

# A Multicenter Trial of Prolonged Prone Ventilation in Severe Acute Respiratory Distress Syndrome

Jordi Mancebo, Rafael Fernández, Lluís Blanch, Gemma Rialp, Federico Gordo, Miquel Ferrer, Fernando Rodríguez, Pau Garro, Pilar Ricart, Immaculada Vallverdú, Ignasi Gich, José Castaño, Pilar Saura, Guillermo Domínguez, Alfons Bonet, and Richard K. Albert

Departments of Intensive Care Medicine and Epidemiology, Hospital de Sant Pau; Department of Intensive Care Medicine, Respiratory Unit, Hospital Clínic, Institut d'Investigacions Biomèdiques August Pi i Sunyer, Barcelona; Department of Intensive Care Medicine, Hospital de Sabadell, Institut Universitari Fundació Parc Taulí, Sabadell; Hospital General de Mallorca, Palma de Mallorca; Department of Intensive Care Medicine, Fundación Hospital de Alcorcón, Alcorcón; Department of Intensive Care Medicine, Clínica San Miguel, Pamplona; Department of Intensive Care Medicine, Hospital de Granollers, Granollers; Department of Intensive Care Medicine, Hospital Germans Trias i Pujol, Badalona; Department of Intensive Care Medicine, Hospital de Sant Joan, Reus; Department of Intensive Care Medicine, Hospital Virgen de las Nieves, Granada; Department of Intensive Care Medicine, Centre Hospitalari de Manresa, Manresa; Department of Intensive Care Medicine, Hospital Josep Trueta, Girona, Spain; Department of Intensive Care Medicine, Instituto Nacional de Ciencias Médicas y de la Nutrición Salvador Zubirán, Mexico Distrito Federal, Mexico; and Denver Health Medical Center, and Department of Medicine, University of Colorado Health Sciences Center, Denver, Colorado

**Rationale:** Ventilation in the prone position for about 7 h/d in patients with acute respiratory distress syndrome (ARDS), acute lung injury, or acute respiratory failure does not decrease mortality. Whether it is beneficial to administer prone ventilation early, and for longer periods of time, is unknown.

**Methods:** We enrolled 136 patients within 48 h of tracheal intubation for severe ARDS, 60 randomized to supine and 76 to prone ventilation. Guidelines were established for ventilator settings and weaning. The prone group was targeted to receive continuous prone ventilation treatment for 20 h/d.

**Results:** The intensive care unit mortality was 58% (35/60) in the patients ventilated supine and 43% (33/76) in the patients ventilated prone ( $p = 0.12$ ). The latter had a higher simplified acute physiology score II at inclusion. Multivariate analysis showed that simplified acute physiology score II at inclusion (odds ratio [OR], 1.07;  $p < 0.001$ ), number of days elapsed between ARDS diagnosis and inclusion (OR, 2.83;  $p < 0.001$ ), and randomization to supine position (OR, 2.53;  $p = 0.03$ ) were independent risk factors for mortality. A total of 718 turning procedures were done, and prone position was applied for a mean of 17 h/d for a mean of 10 d. A total of 28 complications were reported, and most were rapidly reversible.

**Conclusion:** Prone ventilation is feasible and safe, and may reduce mortality in patients with severe ARDS when it is initiated early and applied for most of the day.

**Keywords:** prone position; respiratory distress syndrome, adult; respiration, artificial

Supportive treatment for acute respiratory distress syndrome (ARDS) usually requires tracheal intubation and mechanical ventilation with positive end-expiratory pressure (PEEP) and high concentrations of inspired oxygen. Although these measures are thought to be life-saving, there is increasing concern that mechanical ventilation itself can injure the lungs as a result

of overdistension and/or cyclical airspace opening and closing, and possibly cause or contribute to multisystem organ failure in these patients (1–6).

Ventilating patients with ARDS in the prone position has repeatedly been shown to improve arterial oxygenation and to have few untoward side effects (7–13). Improvement in arterial oxygenation could allow the use of lower, less toxic, inspired oxygen concentrations and lower inflation pressures, and might also help in earlier liberation from mechanical ventilation. The vertical gravitational gradient in pleural pressure is more evenly distributed in prone position than in supine (14), thus implying a better distribution of ventilation in the dorsal areas of the lung (15) where the most impressive morphologic lung lesions are predominantly located (16). The reduction in the gravitational pleural pressure gradient that occurs on turning prone could result in less overdistension and less airspace opening and closing, thereby reducing the incidence of ventilator-induced lung injury and multisystem organ failure (17–20).

Gattinoni and colleagues (21) found no improvement in survival in a randomized trial of prone ventilation applied in the course of ARDS or acute lung injury for an average of 7 h/d for 10 d. On *post hoc* analysis, however, 10-d mortality was found to be significantly lower in the prone group as compared with the supine group in the quartile with the lowest  $Pa_{O_2}:Fi_{O_2}$  ratio (i.e.,  $\leq 88$  mm Hg), the quartile with the highest  $V_T$  (i.e.,  $> 12$  ml/kg), and the quartile with the highest (i.e.,  $> 49$ ) simplified acute physiology score II (SAPS II). In patients with a variety of causes of acute respiratory failure, Guérin and colleagues (22) observed no improvement in survival using prone ventilation instituted shortly after intubation and applied for a mean of 8.6 h/d for a mean of 4.1 d. We hypothesized that prone ventilation would decrease mortality if it were implemented early in the course of ARDS, applied for most of the day, and maintained for a prolonged period of time. Preliminary data have been published in abstract form (23, 24).

## METHODS

### Patients and Randomization

The study was conducted between December 1998 and September 2002. Patients were recruited from 13 intensive care units: 12 in Spain and 1 in Mexico. This study was approved by the Comité Ético de Investigación Clínica of Hospital de Sant Pau (which served as the coordinating center). Informed signed consent was obtained from patients' next of kin.

Inclusion criteria were intubation, mechanical ventilation, over 18 yr of age, and meeting the American–European consensus conference

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Correspondence and requests for reprints should be addressed to Jordi Mancebo, M.D., Servei de Medicina Intensiva, Hospital de Sant Pau, Avinguda Sant Antoni Maria Claret 167, 08025 Barcelona, Spain. E-mail: jmancebo@santpau.es

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definition for ARDS (25). In addition, diffuse bilateral infiltrates on the chest X-ray had to be present. Noninclusion criteria are mentioned in the online supplement.

A sequence of random numbers was computer-generated. This sequence was partitioned into blocks of different size according to the expected number of inclusions at each participating center. Blocks had an equal number of supine and prone position assignments; one center had a block of 30 patients, one center had a block of 24 patients, five centers had blocks of 20 patients each, and six centers had blocks of 16 patients each. Concealment was performed using sealed opaque envelopes prepared by an independent person. All centers had experience in implementing prone ventilation.

The treatment guidelines, including mechanical ventilation settings (maximal  $V_T$  = 10 ml/kg and maximal plateau airway pressure = 35 cm  $H_2O$ , or up to 40 cm  $H_2O$  when chest wall stiffness was clinically suspected), weaning (using T-piece trials or pressure support ventilation), sedation, and data collection are available in the online supplement.

### Outcomes and Statistics

Our primary outcome variable was intensive care unit mortality. Secondary endpoints were hospital mortality, associated complications, and length of stay. On the basis of previous experience (26), we estimated that the mortality in patients ventilated supine would be 50%, and calculated a need to enroll 200 patients, 100 in each arm, to detect a decrease in mortality rate from 50% (supine group) to 30% (prone group) using a two-sided test, a type I error of 0.05, and a power of 80%. Estimates were a compromise between clinical importance (decrease in mortality rate) and feasibility (number of patients to be enrolled).

Analysis was by intention-to-treat. Categorical data were compared by means of the  $\chi^2$  or Fisher's exact test, and the Student's  $t$  test was used for quantitative data. The time course of respiratory variables in the two groups was compared using a two-way analysis of variance for repeated measures. Intensive care unit cumulative survival plots for supine and prone groups were constructed using the Kaplan-Meier method, and the log-rank test was used to determine significance. We also looked for independent risk factors for mortality by entering variables into a multivariate analysis using logistic regression. SAPS IIs were used as a continuous variable in the logistic regression. Like other authors (21), we analyzed our findings for dichotomized SAPS IIs (i.e., SAPS II < 50 and SAPS II  $\geq$  50 at randomization).

All data presented are means ( $\pm$  SD). Additional details are available in the online supplement.

### RESULTS

Because of a marked decrease in the number of patients enrolled in the last year, the study was aborted after 142 participants had been randomized (62 supine and 80 prone). Of these, 136 (60 supine and 76 prone) were evaluated (Figure 1). Five patients allocated to the supine group were crossed-over to prone posi-

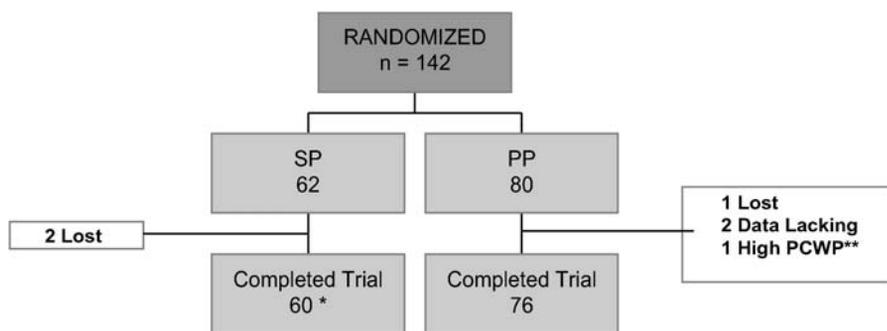
tion, and all of them died. Two patients were crossed-over at Day 1, one patient at Day 6, and two patients at Day 16. No patient allocated to the prone group was crossed-over to receive ventilation in the supine position.

Clinical and physiologic characteristics of the patients at inclusion are described in Table 1. The time between ARDS diagnosis and randomization was  $1.04 \pm 1.30$  d (range, 0–9 d);  $1.23 \pm 1.61$  d in the supine group and  $0.89 \pm 0.97$  in the prone group ( $p = 0.16$ ). The time between meeting inclusion criteria and randomization was  $0.39 \pm 0.54$  d (range, 0–2 d);  $0.47 \pm 0.62$  d in the supine group and  $0.34 \pm 0.48$  d in the prone group ( $p = 0.20$ ).

For patients who received noninvasive ventilation ( $n = 56$ ), the time between ARDS diagnosis and randomization was  $1.73 \pm 1.68$  d (range, 0–9 d), and for those who did not ( $n = 80$ ), it was  $0.56 \pm 0.59$  d (range, 0–2 d) ( $p < 0.001$ ). Noninvasive ventilation was administered as continuous positive airway pressure in 28 patients (13 in the supine group and 15 in the prone group), and as PEEP plus pressure support in another 28 patients (12 in the supine group and 16 in the prone group). The time between ARDS diagnosis and randomization was  $1.25 \pm 1.18$  d (range, 0–6 d) for patients who received continuous positive airway pressure, and  $2.21 \pm 1.97$  d (range, 0–9 d) for patients who received PEEP plus pressure support ( $p = 0.03$ ).

The changes in respiratory variables that occurred over time, from inclusion up to Day 4, are depicted in Figures 2–4. Variables in these figures were subjected to analysis of variance for repeated measures, taking into account time (*horizontal axis*) and the two groups (supine and prone). The *horizontal arrows* indicate whether or not the analyzed variable changes over time. The *vertical arrows* indicate the time interaction (i.e., whether or not the two groups differ over time), but do not indicate at which specific time point the two groups differ. Comparisons of these variables at single time points between the two groups, and up to 3 wk, are shown in the online supplement. Patients ventilated prone had lower  $FI_{O_2}S$  ( $p < 0.001$ ), higher  $Pa_{O_2}:FI_{O_2}$  ratios ( $p < 0.001$ ), and lower levels of plateau airway pressure ( $p = 0.01$ ) and PEEP ( $p = 0.048$ ) than those ventilated supine. Respiratory system compliance did not differ between the two groups, and showed a significant increase over time ( $p < 0.001$ ). Patients remained in the prone position an average of  $10.1 \pm 10.3$  d (range, 0–54 d) and for an average of 17 h/d. A total of 718 turning procedures were performed in the 76 patients who were treated in the prone position. Details about prone position implementation are shown in Table 2.

The long-term evolution, up to Day 20, of respiratory variables is reported in the online supplement. The ventilatory guidelines were violated in 16 patients, and the weaning guidelines



**Figure 1.** Between December 1998 and September 2002, 142 patients were randomized (62 to supine position [SP], and 80 to prone position [PP]) and 136 (60 supine and 76 prone) were evaluated for the study. Case report forms of three patients enrolled in 1999 were lost, two from the supine group and one from the prone group. In two other patients in the prone group (one enrolled in 1998, the other in 1999), data on outcomes were missing from the case report form and could not be recovered. Finally, in one patient allocated to the prone position in 1999, a pulmonary artery catheter was inserted immediately after randomization due to hemodynamic instability, and the pulmonary capillary wedge pressure (PCWP) was 33 mm Hg. This patient was transferred to a referral hospital for possible open heart surgery due to the suspicion of acute mitral regurgitation. \*Five patients allocated to the supine group were crossed over to the prone group. \*\*This patient was lost to follow-up.

mediately after randomization due to hemodynamic instability, and the pulmonary capillary wedge pressure (PCWP) was 33 mm Hg. This patient was transferred to a referral hospital for possible open heart surgery due to the suspicion of acute mitral regurgitation. \*Five patients allocated to the supine group were crossed over to the prone group. \*\*This patient was lost to follow-up.

TABLE 1. CHARACTERISTICS OF THE PATIENTS AT INCLUSION

Characteristic	Supine Group (n = 60)	Prone Group (n = 76)	p Value
Age, yr	54 ± 16	54 ± 17	0.98
Male/Female, n	42/18	44/32	0.10
SAPS II	38 ± 14	43 ± 16	0.08
ARDS etiology, n			0.21
Pneumonia	25	44	
Aspiration	6	9	
Sepsis	16	16	
Multiple trauma	2	1	
Other causes	11	6	
Comorbidities, n			0.42
Immunosuppression	11	16	
Cancer	15	15	
Cirrhosis	6	8	
HIV infection	2	9	
Nonpulmonary organ/system failures*			
Cardiovascular, n (%)	21 (35)	22 (29)	0.50
Gastrointestinal, n (%)	22 (37)	16 (21)	0.06
Renal, n (%)	8 (13)	20 (26)	0.09
Hematologic, n (%)	7 (12)	17 (22)	0.10
Hepatic, n (%)	6 (10)	6 (8)	0.80
Neurologic, n (%)	2 (3)	3 (4)	1
No. of nonpulmonary organ failures	1.1 ± 1.2	1.1 ± 1.1	0.98
No. of patients with vasopressors, n (%)	44 (73)	63 (83)	0.21
No. of patients who received non-invasive ventilation, n (%)	25 (42)	31 (41)	1
No. of patients with chest wall stiffness, n (%)	14 (23)	14 (18)	0.60
Respiratory variables†			
Pa <sub>O<sub>2</sub></sub> , mm Hg	126 ± 94	107 ± 65	0.19
Fi <sub>O<sub>2</sub></sub>	0.79 ± 0.21	0.84 ± 0.19	0.13
Pa <sub>O<sub>2</sub></sub> :Fi <sub>O<sub>2</sub></sub> , mm Hg	161 ± 94	132 ± 74	0.06
Pa <sub>CO<sub>2</sub></sub> , mm Hg	43 ± 11	45 ± 9	0.25
Respiratory rate, breaths/min	19 ± 4	20 ± 4	0.14
V <sub>T</sub> , ml/kg	8.6 ± 1.6	8.3 ± 1.7	0.20
PEEP, cm H <sub>2</sub> O	12.3 ± 2.4	12.4 ± 1.9	0.89
Plateau airway pressure, cm H <sub>2</sub> O	32 ± 4	32 ± 5	0.61
Arterial pH, units	7.35 ± 0.1	7.35 ± 0.08	0.77
Crs, ml/cm H <sub>2</sub> O	32 ± 10	31 ± 11	0.60
Crs/kg, ml/cm H <sub>2</sub> O/kg	0.47 ± 0.16	0.44 ± 0.15	0.28

Definition of abbreviations: ARDS = acute respiratory distress syndrome; Crs = respiratory system compliance; PEEP = positive end-expiratory pressure; SAPS = simplified acute physiology score.

Unless otherwise specified, all values presented are mean ± SD.

\* Some patients had more than one organ/system failure at inclusion.

† All measurements in supine position in both groups and obtained 30–60 min after randomization.

were not followed in 6 patients. These data are reported in the online supplement.

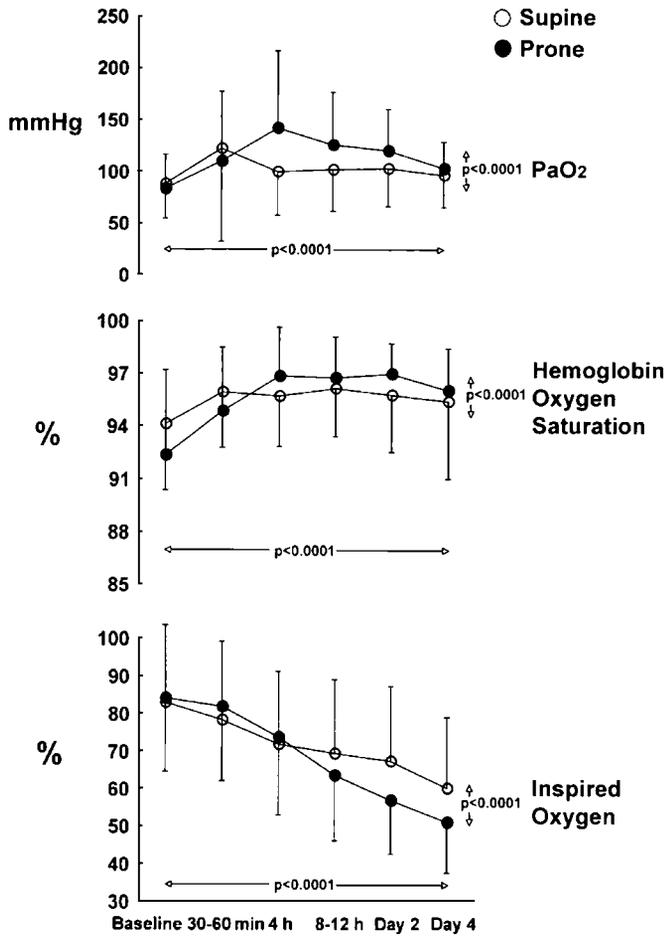
Outcome variables are summarized in Table 3. Intensive care unit mortality was 58% (35/60) in the patients ventilated supine and 43% (33/76) in the patients ventilated prone—a 15% absolute and 25% relative decrease that was not statistically significant ( $p = 0.12$ ). A similar trend was observed for hospital mortality. No statistical difference ( $p = 0.27$ , log-rank test) was observed in the cumulative intensive care unit survival Kaplan-Meier plots between the two groups (Figure 5). Intensive care unit length of stay was shorter in nonsurvivors compared with survivors, but did not differ between the supine and the prone groups. With respect to unplanned extubations, only one occurred during the turn. Five patients needed to be reintubated (one allocated to supine, four allocated to prone). Only one patient (allocated to prone) was diagnosed with ventilator-associated pneumonia after reintubation. None of the patients who had an unplanned extubation died.

Complications related to prone position *per se* were few and clinically mild. Edema (facial, limbs, thorax) was observed in 14 patients, but rapidly improved when patients were turned supine. Conjunctival hemorrhage and pressure sores were observed in

two patients each, and one patient exhibited a vascular catheter malfunction during continuous veno-venous hemofiltration. Complications directly attributable to the turning procedures were as follows: the inadvertent dislodging of a Swan-Ganz catheter during the turn was accompanied by cardiac arrest in one patient, but resuscitation was successful; in two other patients, lines were accidentally displaced (a urinary bladder catheter and a nasogastric feeding tube); and kinking occurred in the endotracheal tube of one patient and the thoracic drain of another. As stated above, one unplanned extubation occurred during the turning procedure, and this patient was rapidly and uneventfully reintubated. All together, a total of 28 complications were noted.

Intensive care unit mortality was 60.7% (34/56; 16/25 supine and 18/31 prone) for patients who received noninvasive ventilation before intubation and mechanical ventilation and 42.5% (34/80; 19/35 supine and 15/45 prone) for those who did not ( $p = 0.055$ ). The SAPS IIs recorded at the time of randomization tended to be higher in patients who did not receive noninvasive ventilation than in those who did ( $42 \pm 15$  and  $38 \pm 15$ , respectively;  $p = 0.10$ ).

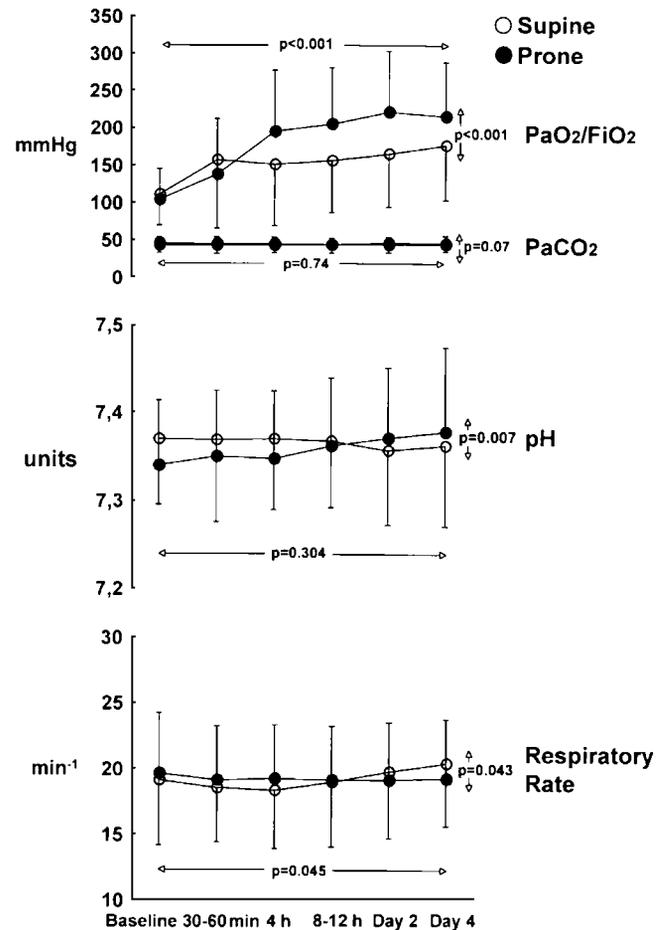
The results of multiple logistic regression analysis indicated three variables that were independently associated with increased



**Figure 2.** Evolution of respiratory variables ( $Pa_{O_2}$ , hemoglobin oxygen saturation and concentration of inspired oxygen) from inclusion (baseline) to Day 4. *Open and closed circles* are mean values for the supine and prone groups, respectively. *Error bars* denote  $\pm 1$  SD. Data at 30–60 min after randomization were collected in supine position after ventilator settings were adjusted according to the guidelines. Data at 4 h, 8–12 h, Day 2, and Day 4 were collected in supine or prone position. *Vertical and horizontal arrows* indicate statistical significance between groups and during the time course, respectively (analysis of variance [ANOVA] for repeated measures). In the supine group, all these variables were available for 49 patients. In the prone group, all these variables were available for 65 patients, except for hemoglobin oxygen saturation, which was available for 63 patients.

risk of mortality: the SAPS II at inclusion (odds ratio [OR], 1.07; 95% confidence interval [CI], 1.04–1.11;  $p < 0.001$ ), the number of days elapsed between ARDS diagnosis and inclusion (OR, 2.83; 95% CI, 1.63–4.90;  $p < 0.001$ ) and random allocation to supine position (OR, 2.53, 95% CI, 1.09–5.89;  $p = 0.03$ ).

The *post hoc* analysis performed in the 103 patients with a SAPS II of less than 50 showed an intensive care unit mortality of 53% (26/49) in the patients ventilated supine and 33% (18/54) in the patients ventilated prone ( $p = 0.049$ ). The SAPS II in the two groups at the time of randomization tended to be higher in the prone group ( $33 \pm 10$  supine,  $36 \pm 9$  prone;  $p = 0.10$ ). The 33 patients with a SAPS II of 50 or greater showed an intensive care unit mortality of 82% (9/11) in the patients ventilated supine and 68% (15/22) in the patients ventilated prone ( $p = 0.68$ ). The SAPS II was similar in both groups at the time of randomization ( $60 \pm 10$  supine,  $62 \pm 15$  prone;  $p =$



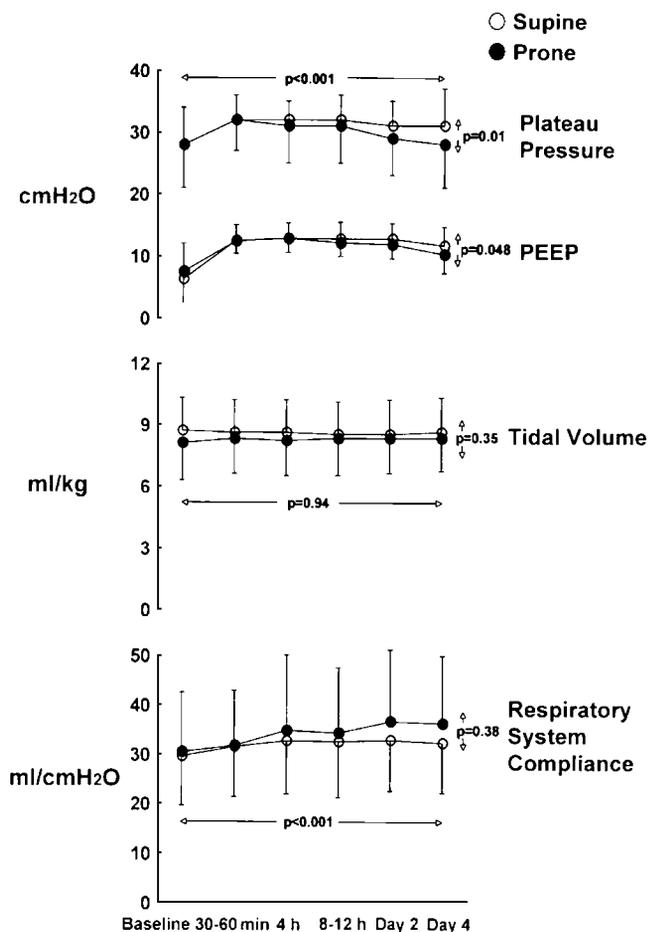
**Figure 3.** Evolution of respiratory variables ( $Pa_{O_2}/F_{iO_2}$ ,  $Pa_{CO_2}$ , arterial pH, and respiratory rate) from inclusion (baseline) to Day 4. *Open and closed circles* are mean values for the supine and prone groups, respectively. *Error bars* denote  $\pm 1$  SD. Data at 30–60 min after randomization were collected in supine position after ventilator settings were adjusted according to the guidelines. Data at 4 h, 8–12 h, Day 2, and Day 4 were collected in supine or prone position. *Vertical and horizontal arrows* indicate statistical significance between groups and during the time course, respectively (ANOVA for repeated measures). In the supine group, all these variables were available for 49 patients. In the prone group, these variables were available for 65 patients, except for arterial pH, which was available for 64 patients.

0.67). Intensive care unit length of stay for the 24 nonsurvivors with SAPS IIs of 50 or greater was  $4 \pm 3.7$  d.

The use of opiates, sedatives, and neuromuscular blocking agents is reported in the online supplement.

## DISCUSSION

The important finding in this study was that patients with ARDS who received mechanical ventilation in the prone position within 48 h of meeting entry criteria, and who remained prone for most of the day and until preset weaning criteria were met, had a 15% absolute and a 25% relative reduction in intensive care unit mortality compared with those who were ventilated supine. Although this improvement did not reach statistical significance, the patients randomized to receive prone ventilation showed a trend toward a higher severity score in comparison with those ventilated supine. The multiple logistic regression analysis



**Figure 4.** Evolution of respiratory variables (plateau airway pressure, PEEP,  $V_t$ , and respiratory system compliance) from inclusion (baseline) to Day 4. Open and closed circles are mean values for the supine and prone groups, respectively. Error bars denote  $\pm 1$  SD. Data at 30–60 min after randomization were collected in supine position after ventilator settings were adjusted according to the guidelines. Data at 4 h, 8–12 h, Day 2, and Day 4 were collected in supine or prone position. Vertical and horizontal arrows indicate statistical significance between groups and during the time course, respectively (ANOVA for repeated measures). In the supine group, plateau airway pressure and  $V_t$  were available for 49 patients, and PEEP and respiratory system compliance were available for 48 patients. In the prone group, PEEP and  $V_t$  were available for 65 patients, and plateau airway pressure and respiratory system compliance were available for 62 patients.

showed, however, that supine position was an independent risk factor for mortality (OR, 2.53). The *post hoc* analysis indicating a subset of patients that benefited from prone position treatment should be interpreted very cautiously.

Two previous trials (21, 22) failed to find improved survival in adult patients ventilated prone compared with those ventilated supine. Both had design issues limiting the strength of their conclusions. Gattinoni and colleagues (21) only applied prone ventilation 7 h/d for a maximum of 10 d, and many of the patients were likely not enrolled until late in the course of ARDS (i.e., nearly 25% had pressure sores at entry). Ventilation and weaning guidelines were not employed, and although 304 patients were enrolled, the study was underpowered and was stopped early because caregivers were unwilling to continue randomizing patients to supine ventilation. On the basis of *post hoc* analysis, Gattinoni and colleagues (21) suggested that prone ventilation had a lower risk of death at Day 10 in patients with the highest

**TABLE 2. PRONE POSITION IMPLEMENTATION**

Day	Patients in Prone Position (n)	Hours in Prone Position (Mean $\pm$ SD)	Patients Undergoing Weaning from the Ventilator (n)	Deaths in the ICU (n)*
1	71	14 $\pm$ 7.1	—	5
2	69	20.4 $\pm$ 3.4	—	7
4	49	18.7 $\pm$ 4.8	13	13
7	23	19.4 $\pm$ 4	32	16
10	16	18.3 $\pm$ 5	33	21
20	5	12.6 $\pm$ 9.9	21	29

Definition of abbreviation: ICU = intensive care unit.

\* Cumulative number of patients.

quartile of SAPS II (i.e., > 49). Our *post hoc* analysis led to a different conclusion. Such a discrepancy can be explained by a number of factors: (1) Gattinoni and colleagues only found a significant difference when they analyzed the 10-d mortality rate; (2) the patients we studied were probably enrolled earlier in the course of ARDS than those studied by Gattinoni and colleagues, as suggested by the high percentage ( $\sim 23\%$ ) of pressure sores at study entry; (3) our patients were treated with prone positioning over a longer period; (4) routine care (for instance, antibiotic policy, strategies to implement other supportive treatment, such as dialysis or vasoactive drugs, decisions to withdraw treatment, etc.) could have differed between these studies; and (5) in the study by Gattinoni and colleagues, the  $V_t$  decreased over time in patients allocated to supine and increased over time in patients allocated to prone (an average change that was statistically significant). This may have been deleterious, and such a change did not arise in our study.  $V_t$  was about 655 ml at baseline in the trial by Gattinoni and coworkers (and increased over time), and about 574 ml in our trial (and remained virtually constant over time). These differences, alone or in combination, could account for the differences in the results. From a clinical point of view, a plausible explanation is that prone position works like any other treatment when it is instituted as early as possible (as probably occurred in our study in comparison to that of Gattinoni and coworkers); given at appropriate doses (our dose per day was higher than that of Gattinoni and colleagues); and given for a sufficient period of time—our treatment was delivered until a major improvement in gas exchange was observed and weaning was envisaged.

Guérin and colleagues (22) enrolled patients earlier, but only applied prone ventilation for a mean of 8.6 h/d for a mean of

**TABLE 3. OUTCOME VARIABLES**

Variable	Supine Group (n = 60)	Prone Group (n = 76)	p Value
ICU mortality, n (%)	35 (58)	33 (43)	0.12
95% CI	45–71%	32–55%	
Hospital mortality, n (%)	37 (62)	38 (50)	0.22
95% CI	48–74%	38–62%	
ICU length of stay, d	19.1 $\pm$ 23.1	20.5 $\pm$ 18.2	0.70
Survivors	22 $\pm$ 14.1	27.9 $\pm$ 18.5	
Nonsurvivors	17 $\pm$ 27.9	10.9 $\pm$ 12.5	0.002
Pneumothorax, n (%)	4 (6.7)	7 (9.2)	0.76
Unplanned tracheal extubation, n (%)	1 (1.7)	6 (7.9)*	0.13
Ventilator-associated pneumonia, n (%)	9 (15)	14 (18.4)	0.65
Days under vasopressors <sup>†</sup>	6.35 $\pm$ 5.03	5.43 $\pm$ 5.22	0.32

Definition of abbreviations: CI = confidence interval; ICU = Intensive care unit. Unless otherwise specified, all values presented are mean  $\pm$  SD.

\* Includes one patient accidentally extubated during the turning procedure.

<sup>†</sup> A total of 54 supine patients and 70 prone patients received vasopressors for at least 1 d.

## Number of patients at risk:

Supine group	40	31	28	28	28	28
Prone group	55	47	46	44	44	44

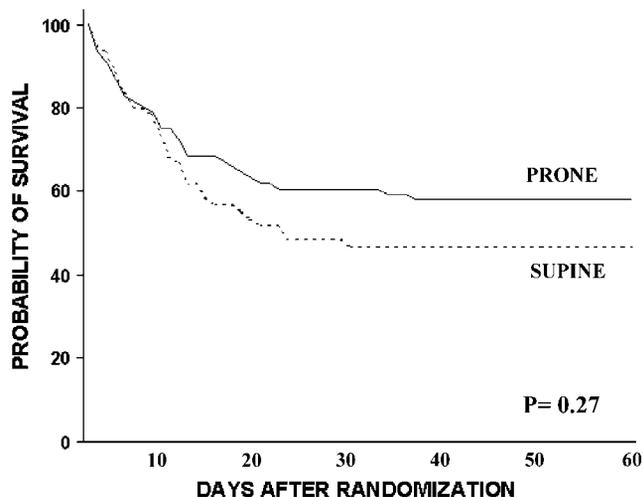


Figure 5. Kaplan-Meier estimates of intensive care unit survival for the supine and the prone groups (up to 60 d).

4.1 d. No ventilation guidelines were reported. However, weaning guidelines were employed. The study was designed to evaluate prone ventilation in treating acute respiratory failure irrespective of cause. Accordingly, only about 50% of the 791 patients had ARDS or acute lung injury, the other half having a wide variety of other causes of respiratory failure. In addition, 81 of the 385 patients (21%) who were randomized to receive supine ventilation were crossed over, and actually received prone ventilation. Our study only included patients with ARDS who were randomized within 48 h of meeting entry criteria and were targeted to receive prone ventilation 20 h/d. Predetermined ventilation and weaning guidelines were employed.

We found that the number of days elapsed between ARDS onset and study entry was an independent risk factor for mortality. This might be attributed to the fact that institution of supportive treatment with mechanical ventilation was delayed in these patients, as they were intubated at a later stage in their illness. We speculate that a potentially harmful scenario may occur. Patients with ARDS exhibit a lower respiratory system compliance in comparison with normal subjects (our patients, at inclusion, had an average respiratory system compliance of  $\sim 31$  ml/cm H<sub>2</sub>O), patients with ARDS have an increased dead-space:V<sub>T</sub> ratio (27), and, on average, spontaneously breathing patients with ARDS (at least in the early phase) show normal Pa<sub>CO<sub>2</sub></sub> values (28, 29). Physiological data (29), obtained in patients with acute lung injury during spontaneous unassisted breathing and spontaneous breathing supported with noninvasive ventilation, indicate that these patients develop a substantial amount of transpulmonary pressure. In addition, end-expiratory lung volume might not increase much when using PEEP during noninvasive ventilation because of the effects of expiratory muscle recruitment (30). All these factors could serve to augment cyclical airspace opening and closing, and precipitate further lung injury (1, 19, 20).

Previous trials by Gattinoni and coworkers (21) and Guérin and coworkers (22) implemented prone position ventilation with the abdomen unsupported. We followed the same approach, and it is not known if by using a different approach (i.e., abdomen supported) our results would have differed. In a recent trial performed in a pediatric population with acute lung injury (31),

supine ventilation was compared with prone ventilation, with the abdomen supported. No differences in outcome were observed.

We observed a low rate of complications relative to that reported by Guérin and colleagues (22). Our investigation involved repositioning the patients only once per day, whereas Guérin and colleagues (22) periodically moved their patients from the left to right lateral decubitus position. This may explain not only why they observed a lower incidence of ventilator-associated pneumonia, but also their higher incidence of selective bronchial intubation in the patients ventilated prone. Contrary to previous reports (21), we found no difference in either the number of patients requiring opiates, sedatives, or neuromuscular blocking agents, or the total cumulative doses of these medications given per patient between the two groups. This discrepancy may be due to the fact that we recommended targeted use of these agents to achieve an objective goal.

Our study included patients with diffuse bilateral radiologic infiltrates, affecting all four quadrants. According to lung morphology studies (32, 33), this group represents about 25% of those patients fulfilling the American-European Consensus Conference definition of ARDS. Despite improving arterial oxygenation with PEEP and prone positioning in these patients, the mortality rates exceed 50% (32, 33), in line with our data. Another factor that could have contributed to the mortality rate in our study is excessive V<sub>T</sub> and/or excessive end-inspiratory plateau airway pressure. Nevertheless, only 4 patients in the supine group and 12 in the prone group received V<sub>T</sub>s and/or developed end-inspiratory plateau airway pressures above the preset limits of our recommended guidelines. The more frequent occurrence of patients receiving a potentially injurious ventilation in the prone group, if anything, negatively biased our results. In a randomized trial performed in patients with ARDS and comparing conventional ventilation with high-frequency oscillatory ventilation (34), the ventilator settings in the conventional ventilation group were similar to ours, and the mortality at Day 30 was 52%.

Our study is limited by the facts that it was stopped due to decreased patient accrual and is underpowered. This may have occurred because of difficulties associated with enrolling patients within the narrow randomization window. Having to evaluate and enroll patients within 48 h of meeting entry criteria required continuous motivation and considerable effort from investigators, and this may have waned with time. In addition, we had only limited funding available to conduct the trial (€9616) at a time when heavily funded pharmaceutical studies were competing for similar patients. Finally, although there were few complications related to prone position *per se* and to the turning procedures, it was unfortunate that the study design did not foresee the need to record complications occurring during routine supine position treatment. The relevance of complications attributable to prone positioning should therefore be interpreted with caution.

In conclusion, using prone ventilation for prolonged periods of time is both feasible and safe. It may reduce mortality in ARDS patients. To date, none of the three trials designed to evaluate the effect of prone ventilation on mortality in adult patients with ARDS have been sufficiently powered to confirm a benefit or the lack thereof. Our results suggest that the duration of prone positioning may be an important determinant of its effectiveness, as may the interval between the onset of ARDS and its application. An appropriately powered trial is needed to reevaluate whether prone ventilation reduces mortality in patients with ARDS.

**Conflict of Interest Statement:** J.M. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. R.F. does not have a financial relationship with a commercial entity that has an interest in

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