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

A Randomized Controlled Trial

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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

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ACUTE RESPIRATORY DISTRESS syndrome (ARDS) is a clinical condition that entails high mortality[1] and may be associated with severe hypoxemia. Prone positioning is currently suggested for patients with ARDS, for whom high fraction of inspired oxygen (FIO_2) 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 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 trial[7] 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-

For editorial comment see p 2030.

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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 trial[9] 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 strategy[11] 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 Pa_{O_2}:F_{IO_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 Pa_{O_2}:F_{IO_2} ratio between 100 mm Hg and 200 mm Hg at enrollment, while the subgroup with severe hypoxemia was defined by a Pa_{O_2}:F_{IO_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, $Pa_{O_2} \leq 55$ mm Hg at $F_{IO_2} = 1.00$ and PEEP ≥ 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, Pa_{O_2} between 70-90 mm Hg), we suggested that F_{IO_2} and PEEP be set according to a table predefined by the investigators (minimal set F_{IO_2}, 0.3 at PEEP = 5 cm H_2O; maximal set F_{IO_2}, 1.0 at 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.

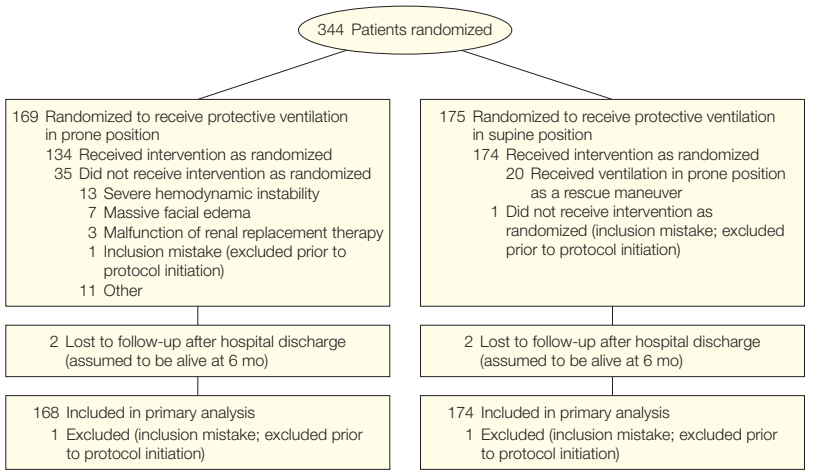
Demographic data, coded primary diagnosis,[15] and severity of illness as assessed with the Simplified Acute Physiology Score II[16] were recorded at study enrollment. During the 28-day study period, Sequential Organ Failure Assessment (SOFA) scores[17] were collected daily to evaluate the severity of 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.

Figure 1. Study Flow



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 al[9] 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 continuous 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 mortality 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)
Pa_{O_2}:F_{IO_2} ratio	113 (39)	141 (27)	77 (16)
PEEP, cm H_2O	10 (3)	9 (2)	11 (3)
F_{IO_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)
Pa_{CO_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; F_{IO_2}, fraction of inspired oxygen; PEEP, positive end-expiratory pressure; SAPS II, Simplified Acute Physiology Score II; SOFA, Sequential Organ Failure Assessment.
[a] Calculated as weight in kilograms divided by height in meters squared.
[b] Used to assess the severity of illness; range, 0 to 194, with higher scores indicating higher risk of death.
[c] Used 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.
[d] Ideal 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 Pa_{O_2}:F_{IO_2} ratio, in the entire population, was significantly higher in the prone group than in the supine group, while F_{IO_2} 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 F_{IO_2} 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 nonsignificant 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 FIO_2 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.

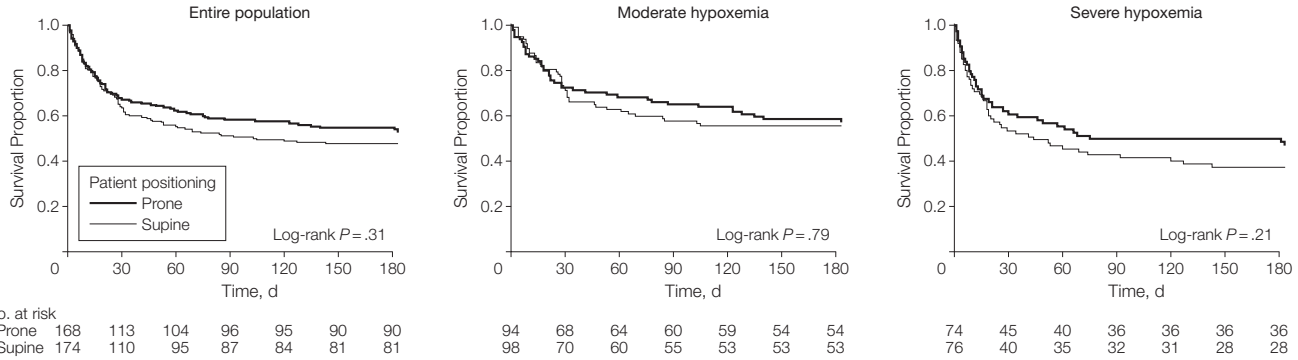
The hypothesis behind the PSII study was that mechanical ventilation could be less injurious if applied in the prone position than if applied in the supine position, owing to the well-recognized greater homogeneity of stress and strain distribution across the lung parenchyma[20] when mechanical ventilation is applied in the prone position. Accordingly, the earlier the application

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

	Entire Population (n = 342)				Moderate Hypoxemia (n = 192)				Severe Hypoxemia (n = 150)			
Outcome	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.
[a] For comparison between prone and supine groups.
[b] Two patients per group (prone and supine) were lost to follow-up at 6 months and were assumed alive for the analysis.
[c] Used 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.
[d] Mean 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]
[e] Days 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 hours[7] or 8 hours[8] 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 H_2O; therefore, in patients treated with a higher level, we decreased the PEEP to 10 cm H_2O (unless the Pa_{O_2}:FI_{O_2} 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	*P* Value[c]	All	Prone	Supine	*P* 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

[a] Percentage of patients who experienced at least 1 episode of the complication considered during the 28-day study period.
[b] Number 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).
[c] For comparison between prone and supine groups.
[d] Percentage 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 PaO_2, which may be a maneuver-induced artifact in some patients, but also by greater $PaCO_2$, 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.

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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)

