Prone Positioning in Severe Acute Respiratory Distress Syndrome

Claude Guérin, M.D., Ph.D., Jean Reignier, M.D., Ph.D., Jean-Christophe Richard, M.D., Ph.D., Pascal Beuret, M.D., Arnaud Gacouin, M.D., Thierry Boulain, M.D., Emmanuelle Mercier, M.D., Michel Badet, M.D., Alain Mercat, M.D., Ph.D., Olivier Baudin, M.D., Marc Clavel, M.D., Delphine Chatellier, M.D., Samir Jaber, M.D., Ph.D., Sylvène Rosselli, M.D., Jordi Mancebo, M.D., Ph.D., Michel Sirodot, M.D., Gilles Hilbert, M.D., Ph.D., Christian Bengler, M.D., Jack Richecoeur, M.D., Marc Gainnier, M.D., Ph.D., Frédérique Bayle, M.D., Gael Bourdin, M.D., Véronique Leray, M.D., Raphaele Girard, M.D., Loredana Baboi, Ph.D., and Louis Ayzac, M.D., for the PROSEVA Study Group*

ABSTRACT

BACKGROUND

Previous trials involving patients with the acute respiratory distress syndrome (ARDS) have failed to show a beneficial effect of prone positioning during mechanical ventilatory support on outcomes. We evaluated the effect of early application of prone positioning on outcomes in patients with severe ARDS.

METHODS

In this multicenter, prospective, randomized, controlled trial, we randomly assigned 466 patients with severe ARDS to undergo prone-positioning sessions of at least 16 hours or to be left in the supine position. Severe ARDS was defined as a ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen ($F_{IO_2}$) of less than 150 mm Hg, with an $F_{IO_2}$ of at least 0.6, a positive end-expiratory pressure of at least 5 cm of water, and a tidal volume close to 6 ml per kilogram of predicted body weight. The primary outcome was the proportion of patients who died from any cause within 28 days after inclusion.

RESULTS

A total of 237 patients were assigned to the prone group, and 229 patients were assigned to the supine group. The 28-day mortality was 16.0% in the prone group and 32.8% in the supine group (P<0.001). The hazard ratio for death with prone positioning was 0.39 (95% confidence interval [CI], 0.25 to 0.63). Unadjusted 90-day mortality was 23.6% in the prone group versus 41.0% in the supine group (P<0.001), with a hazard ratio of 0.44 (95% CI, 0.29 to 0.67). The incidence of complications did not differ significantly between the groups, except for the incidence of cardiac arrests, which was higher in the supine group.

CONCLUSIONS

In patients with severe ARDS, early application of prolonged prone-positioning sessions significantly decreased 28-day and 90-day mortality. (Funded by the Programme Hospitalier de Recherche Clinique National 2006 and 2010 of the French Ministry of Health; PROSEVA ClinicalTrials.gov number, NCT00527813.)
PRONE POSITIONING HAS BEEN USED FOR many years to improve oxygenation in patients who require mechanical ventilatory support for management of the acute respiratory distress syndrome (ARDS). Randomized, controlled trials have confirmed that oxygenation is significantly better when patients are in the prone position than when they are in the supine position. Furthermore, several lines of evidence have shown that prone positioning could prevent ventilator-induced lung injury. In several previous trials, these physiological benefits did not translate into better patient outcomes, since no significant improvement was observed in patient survival with prone positioning. However, meta-analyses have suggested that survival is significantly improved with prone positioning as compared with supine positioning among patients with severely hypoxemic ARDS at the time of randomization. We conducted a prospective, multicenter, randomized, controlled trial to explore whether early application of prone positioning would improve survival among patients with ARDS who, at the time of enrollment, were receiving mechanical ventilation with a positive end-expiratory pressure (PEEP) of at least 5 cm of water and in whom the ratio of the partial pressure of arterial oxygen (Pao2) to the fraction of inspired oxygen (FIO2) was less than 150 mm Hg.

METHODOLOGY

Patients
We included in the study adults who met the following criteria: ARDS, as defined according to the American–European Consensus Conference criteria; endotracheal intubation and mechanical ventilation for ARDS for less than 36 hours; and an FIO2 of ≥0.6, a PEEP of ≥5 cm of water and in whom the ratio of the partial pressure of arterial oxygen (Pao2) to the fraction of inspired oxygen (FIO2) was less than 150 mm Hg.

Protocol
After a patient was determined to be eligible, a stabilization period of 12 to 24 hours was mandated. Inclusion in the study was confirmed only at the end of this period (Fig. S1 in the Supplementary Appendix). Patients assigned to the prone group had to be turned to the prone position within the first hour after randomization. They were placed in a completely prone position for at least 16 consecutive hours. Participants were given guidelines (see the Supplementary Appendix) to ensure standardization of prone placement. Standard ICU beds were used for all patients. Patients assigned to the supine group remained in a semirecumbent position.

Mechanical ventilation was delivered in a volume-controlled mode with constant inspiratory flow, with tidal volume targeted at 6 ml per kilogram of predicted body weight and the PEEP...
level selected from a PEEP–FiO₂ table (Table S1 in the Supplementary Appendix). The goal was to maintain an end-inspiratory plateau pressure of the respiratory system (Pplatₘₙₚ), measured after a 1-second period of no air flow, of no more than 30 cm of water and an arterial plasma pH of 7.20 to 7.45. Physiological variables were measured at predetermined times in both groups. In the supine group, measurements were performed every 6 hours; in the prone group, measurements were performed just before the patient was turned to the prone position, after 1 hour of prone positioning, just before the patient was turned back to the supine position, and 4 hours after the patient was returned to the supine position. Adjustments of ventilator settings in specific situations are detailed in the Supplementary Appendix.

The criteria for stopping prone treatment were any of the following: improvement in oxygenation (defined as a PaO₂:FiO₂ ratio of ≥150 mm Hg, with a PEEP of ≤10 cm of water and an FiO₂ of ≤0.6; in the prone group, these criteria had to be met in the supine position at least 4 hours after the end of the last prone session); a decrease in the PaO₂:FiO₂ ratio of more than 20%, relative to the ratio in the supine position, before two consecutive prone sessions; or complications occurring during a prone session and leading to its immediate interruption. Complications leading to the immediate interruption of prone treatment included nonscheduled extubation, main-stem bronchus intubation, endotracheal-tube obstruction, hemoptysis, oxygen saturation of less than 85% on pulse oximetry or a PaO₂ of less than 55 mm Hg for more than 5 minutes when the FiO₂ was 1.0, cardiac arrest, a heart rate of less than 30 beats per minute for more than 1 minute, a systolic blood pressure of less than 60 mm Hg for more than 5 minutes, and any other life-threatening reason for which the clinician decided to stop the treatment.

After patients in the prone group were turned to the supine position, the prone session could be resumed at any time before the planned assessment at 4 hours in the supine position if the criteria for oxygen saturation level, PaO₂, or both were met. The prone-positioning strategy was applied every day up to day 28, after which it was used at the clinician’s discretion. Patients in the supine group could not be crossed over to the prone group except as a rescue measure in case of life-threatening hypoxemia when all the following criteria were met simultaneously: a PaO₂:FiO₂ ratio of less than 55 mm Hg, with an FiO₂ of 1.0; maximal PEEP according to the PEEP–FiO₂ table; administration of inhaled nitric oxide at a concentration of 10 ppm; infusion of intravenous almitrine bismesylate at a dose of 4 μg per kilogram per minute; and performance of respiratory recruitment maneuvers to increase the amount of aerated lung.

Weaning from mechanical ventilation was conducted in the same way for both groups (see the Supplementary Appendix). Details regarding the management of sedation and the use of neuromuscular blocking agents are also provided in the Supplementary Appendix. The investigators assessed patients at least every morning until day 28 or discharge from the ICU.

**DATA COLLECTION**

At the time of admission, we recorded data on age, sex, the setting from which the patient was admitted to the ICU, the context for admission to the ICU, McCabe score (which ranges from A to C, with A indicating no underlying disease that compromises life expectancy, B an estimated life expectancy with the chronic disease of ≤5 years, and C an estimated life expectancy with the chronic disease of ≤1 year), ventilator settings, time from intubation to randomization, height, predicted body weight, and the Simplified Acute Physiology Score (SAPS) II (which ranges from 0 to 164, with higher scores indicating greater severity of symptoms). We also recorded the number of lung quadrants involved on chest radiography, results of measurements of arterial blood gases, Pplatₘₙₚ, arterial blood lactate levels, the cause of ARDS, the Sepsis-related Organ Failure Assessment (SOFA) score (which ranges from 0 to 24, with higher scores indicating more severe organ failure), the lung injury score (which ranges from 0 to 4, with higher scores indicating more severe lung injury), and the time at which the first prone session was started.

The following events were recorded daily until day 28: attempts at extubation, administration of inhaled nitric oxide, infusion of almitrine bismesylate, use of extracorporeal membrane oxygenation (ECMO), infusion of sedatives and neuromuscular blockers, complications, and the SOFA score. Ventilator settings, Pplatₘₙₚ, static compliance of the respiratory system, and the results of measurements of arterial blood gases were recorded daily during the first week as indicated above. Data quality was verified by the research.
51,189 Patients were admitted to 27 ICUs in the study period, Jan. 1, 2008–July 25, 2011

47,740 Did not have ARDS

3449 Had ARDS

2015 Were not screened

1434 Were screened

858 Were not eligible

576 Were eligible

102 Were excluded
37 Had improved symptoms after 12–24 hr
35 Had organizational problems in study center
10 Were withdrawn by physician

474 Underwent randomization

234 Were assigned to supine group

5 Were excluded
3 Had Pao₂:Fio₂ >150 mm Hg
1 Was enrolled before 12-hr stabilization period was over
1 Had guardianship issues

240 Were assigned to prone group

3 Were excluded
2 Were enrolled before 12-hr stabilization period was over
1 Received NIV >24 hr

466 Were included in the intention-to-treat analysis
229 Were in supine group
237 Were in prone group

466 Were included in the 90-day follow-up
229 Were in supine group
237 Were in prone group

Figure 1. Enrollment, Randomization, and Follow-up of the Study Participants.
ARDS denotes the acute respiratory distress syndrome, ICU intensive care unit, NIV noninvasive ventilation, and Pao₂:Fio₂ the ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen.
outcome measures
The primary end point was mortality at day 28. Secondary end points were mortality at day 90, the rate of successful extubation, the time to successful extubation, the length of stay in the ICU, complications, the use of noninvasive ventilation, the tracheotomy rate, the number of days free from organ dysfunction, and ventilator settings, measurements of arterial blood gases, and respiratory-system mechanics during the first week after randomization.

Successful extubation was defined as no reintubation or use of noninvasive ventilation in the 48 hours after extubation. In patients who had undergone a tracheotomy, successful weaning from the ventilator was defined as the ability to breathe unassisted through the tracheostomy cannula for at least 24 hours.

statistical analysis
The expected 28-day mortality in the supine group was 60%. We estimated that with a sample of 456 patients, the study would have 90% power to detect an absolute reduction of 15 percentage points (to 45%) with prone positioning, at a one-sided type I error rate of 5%.

An interim analysis was planned 28 days after half the patients had been enrolled, and two analyses were scheduled, each with a type I error rate set to 2.5% to maintain an overall type I error rate of 5%. The statistician sent the data from the interim analysis to the data and safety monitoring board, which had to decide whether to continue or discontinue the trial. An absolute difference in mortality of 25 percentage points or more between groups at the time of the interim analysis was the only criterion for early trial termination. There was no stopping rule for futility.

The analysis was performed on an intention-to-treat basis. Continuous variables were expressed as means with standard deviations. Data were compared between groups with the use of the chi-square test or Fisher’s exact test and analysis of variance as indicated. Patient survival was analyzed with the use of the Kaplan–Meier method and compared between groups with the use of the log-rank test. Cox proportional-hazards regression, with stratification according to center,
Table 2. Ventilator Settings, Respiratory-System Mechanics, and Results of Arterial Blood Gas Measurements at the Time of Inclusion in the Study.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Supine Group (N = 229)</th>
<th>Prone Group (N = 237)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tidal volume (ml)</td>
<td>381±66</td>
<td>384±63</td>
</tr>
<tr>
<td>Tidal volume (ml per kg of PBW)</td>
<td>6.1±0.6</td>
<td>6.1±0.6</td>
</tr>
<tr>
<td>Respiratory frequency (breaths per min)</td>
<td>27±5</td>
<td>27±5</td>
</tr>
<tr>
<td>PEEP (cm of water)</td>
<td>10±4</td>
<td>10±3</td>
</tr>
<tr>
<td>Fio2</td>
<td>0.79±0.16</td>
<td>0.79±0.16</td>
</tr>
<tr>
<td>PplatRs (cm of water)</td>
<td>23±5</td>
<td>24±5</td>
</tr>
<tr>
<td>CstRs (ml per cm of water)</td>
<td>35±15</td>
<td>36±23</td>
</tr>
<tr>
<td>Pao2 (mm Hg)</td>
<td>80±18</td>
<td>80±19</td>
</tr>
<tr>
<td>PaO2:FiO2 (mm Hg)</td>
<td>100±20</td>
<td>100±30</td>
</tr>
<tr>
<td>PacO2 (mm Hg)</td>
<td>52±32</td>
<td>50±14</td>
</tr>
<tr>
<td>Arterial pH</td>
<td>7.30±0.10</td>
<td>7.30±0.10</td>
</tr>
<tr>
<td>Plasma bicarbonate (mmol per liter)</td>
<td>25±5</td>
<td>25±5</td>
</tr>
</tbody>
</table>

* Plus–minus values are means ±SD. CstRs denotes static compliance of the respiratory system, Fio2 the fraction of inspired oxygen, PaO2 partial pressure of arterial oxygen, PaCO2 partial pressure of arterial carbon dioxide, PBW predicted body weight, PEEP positive end-expiratory pressure, and PplatRs end-inspiratory plateau pressure of the respiratory system.
† Data are for 227 participants in the supine group and 236 participants in the prone group.

The characteristics of the patients at inclusion in the study were similar in the two groups except for the SOFA score and the use of neuromuscular blockers and vasopressors (Table 1). In more than half the cases, the main cause of ARDS was pneumonia (Table 1). Influenza A (H1N1) virus infection was the main cause of ARDS in 28 patients, with no significant difference between the groups in the rate (5.7% in the supine group and 6.3% in the prone group, P = 0.85). The mean (±SD) time from intubation to randomization was 31±26 hours in the supine group and 33±24 hours in the prone group (P = 0.66). The lung injury score was 3.3±0.4 in both groups, and the rate of use of noninvasive ventilation in the 24 hours before inclusion was similar in the two groups (29.3% and 30.8% in the supine and prone groups, respectively). Ventilator settings, respiratory-system mechanics, and results of arterial blood-gas measurements were also similar in the two groups (Table 2).

PRONE POSITIONING

Patients in the prone group underwent their first prone-positioning session within 55±55 minutes after randomization. The average number of sessions was 4±4 per patient, and the mean duration per session was 17±3 hours. All the patients in this group underwent at least one prone-positioning session. In the prone group, patients were ventilated in the prone position for 73% of the 22,334 patient-hours spent in the ICU from the start of the first session to the end of the last session.

ADJUNCTIVE THERAPIES

The rates of the use of rescue therapies in the supine and prone groups were 2.6% versus 0.8% for ECMO (P = 0.14), 15.7% versus 9.7% for inhaled nitric oxide (P = 0.05), and 6.6% versus 2.5% for almitrine bismesylate (P = 0.04). Neuromuscular blockers were used for 5.6±5.0 days in the supine group and 5.7±4.7 days in the prone group (P = 0.74), and intravenous sedation was given for 9.5±6.8 and 10.1±7.2 days in the two groups, respectively (P = 0.35). The use of antiviral therapy for H1N1 virus infection was similar in the two groups.

RESULTS

PARTICIPANTS

From January 1, 2008, through July 25, 2011, a total of 3449 patients with ARDS were admitted to the participating ICUs, and 474 underwent randomization (Fig. 1). Eight patients were subsequently excluded (Fig. 1), and 466 patients were included in the analysis: 229 in the supine group and 237 in the prone group. After the interim analysis, the data and safety monitoring board recommended that the trial be continued.

CHARACTERISTICS AT INCLUSION

The characteristics of the patients at inclusion in the study were similar in the two groups except...
The partial pressure of arterial carbon dioxide and static compliance of the respiratory system were similar in the two groups.

**Primary and Secondary Outcomes**

Mortality at day 28 was significantly lower in the prone group than in the supine group: 16.0% (38 of 237 participants) versus 32.8% (75 of 229) (P<0.001) (Table 3). The significant difference in mortality persisted at day 90 (Table 3). A comparison of the two survival curves showed the same significant difference (Fig. 2). After adjustment for the SOFA score and the use of neuromuscular blockers and vasopressors at the time of inclusion, mortality remained significantly lower in the prone group than in the supine group (Table S5 in the Supplementary Appendix).

## Table 3. Primary and Secondary Outcomes According to Study Group.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Supine Group (N = 229)</th>
<th>Prone Group (N = 237)</th>
<th>Hazard Ratio or Odds Ratio with the Prone Position (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality — no. (% [95% CI])</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At day 28</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not adjusted</td>
<td>75 (32.8 [26.4–38.6])</td>
<td>38 (16.0 [11.3–20.7])</td>
<td>0.39 (0.25–0.63)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adjusted for SOFA score†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not adjusted</td>
<td>94 (41.0 [34.6–47.4])</td>
<td>56 (23.6 [18.2–29.0])</td>
<td>0.44 (0.29–0.67)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adjusted for SOFA score†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Successful extubation at day 90 — no./total no. (% [95% CI])</td>
<td>145/223 (65.0 [58.7–71.3])</td>
<td>186/231 (80.5 [75.4–85.6])</td>
<td>0.45 (0.29–0.70)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time to successful extubation, assessed at day 90 — days</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Survivors</td>
<td>19±11</td>
<td>17±16</td>
<td>0.87</td>
<td></td>
</tr>
<tr>
<td>Nonsurvivors</td>
<td>16±11</td>
<td>18±14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length of ICU stay, assessed at day 90 — days</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Survivors</td>
<td>26±27</td>
<td>24±22</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>Nonsurvivors</td>
<td>18±15</td>
<td>21±20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ventilation-free days</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At day 28</td>
<td>10±10</td>
<td>14±9</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>At day 90</td>
<td>43±38</td>
<td>57±34</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Pneumothorax — no. (% [95% CI])</td>
<td>13 (5.7 [3.9–7.5])</td>
<td>15 (6.3 [4.9–7.7])</td>
<td>0.89 (0.39–2.02)</td>
<td>0.85</td>
</tr>
<tr>
<td>Noninvasive ventilation — no./total no. (% [95% CI])</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At day 28</td>
<td>10/212 (4.7 [1.9–7.5])</td>
<td>4/228 (1.8 [0.1–3.5])</td>
<td>0.36 (0.07–3.50)</td>
<td>0.11</td>
</tr>
<tr>
<td>At day 90</td>
<td>3/206 (1.5 [0.2–3.2])</td>
<td>4/225 (1.8 [0.1–3.5])</td>
<td>1.22 (0.23–6.97)</td>
<td>1.00</td>
</tr>
<tr>
<td>Tracheotomy — no./total no. (% [95% CI])</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At day 28</td>
<td>12/229 (5.2 [2.3–8.1])</td>
<td>9/237 (3.8 [1.4–6.0])</td>
<td>0.71 (0.27–1.86)</td>
<td>0.37</td>
</tr>
<tr>
<td>At day 90</td>
<td>18/223 (8.1 [4.5–11.7])</td>
<td>15/235 (6.4 [3.3–9.5])</td>
<td>0.78 (0.36–1.67)</td>
<td>0.59</td>
</tr>
</tbody>
</table>

* Plus–minus values are means ±SD. Hazard ratios are shown for mortality and successful extubation; odds ratios are shown for other outcomes. CI denotes confidence interval.
† There were no significant differences between the groups in organ dysfunction as assessed from the SOFA score (Table S4 in the Supplementary Appendix).
of invasive mechanical ventilation, length of stay in the ICU, incidence of pneumothorax, rate of use of noninvasive ventilation after extubation, and tracheotomy rate did not differ significantly between the two groups (Table 3).

COMPLICATIONS

A total of 31 cardiac arrests occurred in the supine group, and 16 in the prone group (P=0.02). There were no significant differences between the groups with respect to other adverse effects (Table S6 in the Supplementary Appendix).

DISCUSSION

Survival after severe ARDS was significantly higher in the prone group than in the supine group. Furthermore, the effect size was large despite the fact that mortality in the supine group was lower than anticipated.

Our results are consistent with findings from previous meta-analyses\(^2,11\) and an observational study\(^9,10\) even though prior randomized trials have failed to show a survival benefit with prone positioning. Meta-analyses of ARDS studies have suggested that the outcomes with prone positioning are better in the subgroup of patients with severe hypoxemia\(^2,11\). However, when we stratified our analysis according to quartile of \(\text{PaO}_2/\text{FiO}_2\) ratio at enrollment, we found no significant differences in outcomes (Table S8 in the Supplementary Appendix).

Several factors may explain our results. First, patients with severe ARDS were selected on the basis of oxygenation together with PEEP and \(\text{FiO}_2\) levels. Second, patients were included after a 12-to-24-hour period during which the ARDS criteria were confirmed. This period may have contributed to the selection of patients with more severe ARDS\(^9\) who could benefit from the advantages of the prone positioning, such as relief of severe hypoxemia and prevention of ventilator-induced lung injury. A previous study has shown that prone positioning, as compared with supine positioning, markedly reduces the overinflated lung areas while promoting alveolar recruitment.\(^5\) These effects (reduction in overdistention and recruitment enhancement) may help prevent ventilator-induced lung injury by homogenizing the distribution of stress and strain within the lungs. In our trial, alveolar recruitment was not directly assessed. However, studies have shown that lung recruitability correlates with the extent of hypoxemia\(^20,21\) and that the transpulmonary pressure along the ventral-to-dorsal axis is more homogeneously distributed in the prone position than in the supine position.\(^22\) We therefore suggest that prone positioning in our patients induced a decrease in lung stress and strain.

Third, as in previous investigations\(^9,10\), we used long prone-positioning sessions. Fourth, the prone position was applied for 73% of the time ascribed to the intervention and was concentrated over a period of a few days. Fifth, in our trial, the tidal volume was lower than in previous trials\(^9,10\) and the \(P_{\text{plat}}\) was kept below 30 cm of water. However, because all patients were returned to the supine position at least once a day, the effect of the prone position itself cannot be distinguished from the effects of being moved from the supine to the prone position over the course of a day.

We should acknowledge that the technical aspects of prone positioning are not simple and that a coordinated team effort is required (see Videos 1 and 2, available at NEJM.org). All centers participating in this study were skilled in the process of turning patients from the supine to the prone position, as shown by the absence of adverse events directly related to repositioning. Because the experience of the units may explain...
the low rate of complications, our results cannot necessarily be generalized to centers without such experience. We should also emphasize that our results were obtained in the subgroup of severely ill patients with ARDS.

It could be argued that our results can be explained by higher mortality in the control group. However, mortality at day 28 in the supine group was similar to that among controls in recent trials. Furthermore, although the mortality in the control group was lower than that used to compute the power of this study, we calculated that the power of our study was 99%.

The study has several limitations. Although we planned to record the data of patients who were eligible but not included, only a few ICUs complied with this request, making it impossible to fully appreciate the physiological condition of the excluded patients. In addition, fluid balance and the cumulative dose of catecholamines were not assessed. The imbalance between the groups in baseline SOFA score, vasopressor use, and the use of neuromuscular blockers could also have influenced the results. However, even after adjustment for these covariates, mortality was significantly lower in the prone group.

In conclusion, this trial showed that patients with ARDS and severe hypoxemia (as confirmed by a PaO₂/FIO₂ ratio of <150 mm Hg, with an FIO₂ of ≥0.6 and a PEEP of ≥5 cm of water) can benefit from prone treatment when it is used early and in relatively long sessions.

Dr. Guérin reports receiving grant support from Air Liquide; Dr. Mercat, receiving consulting fees from Faron Pharmaceuticals, grant support from Covidien and General Electric, patent royalties on a method for evaluating positive end-expiratory pressure that is licensed to General Electric, and reimbursement for travel expenses from Covidien and Maquet; Dr. Jabre, receiving consulting fees from Maquet and Dräger, lecture fees from Fisher and Paykel, Abbott Laboratories, and Philips Respirronics, and reimbursement for travel expenses from Pfizer and Dr. Mancebo, receiving fees for serving on the data and safety monitoring board of Air Liquide, consulting fees from Faron Pharmaceuticals, Alung, and Philips Respirronics, and grant support to his institution from Covidien and General Electric. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank all the physicians, including those on night duty, and nurses in the participating centers for the care provided to patients during the study; the Réseau Européen en Ventilation Artificielle network; and Carolyn Newey for help in editing an earlier version of the manuscript.

APPENDIX

The authors’ affiliations are as follows: Réanimation Médicale, Hôpital de la Croix-Rousse, Hospices Civils de Lyon; Université de Lyon; and Creatis INSERM 1044, Lyon (C.G., J.-C.R., F.B., G.B., V.L., L.B.); Réanimation Polyvalente, and Clinical Research in Intensive Care and Sepsis (CRICS) Group, La Roche-Sur-Yvon (J. Reignet); Réanimation Polyvalente, Roanne (P.B.); Réanimation Médicale, Hôpital Pontchaillou, Rennes (A.G.); Réanimation Polyvalente, and CRICS Group, Hôpital d’Orléans, Orléans (T.B.); Réanimation Médicale, Hôpital Bretonneau, CRICS Group, and Université de Tours, Tours (E.M.); Réanimation Polyvalente, Hôpital de Chambéry, Chambéry (M.B.); L’Université Nantes Angers Le Mans, Université d’Angers, Centre Hospitalier Universitaire Angers, Réanimation Médicale, Angers (A.M.); Réanimation Polyvalente, and CRICS Group, Hôpital d’Angoulême, Angoulême (O.B.); Réanimation Polyvalente Centre d’Investigation Clinique 0801 and CRICS Group, Hôpital de Léonardes, Léonardes (M.C.); Réanimation Médicale, Hôpital de Poitiers, and CRICS Group, and Université de Poitiers, Poitiers (D.C.); Réanimation Chirurgicale, Hôpital Saint-Eloi, INSERM Unité 1046, and Université de Montpellier, Montpellier (S.J.); Réanimation Polyvalente, Hôpital Saint Joseph et Saint Luc, Lyon (S.R.); Réanimation Polyvalente, Hôpital d’Annecy, Annecy (M.B.); Réanimation Médicale, Hôpital Pellegrin, and Université de Bordeaux, Bordeaux (G.H.); Réanimation Polyvalente, Hôpital de Nîmes, et Université de Nîmes-Montpellier, Nîmes (C.B.); Réanimation Polyvalente, Hôpital de Cergy-Pontoise, Cergy-Pontoise (J. Richecoeur); Réanimation des Urgences, Hôpital de la Timone, et Université de la Méditerranée, Marseille (M.G.); Service d’Hypothèse Hospitalière, Groupement Hospitalier Lyon Sud, Hospices Civils de Lyon, Pierre Bénite (R.G.); and Centre de Coopération et de Lutte contre les Infections Nosocomiales Sud-Est, Hôpital Henri Gabrielle, Saint Genis-Laval (L.A.) — all in France; and Servei de Medicina Intensiva, Hospital de Sant Pau, Barcelona (J.M.).

REFERENCES


Copyright © 2013 Massachusetts Medical Society.