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Pascal Beuret
Marie-Jose Carton
Karim Nourdine
Mahmoud Kaaki
Gerard Tramoni
Jean-Claude Ducreux

Prone position as prevention of lung injury in comatose patients: a prospective, randomized, controlled study

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P. Beuret (✉) · M.-J. Carton · K. Nourdine
M. Kaaki · G. Tramoni · J.-C. Ducreux
Intensive Care Unit,
Centre Hospitalier Roanne,
28 rue de Charlieu, 42328 Roanne, France
e-mail: pascal.beuret@ch-roanne.fr
Tel.: +33-4-77443108
Fax: +33-4-77443115

Abstract *Objective*: Comatose patients frequently exhibit pulmonary function worsening, especially in cases of pulmonary infection. It appears to have a deleterious effect on neurologic outcome. We therefore conducted a randomized trial to determine whether daily prone positioning would prevent lung worsening in these patients. *Design*: Prospective, randomized, controlled study. *Setting*: Sixteen-bed intensive care unit. *Patients*: Fifty-one patients who required invasive mechanical ventilation because of coma with Glascow coma scores of 9 or less. *Interventions*: In the prone position (PP) group: prone positioning for 4 h once daily until the patients could get up to sit in an armchair; in the supine position (SP) group: supine positioning. *Measurements and results*: The primary end point was the incidence of lung worsening defined by an increase in the Lung Injury Score of at least 1 point since the time of randomization. The secondary end point was the incidence of ventilator-associated pneumonia (VAP). A total of 25 patients were randomly assigned to the PP group and 26 patients to the SP group. The characteristics of the patients from the two groups were similar at randomization. The incidence of lung worsening was lower in the PP group (12%) than in the SP group (50%) (p=0.003). The incidence of VAP was 20% in the PP group and 38.4% in the SP group (p=0.14). There was no serious complication attributable to prone positioning, however, there was a significant increase of intracranial pressure in the PP. *Conclusion*: In a selected population of comatose ventilated patients, daily prone positioning reduced the incidence of lung worsening.

Keywords Coma · Prone position · Lung injury

Introduction

Pulmonary function worsening is frequent in comatose patients who need mechanical ventilation [1]. The main factors causing this deterioration are pulmonary infection [2, 3, 4] and closure of the small airways with alveolar collapse in the dorsal lung regions [5].

This lung injury was identified as an independent predictor of unfavorable neurologic outcome [2, 6, 7], calling for a preventive strategy. We hypothesized that intermittent prone positioning could prevent this lung deterioration. It has been demonstrated to improve dorsal lung ventilation [8] and then lead to the reopening of collapsed alveoli [9, 10]. We therefore conducted a trial to study the effects in comatose patients requiring mechanical ventilation of daily prone positioning (4 h a day) as compared with remaining in a supine position. The primary end point was the incidence of lung worsening, evaluated by daily measurement of the Lung Injury Score (LIS) [11]. The secondary end point was the incidence of ventilator-associated pneumonia.

Patients and methods

Patients

The study was approved by the committee for the protection of humans in biomedical research of the Rhône Alpes Loire Region. This trial was conducted in our ICU between April 15, 1997, and April 15, 2000. Patients were eligible for the study if their condition required invasive mechanical ventilation because of coma, with a Glasgow coma score of 9 or less. All patients were orally intubated. They were mechanically ventilated using a Siemens 900C (Siemens Elema, Sweden). The ventilatory mode was either volume-controlled or pressure support, according to the decision of the physicians caring for the patient. Initial settings were selected to obtain a tidal volume of 10 ml/kg. They were further adjusted to obtain a $PaCO_2$ between 35 and 40 mmHg, according to published guidelines [12]. The initial level of positive end-expiratory pressure (PEEP) was always 5 cmH_2O. If necessary, patients were sedated with continuous infusion of fentanyl and midazolam. In patients with head injury, the indication of intracranial pressure (ICP) monitoring was based on published guidelines [13]. Exclusion criteria were an age lower than 18 years, expected length of stay in the ICU shorter than 48 h, acute poisoning, severe hypoxemia ($PaO_2/FIO_2 \leq 150$), hemodynamic failure, anterior flail chest, vertebral or long bone fracture that was not stabilized, orthopedic traction or intracranial hypertension (ICP≥20 mmHg). Patients had to be randomized during the first 24 h after intubation. Consent was obtained from relatives before the patients were randomized.

Protocol

Patients were randomized into two groups: the prone position (PP) group: patients recruited in this group were positioned prone for 4 h once daily. The first period in the PP had to begin within 24 h after intubation. Prone positioning was strictly horizontal, head out of bed, with respect to the head-neck-trunk axis to avoid any obstacle to cerebral venous return. Ventilatory settings remained unchanged during PP. If ICP increased over 30 mmHg, prone positioning was stopped and the patient returned to the supine position (SP). The criteria to finish daily periods in PP was the ability of the patient to get up to sit in an armchair. The SP group: these patients stayed in the SP, with the head and trunk positioned at a 20° angle, until they could get up to sit in an armchair. However, they were turned onto the PP if a severe hypoxemia appeared, defined by a $PaO_2/FIO_2$of 150 or less. Lateral positioning was prohibited in the two groups. If PaO_2/FIO_2 fell below 200, the level of PEEP could be increased to improve PaO_2 in both groups. The weaning strategy was the same in the two groups, by pressure support. The level of pressure support was gradually reduced, guided by respiratory rate and minute ventilation.

Data collection

Baseline characteristics of each patient were recorded at the time of randomization. They were: age, sex, SAPS II score during the first 24 h [14], Glasgow coma score, PaO_2/FIO_2 and LIS, etiology of coma, use of antibiotics during the first 24 h, use of sedative drugs, ICP monitoring and mode of mechanical ventilation (Table 1). The following variables were recorded daily in each patient until either extubation or day 28 after randomization, death, or the withholding or withdrawal of life-sustaining therapy. PaO_2 was measured at 8:00 a.m. in the SP group and before turning to the PP in the PP group. The levels of FIO_2 and PEEP were recorded when arterial blood was sampled for PaO_2 measurement. Chest X-ray was also taken at 8:00 a.m. Chest X-rays were reviewed by a physician blinded to the study in order to grade any alterations compared to the initial LIS description [11].

Table 1 Characteristics of the patients at randomization (*PP* prone position, *SP* supine position, *SAPS II* SAPS II score at randomization, *LIS* Lung Injury Score, *Antibiotics* use of antibiotics during the first 24 h, *ICP* intracranial pressure, *VC* volume-controlled mode, *PSV* pressure support ventilation)

Characteristic	PP group (*n*=25)	SP group (*n*=26)
Age (years)[a]	55 (20)	55 (19)
Sex (M/F)	17/8	19/7
SAPS II[b]	48 (27–59)	52 (31–95)
Glascow Coma Score[a]	6.4 (1.8)	5.6 (2.2)
PaO_2/FIO_2[a]	315 (86)	337 (85)
LIS[a]	1.1 (0.4)	0.97 (0.55)
Head trauma	14 (56%)	9 (35%)
Intracranial hemorrhage	5 (20%)	4 (15%)
Ischemic stroke	1 (4%)	2 (8%)
Intracranial infection	2 (8%)	3 (11%)
Anoxic encephalopathy	1 (4%)	4 (15%)
Other etiology of coma[c]	2 (8%)	4 (15%)
Antibiotics	11 (44%)	10 (38%)
Sedation	21 (84%)	21 (80%)
ICP monitoring	6 (24%)	6 (23%)
VC/PSV mode	15/10	21/5

[a] Mean (SD) values
[b] Median (min–max) values
[c] PP group: one patient with coma after surgery for a cerebral neoplasia, one patient with acute poisoning; SP group: one patient with thyrotoxicosis, one with hepatic coma, one with status epilepticus and one with hypoglycemic coma

The values of PaO_2/FIO_2, PEEP and X-ray grading permitted us to calculate daily LIS. Pulmonary worsening was judged to be present for a patient if the LIS increased by at least 1 point when compared to LIS at the time of randomization. Ventilator-associated pneumonia (VAP) was suspected upon the appearance of a new radiographic infiltrate and purulent tracheal secretions [15]. A physician blinded to the study reviewed chest X-rays to verify that the new radiographic infiltrate was not present at the time of intubation. VAP diagnosis was confirmed by a positive quantitative culture of secretions obtained by protected specimen brush with a count of 1000 cfu/ml or more. For the patients with ICP monitoring, the value of ICP was recorded before prone positioning in the SP with the head and trunk elevated at 20 , after 1, 2, 3 and 4 h in the PP, and after return to the SP. Pressure ulcer was judged as a complication if not present at admission and if it was graded 2 or more on Shea's scale [16]; the site of the pressure ulcer was then recorded. The outcome was evaluated by mortality at 28 days after randomization, duration of mechanical ventilation, duration of ICU and neurologic outcome based on the Glasgow Outcome Scale (GOS) [17] 3 months after randomization; neurologic outcome was estimated to be good if the GOS score was either 4 or 5.

Sample size calculation

The study was designed to test the hypothesis that intermittent daily prone positioning would reduce the incidence of pulmonary worsening in the population studied. Using the incidence value obtained from a previous study [18], it was calculated that an inclusion of 66 patients (33 per arm) would provide a reduction in incidence from 60 to 25%, with an alpha level of 5% and a power value of 80% using a two-tailed test.

Statistical analysis

Data were analyzed on an intention-to-treat basis. Confounding factors of distribution between randomized groups were tested using the Fisher exact test and the Student and Wilcoxon tests for qualitative variables, numeric data and SAPS II admission scores, respectively. Incidence rates between groups were compared using a chi-square test. Kaplan-Meier survival curves were also constructed for lung worsening and compared using the Mantel-Cox test. The evolution of PaO_2/FIO_2 was also detailed in the two groups. Changes within groups over time were compared with baseline values, using a one-way analysis of variance for repeated measures, followed by paired *t*-tests. All *p* values are two-sided and the level of significance was set at 5%.

Results

Between April 1997 and April 2000, 279 patients were eligible for the study. Two hundred twenty-four met the exclusion criteria and the relatives of two other patients refused to consent to the patient's participation (Fig. 1). Fifty-three patients were then included in the study: 25 were randomized to the PP group, 28 to the SP group. Two patients randomized to the SP group were excluded from analysis because of death during the first 24 h after randomization, i.e. before the first evaluation time. The remaining 51 patients were kept for analysis. One patient was included with a coma without obvious etiology despite extensive research including cerebral angiography; she was randomized to the PP group and eventually it was revealed that acute poisoning could account for the coma. Despite this etiology, she was not excluded be-

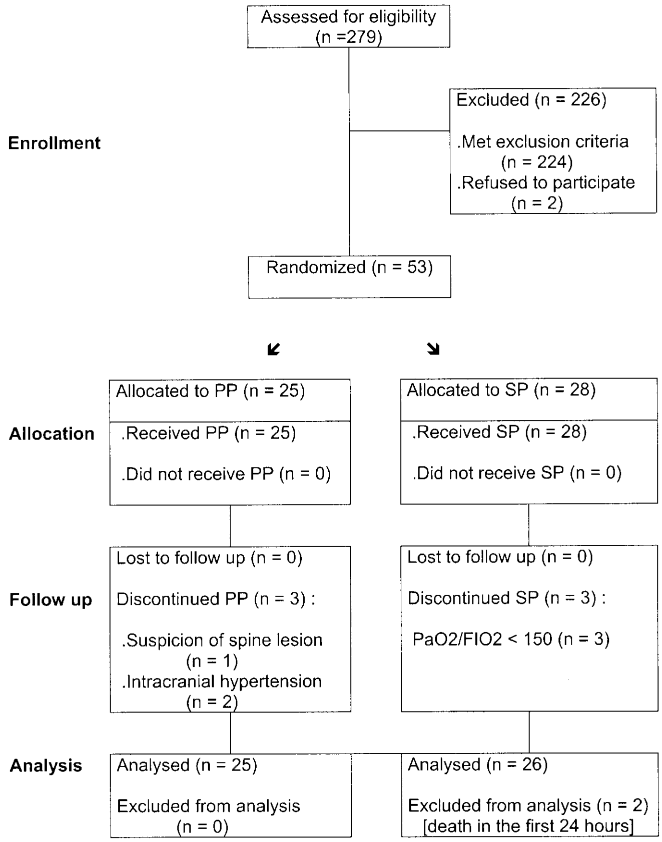
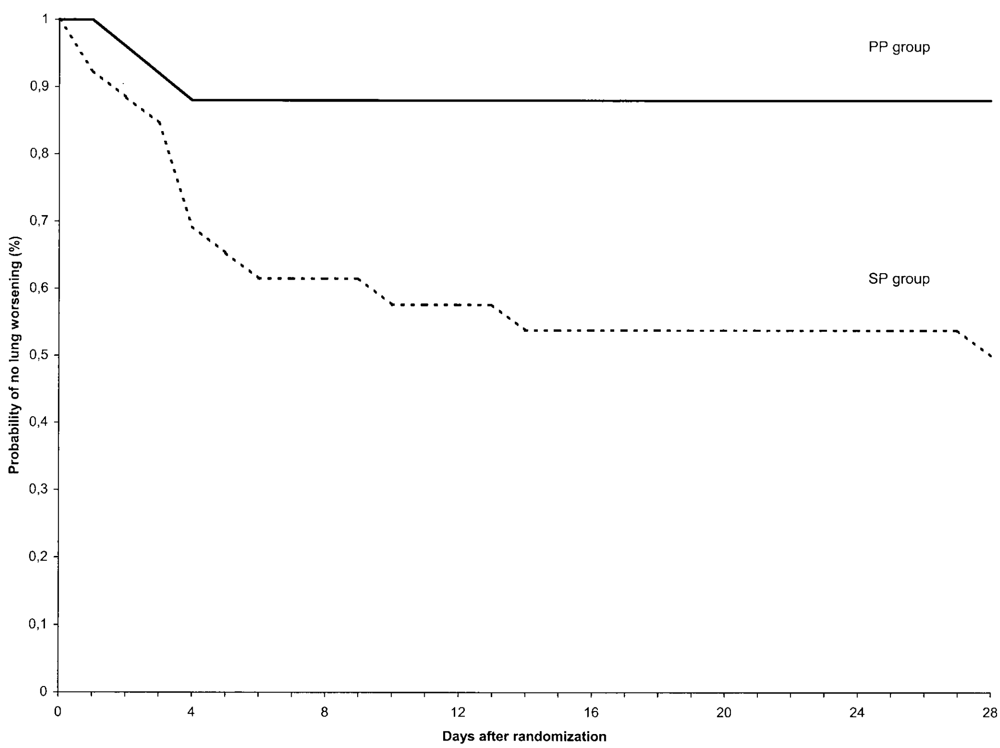


Fig. 1 Diagram showing the flow of the patients through each stage of the study

Fig. 2 Kaplan-Meier estimates of 28day lung worsening



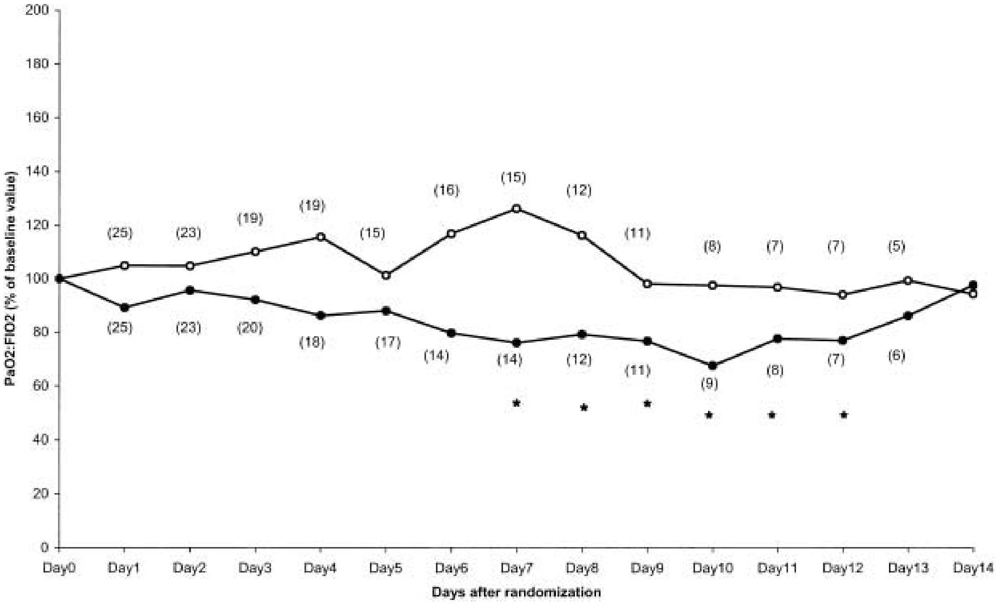


Fig. 3 Evolution of PaO_2/FIO_2 during the first 14 days for patients of PP group (*open circles*) and SP group (*black circles*). Values in parentheses are the number of patients. **p*<0.01 versus day 0

cause our analysis was on an intention-to-treat basis. For one patient randomized to the PP group, prone positioning was stopped on the 3rd day after inclusion, because of clinical suspicion of cervical spine lesion; however, tests were performed which included magnetic resonance imaging and these excluded spine lesion. This patient was therefore included in the analysis in the PP group on an intention-to-treat basis. The characteristics of the patients from the two groups at randomization were similar (Table 1). The first period in the PP began at a mean time of 14 h after intubation for patients from the PP group. The mean total duration in PP was 23.9±14.6 h for the patients in this group.

Thirteen (50%) patients presented lung worsening in the SP group as opposed to three (12%) in the PP group (RR=4.17; 95% CI=1.35–12.89; p=0.003). Using survival analysis, 28day lung worsening was lower in the PP group (p=0.0018) (Fig. 2).

The evolution of PaO_2/FIO_2 in the two groups during the first 14 days is depicted in Fig. 3. Oxygenation was slightly improved in the PP group. Conversely, oxygenation in the patients of the SP group deteriorated significantly after the 6th day ($p<0.01$). Deterioration reached 67.6% of the baseline value on day 10. Among 13 out of 26 patients, PaO_2/FIO_2 decreased below 200 before day 10. Three patients had to be turned onto the PP because PaO_2/FIO_2 fell below 150. Thereafter, oxygenation was progressively restored to baseline values for the entire SP group. PEEP level and chest X-ray grading remained unchanged throughout the first 14 days in the two groups.

Pneumonia was suspected from the clinical and chest X-ray data of 25 patients, 14 of the SP group and 11 of the PP group (NS). The incidence of microbiologically confirmed VAP was 38.4% in the SP group and 20% in the PP group (p=0.148). The duration of mechanical ventilation prior to the development of pulmonary infection was 4.3±1.8 days for the SP group and 5.2±3.5 days for the PP group (NS).

Table 2 Clinical outcome

Variable	PP group (n=25)	SP group (n=26)
Death at day 28	7 (28%)	12 (46%)
Duration of mechanical ventilation (days)[a]	12.7 (10)	14.6 (17.7)
Duration of intensive care unit stay (days)[a]	16.5 (12.9)	19.4 (24.1)
Good neurologic outcome at 3 months[b]	15 (60%)	12 (46%)

[a] Mean (SD) values
[b] Glasgow Outcome Scale 4 or 5

The clinical outcome of patients from each group is depicted in Table 2. Mortality, defined as death at 28 days, duration of mechanical ventilation, duration of intensive care unit stay and neurologic outcome were not significantly different between the two groups. There was no serious complication directly attributable to prone positioning. Values of ICP were recorded during 17 periods in PP (Table 3). There was a significant increase of ICP in PP compared to the values in SP when the head and trunk were elevated to 20°. Prone positioning had to be stopped for two patients because of increases in ICP over 30 mmHg in prone; the ICP decreased after return to the SP. Six patients from the PP group developed a pressure ulcer of grade 2 located on the face and one on the thorax. But the incidence of pres-

Table 3 Intracranial pressure (*ICP*) during prone positioning (*SP 20°* supine position with head and trunk elevated at 20°, *PP 0°* prone position strictly horizontal)

	SP 20°	PP 0° 1 h	PP 0° 2 h	PP 0° 3 h	PP 0° 4 h	SP 20°
ICP	11 (8.8)	23.7 (9.6)[a]	21.5 (4.3)[a]	22 (5.7)[a]	20.2 (5.4)[a]	10 (7.1)

Values are mean (SD) of 17 periods on prone
[a] $p<0.01$ versus values on supine position before prone (SP 20°)

sure ulcer of grade 2 or more, regardless of the site of the lesion, was similar in the two groups: 32% in the PP group and 27% in the SP group (NS).

Discussion

In this study of mechanically ventilated comatose patients, daily prone positioning reduced, by 76%, the incidence of lung worsening and prevented deterioration of oxygenation in comparison with the control group.

The initial objective of our study was to evaluate prone positioning as a strategy for the prevention of lung injury in comatose patients. However, 48 of the 51 patients included in the study had chest X-ray infiltrate at randomization, already showing the presence of a mild degree of lung injury. Here, therefore, prone positioning was evaluated as a preventive measure of lung worsening, which was assessed by the evolution of the LIS. The latter was initially developed to provide a classification of ARDS patients [11]. We chose this score to assess the evolution and the severity of lung injury in comatose patients, because it has been widely used for this in the literature. Moreover, it has been used to assess the evolution of pulmonary function in patients with aneurysmal subarachnoid hemorrhage [6].

The main limitation of our study is the number of patients included, which was smaller than planned by sample size calculation because of a lower rate of enrollment than expected. We had decided to stop enrollment after 3 years, because a longer duration might have introduced changes in the care of these patients.

The difference between the two groups regarding the evolution of LIS seems to be related mainly to differences in oxygenation, since PEEP level and chest X-ray grading did not change over time. This difference between the two groups in oxygenation reveals two important points. First, this study shows a progressive worsening of oxygenation in comatose patients who stay in the SP. This worsening may be harmful since three patients had to be turned onto the PP because their PaO_2/FIO_2 levels were below 150. This worsening might be partially explained by alveolar collapse in dorsal lung regions. There is no morphologic study to confirm this hypothesis, however, in comatose head-injured patients studied on supine at a mean time of 36 h after intubation, shunt was also frequently observed and correlated with the reduction of functional residual capacity (FRC) [5]. It was argued that this reduction of FRC was great enough to expect closure of small airways with alveolar collapse in dorsal lung regions. Moreover, sedative drugs – frequently used for our patients – induce a decrease in FRC [19] and shunt [20], which could be located in dependent lung regions corresponding to atelectatic areas on CT scan [20]. Worsening of oxygenation was probably magnified in patients of the SP group by the occurrence of pneumonia, which was diagnosed after a mean time of 4.3 days on mechanical ventilation. Indeed, the severity of the lung injury in comatose patients has been correlated with the occurrence of pneumonia [18]. Secondly, patients of the PP group exhibited an improvement in oxygenation. This is not a novel observation and has been largely demonstrated in patients with lung injury [21, 22]. However, our results were obtained with only 4 h per day in the PP. Moreover, PaO_2/FIO_2 level was measured daily before turning a patient onto the PP. This implies that the beneficial effect of 4 h on prone persisted after the return to SP. We suggest that the crucial point here could be that the first period on prone was realized very early in the course of the lung injury, so that the time which had elapsed since the onset of coma was short. Alveolar collapse could then be reversed more easily by prone positioning. However, no study has specifically addressed this issue.

Prone positioning did not significantly reduce the incidence of pulmonary infection. Perhaps the study was not powerful enough with regards to this end point. Prone positioning seems to be unable to interfere with bacterial colonization of the tracheobronchial tree. Indeed, the latter occurs early in comatose patients [4] and is probably due to the aspiration of oropharyngeal content before intubation, caused by glottic dysfunction. Thereafter, the impaired muco-ciliary clearance observed in intubated patients under sedative drugs [23] and the decreased cough due to coma favor bacterial colonization of distal lower airways. Prone positioning could limit colonization of the distal lower airways by optimizing bronchial drainage. Indeed, the trachea and main bronchi are directed backwards in the SP. A CT scan study showed the appearance, after prone positioning, of the bronchogram in some dorsal homogeneous densities observed in SP [10]. This means that small airways were reopened by prone, enhancing bronchial drainage. However, no study has demonstrated that PP favors bronchial drainage in comparison with SP.

In our study, PP appeared to be a safe proceeding. However, we observed a significant increase of ICP on prone in head-injured patients. It has to be noted that ICP was not recorded at the same degree of elevation of head and trunk, 20° on supine, 0° on prone. This difference could contribute in part to the increase of ICP observed. The mean value of ICP on prone after 1 h was 23.7 mmHg. These values do not seem to reflect life-threatening intracranial hypertension, since recent guidelines suggested an ICP threshold of 20–25 mmHg above which treatment aimed to reduce ICP was recommended [24]. However, it seems unreasonable to turn onto prone patients who already present intracranial hypertension (if ICP exceeds 20 mmHg, as stated by our protocol) in the SP. Nevertheless, this requires further investigations to clarify the mechanisms and cerebral impact of variations of ICP induced by PP.

In conclusion, our study showed that, in a selected population of comatose patients, daily prone positioning could prevent worsening of oxygenation.

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