



Online article and related content
current as of November 10, 2009.

Prone Positioning in Patients With Moderate and Severe Acute Respiratory Distress Syndrome: A Randomized Controlled Trial

Paolo Taccone; Antonio Pesenti; Roberto Latini; et al.

JAMA. 2009;302(18):1977-1984 (doi:10.1001/jama.2009.1614)

<http://jama.ama-assn.org/cgi/content/full/302/18/1977>

Supplementary material

eTable

<http://jama.ama-assn.org/cgi/content/full/302/18/1977/DC1>

Correction

[Contact me if this article is corrected.](#)

Citations

[This article has been cited 1 time.](#)

[Contact me when this article is cited.](#)

Topic collections

Critical Care/ Intensive Care Medicine; Adult Critical Care; Pulmonary Diseases; Pulmonary Diseases, Other; Randomized Controlled Trial; Prognosis/ Outcomes
[Contact me when new articles are published in these topic areas.](#)

Related Articles published in
the same issue

Improving Outcomes in Critically Ill Patients: The Seduction of Physiology
[Arthur S. Slutsky. JAMA. 2009;302\(18\):2030.](#)

Subscribe

<http://jama.com/subscribe>

Permissions

permissions@ama-assn.org

<http://pubs.ama-assn.org/misc/permissions.dtl>

Email Alerts

<http://jamaarchives.com/alerts>

Reprints/E-prints

reprints@ama-assn.org

Prone Positioning in Patients With Moderate and Severe Acute Respiratory Distress Syndrome

A Randomized Controlled Trial

Paolo Taccone, MD

Antonio Pesenti, MD

Roberto Latini, MD

Federico Polli, MD

Federica Vagginelli, MD

Cristina Mietto, MD

Luisa Caspani, MD

Ferdinando Raimondi, MD

Giovanni Bordone, MD

Gaetano Iapichino, MD

Jordi Mancebo, MD

Claude Guérin, MD

Louis Ayzac, MD

Lluís Blanch, MD

Roberto Fumagalli, MD

Gianni Tognoni, MD

Luciano Gattinoni, MD, FRCP

for the Prone-Supine II Study Group

ACUTE RESPIRATORY DISTRESS syndrome (ARDS) is a clinical condition that entails high mortality¹ and may be associated with severe hypoxemia. Prone positioning is currently suggested for patients with ARDS, for whom high fraction of inspired oxygen (FIO₂) or high plateau pressure makes mechanical ventilation potentially injurious.² Moreover, prone positioning has been advocated as a rescue maneuver for severe hypoxemia, owing to its positive effects on oxygenation,³⁻⁵ which have

Context Post hoc analysis of a previous trial has suggested that prone positioning may improve survival in patients with severe hypoxemia and with acute respiratory distress syndrome (ARDS).

Objective To assess possible outcome benefits of prone positioning in patients with moderate and severe hypoxemia who are affected by ARDS.

Design, Setting, and Patients The Prone-Supine II Study, a multicenter, unblinded, randomized controlled trial conducted in 23 centers in Italy and 2 in Spain. Patients were 342 adults with ARDS receiving mechanical ventilation, enrolled from February 2004 through June 2008 and prospectively stratified into subgroups with moderate (n=192) and severe (n=150) hypoxemia.

Interventions Patients were randomized to undergo supine (n=174) or prone (20 hours per day; n=168) positioning during ventilation.

Main Outcome Measures The primary outcome was 28-day all-cause mortality. Secondary outcomes were 6-month mortality and mortality at intensive care unit discharge, organ dysfunctions, and the complication rate related to prone positioning.

Results Prone and supine patients from the entire study population had similar 28-day (31.0% vs 32.8%; relative risk [RR], 0.97; 95% confidence interval [CI], 0.84-1.13; *P*=.72) and 6-month (47.0% vs 52.3%; RR, 0.90; 95% CI, 0.73-1.11; *P*=.33) mortality rates, despite significantly higher complication rates in the prone group. Outcomes were also similar for patients with moderate hypoxemia in the prone and supine groups at 28 days (25.5% vs 22.5%; RR, 1.04; 95% CI, 0.89-1.22; *P*=.62) and at 6 months (42.6% vs 43.9%; RR, 0.98; 95% CI, 0.76-1.25; *P*=.85). The 28-day mortality of patients with severe hypoxemia was 37.8% in the prone and 46.1% in the supine group (RR, 0.87; 95% CI, 0.66-1.14; *P*=.31), while their 6-month mortality was 52.7% and 63.2%, respectively (RR, 0.78; 95% CI, 0.53-1.14; *P*=.19).

Conclusion Data from this study indicate that prone positioning does not provide significant survival benefit in patients with ARDS or in subgroups of patients with moderate and severe hypoxemia.

Trial Registration clinicaltrials.gov Identifier: NCT00159939

JAMA. 2009;302(18):1977-1984

www.jama.com

been repeatedly documented since its first description in 1976.⁶ However, no randomized clinical trial has yet demonstrated a significant reduction in mortality rate associated with prone positioning.⁷⁻⁹ In a previous randomized trial⁷ we had observed, in a hypothesis-generating post hoc analysis,¹⁰ that in the subgroup of patients with the most

severe hypoxemia and with ARDS, survival was better in the prone than in the supine position. In that study, prone po-

Author Affiliations and Members of the Prone-Supine II Study Group are listed at the end of this article.

Corresponding Author: Luciano Gattinoni, MD, FRCP, Dipartimento di Anestesia e Rianimazione, Fondazione IRCCS—"Ospedale Maggiore Policlinico, Mangiagalli, Regina Elena" di Milano; Via F. Sforza 35, 20122 Milan, Italy (gattinon@policlinico.mi.it).

For editorial comment see p 2030.

sitioning was limited to 6 hours per day for up to 10 days, and no modification of mechanical ventilation settings was allowed when patients were turned from the supine to the prone position.

Since the completion of that study, new evidence has been made available. First, the ARDS Network has definitely demonstrated the potential harm of high tidal volume mechanical ventilation.¹¹ Second, extensive laboratory work has suggested that prone positioning is able to prevent or delay the development of ventilator-induced lung injury, probably because of a more homogeneous distribution of lung stress and strain.^{12,13} Third, another trial⁹ in which prone positioning was prolonged for up to 20 hours per day without the 10-day limit has shown a trend toward survival benefit. This positive signal, however, was not statistically significant, since the population enrolled was smaller than planned because of logistic and economic reasons (enrollment of patients in other, more remunerative, clinical trials).

Therefore, on the basis of the acquired information, we decided to organize a second trial, the Prone-Supine II (PSII) study, to detect the potential survival benefit of prone positioning while avoiding the recognized limitations of previous trials. Accordingly, only patients with ARDS were included and stratified a priori into a subgroup of patients with moderate hypoxemia and a subgroup of patients with severe hypoxemia. Moreover, mechanical ventilation was administered in line with a lung protective strategy¹¹ in both the prone and the supine groups of the study, and daily prone positioning was prolonged for 20 hours, without the 10-day limit.

METHODS

Study Design and Participants

The PSII study prospectively investigated, in a population of patients with ARDS, whether prone positioning—compared to supine positioning—improves survival. In this multicenter, unblinded, randomized controlled trial, we recruited patients from 25 intensive

care units in Italy (23 centers) and Spain (2 centers). The trial was approved by the institutional review boards of each hospital. Written informed consent was obtained according to the national regulations of the participating institutions (consent was delayed in Italy until after the patients had recovered from the effects of sedation and was obtained from the patients' next of kin in Spain; no refusal was registered in either setting).

Patients were considered eligible if they were receiving invasive mechanical ventilation and fulfilled the diagnostic criteria of ARDS,¹⁴ ie, a PaO_2 : FIO_2 ratio equal to or lower than 200 mm Hg, as assessed with a blood gas analysis performed with a positive end-expiratory pressure (PEEP) maintained between 5 and 10 cm H_2O . At randomization, patients were stratified according to the severity of hypoxemia. The subgroup of patients with moderate hypoxemia was defined by a PaO_2 : FIO_2 ratio between 100 mm Hg and 200 mm Hg at enrollment, while the subgroup with severe hypoxemia was defined by a PaO_2 : FIO_2 ratio lower than 100 mm Hg.

Exclusion criteria were age younger than 16 years, more than 72 hours elapsed since the diagnosis of ARDS by the attending physician, history of solid organ or bone marrow transplantation, and any clinical condition contraindicating the use of prone positioning (eg, intracranial hypertension, spine or pelvic fractures).

Patient allocation to the prone or supine groups was assigned with a centralized telephone randomization system operated on a 24-hours-a-day, 7-days-a-week basis. A randomization list was computer-generated with a permuted-block algorithm, with stratification of patients according to the severity of hypoxemia and to participating center.

Procedures and Outcomes

Patients randomized to the prone group remained in the prone position for at least 20 hours per day, until the resolution of acute respiratory failure (according to a protocolized procedure) or

the end of the 28-day study period. Prone positioning was applied using a rotational bed (Rotoprone; KCI Medical Products, San Antonio, Texas) in 20 participating centers and applied manually in the remaining 5 centers. In the supine group, prone positioning could be used only as a rescue maneuver in cases of life-threatening hypoxemia (eg, $\text{PaO}_2 \leq 55$ mm Hg at $\text{FIO}_2 = 1.00$ and $\text{PEEP} \geq 15$ cm H_2O).

Mechanical ventilation was administered according to a prespecified protocol in both study groups. In particular, it was required that tidal volumes be limited to a maximum of 8 mL/kg of ideal body weight and airway plateau pressures be limited to 30 cm H_2O . To reach the oxygenation target (ie, PaO_2 between 70-90 mm Hg), we suggested that FIO_2 and PEEP be set according to a table predefined by the investigators (minimal set FIO_2 , 0.3 at $\text{PEEP} = 5$ cm H_2O ; maximal set FIO_2 , 1.0 at $\text{PEEP} = 20$ -24 cm H_2O). The respiratory rate was set to maintain an arterial blood pH between 7.30 and 7.45. Decisions about other therapeutic interventions (eg, nutrition, sedation, antibiotic therapy, weaning from mechanical ventilation) were not specified in the study protocol. The investigators were required to report the use of nonconventional treatment, eg, high-frequency oscillatory ventilation, use of inhaled nitric oxide, or extracorporeal lung support.

Demographic data, coded primary diagnosis,¹⁵ and severity of illness as assessed with the Simplified Acute Physiology Score II¹⁶ were recorded at study enrollment. During the 28-day study period, Sequential Organ Failure Assessment (SOFA) scores¹⁷ were collected daily to evaluate the severity of organ dysfunction. Adverse events related to repositioning of patients from the supine to the prone position or vice versa (eg, displacement of tubes and lines) or those associated with remaining in the prone position (eg, need for increased sedation) were also recorded on a daily basis. Physiological variables were recorded at 12-hour intervals: in the morning, patients from

both groups were in the supine position, while in the evening patients were in either the prone or the supine position, according to the randomization group.

The primary outcome measure was death from any cause, assessed 28 days after enrollment in the study. Secondary outcome measures were mortality from any cause at intensive care unit discharge and at 6 months, SOFA scores at 28 days of follow-up, and ventilator-free days. The latter represents the number of days, during the 28-day study period, in which the patients had been breathing without any assistance and are defined to be equal to 0 in patients who died during the study period.¹⁸

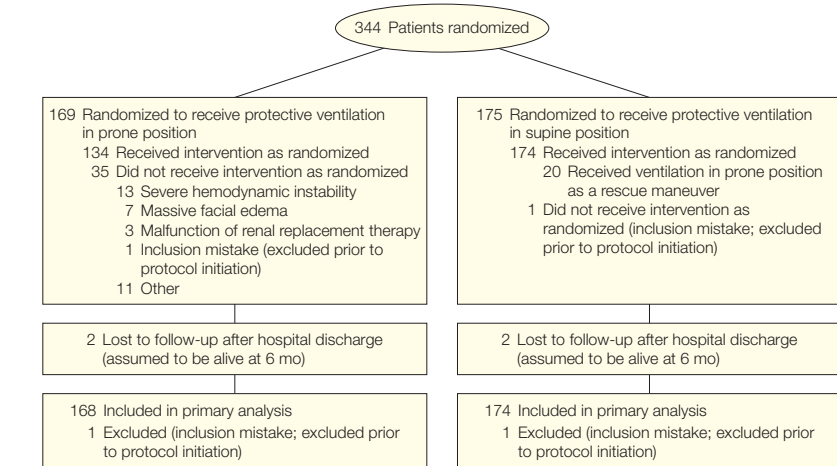
Outcomes data were available during the study only to the members of the data and safety monitoring board for interim analysis. Investigators were blinded to outcomes data until the end of the study.

Statistical Analysis

Expecting a 28-day mortality rate of 50% in the supine group and estimating an absolute 28-day mortality rate reduction of 15% in the prone group (the order of magnitude found in the trial of Mancebo et al⁹ with prolonged prone positioning), we calculated that a sample of 340 patients was required (2-tailed $\alpha = .05$, 80% power). An interim analysis to assess the efficacy and safety of the trial was performed when data of about 170 randomized patients became available (November 2006), using the procedure of Peto.¹⁹ Accordingly, the corresponding significance level to stop the trial was $P < .001$.

The primary analysis was performed on an intention-to-treat basis. All analyses were performed both for the entire population (ie, all patients enrolled in the PSII study) and for the subgroups of patients with moderate and severe hypoxemia. Outcomes and complications were compared, without any adjustment for multiple comparisons, using t tests, χ^2 tests, or Wilcoxon-Mann-Whitney tests, as appropriate. A 2-factor analysis of variance was used to test time and group effects on con-

Figure 1. Study Flow



tinuous variables. Primary outcome was compared using the χ^2 test. Kaplan-Meier curves for the estimated survival rate in both study groups were compared using a log-rank test. Logistic regression analysis was used to test for interaction between hypoxemia severity (ie, moderate vs severe) and treatment (ie, prone vs supine positioning) with regard to mortality.

Continuous variables are shown as mean (SD) or median (interquartile range), as appropriate. Statistical analysis was performed using SAS version 9.1 (SAS Institute Inc, Cary, North Carolina). Two-sided $P < .05$ was considered statistically significant for any test.

RESULTS

Study Population

From February 2004 to June 2008, 344 patients were randomized in the PSII study. As shown in FIGURE 1, 342 patients (168 in the prone group, 174 in the supine group) were included in the analysis: 192 patients were stratified into the subgroup of patients with moderate hypoxemia (94 prone, 98 supine) and 150 into the subgroup with severe hypoxemia (74 prone, 76 supine). The baseline characteristics of the study population are reported in TABLE 1. Of note, patients with severe hypoxemia, independently of the assigned treatment, were characterized by greater clinical severity and higher mor-

tality rates than patients with moderate hypoxemia.

Prone Positioning

Patients enrolled in the prone group were ventilated in the prone position for 1397 of 2760 patient-days (51.0%). Each patient underwent a mean of 8.4 (SD, 6.3) pronation sessions, which lasted for 18 (SD, 4) hours per day. The 20-hour daily target was fully reached in 1086 of 1397 patient-days (77.8%). The main reason for not completing the 20-hour target was related to the need to perform other clinical procedures.

Thirty-four patients (20.2%) in the prone group did not receive the assigned treatment at least once, because of severe hemodynamic instability (13 patients), massive facial edema (7 patients), malfunction of continuous renal replacement therapy (3 patients), or other reason (eg, potential dislodgment of a chest/tracheotomy tube, cerebral edema, massive alveolar hemorrhage) (11 patients), for a total of 160 of 2760 patient-days (5.8%) of protocol violation. Twenty patients (11.5%) in the supine group received prone positioning as a rescue procedure, for a total of 51 of 2764 patient-days (1.9%) of protocol violation. Nonconventional treatments were applied for refractory life-threatening hypoxemia only in 4 patients (2 from each group) and consisted uniquely of extracorporeal lung support.

Table 1. Baseline Characteristics of the Prone-Supine II Study Population

Characteristic	Mean (SD)		
	Entire Population (n = 342)	Moderate Hypoxemia (n = 192)	Severe Hypoxemia (n = 150)
Age, y	60 (16)	61 (16)	59 (17)
BMI ^a	25.3 (4.6)	24.8 (4.4)	25.8 (4.8)
Women, No. (%)	98 (28.7)	59 (30.7)	39 (26.0)
SAPS II score ^b	41.0 (14.6)	39.5 (14.5)	43.0 (14.6)
SOFA score at entry ^c	6.8 (3.9)	6.1 (3.5)	7.7 (4.2)
PaO ₂ :FiO ₂ ratio	113 (39)	141 (27)	77 (16)
PEEP, cm H ₂ O	10 (3)	9 (2)	11 (3)
FiO ₂	0.72 (0.19)	0.62 (0.14)	0.85 (0.16)
Tidal volume per ideal body weight, mL/kg ^d	8.0 (1.7)	8.2 (1.7)	7.7 (1.6)
Minute ventilation, L/min	9.8 (2.8)	9.4 (2.8)	10.2 (2.8)
Paco ₂ , mm Hg	46.5 (11.9)	44.2 (10.0)	49.4 (13.4)
Mechanical ventilation before enrollment, median (IQR), d	0 (0-1)	0 (0-2)	0 (0-1)
Cause of respiratory failure, No. (%)			
Pneumonia	202 (59.1)	110 (57.3)	92 (61.3)
Aspiration	22 (6.4)	15 (7.8)	7 (4.7)
Sepsis	16 (4.7)	8 (4.2)	8 (5.3)
Trauma	6 (1.8)	4 (2.1)	2 (1.3)
Other	80 (23.4)	45 (23.4)	35 (23.3)

Abbreviations: BMI, body mass index; IQR, interquartile range; FiO₂, fraction of inspired oxygen; PEEP, positive end-expiratory pressure; SAPS II, Simplified Acute Physiology Score II; SOFA, Sequential Organ Failure Assessment.

^aCalculated as weight in kilograms divided by height in meters squared.

^bUsed to assess the severity of illness; range, 0 to 194, with higher scores indicating higher risk of death.

^cUsed to assess the degree of dysfunction of 5 organ systems: respiratory, cardiovascular, renal, neurologic, hepatic. Each subscore ranges from 0 (healthy) to 4 (maximum severity); the overall score ranges from 0 to 20.

^dIdeal body weight calculated as 50 + 0.91 · (height in centimeters – 152.4) for men and as 45.5 + 0.91 · (height in centimeters – 152.4) for women.¹¹

Time Course of Respiratory Variables and SOFA Score

The time course in the first 7 days of the most relevant respiratory variables, as well as the SOFA score, is reported in the eTable available at <http://www.jama.com>. As shown, the PaO₂:FiO₂ ratio, in the entire population, was significantly higher in the prone group than in the supine group, while FiO₂ was significantly lower. Positive end-expiratory pressure, tidal volume, and total minute ventilation were similar in the prone and supine groups. A similar pattern was observed in the subgroups of patients with moderate and severe hypoxemia (higher oxygenation in the prone than in the supine group, with a lower FiO₂ at similar PEEP, tidal volume, and minute ventilation). The time course of the SOFA score was similar between the prone and supine groups in the entire population, as well as in the patients with moderate and severe hypoxemia.

Outcomes

Mortality rates of prone and supine patients at 28 days, intensive care unit discharge, and 6 months for the entire PSII study population, and for patients with moderate and severe hypoxemia, are reported in TABLE 2. As shown, the difference in mortality rates between prone and supine patients does not reach statistical significance at any point. However, we observed a statistically non-significant 10% difference in favor of the prone group in the subgroup of patients with severe hypoxemia (risk ratio at 6 months in favor of prone positioning, 0.83; 95% confidence interval, 0.63-1.10). The test for interaction, however, between treatment group and severity of hypoxemia subgroup was not significant ($P = .28$). Six-month survival curves are shown in FIGURE 2.

Median SOFA scores, ventilator-free days, and intensive care unit length of stay were also similar between the prone and the supine patients, both in

the entire PSII study population and in the subgroups of patients with moderate and severe hypoxemia (Table 2).

Complications

TABLE 3 reports the clinically relevant complications observed during the study. A significantly greater proportion of patients in the prone group, as compared with the supine group, experienced at least 1 complication (159/168 [94.6%] in the prone group vs 133/174 [76.4%] in the supine group, $P < .001$). In addition, the incidence of most of the complications (eg, need for increased sedation, muscle paralysis, hemodynamic instability, device displacement) was significantly higher in the prone than in the supine group. The number of complications experienced during the 28-day study period was found to be significantly correlated with the number of days each patient in the prone group ($r^2 = 0.62$, $P < .001$) and the supine group ($r^2 = 0.44$, $P < .001$) remained in the study.

COMMENT

In this study, we found that in an unselected population of patients affected by ARDS—as currently defined—the use of prolonged periods of prone positioning is not associated with any detectable survival advantage. This result is in line with that of previously published studies.⁷⁻⁹

When the present PSII trial was being planned, an effort was made to correct those design issues that had been advocated as possible reasons for the negative findings of previous trials—namely, the lack of standardized mechanical ventilation protocols, the short duration of periods of prone positioning, the delay in instituting prone positioning after the diagnosis of ARDS, and the low degree of severity of the patients enrolled in the trials. Each of these issues deserves some comment.

In the present trial, unlike in the first Prone-Supine study,⁷ a specific protocol was developed to guide continuous modifications in the settings of mechanical ventilation. The rationale of the strategy was that prone positioning may

actually promote the lung-protective ventilation strategy.¹¹ In fact, by taking advantage of the potential improvement in oxygenation and respiratory compliance associated with prone positioning, physicians could possibly reduce potentially harmful levels of oxygen in inspired air, tidal volumes, and positive end-expiratory pressures.¹¹ Our results, however, have shown that only

FIO₂ was significantly lower (about 5%) in the prone than in the supine position. The similarity of PEEP and tidal volume in the prone and supine positions suggests that prone positioning per se did not induce sufficiently large changes in the lung parenchyma to make clinically relevant modifications of the applied mechanical ventilation settings feasible.

The hypothesis behind the PSII study was that mechanical ventilation could be less injurious if applied in the prone position than if applied in the supine position, owing to the well-recognized greater homogeneity of stress and strain distribution across the lung parenchyma²⁰ when mechanical ventilation is applied in the prone position. Accordingly, the earlier the application

Table 2. Primary and Secondary Outcomes in the Prone-Supine II Study

Outcome	Entire Population (n = 342)				Moderate Hypoxemia (n = 192)				Severe Hypoxemia (n = 150)			
	Prone (n = 168)	Supine (n = 174)	RR (95% CI)	P Value ^a	Prone (n = 94)	Supine (n = 98)	RR (95% CI)	P Value ^a	Prone (n = 74)	Supine (n = 76)	RR (95% CI)	P Value ^a
28-d mortality, No. (%)	52 (31.0)	57 (32.8)	0.97 (0.84-1.13)	.72	24 (25.5)	22 (22.5)	1.04 (0.89-1.22)	.62	28 (37.8)	35 (46.1)	0.87 (0.66-1.14)	.31
ICU mortality, No. (%)	64 (38.1)	73 (42.0)	0.94 (0.79-1.12)	.47	30 (31.9)	31 (31.6)	1.00 (0.83-1.22)	.97	34 (45.9)	42 (55.3)	0.83 (0.60-1.15)	.25
6-mo mortality, No. (%) ^b	79 (47.0)	91 (52.3)	0.90 (0.73-1.11)	.33	40 (42.6)	43 (43.9)	0.98 (0.76-1.25)	.85	39 (52.7)	48 (63.2)	0.78 (0.53-1.14)	.19
SOFA score, median (IQR) ^c	6.7 (6.2-7.3)	6.8 (6.3-7.5)		.87	6.0 (5.3-6.8)	6.2 (5.5-6.9)		.52	7.7 (6.8-8.5)	7.6 (6.7-8.9)		.93
Ventilator-free days, median (IQR), d ^d	0 (0-12)	0 (0-14)		.31	0 (0-16)	0 (0-17)		.23	0 (0-9)	0 (0-11)		.87
Duration of mechanical ventilation in 28-d survivors, median (IQR), d ^e	25 (12-28)	19 (9-28)		.12	23 (10-28)	19 (7-28)		.27	27 (12-28)	18 (11-28)		.25
Duration of mechanical ventilation in 28-d nonsurvivors, median (IQR), d ^e	8 (4-16)	9 (4-15)		.92	9 (5-18)	10 (7-14)		.85	8 (3-14)	7 (3-18)		.80
ICU length of stay, median (IQR), d	17.5 (9-31)	16 (8-26)		.17	18 (8-37)	17 (9-27)		.47	17 (9-27)	14 (7-22.5)		.17

Abbreviations: CI, confidence interval; ICU, intensive care unit; IQR, interquartile range; RR, relative risk; SOFA, Sequential Organ Failure Assessment.

^aFor comparison between prone and supine groups.

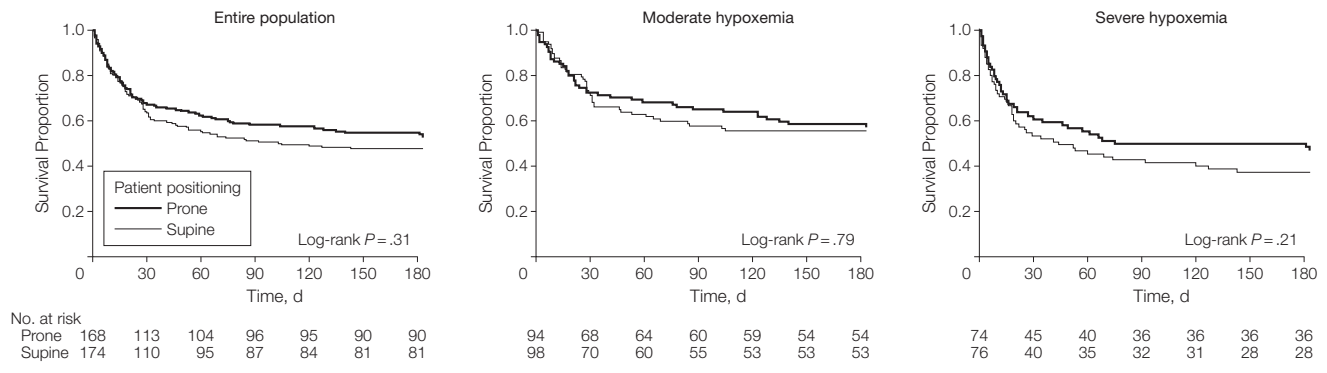
^bTwo patients per group (prone and supine) were lost to follow-up at 6 months and were assumed alive for the analysis.

^cUsed to assess the degree of dysfunction of 5 organ systems: respiratory, cardiovascular, renal, neurologic, hepatic. Each subscore ranges from 0 (healthy) to 4 (maximum severity); the overall score ranges from 0 to 20. Each patient was characterized by his or her own average SOFA score (individual SOFA score = mean of daily SOFA scores). The value reported in the table refers to median (IQR) of the individual SOFA scores.

^dMean number of days from day 1 to day 28 on which patients surviving for at least 28 days had been breathing without any assistance. By definition, ventilator-free days were equal to 0 in patients who died during the 28-day study period.¹⁸

^eDays of mechanical ventilation in the 28-day study period.

Figure 2. Kaplan-Meier Survival Curves of the Prone-Supine II Study Population: Entire Population and Patients With Moderate and Severe Hypoxemia



Time indicates days since randomization.

and the longer the time spent in the prone position, the greater the possible advantage expected. Therefore, in the PSII study, as in the previous trial by Mancebo et al,⁹ prone positioning was applied within 72 hours from diagnosis (early ARDS) and scheduled for up to 20 hours a day. However, in PSII we could not find any significant advantage of this strategy, because similar outcomes were found in the 2 previous trials, in which prone positioning was scheduled for only 6 hours⁷ or 8 hours⁸ per day.

In contrast, the rate of complications was almost 3 times that observed in our previous study.⁷ Because periods of prone positioning also

lasted 3 times as long, it is tempting to attribute the increased complication rate to the longer time spent in the prone position.

Finally, because our previous study suggested that only patients with severe hypoxemia could benefit from prone positioning, we wanted to prospectively test that hypothesis. Accordingly, at randomization in PSII we stratified the patients into subgroups with moderate and severe hypoxemia to ensure similar numbers of patients with severe hypoxemia in both the prone and the supine study groups.

Indeed, in PSII, we tried to realize the best conditions for prone positioning

to work, dealing with the issues of enrollment time, length of application, control of mechanical ventilation, and patient severity. Despite that, we could not show a significant survival benefit, either in the general population or in the predefined study subgroups, although a favorable trend was detected in the subgroup of patients with severe hypoxemia.

Our study has several limitations. First, to standardize the severity of hypoxemia, we assessed the arterial oxygenation while keeping the PEEP between 5 and 10 cm H₂O; therefore, in patients treated with a higher level, we decreased the PEEP to 10 cm H₂O (unless the PaO₂:FiO₂ ratio was already

Table 3. Incidence of Complications During the 28-Day Prone-Supine II Study Period

Complication	Patients, % ^a				Events/100 Days of Study ^b				Events During Positional Changes, % ^d
	All	Prone	Supine	<i>P</i> Value ^c	All	Prone	Supine	<i>P</i> Value ^c	
Entire Population									
Need for increased sedation/muscle relaxants	68.1	80.4	56.3	<.001	15.2	17.9	12.5	<.001	26.9
Airway obstruction	42.1	50.6	33.9	.002	8.4	10.3	6.6	<.001	20.4
Transient desaturation	57.0	63.7	50.6	.01	13.4	15.4	11.3	<.001	21.3
Vomiting	20.8	29.1	12.6	<.001	3.0	4.4	1.7	<.001	35.1
Hypotension, arrhythmias, increased vasopressors	63.2	72.0	54.6	<.001	15.2	18.0	12.4	<.001	22.0
Loss of venous access	9.9	16.1	4.0	<.001	0.7	1.23	0.25	<.001	36.6
Displacement of endotracheal tube	7.6	10.7	4.6	.03	0.6	0.87	0.40	.02	40.0
Displacement of thoracotomy tube	2.9	4.2	1.7	.21	0.2	0.25	0.11	.23	30.0
Moderate Hypoxemia									
Need for increased sedation/muscle relaxants	69.3	79.8	59.2	.002	13.3	15.8	10.9	<.001	26.5
Airway obstruction	40.6	44.7	36.7	.26	7.4	8.5	6.3	<.001	23.3
Transient desaturation	51.0	54.3	48.0	.38	11.2	12.0	10.4	<.001	16.5
Vomiting	19.8	26.6	13.3	.02	2.3	2.8	1.8	<.001	21.9
Hypotension, arrhythmias, increased vasopressors	57.8	64.9	51.0	.05	13.7	17.5	10.2	<.001	18.6
Loss of venous access	10.9	17.0	5.1	.008	0.7	1.1	0.3	.02	27.3
Displacement of endotracheal tube	9.4	12.8	6.1	.11	0.7	0.9	0.5	.18	36.4
Displacement of thoracotomy tube	2.1	3.2	1.0	.36	0.1	0.2	0.1	.35	50.0
Severe Hypoxemia									
Need for increased sedation/muscle relaxants	66.7	81.1	52.6	<.001	17.9	20.5	14.9	.001	27.4
Airway obstruction	44.0	58.1	30.3	<.001	9.9	12.6	7.0	<.001	17.4
Transient desaturation	64.7	75.7	54.0	.005	16.4	19.7	12.8	<.001	25.8
Vomiting	22.0	32.4	11.8	.002	4.1	6.5	1.5	<.001	45.3
Hypotension, arrhythmias, increased vasopressors	70.0	81.1	59.2	.004	17.2	18.6	15.7	.07	25.6
Loss of venous access	8.7	14.7	2.6	.008	0.8	1.4	0.2	<.001	47.4
Displacement of endotracheal tube	5.3	8.1	2.6	.16	0.6	0.8	0.3	.04	46.2
Displacement of thoracotomy tube	4.0	5.4	2.6	.44	0.3	0.3	0.2	.09	16.7

^aPercentage of patients who experienced at least 1 episode of the complication considered during the 28-day study period.

^bNumber of days with at least 1 event, divided by 100 patient-days (2760 patient-days for the prone group and 2764 patient-days for the supine group).

^cFor comparison between prone and supine groups.

^dPercentage of events in the prone group that occurred during the positional changes.

<100). Although the PEEP manipulation may be debatable, its standardization allowed the selection of a rather homogeneous group of patients. In fact, the patients with severe hypoxemia, compared with those with moderate hypoxemia, were not only characterized by lower PaO₂, which may be a maneuver-induced artifact in some patients, but also by greater PaCO₂, greater minute ventilation, greater clinical severity score, and more importantly, higher mortality rate. Second, allowing a 72-hour period for enrollment may be questionable, because earlier intervention could be more effective.⁹ However, the reason for our choice was straightforward: to increase the possibility of enrollment, usually difficult in a study with similar settings. In fact, in our previous study the enrollment rate was as low as 0.28 patients/unit per month. Unfortunately, the 3-day window increases the possibility that some physicians placed patients with severe hypoxemia in the prone position as a rescue maneuver, excluding them from randomization.

Third, we did not have systematic information on patients screened for eligibility but excluded, because only a few units complied with this request. Fourth, our study was likely underpowered; any absolute mortality difference below 15% cannot be detected in our population of 342 patients, and this limitation is even more relevant when considering the subgroups of patients with moderate and severe hypoxemia.

Do the findings of this trial, together with those of previous studies, represent the end of the prone positioning technique? Undoubtedly, the data of the present trial together with previous results clearly indicate that prolonged prone positioning, in the unselected ARDS population, is not indicated as a treatment. However, its potential role in patients with the most severe hypoxemia, for whom the possible benefit could outweigh the risk of complications, must be further investigated, considering the strong pathophysiological background, the

post hoc result of our previous study,⁷ the most recent meta-analysis,⁴ and the favorable trend observed prospectively in this study.

Author Affiliations: Dipartimento di Anestesia e Rianimazione, Fondazione IRCCS—“Ospedale Maggiore Policlinico, Mangiagalli, Regina Elena” di Milano, Milan, Italy (Drs Taccone, Vagginelli, Caspani, and Gattinoni); Dipartimento di Medicina Perioperatoria e Terapie Intensive, Azienda Ospedaliera San Gerardo di Monza, Monza, Italy (Drs Pesenti and Fumagalli); Department of Cardiovascular Research, Istituto di Ricerche Farmacologiche Mario Negri, Milan (Dr Latini); Istituto di Anestesiologia e Rianimazione, Università degli Studi di Milano, Milan (Drs Polli, Miletto, Iapichino, and Gattinoni); U. O. di Anestesia e Rianimazione, Azienda Ospedaliera Polo Universitario San Paolo, Milan (Dr Iapichino); Dipartimento di Medicina Sperimentale, Università degli Studi Milano-Bicocca, Milan (Drs Pesenti and Fumagalli); U. O. di Anestesia e Rianimazione, Polo Universitario Luigi Sacco, Milan (Dr Raimondi); Dipartimento di Anestesia e Rianimazione Generale, Istituto Clinico Humanitas, Rozzano, Italy (Dr Bordone); Servei de Medicina Intensiva, Hospital de Sant Pau, Barcelona, Spain (Dr Mancebo); Service de Réanimation Médicale et Assistance Respiratoire, Hôpital de la Croix-Rousse, Lyon, France (Dr Guérin); Centre de Coordination de la Lutte contre les Infections Nosocomiales Sud-Est, Hôpital Henry Gabrielle, St. Denis Laval, France (Dr Ayzac); Critical Care Center, CIBER Enfermedades Respiratorias, Corporació Sanitaria Parc Taulí, Universitat Autònoma de Barcelona, Sabadell, Spain (Dr Blanch); Consorzio Mario Negri Sud, S. Maria Imbaro, Italy (Dr Tognoni).

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

Study concept and design: Taccone, Pesenti, Latini, Vagginelli, Caspani, Raimondi, Bordone, Iapichino, Fumagalli, Tognoni, Gattinoni.

Acquisition of data: Taccone, Pesenti, Polli, Vagginelli, Caspani, Raimondi, Bordone, Iapichino, Mancebo, Fumagalli.

Analysis and interpretation of data: Taccone, Pesenti, Latini, Polli, Miletto, Mancebo, Guérin, Ayzac, Blanch.

Drafting of the manuscript: Taccone, Polli, Miletto, Gattinoni.

Critical revision of the manuscript for important intellectual content: Pesenti, Latini, Vagginelli, Caspani, Raimondi, Bordone, Iapichino, Mancebo, Guérin, Ayzac, Blanch, Fumagalli, Tognoni.

Statistical analysis: Taccone, Polli, Gattinoni.

Obtained funding: Tognoni, Gattinoni.

Administrative, technical, or material support: Taccone, Pesenti, Latini, Polli, Fumagalli.

Study supervision: Tognoni, Gattinoni.

Financial Disclosures: Dr Gattinoni reported receiving a fee of US \$1500 for a single meeting 5 years ago at KCI Medical Products headquarters, as a member of an advisory board. The other authors reported no financial disclosures.

Funding/Support: KCI Medical Products (San Antonio, Texas) made freely available the Rotoprone rotational bed used by 20 centers in this study. KCI also supported secretarial activity of the coordinating center and periodic meetings of the study investigators.

Role of the Sponsor: KCI Medical Products had no role 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.

The Prone-Supine II Study Group: Steering Committee: Luciano Gattinoni, Gianni Tognoni. **Scientific and Organization Secretariat:** Roberto Fumagalli, Ro-

berto Latini, Antonio Pesenti, Paolo Taccone. **Data and Safety Monitoring Board:** Roberto Malacrida, Maria Grazia Valsecchi, Peter Suter. **Data management and analysis:** Simona Barlera, Federico Polli, Valentina Milani. **Clinical monitoring:** Maria Amigoni, Margherita Scanziani, Chiara Serio. **Investigators:** Belén Cabello and Alberto Lisi (Hospital de la Santa Creu i Sant Pau, Barcelona, Spain); Martino Tino Valetti and Gianmariano Marchesi (Ospedali Riuniti, Bergamo, Italy); Emma Cerchiari and Nicola Cilloni (Ospedale Maggiore, Anestesia e Terapia Intensiva, Bologna, Italy); Giovanni Gordini and Alberto Maioli (Ospedale Maggiore, Rianimazione-118, Bologna, Italy); Giorgio Servadio and Stefano Greco (Ospedale di Circolo, Busto Arsizio, Italy); Maurizio Solca (Ospedale Uboldo, Cernusco sul Naviglio, Italy); Giulio Ronzoni and Eduardo Beck (Presidio Ospedaliero di Desio [AO Vimercate], Desio, Italy); Franco Bobbio Pallavicini and Enrico Ardidì (Ospedale San Martino, Genova, Italy); Danilo Radrizzani and Virginia Porta (Ospedale Civile, Legnano, Italy); Antonio Castelli and Roberto Colombo (Ospedale L. Sacco, Milano, Italy); Riccarda Russo and Monica Savioli (Ospedale Maggiore Policlinico, Milano, Italy); Matteo Zaniboni and Andrea Noto (Ospedale S. Paolo, Milano, Italy); Nicola Rossi and Paola Tagliabue (Ospedale S. Gerardo, Monza, Italy); Gemma Rialp and Sonia Trabanco (Son Llatzer Hospital, Palma de Mallorca, Spain); Giovanni Pittoni and Giuseppina Bonaccorso (Azienda Ospedaliera di Padova, Padova, Italy); Flavio Michielan and Giuseppe Gagliardi (Ospedale S. Antonio, Padova, Italy); Antonio Braschi and Giuseppe Rodi (Policlinico S. Matteo-I Servizio, Pavia, Italy); Andrea Botazzi and Mario Peta (Policlinico S. Matteo-II Servizio, Pavia, Italy); Valentina Bellato and Vittorio Gavazzoni (Istituto Clinico Humanitas, Rozzano, Italy); Giovanni Salati and Walter Bottari (Arcispedale S. Maria Nuova, Reggio Emilia, Italy); Carlo Capra and Fabrizio Frattini (Presidio Ospedaliero di Saronno [AO Busto Arsizio], Saronno, Italy); Maurizio Dan and Germano Zaro (Ospedale Civile, Schio, Italy); Massimo Borelli and Sandra Ferraris (Ospedale Treviglio-Caravaggio, Treviglio, Italy); Sandra Rossi and Silvio Marafon (Ospedale Civile S. Bortolo, Vicenza, Italy); Giorgio Gallioli and Stefano Mutini (Ospedale Civile, Vimercate, Italy).

Additional Information: The eTable is available at <http://www.jama.com>.

Additional Contributions: We thank the Prone-Supine II study participants and the physicians, nurses, members of the involved independent review boards, and administrative staff who assisted with its conduct.

REFERENCES

- Phua J, Badia JR, Adhikari NK, et al. Has mortality from acute respiratory distress syndrome decreased over time? a systematic review. *Am J Respir Crit Care Med*. 2009;179(3):220-227.
- Dellinger RP, Levy MM, Carlet JM, et al; International Surviving Sepsis Campaign Guidelines Committee; American Association of Critical-Care Nurses; American College of Chest Physicians; American College of Emergency Physicians; Canadian Critical Care Society; European Society of Clinical Microbiology and Infectious Diseases; European Society of Intensive Care Medicine; European Respiratory Society; International Sepsis Forum; Japanese Association for Acute Medicine; Japanese Society of Intensive Care Medicine; Society of Critical Care Medicine; Society of Hospital Medicine; Surgical Infection Society; World Federation of Societies of Intensive and Critical Care Medicine. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. *Crit Care Med*. 2008;36(1):296-327.
- Abroug F, Ouannes-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(6):1002-1011.
4. Alsaghir AH, Martin CM. Effect of prone positioning in patients with acute respiratory distress syndrome: a meta-analysis. *Crit Care Med.* 2008;36(2):603-609.
 5. Sud S, Sud M, Friedrich JO, Adhikari NK. Effect of mechanical ventilation in the prone position on clinical outcomes in patients with acute hypoxemic respiratory failure: a systematic review and meta-analysis. *CMAJ.* 2008;178(9):1153-1161.
 6. Piehl MA, Brown RS. Use of extreme position changes in acute respiratory failure. *Crit Care Med.* 1976;4(1):13-14.
 7. Gattinoni L, Tognoni G, Pesenti A, et al; Prone-Supine Study Group. Effect of prone positioning on the survival of patients with acute respiratory failure. *N Engl J Med.* 2001;345(8):568-573.
 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(19):2379-2387.
 9. Mancebo J, Fernandez 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(11):1233-1239.
 10. Slutsky AS. The acute respiratory distress syndrome, mechanical ventilation, and the prone position. *N Engl J Med.* 2001;345(8):610-612.
 11. 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(18):1301-1308.
 12. 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(2):295-303.
 13. Valenza F, Guglielmi M, Maffioletti M, et al. Prone position delays the progression of ventilator-induced lung injury in rats: does lung strain distribution play a role? *Crit Care Med.* 2005;33(2):361-367.
 14. 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(3, pt 1):818-824.
 15. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med.* 1985;13(10):818-829.
 16. 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(24):2957-2963.
 17. Vincent JL, Moreno R, Takala J, et al; Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. *Intensive Care Med.* 1996;22(7):707-710.
 18. Schoenfeld DA, Bernard GR; ARDS Network. Statistical evaluation of ventilator-free days as an efficacy measure in clinical trials of treatments for acute respiratory distress syndrome. *Crit Care Med.* 2002;30(8):1772-1777.
 19. Geller NL, Pocock SJ. Interim analyses in randomized clinical trials: ramifications and guidelines for practitioners. *Biometrics.* 1987;43(1):213-223.
 20. Chiumello D, Carlesso E, Cadringer P, et al. Lung stress and strain during mechanical ventilation for acute respiratory distress syndrome. *Am J Respir Crit Care Med.* 2008;178(4):346-355.

Science is not . . . a perfect instrument, but it is a superb and invaluable tool that works harm only when taken as an end in itself.
—Carl G. Jung (1875-1961)