Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Guérin C, Reignier J, Richard J-C, et al. Prone positioning in severe acute respiratory distress syndrome. N Engl J Med 2013. DOI: 10.1056/NEJMoa1214103

SUPPLEMENTARY APPENDIX

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List of investigators

Lyon: Hôpital de la Croix-Rousse- C Guérin, JC Richard, F Bayle, G Bourdin, V Leray, F Wallet, B Delannoy, S Debord, A Stoian, P Nesme, V Porot; Hôpital Saint-Joseph- S Rosselli; Hôpital Edouard Herriot- L Argaud, O Martin. ***La Roche Sur Yon***: Centre Hospitalier Départemental- J Reignier, E Greau, N Maquigneau. ***Roanne***: Centre Hospitalier- P Beuret. ***Rennes***: Hôpital Ponchaillou- Y Le Tulzo, A Gacouin. ***Orléans***: Hôpital de la source-T Boulain, I Runge, D Benzkri, A Mathonnet, M Skarzynski, A Bretagnol. ***Tours***: Hôpital Bretonneau- D Perrotin, E Mercier, V Simeon-Vieules. ***Angers***: Centre Hospitalier Universitaire- A Mercat, L Masson. ***Chambéry***: Centre hospitalier- M Badet. ***Limoges***: CHU Dupuytren- M Clavel, J Tanty. ***Angoulême***: Centre hospitalier- O Baudin, V Gissot, C Cracco, A Desachy, MA Fally, L Robin. ***Poitiers***: Hôpital Jean Bernard- R Robert, D Chatellier, V Goudet, E Goyheneix, C Guignon. ***Montpellier***: Hôpital Saint-Eloi- S Jaber, B Young, F Belafia, J Carr, N Rossel. ***Barcelone***: Hospital de la Santa Creu i Sant Pau- J Mancebo, M Turella, F Roche-Campo, HM Aguirre-Bermeo. ***Bordeaux***: Hôpital Pellegrin- G Hilbert, S Coz. ***Annecy***: Centre Hospitalier de la région Annecéenne- M Sirodot, A Levrat. ***Marseille***: Hôpital de la Timone- M Gainnier, M Bisbal. ***Cergy-Pontoise***: Centre hospitalier René Dubos- J Richecoeur, D Combaux. ***Nîmes***: Hôpital Caremeau- JY Lefranc, C Bengler, F Casano, S Lloret***.*** ***Grenoble***: CHU la Tronche- JF Timsit, A Bonadonna. ***Avignon***: Centre hospitalier- K Pavaday. ***Saint-Etienne***: Hôpital Nord- F Zeni, E Diconne. ***Dôle***: Centre hospitalier Louis Pasteur- D Perez. ***Clermont-Ferrand***: Hôpital Gabriel Montpied: B Souweine, A Lautrette, AA Hussain. ***Paris***: Hôpital de la Pitié-Salpétrière- A Demoule, L Kontar. ***Annonay***: Centre Hospitalier, V Cadiergue.

Methodology: L Ayzac, R Girard, L Baboi, J Escande, G Flandreau, D Moreau, M Vanhove, M Sidibe, JM Villier.

Steering committee: L Ayzac, R Girard, L Baboi, C Guérin, V Schreiber, J Escande, G Flandreau, D Moreau, M Vanhove, M Sidibe.

Data Safety Management Board: RK Albert MD, Pulmonary and Critical Care Medicine Department, Denver, Colorado, USA ; JD Chiche MD PhD Service de Réanimation Médicale, Groupe Hospitalier Cochin, Paris, France ; D Tassaux MD, Service de Soins Intensifs, Hôpitaux Universitaires de Genève, Geneva, Switzerland.

Patients

Non-inclusion criteria:

1. Contraindication for prone positioning

    a. Intracranial pressure >30 mm Hg or cerebral perfusion pressure <60 mmHg

    b. Massive hemoptysis requiring an immediate surgical or interventional radiology procedure

    c. Tracheal surgery or sternotomy during the previous 15 days

    d. Serious facial trauma or facial surgery during the previous 15 days

    e. Deep venous thrombosis treated for less than 2 days

    f. Cardiac pacemaker inserted in the last 2 days

    g. Unstable spine, femur, or pelvic fractures

    h. Mean arterial pressure lower than 65 mm Hg

    i. Pregnant women

    j. Single anterior chest tube with air leaks

2. Respiratory reason

    a. Inhaled nitric oxide (NO_i) or almitrine bismesylate use before inclusion

    b. Use of extracorporeal membrane oxygenation (ECMO) before inclusion

3. Clinical context

    a. Lung transplantation

    b. Burns on more than 20 % of the body surface

    c. Chronic respiratory failure requiring oxygen therapy or non-invasive ventilation (NIV)

    d. Underlying disease with a life expectancy of less than one year

    e. NIV delivered for more than 24 hours before inclusion

4. Other non-inclusion criteria

a. End-of-life decision before inclusion

b. Inclusion in another research protocol in the previous 30 days with mortality as the main end-point

c. Previous inclusion in the present study

d. Prone positioning before inclusion

e. Subject deprived of freedom, minor, subject under a legal protective measure

f. Opposition from next of kin

Protocol

Study design

C Guérin designed the study, L Baboi, J Escande, G Flandreau, D Moreau, M Vanhove, M Sidibe, JM Villier gathered the data, L Ayzac analysed the data, C Guérin and L Ayzac vouched for the data and the analysis, C Guérin, L Ayzac and R Girard wrote the paper, C Guérin decided to publish the paper.

After checking eligibility, a 12-24-hour stabilization period was observed and inclusion was confirmed only at the end of this period (see Figure S1).

Patients assigned to the prone group had to be turned within the first hour following randomization. They were placed in prone position for at least 16 consecutive hours. Participating centers were provided with guidelines to ensure the best possible standardization of prone positioning . Standard intensive care unit (ICU) beds were used for all patients.

Guidelines for the prone positioning placement

The protocol stated that 3 to 4 persons were required for the procedure, one of them being dedicated to the management of the head of the patient, the endotracheal tube and the ventilator lines. This person at the head of the bed had to coordinate the steps of the procedure. The other persons stood at each side of the bed. In the first step, the direction of the rotation (to the left or to the right) was decided giving priority to the side of the central venous lines. The length of vascular and ventilator lines was checked for appropriateness, the endotracheal tube and gastric tube were secured, and the patient's knees, forehead, chest, and iliac crests were protected using adhesive pads.

The patient was then moved along the horizontal plane to the opposite side of the bed selected for the direction of rotation. In the third step, the patient was moved in the sagittal plane and maintained in that position for a short while to attach the cardiac electrodes to her/his back and to set a new bed sheet. In the last step, the patient was turned to the complete prone position. The body was placed in a horizontal position at 180 degrees. The abdomen was not

supported. The head and neck were turned alternately to the right or left every 2 hours. The upper limbs were placed alongside the body. Particular attention was paid when changing positions to avoid disconnecting the ventilator or kinking in the vascular lines. One video of positioning changes performed at one of the participating centers is available as supplementary material. Another video recording performed by a coauthor can also be downloaded from reference 3).

Patients assigned to supine remained in a semi-recumbent position.

Mechanical ventilation was delivered in volume controlled mode with constant inspiratory flow, with V_T targeted at 6 $ml.kg^{-1}$ predicted body weight (PBW) and positive end-expiratory pressure (PEEP) level selected from a PEEP-F_IO_2 table (Table S1). The goal was to keep end-inspiratory plateau pressure of the respiratory system ($Pplat_{,RS}$), measured after a 1 sec period of no air flow, ≤30 cm H_2O and arterial plasma pH between 7.20 and 7.45. Respiratory frequency (RF) was adjusted to maintain arterial plasma pH within the above range, without exceeding 35 $breaths.min^{-1}$. Ventilator settings could be adjusted at any time regardless of patient position, based on the continuous monitoring of the oxygen saturation by pulse oximetry (SpO_2). Physiological variables were measured at predetermined times in both groups. Measurements were performed every 6 hours in the supine group, and just before turning prone, after 1 hour of proning, just before turning back to supine, and 4 hours later in the prone group. Arterial blood gases and $Pplat_{,RS}$ were measured at these time points. The latter was measured in static conditions in patients with no spontaneous breathing efforts and the NOi was stopped if it was being used. The adjustments made to mechanical ventilation in specific situations are detailed below.

The criteria for stopping prone treatment were: 1) oxygenation improvement defined as $PaO_2/F_IO_2 \geq 150$ mmHg with PEEP ≤ 10 cm H_2O and $F_IO_2 \leq 0.6$; in the prone group, these criteria had to be met in supine at least 4 hours after the end of the last prone session; 2)

PaO_2/F_IO_2 ratio deterioration by more than 20 % relative to supine before two consecutive prone sessions; and 3) complications occurring during a prone session and leading to its immediate interruption, such as non-scheduled extubation, mainstem bronchus intubation, endotracheal tube obstruction, hemoptysis, SpO_2<85% or PaO_2<55mmHg for more than 5 minutes under $F_IO_2$1, cardiac arrest, heart rate <30 beats/min for more than 1 minute, systolic blood pressure<60 mmHg for more than 5 minutes, or any other life-threatening reason for which the clinician decided to stop.

After patients in the prone group were turned to supine, the prone session could be resumed at any time before the planned assessment at 4 hours in supine if the SpO_2 and/or PaO_2 criteria were fulfilled. The proning strategy was applied every day up to day 28 unless the patient met the previously noted criteria for stopping the prone intervention, after which it was used at the clinician's discretion.

Patients in supine were not allowed to cross over to prone except as a rescue therapy in case of life-threatening hypoxemia, when all the following criteria were met simultaneously: PaO_2/F_IO_2<55mmHg under F_IO_2 1, maximal PEEP according to PEEP-F_IO_2 table, 10 ppm inhaled nitric oxide (NOi), 4 $\mu g.kg^{-1}.min^{-1}$ intravenous almitrine bismesylate infusion and performance of recruitment maneuvers.

Management of sedation and neuromuscular blockers (NB) is detailed below. Weaning from mechanical ventilation was conducted in the same way for both groups according to the predetermined strategy explained below.

Data collection

Patient (alive or dead) and respiratory status (successful extubation, NIV use, tracheotomy performed or not) were recorded at days 28 and 90. The times of ICU admission and discharge were also recorded.

Data quality was verified by research fellows, who re-checked every data point.

Adjustments to mechanical ventilation in specific situations

In the event of partial pressure of arterial oxygen (PaO_2)<55 mm Hg or SpO_2 <88 %, the clinician first adjusted the ventilator settings and tested arterial blood gases 15 minutes later:

a. PEEP and F_IO_2 according to the PEEP/F_IO_2 table (Table S1).
b. NB if needed.
c. 10 ppm NO_i with concentration reassessed 48 hours later.
d. Continuous intravenous infusion of 4 $mcg.kg^{-1}.min^{-1}$almitrine bismesylate may be used.
e. Recruitment maneuvers were not recommended but their use was left to the clinician's discretion and recorded in the case report form.

If PaO_2>80 mm Hg or SpO_2> 95 %:

a. NB stopped if being infused .
b. NO_i stopped if in use
c. Almitrine bismesylate stopped if being infused .
d. Recruitment maneuvers stopped if used.
e. PEEP and F_IO_2 management according to PEEP-F_IO_2 table (Table S1).

If $Pplat_{,RS}$>30 cm H_2O :

If spontaneous inspiratory efforts were clinically detected, NB were bolused. If $Pplat_{,RS}$ was still >30 cm H_2O, V_T was decreased by steps of 1 $ml.kg^{-1}$ every 5 minutes as long as $Pplat_{,RS}$>30 cm H_2O until 4 $ml.kg^{-1}$PBW. If pH was < 7.2, V_T was not decreased.

In no spontaneous inspiratory efforts were detected, V_T was decreased by steps of 1 $ml.kg^{-1}$ every 5 minutes as long as $Pplat_{,RS}$>30 cm H_2O until 4 $ml.kg^{-1}$PBW. If pH was < 7.2, V_T was not decreased.

If pH < 7.20, the followings interventions were applied in this order:

a. Sedation and NB regimens were adjusted to obtain a smooth adaptation between the patient and the ventilator.
b. Equipment dead-space was minimized if present.
c. RF was increased by steps of 2 without exceeding 35 breaths.min^{-1}.
d. Sodium bicarbonate was infused intravenously
e. If pH still <7.20 in spite of interventions a-d, V_T was increased by steps of 1 ml.kg^{-1} until pH ≥7.20 without exceeding 8 ml.kg^{-1}PBW.

If pH>7.45:

a. NB was stopped if infused beyond the 48th hour
b. RF was lowered by steps of 2.

If $Pplat_{,RS}$<25 cm H_2O and V_T<6 ml.kg^{-1}PBW:

V_T was increased by steps of 1 ml.kg^{-1} every 5 minutes up to 6 ml.kg^{-1}PBW as long as $Pplat_{,RS}$<30 cm H_2O.

If a pneumothorax was diagnosed:

PEEP level was left to the clinician's discretion as long as the pneumothorax and/or the chest tube was present. The other study recommendations still applied.

Weaning from mechanical ventilation

Weaning was conducted in the same way in the two groups according to a predetermined strategy along the following steps.

First, once PaO_2/ F_IO_2≥150 mmHg, PEEP≤10 cmH_2O and F_IO_2≤ 0.6 were achieved, the NB were stopped if being infused. Sedatives were stopped after NB withdrawal.

Second, as soon as PEEP was ≤10 cm H_2O, PEEP was decreased to 5 cm H_2O in 20 to 30 minutes. If SpO_2 was≤88 % for more than 5 minutes or RF>35.min^{-1}, previous ventilator settings were resumed. If, with PEEP 5 cm H_2O and F_IO_2≤ 0.6, RF was >35 breaths.min^{-1},

previous ventilator settings were resumed. If RF was ≤35.min^{-1} with PEEP 5 cm H_2O and F_IO_2< 0.6, a patient was then qualified as potentially weanable from mechanical ventilation.

Third, potentially weanable patients were weaned using the standardized protocol in pressure support ventilation (PS) as follows. F_IO_2 was set to 0.5 and PEEP to 5 cm H_2O. The objectives were to keep a RF between 26 and 35 breaths.min^{-1} and a SpO_2≥88 %. The PS level was adjusted within the 5 and 20 cm H_2O boundary, by steps of 5 cm H_2O. If the RF<26 breaths.min^{-1}, the PS level was set at 5 cm H_2O. If the RF was between 26 and 35 breaths.min^{-1}, the PS was set to 20 cm H_2O, and subsequently adjusted between 5 and 20 cmH_2O according to the SpO_2 and RF objectives. Patients went back to volume controlled mode or to PS 20 cm H_2O if: a) RF>35 breaths.min^{-1}>5 minutes, b) SpO_2<88 % >5 minutes, c) excessive use of accessory respiratory muscles, d) paradoxical abdominal motion, or e) dyspnea, agitation/altered mental status, or sweating attributable to a clinical intolerance of the withdrawal of ventilator support. The patient could be extubated when he/she tolerated PS 5 cmH_2O with PEEP 5 cmH_2O and F_IO_2 0.5. Tolerance was defined as: SpO_2≥90 % and/or PaO_2≥60 mm Hg, V_T≥4 ml.kg^{-1}PBW, RF≤35 breaths.min^{-1}, absence of signs/symptoms of respiratory distress (RF>35 breaths.min^{-1}>5 minutes, SpO_2<88 %>5 minutes, use of accessory respiratory muscles, paradoxical abdominal motion, dyspnea, sweating, and agitation/altered mental status). The use of non-invasive ventilation in the post-extubation period and the decision to perform a tracheotomy were left to the clinician's discretion. Synchronized intermittent mandatory ventilation and biphasic positive airway pressure modes were not allowed by the protocol.

Management of sedation and neuromuscular blocker agents

Sedation was managed to a target Ramsay score[1] of 6 assessed every 6 hours (1 patient is anxious or agitated or both. 2 patient is co-operative, oriented and tranquil. 3 patient responds to command only. 4 patient exhibits a brisk response to light glabellar plat or loud auditory

stimulus. 5 patient exhibits a sluggish response to light glabellar plat or loud auditory stimulus. 6 patient exhibits no response). Sedative and analgesic drugs were those routinely used in the participating centers. When sedation was stopped, the objective was to keep a Ramsay score of 2.

The protocol strongly recommended the use of a NB during the first 48 hours using cisatracurium besilate administered intravenously with an initial 0.15 $mg.kg^{-1}$ bolus then 0.06 to 0.12 $mg.hour^{-1}$ in continuous drip. NB could be stopped before 48 hours if the improvement criteria were met. NB could be used after the 48^{th} hour if the therapeutic objectives had not been reached. The train-of-four ratio was not used to monitor the effects of NB. Our study was designed before the end of the *Acurasys* trial[2], and we did not change the use of NB in our study after its publication. Sedation was stopped after NB interruption.

Results

Characteristics at inclusion

These are given in table S2.

Prone interruption

Reasons for proning interruption were: oxygenation improvement (n=209), pressure sores (16), end-of life decision (6), PaO_2/F_IO_2 worsening by more than 20% for two consecutive sessions (5), systolic blood pressure <60mmHg for more than 5 minutes (5), SpO_2<85% (3), endotracheal tube obstruction (2), cardiac arrest (2), pneumothorax (2), bladder drainage problem (2), dialysis requirement (2), abdominal reason (2), arrhythmia (2), transport to radiology department (1), hemoptysis (1), venous thrombosis (1), and unknown (4).

Seventeen patients allocated to the supine group (7.4% in this group) were crossed over the prone positioning because of refractory hypoxemia according to the protocol.

Ventilator settings and lung function during the first week

The PaO_2/F_IO_2 ratio recorded in supine position was significantly higher in the prone group than in the supine group at days 3 and 5, whereas PEEP and F_IO_2 were significantly lower (Table S3). $Pplat_{,RS}$ was 2 cm H_2O lower by day 3 in the prone than in the supine group. $PaCO_2$ and static compliance of the respiratory system were similar in both groups (Table S3).

Primary and secondary outcomes

These are given in table S4.

After adjusting for SOFA score, NB and vasopressor use at the time of inclusion, mortality remained significantly lower in the prone group according to the Cox proportional hazards regression (Table S5).

A second mortality analysis was made, taking into account the 8 patients excluded after randomization (figure 1), in order to follow the rule of analysis in "intention-to-treat". In this analysis, mortality rates at day 28 were 32.5% supine and 16.3% prone ($P<0.0001$), and mortality rates at day-90 were 40.6% supine and 23.8% prone ,($P<0.001$).

In 30 of the 75 patients (40%) who died in the supine group and 14 of the 38 (36.8%) who died in the prone group, an end-of life decision was made at some time after inclusion. The difference in the proportion of patients in whom such a decision was made was not statistically significant ($P= 0.74$).

In 21 of the 27 participating ICUs, mortality was lower in the prone group than in the supine group, in agreement with the overall result. In the remaining 6 ICUs (each with fewer than 23 patients) the mortality was not lower in the prone group as compared to the supine group. Furthermore, when the center was entered as a covariate in the Cox proportional hazards regression, no statistically significant effect of center on day 28 and day 90 mortality was found.

The number needed to treat computed from day-28 mortality was 6 (i.e. we need to treat 6 patients in prone to avoid one death).

Complications

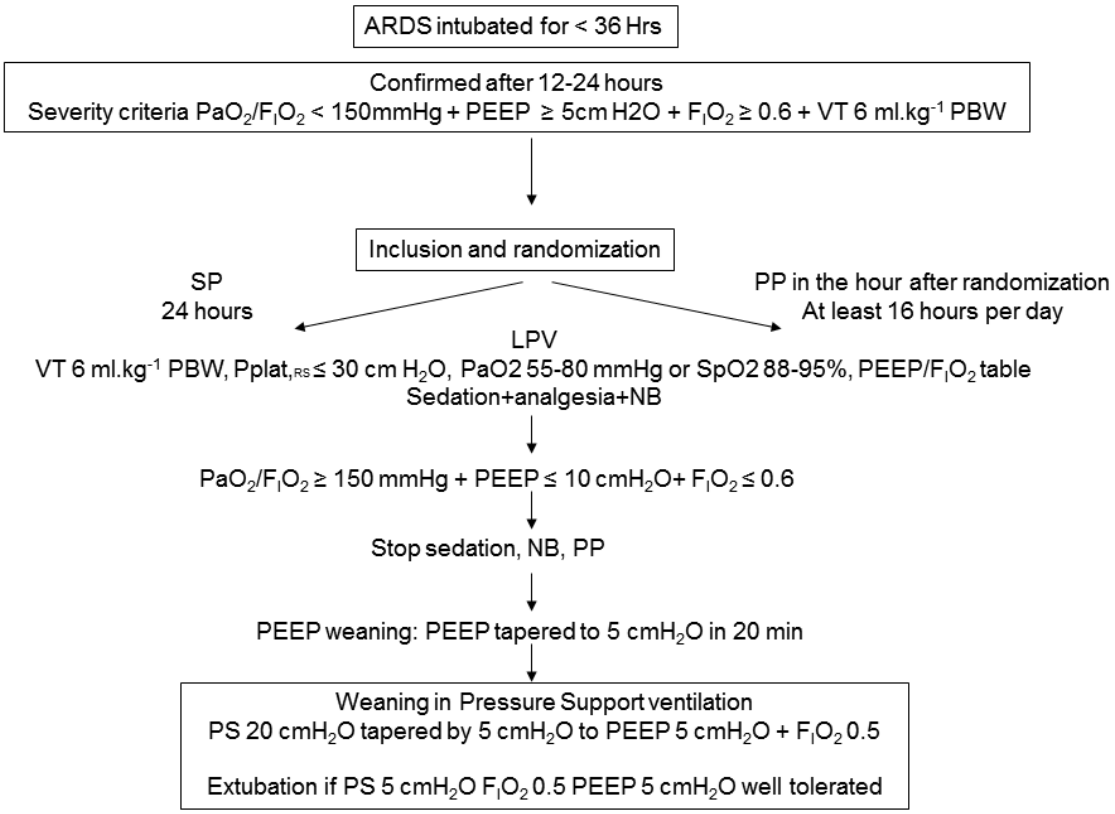
Cardiac arrests occurred significantly more frequently in the supine group than in the prone group. There were no differences between groups for other adverse effects (Table S6).

Causes of death

The causes of death in each group are shown in Table S7.

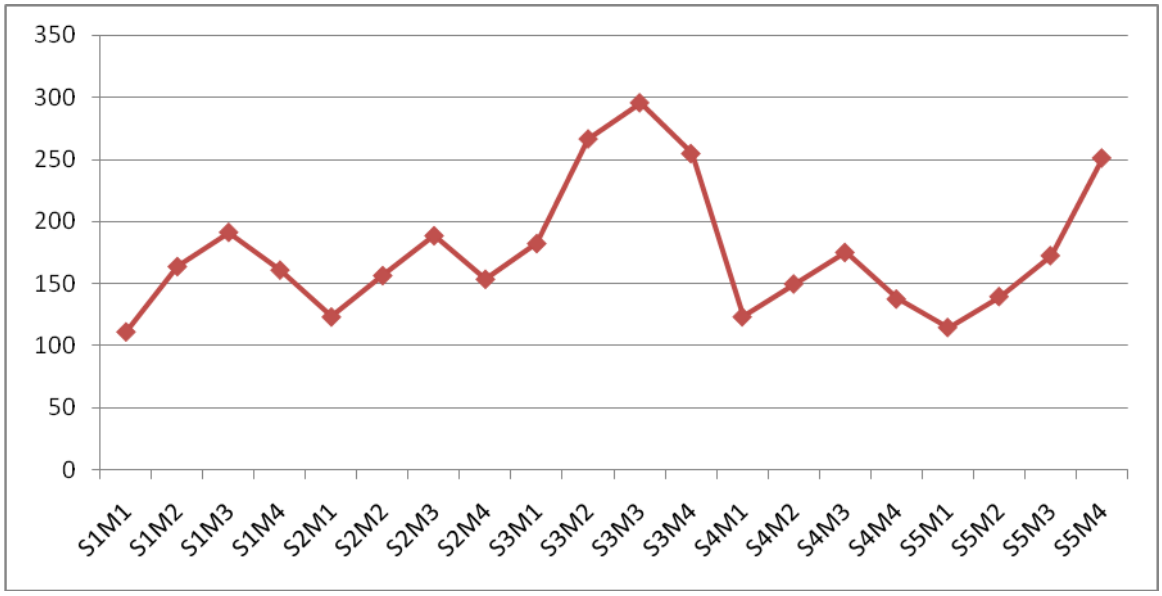
Figures

Figure S1. Study design



ARDS: acute respiratory distress syndrome. PEEP: positive end-expiratory pressure. F_IO_2: fraction of inspired oxygen. V_T: tidal volume. PBW: predicted body weight. SP: supine position. PP: prone position. LPV: lung protective ventilation. $Pplat_{,RS}$: end-inspiratory plateau pressure of the respiratory system. SpO_2: oxygen saturation by pulse oximetry. NB: neuromuscular blockers. PS: pressure support ventilation.

Figure S2. Mean values of PaO_2/F_IO_2 (mm Hg) in the Prone Position group during the first five sessions.



Number of patients per prone session	S1	S2	S3	S4	S5
	170	130	99	71	51

S1 to S5: rank of the prone sessions, M1 to M4: position of the patient and time line of the measurements: M1 supine just before proning, M2 one hour after proning, M3 end of proning just before going back to the supine position and M4 is 4 hours after supine positioning.

Tables

Table S1.Positive end-expiratory pressure (PEEP) - Fractional concentration of inspired oxygen (F_IO_2) table used for both groups

PEEP (cm H_2O)	5	5	8	8	10	10	10	12	14	14	14	16	18	18-24
F_iO_2	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.7	0.7	0.8	0.9	0.9	0.9	1.0

Table S2. Characteristics at inclusion

	Supine group (n=229)	Prone group (n=237)
Age, years	60 ± 16	58 ± 16
Gender, n male (%)	152 (47.8)	166 (52.2)
Patient origin, n (%)		
Emergency room	98 (42.8)	101 (42.6)
Acute care	87 (38.0)	86 (36.3)
Home	26 (11.4)	31 (13.1)
ICU	9 (3.9)	11 (4.6)
Other	9 (3.9)	8 (3.4)
Setting, n (%)		
Medical	203 (88.6)	211 (89.0)
Elective surgery	9 (3.9)	6 (2.5)
Non-elective surgery	15 (6.6)	12 (5.1)
Trauma	2 (0.9)	8 (3.4)
McCabe, n (%)		
A	183 (79.9)	197 (83.1)
B	45 (19.7)	39 (16.5)
C	1 (0.4)	1 (0.4)
Comorbidities, n (%)		
Diabetes, n (%)	39 (17)	50 (21)
Renal failure, n (%)	12 (5)	10 (4)
Hepatic disease, n (%)	16 (7)	15 (6)
Coronaryarterydisease, n (%)	24 (11)	24 (10)
Malignancy, n (%)	30 (13)	24 (10)
COPD, n (%)	29 (13)	23 (10)
Immunodeficiency, n (%)	38 (16.6)	32 (13.5)
SAPS II	47 ± 17	45 ± 15
Sepsis[a], n (%)	195 (85.2)	194 (82.2)
SOFA score	10.4 ± 3.4*	9.6 ± 3.2
Blood lactate (mmol/l)	2.6 ± 3.5 (n=204)	2.5 ± 3.4 (n=201)
ARDS main origin		
Pneumonia	133 (58.1)	148 (62.4)
Aspiration	41 (17.9)	45 (19.0)
Extra-pulmonary sepsis	28 (12.2)	17 (7.2)
Other	27 (11.8)	27 (11.4)
Height (cm)	168 ± 10	168 ± 9
Predicted body weight (kgs)[b]	62 ± 10	63 ± 10
Body mass index ($kg.m^{-2}$)	29 ± 7	28 ± 6
Co-interventions		
Vasopressors, n (%)	190 (83.0)*	172 (72.6)
Neuromuscular blockers, n (%)	186 (82.3)*	212 (91.0)
Renal replacement therapy, n (%)	39 (17.1)	27 (11.4)
Glucocorticoids, n (%)	101 (44.9)	91 (39.6)

ICU: intensive care unit. SAPS II: Simplified Acute Physiology Score II (range 0- 164, higher score greater severity). SOFA: Sepsis-Related Organ Failure Assessment (range 0-24, higher

score greater severity). ARDS: Acute Respiratory Distress Syndrome, COPD: Chronic Obstructive Pulmonary Disease.

McCabe score A. No underlying disease that compromises vital prognosis, B. prognosis of life related to chronic disease less than 5 years, C. prognosis of life related to chronic disease less than 1 year.

[a] according to the consensus conference criteria

[b] according to the following formula: men 50+0.91(cm-152.4); women 45.5+0.91(cm-152.4)

* $P < 0.05$ versus prone group

Table S3. Ventilator settings, arterial blood gases and respiratory system mechanics during the first week, recorded in the supine position in the two groups

	Day 3		Day 5		Day 7	
	SG	PG	SG	PG	SG	PG
Tidal volume (ml)	415±117 (n=201)	411±95 (n=218)	425±115 (n=188)	440±124 (n=197)	440±117 (n=156)	431±102 (n=155)
Tidal volume ($ml.kg^{-1}PBW$)	6.6±1.6 (n=201)	6.5±1.4 (n=218)	6.9±1.8 (n=188)	6.9±1.8 (n=197)	7.0±1.9 (n=156)	6.8±1.4 (n=155)
Respiratory frequency ($breaths.min^{-1}$)	28±6 (n=202)	27±6 (n=218)	27±6 (n=190)	27±7 (n=201)	27±7 (n=157)	27±7 (n=160)
PEEP ($cm\ H_2O$)	9.3±3.3 (n=205)	8.6±2.6* (n=222)	8.9±3.5 (n=191)	8.1±3.0* (n=205)	8.5±3.5 (n=159)	8.1±3.9 (n=165)
F_IO_2	0.58±0.18 (n=203)	0.53±0.14** (n=223)	0.58±0.19 (n=192)	0.51±0.14** (n=206)	0.56± 0.19 (n=160)	0.51±0.13 (n=168)
PaO_2 (mm Hg)	83±25 (n=204)	86±26 (n=219)	82±21 (n=190)	84±24 (n=206)	85±27 (n=160)	84±25 (n=173)
PaO_2 / F_IO_2 (mm Hg)	157±64 (n=200)	172±64* (n=219)	157±68 (n=189)	179±100** (n=203)	170±80 (n=158)	173±62 (n=167)
$PaCO_2$ (mm Hg)	47±14 (n=204)	45±9 (n=219)	47±13 (n=190)	45±10 (n=206)	47±13 (n=160)	44±10 (n=173)
Arterial pH	7.39±0.08 (n=204)	7.40±0.18 (n=219)	7.40±0.09 (n=190)	7.42±0.07 (n=206)	7.41±0.08 (n=160)	7.43±0.07 (n=173)
$Pplat,_{RS}$ ($cm\ H_2O$)	24±5 (n=133)	22±4* (n=135)	24±5 (n=105)	22±5* (n=91)	24±5 (n=73)	22±4** (n=71)
$Cst,_{RS}$ ($ml.cmH_2O^{-1}$)	36±18 (n=133)	38±17 (n=132)	35±16 (n=103)	36±18 (n=89)	35±16 (n=73)	31±17 (n=71)

SG: supine group. PG: prone group. PBW: predicted body weight. PEEP: positive end-expiratory pressure.F_IO_2: inspired oxygen fraction.PaO_2: arterial partial pressure in oxygen.$PaCO_2$: arterial partial pressure in carbon dioxide. $Pplat,_{RS}$: End-inspiratory plateau pressure of the respiratory system.$Cst,_{RS}$: static compliance of the respiratory system.

* $P < 0.05$ ** $P < 0.01$ versus Supine group

Table S4. Primary and secondary outcomes according to study group

	Supine group (n=229)	Prone group (n=237)	Hazard Ratio or Odds Ratio with the prone [95% CI]	P value
Mortality				
at D28, n (% [95% CI])				
Not adjusted	75 (32.8 [26.4-38.6])	38 (16.0 [11.3-20.7])	0.39 [0.25-0.63]	0.0000256
Adjusted for SOFA score			0.42 [0.26-0.66]	0.0002
at D90, n (% [95% CI])				
Not adjusted	94 (41.0 [34.6-47.4])	56 (23.6 [18.2-29.0])	0.44 [0.29-0.67]	0.0000573
Adjusted for SOFA score			0.48 [0.32-0.72]	0.0004
Successful extubation at D90, n (% [95% CI])	145/223 (65.0 [58.7-71.3])	186/231 (80.5 [75.4-85.6])	0.45 [0.29-0.70]	0.0002
Time to successful extubation at D90 (days), (mean±SD)				
Survivors	19 ± 21	17 ± 16		0.873
Non-survivors	16 ± 11	18 ± 14		
ICU length of stay at D90 (days), (mean±SD)				
Survivors	26 ± 27	24 ± 22		0.053
Non-survivors	18 ± 15	21 ± 20		
Ventilator-free days at D28 (mean±SD)	10 ± 10	14 ± 9		0.0003
Ventilator-free days at D90 (mean±SD)	43 ± 38	57 ± 34		0.0001
Pneumothorax, n (% [95% CI])	13 (5.6 [3.9-7.5])	15 (6.3 [4.9-7.7])	0.89 [0.39-2.02]	0.8465
Non-invasive ventilation, n (% [95% CI])				

At D 28	10 (4.7 [1.9-7.5])	4 (1.8 [0.05-3.5])	0.36 [0.07-3.5]	0.1077
At D 90	3 (1.5 [0.2-3.2])	4 (1.8 [0.1-3.5])	1.22 [0.23-6.97]	1.000
Tracheotomy, n (% [95% CI])				
At D 28	12 (5.2 [2.3-8.1])	9 (3.8 [1.4-6.0])	0.71 [0.27-1.86]	0.3668
At D 90	18 (8.1 [4.5-11.7])	15 (6.4 [3.3-9.5])	0.78 [0.36-1.67]	0.5896
Number of extra-pulmonary organ dysfunction-free days up to 28 days after randomization (mean±SD)				
Cardiovascular	10 ± 8	12 ± 7		0.0279
Renal	11 ± 9	12 ± 9		0.1773
Hepatic	13 ± 9	14 ± 8		0.4637
Hematological	13 ± 9	13 ± 8		0.5493
Neurological	12 ± 9	12 ± 3		0.3796

CI: Confidence Interval. ICU: Intensive Care Unit. SOFA: Sepsis-Related Organ Failure Assessment (range 0-164, higher score greater severity).

Table S5. Cox proportional hazards regression model of mortality at day-28 and day-90

Day-28	HR		95% CI	P value
Prone position (reference : supine position)	0.466		0.310-0.699	<0.001
SOFA (per unit SOFA score) at inclusion	1.194		1.106-1.290	<0.001
NB at inclusion (reference: absence)	1.340		0.695-2.583	0.382
Vasopressors at inclusion (reference: absence)	1.217		0.573-2.587	0.609

Day-90	HR		95% CI	P value
Prone (reference : supine)	0.529		0.375-0.747	<0.001
SOFA (per unit SOFA score) at inclusion	1.138		1.066-1.215	<0.001
NB at inclusion (reference: absence)	1.283		0.734-2.243	0.382
Vasopressors at inclusion (reference: absence)	1.630		0.848-3.132	0.609

HR: Hazard ratio. CI: Confidence interval. NB: neuromuscular blockers. SOFA: Sepsis-Related Organ Failure Assessment (range 0-24, higher score greater severity)

Table S6. Adverse events according to study group

	Supine group (n=229)	Prone group (n=237)
Non-scheduled extubation, n (%)	25 (10.9)	31 (13.3)
Mainstem bronchus intubation, n (%)	5 (2.2)	6 (2.5)
Endotracheal tube obstruction, n (%)	5 (2.2)	11 (4.9)
Hemoptysis, n (%)	12 (5.2)	6 (2.5)
Cardiac arrest, n (%)	31 (13.5) *	16 (6.8)
Oxygen saturation by pulse oximetry < 85% or PaO_2 <55 mm Hg > 5 minutes, n (%)	164 (71.6)	155 (65.4)
Heart rate < 30 beats.min^{-1}> 1 minute, n (%)	27 (11.8)	26 (11.0)
Systolic blood pressure<60 mmHg > 5 minutes, n (%)	48 (21.0)	35 (14.8)

* $P < 0.05$ versus the prone group

Table S7. Presumed causes of death in both groups assessed at day-28 (P=0.31, Pearson Chi² test)

	Supine group		Prone group	
	All patients (n=75)	Patients with end-of life decision (n=30)	All patients (n=38)	Patients with end-of life decision (n=14)
Multiple organ dysfunction, n (%)	37 (49)	13 (43)	19 (50)	9 (64)
Refractory shock n (%)	16 (21)	7 (23)	5 (13)	1 (7)
Hypoxemia n (%)	11 (15)	4 (13)	6 (16)	3 (21)
Cardiac arrest n (%)	3 (4)	0 (0)	2 (5)	1 (7)
Other n (%)	7 (9)	5 (17)	4 (10)	0 (0)
Not determined n (%)	1 (1)	1 (4)	2 (5)	0 (0)

The other causes of death were stroke (3), mesenteric ischemia (2), cerebral edema (1), gastro-intestinal bleeding (1) in the supine group and mesenteric ischemia (2), stroke (1), cerebral anoxia (1) in the prone group.

Table S8. Post-hoc analysis.Mortality at day-28 by PaO_2/F_IO_2 quartiles and groups

	Supine group			Prone group		
PaO_2/F_IO_2	n death/total	%	p	n death/total	%	p
1st quartile [45-87]	25/64	39.1	0.51*	15/62	24.2	0.08*
2nd quartile [87-105]	16/57	28.1		10/59	16.9	
3d quartile [105-124]	14/50	30.0		4/59	6.8	
4th quartile [124-150]	20/58	35.1		9/57	16.0	

* Pearson Chi² test

Logistic regression analysis for death at day-28 by PaO_2/F_IO_2 quartiles and groups

	HR	95% CI			p
Quartiles PaO_2/F_IO_2	0.87	0.71	-	1.06	0.14
Prone vs. Supine	0.39	0.25	-	0.61	< 0.00001

HR: Hazard ratio. CI: Confidence interval.

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