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ORIGINAL

A prospective international observational prevalence study on prone positioning of ARDS patients: the APRONET (ARDS Prone Position Network) study

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Abstract

Introduction: While prone positioning (PP) has been shown to improve patient survival in moderate to severe acute respiratory distress syndrome (ARDS) patients, the rate of application of PP in clinical practice still appears low.

Aim: This study aimed to determine the prevalence of use of PP in ARDS patients (primary endpoint), the physiological effects of PP, and the reasons for not using it (secondary endpoints).

Methods: The APRONET study was a prospective international 1-day prevalence study performed four times in April, July, and October 2016 and January 2017. On each study day, investigators in each ICU had to screen every patient. For patients with ARDS, use of PP, gas exchange, ventilator settings and plateau pressure (Pplat) were recorded before and at the end of the PP session. Complications of PP and reasons for not using PP were also documented. Values are presented as median (1st–3rd quartiles).

Results: Over the study period, 6723 patients were screened in 141 ICUs from 20 countries (77% of the ICUs were European), of whom 735 had ARDS and were analyzed. Overall 101 ARDS patients had at least one session of PP (13.7%), with no differences among the 4 study days. The rate of PP use was 5.9% (11/187), 10.3% (41/399) and 32.9% (49/149) in mild, moderate and severe ARDS, respectively ($P = 0.0001$). The duration of the first PP session was 18 (16–23) hours. Measured with the patient in the supine position before and at the end of the first PP session, PaO_2/F_IO_2 increased from 101 (76–136) to 171 (118–220) mmHg ($P = 0.0001$) driving pressure decreased from 14 [11–17] to 13 [10–16] cmH_2O ($P = 0.001$), and Pplat decreased from 26 [23–29] to 25 [23–28] cmH_2O ($P = 0.04$). The most prevalent reason for not using PP (64.3%) was that hypoxemia was not considered sufficiently severe. Complications

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were reported in 12 patients (11.9%) in whom PP was used (pressure sores in five, hypoxemia in two, endotracheal tube-related in two ocular in two, and a transient increase in intracranial pressure in one).

Conclusions: In conclusion, this prospective international prevalence study found that PP was used in 32.9% of patients with severe ARDS, and was associated with low complication rates, significant increase in oxygenation and a significant decrease in driving pressure.

Keywords: ARDS, Prone position, Mechanical ventilation, Epidemiology

Introduction

Acute respiratory distress syndrome (ARDS) is still associated with significant mortality [1]. To date, only three interventions have been proven efficient in improving patient survival [2], namely lower tidal volume (V_T) [3] targeting 6 ml/kg predicted body weight (pbw), continuous intravenous infusion of the neuromuscular blocking agent (NMBA) cisatracurium for 48 h [4] and prolonged sessions of prone positioning [5]. These two latter interventions were, however, performed in selected ARDS patients, i.e. those with PaO_2/F_IO_2 < 150 mmHg. The LUNG SAFE study [1], an international prospective epidemiological study conducted in 459 ICUs across the world in 2014, analyzed the treatment of 2377 ARDS patients and found that the above-mentioned interventions had not been widely adopted by clinicians. Specifically, the median V_T was 7.7 ml/kg pbw and irrespective of the severity of hypoxemia, NMBA and PP were used in 37.8 and 16.3% of severe ARDS, respectively. The rate of prone position use was low despite the results of an individual meta-analysis [6] and a randomized controlled trial [5] that consistently showed benefits in selected patients. It was hypothesized that this low rate of prone positioning in ARDS patients in the LUNG SAFE study might be due in part to selection bias or a clinicians' perception that the evidence level was weak. It is important to assess the prevalence of proning in ARDS patients to quantify the gap between the reality of daily practice and the use of an efficient intervention, and to identify any barriers that could be overcome. As the LUNG SAFE study was not focused specifically on ARDS but on acute hypoxemic respiratory failure, and was also not dedicated entirely to prone positioning, its results may have been biased. For this reason, we undertook a prospective observational international study with the primary aim of measuring the prevalence of use of the prone position in ARDS. Our hypothesis was that it was higher than found in the LUNG SAFE study. We based this assumption on the above considerations and on the fact that the publication of the Proseva trial [5] should be beginning to have an impact on routine clinical practice. Our secondary aims were to identify the reasons for not applying PP, the principal differences between proned and not proned ARDS patients, the physiologic response to and complications of spending extended periods of time in the prone position, and the concurrent treatments. This work was presented at the 2017 LIVES ESICM meeting [7].

Methods

Study design

A 1-day prevalence study was carried out four times: in April 2016, July 2016, October 2016 and January 2017. Each center participated as many times as it could and chose one of four predetermined calendar days (the 5th or 12th or 19th or 26th day of the month) for the study. Because it was a prevalence study, no patient follow-up was mandated. The protocol was drawn up by a steering committee and improved during regular meetings of the Acute Respiratory Failure Section of the European Society of Intensive Care Medicine (ESICM). It had been endorsed by the ESICM clinical trials group. The study was registered at the clinicaltrials.gov website (clinicalTrials.gov identifier: NCT02842788).

Selection of intensive care units

Intensive care units (ICUs) were recruited through the Réseau Européen de Recherche en Ventilation Artificielle (REVA) network and the Réseau recherche de la Société Française d'Anesthésie-Réanimation (SFAR-recherche) both in France and via the ESICM platform once the APRONET had been was endorsed by the ESICM clinical trials group. The ICUs participated on a voluntary basis in any of the four study times. The list of all registered ICUs on the ESICM platform was sent to the University Hospital of Angers France, where study staff were responsible for the electronic case record form (eCRF) and performed data extraction and management. Each center received a protected account and gained access to the system through an individual password to complete the eCRF. At each participating ICU, one physician was designated as investigator.

Inclusion criteria

- ARDS criteria according to the Berlin definition [8] fulfilled on the day of the study. The onset of ARDS could have been established at any time between ICU admission and the study day, but ARDS criteria had to be met on the study day.
- Age ≥ 18 years.

– Intubated or tracheotomized and mechanically ventilated.

Exclusion criteria

– Not intubated on the day of the study.
– No ARDS on the day of the study even if ARDS criteria had been fulfilled between ICU admission and the study day.

Data collection

On each study day the investigator screened every patient who was present in the ICU for the whole day, and checked for ARDS criteria as defined on the first page of the eCRF (Fig. 1 ESM). If ARDS criteria were present, the investigator had to complete the following six sections of the eCRF: (1) general characteristics at the time of ICU admission (gender, age, origin, comorbidities, SAPSII score and anthropometric data), (2) ARDS characteristics at the time of study day (date of ARDS diagnosis, ARDS risk factors, V_T, F_IO_2, PEEP and plateau pressure at the time of worst PaO_2/F_IO_2 ratio in the supine position), (3) proning or not, with the reasons for not proning, (4) concurrent treatments for ARDS, (5) V_T, F_IO_2, positive end-expiratory pressure (PEEP), PaO_2, $PaCO_2$, pH and plateau pressure before and after prone positioning, together with the duration of the session (6) complications during the prone position session. The data pertaining to the onset or to the end of the proning session could be recorded on the day before and/or the day after the scheduled study day (Fig. 1 ESM). If more than one proning session was delivered during the whole study period, items 5 and 6 were documented for each session.

Ethical issues

The protocol was approved by the ethics committee of Lyon, France (IRB identification number 9118) on July 9th, 2015. Informed consent was waived according the French law. This approval was valid for all participating centers in France. Centers in other countries obtained authorization to perform the study according to their national regulations. The database was approved by the CNIL in France. No patient personal data was recorded. The patient identification included ICU number, serial inclusion number and, according to local regulations, the first letter of the last name and first name.

Funding

The study was funded by a research grant from the Hospices Civils de Lyon and a research grant from the ESICM clinical trials group.

Data analysis

The variables are presented as median (1st–3rd quartiles) and absolute numbers (with percentages). The main endpoint, the prevalence of use of PP in ARDS patients, was computed for each center as the number of ARDS patients who were proned divided by the total number of ARDS patients in the ICU on the day of the study. The corresponding proportion was expressed together with its 95% confidence interval. The chi-square test was used to look for any trend across the four study days. If no significant differences were found across the four study days, the data were merged for analysis of the secondary endpoints, namely the reasons for not proning, the characteristics of ARDS patients at the time of ICU admission and study inclusion, the physiological effects of the first proning session, the complications during the first proning session and the concurrent treatments.

Among the reasons for not proning, we placed special emphasis on oxygenation. Based on the previously reported low rate of PP use in severe ARDS, we were expecting that clinicians would not choose to put patients in the prone position because they would judge the hypoxemia as not severe enough. We assessed the reasons for not proning due to insufficiently severe hypoxemia in different ways. First, the rate of use of prone positioning was measured between ARDS stages [8]. Second, we defined patients retrospectively by whether or not they fulfilled the criteria of inclusion in the Proseva trial [5]: $PaO_2/F_IO_2 < 150$ mmHg, PEEP ≥ 5 cm H_2O, $F_IO_2 \geq 0.60$, $V_T = 6$ ml/kg pbw on the day of the study. Third, we split the values of PaO_2/F_IO_2 measured on the study days into quintiles and for each of them, we measured the odds ratio (with 95% confidence intervals, 95% CI) of the PP. In each quintile, the odds ratio was analyzed using the Z test.

Proned and nonproned patients were further compared between European and non-European countries. Driving pressure was computed as plateau pressure minus PEEP. Groups were compared by using parametric or nonparametric tests as appropriate. Variables before and after the proning sessions were compared by using nonparametric or parametric tests for paired values. Binary multivariate logistic regression analysis was performed on the risk factors for not proning ARDS patients, which was the dependent variable, and adjusted for the ICU. The covariates were those which differed at the threshold of 0.20 in the univariate comparison between proned and nonproned ARDS patients during the four periods.

Only the pertaining to the first proning session were analyzed because we expected a very low number of patients with more than one proning session during the study period. The patients with additional proning sessions were, however, counted and are reported in the results section. The database was cleared after two sets of queries were sent to the centers and frozen on June 30 2017. The missing data for each variable can be found in Table 1 in the electronic supplementary material (ESM).

They were checked for missing data at random, which was confirmed. The data were analyzed by one person (LA) using SPSS and EpiINFO softwares. $P < 0.05$ was considered as the threshold of statistical significance.

Results

A total of 6,723 patients were screened over the four study days. Of these, 735 patients in 141 ICUs of 20 countries (ESM Table 2) fulfilled the criteria of ARDS (Fig. 1). ARDS had been diagnosed 4.5 (1-11) days before the study day. The prevalence of ARDS on each study day was 13.3% (11.7–14.9; 240/1808) in April 2016, 8.9% (7.5–10.3; 143/1611) in July 2016, 9.9% (8.4–11.4; 157/1593) in October 2016 and 11.4% (9.9–12.9; 195/1711) in January 2017 ($P = 0.134$).

Prevalence of prone position use

Over the four study days, 101 ARDS patients underwent at least one session of prone positioning (13.7%). Nine patients had a second proning session on the same study day, the data of which were not analyzed. The prevalence of PP in ARDS patients did not differ significantly across study days: it was 13.8% (9.4–18.2; 32/240) in April 2016, 12.6% (7.2–18.0; 18/143) in July 2016, 15.3% (9.7–20.9; 24/157) in October 2016 and 13.8% (9.0–18.6; 27/195) in January 2017 ($P = 0.83$; Fig. 2 ESM). With the four study days merged, the rate of proning use was 5.9% (2.5–9.3; 11/187), 10.3% (7.3–13.3; 41/399) and 32.9% (25.4–40.4; 49/149) in mild, moderate and severe ARDS, respectively ($P = 0.0001$; Fig. 2 ESM). In ARDS patients who met the Proseva criteria as defined for the present study (11.2% of the whole cohort), the rate of proning was 40.2% (29.6–50.8; 33/82) versus 10.4% (8.1–12.7; 68/653) in those who did not meet the Proseva criteria ($P = 0.0001$).

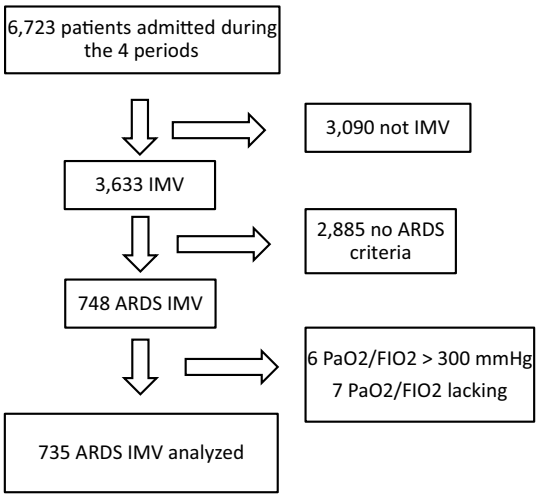

Fig. 1 Flow chart for the four study days. *IMV* invasive mechanical ventilation

Reasons for not proning

The reasons for not proning are listed in Table 1. The primary reason, which accounted for 64.3% of cases, was clinicians' assessment of hypoxemia as not severe enough to justify proning. Its frequency was significantly lower in severe ARDS than in mild or moderate ARDS. The distribution of patients across the five quintiles of PaO_2/F_IO_2 showed that 50.8% of patients with $PaO_2/F_IO_2 < 138$ mmHg received proning (Fig. 2). The quintile with $PaO_2/F_IO_2 < 100$ mmHg was associated with a significant (fivefold) likelihood of proning whilst above a threshold of 139 mmHg, there was a significant probability of not proning (Fig. 2). The second most commonly occurring reason for not proning was having mean arterial pressure lower than 65 mmHg (5.7%) followed by end-of-life decision (4.2%), both of which were significantly more frequent in severe ARDS than in mild or moderate ARDS. The other reasons accounted for less than 4% of the total number of reasons and did not differ among the three stages of ARDS, with the exception of abdominal problems which were cited more often in severe ARDS. In patients meeting the Proseva criteria, the reasons for not proning were insufficiently severe hypoxemia, chest trauma and end-of-life decision (Table 3 ESM).

The patients who were proned differed from those who were not proned in higher frequency of ARDS originating from pneumonia, more severe hypoxemia, higher PEEP and higher plateau pressure at the time of inclusion (Table 2). The multivariate logistic regression analysis found that $PaO_2/F_IO_2 < 150$ mmHg, $V_T < 6$ ml/kg pbw and PEEP > 10 cm H_2O at the time of inclusion were significantly associated with a lower probability of prone positioning not being used, i.e. with a greater likelihood of proning. Conversely, the higher the SAPS II and the higher the plateau pressure, the greater the probability of proning not being used (Table 3).

Physiological response to the session in prone position

The duration of the first prone positioning session over the four study days was 18 (16–23) hours without interruption.

Measured with the patient in the supine position before and after the first PP session, PaO_2/F_IO_2 increased from 101 (76–136) to 171 (118–220) mmHg ($P = 0.0001$) and driving pressure and Pplat decreased from 14 (11–17) to 13 (10–16) cmH_2O ($P = 0.001$) and from 26 (23–29) to 25 (23–28) cmH_2O ($P = 0.04$), respectively (Table 4 ESM). $PaCO_2$ and V_T did not change and PEEP was essentially the same in the supine and prone positions (Table 4 ESM).

Complications of the prone position session

Complications related to sessions of prone positioning were reported in 12 of the 101 proned patients (11.9%)

Table 1 The 734 reasons for not proning 634 ARDS patients

Reason	Mild ARDS (*n* = 197)	Moderate ARDS (*n* = 417)	Severe ARDS (*n* = 120)	All ARDS stages (*n* = 734)	*P* value between ARDS stages
Hypoxemia not severe enough	158 (80.2)	286 (68.6)	28 (23.3)	472 (64.3)	< 0.0001
MAP < 65 mmHg	2 (1.0)	15 (3.6)	25 (20.8)	42 (5.7)	< 0.0001
End of life decision	6 (3.0)	11 (2.6)	14 (11.7)	31 (4.2)	< 0.0001
Tracheotomy	4 (2.0)	11 (2.6)	6 (5.0)	21 (2.9)	0.20000
Abdominal problem	2 (1.0)	9 (2.2)	7 (5.8)	18 (2.5)	0.02250
Weaning from mechanical ventilation	5 (2.5)	11 (2.6)	0	16 (2.2)	0.20100
ECMO	6 (3.0)	5 (1.2)	3 (2.5)	14 (1.9)	0.25800
Elevated ICP	3 (1.5)	9 (2.2)	0	12 (1.6)	0.25660
Pneumothorax	3 (1.5)	7 (1.7)	1 (0.8)	11 (1.5)	0.79760
Unstable bone fracture	2 (1.0)	6 (1.4)	1 (0.8)	9 (1.2)	0.82650
Sternotomy	4 (2.0)	3 (0.7)	1 (0.8)	8 (1.1)	0.32940
Workload	0	6 (1.4)	2 (1.7)	8 (1.1)	0.22180
Face trauma	0	3 (0.7)	3 (2.5)	6 (0.8)	0.05330
Not responsive to previous proning sessions	0	4 (1.0)	2 (1.7)	6 (0.8)	0.24730
Obesity	0	3 (0.7)	2 (1.7)	5 (0.7)	0.21410
Hemoptysis	0	1 (0.2)	2 (1.7)	3 (0.4)	0.05597
Staff undertrained	0	1 (0.2)	2 (1.7)	3 (0.4)	0.05597
Deep venous thrombosis	1 (0.5)	0	1 (0.8)	2 (0.3)	0.23150
Chest trauma	1 (0.5)	0	1 (0.8)	2 (0.3)	0.23150
Surgery	0	0	1 (0.8)	1 (0.1)	0.07700
Other	0	26 (6.2)	18 (15.0)	44 (6.0)	0.00010

Values are counts of complications (percentage points over the total number of complications per group)

MAP mean arterial pressure, *ECMO* extracorporeal oxygenation membrane, *ICP* intracranial pressure

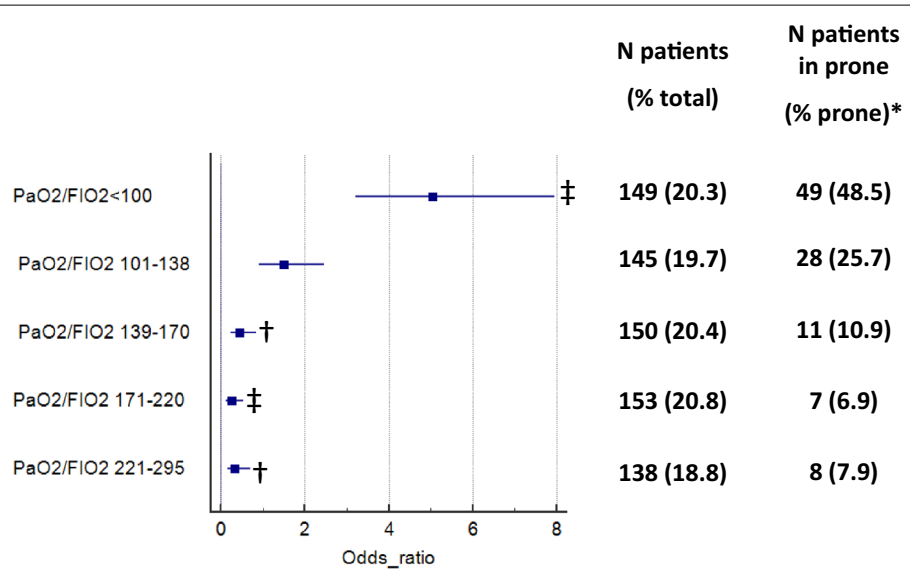

Fig. 2 Odds ratio for the rate of use of prone positioning across PaO_2/FIO_2 quintiles. **P* < 0.0001 for total prone group (χ^2 test), †*P* < 0.05, ‡*P* < 0.001 (Z test). Squares are odds ratio and horizontal bars joining low to high 95% confidence intervals

Table 2 Characteristics of 735 ARDS patients in the proned or not proned group at the time of ICU admission and of inclusion over the four study days

	Total (*N* = 735)	Not proned (*N* = 634)	Proned (*N* = 101)	*P* value
ICU admission				
Age, years	64 (52–73)	64 (53–74)	64 (48–72)	0.255
Gender, male	486 (66.3)	425 (67.1)	61 (61.0)	0.227
Origin of admission				
Emergency room	262 (35.6)	222 (35.0)	40 (39.6)	0.803
Acute care	204 (27.8)	175 (27.6)	29 (28.7)	
Chronic care	32 (4.4)	29 (4.6)	3 (3.0)	
Operating room	86 (11.7)	77 (12.1)	9 (8.9)	
Pre-hospital	80 (10.9)	68 (10.7)	12 (11.9)	
Other	71 (9.7)	63 (9.9)	8 (7.9)	
SAPSII	50 (39–62)	50 (39–63)	47 (37–58)	0.035
Height, m	1.70 (1.64–1.76)	1.70 (1.64–1.76)	1.70 (1.63–1.78)	0.792
Predicted body weight, kg	66 (60–71)	66 (60–71)	66 (56–72)	0.916
Actual body weight, kg	77 (65–87)	77 (65–87)	80 (64–94)	0.311
BMI, kg/m^2	26 (23–30)	26 (23–30)	26 (23–34)	0.608
Comorbidities				
Chronic respiratory failure	73 (9.9)	64 (10.1)	9 (8.9)	0.858
Chronic kidney disease	73 (9.9)	64 (10.1)	9 (8.9)	0.858
Chronic cardiac failure	50 (6.8)	47 (7.4)	3 (3.0)	0.134
Diabetes	140 (19.0)	112 (17.7)	28 (27.7)	0.020
Immunodeficiency	157 (21.1)	137 (21.6)	20 (19.8)	0.794
Onco-hematology	148 (20.2)	131 (20.7)	17 (16.8)	0.424
Chronic liver failure	23 (3.1)	22 (3.5)	1 (1.0)	0.349
Inclusion				
ARDS risk factor				
Pneumonia	457 (62.2)	380 (59.9)	77 (76.2)	0.002
Aspiration	76 (10.3)	68 (10.7)	8 (7.9)	0.39
Smoke inhalation	1 (0.1)	0 (0.0)	1 (1.0)	0.14
Near drowning	2 (0.2)	2 (0.3)	0 (0.0)	1.00
Burns	5 (0.5)	5 (0.8)	0 (0.0)	1.00
Systemic disease	27 (3.7)	23 (3.6)	4 (4.0)	0.78
Chest trauma	14 (1.9)	14 (2.2)	0 (0.0)	0.24
Nonpulmonary sepsis	65 (8.8)	62 (9.8)	3 (3.0)	0.04
Pancreatitis	11 (1.5)	10 (1.6)	1 (1.0)	1.00
Multiple trauma	5 (0.7)	4 (0.6)	1 (1.0)	0.52
TRALI	1 (0.1)	1 (0.2)	0 (0.0)	1.00
Other	46 (6.3)	43(6.8)	3 (3.0)	0.21
Unknown	25 (3.4)	22 (3.5)	3 (3.0)	1.00
PaO_2/F_IO_2, mmHg	156 (110–203)	160 (120–208)	102 (80–143)	0.0001
ARDS stage				
Mild	187 (25.4)	176 (94.1[a])	11 (5.9[a])	0.0001
Moderate	399 (54.3)	358 (89.7[a])	41 (10.3[a])	

Table 2 continued

	Total ($N = 735$)	Not proned ($N = 634$)	Proned ($N = 101$)	*P* value
Severe	149 (20.3)	100 (67.1[a])	49 (32.9[a])	
V_T, ml/kg pbw	6.7 (5.9–7.6)	6.7 (6.0–7.7)	6.1 (5.5–7.0)	0.0001
PEEP, cmH_2O	8 (6–10)	8 (6–10)	12 (9–14)	0.0001
F_IO_2, %	50 (40–70)	50 (40–65)	70 (51–100)	0.0001
Plateau pressure, cmH_2O	23 (20–27)	22 (19–26)	25 (22–28)	0.0001
ΔP, cmH_2O	13 (10–17)	13 (10–17)	13 (11–16)	0.857

Values are median (1st–3rd quartiles) or count (% column). For actual count, see the missing values for each variable in Table 2 of the ESM

Definition of comorbidities: chronic respiratory failure: long-term home noninvasive ventilation or oxygen supplementation; chronic kidney disease: estimated glomerular filtration rate < 60 ml/min; cardiac failure: dyspnea NYHA stage 3 or 4; diabetes requiring insulin supplementation; immunodeficiency: malignant solid tumor or hematologic disease, organ transplant, steroids (for more than 30 days or recent high doses), ongoing chemotherapy or radiotherapy, AIDS, or neutropenia (blood neutrophils less than $500/mm^3$); chronic liver disease: Child C

ARDS acute respiratory distress syndrome, *SAPS* simplified acute physiology score, *BMI* body mass index, *TRALI* transfusion-related acute lung injury, F_IO_2 fraction of oxygen in air, V_T tidal volume, *pbw* predicted body weight, *PEEP* positive end-expiratory pressure, *ΔP* driving pressure of the respiratory system

[a] Among ARDS stage

Table 3 Results of the multivariate logistic regression analysis on the risk factors for not proning ARDS patients

	Odds ratio (95% confidence intervals)	*P* value
Diabetes (reference absent)	0.68 (0.40–1.17)	0.16
Immunodeficiency (reference absent)	1.28 (0.71–2.28)	0.41
SAPS II (per point score)	1.04 (1.03–1.05)	0.0001
Pneumonia (reference absent)	0.74 (0.46–1.19)	0.21
$PaO_2/F_IO_2 < 150$ vs. ≥ 150 mmHg	0.34 (0.19–0.61)	0.0001
$F_IO_2 < 60$ vs. $\geq 60\%$	0.64 (0.37–1.13)	0.13
$V_T < 6$ vs. ≥ 6 ml/kg pbw	0.56 (0.35–0.89)	0.015
PEEP > 10 vs. ≤ 10 cmH_2O	0.38 (0.23–0.64)	0.0001
Plateau pressure (per each cmH_2O increase)	1.07 (1.04–1.11)	0.0001

Odds ratio less than 1 reduces the risk of not being proned and odds ratio greater than 1 increases the risk of not being proned

SAPS simplified acute physiology score, PaO_2 arterial oxygen partial pressure, F_IO_2 inspired fraction of oxygen in air, V_T tidal volume, *PBW* predicted body weight, *PEEP* positive end-expiratory pressure

(ESM Table 5): endotracheal tube-related complications in 2 patients, hypoxemia in 2, ocular complications in 2, pressure sores in 5 and a transient increase in intracranial pressure in 1. One death was notified, which was not due to the procedure.

Concurrent treatments

Proned ARDS patients more frequently received vasopressors, inhaled nitric oxide, sedation and neuromuscular blockade than those who were not proned (Table 6 ESM).

Discussion

The main findings of this study are that: (1) the rate of use of PP was higher than previously reported for severe ARDS in the Lung Safe study, (2) the major reason for not proning was related to the severity of hypoxemia and (3) the rate of complications was much lower than previously reported in trials comparing prone and supine positioning in patients with ARDS or hypoxemic respiratory failure.

This is the first prospective multicenter international study dedicated specifically to the use of PP in ARDS patients. Previous large observational studies on the practice of mechanical ventilation in the ICU provided some information on the rate of use of proning in ARDS patients (Table 7 ESM). The decline in the use of proning observed between the first [9] and the second [10] international survey led by Esteban et al. followed the early negative trials [11, 12]. However, in spite of the positive signals from individual data meta-analysis [6] and three most recent trials [5, 13, 14], PP was still infrequently used in the subsequent international observational studies [1, 15]. The LUNG SAFE study extended these results by showing that actually the use of proning depended on the severity of hypoxemia, from 1% in mild to 5.5% in moderate and to 16.3% in severe ARDS [1]. In the present study, a twofold increase in the rate of use of proning since the LUNG SAFE study was

observed, with similar increases across the ARDS stages culminating in 32.9% in severe ARDS category and 24% in ARDS patients with PaO_2/F_IO_2 < 150 mmHg + PEEP ≥ 10 cmH_2O and $F_IO_2 \geq 60\%$. The rate of use of PP was consistent; it did not vary significantly across the four study days. The difference in the use of the prone position between LUNG SAFE and the present study may reflect a selection bias of centers, as most of the ICUs were located in France, Spain and Italy, where PP has been used for many years in ARDS patients and where most of the large clinical trials on PP have been conducted so far. This is very different from the LUNG SAFE study in which about half of the patients were enrolled in non-European countries. Indeed, a secondary analysis of the LUNG SAFE database [16] has shown that the use of PP in high-income countries is eight times greater in Europe than in the rest of the world. However, we found that the rate of proning use was higher in non-European than in European countries: (28.6 vs. 13%; $P = 0.019$). This is surprising, but should be interpreted with caution, as the proportion of ARDS patients from non-European countries in the present study was small (4.8%) and much lower than in the LUNG SAFE study (46%). One possible explanation for this finding is that the non-European ICUs in our study are strong believers in prone positioning.

It is possible that our results regarding the rate of use of proning (from data collected 2 years after LUNG SAFE) reflect a change in practice. If clinicians are indeed less reluctant to use PP, the reason may be wider better dissemination and a positive perception of the results of the last trial [5]. The Proseva trial showed a significantly improved benefit-to-risk ratio of using PP, a finding that should make clinicians keener to implement this strategy in their ICU. However, this does not explain why the proportion of patients with severe ARDS in whom prone positioning was used was not higher in the present study. The best PaO_2-to-F_IO_2 ratio to use as threshold in determining the indication fore prone positioning is still being debated. The meta-analysis based on individual data found benefit for ARDS patients with PaO_2/F_IO_2 < 100 mmHg [6], in line with a meta-analysis based on grouped data [17], whilst for the Proseva trial, the benefit was obtained below 150 mmHg [5]. The mean PaO_2-to-F_IO_2 ratio at the time of randomization in this trial was 100 mmHg for both groups in the Proseva trial [5]. However, survival was better in the prone group than in the supine group over the whole 49–150-mmHg range of PaO_2/F_IO_2 at the time of randomization [5]. Further grouped-data meta-analyses confirmed the benefit of proning in patients with moderate to severe ARDS [18, 19]. The multivariate analysis of the present data showed that a PaO_2-to-F_IO_2 ratio < 150 mmHg had the lowest odds ratio for prediction of the risk of not being proned. In the present study, 40.2% of the patients meeting the Proseva criteria were proned. This means that 49 patients who fulfilled those criteria were not placed in the prone position. It should be mentioned that our study design obviously did not replicate the Proseva trial. Of note, neither the exclusion criteria of the Proseva trial nor the 12–24-h stabilization period were satisfied by our study design.

The primary reason for not proning ARDS patients in the present study was related to clinicians' judgment of hypoxemia as not being severe enough to justify PP for that specific patient. As would be expected, this reason was observed significantly less frequently in patients with severe ARDS than in those with mild or moderate ARDS. The fact that, even in severe ARDS, many clinicians rated the hypoxemia not severe enough to justify proning suggests that PP is still viewed as a rescue maneuver. However, PP is a method to prevent/attenuate ventilator-induced lung injury [20] and to improve/stabilize hemodynamics [21] and therefore should be applied irrespective of the level of hypoxemia, at least in the subgroup of patients with a PaO_2-to-F_IO_2 ratio < 150 mmHg, in whom benefit was shown. Furthermore, defining ARDS as severe only on the basis of the level of hypoxemia may not be enough. Even if it is true that, on average, the amount of lung tissue increased with the severity of hypoxemia [22], for a given patient the relationship between excess in lung tissue volume and hypoxemia may be less strong. Therefore, and from the specific perspective of PP, other markers for ARDS severity could be used, such as lung morphology as assessed on the CT scan. Further studies are needed to better define ARDS severity and investigate specific interventions such as PP [23]. The second most important reason for not proning patients with severe ARDS was hemodynamic instability. This finding suggests that the possible hemodynamic benefits of proning [24] are still widely unknown among ICU physicians. The other reasons for not using prone positioning were rare, less than 5%. However, the fact that ECMO was the reason for not proning in 1.9% of the cases be related to the rate of use of ECMO in our study, which was half that in the LUNG SAFE study. Obesity was a reason for not using prone positioning in five patients in the present study. However, it has been shown that obese patients can not only be turned prone safely but also benefit from proning more than the non-obese in terms of oxygenation [25]. An increase in the use of proning to treat patients with ARDS may result from evidence showing that using criteria other than oxygenation in deciding whether to prone patients, such as the focal morphological kind of ARDS [26], may be beneficial to the patients. Given that hemodynamic problems are also cited as a reason for not placing patients in the prone position, further data should be provided to confirm the

hemodynamic benefit of proning. Findings showing that proning can be done safely after abdominal surgery [27] should be confirmed by trials in specific settings such as trauma, abdominal or cardiac surgery.

Surprisingly, the rate of complications attributed to PP in the present study was very low. For instance, only two complications related to artificial airways were reported. This differs from the results of previous trials on PP. Mancebo et al. found that 7.9% of proned patients had unplanned extubation [13], Taccone et al. reported a 10.7% rate of endotracheal tube displacement [14] and Guérin et al. described a 13.3% rate of non-scheduled extubation with 2.5% main-stem bronchus intubation and 4.9% endotracheal tube obstruction [5]. The low rate of airways-related complications in the present study may reflect improvement in practice, ICU selection bias or underestimation. The rate of pressure sores found in the present study is also very much lower than previously reported. However, we did not assess the rate of complications in patients who were not proned. It should be mentioned that the one death reported was not related to the procedure.

The physiological response to the first session of prone positionning confirms the well-known finding of significant improvement in oxygenation. In our sample, the reduction in driving pressures at similar V_T presumably reflects improvement in respiratory system compliance. The effect of PP on respiratory mechanics is complex and not consistent across trials. Respiratory system compliance was found to be increased in the prone versus the supine position in one trial [13] but unchanged in another [5]. We found a significant decrease in respiratory driving pressure in the prone position. This is an important finding as driving pressure has recently been suggested to be the strongest predictor of death in ARDS patients [28]. It is worth mentioning that in the present study, plateau pressure was measured in 90.7% of patients (667/735 ARDS patients), a much higher proportion than in the LUNG SAFE study where Pplat was determined in 40% of patients overall and 48.5% of those undergoing controlled ventilation. This result may reflect ICU selection bias or improvement in practice since the publication of the LUNG SAFE study.

Our study has limitations. Centers were informed in advance about the study days and, hence, may have adapted their practice accordingly. There may well be a selection bias in the participating ICUs, whose staff are likely to be proponents of and trained in proning. Furthermore, the data were not recorded during a long prospective period but only on four (separate) days. However, the fact that the rate of proning was not different across the four study days is an argument against any real bias in the present study. Our study was underpowered. We computed a posterior that, at α and β risks of 5 and 20%, respectively, 884 patients with ARDS would have needed to be enrolled for the overall prevalence of PP of 13.7% in this and 7.9% in the Lung SAFE study to be shown to be significantly different.

In conclusion, this prospective international prevalence study found that PP was used in 32.9% of severe ARDS and was associated with a low rate of complications, a significant increase in oxygenation, and a significant decrease in driving pressure.

Electronic supplementary material

The online version of this article (https://doi.org/10.1007/s00134-017-4996-5) contains supplementary material, which is available to authorized users.

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Acknowledgments

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Country	City	Name of the ICU	Name of the hospital	Collaborator #1	Collaborator #2	Head of the ICU or department
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UK	Carlisle	Intensive Care	Cumberland Infirmary	BARBERIS Luigi		STURMAN J
Greece	Athens	Intensive Care Unit	Hippokrateion General Hospital of Athens	MAINAS Efstratios		KARATZAS S

Country	City	Name of the ICU	Name of the hospital	Collaborator #1	Collaborator #2	Head of the ICU or department
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Belgium	Gosselies	Intensive Care Unit	Clinique Notre-Dame de Grâce	SOTTIAUX Thierry		ADAM JF
Poland	Opole	Department of Anesthesiology and Critical Care	PS ZOZ Wojewodzkie Centrum Medyczne w Opolu	GAWDA Ryszard		GAWOR M
Canada	Moncton	Respirology Critical Care	The Moncton Hospital	ALQDAH Maen		ALQDAH M and COHEN D
Canada	Toronto	Intensive Care Unit	St. Michael's Hospital	BROCHARD Laurent		BAKER A
Mexico	Mexico City	Department of Critical Care Unit	Instituto Nacional de Cancerología	ÑAMENDYS-SILVA Silvio Antonio	GARCIA-GUILLEN Francisco Javier	
Ecuador	Quito	Unidad de Terapia Intensiva	Hospital de Especialidades Eugenio Espejo	MOROCHO TUTILLO Diego Rolando	JIBAJA VEGA Manuel	JIBAJA VEGA MANUEL
Argentina	Mendoza	Terapia intensiva	Hospital Luis Carlos Lagomaggiore	ZAKALIK Graciela	PAGELLA Gonzalo	MARENGO J

Compliance with ethical standards

Conflicts of interest
On behalf of all authors, the corresponding author states that there is no conflict of interest.

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