Positive End-Expiratory Pressure Setting in Adults With Acute Lung Injury and Acute Respiratory Distress Syndrome

A Randomized Controlled Trial

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Context The need for lung protection is universally accepted, but the optimal level of positive end-expiratory pressure (PEEP) in patients with acute lung injury (ALI) or acute respiratory distress syndrome remains debated.

Objective To compare the effect on outcome of a strategy for setting PEEP aimed at increasing alveolar recruitment while limiting hyperinflation to one aimed at minimizing alveolar distension in patients with ALI.

Design, Setting, and Patients A multicenter randomized controlled trial of 767 adults (mean [SD] age, 59.9 [15.4] years) with ALI conducted in 37 intensive care units in France from September 2002 to December 2005.

Intervention Tidal volume was set at 6 mL/kg of predicted body weight in both strategies. Patients were randomly assigned to a moderate PEEP strategy (5-9 cm H_2O) (minimal distension strategy; n=382) or to a level of PEEP set to reach a plateau pressure of 28 to 30 cm H_2O (increased recruitment strategy; n=385).

Main Outcome Measures The primary end point was mortality at 28 days. Secondary end points were hospital mortality at 60 days, ventilator-free days, and organ failure–free days at 28 days.

Results The 28-day mortality rate in the minimal distension group was 31.2% (n=119) vs 27.8% (n=107) in the increased recruitment group (relative risk, 1.12 [95% confidence interval, 0.90-1.40]; *P*=.31). The hospital mortality rate in the minimal distension group was 39.0% (n=149) vs 35.4% (n=136) in the increased recruitment group (relative risk, 1.10 [95% confidence interval, 0.92-1.32]; *P*=.30). The increased recruitment group compared with the minimal distension group had a higher median number of ventilator-free days (7 [interquartile range {IQR}, 0-19] vs 3 [IQR, 0-17]; *P*=.04) and organ failure–free days (6 [IQR, 0-18] vs 2 [IQR, 0-16]; *P*=.04). This strategy also was associated with higher compliance values, better oxygenation, less use of adjunctive therapies, and larger fluid requirements.

Conclusions A strategy for setting PEEP aimed at increasing alveolar recruitment while limiting hyperinflation did not significantly reduce mortality. However, it did improve lung function and reduced the duration of mechanical ventilation and the duration of organ failure.

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POSITIVE END-EXPIRATORY PRESsure (PEEP) is an essential component of the management of acute lung injury (ALI) and acute respiratory distress syndrome (ARDS).[1] PEEP improves hypoxemia and decreases intrapulmonary shunting, and these effects have been the basis for titrating PEEP in clinical practice.[2]

Numerous experimental studies showed that PEEP protected the lung in various models of ventilation-induced lung injury.[3-6] Although the mechanisms of this protective effect are not fully elucidated, they may be mediated by PEEP-induced alveolar recruitment, which avoids cyclic air-

See also pp 637, 691, and 693.

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way collapse and reopening, protects lung surfactant, and improves ventilation homogeneity. Although oxygenation and alveolar recruitment are often associated, the former is influenced by many other factors, including hemodynamics, and is therefore a poor surrogate for recruitment. Analysis of the volume-pressure relationship of the respiratory system has shown that alveolar recruitment occurs all along the volume-pressure relationship and depends on the airway pressure reached.[7-9] Also, a combination of small tidal volume and high PEEP was more effective than the opposite in promoting recruitment at a given maximal airway pressure.[10,11]

The recognition that tissue stress leads to ventilator-induced lung injury was a major breakthrough in the management of patients with ALI and ARDS.[12,13] The use of low tidal volumes and maintaining a plateau pressure of no more than 30 cm H_2O was found to increase survival among such patients.[12] Despite persisting controversy about the best clinical approach, limiting hyperinflation has become a major objective when selecting ventilator settings. Because higher PEEP levels may increase hyperinflation, a compromise must be found between PEEP-induced alveolar recruitment and hyperinflation.

We therefore designed a strategy using high PEEP levels to increase alveolar recruitment while avoiding excessive hyperinflation by limiting plateau pressure and using low tidal volumes. The objective of this study was to determine whether trying to increase recruitment by giving the highest possible PEEP level until a maximal plateau pressure was reached was better than a moderate PEEP level and low tidal volumes aimed at minimizing alveolar distension to manage patients with ALI and ARDS. To this end, we compared our low tidal volume plus high PEEP strategy with a low tidal volume plus moderate PEEP strategy. Mortality within the first 28 days was the primary end point of the study.

METHODS

Patients

Patients receiving endotracheal mechanical ventilation for hypoxemic acute respiratory failure were eligible if the following criteria were met for no more than 48 hours before enrollment: ratio of partial pressure of arterial oxygen over fraction of inspired oxygen (PaO_2:FIO_2) no greater than 300 mm Hg at time of enrollment, recent appearance of bilateral pulmonary infiltrates consistent with edema, and no clinical evidence of left atrial hypertension (pulmonary-capillary wedge pressure ≤18 mm Hg, when available).

Exclusion criteria were age younger than 18 years, known pregnancy, participation in another trial within 30 days before meeting the eligibility criteria, increased intracranial pressure, sickle cell disease, severe chronic respiratory disease requiring long-term oxygen therapy or home mechanical ventilation, actual body weight exceeding 1 kg/cm of height, severe burns, severe chronic liver disease (Child-Pugh class C), bone marrow transplant or chemotherapy-induced neutropenia, pneumothorax, expected duration of mechanical ventilation shorter than 48 hours, and decision to withhold life-sustaining treatment.

Design

Patients were enrolled from September 16, 2002, to December 12, 2005, at 37 intensive care units in France. The study protocol was approved for all centers by the ethics committee of the Angers University Hospital (Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale), according to French law. Written informed consent was obtained from the patients or their surrogates before study inclusion. The trial was monitored by an independent data and safety monitoring board. Patients were randomly assigned in permuted blocks stratified by center to receive either the minimal distension or the increased recruitment strategy. Patients were enrolled by designated investigators at each center. Investigators used a centralized interactive telephone system to implement random allocation. Blinding treating clinicians to group assignment was not feasible. The main analyses were conducted blindly, in particular in regard to the information given to the data and safety monitoring board.

Ventilation Strategies. In both ventilation strategies, the oxygenation goal was obtained by adjusting FIO_2 (**TABLE 1**) and tidal volume was set at 6 mL/kg of predicted body weight.[14]

In the minimal distension strategy, PEEP and inspiratory plateau pressure were kept as low as possible without falling below oxygenation targets. External PEEP was set to maintain total PEEP (the sum of external and intrinsic PEEP) between 5 and 9 cm H_2O, which are levels consistent with large surveys.[15,16]

In the increased recruitment strategy, PEEP was adjusted based on airway pressure and was kept as high as possible without increasing the maximal inspiratory plateau pressure above 28 to 30 cm H_2O, a value shown in several studies to limit the risk of distension-related lung injury[17,18]; PEEP was individually titrated based on plateau pressure, regardless of its effect on oxygenation in contrast to the PEEP FIO_2 scales used in other studies.[2,19]

All other ventilatory settings were adjusted in the same manner in the 2 groups. The volume-assist control mode was used with a low tidal volume of 6 mL/kg of predicted body weight. PEEP was reduced to 5 cm H_2O if needed to keep plateau pressure no greater than 30 cm H_2O. When plateau pressure nevertheless exceeded 32 cm H_2O, tidal volume was reduced by steps of 1 to 4 mL/kg of predicted body weight. When this procedure failed to reduce plateau pressure below 32 cm H_2O with a pH above 7.15, PEEP could be reduced below 5 cm H_2O in the minimal distension strategy only. When the oxygenation target was not achieved despite an FIO_2 of 1, PEEP was increased until total PEEP was 12 cm H_2O in the minimal distension group and until plateau pressure

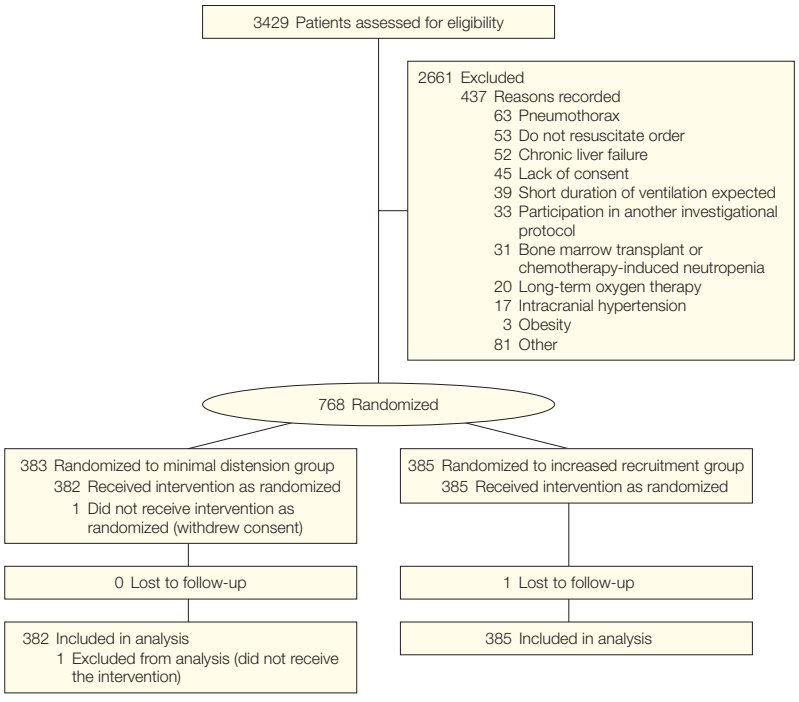
was 32 cm H_2O in the increased recruitment group. Decision trees were used to manage acidosis and hypotension secondary to ventilatory settings (the protocol can be found at http://www.chu-angers.fr/expresstrial).[20] In both groups, recruitment maneuvers were allowed but not recommended.

Table 1. Ventilation Characteristics in the Minimal Distension and Increased Recruitment Groups

Ventilator Mode	Volume-Assist Control
Tidal volume goal	6 mL/kg of predicted body weight[a]
Plateau pressure limit	≤30 cm H_2O
Ventilation rate and pH goals	≤35; adjusted for a pH between 7.30 and 7.45
Oxygenation goals	
Pa_{O_2}	55-80 mm Hg
Sp_{O_2}	88%-95%
PEEP[b]	
Minimal distension group[c]	Total PEEP between 5 and 9 cm H_2O
Increased recruitment group[d]	Plateau pressure between 28 and 30 cm H_2O
Recruitment maneuvers	Allowed but not recommended
Adjunctive therapies (prone position or inhaled nitric oxide or almitrine bismesylate)	Allowed when the oxygenation goal was not met despite F_{IO_2} ≥0.8
PEEP weaning test	
In patients with Pa_{O_2}:F_{IO_2} >150 mm Hg with F_{IO_2} ≤0.6 daily from day 4 onward; F_{IO_2} of 0.5 and PEEP of 5 cm H_2O for 20-30 min	Successful if Pa_{O_2} ≥100 mm Hg; subsequent ventilation with PEEP of 5 cm H_2O, tidal volume <10 mL/kg predicted body weight, and plateau pressure <30 cm H_2O

Abbreviations: F_{IO_2}, fraction of inspired oxygen; PEEP, positive end-expiratory pressure; Sp_{O_2}, oxygen saturation as measured by pulse oximetry.
[a]Tidal volume could be decreased to a minimal value of 4 mL/kg of predicted body weight in both groups in case of plateau pressure higher than 32 cm H_2O or it could be increased to a maximal value of 8 mL/kg of predicted body weight in case of severe acidosis defined as arterial pH lower than 7.15.
[b]Total PEEP was defined as the sum of applied PEEP and intrinsic PEEP.
[c]PEEP could be increased up to a total PEEP of 12 cm H_2O if the oxygenation goal was not met despite an F_{IO_2} of 1.
[d]PEEP could not be increased to a value resulting in a total PEEP higher than 20 cm H_2O unless the oxygenation goals were not met despite an F_{IO_2} of 1.

Figure 1. Flow Diagram of the Trial



Weaning Protocol. In both groups, weaning from the ventilator and from PEEP followed the same protocol. Although weaning could be started before day 4 if deemed appropriate by the attending physician, the protocol required that from day 4 onward, a daily PEEP weaning trial was performed if the Pa_{O_2}:F_{IO_2} ratio was greater than 150 mm Hg and F_{IO_2} was no greater than 0.6 (Table 1). The F_{IO_2} was set at 0.5 and PEEP decreased to 5 cm H_2O. Arterial blood gas was sampled after 20 to 30 minutes. Previous ventilatory settings were resumed if transcutaneous oxyhemoglobin saturation decreased below 88% during the procedure or if Pa_{O_2}:F_{IO_2} was below 200 mm Hg. When Pa_{O_2}:F_{IO_2} was no lower than 200 mm Hg, the patient was considered to have acceptable gas exchange on 5 cm H_2O of PEEP. The physician decided whether to use assist-control or pressure-support ventilation and chose settings that kept tidal volume below 10 mL/kg of predicted body weight and inspiratory pressure (in pressure support ventilation) or plateau pressure (in assist-control mode) below 30 cm H_2O with a PEEP of 5 cm H_2O.

The weaning trigger value (Pa_{O_2}:F_{IO_2} >150 mm Hg) and the abort value (<200 mm Hg) were different for 2 reasons. First, the weaning trigger value was set to avoid inducing an unwanted disadvantage in the low PEEP group, which was expected to have lower levels of oxygenation. Second, the values were different because it was possible that oxygenation could improve when removing higher levels of PEEP because the original PEEP setting was not titrated based on oxygenation.

Criteria for a spontaneous breathing test were a successful PEEP weaning test and presence of the following: no infusion of vasopressor agents or sedatives, adequate responses to simple commands, and cough during suctioning. The test consisted of breathing spontaneously for up to 2 hours dis-

connected from the ventilator on a T-piece providing humidified oxygen, or in pressure-support ventilation with an inspiratory pressure of 7 cm H_2O. Based on the results of the test, the physician decided whether to extubate the patient.

Outcome Measures and Data Collection

The primary evaluation criterion was the proportion of patients who died within 28 days after randomization. Secondary criteria were 60-day mortality, hospital mortality censored on day 60, numbers of ventilator-free days and organ failure–free days from day 1 to day 28, and the proportion of patients who experienced pneumothorax requiring chest tube drainage between day 1 and day 28.

Data were collected at the time of randomization to characterize severity of underlying medical conditions, severity of acute illness,[21] ventilatory settings, arterial blood gases, and history and cause of lung injury. In patients experiencing pneumonia and septic shock, pneumonia was considered the main cause of lung injury. Patients were monitored daily for 28 days for ventilatory conditions, arterial blood gases, cointerventions, and organ failures. Septic shock was defined according to international consensus conference criteria.[22] Organ failures were defined using the organ dysfunctions and infection (ODIN) score.[23] Patients were followed up until day 60 after randomization or death. The number of ventilator-free days to day 28 was defined as the number of days of unassisted breathing to day 28 after randomization, assuming a patient survives and remains free of invasive or noninvasive assisted breathing for at least 2 consecutive calendar days after extubation, whatever the vital status at day 28. For all other organ failures, the number of organ failure–free days was defined as the number of days alive and free of organ failure as defined in the ODIN score, whatever the vital status at day 28. Vital status at day 60 was assessed by telephone contact for patients discharged home before day 60.

Statistical Analysis

Sample size calculations showed that assuming a 40% mortality rate in the control group, 400 patients per group would provide 80% power at a 2-sided α level of .05 to detect a 10% absolute reduction in mortality. This sample size estimate and power calculation were based on conventional calculation for fixed-sample design.

We conducted a sequential, symmetric trial analysis using the double triangular test[24] to monitor the primary end point. With this sequential design, the data are examined periodically throughout patient recruitment. We conducted an interim analysis at each increment of 40 new individuals with available primary end points. Each interim analysis consisted of calculating test statistics and comparing the results with straight-line stopping boundaries; the Christmas tree correction[24] was applied to the continuous boundaries to adjust for discrete monitoring. After the 18th interim analysis, the data and safety monitoring board decided to terminate the study.

All analyses were conducted on an intention-to-treat basis. Differences between groups were assessed with the *t* test or the Mann-Whitney test for continuous variables and the χ^2 test or Fisher exact test for categorical variables. Probability of mortality and time-

Table 2. Baseline Characteristics of the Patients

Characteristic	Minimal Distension (n = 382)	Increased Recruitment (n = 385)
Age, mean (SD), y	60 (15)	60 (16)
Female sex, No. (%)	126 (33)	125 (32)
SAPS II score, mean (SD)[a]	49 (16)	50 (16)
Septic shock, No. (%)[b]	229 (60)	242 (63)
No. of organ failures in addition to respiratory failure, mean (SD)[c]	1.4 (1.0)	1.4 (1.0)
Time since onset of acute lung injury or ARDS, mean (SD), h	27.1 (24.5)	25.1 (21.7)
Respiratory measures, mean (SD)		
Tidal volume, mL/kg of predicted body weight	7.5 (1.5)	7.4 (1.4)
Minute ventilation, L/min	11.5 (3.1)	11.5 (2.8)
Respiratory rate, cycles/min	24.7 (5.8)	24.4 (6.0)
PEEP, cm H_2O	7.9 (3.3)	8.2 (3.7)
Plateau pressure, cm H_2O	22.9 (5.3)	23.7 (4.9)
Respiratory system compliance, mL/cm H_2O[d]	36.1 (13.8)	36.4 (14.6)
Pa_{O_2}:F_{IO_2}, mm Hg	143 (57)	144 (58)
Cause of lung injury, No. (%)		
Pneumonia	198 (52)	194 (50)
Aspiration	88 (23)	76 (20)
Intra-abdominal sepsis	28 (7)	32 (8)
Other sepsis	18 (5)	21 (5)
Acute pancreatitis	12 (3)	10 (3)
Other[e]	38 (10)	52 (14)

Abbreviations: ARDS, acute respiratory distress syndrome; F_{IO_2},fraction of inspired oxygen; PEEP, positive end-expiratory pressure; SAPS II, Simplified Acute Physiologic Score.

[a] Used to assess severity of illness and can range from 0 to 163, with higher scores indicating a higher probability of death.[21]

[b] Defined according to international consensus conference criteria.[22]

[c] Cardiovascular, neurological, hepatic, renal, and hematological failures were defined according to the ODIN (organ dysfunctions and/or infection) score.[23]

[d] Calculated as the tidal volume divided by the difference between plateau pressure and total PEEP (applied PEEP + intrinsic PEEP) or PEEP if total PEEP was not measured.

[e] Multiple transfusions of blood products (n = 10), shock (n = 7), intra-alveolar hemorrhage (n = 7), cardiopulmonary bypass (n = 5), severe trauma (n = 5), near drowning (n = 4), vasculitis (n = 3), heat stroke (n = 2), drug-induced pneumonia (n = 2), pulmonary contusion (n = 2), miscellaneous (n = 20), indeterminate (n = 23).

to-unassisted breathing curves were constructed and differences between the groups were compared using the log-rank test. Continuous data are reported as mean (SD) or median (interquartile range [IQR]) and categorical data as percentages with 95% confidence intervals (CIs) calculated with normal approximation. The sequential analysis was conducted using the statistical software PEST, version 4 (MPS, Reading, England). All reported *P* values are 2-sided. *P* values no greater than .05 were taken to indicate statistical significance.

RESULTS

Study Population

We prospectively screened patients at 37 intensive care units in France between September 16, 2002, and December 12, 2005. Among 3429 screened patients, 768 were enrolled (mean [SD] age, 59.9 [15.4 years]) (FIGURE 1). The study was stopped by the data and safety monitoring board at the 18th interim analysis because according to the triangular test a stopping boundary indicating an absence of 10% absolute reduction in mortality was crossed. One patient's family withdrew consent after randomization and the patient was excluded. Complete follow-up data were available for all 382 patients in the minimal distension group. One of the 385 patients in the increased recruitment group was lost to follow-up after discharge on day 29.

Baseline characteristics of the patients are indicated in TABLE 2. At inclusion, 95% of the patients were ventilated with a total PEEP equal or higher than 5 cm H_2O, and 84% had a PaO_2:FIO_2 equal to or lower than 200 mm Hg, indicating ARDS. The 2 study groups were balanced at baseline with regard to age, severity of illness, number of organ failures, proportion in septic shock, ventilation and oxygenation parameters, and causes of lung injury.

Respiratory Variables

Respiratory variables on days 1, 3, and 7 are reported in TABLE 3. Tidal volume was close to 6 mL/kg of predicted body weight in both groups as planned by the study design. Respiratory rate, minute ventilation, pH, and $PaCO_2$ did not differ except for a small pH difference on day 1. In the increased recruit-

Table 3. Respiratory Variables During the First 7 Days of Treatment[a]

	Day 1			Day 3			Day 7		
Variable	Minimal Distension	Increased Recruitment	*P* Value	Minimal Distension	Increased Recruitment	*P* Value	Minimal Distension	Increased Recruitment	*P* Value
Tidal volume, mL/kg of predicted body weight	6.1 (0.4)	6.1 (0.3)	.57	6.2 (0.6)	6.2 (0.5)	.83	6.4 (0.9)	6.8 (1.3)	.001
No. of patients	372	379		322	332		210	192	
Plateau pressure, cm H_2O	21.1 (4.7)	27.5 (2.4)	<.001	20.7 (5.0)	26.5 (4.2)	<.001	21.1 (5.6)	24.3 (5.8)	<.001
No. of patients	365	378		314	329		173	163	
Respiratory rate, cycles/min	27.8 (5.4)	28.2 (5.4)	.32	27.8 (5.7)	28.2 (6.1)	.39	27.4 (6.4)	26.5 (7.1)	.13
No. of patients	371	377		331	346		250	242	
Minute ventilation, L/min	11.2 (2.8)	11.3 (2.7)	.39	11.3 (2.8)	11.5 (2.7)	.36	12.0 (3.0)	12.2 (3.0)	.55
No. of patients	369	376		331	348		245	233	
FIO_2	0.66 (0.21)	0.55 (0.19)	<.001	0.58 (0.20)	0.46 (0.17)	<.001	0.54 (0.20)	0.49 (0.17)	.001
No. of patients	372	380		333	351		266	252	
PEEP, cm H_2O	7.1 (1.8)	14.6 (3.2)	<.001	6.7 (1.8)	13.4 (4.7)	<.001	6.2 (2.1)	8.9 (5.1)	<.001
No. of patients	372	380		333	351		264	252	
Total PEEP, cm H_2O[b]	8.4 (1.9)	15.8 (2.9)	<.001	8.1 (2.0)	15.1 (4.3)	<.001	8.0 (2.5)	12.0 (5.4)	<.001
No. of patients	336	343		274	284		154	138	
PaO_2/FIO_2	150 (69)	218 (97)	<.001	175 (81)	245 (98)	<.001	184 (79)	206 (85)	.003
No. of patients	371	378		331	350		262	247	
Respiratory system compliance, mL/cm H_2O[c]	33.7 (14.3)	37.2 (22.7)	.01	35.2 (16.5)	37.9 (16.7)	.04	35.5 (17.0)	40.1 (29.1)	.08
No. of patients	365	378		314	329		171	163	
PaO_2, mm Hg	89 (34)	108 (43)	<.001	91 (37)	102 (38)	<.001	89 (30)	91 (27)	.30
No. of patients	371	378		331	351		262	247	
$PaCO_2$, mm Hg	43 (9)	44 (8)	.64	43 (10)	43 (8)	.68	43 (10)	42 (11)	.41
No. of patients	371	379		331	351		262	248	
Arterial pH	7.36 (0.10)	7.34 (0.10)	.03	7.40 (0.08)	7.39 (0.08)	.09	7.42 (0.07)	7.42 (0.09)	.95
No. of patients	371	379		331	351		262	248	

Abbreviations: FIO_2, fraction of inspired oxygen; PEEP, positive end-expiratory pressure.
[a] Data are presented as mean (SD) of values recorded from 6 AM to 12 AM on days 1, 3, and 7 after enrollment among patients who were receiving mechanical ventilation.
[b] Defined as the sum of applied PEEP and intrinsic PEEP.
[c] Calculated as the tidal volume divided by the difference between the inspiratory plateau pressure and total PEEP or PEEP if total PEEP was not measured.

ment group, PEEP, total PEEP, and plateau pressure were considerably higher at each time point, and respiratory system compliance and oxygenation were significantly better, explaining the lower F_{IO_2} value. On day 1, the mean (SD) total PEEP was 15.8 (2.9) cm H_2O in the increased recruitment group vs 8.4 (1.9) cm H_2O in the minimal distension group ($P<.001$). The mean (SD) plateau pressure was 27.5 (2.4) cm H_2O in the increased recruitment group vs 21.1 (4.7) cm H_2O in the minimal distension group ($P<.001$). Within each group, patients with ALI but without ARDS and patients with ARDS received the same levels of PEEP (mean [SD] day 1 PEEP level for patients without ARDS was 6.9 [1.4] and for patients with ARDS was 7.2 [1.9] cm H_2O in the minimal distension group [$P=.22$] and 15.0 [2.8] and 14.6 [3.2] cm H_2O, respectively, in the increased recruitment group [$P=.35$]). Only 13 patients (3.4%) in the minimal distension group and 18 patients (4.7%) in the increased recruitment group had successfully passed the PEEP weaning test before day 4 ($P=.37$).

Adverse Events

The incidence of pneumothorax requiring drainage was low and similar in both groups (TABLE 4). In the increased recruitment group, more patients required fluid loading for hemodynamic support, and the amount of fluid was higher by approximately 400 mL over the first 72 hours (TABLE 5). There was no difference, however, in the number of patients requiring vasopressive therapy. The total rate of extubation failure was not different between the 2 groups (23.1% in the minimal distension group vs 21.1% in the increased recruitment group; $P=.61$).

Prespecified Evaluation Criteria

The 28-day mortality rate for the minimal distension group was 31.2% (95% CI, 26.5%-35.8%) vs 27.8% (95% CI, 23.3%-32.3%) in the increased recruitment group (relative risk [RR], 1.12 [95% CI, 0.90-1.40] [$P=.31$]; Table 4 and FIGURE 2). Differences were not found between the groups for 60-day mortality (RR, 1.10 [95% CI, 0.92-1.32]) or hospital mortality (RR, 1.10 [95% CI, 0.92-1.32]). In the increased recruitment group compared with the minimal distension group, there were significantly more ventilator-free days (median, 7 [IQR, 0-19] vs 3 [IQR, 0-17]; $P=.04$) and organ failure–free days (median, 6 [IQR, 0-18]) vs 2 [IQR, 0-16]; $P=.04$).

FIGURE 3 shows day 28 mortality rates in the 2 groups according to the Pa_{O_2}:F_{IO_2} quartile before randomization. There was no significant interaction between the Pa_{O_2}:F_{IO_2} quartile and the randomization group ($P=.40$). Outcome results for patients with ARDS only are shown in Figure 2. The difference for the probability of breathing without assistance between the 2 groups was more pronounced ($P=.003$), but the

Table 4. Main Outcome Variables

Outcome	Minimal Distension (n = 382)	Increased Recruitment (n = 385)	*P* Value
	No. (%)		
Death in the first 28 d[a]	119 (31.2)	107 (27.8)	.31
Death before hospital discharge	149 (39.0)	136 (35.4)	.30
Death in the first 60 d	151 (39.5)	138 (35.9)	.31
Pneumothorax between day 1 and day 28[b]	22 (5.8)	26 (6.8)	.57
	Median (IQR)		
No. of days between day 1 and day 28			
Ventilator-free[c]	3 (0-17)	7 (0-19)	.04
Organ failure–free[d]	2 (0-16)	6 (0-18)	.04
Cardiovascular failure–free[d]	21 (4-26)	23 (10-26)	.09
Renal failure–free[d]	27.5 (8.0-28.0)	28.0 (11.0-28.0)	.23

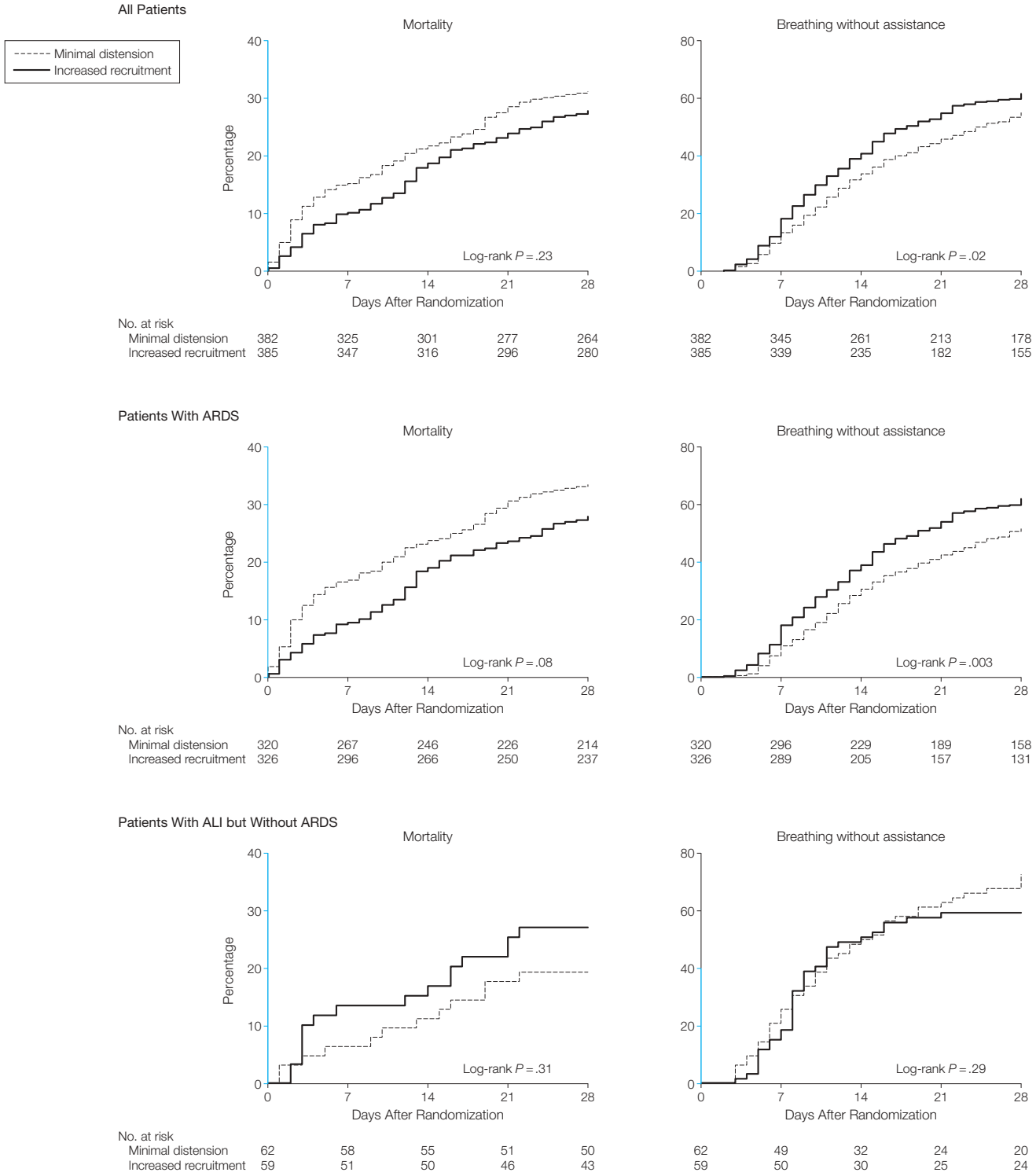
Abbreviation: IQR, interquartile range.
[a] The primary evaluation criterion was the proportion of patients who died within 28 days after inclusion.
[b] Defined as the need for chest tube drainage.
[c] Median number of days of unassisted breathing to day 28 after randomization, assuming a patient survives and remains free of assisted breathing for at least 2 consecutive calendar days after extubation.
[d] Median number of days between day 1 and day 28 on which patients were free of respiratory, cardiovascular, renal, neurological, hepatic, and hematological failure as defined by the ODIN (organ dysfunctions and infection) score.[23]

Table 5. Cointerventions and Adjunctive Therapies

Intervention	No. (%)[a] Minimal Distension (n=382)	No. (%)[a] Increased Recruitment (n=385)	*P* Value
During the first 72 h			
Fluid loading	255 (66.8)	290 (75.3)	.01
Volume of fluids, median (IQR), L[b]	0.5 (0-1.5)	1.0 (0.1-2.2)	<.001
During the first 7 d			
Epinephrine or norepinephrine	286 (74.9)	289 (75.1)	.95
Corticosteroids	198 (51.8)	199 (51.7)	.97
Neuromuscular blockade	209 (54.7)	204 (53)	.63
Recruitment maneuvers	49 (12.8)	27 (7.0)	.007
Adjunctive therapies during the first 7 d			
Prone position	72 (18.8)	34 (8.8)	<.001
Inhaled nitric oxide	98 (25.7)	57 (14.8)	<.001
Almitrine bismesylate	25 (6.5)	14 (3.6)	.07
Any therapy	132 (34.6)	72 (18.7)	<.001
Mortality in patients who received rescue therapy	62 (47.0)	37 (51.4)	.55

Abbreviation: IQR, interquartile range.
[a] Unless otherwise indicated.
[b] Total volume of colloids and/or crystalloids given as bolus injections.

Figure 2. Probabilities of Death and Breathing Without Assistance From the Day of Randomization (Day 0) to Day 28



Among patients with acute lung injury (ALI) and acute respiratory distress syndrome (ARDS), positive end-expiratory pressure (PEEP) was set to achieve minimal distension or increased recruitment. Among patients with ARDS only, PEEP was set to achieve minimal distension (n=320) or increased recruitment (n=326). Among patients with ALI but without ARDS, PEEP was set to achieve minimal distension (n=62) or increased recruitment (n=59). Regions of y-axes shown in blue indicate range of 0% to 40%.

difference in mortality failed to reach statistical significance ($P=.08$).

Adjunctive Treatments

Compared with the minimal distension group, significantly less patients in the increased recruitment group received rescue therapy for severe hypoxemia (34.6% vs 18.7; $P<.001$; Table 5). Patients receiving rescue therapy had a high 28-day mortality rate in both of the study groups (47.0% in the minimal distension group vs 51.4% in the increased recruitment group; $P=.55$). Steroids, which were used mainly for septic shock, were given to similar numbers of patients in the 2 groups (Table 5).

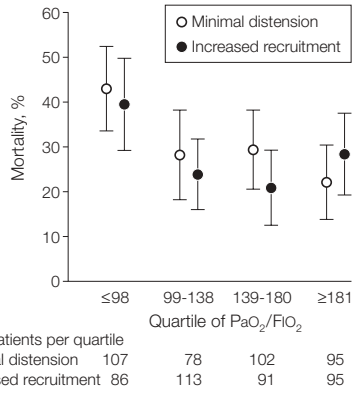
COMMENT

In a large cohort of patients with ALI and ARDS, a ventilatory strategy designed to increase recruitment while limiting overdistension significantly reduced the time spent on mechanical ventilation and with organ failures but failed to reduce 28-day or 60-day mortality. Oxygenation and respiratory system compliance also were improved with this strategy, which was associated with reduced use of rescue techniques for improving oxygenation, such as the prone position or inhaled nitric oxide. The increased recruitment strategy was not associated with increased barotrauma. It induced a modest but significant increase in fluid requirements. This strategy used a tidal volume of 6 mL/kg of predicted body weight, which is currently recommended for lung protection.

A unique feature of the ventilation strategies used in our study was PEEP titration based on plateau pressure, which was used as a surrogate for alveolar distension as opposed to oxygenation. The improvements in secondary evaluation criteria achieved using the increased recruitment strategy in our study can be compared with the results of randomized controlled studies in which the tested strategy involved setting PEEP according to individual pressure volume curves.[25-27] In these studies, a higher level of PEEP was associated with better outcomes. By contrast, the largest trial to date comparing 2 approaches for titrating PEEP and FIO_2 relied solely on oxygenation criteria and found no significant difference in favor of a higher level of PEEP.[2] Although recruitment and oxygenation often vary in tandem, some patients with limited ability to recruit alveoli may receive higher PEEP levels because of a poor oxygenation response to PEEP; in these patients, higher PEEP levels may be deleterious. A recent physiological study in a small group of patients with ARDS showed that using a scale of PEEP vs FIO_2 may fail to induce recruitment in some patients, leading to overdistension instead.[19] We chose not to incorporate recruitment maneuvers in our strategy because both their efficacy and their safety have been challenged.[28,29] Another advantage of the strategy is its applicability at the bedside because PEEP settings and plateau pressure are determined from simple measurements available on all modern ventilators.

A potential strength of the increased recruitment strategy is the PEEP weaning procedure. On the one hand, we did not immediately wean off high levels of PEEP to maintain alveolar recruitment for a sufficient period, which may have contributed to its beneficial effects. On the other hand, this PEEP weaning procedure may have protected patients from unnecessarily prolonged periods of ventilation with high levels of PEEP, which may induce adverse effects. Also, because patients receiving higher levels of PEEP had higher PaO_2:FIO_2 ratios, one may suspect that they could qualify for a PEEP weaning trial sooner than would have occurred had they been randomized to the study group with lower levels of PEEP. The PEEP levels in the low distension group (mean [SD], 6.7 [1.8] cm H_2O at day 3), however, were on average very close to the 5 cm H_2O level chosen for weaning from PEEP. Because the threshold for testing PEEP was relatively low (PaO_2:FIO_2 ratio >150 mm Hg), this could have been easily achieved at the same rate in this group if PEEP had only a cosmetic effect. An easier weaning from PEEP could also reflect a specific effect of higher levels of PEEP, allowing a better lung recruitment and a better tolerance of a decreased PEEP level than in the minimal distension group.

Figure 3. Day 28 Mortality Rates in Patients With Acute Lung Injury and Acute Respiratory Distress Syndrome



No. of patients per quartile				
Minimal distension	107	78	102	95
Increased recruitment	86	113	91	95

Error bars indicate 95% confidence intervals. A total of 382 were assigned to the minimal distension strategy and 385 to the increased recruitment strategy. Day 28 mortality according to the quartile of the ratio of partial pressure of arterial oxygen over fraction of inspired oxygen (PaO_2:FIO_2) before randomization. The interaction between the study group and the PaO_2:FIO_2 quartile at baseline was not significant ($P=.40$).

The increased recruitment strategy was not associated with a significant improvement in mortality. We cannot rule out a survival benefit, which would require greater statistical power to detect than that afforded by our study. Alternatively, benefits from higher levels of PEEP in a subset of patients may have been canceled out by adverse effects in another subset. Although the mean hemodynamic effects were small, the significant increase in fluid requirements possibly reflected poor tolerance of higher levels of PEEP in some patients. The need for vasopressors or number of days free from cardiovascular failure, however, did not suggest worse hemodynamics in the higher level of PEEP strategy. Higher levels of PEEP may benefit only those patients with a high potential for alveolar recruitment.[30] The potential for PEEP-induced recruitment varies widely

across patients and correlates with lung injury severity, most notably oxygenation impairment.[30] Analysis of patients with ALI without ARDS and the post hoc analysis based on oxygenation impairment at study enrollment (Figure 2 and Figure 3) suggests that compared with ARDS, mild lung injury may be associated with less benefits and more adverse effects from high levels of PEEP. Mortality tended to improve and extubation occurred earlier in the ARDS group, whereas the opposite trend was observed in the group with ALI but without ARDS. These results suggest that the strategy of a high level of PEEP and low tidal volume should be used with caution in patients with ALI not reaching the criteria for ARDS.

Despite higher plateau pressures, several secondary outcomes were significantly better in the increased recruitment group than in the minimal distension group. Although firm recommendations for using a lung protective strategy are still essential, this finding suggests that lowering the plateau pressure may not be the sole priority in all patients with ARDS. At a given plateau pressure, different PEEP tidal volume combinations have different effects on recruitment and lung injury.[5,10,11] Whether the plateau pressure used in our study is safe cannot be determined from our data however, and the benefits of reducing overdistension with lower plateau pressures must be weighed against the adverse effects of reduced alveolar recruitment and lung homogenization. Further studies may be required to search for the best compromise.

Our study has a number of limitations. The unblinded nature of the study, coupled with the use of adjunctive interventions left to the discretion of the attending physician in case of severe hypoxemia, could confound our results. We believe that the high use of rescue therapy reflects current practice in France,[31] and that inhaled nitric oxide and prone therapy were used by physicians when faced with hypoxemia that they considered to be life threatening. As such, the significant reduction in the use of rescue therapy is of great interest, especially with regard to the high mortality of these patients. In comparison with prior studies of ALI and ARDS, relatively few of our patients presented with ARDS secondary to nonpulmonary causes. However, part of the explanation may be because any patient with pneumonia was considered to have ARDS due to pneumonia, even if there was septic shock or other nonpulmonary ARDS risk factors.

In conclusion, we could not demonstrate that a lung recruitment strategy of increasing level of PEEP to maintain plateau pressures at 28 to 30 cm H_2O improved mortality in adults with ALI undergoing low tidal volume mechanical ventilation. Nevertheless, secondary outcomes suggest morbidity may be improved, as reflected by improved ventilator-free and organ failure–free days. Furthermore, although individuals randomized to higher levels of PEEP required more intravenous fluid, there was no evidence of harm and reduced use of rescue therapies.

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