EFFECT OF PRONE POSITIONING ON THE SURVIVAL OF PATIENTS WITH ACUTE RESPIRATORY FAILURE

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ABSTRACT

Background Although placing patients with acute respiratory failure in a prone (face down) position improves their oxygenation 60 to 70 percent of the time, the effect on survival is not known.

Methods In a multicenter, randomized trial, we compared conventional treatment (in the supine position) of patients with acute lung injury or the acute respiratory distress syndrome with a predefined strategy of placing patients in a prone position for six or more hours daily for 10 days. We enrolled 304 patients, 152 in each group.

Results The mortality rate was 23.0 percent during the 10-day study period, 49.3 percent at the time of discharge from the intensive care unit, and 60.5 percent at 6 months. The relative risk of death in the prone group as compared with the supine group was 0.84 at the end of the study period (95 percent confidence interval, 0.56 to 1.27), 1.05 at the time of discharge from the intensive care unit (95 percent confidence interval, 0.84 to 1.32), and 1.06 at six months (95 percent confidence interval, 0.88 to 1.28). During the study period the mean (±SD) increase in the ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen, measured each morning while patients were supine, was greater in the prone than the supine group (63.0±66.8 vs. 44.6±68.2, P=0.02). The incidence of complications related to positioning (such as pressure sores and accidental extubation) was similar in the two groups.

Conclusions Although placing patients with acute respiratory failure in a prone position improves their oxygenation, it does not improve survival. (N Engl J Med 2001;345:568-73.)

THE prone position is increasingly being used to treat patients with acute lung injury or the acute respiratory distress syndrome, since a 1976 study reported that placing such patients in the prone position improves oxygenation.[1] Several mechanisms have been proposed to account for this effect, including an increase in end-expiratory lung volume,[2] better ventilation–perfusion matching,[3] and regional changes in ventilation[4] associated with alterations in chest-wall mechanics.[5] Whatever the mechanism, in 60 to 70 percent of patients, the prone position improves oxygenation, sometimes dramatically. Moreover, it has also been shown in studies in animals to protect against ventilator-induced lung injury.[6] However, the effect of pronation on survival is unknown. In a multicenter randomized trial, we assessed the effect of a predefined strategy of prone positioning on the survival of patients with acute lung injury or the acute respiratory distress syndrome.

METHODS

Enrollment

Patients who were receiving mechanical ventilation were considered eligible if they met the following modified criteria for acute lung injury or the acute respiratory distress syndrome[7]: a ratio of partial pressure of arterial oxygen (PaO_2) to fraction of inspired oxygen (FiO_2) of 200 or less (a finding characteristic of the acute respiratory distress syndrome) with a positive end-expiratory pressure of at least 5 cm of water or a PaO_2:FiO_2 ratio of 300 or less (a finding characteristic of acute lung injury) with a positive end-expiratory pressure of at least 10 cm of water, radiographic evidence of bilateral pulmonary infiltrates, and (if measured) a pulmonary-capillary wedge pressure of 18 mm Hg or less or the absence of clinical evidence of left atrial hypertension. Patients were excluded from the study if they were younger than 16 years of age; had evidence of cardiogenic pulmonary edema, cerebral edema, or intracranial hypertension; or had clinical conditions that might have contraindicated the use of the prone position, such as fractures of the spine or severe hemodynamic instability.

Study Design and Treatment Protocol

Patients were recruited from 28 intensive care units in Italy and 2 in Switzerland and were randomly assigned to a supine or prone group. Randomization was conducted centrally by telephone on a 24-hour-a-day, 7-day-a-week basis and was based on a permuted-block algorithm, which allowed stratification according to the intensive care unit. Patients in the prone group were continuously kept prone for at least six hours per day for a period of 10 days. Patients were assessed each morning while they were supine. A change to the prone position was triggered by a finding during the morning assessment of a PaO_2:FiO_2 ratio of 200 or less with a positive end-expiratory pressure of at least 5 cm of water or a PaO_2:FiO_2 ratio of 300 or less with a positive end-expiratory pressure of at least 10 cm of water.

The physicians caring for the patients in both groups were

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asked to comply with the guidelines of the American–European Consensus Conference on mechanical ventilation for routine ventilatory treatment[8] and not to change the ventilatory settings during the period of pronation in order to standardize the assessment of the changes in gas exchange induced by the maneuver. Decisions about care were otherwise not specified by the study protocol.

The study protocol was approved by the human-experimentation committee of the health authority of the Regione Lombardia as well as by local ethics committees. The trial was monitored by an independent, external safety and efficacy monitoring board. Clinical staff members were solely responsible for including patients in the study. Informed-consent procedures complied with the European guidelines for good clinical practice.[9] As soon as their clinical condition allowed them to understand adequately, patients were duly informed of the study and of their right to withdraw.

Outcome Measures and Data Collection

The primary end point was death at 10 days (the end of the period involving prone positioning), at the time of discharge from the intensive care unit, and 6 months after randomization (data were obtained from the census offices). Secondary end points were improvement in respiratory failure and improvement in organ dysfunction at 10 days.

At the time of enrollment, demographic data, the diagnostic code (according to the Knaus classification[10]), and the Simplified Acute Physiology Score II[11] were obtained for each patient. The Simplified Acute Physiology Score assesses the severity of illness on the basis of 12 physiological variables, age, the type of admission (urgent or nonurgent), and 3 variables related to the underlying disease. Scores can range from 0 to 194; higher scores are correlated with a higher risk of death during hospitalization.

During each morning assessment in both groups we recorded (with the patients in the supine position) the respiratory and the biochemical variables used to monitor patients for nonpulmonary organ or system failure (renal, hepatic, circulatory, and coagulation failure), defined as in the Acute Respiratory Distress Syndrome Network trial of the National Heart, Lung, and Blood Institute.[12] We calculated the number of days without nonpulmonary organ or system failure by subtracting the number of days with organ failure from the lesser of 10 days or the number of days to death. Organs were considered failure-free after patients were discharged from the hospital.

The presence, site, and severity of pressure sores, classified according to the four-stage system of the National Pressure Ulcers Advisory Panel,[13] were recorded at base line and daily during each morning assessment. According to this system, stage I indicates a reddened area with intact skin; stage II a superficial abrasion, blister, or shallow crater involving the epidermis, dermis, or both; stage III a deep crater involving damage to or necrosis of subcutaneous tissue that may extend to, but not through, underlying fascia and may undermine adjacent tissue; and stage IV a very deep sore that extends into muscle, bone, and supporting structures (e.g., tendons). In the prone group we recorded for each period of pronation (immediately before, after one hour, and at the end of the scheduled period) arterial blood gas tension, the ventilator setting, and any adverse event associated with the maneuver, as well as the number of personnel involved in positioning the patient.

The clinicians and nurses from the coordinating centers made periodic site visits during the study. The original clinical forms were sent to the coordinating center at Mario Negri Institute in Milan, where the records were checked for internal consistency and completeness by specially trained clinical data managers. Any queries about missing or inconsistent data were sent directly to the investigator at the original center before the information was entered in the data base. The analysis and the interpretation of the data were the joint responsibility of the statisticians of the study and the steering committee.

Statistical Analysis

In the absence of reliable information on the expected mortality rate in the target population, we planned to calculate the sample size needed to assess a clinically relevant benefit — a 20 percent decrease in the mortality rate with the use of prone positioning — during the first interim analysis of 10-day mortality (after the randomization of 150 patients). We estimated that the study would be able to detect a 20 percent decrease in 10-day mortality (with a two-tailed α level of 0.05) at a power of 80 percent if the total number of deaths at this time was at least 95. We decided to stop the trial after the enrollment of 304 patients and 70 deaths, in agreement with the data and safety monitoring board, given a progressively slower rate of recruitment in the preceding 12 months, ascribed by the steering committee largely to an increasing unwillingness among caregivers to forgo the use of prone positioning.

The primary analysis was carried out on an intention-to-treat basis. A per-protocol analysis was also planned. The base-line characteristics, complications, and outcomes in the two groups were compared with the use of Fisher's exact test, Student's t-test, or the Wilcoxon–Mann–Whitney test, as appropriate. The survival rate was analyzed according to the Kaplan–Meier method, and the results were compared with the use of the log-rank test.

To compare the changes in continuous variables between the prone and supine groups, we used the incremental area under the curve during the period of the study.[14] For each patient and for each day, the value for each variable obtained during the morning assessment was used to compute the area under the curve. Since the time spent in the study differed from patient to patient, we standardized the time scale (expressed in days) by dividing the individual area under the curve by the number of days the patient spent in the study.

We performed a post hoc exploratory analysis by stratifying the population into quartiles for the relevant physiological and treatment variables recorded at entry (the PaO_2:FiO_2 ratio, the Simplified Acute Physiology Score II, and tidal volume), with no formal adjustments for multiple comparisons. All analyses were performed with SAS software (version 8.0, SAS Institute, Cary, N.C.). A two-tailed P value of less than 0.05 was considered to indicate statistical significance. Data are presented as means ±SD unless otherwise specified.

RESULTS

Study Population

From December 1996 to October 1999, 152 patients were randomly assigned to the prone group and 152 patients to the supine (control) group. Characteristics of the patients at entry are summarized in Table 1. A registry of patients who fulfilled the admission criteria but who were not enrolled was kept at 21 of the centers from December 1996 to June 1998. Of the 214 patients in the registry, 106 (49.5 percent) died in the intensive care unit. During the same period 144 patients were enrolled in the study, 76 of whom (52.8 percent) died in the intensive care unit.

In the case of 12 patients (43 maneuvers) in the supine group, a decision was made, despite randomization, to use the prone position because of the severity of arterial hypoxemia. In the prone group, logistic problems, mainly staffing limitations, caused various degrees of noncompliance in the case of 41 patients, resulting in a total of 91 missed periods of pronation over the 10-day period.

Mortality

The mortality rate did not differ significantly between the prone group and the supine group at the end of the 10-day study period (21.1 percent vs. 25.0 percent [32 vs. 38 deaths]; relative risk of death, 0.84

TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS.*

CHARACTERISTIC	SUPINE GROUP (N=152)	PRONE GROUP (N=152)
Age (yr)	57±16	59±17
Female sex (%)	25.0	34.2
SAPS II†	40±16	40±14
Acute lung injury (%)‡	6.6	5.3
Acute respiratory distress syndrome (%)§	93.4	94.7
No. of nonpulmonary organ or system failures	1.4±1.0	1.3±1.0
Cause of lung injury (%)¶		
Pneumonia	48.3	48.3
Aspiration	4.6	1.3
Other types of respiratory disease	16.6	11.9
Respiratory tract infection after surgery	11.9	9.9
Sepsis	8.6	9.9
Trauma	1.3	3.3
Other causes	8.6	15.2

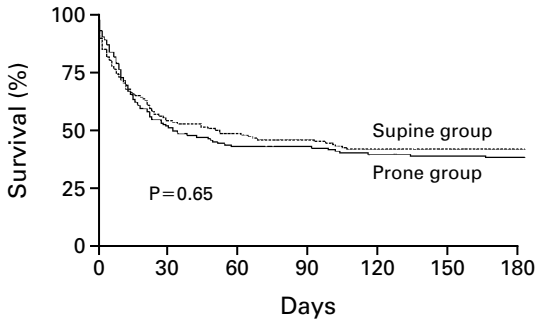
*Plus–minus values are means ±SD. There were no significant differences between groups.

†The Simplified Acute Physiology Score (SAPS) II is used to assess the severity of illness and can range from 0 to 194, with higher scores indicating a higher risk of death.[11]

‡Acute lung injury is characterized by a ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen of 300 or less.[7]

§The acute respiratory distress syndrome is characterized by a ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen of 200 or less.[7]

¶Because of rounding, percentages do not total 100.



NO. AT RISK

Supine group	152	82	72	68	62	62	62
Prone group	152	78	63	63	58	57	56

Figure 1. Kaplan–Meier Estimates of Survival at Six Months.

The status at 183 days was known for all but seven patients (four in the prone group and three in the supine group). The difference between groups was not significant (P=0.65 by the log-rank test).

in the prone group; 95 percent confidence interval, 0.56 to 1.27), at the time of discharge from the intensive care unit (50.7 percent vs. 48.0 percent [77 vs. 73 deaths]; relative risk of death, 1.05; 95 percent confidence interval, 0.84 to 1.32), or at 6 months (62.5 percent vs. 58.6 percent [95 vs. 89 deaths]; relative risk of death, 1.06; 95 percent confidence interval, 0.88 to 1.28) (Fig. 1). A per-protocol analysis, from which patients in each group with at least one protocol violation were excluded, produced similar results: respective mortality rates of 22.5 percent and 27.9 percent at 10 days (relative risk of death, 0.83; 95 percent confidence interval, 0.53 to 1.29), 52.2 percent and 49.3 percent at the time of discharge from the intensive care unit (relative risk of death, 1.06; 95 percent confidence interval, 0.83 to 1.35), and 62.4 percent and 59.1 percent at 6 months (relative risk of death, 1.05; 95 percent confidence interval, 0.86 to 1.29).

Secondary End Points

Table 2 shows the base-line values of the major respiratory variables, as well as their average change during the 10-day study period. The PaO_2:FiO_2 ratio, which was obtained during the morning assessment while patients were supine, increased slightly but significantly more in the prone group than in the supine group. This was due both to a significant increase in the PaO_2 and to a significant decrease in the FiO_2. The tidal volume increased in the prone group and decreased in the supine group (average difference between the groups, 0.5 ml per kilogram of predicted body weight).

We found no difference in the incidence of dysfunction of the various organs and systems considered. The number of days without any nonpulmonary organ failure was similar in the two groups (2.7±3.7 days in the prone group and 2.8±3.6 days in the supine group, P=0.83).

Complications Related to the Prone or Supine Position

At entry, the number of patients with pressure sores of stage II, III, or IV according to the classification of the National Pressure Ulcers Advisory Panel and the number of pressure sores per patient were similar in the two groups (Table 3). The percentage of patients who had new or worsening pressure sores was similar in the two groups. The number of new or worsening pressure sores per patient was significantly higher in the prone group than in the supine group during the 10-day study period, whereas the number of days with pressure sores per patient was similar in the two groups. As expected, the weight-bearing sites in the prone position (thorax, cheekbone, iliac crest, breast, and knee) were significantly more likely to be affected in the prone group (70 of 188 sores were at these sites, as compared with 12 of 102 in the supine group; P<0.001).

The percentages of patients with accidental displacement of the tracheal or a thoracotomy tube or

TABLE 2. CHANGES IN RESPIRATORY VARIABLES DURING THE 10-DAY TREATMENT PERIOD.*

VARIABLE	BASE-LINE VALUE			AVERAGE CHANGE†		
	SUPINE GROUP	PRONE GROUP	P VALUE	SUPINE GROUP	PRONE GROUP	P VALUE
PaO_2 (mm Hg)	88.3±25.9	85.7±24.6	0.38	8.5±26.8	15.0±26.4	0.04
FiO_2 (%)	72.7±18.7	73.4±18.3	0.72	−7.6±17.6	−12.7±18.7	0.02
PaO_2:FiO_2	129.5±47.5	125.3±48.8	0.45	44.6±68.2	63.0±66.8	0.02
PEEP (cm of water)	9.6±3.2	9.7±2.9	0.79	0.0±2.9	−0.1±2.5	0.81
Peak inspiratory pressure (cm of water)	32.6±7.4	32.4±7.5	0.86	−0.6±5.3	−0.1±6.6	0.85
Tidal volume						
Milliliters	658±192	652±177	0.80	−11±138	25±128	0.02
Milliliters per kilogram of predicted body weight‡	10.3±2.9	10.3±2.7	0.92	−0.1±2.2	0.4±2.1	0.03
Respiratory rate (breaths/min)	17.2±5.1	17.1±5.3	0.91	1.3±4.5	0.7±4.2	0.20
Minute ventilation (liters/min)	10.4±3.3	10.4±3.2	0.96	0.5±2.6	0.5±2.3	0.96
$PaCO_2$ (mm Hg)	44.2±11.8	45.1±11.0	0.50	2.5±9.9	0.6±11.2	0.11

*Plus–minus values are means ±SD. PaO_2 denotes partial pressure of arterial oxygen, FiO_2 fraction of inspired oxygen, PEEP positive end-expiratory pressure, and $PaCO_2$ partial pressure of arterial carbon dioxide.

†The values are the difference between the mean value during treatment, calculated as the area under the curve of the variable plotted against time (days 2 to 10) divided by the number of days a patient was in the study, and the base-line value (day 1).

‡The predicted body weight was calculated as 50 + 0.91(height in centimeters − 152.4) for male patients and as 45.5 + 0.91(height in centimeters − 152.4) for female patients.[12]

loss of venous access were similar in the two groups (Table 3).

Prone Positioning

Patients who were randomly assigned to the prone group remained in a prone position for an average of 7.0±1.8 hours per day. The response of the PaO_2:FiO_2 ratio to pronation is summarized in Figure 2. For all 721 maneuvers, the median change in the PaO_2:FiO_2 ratio was 28 at one hour (range, −128 to 303) and 44 (range, −101 to 319) at the end of the period of pronation. In 73.2 percent of the pronation procedures, the PaO_2:FiO_2 ratio increased more than 10, with 69.9 percent of the total response observed during the first hour. Each maneuver (i.e., placing the patient in the prone position or returning the patient to the supine position) required a mean of 10±12 minutes and involved a mean of 4.6±0.9 persons. The adverse effects that occurred during these maneuvers are listed in Table 3.

Post Hoc Analysis

We found a significantly lower 10-day mortality rate in the prone group than in the supine group in the quartile with the lowest PaO_2:FiO_2 ratio (≤88; 23.1 percent vs. 47.2 percent; relative risk of death, 0.49; 95 percent confidence interval, 0.25 to 0.95), the quartile with the highest Simplified Acute Physiology Score II (>49; 19.4 percent vs. 48.5 percent; relative risk of death, 0.40; 95 percent confidence

TABLE 3. INCIDENCE OF COMPLICATIONS.*

COMPLICATION	SUPINE GROUP	PRONE GROUP	P VALUE
Related to position			
Pressure sores at entry (% of patients)	22.5	24.0	0.78
No. of pressure sores/patient at entry†	1.6±0.9	1.9±1.4	0.23
New or worsening pressure sores during the 10-day study period (% of patients)	27.5	36.0	0.13
No. of new or worsening pressure sores/patient‡	1.9±1.3	2.7±1.7	0.004
No. of days with pressure sores/patient	2.5±3.7	3.0±3.8	0.28
Displacement of tracheal tube (% of patients)	9.9	7.9	0.68
Loss of venous access (% of patients)	9.2	5.3	0.27
Displacement of a thoracotomy tube (% of patients)	0.7	3.9	0.12
Related to prone positioning (% of patients)§			
Need for increased sedation		55.2	
Airway obstruction		39.3	
Facial edema		29.8	
Increased need for muscle relaxants		27.7	
Ventilator discoordination		19.6	
Transient desaturation		18.7	
Hypotension		12.3	
Vomiting		7.6	
Arrhythmias		4.2	
Loss of venous access		0.7	
Displacement of a thoracotomy tube		0.5	
Accidental extubation		0.5	

*Plus–minus values are means ±SD.

†Only the patients with sores were included.

‡Only the patients with new or worsening sores were included.

§There was a total of 721 maneuvers. More than one complication could occur during a maneuver.

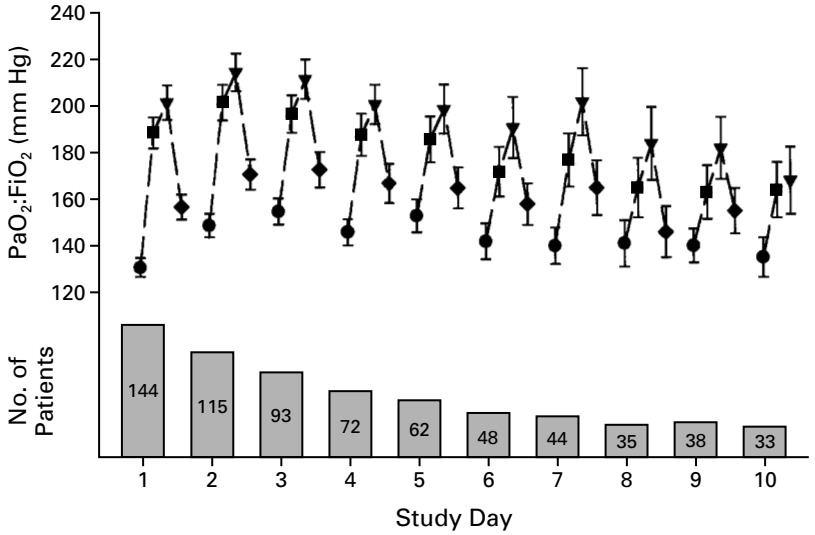


Figure 2. Mean (±SE) Ratios of the Partial Pressure of Arterial Oxygen (PaO_2) to the Fraction of Inspired Oxygen (FiO_2) Immediately before Prone Positioning (Circles), after One Hour (Squares), at the End of the Period of Pronation (Triangles), and on the Morning of the Following Day (Diamonds) during the 10-Day Study Period.

Each calculation includes only data from patients for whom values for all four measurements were available. The bars show the number of patients who were placed in the prone position each day and for whom values for all four measurements were available.

interval, 0.19 to 0.85), and the quartile with the highest tidal volume (>12 ml per kilogram of predicted body weight; 18.2 percent vs. 41.0 percent; relative risk of death, 0.44; 95 percent confidence interval, 0.20 to 1.00). In the subgroup of 162 patients with at least one of these three characteristics (83 in the prone group and 79 in the supine group; 111 with one characteristic and 51 with two or three), the mortality rate at 10 days was significantly lower in the prone group than in the supine group (20.5 percent vs. 40.0 percent; relative risk of death, 0.54; 95 percent confidence interval, 0.32 to 0.90). These differences in the mortality rate did not persist beyond discharge from the intensive care unit (data not shown).

DISCUSSION

In this controlled assessment of the clinical efficacy of the prone position in a randomized cohort of 304 patients with acute lung injury or the acute respiratory distress syndrome, we found no significant differences in the mortality rate at the end of the 10-day study period, at the time of discharge from the intensive care unit, or at 6 months. Despite the limitations related to having a smaller number of patients than planned, our data suggest that the use of the prone position, as defined by this study protocol, in the general population of patients with acute lung injury or the acute respiratory distress syndrome does not improve survival.

We found, however, that the use of the prone position improved oxygenation in more than 70 percent of the instances in which it was used, with about 70 percent of the effect occurring during the first hour of pronation. Indeed, when we compared the PaO_2:FiO_2 ratio in the two groups, which was obtained during the morning assessment while the patients were supine, we found that the prone position increased the ratio significantly more than did the supine position (by 63.0, as compared with 44.6). This finding suggests that the prone position alters the conditions of the respiratory system and leads to improved gas exchange, an effect that persists in part beyond the six-hour period of pronation.

When we compared the incidence of complications that were most likely related to positioning during the 10-day study period (pressure sores and the displacement of devices), we found, as expected, a greater number of pressure sores per patient in the prone group and a higher proportion of sores in the sites more subject to pressure in the prone position. Surprisingly, the percentages of patients with new or worsening pressure sores or with displacement of endotracheal tubes, vascular catheters, or thoracotomy tubes were similar in the two groups. Since these events were expected to be more frequent in the prone

group than in the supine group, our findings suggest that the use of appropriate nursing precautions may prevent them. The most frequent adverse effects of pronation were the need for increased sedation, the need for immediate suctioning of the airway, and facial edema. The most severe adverse effect — accidental extubation — occurred during 4 of 721 maneuvers.

The post hoc analysis of subgroups indicated that prone positioning of the patients who were at highest risk, as reflected by a low PaO_2:FiO_2 ratio ($\leq$88), a high Simplified Acute Physiology Score II (>49), a high tidal volume (>12 ml per kilogram of predicted body weight), or all three, may have resulted in a survival advantage during the 10-day study period that was subsequently lost at the time of discharge from the intensive care unit. The transience of the potential advantage may indicate that the duration of pronation was insufficient. On the other hand, the use of the prone position could simply have delayed the inevitable outcome of death. Our data, however, must be interpreted cautiously, since the higher survival rate at 10 days in the prone group may have been a chance finding associated with the application of multiple statistical tests.

In conclusion, our study confirms that the use of the prone position improves arterial oxygenation and demonstrates that this approach has a limited number of complications. However, routine use of the prone position in patients with acute respiratory failure is not justified. The prone position might be considered useful for patients with severe hypoxemia. The results of the post hoc analysis indicate the need for another trial designed to clarify the role of the prone position in patients with particularly severe acute respiratory distress syndrome.

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APPENDIX

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