among patients with acute lung injury and ARDS who were receiving mechanical ventilation with lower tidal volumes and inspiratory airway pressures.

METHODS

Patients were enrolled from October 1999 through February 2002 at 23 hospitals of the National Heart, Lung, and Blood Institute (NHLBI) ARDS Clinical Trials Network (listed in the Appendix). The trial was approved by the institutional review board of each hospital. Written informed consent was obtained from the patients or their surrogates. A complete description of the methods is available at www.ardsnet.org and in the Supplementary Appendix, available with the full text of this article at www.nejm.org.

PATIENTS

Patients who were intubated and receiving mechanical ventilation were eligible if there was a sudden decrease in the ratio of the partial pressure of arterial oxygen (PaO_2) to the FiO_2 of 300 or less (adjusted to 253 in Denver and Salt Lake City because of the altitude), a recent appearance of bilateral pulmonary infiltrates consistent with the presence of edema, and no clinical evidence of left atrial hypertension (defined by a pulmonary-capillary wedge pressure of 18 mm Hg or less, if measured). Patients were excluded if 36 hours had elapsed since the eligibility criteria were met; they were younger than 13 years of age; they had participated in other trials involving acute lung injury within the preceding 30 days; they were pregnant; they had increased intracranial pressure, severe neuromuscular disease, sickle cell disease, severe chronic respiratory disease, a body weight greater than 1 kg per centimeter of height, burns over more than 40 percent of their body-surface area, severe chronic liver disease, vasculitis with diffuse alveolar hemorrhage, or a coexisting condition associated with an estimated 6-month mortality rate greater than 50 percent; had received a bone marrow or lung transplant; or their attending physician refused to allow enrollment. We used a centralized interactive voice system to randomly assign eligible patients in permuted blocks to either a lower- or a higher-PEEP strategy. Patients were stratified according to hospital before randomization.

VENTILATOR PROCEDURES

We designed two different strategies for adjusting PEEP and FiO_2 in discrete steps to maintain an arterial oxyhemoglobin saturation (measured by pulse oximetry) of 88 to 95 percent or a PaO_2 of 55 to 80 mm Hg (Table 1). The lower-PEEP strategy represents a consensus of how the investigators and clinical colleagues balanced beneficial and adverse effects of PEEP in 1995. This strategy was used in our previous trial,[21] which compared ventilator strategies involving traditional and lower tidal volumes and resulted in PEEP levels that were consistent with those reported in surveys of clinicians' practices.[14-16] The higher-PEEP strategy was designed to use PEEP levels that were similar to those used in a previous trial in which higher PEEP levels and smaller tidal volumes were associated with better survival.[19] When our trial started, we required a PEEP of at least 12 cm of water for at least 12 hours after randomization to the higher-PEEP group. However, after 171 patients had been enrolled in the trial, the difference in mean PEEP levels between study groups on days 1 through 7 was less than the difference in the previous study that tested the effects of higher PEEP levels and smaller tidal volumes.[19] To approximate more closely the separation in PEEP between study groups as in this previous trial, we modified the higher-PEEP strategy by eliminating the steps with a PEEP of less than 12 cm of water and requiring a minimum PEEP of 14 cm of water for the first 48 hours (Table 1). These changes in the protocol were made by the steering committee without knowledge of the clinical outcome data.

Other ventilator variables were adjusted in the same manner in both groups. In all patients, we used a tidal-volume goal of 6 ml per kilogram of predicted body weight and an inspiratory plateau pressure of 30 cm of water or less.[21] Weaning was initiated when acceptable arterial oxygenation could

Table 1. Summary of Ventilator Procedures in the Lower- and Higher-PEEP Groups.*

Procedure	Value
Ventilator mode	Volume assist/control
Tidal-volume goal	6 ml/kg of predicted body weight
Plateau-pressure goal	≤30 cm of water
Ventilator rate and pH goal	6–35, adjusted to achieve arterial pH ≥7.30 if possible
Inspiration:expiration time	1:1–1:3
Oxygenation goal	
PaO_2	55–80 mm Hg
SpO_2	88–95%
Weaning	Weaning attempted by means of pressure support when level of arterial oxygenation acceptable with PEEP ≤8 cm of water and FiO_2 ≤0.40

Allowable combinations of PEEP and FiO_2†														
Lower-PEEP group														
FiO_2	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.7	0.7	0.8	0.9	0.9	0.9	1.0
PEEP	5	5	8	8	10	10	10	12	14	14	14	16	18	18–24
Higher-PEEP group (before protocol changed to use higher levels of PEEP)														
FiO_2	0.3	0.3	0.3	0.3	0.3	0.4	0.4	0.5	0.5	0.5–0.8	0.8	0.9	1.0	
PEEP	5	8	10	12	14	14	16	16	18	20	22	22	22–24	
Higher-PEEP group (after protocol changed to use higher levels of PEEP)														
FiO_2	0.3	0.3	0.4	0.4	0.5	0.5	0.5–0.8	0.8	0.9	1.0				
PEEP	12	14	14	16	16	18	20	22	22	22–24				

* Complete ventilator procedures and eligibility criteria are listed in the Supplementary Appendix (available with the full text of this article at www.nejm.org) and at www.ardsnet.org. PaO_2 denotes partial pressure of arterial oxygen, SpO_2 oxyhemoglobin saturation as measured by pulse oximetry, FiO_2 fraction of inspired oxygen, and PEEP positive end-expiratory pressure.

† In both study groups, additional increases in PEEP to 34 cm of water were allowed but not required after the FiO_2 had been increased to 1.0 according to the protocol. The combinations of PEEP and FiO_2 used with PEEP values of less than 12 cm of water were eliminated in the higher-PEEP group after 171 patients had been enrolled in this group.

be maintained at the same or similar PEEP and FiO_2 steps. The same weaning procedures were used in both study groups.

ORGAN FAILURES

We monitored patients daily for cardiovascular, coagulation, renal, and hepatic failure for 28 days.[21] For each organ we calculated the number of days without organ failure by subtracting the number of days of organ failure from the lesser of 28 or the number of days to death. Organs were considered failure-free after hospital discharge.

RECRUITMENT MANEUVERS

In the first 80 patients randomly assigned to the higher-PEEP group, we assessed the safety and efficacy of recruitment maneuvers — that is, single sustained inflations of the lungs to higher airway pressures and volumes than are obtained during tidal ventilation — in an effort to improve arterial oxygenation. One or two such maneuvers were conducted during the first four days after randomization by applying continuous positive airway pressure of 35 to 40 cm of water for 30 seconds. The subsequent mean increase in arterial oxygenation was small and transient.[22] Therefore, we discontinued recruitment maneuvers for the remainder of the trial.

PLASMA LEVELS OF BIOLOGIC MARKERS

Blood samples were obtained in sterile, EDTA-treated glass tubes before randomization (day 0) and on day 3 for measurements by enzyme-linked immunoassays of plasma interleukin-6,[23] surfactant protein D,[24] and intercellular adhesion molecule 1.[25] These markers were selected to reflect mechanisms of lung inflammation and injury.[20,21]

DATA COLLECTION

Data on demographic, physiological, and radiographic characteristics; coexisting conditions; and medications were recorded within four hours before initial changes were made in the ventilator settings and between 6 a.m. and 10 a.m. on days 1, 2, 3, 4, 7, 14, 21, and 28. Patients were followed until day 90 or until they were discharged home while breathing without assistance.

STATISTICAL ANALYSIS

The primary outcome measure was the proportion of patients who died before they were discharged home while breathing without assistance. Patients alive in health care facilities at 60 days, regardless of their requirement for ventilation assistance, were considered to have been discharged home while breathing without assistance. Our estimates indicated that a sample size of 750 patients would yield a statistical power of 89 percent to detect a reduction in mortality from 28 percent in the lower-PEEP group to 18 percent in the higher-PEEP group. An independent data and safety monitoring board conducted interim analyses after the enrollment of successive groups of approximately 250 patients. Asymmetric stopping boundaries (with a two-sided α=0.05) were designed to allow early termination of the trial if the use of higher PEEP was found to reduce mortality or if there was a low probability that the trial could demonstrate a lower mortality rate in the higher-PEEP group than in the lower-PEEP group (futility stopping rule).[26] Secondary outcome variables included the number of ventilator-free days (the number of days a patient breathed without assistance for at least 48 consecutive hours from day 1 to day 28),[27] the number of days a patient was not in the intensive care unit (ICU) from day 1 to day 28, and the number of days without organ failure from day 1 to day 28.

We report means (±SD), 95 percent confidence intervals, and interquartile ranges where appropriate. We compared baseline variables using Student's t-test or Fisher's exact test. We used Wilcoxon's test to compare day 0 and day 3 plasma levels of biologic marker, the number of ventilator-free days, the number of ICU-free days, and the number of organ-failure–free days, all of which had skewed distributions. We used the 60-day cumulative mortality rate to compare the proportion of patients in each group who died before being discharged from the hospital while breathing without assistance.[28] All reported P values are two-sided.

To adjust for baseline imbalances in covariates between study groups, we used a forward stepwise selection scheme to identify predictors of mortality from the 27 baseline variables recorded for 473 patients who received the strategy of mechanical ventilation involving lower tidal volumes in our two previous trials.[21,29] Missing values were replaced by group mean values. Dummy variables indicated missing values. We used P values of 0.05 to enter and remove variables from the regression. We identified the following predictors: age, score on the Acute Physiology and Chronic Health Evaluation (APACHE III; scores can range from 0 to 299, with higher scores indicating a higher probability of

death),[30] plateau pressure, missing plateau pressure, number of organ failures, number of hospital days before enrollment in the trial, and the alveolar–arterial difference in the partial pressure of oxygen. We then fit a logistic model to the data in the current trial with the use of these seven covariates and study-group assignment. The estimates from this model were used to calculate a predicted mortality for each patient if treated with lower PEEP and also if treated with higher PEEP. The averages of these predictions for all patients provide adjusted mortality rates, which represent estimated mortality rates for the lower- and higher-PEEP study groups if the distributions of the covariates had been completely balanced between groups. The standard error of these rates and their difference was calculated by means of the bootstrap technique.[31]

RESULTS

The data and safety monitoring board stopped the trial at the second interim analysis, after 549 patients had been enrolled, on the basis of the specified futility stopping rule. At this time it was calculated that if the study had continued to the planned maximal enrollment of 750 patients, the probability of demonstrating the superiority of the higher-PEEP strategy was less than 1 percent under the alternative hypothesis based on the unadjusted mortality difference.

Most of the baseline characteristics of the two study groups were similar (Table 2). However, in the higher-PEEP group, the mean age was significantly higher (P=0.004) and the mean PaO_2:FiO_2 was significantly lower (P=0.03).

The mean PEEP values on days 1 through 4 were 8.3±3.2 cm of water in the lower-PEEP group and 13.2±3.5 cm of water in the higher-PEEP group (P<0.001). Values of the PaO_2:FiO_2 were higher in the higher-PEEP group than in the lower-PEEP group (Table 3). The mean differences in these ratios were 52 (95 percent confidence interval, 39 to 66) on day 1, 37 (95 percent confidence interval, 22 to 52) on day 3, and 37 (95 percent confidence interval, 9 to 65) on day 7. Respiratory-system compliance was significantly higher in the higher-PEEP group than in the lower-PEEP group on days 1, 2, and 4. Tidal volumes were significantly but only slightly lower and plateau pressures were significantly higher in the higher-PEEP group on days 1 through 3 (Table 3). PaO_2 values were higher in the higher-PEEP group on day 1 but were similar to those in the lower-PEEP group on days 2 through 7. Respiratory rates and the values of the partial pressure of carbon dioxide and pH in arterial blood were similar in the two groups on all days.

Table 2. Baseline Characteristics of the Patients.*

Characteristic	Lower-PEEP Group (N=273)	Higher-PEEP Group (N=276)
Age (yr)	49±17	54±17†
Female sex (%)	47	43
Race or ethnic group (%)‡		
White	73	77
Black	14	14
Hispanic	6	7
Other or not available	7	2
APACHE III score§	91±30	96±33
Tidal volume (ml/kg of predicted body weight)	8.2±2.0	8.0±2.0
Minute ventilation (liters/min)	12.1±4.2	12.0±3.4
Respiratory rate (breaths/min)	22.8±7.8	23.2±7.6
No. of nonpulmonary organ or system failures¶	1.0±0.9	1.0±0.9
PaO_2:FiO_2	165±77	151±67‖
Cause of lung injury (%)		
Pneumonia	38	42
Sepsis	24	20
Aspiration	15	16
Trauma	10	7
Multiple transfusions	4	6
Other	10	9

* Plus–minus values are means ±SD. Because of rounding, percentages may not total 100. PaO_2 denotes partial pressure of arterial oxygen tension, and FiO_2 fraction of inspired oxygen.
† P=0.004.
‡ Race or ethnic group was assigned by the investigators.
§ Scores for the Acute Physiology, Age, and Chronic Health Evaluation (APACHE III)[30] can range from 0 to 299, with higher scores indicating a higher probability of death.
¶ Patients were monitored daily for 28 days for cardiovascular, coagulation, renal, and hepatic failure.
‖ P=0.003.

The probabilities of survival and of being discharged home while breathing without assistance during the first 60 days after randomization are shown in Figure 1. The rate of death from any cause was 24.9 percent in the lower-PEEP group and 27.5 percent in the higher-PEEP group (P=0.48; 95 percent confidence interval for the difference between groups, –10.0 to 4.7 percent). After adjustments for differences in the baseline variables, the mortality rate was 27.5 percent in the lower-PEEP

Table 3. Respiratory Values during the First Seven Days of Treatment.*

Variable	Day 1		Day 3		Day 7	
	Lower-PEEP Group	Higher-PEEP Group	Lower-PEEP Group	Higher-PEEP Group	Lower-PEEP Group	Higher-PEEP Group
Tidal volume (ml/kg of predicted body weight)	6.1±0.8	6.0±0.9†	6.1±1.1	5.8±1.0†	6.2±1.3	5.8±1.2
No. of patients	236	258	171	160	83	97
Plateau pressure (cm of water)	24±7	27±6†	24±6	26±7†	26±8	26±6
No. of patients	230	252	165	155	78	96
Mean airway pressure (cm of water)	15±5	20±5†	15±5	18±5†	15±7	19±6†
No. of patients	233	261	167	164	82	94
Respiratory rate (breaths/min)	29±7	29±7	30±7	30±7	28±7	30±7
No. of patients	248	263	180	173	98	102
Minute ventilation (liters/min)	12±4	12±3	12±4	12±3	12±4	12±3
No. of patients	247	264	178	171	96	104
FiO_2	0.54±0.18	0.44±0.17†	0.52±0.18	0.40±0.14†	0.52±0.20	0.40±0.11†
No. of patients	249	264	179	173	98	103
PEEP (cm of water)						
All patients	8.9±3.5	14.7±3.5‡	8.5±3.7	12.9±4.5‡	8.4±4.3	12.9±4.0‡
No. of patients	249	264	180	173	98	104
First 171 patients	9.1±3.3	14.2±3.2	8.7±3.6	11.3±4.6	7.6±3.0	12.0±5.0
No. of patients	76	82	60	62	40	32
Subsequent 378 patients	8.9±3.6	14.9±3.6	8.4±3.7	13.8±4.2	9.1±4.9	13.4±3.4
No. of patients	173	182	120	111	58	72
PaO_2/FiO_2	168±66	220±89‡	169±69	206±76‡	181±115	218±85†
No. of patients	230	244	159	152	87	91
Respiratory-system compliance (ml/cm of water)§	31±15	39±34‡	29±16	32±34	28±16	32±22
No. of patients	227	251	165	152	77	94
PaO_2 (mm Hg)	78±22	85±28‡	77±22	74±20	77±27	78±26
No. of patients	230	244	159	152	87	92
$PaCO_2$ (mm Hg)	41±11	41±11	43±13	43±13	48±14	47±16
No. of patients	230	244	159	152	87	92
Arterial pH	7.4±0.1	7.4±0.1	7.4±0.1	7.4±0.1	7.4±0.1	7.4±0.1
No. of patients	230	244	160	153	87	92

* Plus–minus values are means ±SD of the values recorded from 6 a.m. to 10 a.m. on days 1, 3, and 7 after enrollment in patients who were receiving mechanical ventilation in the volume-assist/control mode. PEEP denotes positive end-expiratory pressure, FiO_2 fraction of inspired oxygen, $PaCO_2$ partial pressure of arterial carbon dioxide, and PaO_2 partial pressure of arterial oxygen.
† $P<0.05$.
‡ $P<0.01$.
§ Respiratory-system compliance was calculated as the tidal volume divided by the difference between the inspiratory plateau pressure and PEEP.

group and 25.1 percent in the higher-PEEP group ($P=0.47$; 95 percent confidence interval for the difference between groups, –3.6 to 8.4 percent).

The numbers of ventilator-free and ICU-free days were similar in the two groups (Table 4). There were no significant differences in the number of days without circulatory, coagulation, hepatic, or renal failure or in the incidence of barotrauma. Changes in plasma levels of interleukin-6, surfactant protein D, and intercellular adhesion molecule

1 from day 0 to day 3 did not differ significantly between study groups (Table 5 in the Supplementary Appendix).

Because we modified the higher-PEEP protocol after 171 patients had undergone randomization, we analyzed separately the results for these 171 patients and the results for the subsequent 378 patients (Fig. 2). The differences in unadjusted and adjusted mortality rates in both phases of the trial were small and not significant. The overall mortality rate among the first 171 patients was lower than that among the subsequent 378 patients. This difference in overall mortality was associated with significant differences in several baseline characteristics that predict mortality. There was no apparent reason for these differences in baseline characteristics in the two phases of the trial other than chance variation. Baseline variables, main outcomes, and changes in plasma levels of interleukin-6, surfactant protein D, and intercellular adhesion molecule 1 from day 0 to day 3 were not significantly different between study subgroups in either the first 171 patients or the subsequent 378 patients. These analyses are available in the Supplementary Appendix. There was no significant relationship between mortality and either sex or racial or ethnic group. There was no significant interaction between study group and either sex and racial or ethnic group.

DISCUSSION

In this truncated study of 549 patients with acute lung injury and ARDS, there were no significant differences in mortality rates or the numbers of ventilator-free days, ICU-free days, or organ-failure–free days between the lower- and higher-PEEP study groups. Imbalances between the groups in some baseline characteristics (resulting from chance) could have influenced these results. However, we identified predictors of mortality in previous studies of similar patients and used this information to adjust for effects of the imbalances in baseline characteristics in the present study. Even after this adjustment, the difference in mortality between study groups was not significant. Consistent with the absence of significant differences between the study groups in clinical outcomes, we found no significant differences between study groups in the changes in plasma levels of biologic markers of inflammation and lung injury (Table 5 in the Supplementary Appendix).

It is possible that higher PEEP values reduced

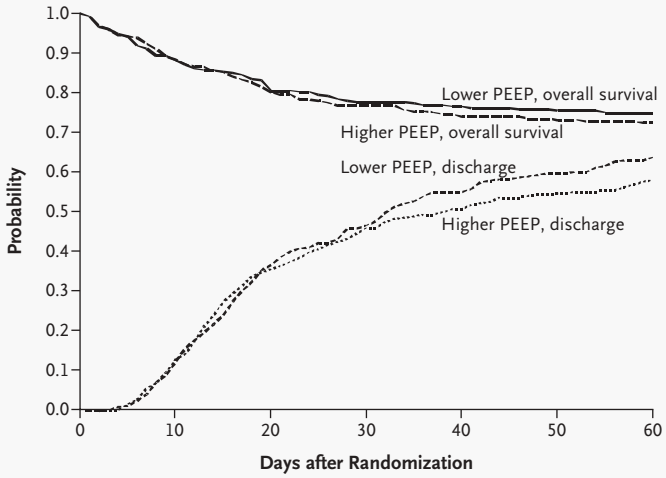

Figure 1. Probabilities of Survival and of Discharge Home While Breathing without Assistance, from the Day of Randomization (Day 0) to Day 60 among Patients with Acute Lung Injury and ARDS, According to Whether Patients Received Lower or Higher Levels of PEEP.

Table 4. Main Outcome Variables.*

Outcome	Lower-PEEP Group	Higher-PEEP Group	P Value
Death before discharge home (%)†			
Unadjusted	24.9	27.5	0.48
Adjusted for differences in baseline covariates	27.5	25.1	0.47
Breathing without assistance by day 28 (%)	72.8	72.3	0.89
No. of ventilator-free days from day 1 to day 28‡	14.5±10.4	13.8±10.6	0.50
No. of days not spent in intensive care unit from day 1 to day 28	12.2±10.4	12.3±10.3	0.83
Barotrauma (%)§	10	11	0.51
No. of days without failure of circulatory, coagulation, hepatic, and renal organs from day 1 to day 28	16±11	16±11	0.82

* Plus–minus values are means ±SD.
† The primary outcome measure was the proportion of patients who died before they were discharged home while breathing without assistance. Patients who were in health care facilities at 60 days were considered to have been discharged home while breathing without assistance.
‡ The number of ventilator-free days is the mean number of days from day 1 to day 28 on which patients had been breathing without assistance for at least 48 consecutive hours.
§ Barotrauma was defined as any new pneumothorax, pneumomediastinum, subcutaneous emphysema, or pneumatocele with a diameter of more than 2 cm after randomization.

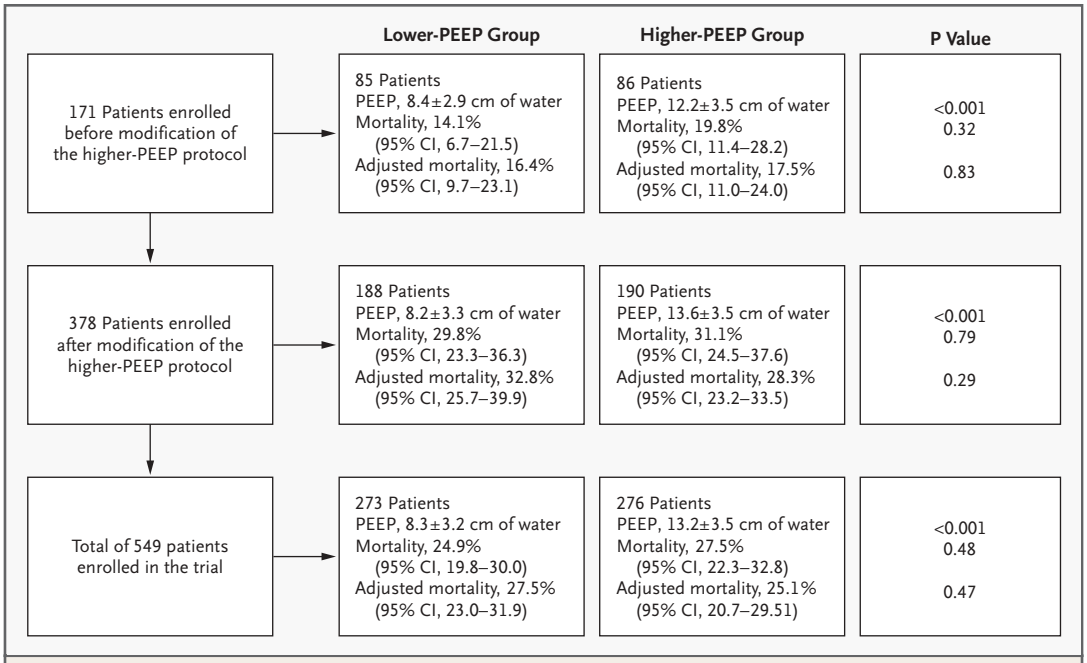

Figure 2. PEEP Levels and Mortality Rates before and after the Higher-PEEP Protocol Was Modified to Use Higher Levels of PEEP.

Values of PEEP represent means (±SD) for the first four days after randomization in patients who were receiving mechanical ventilation in the volume-assist/control mode. CI denotes confidence interval. Mortality rates were adjusted for differences between the study groups at baseline in covariates that predict mortality.

ventilator-induced lung injury from ventilation with nonaerated lung regions but that the adverse effects of higher PEEP counteracted the beneficial effects. Plateau pressures were higher in the higher-PEEP group (Table 3), suggesting that there could have been more ventilator-induced lung injury from overdistention. The mean plateau pressure in the higher-PEEP group was less than 30 cm of water, which some investigators have suggested is a safe limit. However, overdistention may occur in some patients at plateau pressures below 30 cm of water.[32-34] Higher PEEP values may also decrease cardiac output[11] and increase pulmonary edema.[12,13]

Our method for setting higher PEEP levels differed from the method used in previous studies in which higher PEEP levels were associated with better outcomes.[19,20] In those studies, higher PEEP levels were set according to the pressure-volume characteristics of each patient's respiratory system. This approach resulted in mean PEEP levels of approximately 16 cm of water during the first 36 hours and 13 cm of water on days 2 through 7. In our trial, higher PEEP levels were set and adjusted according to each patient's arterial-oxygenation response to the protocol PEEP–FiO_2 settings. This approach resulted in mean PEEP levels of approximately 15 cm of water on day 1 and 13 cm of water on days 2 through 7. The differences in PEEP levels between these trials are small. However, it is possible that higher PEEP levels in our trial would have resulted in better clinical outcomes.

In a previous study in which higher PEEP levels were associated with better survival, recruitment maneuvers (single sustained inflations of the lungs to higher airway pressures and volumes than are obtained during tidal ventilation) were conducted early in the course of the disease in the higher-PEEP group.[19] We did not conduct recruitment maneuvers in most patients in our higher-PEEP group because the effects of recruitment maneuvers on arterial oxygenation were small and transient in the first 80 patients we studied, and the practice was removed from the trial protocol.[22] It is possible that the combination of our higher-PEEP strategy and different recruitment maneuvers could have resulted in greater lung recruitment and thus

offered increased protection against ventilator-induced lung injury.

Patients in both groups received lower tidal volumes and inspiratory airway pressures, as in our previous study.[21] The resulting smaller tidal changes in lung volume and airway pressure could also have reduced the injurious mechanical forces that occur during ventilation when substantial portions of the lung are not aerated at end-expiration. If so, then the effects of higher PEEP on mortality, if any, may be small when added to a mechanical-ventilation strategy that uses lower tidal volumes and inspiratory pressures. The current trial was designed to detect larger effects, as suggested to occur in previous studies.[19,20]

Our results suggest that in patients with acute lung injury and ARDS who receive mechanical ventilation with lower tidal volumes and inspiratory pressures, raising PEEP to levels that exceed those used in our lower-PEEP strategy does not improve important clinical outcomes. In our previous study of mechanical-ventilation strategies,[21] the mortality rate before discharge home or to day 60 was 30 percent among patients who received the same lower-tidal-volume and pressure-limited strategy as was used in this study. This mortality rate is lower than the rates among patients with acute lung injury and ARDS who received mechanical ventilation with higher tidal volumes.[19,21,35,36] The mortality rate before discharge home or to day 60 for all patients in the current study was 26 percent. This finding further emphasizes the value of a strategy that uses lower tidal volumes and inspiratory pressures than were used in the past.

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APPENDIX

Participants in the National Heart, Lung, and Blood Institute (NHLBI) ARDS Clinical Trials Network were as follows: *Investigators (principal investigators are marked with an asterisk): Cleveland Clinic Foundation* — H.P. Wiedemann,* A.C. Arroliga, C.J. Fisher, Jr., J.J. Komara, Jr., P. Perez-Trepichio; *Denver Health Medical Center* — P.E. Parsons; *Denver Veterans Affairs Medical Center* — C. Welsh; *Duke University Medical Center* — W.J. Fulkerson, Jr.,* N. MacIntyre, L. Mallatratt, M. Sebastian, J. Davies, E. Van Dyne, J. Govert; *Johns Hopkins Bayview Medical Center* — J. Sevransky, S. Murray; *Johns Hopkins Hospital* — R.G. Brower, D. Thompson, H.E. Fessler, S. Murray; *LDS Hospital* — A.H. Morris,* T. Clemmer, R. Davis, J. Orme, Jr., L. Weaver, C. Grissom, F. Thomas, M. Gleich (deceased); *McKay-Dee Hospital* — C. Lawton, J. D'Hulst; *MetroHealth Medical Center of Cleveland* — J.R. Peerless, C. Smith; *San Francisco General Hospital Medical Center* — R. Kallet, J.M. Luce; *Thomas Jefferson University Hospital* — J. Gottlieb, P. Park, A. Girod, L. Yannarell; *University of California, San Francisco* — M.A. Matthay,* M.D. Eisner, J. Luce, B. Daniel, T.J. Nuckton; *University of Colorado Health Sciences Center* — E. Abraham,* F. Piedalue, R. Jagusch, P. Miller, R. McIntyre, K.E. Greene; *University of Maryland* — H.J. Silverman,* C. Shanholtz, W. Corral; *University of Michigan* — G.B. Toews,* D. Arnoldi, R.H. Bartlett, R. Dechert, C. Watts; *University of Pennsylvania* — P.N. Lanken,* J.D. Christie, B. Finkel, B.D. Fuchs, C.W. Hanson, III, P.M. Reilly, M.B. Shapiro; *University of Utah Hospital* — R. Barton, M. Mone; *University of Washington/Harborview Medical Center* — L.D. Hudson,* G. Carter, C.L. Cooper, A. Hiemstra, R.V. Maier, K.P. Steinberg, Margaret Neff, Patricia Berry-Bell; *Utah Valley Regional Medical Center* — T. Hill, P. Thaut; *Vanderbilt University* — A.P. Wheeler,* G. Bernard,* B. Christman, S. Bozeman, T. Swope, L.B. Ware; *Clinical Coordinating Center, Massachusetts General Hospital, Harvard Medical School* — D.A. Schoenfeld,* B.T. Thompson, M. Ancukiewicz, D. Hayden, MA, F. Molay, N. Ringwood, C. Oldmixon, A. Korpak, R. Morse; *NHLBI Staff* — D.B. Gail, A. Harabin,* P. Lew, M. Waclawiw*; *Steering Committee* — G.R. Bernard (chair); *Data and Safety Monitoring Board* — R.G. Spragg (chair), J. Boyett, J. Kelley, K. Leeper, M. Gray Secundy, A.S. Slutsky, B. Turnbull; *Protocol Review Committee* — J.G.N. Garcia (chair), S.S. Emerson, S.K. Pingleton, M.D. Shasby, W.J. Sibbald.

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