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

Maureen O. Meade, MD, MSc
Deborah J. Cook, MD, MSc
Gordon H. Guyatt, MD, MSc
Arthur S. Slutsky, MD
Yaseen M. Arabi, MD
D. James Cooper, MD
Andrew R. Davies, MD
Lori E. Hand, RRT, CCRA
Qi Zhou, PhD
Lehana Thabane, PhD
Peggy Austin, CCRA
Stephen Lapinsky, MD
Alan Baxter, MD
James Russell, MD
Yoanna Skrobik, MD
Juan J. Ronco, MD
Thomas E. Stewart, MD

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.

Trial Registration clinicaltrials.gov Identifier: NCT00182195

©2008 American Medical Association. All rights reserved.

Author Affiliations are listed at the end of this article.

Corresponding Author: Maureen O. Meade, MD, MSc, Departments of Medicine and Epidemiology and Biostatistics, McMaster University, 1200 Main St W, Room 210C, Hamilton, ON L8N 3Z5, Canada (meadema@hhsc.ca).
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. 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. This specific low-tidal-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. 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. 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. 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-tidal-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 (Pao2/FiO2) 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**

<table>
<thead>
<tr>
<th>Component Variables</th>
<th>Control Ventilation Strategy</th>
<th>Lung Open Ventilation Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventilator mode</td>
<td>Volume-assist control</td>
<td>Pressure control</td>
</tr>
<tr>
<td>Tidal volume target, mL/kg predicted body weight</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Tidal volume range, mL/kg predicted body weight</td>
<td>4-8</td>
<td>4-8</td>
</tr>
<tr>
<td>Plateau airway pressure, cm H2O</td>
<td>≤30</td>
<td>≤40</td>
</tr>
<tr>
<td>Positive end-expiratory pressure, cm H2O</td>
<td>See Table 2</td>
<td>See Table 2</td>
</tr>
<tr>
<td>Partial pressure of oxygen, arterial, mm Hg</td>
<td>55-80</td>
<td>55-80</td>
</tr>
<tr>
<td>Oxygen saturation as measured by pulse oximetry, %</td>
<td>88-93</td>
<td>88-93</td>
</tr>
<tr>
<td>pH</td>
<td>≥7.30</td>
<td>≥7.30</td>
</tr>
<tr>
<td>Ventilator rate, breaths/min</td>
<td>≤35</td>
<td>≤35</td>
</tr>
<tr>
<td>Inspiration:expiration time</td>
<td>1:1-1:3</td>
<td>1:1-1:3</td>
</tr>
<tr>
<td>Recruitment maneuvers</td>
<td>Not permitted</td>
<td>After ventilator disconnects</td>
</tr>
</tbody>
</table>

**Table 2. Allowable PEEP Ranges at Specified Levels of FiO2**

<table>
<thead>
<tr>
<th>Fraction of Inspired Oxygen (FiO2)</th>
<th>0.3</th>
<th>0.4</th>
<th>0.5</th>
<th>0.6</th>
<th>0.7</th>
<th>0.8</th>
<th>0.9</th>
<th>1.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control PEEP ranges, cm H2O</td>
<td>5</td>
<td>5-8</td>
<td>8-10</td>
<td>10</td>
<td>10-14</td>
<td>14</td>
<td>14-18</td>
<td>18-24</td>
</tr>
<tr>
<td>Lung open ventilation PEEP ranges, cm H2O</td>
<td>Before protocol change</td>
<td>5-10</td>
<td>10-14</td>
<td>14-20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20-22</td>
</tr>
<tr>
<td></td>
<td>After protocol change</td>
<td>5-10</td>
<td>10-18</td>
<td>18-20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20-22</td>
</tr>
</tbody>
</table>

Abbreviation: PEEP, positive end-expiratory pressure.

*Both 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” 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, 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, 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.

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, 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, 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 randomization. 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. We also assumed a relative risk reduction of 20%, 80% power, and a 2-sided t test at a significance level of α < 0.05 and applied a continuity correction (the Fleiss approxi-
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 Physiology Score component of the Acute Physiologic 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 injury at baseline, defined by quartiles of PaO2/FIO2, 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 hospitalization.

### Table 4. Respiratory Data

<table>
<thead>
<tr>
<th>Variables</th>
<th>Day 1</th>
<th>Day 3</th>
<th>Day 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tidal volume, mean (SD), mL/kg predicted body weight</td>
<td>Lung Open Ventilation</td>
<td>Control</td>
<td>P Value</td>
</tr>
<tr>
<td>No. of patients</td>
<td>436</td>
<td>469</td>
<td>.08</td>
</tr>
<tr>
<td>Total respiratory rate, mean (SD), /min</td>
<td>25.2 (6.6)</td>
<td>26.0 (6.5)</td>
<td>.08</td>
</tr>
<tr>
<td>Plateau pressure, mean (SD), cm H2O</td>
<td>30.2 (6.3)</td>
<td>24.9 (5.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>P/F ratio, mean (SD)</td>
<td>0.50 (0.16)</td>
<td>0.58 (0.17)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Set PEEP, mean (SD), cm H2O</td>
<td>All patients</td>
<td>15.6 (3.9)</td>
<td>10.1 (3.0)</td>
</tr>
<tr>
<td>No. of patients</td>
<td>471</td>
<td>507</td>
<td>.001</td>
</tr>
<tr>
<td>First 161 patients</td>
<td>15.3 (3.6)</td>
<td>10.6 (2.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>No. of patients</td>
<td>77</td>
<td>82</td>
<td>.001</td>
</tr>
<tr>
<td>Subsequent 822 patients</td>
<td>15.7 (4.0)</td>
<td>10.0 (3.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>No. of patients</td>
<td>394</td>
<td>425</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>I/E ratio, mean (SD)</td>
<td>0.62 (0.19)</td>
<td>0.56 (0.19)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>No. of patients</td>
<td>410</td>
<td>420</td>
<td>.001</td>
</tr>
<tr>
<td>P/F ratio, mean (SD)</td>
<td>187.4 (68.8)</td>
<td>149.1 (60.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>No. of patients</td>
<td>464</td>
<td>498</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>P/F ratio, mean (SD), mm Hg</td>
<td>88.1 (32.6)</td>
<td>80.1 (25.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>No. of patients</td>
<td>464</td>
<td>498</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>P/F ratio, mean (SD), mm Hg</td>
<td>45.5 (12.0)</td>
<td>44.6 (10.9)</td>
<td>.22</td>
</tr>
<tr>
<td>No. of patients</td>
<td>464</td>
<td>498</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>pH, mean (SD)</td>
<td>7.33 (0.10)</td>
<td>7.35 (0.09)</td>
<td>.17</td>
</tr>
<tr>
<td>No. of patients</td>
<td>464</td>
<td>498</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>24-h fluid balance, mean (SD), mL</td>
<td>2131.4 (2506.6)</td>
<td>2110.6 (2641.7)</td>
<td>.90</td>
</tr>
<tr>
<td>No. of patients</td>
<td>465</td>
<td>500</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: P, 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.

Data 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 P/F 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 predefined 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 software, 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 patients 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 (PaO2/FIO2 ≤ 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 H2O 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

**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.

©2008 American Medical Association. All rights reserved.
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

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

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

<table>
<thead>
<tr>
<th>PaO2/FIO2</th>
<th>Lung Open Ventilation</th>
<th>Control</th>
<th>Relative Risk (95% Confidence Interval)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quartile 1: 41-106</td>
<td>57 (50)</td>
<td>77 (58)</td>
<td>0.86 (0.68-1.09)</td>
<td>.94</td>
</tr>
<tr>
<td>Quartile 2: &gt;106-142</td>
<td>46 (39)</td>
<td>55 (43)</td>
<td>0.92 (0.68-1.24)</td>
<td>.94</td>
</tr>
<tr>
<td>Quartile 3: &gt;142-180</td>
<td>43 (33)</td>
<td>40 (33)</td>
<td>0.99 (0.69-1.41)</td>
<td>.94</td>
</tr>
<tr>
<td>Quartile 4: &gt;180-250</td>
<td>27 (25)</td>
<td>33 (26)</td>
<td>0.90 (0.68-1.40)</td>
<td>.94</td>
</tr>
</tbody>
</table>

Abbreviations: FIO2, fraction of inspired oxygen; PaO2, partial pressure of arterial oxygen.  
\( P \) value for homogeneity among the quartiles.
lungenopenventilationstrategymayberestrictedtoanasyetundefinedsub-
grouppopulationofpatients,withnoeffectortharm
toothersubgroups.

Earlyprereclınicalandclinicaltrialsprovidingindirectevidencethattopen-
lungs strategies improve survival were restricted to animal models,7,8 of ARDS
andtopatientswithsevereARDS9orpersistentARDS.10 Findingsin
this study did not suggest that the inclu-
sion of patients with acute lung injury diluted a survival benefit that is
restricted topatientswithARDS;wefailed
todetectaninteractionbetweenbas-
eline 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 ex-
perimental study protocol. This theory
is supported by recent computed tomo-
graphy evidence demonstrating that
response to PEEP in a heterogeneous
population of ARDS patients is highly
variable and frequently leads to over-
distention as opposed to lung recruit-
ment.18 Thus, the benefits of recruit-
ment maneuvers and higher levels of
PEEP for some might have been offset
by harm to others, particularly among
the relatively fewpatientsexposed to
higher plateau airway pressures.19,20 The
experimental strategy permitted pla-
ateau airway pressures up to 40 cm H\textsubscript{2}O
compared with 30 cm H\textsubscript{2}O in the con-
trol group; however, plateau airway
pressures rarely exceeded 35 cm H\textsubscript{2}O
with the experimental strategy.

This is the largest of 3 trials testing
the incremental benefit of maneuvers
aimed to minimize atelectrauma com-
pared with low-tidal-volume ventila-
tion alone in patients with acute lung
injuryandARDS.Inapreviouslypub-
lished trial, the compared ventilation
strategies differed primarily with re-
spect to PEEP levels.11 The investiga-
tors stopped the trial early for futility
when the unadjusted analysis re-
vealed a trend toward increased mor-
talitywiththelungopenstrategy;how-
ever, the adjusted analysis addressing
large baseline imbalances revealed a
nonsignificantreductioninmortality.

A third large trial, which has been com-
pleted and published in abstract form,
tested an innovative strategy in which
the primary difference from the con-
trol strategy was the management of
PEEP.21 This trial, similar to the pres-
tent trial, observed a trend toward lower
mortality with the high-PEEP strat-
ey. None of these 3 trials directly mea-
sured lung recruitment with the exper-
imental strategies. On balance, how-
ever, the results of these trials sup-
port the notion that open-lung venti-
lation strategies, which combine low
tidal volumes with additional efforts
to open the lung, are an acceptable alter-
native to the current standard of care.
Evidence that critical care clinicians
do not fully accept the currently recom-
manded lung-protective ventilation
strategy makes the finding of an ac-
ceptable alternative strategy particu-
larly relevant.22

Strengths of this trial include rigorous
methods to minimize bias (con-
cealed randomization, explicit study
protocols, complete follow-up, and
analyses based on the intention-to-
treat principle). Recruitment of a large
sample from 30 multidisciplinary in-
tensive care units with international
representation enhances the general-
izability 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, rec-
cruitment maneuvers, or pressure con-
tral mode in lung protection. We ob-
erved modest baseline imbalances in
age and sepsis, and whether our sec-
ondary analysis adjusting for age, sep-
sis, acute physiology, and duration of
hospitalization represents a more ac-
curate estimate—vs an overadjusted es-
imate—of the treatment effect re-
mains uncertain. The relevance of our
observations of reduced use of rescue
therapies in the experimental group and
fewer deaths associated with refrac-
tory hypoxemia are unclear.

lnsummary, for patients with acute
lung injury and ARDS, we found simi-
lar mortality in patients with a multi-

ventilationstrategydesignedtoopen
the lung compared with an estab-
lished low-tidal-volume protociled
ventilationstrategy.Wefoundno evi-
dence of significant harm or increased
risk of barotrauma despite the use of
higher PEEP. In addition, the “open-
lung” strategy appeared to improve oxy-
genation, 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 estab-
lished low-PEEP, low-tidal-volume
strategy.

Author Affiliations: McMaster University, Hamilton,
Ontario, Canada (Drs Meade, Cook, Guyatt, Zhou,
and ThomandMssHandandAustin);University of
Toronto, Toronto, Ontario, Canada (Drs Slutsky,
Lapinsky, and Stewart); King Saud Bin Abdulaziz Uni-
versity, Riyadh, Saudi Arabia (Drs Arabi); Monash Uni-
versity, Melbourne, Australia (Drs Cooper and Dav-
ies); Ottawa University, Ottawa, Ontario, Canada (Dr
Baxter); University of British Columbia, Vancouver, Brit-
ish Columbia, Canada (Drs Russell and Ronco); and
University of Montreal, Montreal, Quebec, Canada
(Dr Skrobik).

Author Contributions: Dr Meade had full access to all of
the data in the study and takes responsibility for the
integrity of the data and the accuracy of the data
analysis.

Study concept and design: Meade, Cook, Guyatt,
Slutsky, Lapinsky, Stewart.

Acquisition of data: Meade, Arabi, Cooper, Davies,
Hand, Austin, Lapinsky, Baxter, Skrobik, Ronco,
Stewart.

Analysis and interpretation of data: Meade, Cook,
Guyatt, Slutsky, Davies, Zhou, Thabane, Austin,
Russell, Skrobik, Ronco, Stewart.

Drafting of the manuscript: Meade, Cook, Guyatt,
Stewart.

Critical revision of the manuscript for important in-
tellectual content: Meade, Slutsky, Arabi, Cooper,
Davies, Hand, Zhou, Thabane, Austin, Lapinsky,
Baxter, Russell, Skrobik, Ronco, Stewart.

Statistical analysis: Zhou, Thabane.

Obtained funding: Meade, Stewart.

Administrative, technical, or material support: Meade,
Cook, Guyatt, Slutsky, Arabi, Hand, Austin, Lapinsky,
Skrobik, Ronco, Stewart.

Study supervision: Meade, Arabi, Cooper, Austin,
Baxter, Russell, Ronco, Stewart.

Financial Disclosures: None reported.

Lung Open Ventilation Study Investigators: principal
investigators: M. O. Meade, T. E. Stewart; steering com-
nittee: D. J. Cook, G. H. Guyatt, M. O. Meade, T. E.
Stewart, A. S. Slutsky; site investigators: Canada: Cen-
tre Hospitalier Universitaire de Sherbrooke—O. Lesur;
Charles LeMoyne Hospital, Montreal—C. Corbeil, G.
Poirier; Hamilton Health Sciences, General Hospi-
tal—C. Bradley, M. O. Meade; Hamilton Health Sci-
ences, Henderson Hospital—G. Jones; Hamilton Health
Sciences, McMaster—A. Freitag; Hôpital de l’enfant
Jesus, Quebec City—M. Lessard, S. Langevin; Hôpital
Maisonneuve Rosemont, Montreal—B. Laufer, Y.
Skrobik; Hotel Dieu Grace, Windsor—J. Muscedere;
Jewish General Hospital, Montreal—D. Laporta; Lon-
don Health Sciences Centre, University Hospital—D.
Leasa; London Health Sciences Centre, Victoria Hos-
pital—L. Martin; Montreal General Hospital—D. Evans;
Mount Sinai Hospital, Toronto—S. Lapinsky, T. E. Stewart; Ottawa Hospital, Civic Campus—R. Hodder; Ottawa Civic Hospital, General Campus—A. Baxter; Royal Columbian Hospital, New Westminster—S. Keenan; Royal Victoria Hospital, Montreal—S. Magder; St Joseph’s Healthcare, Hamilton—C. D. Mazer, M. Ward; St Paul’s Hospital, Vancouver—J. A. Russell; Sunnybrook Hospital—A. B. Cooper; Toronto General Hospital—J. T. Granton; Toronto Western Hospital—N. D. Ferguson; University of Alberta Hospital, Edmonton—M. Jacka; Vancouver General Hospital—J. J. Ronco; Vancouver Island Health Research Centre, Victoria—G. Wood; Australia: Alfred Hospital, Melbourne—A. Davies, D. J. Cooper; Royal Prince Alfred Hospital, Camperdown—C. Wooff; Western Hospital, Victoria—C. French; Saudi Arabia: Medical City King Fahad National Guard Hospital, Riyadh—A. A. Al-Shimemeri, Y. M. Arabi, O. Dabbagh; McMaster University, Hamilton—P. Austin, D. J. Cook, G. H. Guyatt, L. E. Hand, M. O. Meade, L. Thabane, N. Zytaruk, Q. Zhou; protocol review: R. Kaczmarek, R. McDonald, data monitoring committee: R. Roberts (chair), R. Jaeschke, H. Kirplani, N. MacIntyre; writing committee: D. J. Cook, G. H. Guyatt, L. E. Hand, M. O. Meade, T. E. Stewart, L. Thabane, A. S. Slutsky.

**Funding/Support:** This study was supported by grants from the Canadian Institutes for Health Research and Hamilton Health Sciences Foundation. Dr Meade was a Peter Lougheed Scholar of the Medical Research Council of Canada during the period of this study. Drs Cook and Thabane are clinical trials mentors for the Canadian Institutes of Health Research.

**Role of the Sponsors:** The funding agencies had no role in the design and conduct of the study, in the collection, analysis, or interpretation of data, or in the preparation, review, or approval of the manuscript.

**REFERENCES**


©2008 American Medical Association. All rights reserved.