Effects of Systematic Prone Positioning in Hypoxemic Acute Respiratory Failure

A Randomized Controlled Trial

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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 (PaO_2) to fraction of inspired oxygen (FIO_2) 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 PaO_2/FIO_2 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

PRONE POSITIONING WAS ADVOcated 30 years ago[1] to improve oxygenation in patients with hypoxemic acute respiratory failure (ARF) receiving mechanical ventilation. Dramatic oxygenation improvement using prone positioning was reported in severely hypoxemic patients.[2]

The mechanism of how the prone position improves oxygenation in this setting is still unclear. Postulated hypotheses in humans include alveolar recruitment,[3] redistribution of ventilation[4] toward dorsal areas that remain well

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Caring for the Critically Ill Patient Section Editor: Deborah J. Cook, MD, Consulting Editor, *JAMA*.

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perfused,[5] homogenization of tidal volume (VT) distribution as a result of a better fitting of the lungs with the chest wall,[6] and redirection of compressive force exerted by heart weight on lungs toward the sternum.[7] In addition prone positioning has a drainage effect of respiratory secretions, which has not been systematically investigated. Whereas most experience with the prone position has been for patients with acute lung injury (ALI) or acute respiratory distress syndrome (ARDS), oxygenation may also improve using the prone position for other serious respiratory illness, such as chronic obstructive pulmonary disease[8,9] or acute cardiogenic pulmonary edema.[10]

In patients with chronic obstructive pulmonary disease, the improvement of oxygenation from prone position placement was associated with a reduction in static lung elastance,[9] suggesting that tidal ventilation was operating above closing volume. In patients with cardiogenic pulmonary edema, oxygenation improvement may result from less lung compression by the heart, which is frequently enlarged in this condition. Therefore, translation of these physiological effects into clinical benefits, ie, reduction in mortality, was expected. Speculated mechanisms for this can be reduction in the length of mechanical ventilation and, hence, of its associated adverse effects, such as nosocomial infections and reduction of ventilator-induced lung injury[11] and multiple organ failure.[12]

However, in a randomized controlled trial, Gattinoni et al[13] found that patients with ALI experienced no clinical benefit from prone position placement. This may be due to insufficient statistical power resulting from an interruption of enrollment before reaching the required number of patients (prone position group, 152; control group, 152) or because the average of 7 hours per day that patients were in the prone position may have been an insufficient amount of time to determine efficacy. Another randomized controlled trial of prone position in ARDS patients (only reported in abstract form to date) also showed no significant improvement in patient outcome.[14]

We designed this protocol in 1997 before the results of the trial by Gattinoni et al[13] 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 (PaO_2) to fraction of inspired oxygen (FIO_2) ratio of 300 or less, from various etiologies, was 41% in France.[15] 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 patients[16] 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 PaO_2/FIO_2 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 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-venous thrombosis (to minimize risk for pulmonary embolism from being in a prone position), pacemaker inserted for fewer than 2 days, and unstable fracture; (3) therapeutic limitation indicated in the first 24 hours of ICU admission; (4) high risk of death in the next 48 hours; (5) chronic respiratory failure requiring mechanical ventilation; and (6) inclusion in another protocol with mortality as a primary end point.

Design

The patients were consecutively recruited from 21 ICUs in France. The participating centers had used this maneuver for more than a year. Before inclusion, each center had been formally visited by 2 of us (S.G. and C.G.) during rounds and interview the nursing and physician staff about prone positioning practice and assess interest in the trial. The randomization was computer-generated and separately generated for each ICU. Patients were randomly assigned to the prone position or the supine position group using sequentially numbered, opaque, and sealed envelopes.

The protocol was approved by an ethics committee (Comité Consultatif de Protection des Personnes dans la Recherche Biomedicale Lyon B, Lyon, France) on March 18, 1998. Written informed consent was read and signed by patients' surrogate in every instance. Once patients improved to the point at which they could read a written informed consent, they were approached to confirm trial participation.

A register of admissions to ICUs was maintained, recording the reason for noninclusion of eligible patients. An investigator in each center was responsible for including the patients following the protocol and completing the case record forms (CRFs). The trial was monitored by 2 research fellows (S.G., S.L.) who made periodic site visits. Data collectors and outcomes assessors were not blinded. The trial was overseen by a steering committee that convened monthly meetings.

Protocol

After verification of eligibility, patients were allowed a 12- to 24-hour pe-

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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 FIO_2 were selected to obtain arterial oxygen saturation (SaO_2) 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 FIO_2.

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 placement would be 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 PaO_2/FIO_2 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 PaO_2/FIO_2 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, hemoptysis, transcutaneous oxygen saturation [SpO_2] <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 ventillator-associated pneumonia [VAP]). In both groups, improvement was defined by 1 major (relative improvement of PaO_2/FIO_2 ≥30% relative to randomization, with FIO_2 ≤60%) and at least 1 minor criterion (PEEP ≤8 cm H_2O, no sepsis,[18] cause of ARF under control [BOX, stable or improving chest x-ray, and <3 organ dysfunctions, including lung dysfunction[19]). 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.[21,22] Patients were

Box. Definitions of the Causes of Hypoxemic Acute Respiratory Failure

Pneumonia. Sepsis[18] in which at least 1 primary location is the lower respiratory tract

Shock. Defined by criteria established by Fagon et al[19] 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[20] 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 (PaO_2) to fraction of inspired oxygen (FIO_2) ratio lower than 200 mm Hg, and no concern about elevated left atrial pressure

Acute lung injury. Defined by the American-European Consensus Conference[20] as the following being present in patients without chronic respiratory failure: acute onset, bilateral diffuse alveolar infiltrates on chest-x-ray, PaO_2/FIO_2 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[18]

Acute on chronic respiratory failure. Acute respiratory failure in patients with restrictive, obstructive, or mixed chronic respiratory failure previously documented with PaO_2 lower than 55 mm Hg and/or $PaCO_2$ 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[18] 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

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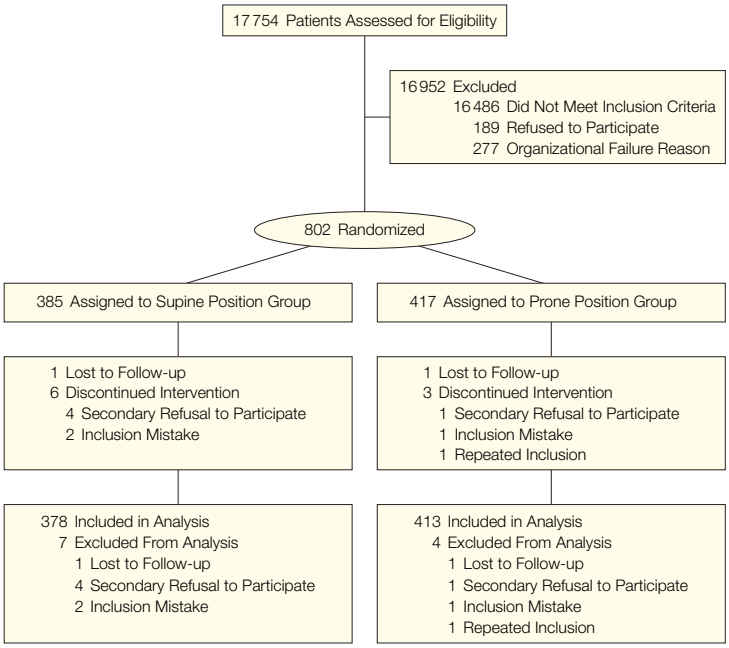
Figure 1. Flow Diagram of the Trial



screened daily for the following criteria: SpO_2 92% or higher with FIO_2 no higher than 40%, PEEP no higher than 5 cm H_2O, normal mental status, adequate cough during tracheal aspiration, no swallowing disorder, no sepsis, no continuous intravenous sedation, no vasoactive support except for dopamine and/or dobutamine of 5 µg/kg per minute or less. Once all of these criteria were present, the patient was disconnected from the ventilator and a 2-hour T-piece trial was initiated with or without a PEEP of 5 cm H_2O. The patient was reconnected to the ventilator if any of the following criteria occurred at any time during the T-piece trial: respiratory rate of 35/min or higher for more than 5 minutes, SpO_2 of less than 90%, heart rate higher than 140/min or changing by more than 20%, systolic arterial blood pressure higher than 180 mm Hg, or anxiety. If none of the above criteria occurred, the patient was extubated.

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 between 7 and 10 AM daily in both patient groups, just before each position change: PaO_2, $PaCO_2$, 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 $4000 \times 10^3/\mu L$ or greater than $12\,000 \times 10^3/\mu L$. It was confirmed by quantitative cultures from fiberoptic or not fiberoptic bronchoalveolar lavage ($\geq 10^4$ colony-forming units/mL) and/or from Wimberley brush ($\geq 10^3$ 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 Epi-Info 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.[15] 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 χ^2 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

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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 participants[24] 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 group 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.

Table 1. Baseline Characteristics at Inclusion

Characteristics	Supine Position (n = 378)	Prone Position (n = 413)
Age, mean (SD), y	62.5 (14.7)	62.0 (15.7)
BMI, mean (SD)	26.1 (6.2)	26.2 (6.1)
Men, No. (%)	289 (76.5)	304 (73.6)
Simplified Acute Physiology Score II,[25] mean (SD)	46.1 (16.4)	45.1 (15.4)
Origin, No. (%)		
Home	126 (33.3)	143 (34.6)
Other hospital	97 (25.7)	92 (22.3)
Other ward in same hospital	108 (28.6)	120 (29.1)
Operating room	27 (7.1)	32 (7.7)
Other ICU	20 (5.3)	26 (6.3)
Admission classification, No. (%)		
Medical or poisoning	304 (80.4)	322 (78.0)
Nonelective surgery	33 (8.7)	41 (9.9)
Elective surgery	15 (4.0)	20 (4.8)
Trauma	26 (6.9)	30 (7.3)
Immunosuppression*	52 (13.8)	59 (14.3)
McCabe score,[26] No. (%)		
No underlying fatal illness	244 (64.6)	286 (69.4)
Non–rapidly fatal underlying illness	109 (28.8)	102 (24.8)
Rapidly fatal underlying illness	25 (6.6)	24 (5.8)
Causes of acute respiratory failure†		
Pneumonia	228 (60.3)	255 (61.7)
Shock	121 (32.0)	130 (31.5)
Acute respiratory distress syndrome	106 (28.0)	140 (33.9)
Acute lung injury	77 (20.4)	90 (21.8)
Aspiration	86 (22.8)	95 (23.0)
Septic shock	102 (27.1)	106 (25.7)
Acute on chronic	84 (22.2)	104 (25.2)
Coma	76 (20.1)	84 (20.3)
Postoperative	48 (12.7)	62 (15.0)
Nonpulmonary sepsis	33 (8.7)	42 (10.2)
Acute cardiogenic pulmonary edema	25 (6.6)	31 (7.5)
Noninvasive ventilation before inclusion, No. (%)	96 (25.4)	106 (25.7)
No. of organ dysfunctions including lung,[19] mean (SD)	2.3 (1.0)	2.2 (1.0)
Respiratory measures, mean (SD)		
Pa_{O_2}/Fi_{O_2}	155 (59)	150 (59)
Pa_{CO_2}, mm Hg	44 (11)	44 (12)
pH	7.38 (0.09)	7.39 (0.10)
Static compliance of respiratory system, mL/cm H_2O	41 (15) [n = 222]	40 (20) [n = 251]
Inspired fraction of oxygen in air, %	65.7 (20.4)	65.7 (20.9)
Positive end-expiratory pressure, cm H_2O	7.5 (3.2)	7.9 (3.4)
Tidal volume in volume controlled, mL/kg mBW	8.1 (1.9) [n = 326]	8.1 (2.0) [n = 369]
Respiratory rate, cycles/min in volume controlled	16 (4) [n = 326]	16 (4) [n = 369]
Inspiratory or total duration of respiratory cycle (%) in volume controlled	37 (8) [n = 322]	38 (8) [n = 367]
Tidal volume in pressure controlled, mL/kg mBW	11 (3) [n = 38]	10 (3) [n = 28]
Level of pressure support, cm H_2O	20 (5) [n = 48]	21 (6) [n = 41]

Abbreviations: BMI, body mass index, calculated as weight in kilograms divided by the square of height in meters; Fi_{O_2}, fraction of oxygen in air; ICU, intensive care unit; mBW, measured body weight; Pa_{CO_2}, partial pressure of carbon dioxide in arterial blood; Pa_{O_2}, partial pressure of oxygen in arterial blood.

*Disseminated cancer, hematological malignancy, organ transplantation, steroids given for at least 30 days or at high dosage for less than 30 days, ongoing chemotherapy or radiotherapy, AIDS, or neutropenia (<500 polymorphonuclear cells/mm^3).

†Patients could have more than 1 cause.

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Table 2. Cointerventions at Inclusion

Cointervention	No. (%) of Patients	
	Supine Position (n = 378)	Prone Position (n = 413)
Continuous intravenous sedation	351 (92.9)	393 (95.2)
Vasopressor/ inotropic agents	287 (75.9)	292 (70.7)
Enteral nutrition	138 (36.5)	148 (35.8)
Parenteral nutrition	91 (24.1)	98 (23.7)
Neuromuscular blockade	79 (20.9)	85 (20.6)
Pulmonary artery catheter	56 (14.8)	59 (14.3)
Inhaled nitric oxide	41 (10.8)	37 (9.0)
Renal replacement therapy	16 (4.2)	21 (5.1)
Intravenous almitrine	7 (1.9)	8 (1.9)

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, PaO_2/FIO_2 ratio was significantly higher (Table 3), but VT, PEEP, and FIO_2 readings were significantly lower than those in the supine group (TABLE 4). The $PaCO_2$ 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=.79), 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[27] 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 by Gattinoni et al[13] 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 ex-

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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 position[28] 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 VAP[30] 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 F_{IO_2} were slightly lower in the prone group, suggesting that VILI may have been reduced.

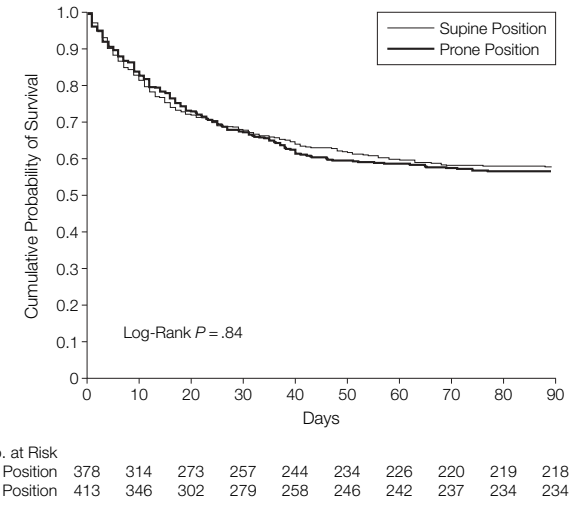
In our study, as in the trial conducted by Gattinoni et al,[13] oxygenation was improved by the prone position placement without mortality reduction. In our study, this was obtained with lower VT, PEEP, and F_{IO_2} in the prone position group than in the supine group. Oxygenation cannot accurately predict mor-

Table 3. Outcome Measures

Outcome Measures	Supine (n = 378)	Prone (n = 413)	Relative Risk (95% Confidence Interval)	*P* Value†
Mortality, No./Total (%) of patients				
28 Day	119/378 (31.5)	134/413 (32.4)	0.97 (0.79-1.19)	.77
90 Day	159/377 (42.2)	179/413 (43.3)	0.98 (0.84-1.13)	.74
Mechanical ventilation assessed at 90 days				
Mechanical ventilation, mean (SD), d*	14.1 (8.6)	13.7 (7.8)		
Patients successfully extubated, No./total (%)	248/378 (65.8)	266/413 (64.4)		
Inclusion to successful extubation, mean (SD), d	16.0 (13.6)	14.9 (11.2)		
Intubation to successful extubation, mean (SD), d	17.6 (13.7)	16.9 (11.4)		
First episode of VAP				
Episodes of VAP/patient days of intubation (rate per 100-patient days of intubation)	91/4247 (2.14)	85/5120 (1.66)		.045
Patients with VAP, No. (%)	91 (24.1)	85 (20.6)		
Inclusion to VAP, median IQR, d	10 (6-16)	10.5 (6-17)		
Pa_{O_2}/F_{IO_2}, mean (SD)				<.001
Day				
1	182 (78) [n = 365]	188 (78) [n = 305]		
2	193 (76) [n = 338]	210 (82) [n = 317]		
3	199 (78) [n = 325]	213 (85) [n = 310]		
4	206 (84) [n = 311]	227 (87) [n = 286]		
5	205 (79) [n = 278]	224 (88) [n = 286]		
6	204 (78) [n = 265]	223 (91) [n = 274]		
7	206 (78) [n = 238]	228 (91) [n = 254]		

Abbreviations: F_{IO_2}, 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 and prone position groups and compares days.

Figure 2. Cumulative Probability of Patient Survival After Randomization



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tality in trials studying the effects of prone positioning on either patients who are severely hypoxemic[13] or unselected mild hypoxemic patients.

In conclusion, the results of this multicenter trial of prone positioning in patients with hypoxemic ARF demonstrated improved oxygenation and a lower incidence of VAP but significant harmful effects and no mortality benefit. Further prone positioning research should address the treatment sessions and timing of the intervention; prone positioning in combination with optimal VT and PEEP; and different target populations, evaluating outcomes such as major morbidities, patient safety, and mortality.

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

	Mean (SD)							
	Day 1		Day 2		Day 3		Day 4	
	Supine	Prone	Supine	Prone	Supine	Prone	Supine	Prone
$Paco_2$, mm Hg*	43 (10) [n = 365]	43 (11) [n = 305]	43 (10) [n = 338]	42 (9) [n = 317]	43 (10) [n = 325]	43 (11) [n = 310]	43 (10) [n = 311]	42 (10) [n = 286]
pH	7.38 (0.4) [n = 365]	7.35 (2.5) [n = 305]	7.40 (0.5) [n = 338]	7.47 (2.3) [n = 317]	7.43 (1.2) [n = 325]	7.16 (1.9) [n = 310]	7.40 (0.2) [n = 311]	7.48 (1.5) [n = 286]
PEEP, cm H_2O†	7.8 (3.4) [n = 365]	7.5 (3.5) [n = 312]	7.9 (3.4) [n = 340]	7.5 (3.4) [n = 320]	7.8 (3.3) [n = 325]	7.4 (3.2) [n = 313]	7.6 (3.4) [n = 312]	7.4 (3.1) [n = 291]
VT, mL/kg‡	8.3 (2.3) [n = 336]	8.2 (2.4) [n = 299]	8.3 (2.3) [n = 299]	8.2 (2.3) [n = 302]	8.4 (2.3) [n = 272]	8.2 (2.3) [n = 282]	8.2 (2.3) [n = 241]	8.2 (2.3) [n = 245]
Fio_2, %§	59 (18) [n = 365]	57 (19) [n = 312]	55 (17) [n = 340]	52 (17) [n = 320]	53 (18) [n = 325]	51 (18) [n = 313]	51 (18) [n = 312]	48 (17) [n = 291]

	Day 5		Day 6		Day 7	
	Supine	Prone	Supine	Prone	Supine	Prone
$Paco_2$, mm Hg*	43 (10) [n = 278]	42 (11) [n = 286]	42 (10) [n = 265]	42 (11) [n = 274]	42 (10) [n = 238]	42 (10) [n = 254]
pH	7.41 (0.1) [n = 278]	7.26 (1.1) [n = 286]	7.40 (0.5) [n = 265]	7.40 (1.8) [n = 274]	7.43 (0.6) [n = 238]	7.33 (1.2) [n = 254]
PEEP, cm H_2O†	7.6 (3.3) [n = 278]	7.2 (3.0) [n = 287]	7.4 (3.0) [n = 266]	7.3 (3.0) [n = 275]	7.3 (3.0) [n = 238]	7.2 (3.0) [n = 257]
VT, mL/kg‡	8.5 (2.5) [n = 216]	8.1 (22) [n = 224]	8.6 (2.3) [n = 198]	8.3 (2.4) [n = 201]	8.7 (2.9) [n = 167]	8.4 (2.5) [n = 183]
Fio_2, %§	50 (17) [n = 278]	47 (17) [n = 287]	50 (18) [n = 266]	47 (17) [n = 275]	49 (18) [n = 239]	47 (16) [n = 257]

Abbreviations: Fio_2, fraction of oxygen in air; $Paco_2$, partial pressure of carbon dioxide in arterial blood; PEEP, positive end-expiratory pressure; VT, tidal volume.
*P=.005 when comparing days.
†P<.001 when comparing supine and prone groups at any time and P = .006 when comparing days for any group.
‡P=.005 when comparing supine and prone groups.
§P=.01 between supine and prone position groups and P<.001 between days after inclusion.

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

	Supine Position			Prone Position		
	Patient-Days	No. of Occurrences	Incidence per 100 Days (95% CI)	Patient-Days	No. of Occurrences	Incidence per 100 Days (95% CI)
Unplanned extubation	5188	47	0.91 (0.65-1.16)	5756	44	0.76 (0.54-0.99)
Selective intubation*	5188	0	0	5755	6	0.10 (0.02-0.19)
ETT obstruction†	5188	12	0.23 (0.10-0.36)	5755	34	0.59 (0.39-0.79)
Hemoptysis	5188	34	0.66 (0.44-0.88)	5755	45	0.78 (0.55-1.01)
Spo_2 <85%	5188	207	3.99 (3.45-4.53)	5755	236	4.10 (3.58-4.62)
Cardiac arrest	5188	88	1.70 (1.34-2.05)	5754	87	1.51 (1.19-1.83)
Heart rate <30/min	5188	72	1.39 (1.07-1.71)	5755	81	1.41 (1.10-1.71)
SAP <60 mm Hg	5188	148	2.85 (2.39-3.31)	5754	135	2.35 (1.95-2.74)
Pressure sores‡	5188	157	3.03 (2.55-3.50)	5756	208	3.61 (3.12-4.10)
Atelectasis	5188	28	0.54 (0.34-0.74)	5756	28	0.49 (0.31-0.67)
Intracranial hypertension	5188	3	0.06 (0.00-0.12)	5756	9	0.16 (0.05-0.26)
Pneumothorax	5188	28	0.54 (0.34-0.74)	5756	22	0.38 (0.22-0.54)

Abbreviations: CI, confidence interval; ETT, endotracheal tube; SAP, systolic arterial pressure; 95% Spo_2, transcutaneous oxygen saturation of arterial blood.
*P=.01.
†P=.002.
‡P=.005 between supine and prone position groups.

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Obtained funding: Guerin, Ayzac, Girard.

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Funding/Support: This work was promoted by the Hospices Civils de Lyon (HCL) and supported by grants HCL-PHRC 97.053 and HCL-PHRC 97.00.053 from the Ministère de la Santé of France (Programme Hospitalier de Recherche Clinique) and the Hospices Civils de Lyon (Appel d'Offres de Recherche 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.

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