



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

C. Guérin^{1,2,3,30*}, P. Beuret⁴, J. M. Constantin^{5,6}, G. Bellani⁷, P. Garcia-Olivares⁸, O. Roca^{9,10}, J. H. Meertens¹¹, P. Azevedo Maia¹², T. Becher¹³, J. Peterson^{14,15}, A. Larsson^{16,17}, M. Gurjar¹⁷, Z. Hajjej¹⁸, F. Kovari¹⁹, A. H. Assiri²⁰, E. Mainas²¹, M. S. Hasan²², D. R. Morocho-Tutillo²³, L. Baboi¹, J. M. Chrétien²⁴, G. François²⁵, L. Ayzac²⁶, L. Chen²⁷, L. Brochard²⁷ and A. Mercat^{28,29} for the investigators of the APRONET Study Group, the REVA Network, the Réseau recherche de la Société Française d'Anesthésie-Réanimation (SFAR-recherche) and the ESICM Trials Group

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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, $\text{PaO}_2/\text{F}_i\text{O}_2$ 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

*Correspondence: claude.guerin@chu-lyon.fr

¹ Réanimation Médicale Hôpital de la Croix Rousse, Hospices Civils de Lyon, Lyon, France

Full author information is available at the end of the article

The complete list of investigators and centers can be found in the Acknowledgments and in ESM file 10.

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 $\text{PaO}_2/\text{F}_i\text{O}_2 < 150$ 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 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.

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- 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 , $F_{I}O_2$, PEEP and plateau pressure at the time of worst $PaO_2/F_{I}O_2$ ratio in the supine position), (3) proning or not, with the reasons for not proning, (4) concurrent treatments for ARDS, (5) V_T , $F_{I}O_2$, 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 prone 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]: $PaO_2/F_{I}O_2 < 150$ mmHg, $PEEP \geq 5$ cm H_2O , $F_{I}O_2 \geq 0.60$, $V_T = 6$ ml/kg pbw on the day of the study. Third, we split the values of $PaO_2/F_{I}O_2$ 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 prone and non-prone 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).

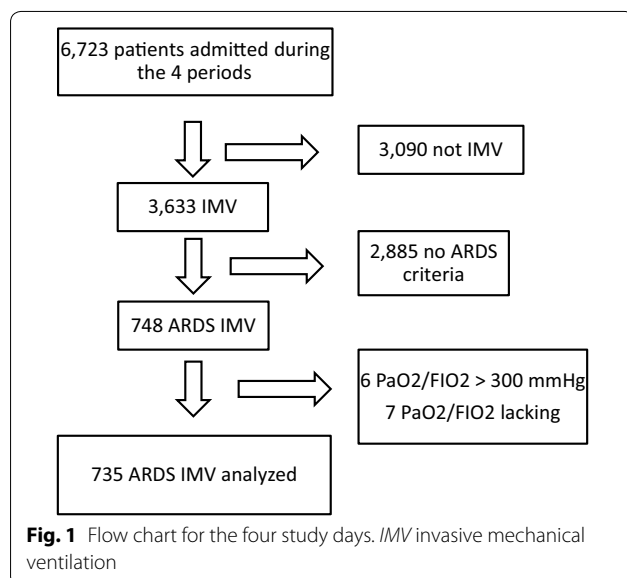
They were checked for missing data at random, which was confirmed. The data were analyzed by one person (LA) using SPSS and EpiINFO softwares. $P < 0.05$ was considered as the threshold of statistical significance.

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 ($P = 0.0001$).



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 $\text{PaO}_2/\text{F}_i\text{O}_2$ showed that 50.8% of patients with $\text{PaO}_2/\text{F}_i\text{O}_2 < 138$ mmHg received proning (Fig. 2). The quintile with $\text{PaO}_2/\text{F}_i\text{O}_2 < 100$ 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 $\text{PaO}_2/\text{F}_i\text{O}_2 < 150$ mmHg, $V_T < 6$ ml/kg pbw and $\text{PEEP} > 10$ 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, $\text{PaO}_2/\text{F}_i\text{O}_2$ increased from 101 (76–136) to 171 (118–220) mmHg ($P = 0.0001$) and driving pressure and P_{plat} decreased from 14 (11–17) to 13 (10–16) cm H_2O ($P = 0.001$) and from 26 (23–29) to 25 (23–28) cm H_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

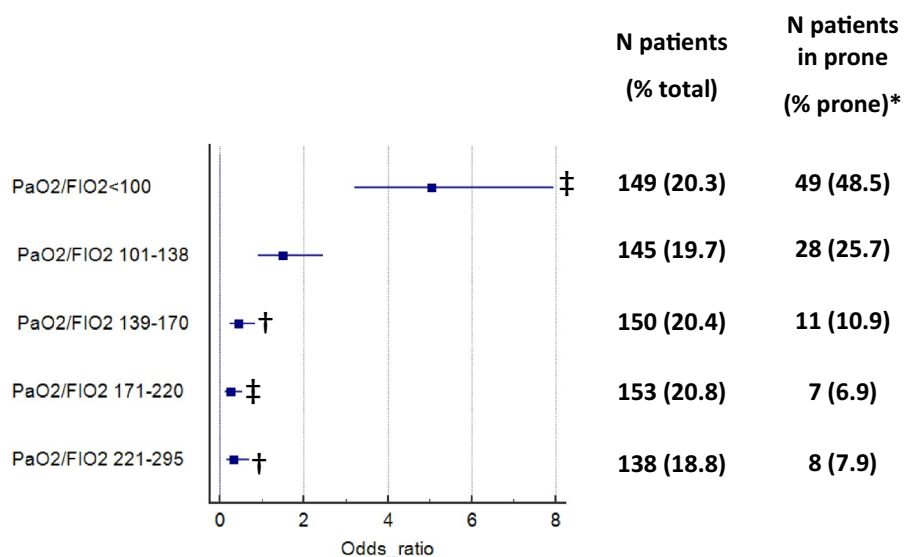


Fig. 2 Odds ratio for the rate of use of prone positioning across PaO₂/FIO₂ quintiles. *P < 0.0001 for total prone group (χ² test), †P < 0.05, ‡P < 0.001 (Z test). Squares are odds ratio and horizontal bars joining low to high 95% confidence intervals

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

	Total (N = 735)	Not prone (N = 634)	Prone (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 _i O 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 prone (N = 634)	Prone (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 ₂ O	8 (6–10)	8 (6–10)	12 (9–14)	0.0001
F _I O ₂ , %	50 (40–70)	50 (40–65)	70 (51–100)	0.0001
Plateau pressure, cmH ₂ O	23 (20–27)	22 (19–26)	25 (22–28)	0.0001
ΔP, cmH ₂ O	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/mm³); 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_IO₂ 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 _I O ₂ < 150 vs. ≥ 150 mmHg	0.34 (0.19–0.61)	0.0001
F _I O ₂ < 60 vs. ≥ 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 ₂ O	0.38 (0.23–0.64)	0.0001
Plateau pressure (per each cmH ₂ O increase)	1.07 (1.04–1.11)	0.0001

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

SAPS simplified acute physiology score, PaO₂ arterial oxygen partial pressure, F_IO₂ 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

Prone ARDS patients more frequently received vasopressors, inhaled nitric oxide, sedation and neuromuscular blockade than those who were not prone (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 $\text{PaO}_2/\text{F}_1\text{O}_2 < 150$ mmHg + $\text{PEEP} \geq 10$ cmH₂O and $\text{F}_1\text{O}_2 \geq 60\%$. 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_1O_2 ratio to use as threshold in determining the indication for prone positioning is still being debated. The meta-analysis based on individual data found benefit for ARDS patients with $\text{PaO}_2/\text{F}_1\text{O}_2 < 100$ 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_1O_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 $\text{PaO}_2/\text{F}_1\text{O}_2$ 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_1O_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 prone. 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_1O_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 positioning 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.

Author details

¹ Réanimation Médicale Hôpital de la Croix Rousse, Hospices Civils de Lyon, Lyon, France. ² Université de Lyon, Lyon, France. ³ IMRB INSERM 955 Créteil, Créteil, France. ⁴ Réanimation polyvalente Roanne, Roanne, France. ⁵ Department of Preoperative Medicine, University Hospital of Clermont-Ferrand, Clermont-Ferrand, France. ⁶ Faculté de médecine, GReD, UMR, CNRS 6293, UCA, INSERM, U1103 R2D2 EA-7281, Université d'Auvergne, Clermont-Ferrand, France. ⁷ Dipartimento di Medicina e Chirurgia Monza, Università degli Studi Milano Bicocca, Milan, Italy. ⁸ Intensive Care Unit, H.G.U Gregorio Marañón, Madrid, Spain. ⁹ Critical Care Department, Vall d'Hebron University Hospital, Vall d'Hebron Research Institute, Barcelona, Spain. ¹⁰ Ciber Enfermedades Respiratorias (Ciberes), Instituto de Salud Carlos III, Madrid, Spain. ¹¹ Department of Critical Care, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands. ¹² Cuidados intensivos-Centro Hospitalar do Porto, Porto, Portugal. ¹³ Universitätsklinikum Schleswig-Holstein, Campus Kiel, Kiel, Germany. ¹⁴ Function Perioperative Medicine and Intensive Care, Karolinska University Hospital Solna, Stockholm, Sweden. ¹⁵ Department of Physiology and Pharmacology, Section of Anesthesiology and Intensive Care Medicine, Karolinska Institutet, 171 77 Stockholm, Sweden. ¹⁶ Hedenstierna Laboratory, Department of Surgical Sciences, Uppsala University, Uppsala, Sweden. ¹⁷ Department of Critical Care Medicine, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India. ¹⁸ Department of Critical Care Medicine and Anesthesiology, Military Hospital of Tunis, Tunis, Tunisia. ¹⁹ The North Middlesex University Hospital Trust, London, UK. ²⁰ Aseer Central Hospital, Abha, Saudi Arabia. ²¹ Hippokrateion General Hospital of Athens, Athens, Greece. ²² University Malaya Medical Centre, Kuala Lumpur, Malaysia. ²³ Unidad de Terapia Intensiva Hospital de Especialidades Eugenio Espejo, Quito, Ecuador. ²⁴ CHU Angers-DRCI-Cellule Gestion des Données et Evaluation, Angers, France. ²⁵ Division of Scientific Affairs—Research, ESICM, Brussels, Belgium. ²⁶ Centre de coordination et de lutte contre les infections nosocomiales (C-CLIN) Sud-Est, Pierre Bénite, France. ²⁷ Saint Michael's Hospital, Toronto, Canada. ²⁸ Médecine Intensive et Réanimation, CHU Angers, Angers, France. ²⁹ Université d'Angers, Angers, France. ³⁰ INSERM, 955, Creteil, France.

Acknowledgments

The investigators of the APRONET Study Group (listed in the accompanying table of investigators), the REVA Network, the Réseau recherche de la Société Française d'Anesthésie-Réanimation (SFAR-recherche) and the ESICM Trials Group.

Table of investigators

Country	City	Name of the ICU	Name of the hospital	Collaborator #1	Collaborator #2	Head of the ICU or department
Tunisia	Tunis	Critical Care Medicine and Anesthesiology	Military hospital for instruction of Tunisia	HAJJEJ Zied	SELLAMI Walid	FERJANI M
India	Lucknow	Critical Care Medicine	Sanjay Gandhi Postgraduate Institute of Medical Sciences	GURJAR Mohan		
Saudi Arabia	Abha	Intensive care unit	Asher Central Hospital	ASSIRI Amer	AL BSHABSHE Ali	
Saudi Arabia	Riyadh	Intensive care unit	Prince Sultan Military Medical City	ALMEKHLAFI Ghaleb	MANDOURAH Yasser	
Malaysia	Kuala Lumpur	Intensive Care Unit	University Malaya Medical Centre	HASAN Mohd Shahnaz	RAI Vineya	MARZIDA M
Spain	Albacete	Servicio Medicina intensiva	Hospital General de Albacete	CORCOLES GONZALEZ Virgilio	SANCHEZ INIESTA Rafael	
Spain	Madrid	Intensive Care Unit	H.G.U Gregorio Marañón	GARCIA Pablo		
Spain	Pamplona	Intensive Care Unit	Complejo Hospitalario De Navarra	GARCIA-MONTESINOS DE LA PEÑA Manuel	GARCIA HERRERA Adriana	
Spain	Barcelona	Vall d'Hebron—Critical Care Department	Hospital Universitari Vall d'Hebron	ROCA Oriol	GARCIA-de-ACILU Marina	
Spain	Barcelona	Del Mar—Anestesiología y Reanimación	Hospital del Mar	MASCLANS ENVIJ Joan Ramon		
Spain	Barcelona	San Pau—Anestesiología y Reanimación	Hospital Sant Pau	MANCEBO Jordi		
Spain	Madrid	Unidad de Cuidados Intermedios Respiratorios	Hospital Fundación Jiménez Díaz-Quirón Calvo NATIVIDAD Arias Cesar Peset		HEILI Sarah Frades	
Spain	Sabadell	Intensive Medicine Service	Hospital Parc Tauli	ARTIGAS RAVENTOS Antonio	BLANCH TORRA Lluís	
Spain	Tortosa	Medicina intensiva	Hospital Verge de la Cinta	ROCHE-CAMPO Ferran		
Spain	Palma de Mallorca	Intensive Care Department	Hospital Son Llàtzer	RIALP Gemma	FORTEZA Catalina	
Spain	Burgos	Intensive Care Unit	Hospital Universitario de Burgos	BERRAZUETA Ana	MARTINEZ Esther	
Spain	Getafe	Intensive Care Unit	Hospital Universitario de Getafe	PENUELAS Oscar		
Spain	Murcia	Servicio de Medicina Intensiva	Hospital Clínico Universitario Virgen de la Arrixaca	JARA-RUBIO Ruben		
France	Lens	Réanimation Polyvalente	Centre Hospitalier de Lens	MALLAT Jihad		THEVENIN D
France	Amiens	Réanimation Chirurgicale	Centre Hospitalier universitaire d'Amiens	ZOGHEIB Elie		
France	Angers	Réanimation Médicale	Centre Hospitalier universitaire d'Angers	MERCAT Alain		
France	Anncy	Réanimation Polyvalente	Centre Hospitalier Anncy Genevois	LEVRAT Albrice		
France	Annonay	Réanimation Polyvalente	Centre Hospitalier Annonay	POROT Veronique		BEDOCK B
France	Antibes	Réanimation Polyvalente	Centre Hospitalier Antibes	GRECH Ludovic		
France	Argenteuil	Réanimation Polyvalente	Hopital Victor Dupouy	PLANTEFEVE Gaetan		
France	Belfort	Réanimation Polyvalente	Hopital Nord Franche Comté	BADIE Julio		
France	Besançon	Réanimation Chirurgicale	Centre Hospitalier Universitaire Jean Minjot	BESCH Guillaume	PILLI-FOURY Sébastien	
France	Bordeaux	Réanimation Médicale	Hopital Saint André	GUISSET Olivier		

Country	City	Name of the ICU	Name of the hospital	Collaborator #1	Collaborator #2	Head of the ICU or department
France	Bourg en Bresse	Réanimation Médicale	Centre hospitalier Bourg en Bresse	ROBINE Adrien		
France	Brest	Réanimation Médicale	CHRU Cavale Blanche	PRAT Gwenael		
France	Chalon sur Saone	Réanimation Médicale	Centre Hospitalier de Chalon sur Saone	DOISE Jean-Marc		
France	Chambéry	Réanimation Polyvalente	Centre Hospitalier Metropole Savoie	BADET Michel		THOURET JM
France	Charleville-Mézières	Réanimation Polyvalente	Centre Hospitalier de Charleville-Mézières	JUST Bernard		
France	Clermond-Ferrand	Réanimation Médico-Chirurgicale	Centre Hospitalier Universitaire Clermond-Ferrand	PERBET Sébastien		
France	Clermond-Ferrand	Réanimation Médicale Polyvalente	Centre Hospitalier Universitaire Clermond-Ferrand	LAUTRETTE Alexandre		SOUWEINE B
France	Clermond-Ferrand	Neuro Réanimation	Centre Hospitalier Universitaire Clermond-Ferrand	CHABANNE Russell		
France	Brest	Réanimation Polyvalente	Hôpital d'Instruction des Armées Clermont Tonnerre	DANGUY DES DÉSERTS Maic		
France	Dieppe	Réanimation Polyvalente	Centre Hospitalier de Dieppe	RIGAUD Jean-Philippe	MARCHALOT Antoine	RIGAUD JP
France	Draguignan	Réanimation Polyvalente	Centre Hospitalier de Draguignan	BELE Nicolas		
France	Dunkerque	Réanimation Chirurgicale	Centre Hospitalier de Dunkerque	BEAGUE Sébastien		
France	Corbeil-Essones Cedex	Réanimation Polyvalente	Centre Hospitalier Sud Francilien	HOURS Sandrine	MARQUE Sophie	
France	Grenoble	Réanimation Cardiovasculaire et Thoracique	Hopital Michallon	DURAND Michel		PAYEN JF
France	Villejuif	Réanimation USCM	Institut Gustave Roussy Cancer Campus	STOCLIN Annabelle	GAFFINEL Alain	
France	La Réunion	Réanimation Polyvalente	Centre Hospitalier Universitaire de la Réunion	WINER Arnaud		
France	LeMans	Réanimation Médico—Chirurgicale	Centre Hospitalier de LeMans	CHUDEAU Nicolas	TIROT Patrice	
France	Longjumeau	Réanimation Polyvalente	Centre Hospitalier des Deux Vallées	THYRAULT Martial	PAULET Rémi	THYRAULT M
France	Lyon	Reanimation chirurgicale	Hospices Civils de Lyon, Hôpital Croix Rousse	AUBRUN Frederic		
France	Lyon	Réanimation Médicale	Hospices Civils de Lyon, Hôpital Croix Rousse	GUERIN Claude		
France	Lyon	Réanimation HEH Gréa	Hospices Civils de Lyon, Hôpital Edouard Herriot	FLOCCARD Bernard		RIMMELET
France	Lyon	Réanimation HEH Nréa	Hospices Civils de Lyon, Hôpital Edouard Herriot	ARGAUD Laurent	HERNU Romain	
France	Lyon	Réanimation HEH Préa	Hospices Civils de Lyon, Hôpital Edouard Herriot	CROZON Clauzel Jullien		
France	Lyon	Réanimation Desgenettes	Hôpital d'Instruction des armées Desgenettes	WEY Pierre-François		
France	Lyon	Réanimation Polyvalente Saint Joseph	Centre Hospitalier Saint Joseph—Saint Luc	BOURDIN Gael		POMMIER C

Country	City	Name of the ICU	Name of the hospital	Collaborator #1	Collaborator #2	Head of the ICU or department
France	Mâcon	Réanimation Médicale	Centre Hospitalier des Chanaux	CUEVILLE Nadège		DEVARAX
France	Marseille	Réanimation DRIS	Hopital Nord	MARCHI Elisa		PAPAZIAN L
France	Melun	Médecine Intensive	Centre Hospitalier de Melun	JOCHIMANS Sebastien		MONCHI M
France	Montpellier	Réanimation Chirurgicale	Centre Hospitalier de Montpellier	JABER Samir	DE JONG Audrey	
France	Montpellier	Réanimation Médicale	Centre Hospitalier de Montpellier	MOULAIRE Valerie		JARRIGE L
France	Moulins	Réanimation Polyvalente	Centre Hospitalier Moulins Yzeure	CAPRON Matthieu		
France	Mulhouse	Réanimation Médicale	Centre Hospitalier de Mulhouse	BARBERET Guillaume	IOIDEVIN Autoine	
France	Nantes	Réanimation chirurgicale polyvalente HGRL	de Nantes	LAKHAL Karim		ROZEC B
France	Nice	Réanimation Médicale	Centre Hospitalier Universitaire I'ARCHET ¹	DELLAMONICA Jean	ROBERT Alexandre	BERNARDIN G
France	Nice	Réanimation Médico-Chirurgicale	Centre Hospitalier Universitaire I'ARCHET ²	DANIN Pierre-Eric		RAUCOULES M
France	Orleans	Réanimation Médicale	Centre Hospitalier Régional d'Orleans	RUNGE Isabelle		
France	Paris	Réanimation Chirurgicale Polyvalente	Hôpital Beaujon (Clichy) APHP	FOUCRIER Arnaud		
France	Paris	Réanimation Chirurgicale	Hôpital Bicêtre APHP	HAMADA Sophie		
France	Paris	Réanimation Chirurgicale Digestive	Hôpital Cochin APHP	TESNIERE Antoine	FROMENTIN Mélanie	SAMAMA CM
France	Paris	Réanimation Médicale	Hôpital Cochin APHP	MIRA Jean-Paul		
France	Paris	Réanimation	Hôpital George Pompidou APHP	DIEHL Jean-Luc		
France	Créteil	Réanimation Médicale—Créteil	Hôpital Henri-Mondor APHP	MEKONTO DESSAP Armand		
France	Paris	Réanimation Chirurgicale	Hôpital Pitié-Salpêtrière APHP	ARBELOT Charlotte		
France	Paris	Réanimation médicale Montyon	Hôpital Pitié-Salpêtrière APHP	DEMOULE Alexandre	ROCHE Anne	SIMILOWSKIT
France	Colombes	Réanimation Médico Chirurgicale—Louis mourier	Hopitaux Universitaires Paris Nord Val de Seine APHP	RICARD Jean-Damien	GAUDRY Stéphane	DREYFUSS D
France	Saint Denis	Réanimation Médicale—Saint Denis	Centre Hospitalier Saint Denis	de MONTMOLIN Etienne	Da SILVA Daniel	VERDIERE B
France	Paris	Réanimation Médicale—Saint Louis	Hôpital Saint Louis APHP	ARDISSON Fanny	LEMIALE Virginie	AZOULAY Elie
France	Paris	Réanimation Médicale—St Joseph	Hôpital Paris Saint Joseph	BRUEL Cédric	TIERCELET Kelly	
France	Paris	Réanimation Médico-Chirurgicale	Hôpital Tenon APHP	FARTOUKH Muriel	VOIRIOT Guillaume	
France	Clamart	Centre de Traitement des Brûlés	Percy Military Teaching Hospital	HOFFMANN Clement		LECLERC T
France	Poitiers	Réanimation Médicale	Centre Hospitalier Universitaire Poitiers	THILLE Arnaud	ROBERT René	
France	Roanne	Réanimation Médicale	Centre Hospitalier de Roanne	BEURET Pascal		
France	Rouen	Réanimation Médicale	Centre Hospitalier Universitaire de Rouen	BEDUNEAU Gaëtan	BEUZELIN Marion	TAMION F
France	Saint-Priest en Jarez	Réanimation Polyvalente	Centre Hospitalier Universitaire de Saint Etienne	MOREL Jérôme	TREMBLAY Aymeric	MOLLIEX S
France	Toulon	Réanimation Polyvalente	Centre Hospitalier de Toulon	AMAL Jean-Michel		
France	Toulon	Réanimation HIA	HIA SAINTE-ANNE	MEAUDRE Eric	GOUTORBE Philippe	

Country	City	Name of the ICU	Name of the hospital	Collaborator #1	Collaborator #2	Head of the ICU or department
France	Tours	Anesthésie Réanimation	Centre Hospitalier Régional Universitaire de Tours	LAFFON Marc		
France	Le Chesnay (Versailles)	Réanimation Médico-Chirurgicale	Centre Hospitalier de Versailles	GROS Antoine		
France	Compiègne	Réanimation	Centre Hospitalier de Compiègne	NOYON NICA Alexandru	BARJON Genevieve	
France	Poitiers	Réanimation Chirurgicale	Centre Hospitalier Universitaire Poitiers	DAHYOT-FIZELIER Claire	IMZI Nadia	
France	Mulhouse	Réanimation Chirurgicale	Groupe hospitalier de la région Mulhouse et sud Alsace	GALLY Josette		REAL
France	Cherbourg en Cotentin	Réanimation Polyvalente	Centre Hospitalier Public du Cotentin	SAUNEUF Bertrand	SOULOY Xavier	
The Netherlands	The Neth-Amsterdam	Department of Intensive Care	University Hospital VU medical centre	GIRBES Armand	TUINMAN Pieter Roel	
The Netherlands	The Neth-Amsterdam	Intensive Care Unit	Academic medical Center	SCHULTZ Marcus	WINTERS Tineke	
The Netherlands	The Neth-Roermond	Intensive Care Unit	Laurentius Ziekenhuis Roermond	MUIZEN Lisa		ROEKAERTS
The Netherlands	The Neth-Enschede	Intensive Care Centrum	Medisch Spectrum Twente	VERMEIJDEN Wytze	BEISHUIZEN Albertus	TROF R.
The Netherlands	The Neth-Nijmegen	Intensive Care afdeling	Canisius Wilhelmina Ziekenhuis	CORSTEN Stijn		
The Netherlands	The Neth-Utrecht	Department of Intensive Care Medicine	University Medical Center Utrecht	KESECIOGLU Jozef		
The Netherlands	The Neth-Groningen	Critical Care	University Medical Center Groningen	MEERTENS John	DIEPERINK Wim	
The Netherlands	The Neth-Nijmegen	Intensive Care Unit	Radboudumc	PICKERS Peter	ROOVERS Noortje	
Portugal	Porto	Cuidados intensivos	Hospital Santo António	MAIA Paulo	DUQUE Melanie	FERNANDO RUA
Portugal	Cascais	Intensive Care	Hospital de Cascais	PEREIRA DE FIGUEIRED António Manuel	RAMOS Armindo	
Portugal	Lisboa	Unidade de Cuidados Intensivos Respiratórios (UCIR)—Serviço de Pneumologia	Hospital de Santa Maria—Centro Hospitalar de Lisboa Norte	FRAGOSO Elsa	AZEVEDO Pilar	AZEVEDO P
Portugal	Lisboa	Serviço de Medicina Intensiva—UCIP	Hospital Santa Maria	GOUVEIA Joao		Zélia Costa e Silva
Portugal	Funchal	Serviço de Medicina Intensiva	Hospital Central do Funchal	SILVA Goncalo	CHAVES Susana	NOBREGA JJ
Portugal	Porto	Unidade de Cuidados Intensivos Polivalentes da Urgência (UCIPU); Unidade de Cuidados Intensivos Polivalente Geral (UCIPG)	Hospital São João	LOPES Luis	NUNO Iriucipe	
Portugal	Lisboa		Hospital de São Francisco Xavier	VALERIO Bernardino		
Portugal	Amadora		Hospital Amadora-Sintra	ARAUJO Ana Carolina		Dr. Paulo Telles de Freitas
Portugal	Lisboa		IPO Lisboa	BOUW Maria Jose		

Country	City	Name of the ICU	Name of the hospital	Collaborator #1	Collaborator #2	Head of the ICU or department
Portugal	Faro	UCIP Unidade de Cuidados Intensivos Polivalente	Centro Hospitalar do Algarve	MELAO Maria		GRANJA C
Portugal	Gaia		CHWNG Centro Hospitalar Vila Nova de Gaia	MARCAL Paulo		
Portugal	Almada	Hospital Almada	Hospital Almada	FERNANDES Antero		
Portugal	Vila Franca Xira	Hospital Vila Franca Xira	Hospital Vila Franca Xira	JOAO Gonçalves Pereira		
Portugal	Ponta Delgada—Açores Islands	Hospital Ponta Delgada	Hospital Ponta Delgada	FARIA MAIA Dionísio		
Italy	Ferrara	Intensive care unit	Arcispedale Sant'Anna	SPADARO Savino	VOLTA Carlo Alberto	
Italy	Monza	General ICU	Hospital San Gerardo	BELLANI Giacomo		CITERIO G
Italy	Milano	Terapia Intensiva Postoperatoria	Fondazione IRCCS Ospedale Maggiore Policlinico	MAURI Tommaso	ALBAN Laura	PESENTI A
Italy	Milano	U.O.C. Anestesia e Rianimazione	Ospedale San Paolo—Polo Universitario	MISTRALETTI Giovanni	FORMENTI Paolo	TOMMASINO C
Italy	Milano	Terapia Intensiva Generale 1	ASST Grande Ospedale Metropolitano Niguarda	TARDINI Francesca		FUMAGALLI R
Italy	Milano	Terapia Intensiva	Ospedale Luigi Sacco	COLOMBO Riccardo	FOSSALI Tommaso	CATENA E
Italy	Chiari	Unità di terapia intensiva	ASST FRANCIACORTA Chiani Hospital	TODESCHINI Manuel	GNESINI Paolo	
Italy	Palermo	Terapia Intensiva Polivalente 2	ARNAS Ospedale Civico Di Cristina BENFRATELLI	CRACCHIOLO Andrea Neville	PALMA Daniela	TETAMO R
Italy	Rozzano	Terapia Intensiva Generale	Humanitas Research Hospital	ALBIERO Daniela	COSTANTINI Elena	RAIMONDI F
Italy	Lecco	Rianimazione Generale	A. Manzoni Hospital	COPPADORO Andrea	VASCOTTO Ettore	LUSENTI F
Germany	Kiel	Anesthesiology and Intensive Care Medicine	Universitätsklinik Schleswig-Holstein, Campus Kiel	BECHER Tobias	SCHÄDLER Dirk	WEILER N
Germany	Cologne	ARDS and ECMO centre Cologne	ARDS and ECMO centre Cologne-Merheim/University Witten/Herdecke	KARAGIANNIDIS Christian		
Sweden	Stockholm	Karolinska Universitetssjukhuset, Solna	Karolinska University Hospital Solna	PETERSSON Johan		KONRAD D
Sweden	Uppsala	Central intensive care	Akademiska sjukhuset	KAWATI Rafael	WESSBERGH Joanna	VALTYSSON J
Sweden	Kalmar	ICU	Länssjukhuset i Kalmar	ROCKSTROH Matthias	BORGSTROM Sten	
Sweden	Umeå	Centrum för intensiv och postoperativ vård	Umeå University Hospital	LARSSON Niklas		THUNBERG J
UK	Poole	Critical Care Unit	Poole Hospital	CAMSOOKSAI Julie		BRIGGS
UK	London	Critical care complex	The North Middlesex University Hospital Trust	KOVARI Ferenc		CUESTA J
UK	London	Barts Heart Centre	Barts Heart Centre- St. Bartholomew's Hospital	ANWAR Sibis		O'BRIEN B
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
Czech Republic	Prague	Intensive Care Unit	IKEM Institute of Clinical and Experimental Medicine	PIZA Petr		
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		GAWORM
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 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	MARENCO J

Compliance with ethical standards

Conflicts of interest

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

Received: 13 October 2017 Accepted: 11 November 2017

Published online: 07 December 2017

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