The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 | JUNE 6, 2013 | VOL. 368 NO. 23

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 (FIO_2) of less than 150 mm Hg, with an FIO_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.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Guérin at Service de Réanimation Médicale, Hôpital de la Croix-Rousse, 103 Grande Rue de la Croix-Rousse, 69004 Lyon, France, or at claude.guerin@chu-lyon.fr.

*The Proning Severe ARDS Patients (PROSEVA) study investigators are listed in the Supplementary Appendix, available at NEJM.org.

This article was published on May 20, 2013, at NEJM.org.

N Engl J Med 2013;368:2159-68.
DOI: 10.1056/NEJMoa1214103

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.[1,2] Furthermore, several lines of evidence have shown that prone positioning could prevent ventilator-induced lung injury.[3-6] 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.[7-10] However, meta-analyses[2,11] 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 (PaO_2) to the fraction of inspired oxygen (FIO_2) was less than 150 mm Hg.

METHODS

PATIENTS

We included in the study adults who met the following criteria: ARDS, as defined according to the American–European Consensus Conference criteria[12]; endotracheal intubation and mechanical ventilation for ARDS for less than 36 hours; and severe ARDS (defined as a PaO_2:FIO_2 ratio of <150 mm Hg, with an FIO_2 of ≥0.6, a PEEP of ≥5 cm of water, and a tidal volume of about 6 ml per kilogram of predicted body weight; the criteria were confirmed after 12 to 24 hours of mechanical ventilation in the participating intensive care unit [ICU]). Exclusion criteria are listed in the Supplementary Appendix, available with the full text of this article at NEJM.org.

TRIAL DESIGN

Patients were recruited from 26 ICUs in France and 1 in Spain, all of which have used prone positioning in daily practice for more than 5 years. Randomization was computer-generated and stratified according to ICU. Patients were randomly assigned to the prone group or supine group with the use of a centralized Web-based management system (Clininfo). The protocol, available at NEJM.org, was approved by the ethics committee Comité Consultatif de Protection des Personnes dans la Recherche Biomedicale Sud-Est IV in Lyon, France, and by the Clinical Investigation Ethics Committee at Hospital de Sant Pau in Barcelona. Written informed consent was obtained after the patients' next of kin read the informational leaflet. If patients were able to read the leaflet at some point after inclusion in the study, they were approached to confirm participation in the trial. An investigator at each center was responsible for enrolling patients in the study, following the protocol, and completing the case-report form. Centers were regularly monitored by research fellows. Data collectors were aware of the study-group assignments, but outcomes assessors were not.

The trial was overseen by a steering committee that met monthly. An independent data and safety monitoring board, comprising three experts in the field, was also set up (a list of board members is provided in the Supplementary Appendix). There was no commercial support. No one who is not listed as an author contributed to the writing of this manuscript. All authors vouch for the accuracy of the data and analysis and the fidelity of the study to the protocol.

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. Participating centers 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[13] was delivered in a volume-controlled mode with constant inspiratory flow, with tidal volume targeted at 6 ml per kilogram of predicted body weight[13] and the PEEP level selected from a PEEP–FIO_2 table[14] (Table S1 in the Supplementary Appendix). The goal was to maintain an end-inspiratory plateau pressure of the respiratory system ($Pplat_{RS}$), 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 PaO_2:FIO_2 ratio of ≥150 mm Hg, with a PEEP of ≤10 cm of water and an FIO_2 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 PaO_2:FIO_2 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 PaO_2 of less than 55 mm Hg for more than 5 minutes when the FIO_2 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, PaO_2, 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 PaO_2:FIO_2 ratio of less than 55 mm Hg, with an FIO_2 of 1.0; maximal PEEP according to the PEEP–FIO_2 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[14] (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[15] (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, $Pplat_{RS}$, arterial blood lactate levels, the cause of ARDS, the Sepsis-related Organ Failure Assessment (SOFA) score[16] (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),[17] 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, $Pplat_{RS}$, 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

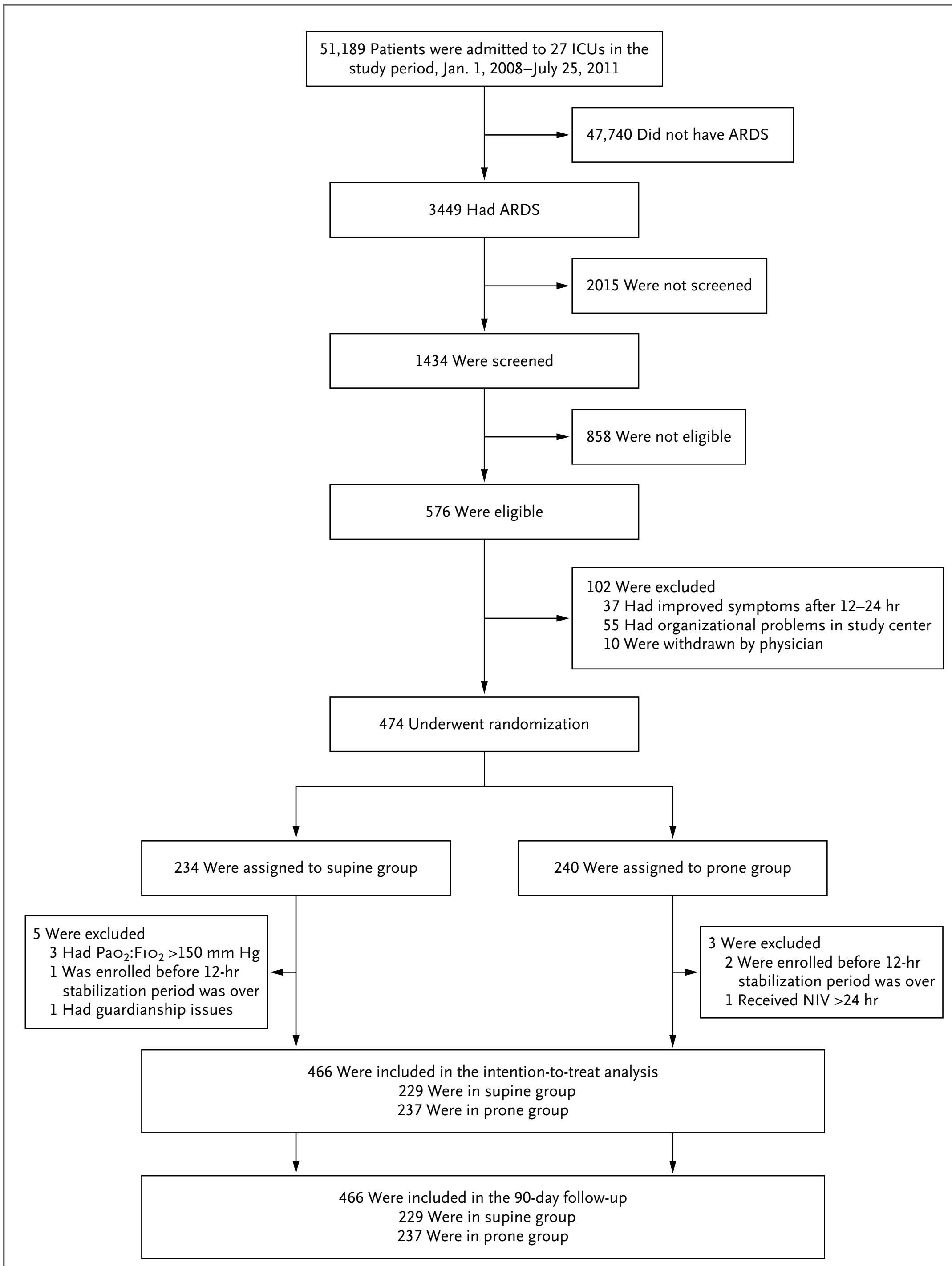


Figure 1. Enrollment, Randomization, and Follow-up of the Study Participants.

ARDS denotes the acute respiratory distress syndrome, ICU intensive care unit, NIV noninvasive ventilation, and Pa_{O_2}:F_{IO_2} the ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen.

fellows, and data were stored in a database (Clininfo) that was specifically developed for the study with the use of Epi Info software, version 3.4.3.

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 1. Characteristics of the Participants at Inclusion in the Study.*

Characteristic	Supine Group (N=229)	Prone Group (N=237)
Age — yr	60±16	58±16
Male sex — no. (%)	152 (66.4)	166 (70.0)
Setting from which patient was admitted to ICU — no. (%)		
Emergency room	98 (42.8)	101 (42.6)
Acute care facility	87 (38.0)	86 (36.3)
Home	26 (11.4)	31 (13.1)
ICU	9 (3.9)	11 (4.6)
Other	9 (3.9)	8 (3.4)
McCabe score — no. (%)†		
A	183 (79.9)	197 (83.1)
B	45 (19.7)	39 (16.5)
C	1 (0.4)	1 (0.4)
Coexisting conditions — no. (%)		
Diabetes	39 (17.0)	50 (21.1)
Renal failure	12 (5.2)	10 (4.2)
Hepatic disease	16 (7.0)	15 (6.3)
Coronary artery disease	24 (10.5)	24 (10.1)
Cancer	30 (13.1)	24 (10.1)
COPD	29 (12.7)	23 (9.7)
Immunodeficiency — no. (%)	38 (16.6)	32 (13.5)
SAPS II‡	47±17	45±15
Sepsis — no./total no. (%)§	195/229 (85.2)	194/236 (82.2)
SOFA score¶	10.4±3.4	9.6±3.2
ARDS due to pneumonia	133 (58.1)	148 (62.4)
Body-mass index‖	29±7	28±6
Other interventions — no./total no. (%)		
Vasopressors	190/229 (83.0)	172/237 (72.6)
Neuromuscular blockers	186/226 (82.3)	212/233 (91.0)
Renal-replacement therapy	39/228 (17.1)	27/237 (11.4)
Glucocorticoids	101/225 (44.9)	91/230 (39.6)

* Plus–minus values are means ±SD. There were no significant differences between the groups in any of the characteristics listed, with the exception of the Sepsis-related Organ Failure Assessment (SOFA) score, the use of vasopressors, and the use of neuromuscular blockers. ARDS denotes the acute respiratory distress syndrome, COPD chronic obstructive pulmonary disease, and ICU intensive care unit. A version of this table with additional information is available as Table S2 in the Supplementary Appendix.

† A McCabe score of A indicates no underlying disease that compromises life expectancy, B an estimated life expectancy with the chronic disease of less than 5 years, and C an estimated life expectancy with the chronic disease of less than 1 year.

‡ The Simplified Acute Physiology Score (SAPS) II ranges from 0 to 164, with higher scores indicating greater severity of symptoms.

§ Sepsis was defined according to the American–European Consensus Conference criteria.

¶ SOFA scores range from 0 to 24, with higher scores indicating more severe organ failure.

‖ The body-mass index is the weight in kilograms divided by the square of the height in meters.

Table 2. Ventilator Settings, Respiratory-System Mechanics, and Results of Arterial Blood Gas Measurements at the Time of Inclusion in the Study.*

Variable	Supine Group (N=229)	Prone Group (N=237)
Tidal volume (ml)	381±66	384±63
Tidal volume (ml per kg of PBW)	6.1±0.6	6.1±0.6
Respiratory frequency (breaths per min)	27±5	27±5
PEEP (cm of water)	10±4	10±3
F_{IO_2}	0.79±0.16	0.79±0.16
$Pplat_{RS}$ (cm of water)	23±5	24±5
Cst_{RS} (ml per cm of water)	35±15	36±23
Pa_{O_2} (mm Hg)	80±18	80±19
Pa_{O_2}:F_{IO_2} (mm Hg)	100±20	100±30
Pa_{CO_2} (mm Hg)	52±32	50±14
Arterial pH	7.30±0.10	7.30±0.10
Plasma bicarbonate (mmol per liter)†	25±5	25±5

* Plus–minus values are means ±SD. Cst_{RS} denotes static compliance of the respiratory system, F_{IO_2} the fraction of inspired oxygen, Pa_{CO_2} partial pressure of arterial carbon dioxide, Pa_{O_2} partial pressure of arterial oxygen, PBW predicted body weight, PEEP positive end-expiratory pressure, and $Pplat_{RS}$ end-inspiratory plateau pressure of the respiratory system.

† Data are for 227 participants in the supine group and 236 participants in the prone group.

was planned to adjust the between-group differences in mortality at day 28 and day 90 for significant baseline covariates. The statistical analysis was performed with the use of SPSS software (SPSS for Windows, version 17.0). The investigators had no access to the database until the study was completed. All reported P values are two-sided, and have not been adjusted for multiple comparisons. A P value of less than 0.05 was considered to indicate statistical significance.

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 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.

VENTILATOR SETTINGS AND LUNG FUNCTION DURING THE FIRST WEEK

The Pa_{O_2}:F_{IO_2} ratio recorded in the supine position was significantly higher in the prone group than in the supine group at days 3 and 5, whereas the PEEP and F_{IO_2} were significantly lower (Table S3 in the Supplementary Appendix). The $Pplat_{RS}$ was 2 cm of water lower by day 3 in the

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

Outcome	Supine Group (N=229)	Prone Group (N=237)	Hazard Ratio or Odds Ratio with the Prone Position (95% CI)	P Value
Mortality — no. (% [95% CI])				
At day 28				
Not adjusted	75 (32.8 [26.4–38.6])	38 (16.0 [11.3–20.7])	0.39 (0.25–0.63)	<0.001
Adjusted for SOFA score†			0.42 (0.26–0.66)	<0.001
At day 90				
Not adjusted	94 (41.0 [34.6–47.4])	56 (23.6 [18.2–29.0])	0.44 (0.29–0.67)	<0.001
Adjusted for SOFA score†			0.48 (0.32–0.72)	<0.001
Successful extubation at day 90 — no./total no. (% [95% CI])	145/223 (65.0 [58.7–71.3])	186/231 (80.5 [75.4–85.6])	0.45 (0.29–0.70)	<0.001
Time to successful extubation, assessed at day 90 — days				
Survivors	19±21	17±16		0.87
Nonsurvivors	16±11	18±14		
Length of ICU stay, assessed at day 90 — days				
Survivors	26±27	24±22		0.05
Nonsurvivors	18±15	21±20		
Ventilation-free days				
At day 28	10±10	14±9		<0.001
At day 90	43±38	57±34		<0.001
Pneumothorax — no. (% [95% CI])	13 (5.7 [3.9–7.5])	15 (6.3 [4.9–7.7])	0.89 (0.39–2.02)	0.85
Noninvasive ventilation — no./total no. (% [95% CI])				
At day 28	10/212 (4.7 [1.9–7.5])	4/228 (1.8 [0.1–3.5])	0.36 (0.07–3.50)	0.11
At day 90	3/206 (1.5 [0.2–3.2])	4/225 (1.8 [0.1–3.5])	1.22 (0.23–6.97)	1.00
Tracheotomy — no./total no. (% [95% CI])				
At day 28	12/229 (5.2 [2.3–8.1])	9/237 (3.8 [1.4–6.0])	0.71 (0.27–1.86)	0.37
At day 90	18/223 (8.1 [4.5–11.7])	15/235 (6.4 [3.3–9.5])	0.78 (0.36–1.67)	0.59

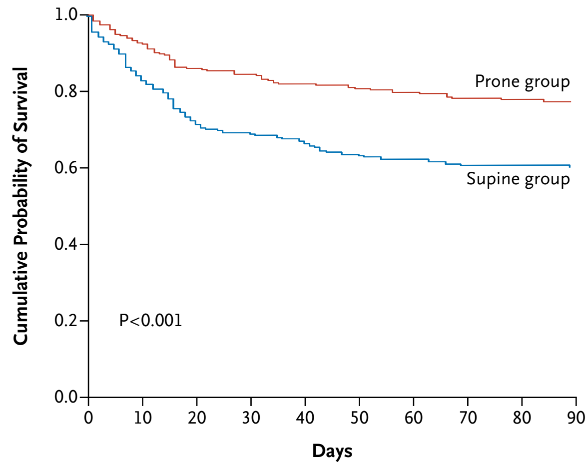
* Plus–minus values are means ±SD. Hazard ratios are shown for mortality and successful extubation; odds ratios are shown for other outcomes. CI denotes confidence interval.

† There were no significant differences between the groups in organ dysfunction as assessed from the SOFA score (Table S4 in the Supplementary Appendix).

prone group than in the supine group. 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). The rate of successful extubation was significantly higher in the prone group (Table 3). The duration



No. at Risk					
Prone group	237	202	191	186	182
Supine group	229	163	150	139	136

Figure 2. Kaplan–Meier Plot of the Probability of Survival from Randomization to Day 90.

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.

Videos showing prone positioning of patients with ARDS are available at NEJM.org

Our results are consistent with findings from previous meta-analyses[2,11] and an observational study,[18] 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 PaO_2: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 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[19] 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 $Pplat_{RS}$ 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.[23,24] 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 PaO_2:FIO_2 ratio of <150 mm Hg, with an FIO_2 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. Jaber, receiving consulting fees from Maquet and Dräger, lecture fees from Fisher and Paykel, Abbott Laboratories, and Philips Respironics, 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 Respironics, 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-Yon (J. Reignier); Réanimation Polyvalente, Roanne (P.B.); Réanimation Médicale, Hôpital Pontchaillou, Rennes (A.G.); Réanimation Polyvalente, and CRICS Group, Hôpital d'Orléans, Orleans (T.B.); Réanimation Médicale, Hôpital Bretonneau, CRICS Group, and Université de Tours, Tours (E.M.); Réanimation Polyvalente, Hôpital de Chambéry, Chambery (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, Angouleme (O.B.); Réanimation Polyvalente Centre d'Investigation Clinique 0801 and CRICS Group, Hôpital de Limoges, Limoges (M.C.); Réanimation Médicale, Hôpital de Poitiers, and CRICS Group, and University of 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.S.); Réanimation Médicale, Hôpital Pellegrin, and Université de Bordeaux, Bordeaux (G.H.); Réanimation Polyvalente, Hôpital de Nîmes, and Université de Nîmes-Montpellier, Nimes (C.B.); Réanimation Polyvalente, Hôpital de Cergy-Pontoise, Cergy-Pontoise (J. Richecoeur); Réanimation des Urgences, Hôpital de la Timone, and Université de la Méditerranée, Marseille (M.G.); Service d'Hygiène Hospitalière, Groupement Hospitalier Lyon Sud, Hospices Civils de Lyon, Pierre Bénite (R.G.); and Centre de Coordination 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

1. Abroug F, Ouanes-Besbes L, Elatrous S, Brochard L. The effect of prone positioning in acute respiratory distress syndrome or acute lung injury: a meta-analysis: areas of uncertainty and recommendations for research. Intensive Care Med 2008;34:1002-11.

2. Sud S, Friedrich JO, Taccone P, et al. Prone ventilation reduces mortality in patients with acute respiratory failure and severe hypoxemia: systematic review and meta-analysis. Intensive Care Med 2010; 36:585-99.

3. Broccard A, Shapiro RS, Schmitz LL, Adams AB, Nahum A, Marini JJ. Prone positioning attenuates and redistributes ventilator-induced lung injury in dogs. Crit Care Med 2000;28:295-303.

4. Mentzelopoulos SD, Roussos C, Zakynthinos SG. Prone position reduces lung stress and strain in severe acute respiratory distress syndrome. Eur Respir J 2005; 25:534-44.

5. Galiatsou E, Kostanti E, Svarna E, et al. Prone position augments recruitment and prevents alveolar overinflation in acute lung injury. Am J Respir Crit Care Med 2006;174:187-97.

6. Papazian L, Gainnier M, Marin V, et al. Comparison of prone positioning and high-frequency oscillatory ventilation in patients with acute respiratory distress syndrome. Crit Care Med 2005;33:2162-71.

7. Gattinoni L, Tognoni G, Pesenti A, et al. Effect of prone positioning on the survival of patients with acute respiratory failure. N Engl J Med 2001;345:568-73.

8. Guerin C, Gaillard S, Lemasson S, et al. Effects of systematic prone positioning in hypoxemic acute respiratory failure: a randomized controlled trial. JAMA 2004;292:2379-87.

9. Mancebo J, Fernández R, Blanch L, et al. A multicenter trial of prolonged prone ventilation in severe acute respiratory distress syndrome. Am J Respir Crit Care Med 2006;173:1233-9.
10. Taccone P, Pesenti A, Latini R, et al. Prone positioning in patients with moderate and severe acute respiratory distress syndrome: a randomized controlled trial. JAMA 2009;302:1977-84.
11. Gattinoni L, Carlesso E, Taccone P, Polli F, Guérin C, Mancebo J. Prone positioning improves survival in severe ARDS: a pathophysiologic review and individual patient meta-analysis. Minerva Anestesiol 2010;76:448-54.
12. Bernard GR, Artigas A, Brigham KL, et al. The American-European Consensus Conference on ARDS: definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med 1994;149:818-24.
13. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 2000;342:1301-8.
14. McCabe WR, Treadwell TL, De Maria A Jr. Pathophysiology of bacteremia. Am J Med 1983;75:7-18.
15. Le Gall JR, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. JAMA 1993;270:2957-63. [Erratum, JAMA 1994;271:1321.]
16. Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. Intensive Care Med 1996;22:707-10.
17. Murray JF, Matthay MA, Luce JM, Flick MR. An expanded definition of the adult respiratory distress syndrome. Am Rev Respir Dis 1988;138:720-3. [Erratum, Am Rev Respir Dis 1989:139:1065.]
18. Charron C, Bouferrache K, Caille V, et al. Routine prone positioning in patients with severe ARDS: feasibility and impact on prognosis. Intensive Care Med 2011;37:785-90.
19. Villar J, Pérez-Méndez L, López J, et al. An early PEEP/FiO2 trial identifies different degrees of lung injury in ARDS patients. Am J Respir Crit Care Med 2007;176:795-804.
20. Gattinoni L, Caironi P, Cressoni M, et al. Lung recruitment in patients with the acute respiratory distress syndrome. N Engl J Med 2006;354:1775-86.
21. Ranieri VM, Rubenfeld GD, Thompson BT, et al. Acute respiratory distress syndrome: the Berlin Definition. JAMA 2012;307:2526-33.
22. Mutoh T, Guest RJ, Lamm WJ, Albert RK. Prone position alters the effect of volume overload on regional pleural pressures and improves hypoxemia in pigs in vivo. Am Rev Respir Dis 1992;146:300-6.
23. Papazian L, Forel J-M, Gacouin A, et al. Neuromuscular blockers in early acute respiratory distress syndrome. N Engl J Med 2010;363:1107-16.
24. Ferguson ND, Cook DJ, Guyatt GH, et al. High-frequency oscillation in early acute respiratory distress syndrome. N Engl J Med 2013;368:795-805.