Effects of Systematic Prone Positioning in Hypoxemic Acute Respiratory Failure
A Randomized Controlled Trial

Claude Guerin, MD
Sandrine Gaillard, MD
Stephane Lemasson, MD
Louis Ayzac, MD
Raphaele Girard, MD
Pascal Beuret, MD
Bruno Palmier, MD
Quoc Viet Le, MD
Michel Sirodot, MD
Sylvaine Rosselli, MD
Vincent Cadiergue, MD
Jean-Marie Sainty, MD
Philippe Barbe, MD
Emmanuel Combourieu, MD
Daniel Debatty, MD
Jean Rouffineau, MD
Eric Ezingeard, MD
Olivier Millet, MD
Dominique Guelon, MD
Luc Rodriguez, MD
Olivier Martin, MD
Anne Renault, MD
Jean-Paul Sibille, MD
Michel Kaidomar, MD

Context A recent trial showed that placing patients with acute lung injury in the prone position did not increase survival; however, whether those results hold true for patients with hypoxemic acute respiratory failure (ARF) is unclear.

Objective To determine whether prone positioning improves mortality in ARF patients.

Design, Setting, and Patients Prospective, unblinded, multicenter controlled trial of 791 ARF patients in 21 general intensive care units in France using concealed randomization conducted from December 14, 1998, through December 31, 2002. To be included, patients had to be at least 18 years, hemodynamically stable, receiving mechanical ventilation, and intubated and had to have a partial pressure of arterial oxygen (PaO2) to fraction of inspired oxygen (FiO2) ratio of 300 or less and no contraindications to lying prone.

Interventions Patients were randomly assigned to prone position placement (n = 413), applied as early as possible for at least 8 hours per day on standard beds, or to supine position placement (n = 378).

Main Outcome Measures The primary end point was 28-day mortality; secondary end points were 90-day mortality, duration of mechanical ventilation, incidence of ventilator-associated pneumonia (VAP), and oxygenation.

Results The 2 groups were comparable at randomization. The 28-day mortality rate was 32.4% for the prone group and 31.5% for the supine group (relative risk [RR], 0.97; 95% confidence interval [CI], 0.79-1.19; P = .77). Ninety-day mortality for the prone group was 43.3% vs 42.2% for the supine group (RR, 0.98; 95% CI, 0.84-1.13; P = .74). The mean (SD) duration of mechanical ventilation was 13.7 (7.8) days for the prone group vs 14.1 (8.6) days for the supine group (P = .93) and the VAP incidence was 1.66 vs 2.14 episodes per 100-patients days of intubation, respectively (P = .045). The PaO2/FiO2 ratio was significantly higher in the prone group during the 28-day follow-up. However, pressure sores, selective intubation, and endotracheal tube obstruction incidences were higher in the prone group.

Conclusions This trial demonstrated no beneficial outcomes and some safety concerns associated with prone positioning. For patients with hypoxemic ARF, prone position placement may lower the incidence of VAP.

JAMA. 2004;292:2379-2387 www.jama.com

©2004 American Medical Association. All rights reserved.
PRONE POSITIONING IN HYPOXEMIC ACUTE RESPIRATORY FAILURE

perfused, also showed no significant improvement in patient outcome.19

We designed this protocol in 1997 before the results of the trial by Gattinoni et al13 were reported. At that time, the intensive care unit (ICU) mortality of hypoxemic ARF in intubated patients, as defined as a partial pressure of arterial oxygen (Pao2) to fraction of inspired oxygen (FIO2) ratio of 300 or less, from various etiologies, was 41% in France.13 We selected 8-hour prone position sessions because no clearly optimal time frame had yet been determined. Also, prone position sessions as short as 4 hours resulted in significant oxygenation improvement.8

We chose to investigate the effect of prone position placement to outcome in unselected patients with hypoxemic ARF to delineate the role of prone positioning in the management of hypoxemic patients. Prone positioning has been routinely used in several centers, such as ours, for many years, not only in ARDS patients14 but also in comatose patients mechanically ventilated without significant hypoxemia.17 Accordingly, the objective of this study was to determine whether systematic use of prone position in patients receiving mechanical ventilation with hypoxemic ARF from various etiologies would decrease mortality.

METHODS

Patients

Patients were considered eligible if they met all the following criteria: mechanical ventilation through either oral or nasal tracheal intubation or tracheostomy; a PaO2/FIO2 of 300 or less; at least 18 years; expected duration of mechanical ventilation of longer than 48 hours; and written informed consent obtained from next of kin. Patients were excluded for any of the following reasons: (1) prone position for at least 6 hours per day in the 4 days preceding enrollment; (2) contraindications to prone position, such as intracranial pressure of more than 30 mm Hg or cerebral perfusion pressure of less than 60 mm Hg, massive hemoptysis, broncho-pleural fistula, tracheal surgery or sternotomy in the last 15 days, mean arterial blood pressure of less than 65 mm Hg with or without vasopressors, deep-
riod during which their clinical condition could stabilize. During this period, clinicians were free to choose the ventilatory mode. Positive end-expiratory pressure (PEEP) and FiO₂ were selected to obtain arterial oxygen saturation (SaO₂) of 90% or more. Sedation and neuromuscular blockade were administered according to clinician preference. If patients still satisfied inclusion criteria, were hemodynamically stable (mean arterial blood pressure ≥ 65 mm Hg with or without vasopressors), and no exclusion criteria were present after this stabilization period, they were enrolled. Time of randomization (day 0) and of the first prone position session were recorded on the CRF. Physicians were asked to follow the standard of care of their ICU and not to change ventilatory settings during the prone position session except for FiO₂.

Patients assigned to the prone position group were placed in a complete prone position for at least 8 hours per day. We provided participating centers with guidelines so that prone position was performed in as standard of a protocol as possible. The beds used for prone positioning were standard hospital beds. While in the prone position, the patients were lying with their heads inclined up and with both arms by their sides, they were given protective pads to minimize pressure sores, and their heads were alternatively turned to right or left every 2 hours.

Patients assigned to the supine group stayed in a semirecumbent position (30° angle, mandated by protocol but not actually measured). Patients in the supine group could cross over to the prone position in case of severe hypoxemia as defined as PaO₂/FiO₂ lower than 100 for more than 12 hours or lower than 60 for more than 1 hour, both receiving pure oxygen.

In both groups, periodic left and right lateral decubitus for nursing care was allowed. The investigator assessed all patients every morning. Prone position was stopped if the physician deemed it necessary if after 2 consecutive prone position sessions they experienced a decrease of PaO₂/FiO₂ by 20% after switching from the supine position or if a major complication attributable to prone position occurred (unplanned extubation, selective intubation, endotracheal tube obstruction, hemothysis, transcutaneous oxygen saturation [SpO₂] < 85% for more than 5 minutes, cardiac arrest, heart rate < 30/min for more than 1 minute, arterial systolic blood pressure < 60 mm Hg for more than 5 minutes, pressure sores, lobar atelectasis, intracranial hypertension, pneumothorax, and ventilator-associated pneumonia [VAP]). In both groups, improvement was defined by 1 major (relative improvement of PaO₂/FiO₂ ≥ 30% relative to randomization, with FiO₂ ≥ 60%) and at least 1 minor criterion (PEEP ≤ 8 cm H₂O, no sepsis, cause of ARF under control [Box], stable or improving chest x-ray, and ≤ 3 organ dysfunctions, including lung dysfunction). Once this improvement was established, sedation and neuromuscular blockade were stopped in both groups and prone position sessions were interrupted.

Weaning from mechanical ventilation was performed according to modified standard criteria. Patients were

Box. Definitions of the Causes of Hypoxemic Acute Respiratory Failure

Pneumonia. Sepsis in which at least 1 primary location is the lower respiratory tract.

Shock. Defined by criteria established by Fagon et al as at least 1 of the following: arterial systolic pressure lower than 90 mm Hg with signs of peripheral hypoperfusion, urine output lower than 500 mL/24 h or lower than 180 mL/8 h, or blood lactate levels higher than 3 mmol/L, or confusion; and use of inotropic or vasopressive agents to maintain arterial systolic pressure higher than 90 mm Hg.

Acute respiratory distress syndrome. Defined by the American-European Consensus Conference as the presence in patients without chronic respiratory failure of acute onset, bilateral diffuse alveolar infiltrates on chest x-ray, partial pressure of oxygen in arterial blood (PaO₂) to fraction of inspired oxygen (FiO₂) ratio lower than 200 mm Hg, and no concern about elevated left atrial pressure.

Acute lung injury. Defined by the American-European Consensus Conference as the following being present in patients without chronic respiratory failure: acute onset, bilateral diffuse alveolar infiltrates on chest-x-ray, PaO₂/FiO₂ lower than 300 mm Hg, no concern about elevated left atrial pressure.

Aspiration. Alveolar infiltrates on chest-x-ray associated with suspicion or clinical evidence for gastric content aspiration.

Septic shock. Shock-induced sepsis according to the definition established by Bone et al.

Acute on chronic respiratory failure. Acute respiratory failure in patients with restrictive, obstructive, or mixed chronic respiratory failure previously documented with PaO₂ lower than 55 mm Hg and/or PaCO₂ higher than 45 mm Hg breathing room air.

Coma. Glasgow coma score less than 6 (score range, 3 to 15 with 3 being the worst).

Postoperative. Acute respiratory failure following surgery including diagnostic or therapeutic endoscopic procedures and interventional radiological procedures.

Nonpulmonary sepsis. Sepsis in which at least 1 primary location is outside the lower respiratory tract, including bacteremia.

Acute cardiogenic pulmonary edema. Unilateral or bilateral alveolar infiltrates on chest x-ray with evidence for elevated left atrial pressure from echocardiography or pulmonary artery catheter.
Figure 1. Flow Diagram of the Trial

Outcome Measures

The primary end point was mortality at 28 days. Secondary end points were mortality at 90 days (to evaluate long-term patient outcome); incidence of VAP and duration of mechanical ventilation (to assess factors that may explain the primary end point); and oxygenation (to evaluate whether the prone position influences oxygenation in hypoxemic patients).

From day 0 to the end of the protocol, the following were recorded before each position change: PaO₂, PaCO₂, pH, and ventilatory settings (up to day 7).

Ventilator-associated pneumonia was defined as a pneumonia occurring more than 48 hours after patients received invasive mechanical ventilation. It was suspected in the presence of a new radiographic infiltrate and at least 1 of the following criteria: temperature higher than 100.4°F (>38°C) or lower than 96.8°F (<36°C), purulent tracheal aspirates, and total white blood cells count lower than 4000/µL or greater than 10,000/µL. It was confirmed by quantitative cultures from fiberoptic or not fiberoptic bronchoalveolar lavage (≥10³ colony-forming units/mL) and/or from Wimberley brush (≥10³ colony-forming units/mL). Ventilator-associated pneumonia was assessed by an investigator in each center, and its determination adjudicated by research fellows.

Successful extubation was defined as no reintubation, survival, or noninvasive ventilation for less than 8 hours per day during the 48 hours following scheduled extubation. In tracheostomized patients, a successful weaning from ventilator was defined as the ability to breathe spontaneously through a T-tube without ventilatory assistance. Duration of mechanical ventilation was defined as the number of days between randomization and successful extubation.

Data Collection

Data were collected at randomization to characterize context of ICU admission, underlying disease, severity of acute illness, ventilatory settings, arterial blood gases, ARF causes, and cointerventions. The duration and number of prone position sessions were recorded during the first week only to improve the efficiency of adequate recording and because fewer patients received prone position as the days passed. Data were verified by the research fellows and stored in a database specifically developed (L.A.) on EpiInfo software (Epi-Info for DOS version 6.3, Centers for Disease Control and Prevention, Atlanta, Ga).

Statistical Analysis

Study sample size was calculated to detect a 10% reduction in 28-day mortality using the prone position with a 2-tailed α error set at 5% and power of 80%. The mortality in the supine group was estimated to be 40% according to a French epidemiological survey. It was calculated that 376 patients needed to be randomized to each group.

The analysis was performed on an intention-to-treat basis. The continuous variables were expressed as mean (SD) and median (SD) if appropriate. The data were compared between the 2 groups using Pearson χ² or Fisher exact test, t test, or Mann-Whitney test as indicated. Patient survival was analyzed using the Kaplan-Meier method and compared with the log-rank test. A 2-factor analysis of variance was used.
to test time and group effects on continuous variables.

The incidence of complications in each group was expressed as ratio of number of events divided by number of patient-days and compared between the supine and prone groups using the Z test.23 The mortality rates among different centers were compared using stratified Mantel-Haenszel analysis. Statistical analysis was performed using SPSS software (SPSS for Windows version 11.0, SPSS Inc, Chicago, Ill). The interim analysis was performed once half the patients had been included to detect a significant excess in 28-day mortality or in serious adverse events in the prone position group. It did not include any stopping rule for futility. This showed no statistically significant difference in the 28-day mortality and serious adverse event occurrence between the 2 groups; therefore, the study continued to its planned end. Reported P values were 2-sided; no adjustments were made for multiple comparisons. Statistical significance was P<.05.

RESULTS

Study Population

The trial was carried out from December 14, 1998, through December 31, 2002. The flow of participants24 was computed from a representative sampling of 12,884 consecutive admissions corresponding to 72.6% of the final included number of patients (FIGURE 1). Because the design of the trial allowed for crossover, we included in the supine group data analysis the 81 patients who had crossed over from the supine group to the prone position. Since this analysis was performed on an intention-to-treat basis, the 6 patients assigned to the prone position but who did not undergo the prone position regimen remained in the final data analysis. These patients did not undergo the prone position regimen because they died (n = 2) or because of a secondary contraindication to being placed in a prone position (n = 4). The final analysis included 791 patients, 378 in the supine group and 413 in prone group. The rate of missing values was less than 1% for all data.

©2004 American Medical Association. All rights reserved.

PRONE POSITIONING IN HYPOXEMIC ACUTE RESPIRATORY FAILURE

Table 1. Baseline Characteristics at Inclusion

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Supine Position (n = 378)</th>
<th>Prone Position (n = 413)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>62.5 (14.7)</td>
<td>62.0 (15.7)</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>26.1 (6.2)</td>
<td>26.2 (6.1)</td>
</tr>
<tr>
<td>Men, No. (%)</td>
<td>289 (76.5)</td>
<td>304 (73.6)</td>
</tr>
<tr>
<td>Simplified Acute Physiology Score II, mean (SD)</td>
<td>46.1 (16.4)</td>
<td>45.1 (15.4)</td>
</tr>
<tr>
<td>Origin, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Home</td>
<td>126 (33.3)</td>
<td>143 (34.6)</td>
</tr>
<tr>
<td>Other hospital</td>
<td>97 (25.7)</td>
<td>92 (22.3)</td>
</tr>
<tr>
<td>Other ward in same hospital</td>
<td>108 (28.6)</td>
<td>120 (29.1)</td>
</tr>
<tr>
<td>Operating room</td>
<td>27 (7.1)</td>
<td>32 (7.7)</td>
</tr>
<tr>
<td>Other ICU</td>
<td>20 (5.3)</td>
<td>26 (6.3)</td>
</tr>
<tr>
<td>Admission classification, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical or poisoning</td>
<td>304 (80.4)</td>
<td>322 (78.0)</td>
</tr>
<tr>
<td>Nonelective surgery</td>
<td>33 (8.7)</td>
<td>41 (9.9)</td>
</tr>
<tr>
<td>Elective surgery</td>
<td>15 (4.0)</td>
<td>20 (4.8)</td>
</tr>
<tr>
<td>Trauma</td>
<td>26 (6.8)</td>
<td>30 (7.3)</td>
</tr>
<tr>
<td>McCabe score, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No underlying fatal illness</td>
<td>244 (64.6)</td>
<td>286 (69.4)</td>
</tr>
<tr>
<td>Non–rapidly fatal underlying illness</td>
<td>109 (28.9)</td>
<td>102 (24.8)</td>
</tr>
<tr>
<td>Rapidly fatal underlying illness</td>
<td>25 (6.6)</td>
<td>24 (5.8)</td>
</tr>
<tr>
<td>Causes of acute respiratory failure†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>228 (60.3)</td>
<td>255 (61.7)</td>
</tr>
<tr>
<td>Shock</td>
<td>121 (32.0)</td>
<td>130 (31.5)</td>
</tr>
<tr>
<td>Acute respiratory distress syndrome</td>
<td>106 (28.0)</td>
<td>140 (33.9)</td>
</tr>
<tr>
<td>Acute lung injury</td>
<td>77 (20.4)</td>
<td>90 (21.8)</td>
</tr>
<tr>
<td>Aspiration</td>
<td>86 (22.8)</td>
<td>95 (23.0)</td>
</tr>
<tr>
<td>Septic shock</td>
<td>102 (27.1)</td>
<td>106 (25.7)</td>
</tr>
<tr>
<td>Acute on chronic</td>
<td>84 (22.2)</td>
<td>104 (25.2)</td>
</tr>
<tr>
<td>Coma</td>
<td>76 (20.1)</td>
<td>84 (20.3)</td>
</tr>
<tr>
<td>Postoperative</td>
<td>48 (12.7)</td>
<td>62 (15.0)</td>
</tr>
<tr>
<td>Nonpulmonary sepsis</td>
<td>33 (8.7)</td>
<td>42 (10.2)</td>
</tr>
<tr>
<td>Acute cardiogenic pulmonary edema</td>
<td>25 (6.6)</td>
<td>31 (7.5)</td>
</tr>
<tr>
<td>Noninvasive ventilation before inclusion, No. (%)</td>
<td>96 (25.4)</td>
<td>106 (25.7)</td>
</tr>
<tr>
<td>No. of organ dysfunctions including lung†, mean (SD)</td>
<td>2.3 (1.0)</td>
<td>2.2 (1.0)</td>
</tr>
<tr>
<td>Respiratory measures, mean (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\text{PaO}_2$/FiO$_2$</td>
<td>155 (59)</td>
<td>150 (59)</td>
</tr>
<tr>
<td>$\text{PaCO}_2$, mm Hg</td>
<td>44 (11)</td>
<td>44 (12)</td>
</tr>
<tr>
<td>pH</td>
<td>7.38 (0.09)</td>
<td>7.39 (0.10)</td>
</tr>
<tr>
<td>Static compliance of respiratory system, mL/cm H$_2$O</td>
<td>41 (15) [n = 222]</td>
<td>40 (20) [n = 251]</td>
</tr>
<tr>
<td>Inspired fraction of oxygen in air, %</td>
<td>65.7 (20.4)</td>
<td>65.7 (20.9)</td>
</tr>
<tr>
<td>Positive end-expiratory pressure, cm H$_2$O</td>
<td>7.5 (3.2)</td>
<td>7.9 (3.4)</td>
</tr>
<tr>
<td>Tidal volume in volume controlled, mL/kg mBW</td>
<td>8.1 (1.9) [n = 326]</td>
<td>8.1 (2.0)</td>
</tr>
<tr>
<td>Respiratory rate, cycles/min in volume controlled</td>
<td>16 [n = 326]</td>
<td>16 [n = 369]</td>
</tr>
<tr>
<td>Inspiratory or total duration of respiratory cycle (s) in volume controlled</td>
<td>37 [n = 322]</td>
<td>38 [n = 367]</td>
</tr>
<tr>
<td>Tidal volume in pressure controlled, mL/kg mBW</td>
<td>11 [n = 38]</td>
<td>10 [n = 28]</td>
</tr>
<tr>
<td>Level of pressure support, cm H$_2$O</td>
<td>20 [n = 48]</td>
<td>21 [n = 41]</td>
</tr>
</tbody>
</table>

*Abbreviations: BMI, body mass index, calculated as weight in kilograms divided by the square of height in meters; FIO$_2$, inspired fraction of oxygen in air; ICU, intensive care unit; mBW, measured body weight; PaCO$_2$, partial pressure of carbon dioxide in arterial blood; PaO$_2$, partial pressure of oxygen in arterial blood.

†Patients could have more than 1 cause.
Baseline
Baseline characteristics were not significantly different between groups (Table 1). Mechanical ventilation was delivered through an oral route in 93.1% of those in the supine group and in 90.8% of those in the prone group (P = .39). The numbers of patients treated with hemodialysis, inotropic support, sedation, neuromuscular blockade, enteral or parenteral nutrition, inhaled nitric oxide, or almitrine were similar in both groups (Table 2). The mean (SD) time between ICU admission and randomization was 54.8 (72.7) hours for the supine group vs 58.6 (84.3) hours for the prone group (P = .23) and length of ICU stay 24.5 (21.9) and 26.6 (29.6) days (P = .35), respectively. The mean (SD) delay between intubation and initiating the first prone position session was 50.8 (74.1) hours and between randomization and the first prone position session was 4.3 (4.6) hours.

Prone Position
Patients were in the prone position for a median of 4.0 (interquartile range, 2.0-6.0) days. During the first week after randomization, the median amount of time patients were in the prone position was 8.0 (interquartile range, 7.7-9.8) hours per day and 0.0 hours per day for the 81 patients who had crossed over to the prone group (P < .001).

Mortality
Crude 28-day mortality rates were 31.5% in the supine group and 32.4% in the prone group (relative risk [RR], 0.97; 95% confidence interval [CI], 0.79-1.19; P = .77; Table 3). The estimate of survival (Figure 2) was not different between the groups. At day 28, 83 (27.9%) of 297 patients in the supine group died, 36 (44.4%) of the 81 patients who had crossed over from the supine group died, 76 (31.3%) of 243 patients in the prone group died, and 58 (34.1%) of 170 patients who crossed over from the prone group died (P = .85).

Secondary End Points
Crude 90-day mortality rates were 42.2% in the supine group and 43.3% in the prone group (RR, 0.98; 95% CI, 0.84-1.13; P = .74; Table 3). The 90-day mortality was 39.2% in the supine group, 53.1% in patients who crossed over to the prone group, 40.3% in prone group, and 47.6% in patients who crossed over to the supine group (P = .83). Mechanical ventilation length and successful extubation rate were not statistically significantly different. Ventilator-associated pneumonia incidence was significantly lower in prone group (Table 3).

In the prone group, PaCO2/FiO2 ratio was significantly higher (Table 3), but VT, PEEP, and FiO2 readings were significantly lower than those in the supine group (Table 4). The Pao2 and pH levels were not significantly different over time between groups (Table 4).

Selective intubation, endotracheal tube obstruction, and incidences of pressure sores were significantly greater in prone group than in the supine group (Table 5). Incidence of other adverse events was not significantly different. The mean (SD) reduction in organ dysfunction was 0.36 (0.95) per day in the supine group and by 0.34 (1.01) per day in the prone group (P = .30).

The 28-day mortality (P = .73), 90-day mortality (P = .70), VAP incidence (P = .42), and successful extubation rate (P = .84) did not differ among centers.

COMMENT
The main findings of this concealed, unblinded, multicenter, randomized trial of hypoxemic ARF patients showed that early prone positioning did not reduce mortality and was associated with harmful effects although it improved oxygenation and reduced the incidence of VAP.

However, several limitations must be acknowledged. First, most hypoxemic patients assigned to the supine group were allowed to be placed in the prone position. When the protocol was designed, even though the effect of prone positioning on patient outcome was not proven, coinvestigators considered it unethical not to allow severely hypoxemic patients to be placed in a prone position. Second, mechanical ventilation was not performed using a predetermined algorithm. This can be explained because present protocol was set up in 1997 and 1998 before results of the ARDSnet trial were available. Hence, mechanical ventilation practice in our trial was at the discretion of each center. However, per center randomization should have balanced this factor between groups. Third, we planned that patients assigned to the prone group would be in the prone position for at least 8 hours per day until their conditions had improved, which had been defined by predetermined criteria. In our study, prone positioning was applied for a mean (SD) of 8.6 (6.6) hours per day for 4.1 (4.7) days. Nevertheless, the prone position regimen was not adequate because 25% of patients were so placed for fewer than 8 hours. Fourth, whereas eligibility of patients other than those with ARDS or ALI could be seen as a limitation, our basic question was “Should we systematically try prone positioning in hypoxemic patients?” Hence, the protocol was designed to directly address our research question.

Our findings confirm the results of the trial byGattinoni et al in which 304 ARF patients, mostly with ARDS, received no benefit from prone position placement in terms of survival and duration of mechanical ventilation. These investigators had planned to use prone positioning for at least 6 hours per day for 10 days. In fact, patients were in the prone position for a mean (SD) of 7.0 (1.8) hours per day, and 41 (27%) of 152 patients in the prone group were so placed for fewer hours than were expected.

Table 2. Cointerventions at Inclusion

<table>
<thead>
<tr>
<th>Cointervention</th>
<th>Supine Position (n = 370)</th>
<th>Prone Position (n = 413)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous intravenous sedation</td>
<td>351 (92.9)</td>
<td>393 (95.2)</td>
</tr>
<tr>
<td>Vasopressor/ inotropic agents</td>
<td>287 (75.9)</td>
<td>292 (70.7)</td>
</tr>
<tr>
<td>Enteral nutrition</td>
<td>138 (36.5)</td>
<td>148 (35.8)</td>
</tr>
<tr>
<td>Parenteral nutrition</td>
<td>91 (24.1)</td>
<td>98 (23.7)</td>
</tr>
<tr>
<td>Neuromuscular blockade</td>
<td>79 (20.9)</td>
<td>85 (20.6)</td>
</tr>
<tr>
<td>Pulmonary artery catheter</td>
<td>56 (14.8)</td>
<td>59 (14.3)</td>
</tr>
<tr>
<td>Inhaled nitric oxide</td>
<td>41 (10.8)</td>
<td>37 (9.0)</td>
</tr>
<tr>
<td>Renal replacement therapy</td>
<td>16 (4.2)</td>
<td>21 (5.1)</td>
</tr>
<tr>
<td>Intravenous almitrine</td>
<td>7 (1.9)</td>
<td>8 (1.9)</td>
</tr>
</tbody>
</table>
pected. Therefore, limited compliance with the scheduled prone position sessions are shared by these 2 studies. The timing of the intervention may differ between the 2 trials because we applied prone position early during the ICU course.

We found that the incidence of pressure sores was higher in the prone group. Neither trial reported whether pressure sore intensity was different between groups. Furthermore, in our study, selective intubation and endotracheal tube obstruction occurred more frequently in patients in the prone group. These adverse events seemed less frequent in our study than in the study by Gattinoni et al.13 However, in both trials, mortality was not affected. Prone positioning is still approached with some reluctance by ICU staff due to the risks of changing position28 and the apparent lack of overall benefit. Therefore, the harmful effects of prone positioning should be reduced by developing guidelines to safely optimize prone position implementation.29

In our trial, we found lower VAP incidence in the prone group. In a small randomized controlled trial of 51 comatose patients, 1 of us (P.B.)17 reported that VAP incidence was 20% in the prone group and 38.4% in the supine group \[P = .14\]. Our study suggests that prone position may be considered as a means of preventing VAP30 along with postural changes and semirecumbent position. It should be noted that there may have been bias in VAP diagnosis since central blinded adjudication was not used. Postulated mechanisms for prone position–induced VAP reduction are drainage effect, reduction of bacterial translocation in experimental ALI,31 and reduction of VILI.11 In our study, VT and FIO2 were slightly lower in the prone group, suggesting that VILI may have been reduced.

In our study, as in the trial conducted by Gattinoni et al,13 oxygenation was improved by the prone position placement without mortality reduction. In our study, this was obtained with lower VT, PEEP, and FIO2 in the prone position group than in the supine group. Oxygenation cannot accurately predict mor-

<table>
<thead>
<tr>
<th>Table 3. Outcome Measures</th>
<th>Supine (n = 378)</th>
<th>Prone (n = 413)</th>
<th>Relative Risk (95% Confidence Interval)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality, No./Total (%) of patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>28 Day</td>
<td>119/378 (31.5)</td>
<td>134/413 (32.4)</td>
<td>0.97 (0.79-1.19)</td>
<td>.77</td>
</tr>
<tr>
<td>90 Day</td>
<td>159/377 (42.2)</td>
<td>179/413 (43.3)</td>
<td>0.98 (0.84-1.13)</td>
<td>.74</td>
</tr>
<tr>
<td>Mechanical ventilation assessed at 90 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mechanical ventilation, mean (SD), d*</td>
<td>14.1 (8.6)</td>
<td>13.7 (7.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients successfully extubated, No./total (%)</td>
<td>248/378 (65.8)</td>
<td>266/413 (64.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inclusion to successful extubation, mean (SD), d</td>
<td>16.0 (13.6)</td>
<td>14.9 (11.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intubation to successful extubation, mean (SD), d</td>
<td>17.6 (13.7)</td>
<td>16.9 (11.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First episode of VAP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Episodes of VAP/patient days of intubation (rate per 100-patient days of intubation)</td>
<td>91/4247 (2.14)</td>
<td>85/5120 (1.66)</td>
<td>.045</td>
<td></td>
</tr>
<tr>
<td>Patients with VAP, No. (%)</td>
<td>91 (24.1)</td>
<td>85 (20.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inclusion to VAP, median IQR, d</td>
<td>10 (6-16)</td>
<td>10.5 (6-17)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: FIO2, fraction of oxygen in air; IQR, interquartile range; VAP, ventilator-associated pneumonia.

*Either invasive or noninvasive for 8 hours or more per day between inclusion and successful extubation.

†P value compares supine and prone position groups and compares days.

Table 3. Outcome Measures

©2004 American Medical Association. All rights reserved.

Figure 2. Cumulative Probability of Patient Survival After Randomization

![Cumulative Probability of Survival](image-url)
PRONE POSITIONING IN HYPOXEMIC ACUTE RESPIRATORY FAILURE

Table 4. Time Course of Arterial Carbon Dioxide, Arterial pH, and Ventilatory Settings During the First Week of Mechanical Ventilation

<table>
<thead>
<tr>
<th>Mean (SD)</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Supine</strong></td>
<td><strong>Prone</strong></td>
<td><strong>Supine</strong></td>
<td><strong>Prone</strong></td>
<td><strong>Supine</strong></td>
</tr>
<tr>
<td>PaCO₂, mm Hg*</td>
<td>43 (10)</td>
<td>43 (11)</td>
<td>43 (10)</td>
<td>42 (9)</td>
</tr>
<tr>
<td>[n = 365]</td>
<td>[n = 308]</td>
<td>[n = 338]</td>
<td>[n = 317]</td>
<td>[n = 326]</td>
</tr>
<tr>
<td>pH</td>
<td>7.38 (0.4)</td>
<td>7.35 (0.5)</td>
<td>7.40 (0.5)</td>
<td>7.47 (2.3)</td>
</tr>
<tr>
<td>[n = 365]</td>
<td>[n = 305]</td>
<td>[n = 338]</td>
<td>[n = 317]</td>
<td>[n = 326]</td>
</tr>
<tr>
<td>PEEP, cm H₂O†</td>
<td>7.8 (3.4)</td>
<td>7.5 (3.5)</td>
<td>7.9 (3.4)</td>
<td>7.5 (3.4)</td>
</tr>
<tr>
<td>[n = 365]</td>
<td>[n = 312]</td>
<td>[n = 340]</td>
<td>[n = 320]</td>
<td>[n = 325]</td>
</tr>
<tr>
<td>VT, mL/kg‡</td>
<td>8.3 (2.3)</td>
<td>8.3 (2.4)</td>
<td>8.3 (2.3)</td>
<td>8.2 (2.3)</td>
</tr>
<tr>
<td>[n = 336]</td>
<td>[n = 299]</td>
<td>[n = 302]</td>
<td>[n = 272]</td>
<td>[n = 282]</td>
</tr>
<tr>
<td>FIO₂, % §</td>
<td>59 (18)</td>
<td>57 (19)</td>
<td>56 (17)</td>
<td>52 (17)</td>
</tr>
<tr>
<td>[n = 365]</td>
<td>[n = 312]</td>
<td>[n = 340]</td>
<td>[n = 320]</td>
<td>[n = 325]</td>
</tr>
</tbody>
</table>

*P<.001 when comparing days.
†P<.005 when comparing supine and prone groups.
‡P<.05 when comparing supine and prone groups.
§P<.01 between supine and prone position groups.

Table 5. Incidence of Complications During the 28 Days After Randomization

<table>
<thead>
<tr>
<th>Incidence per 100 Days (95% CI)</th>
<th>Supine Position</th>
<th>Prone Position</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Unplanned extubation</strong></td>
<td>5188</td>
<td>47</td>
</tr>
<tr>
<td><strong>Selective intubation</strong></td>
<td>5188</td>
<td>0</td>
</tr>
<tr>
<td><strong>ETT obstruction†</strong></td>
<td>5188</td>
<td>12</td>
</tr>
<tr>
<td><strong>Hemoptysis</strong></td>
<td>5188</td>
<td>34</td>
</tr>
<tr>
<td><strong>SpO₂ &lt;85%</strong></td>
<td>5188</td>
<td>207</td>
</tr>
<tr>
<td><strong>Cardiac arrest</strong></td>
<td>5188</td>
<td>88</td>
</tr>
<tr>
<td><strong>Heart rate &lt;30/min</strong></td>
<td>5188</td>
<td>72</td>
</tr>
<tr>
<td><strong>SAP &lt;60 mm Hg</strong></td>
<td>5188</td>
<td>148</td>
</tr>
<tr>
<td><strong>Pressure sores‡</strong></td>
<td>5188</td>
<td>157</td>
</tr>
<tr>
<td><strong>Atelectasis</strong></td>
<td>5188</td>
<td>28</td>
</tr>
<tr>
<td><strong>Intracranial hypertension</strong></td>
<td>5188</td>
<td>3</td>
</tr>
<tr>
<td><strong>Pneumothorax</strong></td>
<td>5188</td>
<td>28</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; ETT, endotracheal tube; SAP, systolic arterial pressure; 95% SpO₂, transcutaneous oxygen saturation of arterial blood.

©2004 American Medical Association. All rights reserved.
Author Affiliations: Service de Réanimation Médicale, Hôpital De La Croix-Rousse, Lyon (Dr Guerin, Gallard, and Lemasson); C-Clin Sud-Est, Centre Hospitalier Lyon-Sud, Pierre Bénite (Dr Ayazc); Service d’hygiène et d’épidémiologie, Centre Hospitalier Lyon-Sud, Pierre Bénite (Dr Girard); Service de Réanimation Polyvalente, Roanne (Dr Beurret); Service de Réanimation, Hôpital D’instruction Des Armées, Toulon (Dr Palmer); Service de Réanimation Polyvalente, Chalon-sur-Saône (Dr Viet Le); Service de Réanimation Polyvalente, Annecy (Dr Sirodot); Service de Réanimation Médicale, Centre Hospitalier Saint Joseph, Lyon (Dr Ro- selli); Service de Réanimation Médicale, Centre Hospitalier Lyon-Sud, Lyon (Dr Cadiergue); Service de Réanimation Polyvalente, Hôpital Sainte Marguerite, Marseille (Dr Sainty); Service de Réanimation Polyvalente, Chambéry (Dr Barbe); Service de Réanimation, Hôpital D’instruction Des Armées, Lyon (Dr Cormeau); Service de Réanimation Polyvalente, Mâcon (Dr De batty); Service de Réanimation Médicale, CHU, Poitiers (Dr Rouffineau); Service de Réanimation, Clinique Mutualiste, Saint-Etienne (Dr Ezingeard); Service de Réanimation, Hopital Edouard-Herriot, Lyon (L. Argaud, O. Mansoor, P. Schoeffler); Service de Réanimation Polyvalente, Lyon-Sud (Dr Sainty); Service de Réanimation Médicale, hôpital de la Croix-Rousse, Lyon (M. Badet, M. Sirodot, Dr Noel, F. Pho- lit); Service de Réanimation Médicale, Hôpital Edouard-Herriot, Lyon (L. Argaud, O. Mansoor, M. Mohamedi, D. Robert); Service de Réanimation Chirurgicale, Hôpital de la Croix-Rousse, Lyon (F. P. Viale); Service deRéanimation Médicale, center hospitalier Saint Joseph, Lyon (P. Dorne, M. Manchoñ, C. Pomier, S. Rosselli); Service de Réanimation, Hôpital d’instruction des armées, Lyon (C. Escarmient, R. G. Patrignon, J. L. Soubricou); Service de Réanimation Polyvalente, Mâcon (M. Clavier, D. Debatty, J. Labrasse); Service de Réanimation Médicale, hôpital Sainte Marie, Marseille (J. M. Forel, L. Papazian, J. M. Sainty); Service de Réanimation Médicale, Centre Hospitalier Lyon-Sud, Pierre Bénite (J. Bohé, V. Cadiergue, D. Jacques, G. Fournier); Service de Réanimation Médicale, CHU, Poitiers (R. Robert, J. Rouffineau); Service de Réanimation Polyvalente, Roanne (M. P. Carton, J. C. Duceux, M. Kaaki, Nourdine K); Service de Réanimation, Clinique Mutualiste, Saint-Etienne (É. Ezingeard, B. Stimmesse); Service de Réanimation, hôpital d’instruction des armées, Toulon (E. Cantais, E. Kaiser, B. Palmier, J. F. Quinto, L. Salinier).

Funding/Support: This work was supported by the Hospices Civils de Lyon (HCL) and by grants HCL-PHR 97.053 and HCL-PHR 97.00.053 from the Ministère de la Santé de France (Programme Hospitalier de Recherche Clinique) and the Hospices Civils de Lyon (Appel d’Investissement Clinique). The project protocol was recorded at the Direction Générale de la Santé (Ministère de l’emploi et de la solidarité) of France and identified as No. DGS 980279.

Role of the Sponsors: The funding agencies were not involved in the design and conduct of the study; the collection, management, analysis, and interpretation of the data; or the preparation, review, or approval of the manuscript.

Acknowledgment: We thank Isabelle Sabaud for review of the language.

REFERENCES


