

Ventilation Strategy Using Low Tidal Volumes, Recruitment Maneuvers, and High Positive End-Expiratory Pressure for Acute Lung Injury and Acute Respiratory Distress Syndrome

A Randomized Controlled Trial

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ACU TE LUNG INJURY AND ACUTE respiratory distress syndrome (ARDS, the most severe form of acute lung injury), are potentially devastating complications of critical illness.¹ Arising in response to direct lung injury (eg, pneumonia) or intense systemic inflammation (eg, sepsis),² the pathogenesis involves pulmonary edema, diffuse cellular destruction, alveolar collapse, and disordered repair. Mor-

See also pp 646, 691, and 693.

Context Low-tidal-volume ventilation reduces mortality in critically ill patients with acute lung injury and acute respiratory distress syndrome. Instituting additional strategies to open collapsed lung tissue may further reduce mortality.

Objective To compare an established low-tidal-volume ventilation strategy with an experimental strategy based on the original "open-lung approach," combining low tidal volume, lung recruitment maneuvers, and high positive-end-expiratory pressure.

Design and Setting Randomized controlled trial with concealed allocation and blinded data analysis conducted between August 2000 and March 2006 in 30 intensive care units in Canada, Australia, and Saudi Arabia.

Patients Nine hundred eighty-three consecutive patients with acute lung injury and a ratio of arterial oxygen tension to inspired oxygen fraction not exceeding 250.

Interventions The control strategy included target tidal volumes of 6 mL/kg of predicted body weight, plateau airway pressures not exceeding 30 cm H₂O, and conventional levels of positive end-expiratory pressure (n=508). The experimental strategy included target tidal volumes of 6 mL/kg of predicted body weight, plateau pressures not exceeding 40 cm H₂O, recruitment maneuvers, and higher positive end-expiratory pressures (n=475).

Main Outcome Measure All-cause hospital mortality.

Results Eighty-five percent of the 983 study patients met criteria for acute respiratory distress syndrome at enrollment. Tidal volumes remained similar in the 2 groups, and mean positive end-expiratory pressures were 14.6 (SD, 3.4) cm H₂O in the experimental group vs 9.8 (SD, 2.7) cm H₂O among controls during the first 72 hours ($P < .001$). All-cause hospital mortality rates were 36.4% and 40.4%, respectively (relative risk [RR], 0.90; 95% confidence interval [CI], 0.77-1.05; $P = .19$). Barotrauma rates were 11.2% and 9.1% (RR, 1.21; 95% CI, 0.83-1.75; $P = .33$). The experimental group had lower rates of refractory hypoxemia (4.6% vs 10.2%; RR, 0.54; 95% CI, 0.34-0.86; $P = .01$), death with refractory hypoxemia (4.2% vs 8.9%; RR, 0.56; 95% CI, 0.34-0.93; $P = .03$), and previously defined eligible use of rescue therapies (5.1% vs 9.3%; RR, 0.61; 95% CI, 0.38-0.99; $P = .045$).

Conclusions For patients with acute lung injury and acute respiratory distress syndrome, a multifaceted protocolized ventilation strategy designed to recruit and open the lung resulted in no significant difference in all-cause hospital mortality or barotrauma compared with an established low-tidal-volume protocolized ventilation strategy. This "open-lung" strategy did appear to improve secondary end points related to hypoxemia and use of rescue therapies.

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tal and health care costs are high,³ and long-term survivors experience serious morbidity.⁴

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Although mechanical ventilation provides essential life support, it can worsen lung injury. Mechanisms include regional alveolar overdistention, repetitive alveolar collapse with shearing (atelectrauma), and oxygen toxicity.⁵ A pivotal multicenter trial established the importance of overdistention by demonstrating that ventilation with lower tidal volumes vs traditional tidal volumes (6 vs 12 mL/kg) improves survival.⁶ This specific low-tilal-volume strategy has become the standard for comparison in evaluations of newer strategies for lung protection. Experimental data suggest that atelectrauma is prominent in ARDS.^{7,8} Consequently, atelectrauma might be another important contributor to ARDS mortality. Atelectrauma may be mitigated by recruitment maneuvers (periodic hyperinflations) to open collapsed lung tissue and high levels of positive end-expiratory pressure (PEEP) to prevent further collapse. In theory,

ventilation strategies that combine low tidal volumes with prevention of atelectrauma would be ideal for lung protection.

Support for this theory comes from 2 randomized trials that combined low tidal volumes with high PEEP (and, in 1 study, recruitment maneuvers) and observed significant mortality reductions in patients with established ARDS.^{9,10} Both trials used more traditional tidal volumes in the control group; thus, the incremental benefit of high levels of PEEP and recruitment maneuvers, beyond that achieved with low tidal volumes and lower PEEP, remains uncertain. A third trial specifically investigated the incremental effect of high levels of PEEP.¹¹ After stopping early for perceived futility, the sample of 549 patients provided a result that could not rule out either an important mortality reduction or an increase with the high PEEP strategy.

The objective of the present trial was to examine the effect on mortality of a

multifaceted “lung open ventilation” (LOV) strategy combining low tidal volumes, recruitment maneuvers, and high levels of PEEP compared with an established low-tilal-volume strategy in patients with moderate and severe lung injury.

METHODS

We enrolled patients from August 2000 to March 2006 in 30 hospitals in Canada, Australia, and Saudi Arabia. The research ethics board of each hospital approved the trial, and legal substitute decision makers for each patient provided either written or oral informed consent.

Participants

We included patients with both acute lung injury and ARDS, defined by the onset of new respiratory symptoms within 28 days and bilateral opacifications on chest radiograph, and requiring a ratio of arterial oxygen tension to inspired oxygen fraction ($\text{PaO}_2/\text{FiO}_2$) less than or equal to 250 during invasive mechanical ventilation. The launch of this trial preceded recent studies suggesting the desirability of patient assessments on standard ventilator settings. We excluded patients with left atrial hypertension, as diagnosed by the attending physician, as the primary cause of respiratory failure; anticipated duration of mechanical ventilation of less than 48 hours; inability to wean from experimental strategies (eg, nitric oxide); severe chronic respiratory disease; neuromuscular disease that would prolong mechanical ventilation; intracranial hypertension; morbid obesity; pregnancy; lack of commitment to life support; premorbid

Table 1. Protocol Components

Component Variables	Control Ventilation Strategy	Lung Open Ventilation Strategy
Ventilator mode	Volume-assist control	Pressure control
Tidal volume target, mL/kg predicted body weight	6	6
Tidal volume range, mL/kg predicted body weight	4-8	4-8
Plateau airway pressure, cm H ₂ O	≤30	≤40
Positive end-expiratory pressure, cm H ₂ O	See Table 2	See Table 2
Partial pressure of oxygen, arterial, mm Hg	55-80	55-80
Oxygen saturation as measured by pulse oximetry, %	88-93	88-93
pH	≥7.30	≥7.30
Ventilator rate, breaths/min	≤35	≤35
Inspiration:expiration time	1:1-1:3	1:1-1:3
Recruitment maneuvers	Not permitted	After ventilator disconnects

Table 2. Allowable PEEP Ranges at Specified Levels of FiO_2 ^a

	Fraction of Inspired Oxygen (FiO_2)							
	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0
Control PEEP ranges, cm H ₂ O	5	5-8	8-10	10	10-14	14	14-18	18-24
Lung open ventilation PEEP ranges, cm H ₂ O								
Before protocol change	5-10	10-14	14-20	20	20	20	20	20-24
After protocol change	5-10	10-18	18-20	20	20	20-22	22	22-24

Abbreviation: PEEP, positive end-expiratory pressure.

^aBoth ventilation strategies included a protocol for reducing PEEP when plateau pressure exceeded the assigned plateau pressure limit or when mean arterial pressure decreased to less than 60 mm Hg, whether or not this occurred in the setting of an increase in PEEP.

conditions with an expected 6-month mortality risk exceeding 50%; greater than 48 hours of eligibility; and participation in a confounding trial.

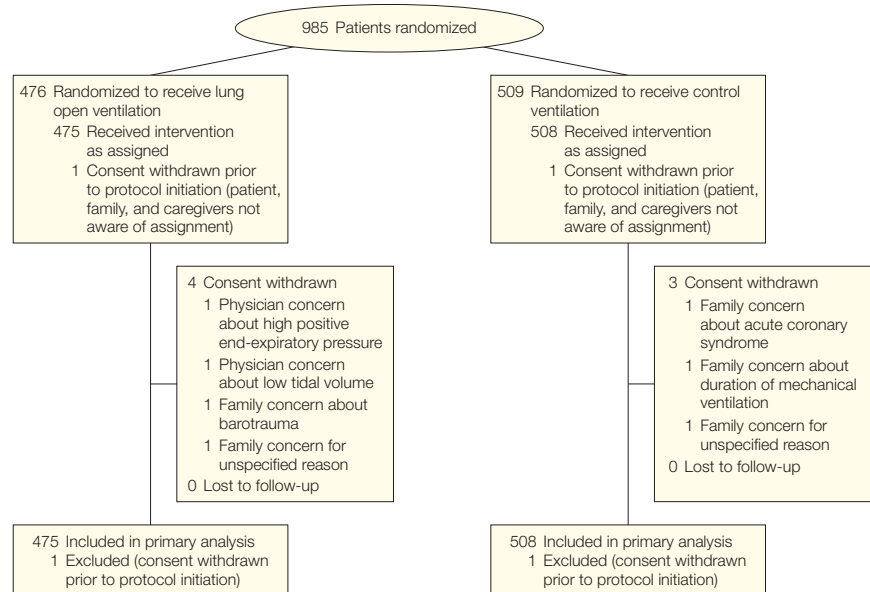
We concealed randomization using a central computerized telephone system and stratified enrollment by site using variable permuted blocks. At the end of the trial, we noted an unexpected difference in the number of patients allocated to each group and found that in high-volume hospitals with rapid enrollment and in newly participating centers, a programming error occurring late in the study had disrupted the specified randomization blocks. Sensitivity analyses indicated that this error did not undermine randomization.

Ventilator Procedures

The experimental ventilation strategy was based on a previously defined "open-lung approach"⁹ including pressure control mode; target tidal volume of 6 mL/kg of predicted body weight, with allowances for 4 mL/kg to 8 mL/kg; and plateau airway pressures not exceeding 40 cm H₂O. Patients started with a recruitment maneuver, which included a 40-second breath-hold at 40 cm H₂O airway pressure, on an FIO₂ of 1.0.

In contrast with the previous open-lung approach, which determined PEEP levels for individual study patients by a single pressure-volume curve analysis at enrollment,⁹ we adjusted PEEP levels according to FIO₂. Based on a standard PEEP protocol that reflected usual care and was successfully implemented in an earlier multicenter trial,⁶ we introduced modifications to ensure higher PEEP levels in the experimental group. Protocols for reducing PEEP levels in the setting of hypotension (mean arterial pressure <60 mm Hg), high plateau airway pressures (>40 cm H₂O), or refractory barotrauma (see below) allowed us to further modify PEEP levels according to individual patient needs. After the initial recruitment maneuver, starting with PEEP at 20 cm H₂O, both FIO₂ and PEEP were reduced as outlined in TABLE 1 and TABLE 2.

Figure 1. Study Flow



Data related to the number of patients screened, eligible, and excluded were not collected consistently at some sites and are not shown. Seven patients who were withdrawn from the study at various time points (ranging from study days 1-11) were included in the primary analysis and contributed partial data for secondary analyses.

An additional recruitment maneuver followed each disconnect from the ventilator, up to 4 times daily, until FIO₂ was 0.40 or less. We withheld recruitment maneuvers when mean arterial pressure was less than 60 mm Hg, and for barotrauma. At the first investigators' meeting, 8 months after the launch of the trial, we reviewed PEEP levels in each group. While PEEP levels clearly differed between the 2 study groups, clinicians at participating hospitals were increasingly comfortable with higher levels of PEEP. Reasoning that the goal of the study was to maximize this separation while staying within the bounds of clinical equipoise and usual clinical practice, we increased PEEP levels in the experimental strategy (Table 1 and Table 2).

Using the Acute Respiratory Distress Syndrome Network's low-tidal-volume ventilation protocol,⁶ the control strategy included volume-assist control mode; target tidal volumes of 6 mL/kg of predicted body weight, with allowances for 4 mL/kg to 8 mL/kg; plateau airway pressures up to 30 cm

H₂O; and the PEEP strategy shown in Table 1 and Table 2. Recruitment maneuvers were not permitted in the control group.

When patients met specific criteria denoting either refractory hypoxemia (PaO₂ <60 mm Hg for at least 1 hour while receiving an FIO₂ of 1.0), refractory acidosis (pH ≤7.10 for at least 1 hour), or refractory barotrauma (persistent pneumothorax with 2 chest tubes on the involved side or increasing subcutaneous or mediastinal emphysema with 2 chest tubes), clinicians could, at their discretion, deviate from the assigned ventilation protocols or institute "rescue therapies" (including prone ventilation, inhaled nitric oxide, high-frequency oscillation, jet ventilation, or extracorporeal membrane oxygenation). The protocol called for recommencement of the assigned protocol as soon as possible. In addition, if patient discomfort was difficult to control, clinicians could institute pressure support mode, adhering to the assigned targets for tidal volume and airway pressure until FIO₂ was

titrated to 0.40 or less and PEEP was 10 cm H₂O or less.

The study weaning protocol, supported by current recommendations,¹² included explicit daily assessments of patients' readiness to undergo a trial of unassisted breathing. Following a successful trial and ensuring the presence of a cuff leak, respiratory therapists notified the attending physician with a view to prompt extubation. Use of sedation and neuromuscular blockade and the timing of tracheostomy were at the discretion of intensive care unit clinicians.

Strategies to facilitate adherence to protocol throughout the trial included educational in-service sessions, bedside prompts, daily assessments by research personnel, and standardized real-time center-specific audit and feedback.

Data Collection and Outcome Measurements

Research personnel recorded demographic characteristics, physiological data, relevant intensive care unit interventions, and radiographic characteristics from the 24 hours preceding ran-

domization. We recorded respiratory data at baseline and at 8-hour intervals thereafter until extubation. Daily, we documented physiological data, radiographic findings, and relevant therapeutic interventions. We followed all patients up to the time of hospital discharge.

The primary outcome was all-cause hospital mortality. We classified patients discharged to an alternative level of care facility as alive at discharge. We also documented mortality during mechanical ventilation, intensive care unit mortality, and 28-day mortality.

We defined barotrauma as pneumothorax, pneumomediastinum, pneumoperitoneum, or subcutaneous emphysema on chest radiograph or chest tube insertions for known or suspected spontaneous pneumothorax. Additional predefined secondary outcomes included eligible use and total use of rescue therapies in response to refractory hypoxemia, refractory acidosis, or refractory barotrauma (defined above). We classified deaths that occurred during or following a period of refractory hypoxemia as death associated with refractory hypoxemia. The duration of mechanical ventilation includes the day of enrollment to the day of (1) extubation that was successful for at least 24 hours or (2) passing a trial of unassisted breathing and ultimately continuing with unassisted breathing (including tracheostomy mask, T-piece, or continuous positive airway pressure and pressure support ≤ 5 cm H₂O) for at least 48 hours. The duration of hospital stay includes the date of enrollment to the date of discharge from the study hospital.

Statistical Analysis

The target sample size of 980 patients assumed a control group hospital mortality rate of 45%, based on finding a 50% mortality rate in a similar population that did not receive the current standard for lung-protective ventilation.¹³ We also assumed a relative risk reduction of 20%, 80% power, and a 2-sided *t* test at a significance level of $\alpha < .05$ and applied a continuity correction (the Fleiss approxi-

Table 3. Baseline Characteristics^a

Characteristics	Lung Open Ventilation (n = 475)	Control Ventilation (n = 508)
Age, mean (SD), y	54.5 (16.5)	56.9 (16.5)
Female sex	193 (40.6)	201 (39.6)
Hospital stay, median (IQR), d	3 (1-6)	3 (2-6)
Mechanical ventilation, median (IQR), d	1 (0-3)	1 (0-3)
APACHE II score, mean (SD) ^b	24.8 (7.8)	25.9 (7.7)
Nonpulmonary MOD score, mean (SD) ^c	6.5 (3.4)	6.6 (3.3)
PaO ₂ /Fio ₂ , mean (SD)	144.8 (47.9)	144.6 (49.2)
PaO ₂ /Fio ₂ <200	409 (86.1)	427 (84.1)
Oxygenation index, median (IQR) ^d	12.1 (8.7-17.2)	11.9 (8.5-18.0)
Set PEEP, mean (SD), cm H ₂ O	11.5 (3.5)	11.2 (3.3)
Plateau pressure, mean (SD), cm H ₂ O ^e	30.4 (5.5)	29.3 (6.0)
Tidal volume, mL/kg predicted body weight, mean (SD)	8.4 (2.1)	8.4 (2.2)
Minute ventilation, mean (SD), L/min	11.4 (3.4)	11.6 (3.5)
Total respiratory rate, mean (SD), breaths/min	22.1 (6.4)	22.4 (4.3)
Barotrauma	17 (3.6)	19 (3.7)
Cause of lung injury ^f		
Sepsis	214 (45.1)	248 (48.8)
Pneumonia (non- <i>Pneumocystis jiroveci</i>)	207 (43.7)	233 (45.9)
Gastric aspiration	85 (17.9)	106 (20.9)
Multiple transfusion	45 (9.5)	40 (7.9)
Prolonged shock	35 (7.4)	24 (4.7)
Pulmonary contusion	18 (3.8)	26 (5.1)
Multiple major fractures	22 (4.6)	27 (5.3)
Acute pancreatitis	20 (4.2)	27 (5.3)
Drug overdose	20 (4.2)	19 (3.7)
<i>P jiroveci</i>	12 (2.5)	15 (3.0)
Burn injury	14 (3.0)	8 (1.6)
Inhalation injury	5 (1.1)	5 (1.0)

Abbreviations: APACHE II, Acute Physiology, Age and Chronic Health Evaluation; Fio₂, fraction of inspired oxygen; IQR, interquartile range; MOD, Multiple Organ Dysfunction scale; PaO₂, partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure.

^a Data are presented as No. (%) unless otherwise indicated.

^b Higher scores indicate more severe illness.¹⁵

^c Higher scores indicate more severe illness.¹⁷

^d Oxygenation index is calculated as mean airway pressure \times Fio₂ \times 100/PaO₂.

^e Plateau pressure was not measurable for 315 patients because of high respiratory rates.

^f Cause of lung injury was determined by the attending physician, without the provision of study definitions. Individual patients frequently had more than 1 cause of lung injury.

mation to the exact binomial method of Cassagrande et al).¹⁴ An independent data monitoring committee conducted 2 interim analyses using a nominal $P < .001$ as a threshold to consider early stopping.

The primary analysis was a Mantel-Haenszel analysis of hospital mortality, using center as the single stratification variable.

In a planned secondary analysis of hospital mortality, we adjusted for 4 baseline variables: age, the Acute Physi-

ology Score component of the Acute Physiology and Chronic Health Evaluation (APACHE) II score,¹⁵ sepsis, and duration of hospitalization. To present study results as relative risks, we planned to use the exact log-binomial approach. With failure to converge using this method, we used an indirect logistic regression analysis, using the bootstrap method to derive confidence intervals.¹⁶ We also conducted a subgroup analysis to investigate an interaction between severity of lung in-

jury at baseline, defined by quartiles of $\text{PaO}_2/\text{FiO}_2$, and treatment effect.

Four sensitivity analyses addressing the outcome of hospital mortality examined potential bias introduced by the blocked randomization programming error; these results did not differ from our primary analysis. Formal comparisons of 25 baseline characteristics using the Bonferroni correction revealed no statistically significant imbalances. Analyses of the duration of mechanical ventilation and hospital-

Table 4. Respiratory Data^a

Variables	Day 1			Day 3			Day 7		
	Lung Open Ventilation	Control	P Value	Lung Open Ventilation	Control	P Value	Lung Open Ventilation	Control	P Value
Tidal volume, mean (SD), mL/kg predicted body weight	6.8 (1.4)	6.8 (1.3)	.76	6.9 (1.5)	6.7 (1.5)	.02	6.9 (1.3)	7.0 (1.6)	.53
No. of patients	436	469		337	395		177	243	
Total respiratory rate, mean (SD), /min	25.2 (6.6)	26.0 (6.5)	.08	25.1 (6.6)	27.1 (8.0)	<.001	25.5 (8.0)	26.1 (7.6)	.26
No. of patients	471	507		447	479		316	351	
Plateau pressure, mean (SD), cm H ₂ O	30.2 (6.3)	24.9 (5.1)	<.001	28.6 (6.0)	24.7 (5.7)	<.001	28.8 (6.3)	25.1 (6.8)	<.001
No. of patients	435	424		334	380		174	232	
30.1-35.0	112	33		76	38		37	27	
35.1-40.0	88	4		41	12		27	13	
>40.0	8	1		8	3		4	4	
FiO ₂ , mean (SD)	0.50 (0.16)	0.58 (0.17)	<.001	0.41 (0.12)	0.52 (0.16)	<.001	0.39 (0.12)	0.48 (0.17)	<.001
No. of patients	471	507		447	482		319	356	
Set PEEP, mean (SD), cm H ₂ O									
All patients	15.6 (3.9)	10.1 (3.0)	<.001	11.8 (4.1)	8.8 (3.0)	<.001	10.3 (4.3)	8.0 (3.1)	<.001
No. of patients	471	507		447	479		316	348	
First 161 patients	15.3 (3.6)	10.6 (2.9)	<.001	12.1 (4.1)	9.3 (3.0)	<.001	10.4 (4.3)	8.2 (3.1)	.005
No. of patients	77	82		72	79		47	63	
Subsequent 822 patients	15.7 (4.0)	10.0 (3.0)	<.001	11.8 (4.1)	8.7 (3.0)	<.001	10.3 (4.3)	8.0 (3.1)	<.001
No. of patients	394	425		375	400		269	285	
I:E ratio, mean (SD)	0.62 (0.19)	0.56 (0.19)	<.001	0.64 (0.21)	0.56 (0.21)	<.001	0.64 (0.19)	0.59 (0.22)	.02
No. of patients	410	420		329	373		170	212	
PaO ₂ /FiO ₂ , mean (SD)	187.4 (68.8)	149.1 (60.6)	<.001	196.8 (60.6)	164.1 (63.5)	<.001	212.7 (70.5)	180.8 (73.0)	<.001
No. of patients	464	498		444	472		314	342	
PaO ₂ , mean (SD), mm Hg	88.1 (32.0)	80.1 (25.2)	<.001	75.3 (14.8)	76.4 (16.2)	.30	76.3 (15.6)	77.0 (17.1)	.56
No. of patients	464	498		444	472		314	342	
Paco ₂ , mean (SD), mm Hg	45.5 (12.0)	44.6 (10.9)	.22	44.8 (9.5)	45.3 (9.8)	.41	44.8 (10.3)	46.6 (11.7)	.04
No. of patients	464	498		444	472		314	342	
pH, mean (SD)	7.33 (0.10)	7.35 (0.09)	.17	7.38 (0.07)	7.37 (0.08)	.11	7.40 (0.07)	7.39 (0.08)	.03
No. of patients	464	498		444	472		314	342	
24-h fluid balance, mean (SD), mL	2131.4 (2506.6)	2110.6 (2641.7)	.90	1029.0 (2222.9)	722.9 (2201.4)	.04	270.6 (2078.2)	102.4 (1808.4)	.26
No. of patients	465	500		445	473		326	363	

Abbreviations: FiO₂, fraction of inspired oxygen; I:E, inspiration:expiration; PEEP, positive end-expiratory pressure; PaO₂, partial pressure of arterial oxygen; Paco₂, partial pressure of arterial carbon dioxide.

^aData shown were derived from the average value obtained for each patient over 3 measurements each day. Values were recorded on days 1, 3, and 7 after enrollment. For tidal volume and plateau airway pressure measurements, data exclude patients weaning in pressure support mode, with FiO₂ less than or equal to 0.40 and PEEP less than or equal to 10 cm H₂O.

ization excluded 3 patients transferred to long-term ventilation facilities and all patients who died prior to extubation or hospital discharge. We compared non-normally distributed data using the Wilcoxon rank-sum test.

All final analyses followed pre-defined protocols based on the intention-to-treat principle, were stratified by center (except duration of ventilation and hospitalization), and were conducted independently by 2 analysts at the CLARITY Methods Centre in Hamilton, Ontario, using SAS soft-

ware, version 9.1 (SAS Institute Inc, Cary, North Carolina). One analyst was blinded to allocation.

RESULTS

We enrolled 985 patients (FIGURE 1). Physicians refused enrollment for 58 eligible patients; these patients were never randomized. Families withdrew consent for 1 patient in each group immediately after randomization, without knowledge of group allocation and prior to any initiation of study procedures. We did not collect data on these pa-

tients and they did not contribute to any analyses. Primary outcome data were available from all patients. Seven patients, withdrawn from the study at various time points (ranging from study days 1-11), contributed partial data for secondary analyses.

The majority of patients (85.0%) met criteria for ARDS at study entry ($\text{PaO}_2/\text{FiO}_2 \leq 200$; TABLE 3). Control group patients were, on average, 2.4 years older than patients in the experimental group, and their rate of sepsis at baseline was 3.7% higher. The most common causes of lung injury were sepsis (47.0%), pneumonia (44.8%), and gastric aspiration (19.4%).

TABLE 4 shows the evolution of respiratory data. Mean tidal volumes were similar in the 2 groups and within the target range. Results showed a consistent and significant difference in PEEP levels between groups. Control group patients had more hypoxemia and required higher inspired oxygen levels. Plateau airway pressures were higher in the experimental group, though observations above 35 cm H_2O were infrequent in both groups (Table 4).

Among patients in the experimental group, 366 received at least 1 recruitment maneuver following the initial recruitment maneuver at study initiation. Eighty-one patients (22.1%) developed a complication associated

Table 5. Cointerventions During the First 28 Days of Study^a

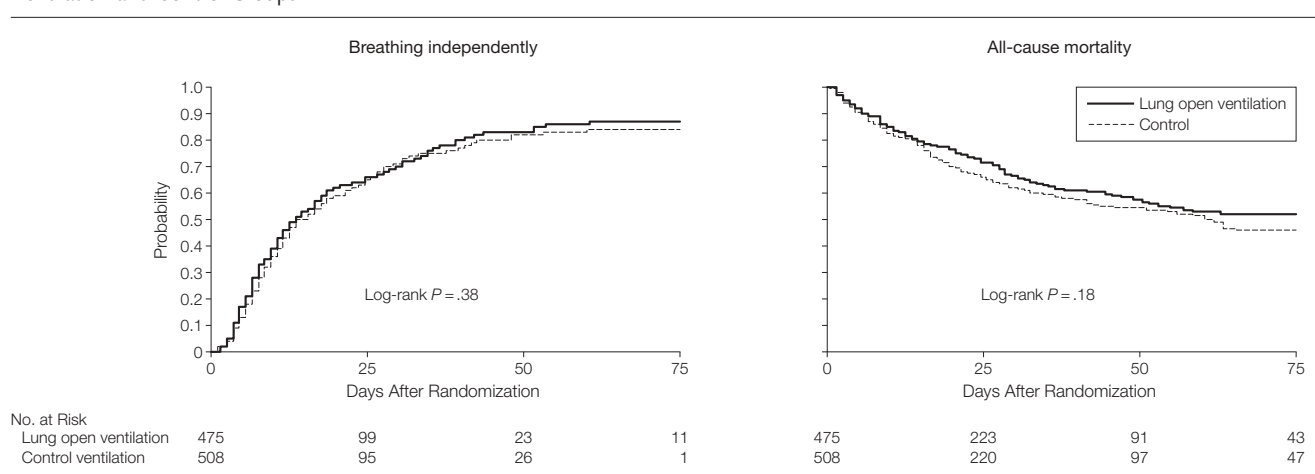
Cointerventions	Lung Open Ventilation	Control Ventilation
Sedative infusion	423 (89.1)	457 (90.0)
Days of sedative infusion, median (IQR)	7 (3-12)	7 (4-12)
Sedative or narcotic infusion	449 (94.5)	476 (93.7)
Days of sedative or narcotic infusion, median (IQR)	7 (4-13)	8 (5-14)
Neuromuscular blockade	208 (43.8)	223 (43.9)
Days of neuromuscular blocker use, median (IQR)	2 (1-5)	3 (1-6)
Vasopressors	339 (71.4)	377 (74.2)
Days of vasopressor use, median (IQR)	4 (2-8)	5 (2-9)
No. of vasopressors each day in use, median (IQR)	5 (3-10)	6 (3-12)
Pulmonary artery catheter	164 (34.5)	180 (35.4)
Corticosteroids	194 (40.8)	216 (42.5)
Hemodialysis ^b	71 (16.6)	85 (18.5)

Abbreviation: IQR, interquartile range.

^aData are expressed as No. (%) unless otherwise indicated. For median data, values reflect either the duration or amount of drug in patients who ever received the specified intervention.

^bDialysis rates exclude patients receiving dialysis at the time of enrollment.

Figure 2. Probabilities of Survival and Unassisted Breathing From Day of Randomization (Day 0) to Day 75 Among Patients in the Lung Open Ventilation and Control Groups



Patients were censored at hospital discharge and at death in the 2 analyses, respectively.

with a recruitment maneuver: 61 (4.5%) resulted in a mean arterial pressure of less than 60 mm Hg, 58 (4.2%) were associated with a decrease in oxygen saturation to less than 85%, 24 (1.8%) were associated with bradycardia or tachycardia, 4 (0.3%) were associated with cardiac arrhythmia, and 4 (0.3%) were associated with a new air leak through an existing thoracostomy tube. In 3 patients, clinicians detected new barotrauma immediately following a recruitment maneuver. TABLE 5 summarizes the use of selected intensive care unit interventions, which clinicians administered similarly in both groups.

There were 173 hospital deaths (36.4%) in the experimental group and 205 (40.4%) in the control group. The relative risk of death in the hospital was 0.90 (95% confidence interval, 0.77-1.05; $P=.19$) (FIGURE 2 and TABLE 6). The secondary adjusted analysis of hospital mortality showed a relative risk of 0.97 (95% confidence interval, 0.84-1.12; $P=.74$). We found no interaction between severity of baseline lung injury and response to treatment (TABLE 7).

There were 53 experimental patients vs 47 controls who developed an episode of barotrauma, for an absolute difference of 6 events. There was a lower incidence of refractory hypoxemia as a cause for deviation from the assigned ventilation settings, and a lower rate of associated deaths, among patients in the experimental group (Table 6). The median duration of mechanical ventilation among survivors of mechanical ventilation was 10 days (interquartile range, 6-17 days) in the experimental group and 10 days (interquartile range, 6-16 days) in the control group ($P=.92$). The median duration of hospitalization among survivors was 28 days (interquartile range, 17-48 days) vs 29 days (interquartile range, 16-51 days) ($P=.96$).

COMMENT

This trial comparing 2 lung-protective ventilation strategies, an established low-tidal-volume strategy and an

experimental lung open ventilation strategy that includes low tidal volumes, recruitment maneuvers, and higher levels of PEEP, resulted in no statistically significant difference in rates of all-cause hospital mortality. The lower mortality rate observed in the experimental group was not statistically significant and became negligible in a secondary adjusted analysis. The 2 strategies resulted in similar rates of barotrauma and similar duration of mechanical ventilation. The experimental strategy was associated with less use of

rescue therapies and fewer deaths associated with refractory hypoxemia.

A number of hypotheses could explain the similar mortality rates we observed. First, our experimental strategy may have no appreciable impact on survival beyond that achieved with low tidal volumes and standard PEEP levels alone. Alternatively, the experimental strategy may reduce deaths among patients similar to those studied; however, our trial did not have sufficient power to detect a relatively small mortality reduction. Finally, benefits to the

Table 6. Outcomes^a

Outcomes	No. (%)		Relative Risk (95% Confidence Interval)	P Value
	Lung Open Ventilation (n = 475)	Control Ventilation (n = 508)		
Death in hospital	173 (36.4)	205 (40.4)	0.90 (0.77-1.05)	.19
Death in intensive care unit	145 (30.5)	178 (35.0)	0.87 (0.73-1.04)	.13
Death during mechanical ventilation	136 (28.6)	168 (33.1)	0.87 (0.72-1.04)	.13
Death during first 28 d	135 (28.4)	164 (32.3)	0.88 (0.73-1.07)	.20
Barotrauma ^b	53 (11.2)	47 (9.1)	1.21 (0.83-1.75)	.33
Refractory hypoxemia	22 (4.6)	52 (10.2)	0.54 (0.34-0.86)	.01
Death with refractory hypoxemia	20 (4.2)	45 (8.9)	0.56 (0.34-0.93)	.03
Refractory acidosis	29 (6.1)	42 (8.3)	0.81 (0.51-1.31)	.39
Death with refractory acidosis	27 (5.7)	38 (7.5)	0.85 (0.51-1.40)	.52
Refractory barotrauma	14 (3.0)	12 (2.4)	1.10 (0.54-2.26)	.80
Death with refractory barotrauma	8 (1.7)	8 (1.6)	1.00 (0.41-2.40)	.99
Eligible use of rescue therapies ^c	24 (5.1)	47 (9.3)	0.61 (0.38-0.99)	.045
Total use of rescue therapies ^c	37 (7.8)	61 (12.0)	0.68 (0.46-1.00)	.05
Days of mechanical ventilation ^d	10 (6-17)	10 (6-16)		.92
Days of intensive care ^d	13 (8-23)	13 (9-23)		.98
Days of hospitalization ^d	28 (17-48)	29 (16-51)		.96

^aAll analyses of relative risk are stratified by hospital.

^bBarotrauma includes study onset of pneumothorax, pneumomediastinum, pneumoperitoneum, subcutaneous emphysema, and chest tubes inserted for spontaneous pneumothorax.

^cEligible use of rescue therapies refers to use among patients who met a priori criteria. Total use of rescue therapies refers to use among all patients whether or not they met criteria. Rescue therapies included inhaled nitric oxide, prone ventilation, high-frequency oscillation, high-frequency jet ventilation, and extracorporeal membrane oxygenation.

^dContinuous data are presented as median (interquartile range) among survivors of mechanical ventilation, intensive care, and hospitalization, respectively.

Table 7. Hospital Mortality Based on Severity of Lung Injury at Baseline

Pao ₂ /Fio ₂	No. (%)		Relative Risk (95% Confidence Interval)	P Value ^a
	Lung Open Ventilation	Control		
Quartile 1: 41-106	57 (50)	77 (58)	0.86 (0.68-1.09)	.94
Quartile 2: >106-142	46 (39)	55 (43)	0.92 (0.68-1.24)	
Quartile 3: >142-180	43 (33)	40 (33)	0.99 (0.69-1.41)	
Quartile 4: >180-250	27 (25)	33 (26)	0.90 (0.58-1.40)	

Abbreviations: Fio₂, fraction of inspired oxygen; Pao₂, partial pressure of arterial oxygen.

^aP value for homogeneity among the quartiles.

lung open ventilation strategy may be restricted to an as-yet undefined subgroup of patients, with no effect or harm to other subgroups.

Early preclinical and clinical trials providing indirect evidence that open-lung strategies improve survival were restricted to animal models^{7,8} of ARDS and to patients with severe ARDS⁹ or persistent ARDS.¹⁰ Findings in this study did not suggest that the inclusion of patients with acute lung injury diluted a survival benefit that is restricted to patients with ARDS; we failed to detect an interaction between baseline severity of lung injury and treatment effect. Nevertheless, a significant proportion of patients receiving the experimental strategy may have failed to achieve an open lung with the experimental study protocol. This theory is supported by recent computed tomography evidence demonstrating that response to PEEP in a heterogeneous population of ARDS patients is highly variable and frequently leads to overdistention as opposed to lung recruitment.¹⁸ Thus, the benefits of recruitment maneuvers and higher levels of PEEP for some might have been offset by harm to others, particularly among the relatively few patients exposed to higher plateau airway pressures.^{19,20} The experimental strategy permitted plateau airway pressures up to 40 cm H₂O compared with 30 cm H₂O in the control group; however, plateau airway pressures rarely exceeded 35 cm H₂O with the experimental strategy.

This is the largest of 3 trials testing the incremental benefit of maneuvers aimed to minimize atelectrauma compared with low-tidal-volume ventilation alone in patients with acute lung injury and ARDS. In a previously published trial, the compared ventilation strategies differed primarily with respect to PEEP levels.¹¹ The investigators stopped the trial early for futility when the unadjusted analysis revealed a trend toward increased mortality with the lung open strategy; however, the adjusted analysis addressing large baseline imbalances revealed a nonsignificant reduction in mortality.

A third large trial, which has been completed and published in abstract form, tested an innovative strategy in which the primary difference from the control strategy was the management of PEEP.²¹ This trial, similar to the present trial, observed a trend toward lower mortality with the high-PEEP strategy. None of these 3 trials directly measured lung recruitment with the experimental strategies. On balance, however, the results of these trials support the notion that open-lung ventilation strategies, which combine low tidal volumes with additional efforts to open the lung, are an acceptable alternative to the current standard of care. Evidence that critical care clinicians do not fully accept the currently recommended lung-protective ventilation strategy makes the finding of an acceptable alternative strategy particularly relevant.²²

Strengths of this trial include rigorous methods to minimize bias (concealed randomization, explicit study protocols, complete follow-up, and analyses based on the intention-to-treat principle). Recruitment of a large sample from 30 multidisciplinary intensive care units with international representation enhances the generalizability of our findings.

Limitations of the trial include our inability to differentiate among the specific effects of higher levels of PEEP, higher plateau airway pressures, recruitment maneuvers, or pressure control mode in lung protection. We observed modest baseline imbalances in age and sepsis, and whether our secondary analysis adjusting for age, sepsis, acute physiology, and duration of hospitalization represents a more accurate estimate—vs an overadjusted estimate—of the treatment effect remains uncertain. The relevance of our observations of reduced use of rescue therapies in the experimental group and fewer deaths associated with refractory hypoxemia are unclear.

In summary, for patients with acute lung injury and ARDS, we found similar mortality in patients with a multifaceted protocolized lung-protective

ventilation strategy designed to open the lung compared with an established low-tidal-volume protocolized ventilation strategy. We found no evidence of significant harm or increased risk of barotrauma despite the use of higher PEEP. In addition, the “open-lung” strategy appeared to improve oxygenation, with fewer hypoxemia-related deaths and a lower use of rescue therapies by the treating clinicians. Our results, in combination with the 2 other major trials, justify use of higher PEEP levels as an alternative to the established low-PEEP, low-tidal-volume strategy.

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