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Prone positioning in spontaneously breathing patients with moderate or severe ARDS under invasive mechanical ventilation: a monocentric retrospective study.

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Title

Prone positioning in spontaneously breathing patients with moderate or severe ARDS under invasive mechanical ventilation: a monocentric retrospective study.

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Author's contributions

AW collected the data and was a major contributor in writing the manuscript.

DC contributed to the acquisition of the data, performed statistical analysis and was a minor contributor in writing the manuscript.

GD collected the data and extensively revised the manuscript.

XW contributed to the acquisition of the data and extensively revised the manuscript.

GM contributed to the acquisition of the data and extensively revised the manuscript.

PFL contributed to the acquisition of the data and extensively revised the manuscript.

LG drafted the work, contributed to the acquisition and collection of data, and was a major contributor in writing the manuscript.

All authors read and approved the final manuscript

Conflicts of interest

The authors declare that they have no competing interests.

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Abstract

Objectives: Prone positioning (PP) during invasive mechanical ventilation (MV) improves outcomes of patients with severe ARDS. Recent studies suggest that PP in spontaneously breathing non-intubated patients with acute respiratory failure is well tolerated and improves oxygenation. However, little is known regarding assisted ventilation in intubated patients with ARDS undergoing PP. We conducted a retrospective review of our experience proning two clinical series of patients with moderate and severe ARDS (related to COVID-19 in one cohort, unrelated in the other), many of whom were under pressure support ventilation (PSV).

Methods: Retrospective analysis, in one 22-bed mixed ICU. The patients included in the analysis were aged ≥18 years, met the Berlin definition for moderate or severe ARDS (related or not to COVID-19) and underwent prone positioning under invasive mechanical ventilation.

Results: Thirty nine patients were included in the analysis. 20 patients had COVID-19 related ARDS while 19 had ARDS related to other etiologies. A total of 113 prone positioning episodes were analyzed, 84 in PSV and 29 in volume assist-control ventilation (VAC). Prone positioning under PSV was well tolerated and was effective in improving arterial oxygenation (increase of the median paO2/FiO2 ratio from 100 [75-120] to 135 [111-161], p<0.0001). No significant difference between VAC and PSV was noted regarding arterial oxygenation during PP. Compared with VAC mode, PP in PSV was associated with a significant decrease in the use of neuromuscular blocking agents (NMBA) (4 vs 69% of patients, p<0.0001), while sedative requirements remained unchanged.

Conclusions: In a retrospective analysis of consecutive patients with moderate or severe ARDS related or not to COVID-19 spontaneous breathing in intubated patients undergoing PP invasive was well tolerated and achieved significant improvement in arterial oxygenation.

Keywords

Acute respiratory distress syndrome; COVID19; SARS-CoV2; Prone positioning; spontaneous breathing; pressure support ventilation

Background

Acute respiratory distress syndrome (ARDS) is common in critically ill patients, whilst associated with high mortality and morbidity(1).

Prone positioning (PP) during invasive mechanical ventilation has been shown to improve oxygenation and to decrease mortality of the most severe ARDS patients(2). Therefore, prone positioning for more than 12 hours a day is recommended in patients with severe ARDS (3). Whereas the benefits of prone positioning are well established, the ideal ventilatory management of patients with moderate and severe ARDS patients is less well defined. In particular, the benefits and risks of spontaneous breathing in ARDS are debated. Experimental evidence is conflicting, and no clinical trial to date has compared assisted with controlled mechanical ventilation.

Several studies, mainly retrospective, suggested that prone positioning was safe and could improve oxygenation in spontaneously breathing non intubated patients with respiratory failure of various origins(4-6) (some of them fulfilling ARDS criteria), and, recently, in patients with severe hypoxemia due to coronavirus disease 2019 (COVID-19) (7-9).

However, none of the clinical studies who focused on the effects of prone positioning during invasive mechanical ventilation was conducted in patients under an assisted mode. Therefore, we aimed to evaluate the feasibility, the tolerance and the effects on oxygenation of prone positioning during moderate to severe ARDS, (related or not to COVID-19), in patients under pressure support mechanical ventilation (PSV). In our group, we tend to favour spontaneous breathing whenever possible in mechanically ventilated patients, as part of a global strategy to decrease sedation requirements, promote early mobilization and to prevent muscular atrophy, including diaphragm dysfunction (10-13). In this regard, we try to maintain spontaneous breathing, most often in the pressure support mode (PSV), while moderate or severe ARDS patients undergo prone positioning.

We conducted a retrospective review of our experience proning two clinical series of patients with moderate and severe ARDS, many of whom were under assisted invasive mechanical ventilation.

Methods

The appropriate ethics committee (Comité d'Ethique Hospitalo-Facultaire, Saint-Luc, UCL N°2019/16JAN/022 and N°2020/27AVR/247) approved the reporting of our study results. Informed consent from the patients or their next of kin was waived due to the retrospective nature of the analysis.

Patients

The medical files of patients with a discharge diagnosis code 518.50 ("Acute Respiratory Distress Syndrome") and/or A03.5 ("ARDS"), according to the International Classification of Diseases, 9th Revision (ICD-9), admitted from July 2012 to March 2018 in a 22-bed tertiary care mixed ICU were reviewed for possible inclusion in this study. The inclusion criteria were as follows: age equal or greater than 18 years at the time of diagnosis, findings consistent with the Berlin ARDS definition of moderate or severe ARDS(14), and prone positioning > 12 hours during the first 72 hours of invasive mechanical ventilation. All consecutive patients following inclusion criteria were included in the first cohort. In addition, in a second cohort, all consecutive patients under invasive mechanical ventilation for COVID-19 related ARDS and undergoing at least one session of prone positioning (> 12 hours) between the 15th of March 2020 to the 15th of April 2020 were included in the analysis.

Data collection

Data were retrieved from Electronic Medical Recording (Qcare ICU, HIM). Demographic data, underlying conditions, adjuvant therapies and cause of ARDS were recorded. Acute Physiology and

Chronic Health Evaluation II (APACHE II) score and Sequential Organ Failure Assessment (SOFA) score were calculated at the day of ARDS diagnosis. For all patients, the first 4 sessions of prone positioning following initiation of MV were carefully considered. For each PP session, the occurrence of adverse events, respiratory and hemodynamic parameters (including vasoactive drugs use and dosing) and sedation related variables (RASS score, and the use and average dose of sedative drugs) were recorded. Were considered as adverse events: cardiac arrest, unplanned extubation and mainstem bronchus intubation due to endotracheal tube displacement. Hemodynamic instability was defined as a bradycardia < 30 bpm for > 1 min, or a decrease of mean arterial pressure of 20 mmHg or an increase of norepinephrine dose of 0.1 mcg/kg/min in the 15 minutes following turning to prone position. We assessed each variable retrieved from the EMR at 4 timepoints: immediately before PP, at the beginning of PP (first available values 1 hour after initiation of PP for respiratory variables and values 15 min after initiation of PP for hemodynamic variables), at the end of PP (last value before turning back to supine) and after PP (first available values > 1 hour after turning back to supine position). For each session of PP, the duration of spontaneous breathing (under pressure support ventilation) was recorded. When the duration of PSV exceeded 50% of the total duration of PP, the PP session was recorded in the PSV group, otherwise it was recorded in the VAC group. Patients were followed up until hospital discharge, and outcome was recorded at 28 days and ICU discharge.

Statistical Analysis

Statistical analyses were performed using the SPSS 21 software (IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY), with graphs drawn using Graphpad Prism 8 (GraphPad Software, LaJolla, CA). Values were expressed as median (first–third quartiles) or mean (SD) for continuous values and counts (per percent of group) for qualitative variables. The data were subjected to Kolmogorov-Smirnov normality test and Bartlett's test for homogeneity of variance. We compared outcome and demographic variables, sedation and adverse events between patients groups using the chi-square test (or Fisher exact test when appropriate) and unpaired t test (or the

Mann-Whitney test according to statistical distribution) for quantitative data, respectively. Furthermore, we compared the evolution of respiratory and hemodynamic parameters during PP sessions within each group using paired t test (or Wilcoxon rang-sum test according to statistical distribution). All tests were two-sided, with significance level set at 0.05.

Results

From July 2012 to March 2018, 107 patients were admitted in the ICU with moderate or severe ARDS and underwent mechanical ventilation for 72 hours at least. 38 patients underwent PP, but full data (mainly regarding sedation and hemodynamic parameters) was available in only 19 of them, who were included in the first cohort (Fig.1). Besides, from the 15th of March to the 15th of April 2020, 52 patients were admitted in the ICU with severe COVID-19. Among them, 23 underwent mechanical ventilation and 20 underwent at least 12 hours of PP. Full data was available for all patients, who were included in the second cohort. The patients' characteristics at baseline, cause of ARDS and main outcome data are summarized in Table 1. The Median age in the whole cohort was 59 years old. Patients undergoing PP for COVID-19 related ARDS were more likely to be male (65 vs 37%, p=0.07), had lower APACHE II (11 [IQR 9-21] vs 25 [18-28], p0.001) and SOFA score (5 [IQR 4-9] vs 9 [IQR 5-12], p=0.01). 28-day and ICU mortality were 31 and 42% in the whole cohort respectively, with no difference between COVID and ARDS patients. There was a total of 113 sessions of PP, with more PP sessions in PSV (n=84) than in VAC (n=29). Thirty-four patients (87%) experienced at least one session of PP in PSV. Patients with COVID had significantly more sessions of PP (4 vs 2, p=0.015), and were less likely to have PP under PSV (66 vs 87% of PP sessions, p=0.01).

Baseline characteristics and outcomes of patients classified into a "full PSV group" (all PP sessions in PSV, n=25), a full control group (all PP sessions in VAC, n=5) or in a "combination" group (mix of PSV and VAC PP sessions [n=9]) are shown in table S1 (supplemental digital content).

As shown in **table 2**, PP duration was significantly shorter in the PSV group (14.6 vs 17 hours, p=0.016). There was no difference regarding the number of sedative drugs nor the average dose during PP between VAC and PSV. Neuromuscular blocking agent (NMBA) use was more frequent in the VAC group than in the PSV group (4 vs 69% of sessions, p<0.0001). Four sessions of PP were terminated prematurely due to a severe adverse event (1 cardiac arrest, 2 unplanned extubations and 1 mainstem bronchus intubation during PP procedure), all in the PSV group.

The evolution of respiratory parameters before, during and after prone positioning is shown in figure 2 and detailed in table S2 (supplemental digital content). As expected, PaO2/FiO2 ratio increased with PP. Other respiratory parameters remained unchanged throughout PP sessions, out of a significant decrease in median respiratory rate (RR) from 30 (IQR 22-36) to 26 (IQR 21-32) breaths per minute in the PSV group (p=0.03). The detailed evolution of PaO2/FiO2 throughout all 4 sessions of PP in VAC and PSV group is provided in figure S1 (supplemental digital content).

In addition, the evolution of hemodynamic parameters during PP sessions is shown in Figure S2 (supplemental digital content). We did not find any significant change in mean arterial pressure, heart rate or norepinephrin dose during PP either in PSV or in VAC.

Discussion

To our knowledge, the present study is the first to focus on PP in the early phase of moderate and severe ARDS, related or not to COVID-19, in patients spontaneously breathing under invasive mechanical ventilation. In our work, we describe the early application of PP in 39 patients with moderate to severe ARDS, among whom 34 experienced at least 1 session of PP in PSV. Eighty-four PP procedures were performed under assisted ventilation, and were compared with 29 PP procedures performed under controlled mechanical ventilation. Our findings show that PP in PSV

was effective in improving arterial oxygenation, well tolerated, and associated with a significant decrease in NMBA consumption compared with PP in VAC, without change in sedative requirements.

Few interventions have demonstrated a survival benefit in patients with moderate or severe ARDS. Among them, prone positioning is a cheap, well-tolerated intervention whose benefits on the outcomes of moderate or severe ARDS patients have been demonstrated in recent trials(2, 15-17). Prone positioning improves oxygenation by optimizing lung recruitment and ventilation-perfusion matching, helps preventing ventilator-induced lung injury (VILI) by improving the distribution of mechanical forces through the lung, and encourages secretion drainage(18). Despite recognized benefits, PP is still underused(1, 15). A recent prevalence study showed that PP was used in only 33% of patients with severe ARDS(15). The main reasons not to use PP in severe ARDS patients were mainly the rating of hypoxemia as “not severe enough” and hemodynamic instability.

In our study, PP was well tolerated, with a rate of severe complications of 3%, lower than previously reported in clinical trials(2, 17) and comparable to the rate of complications recorded in a recent prevalence study (15). One patient had a cardiac arrest while undergoing PP, but it happened more than 4 hours after being turned to prone. The patient ultimately survived. Transient hemodynamic instability at the initiation of PP was frequent (26% of patients) but limited in time. Besides, norepinephrine doses remained stable through PP procedure. Our results show that, with an experienced team, PP can be safely managed even while patients are spontaneously breathing under mechanical ventilation.

We show that, unsurprisingly, maintaining pressure support ventilation during PP procedures allowed to limit NMBA consumption (transient muscular paralysis for the turning was realized in a few patients, explaining the 4% of PP procedures with NMBA use in the PSV group), without difference regarding sedatives. The use of NMBA in ARDS is still debated. Whereas the ACURASYS trial showed a decrease in mortality in severe ARDS patients treated with cisatracurium for 48 hours(19), those results were not replicated in a recent larger trial(20). Moreover, prolonged use of

NMBA is discouraged(21) because of their potential to contribute to sustained neuromuscular weakness(22), ventilator-associated diaphragm dysfunction(23, 24) and impaired coughing and secretion clearance. A significant proportion of patients with ARDS, particularly in the case of COVID-19, experience severe hypoxemia for prolonged periods and might benefit from multiple sessions of PP, with potential exposure to the deleterious effects of long-term neuromuscular blockade. Moreover, due to the recent pandemic of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), ICUs across the world are faced with a dramatic increase of patients with severe ARDS. In many areas, supplies of critical care medications, including NMBA, are currently extremely limited, with expected or effective shortages (25). For those reasons, realizing PP procedures under assisted ventilation, without NMBA, might prove useful.

Furthermore, we showed that PP performed under assisted ventilation was effective in improving arterial oxygenation. The increase of PaO2/FiO2 ratio in our cohort was not different between PSV and VAC group. Interestingly, in patients undergoing PP under PSV, there was a significant decrease of respiratory rate with no change in tidal volume, suggesting a reduced work of breathing.

Beyond the effectiveness of PP to improve oxygenation in ARDS patients under assisted MV, the question of the use of spontaneous ventilation in ARDS remains open. Experimental evidence is conflicting and clinical evidence is scarce. Therefore, it is still unknown whether the potential benefits of spontaneous breathing (including better patient-ventilator interaction, prevention of diaphragmatic atrophy and atelectasis, better ventilation of dorsal lung units, decreased sedation requirements(13, 26-28)) outplace the harms (higher rate of respiratory asynchronies, increase in transpulmonary pressure and Pendelluft phenomenon(26, 29)) in a given patient. Despite this uncertainty, it was reported in a secondary analysis of the LUNG SAFE database that spontaneous breathing was common in the first 48h of ARDS, with 79% and 21% of patients with transient or continuous SB, respectively(30). In an adjusted analysis, SB was not associated with deleterious outcomes.

Our study was not designed nor powered to evaluate the effects of SB on outcomes. However, the ICU mortality in non-COVID and COVID ARDS patients (42% in both cohorts) were similar to those reported in recent large series in which the patients were managed with conventional ventilation strategies(1, 31, 32).

We acknowledge that our results should be interpreted with caution. First, it is a retrospective analysis, in a single referral centre, involving a small number of patients. Second, in our analysis, we pooled patients with ARDS secondary to COVID-19 and patients with ARDS from other aetiologies, despite the fact the underlying pathophysiology might be different(33). It has been suggested that only a proportion of patients with COVID-19 pneumonia can be qualified as ARDS, based on the fact that respiratory system compliance remains initially normal in a large proportion of patients(33, 34). Therefore, according to this hypothesis, the expected benefits in the two sub-populations of COVID patients may be related to different physiopathologic phenomenon and should be analysed separately. However, it has to be noted that post-mortem examinations of most COVID patients reveal the presence of diffuse alveolar damage, the hallmark of ARDS(35, 36), irrespective of the fact that patients were under MV at the time of death. Moreover, we observed comparable results when we analysed the effects of PP within each of the two cohorts. Third, there was an imbalance between patients in the PSV mode and patients in the VAC mode, with a large majority in the former. Our habit is to favour spontaneous breathing whenever possible. The use of VAC is usually restricted to asynchronies or poor tolerance under assisted ventilation, or large tidal volumes despite adaptation of ventilator settings. This could constitute a selection bias towards the use of VAC in more severe patients. However, P/F ratio was similar between groups. Fourth, in the first cohort, only 35% of all moderate to severe ARDS patients underwent PP. However, an equally low prevalence of PP among severe ARDS was reported in the APRONET study{(15). Lastly, data was missing in many non-COVID ARDS patients. Those patients were not included in the analysis, which constitute another possible selection bias.

Conclusion

In this retrospective analysis of consecutive patients with moderate or severe ARDS related or not to COVID-19, PP under assisted mechanical ventilation was well tolerated, and effective in improving oxygenation. When compared with controlled mechanical ventilation, PP procedures under assisted MV were associated with a significant decrease in NMBA consumption, while sedative requirements remained unchanged. Large prospective randomized controlled trials are needed to compare assisted to controlled MV in ARDS, particularly in patients undergoing prone positioning. Moreover, physiologic studies focusing on the effects of spontaneous breathing during prone positioning should help to identify patients in whom benefits of SB are likely to outplace harms.

DECLARATIONS

Ethics approval and consent to participate

The appropriate ethics committee (Comité d'Ethique Hospitalo-Facultaire, Saint-Luc, UCL N°2019/16JAN/022 and N°2020/27AVR/247) approved the reporting of our study results. Informed consent from the patients or their next of kin was waived due to the retrospective nature of the analysis.

Consent for publication

Not applicable

Availability of data

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Quick look

Current knowledge

Prone positioning (PP) during invasive mechanical ventilation (MV) improves outcomes of patients with severe ARDS. Recent studies suggest that PP in spontaneously breathing non-intubated patients with acute respiratory failure is well tolerated and improves oxygenation. No study has been conducted in intubated patients undergoing PP for ARDS.

What This Paper Contributes To Our Knowledge

In this retrospective analysis of consecutive patients with moderate or severe ARDS related or not to COVID-19, PP under assisted mechanical ventilation was well tolerated, and effective in improving oxygenation.

Tables

Table 1. Baseline characteristics, respiratory parameters and outcomes for 39 mild and moderate ARDS patients mechanically ventilated undergoing prone positioning for COVID-unrelated ARDS (1st cohort) or COVID-related ARDS (2nd cohort)

Table 2. Comparison between sedative use and adverse events during prone positioning (PP) in pressure support ventilation (PSV) and in Volume Assist-Control Ventilation (VAC)

Figure legends

Figure 1. Flow chart of the study population in the two cohorts.

Figure 2. Evolution of respiratory parameters throughout prone position sessions in pressure support ventilation (PSV, continuous line) and in Volume assist-control ventilation (VAC, dashed line).

Additional files

Figures

Figure S1. Detailed evolution of PaO2/FiO2 ratio throughout the first 4 prone position sessions in support ventilation (PSV, continuous line) and in Volume assist-control ventilation (VAC, dashed line).

P1 to P4: rank of the prone sessions ; M1 to M4: time 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

Figure S2. Evolution of hemodynamic parameters throughout prone position sessions in pressure support ventilation (PSV, continuous line) and in Volume assist-control ventilation (VAC, dashed line).

* indicates statistical significance in the comparison with « before PP »: * $p<0.05$; ** $p<0.005$; $^{***}p<0.0005$.

Tables

Table S1. Baseline characteristics and outcomes for 39 mild and moderate ARDS patients mechanically ventilated undergoing prone positioning (PP) in pressure support mode (PSV), Volume assist-control mode (VAC) or a combination of both.

Table S2. Evolution of respiratory parameters before, during and after prone positioning.

Table S3. Comparison between sedative use during prone positioning (PP) in pressure support ventilation (PSV) and in Volume Assist-Control Ventilation (VAC) in COVID-related ARDS.

Table S4. Comparison between sedative use prone positioning (PP) in pressure support ventilation (PSV) and in Volume Assist-Control Ventilation (VAC) in COVID-unrelated ARDS.

Table 1. Baseline characteristics, respiratory parameters and outcomes for 39 mild and moderate ARDS patients mechanically ventilated undergoing prone positioning for COVID-unrelated ARDS (1st cohort) or COVID-related ARDS (2nd cohort)

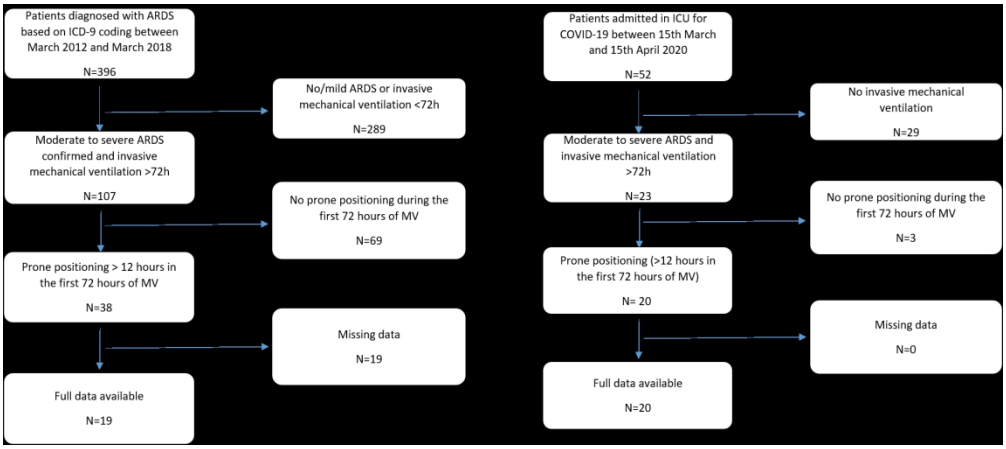
Variables	All patients (n=39)	COVID-unrelated ARDS (n=19)	COVID-related ARDS (n=20)	p
Age, median (IQR), years	59 (46-68)	53 (31—66)	61 (53-70)	0.16
Male, n (%)	20 (51.3)	7 (37)	13 (65)	0.07
Body Mass Index (kg/m²), median (IQR)	26.6 (23.1-29.2)	26 (21-32)	27 (23-29)	0.5
Immunocompromised, n (%)	13 (33.3)	8 (42)	5 (25)	0.21
Chronic respiratory disease, n (%)	9 (22)	6 (31)	3 (15)	0.23
APACHE II (ARDS diagnosis day), median (IQR)	19 (11-26)	25 (18-28)	11 (9-21)	0.001
SOFA (ARDS diagnosis day), median (IQR)	7 (5-11)	9 (5.5-12)	5 (4-9)	0.01
Cause of ARDS, n (%)				<0.0001
COVID-19	20 (51.3)	0	20 (100)	
Pneumonia	10 (25.6)	10 (53)	0	
Sepsis (of extra-pulmonary origin)	7 (18)	7 (37)	0	
Other	2 (5.1)	2 (10)	0	
PaO2/FiO2 ratio baseline, median (IQR), mmHg	76 (65-109)	75 (66-99)	85 (61-118)	0.47
PaCO2 baseline, median (IQR), mmHg	41 (34-47)	43 (37-59)	36 (33-44)	0.07
PEEP baseline, median (IQR), cmH2O	12 (10-12)	12 (10-12)	12 (10-12)	0.62
Peak inspiratory pressure, median (IQR), cmH2O	22 (18-25)	23 (19-27)	22 (15-26)	0.45
VT, median (IQR), ml/kg PBW	6.7 (5.6-7.8)	6.7 (5.3-8)	6.7 (5.6-7)	0.87
Respiratory rate, median (IQR), breaths/min	31 (24-40)	35 (28-41)	28 (22-37)	0.08
28-d mortality, n (%)	12 (31)	6 (32)	6 (30)	0.87
ICU mortality, n (%) (n=38)	16 (42)	8 (42)	8 (42)	1
VFdays D28, median (IQR)	1 (0-9)	2 (0-20)	1 (0-3)	0.34
Number of patients with at least one PP session in PSV, n (%)	34 (87)	18 (95)	16 (80)	0.77
Number of PP sessions	113	45	68	
Number of PP sessions in PSV, n (%)	84 (74)	39 (87)	45 (66)	0.01
Number of PP sessions/patient, median (IQR)	4 (2-4)	2 (1-4)	4 (2-4)	0.015

ARDS: acute respiratory distress syndrome, IQR: interquartile range; SOFA: Sequential Organ Failure Assessment; APACHE II: Acute Physiology and Chronic Health Evaluation II; PEEP: Positive End-Expiratory Pressure; VT: Tidal Volume; PSV: Pressure support ventilation; PP: Prone positioning; ICU: Intensive Care Unit; VFdays D28: Ventilation Free days by day 28.

Table 2. Comparison between sedative use and adverse events during prone positioning (PP) in pressure support ventilation (PSV) and in Volume Assist-Control Ventilation (VAC)

Variables	All PP (n=113)	PP in PSV (n=84)	PP in VAC (n=29)	p
PP duration, mean ± SD, hours	15.3 ± 4	14.6 ± 4.2	17 ± 4.3	0.016
Number of sedative drugs during PP, mean ± SD	3 ± 1	3 ± 1	3 ± 1	0.26
Sedative use, n (%)				
Propofol	112 (99)	84 (100)	28 (96)	0.257
Ketamine	88 (78)	63 (75)	25 (86)	0.16
Clonidine	48 (43)	35 (42)	13 (45)	0.46
Midazolam	34 (30)	26 (31)	8 (28)	0.46
Sufentanil	55 (49)	37 (44)	18 (62)	0.07
Average sedative dose, mean ± SD				
Propofol (mg/kg/h)	2.7 ± 1	2.8 ± 0.9	2.5 ± 1.1	0.14
Ketamine (mg/kg/h)	0.3 ± 0.2	0.29 ± 0.2	0.32 ± 0.2	0.49
Clonidine (mcg/kg/h)	0.13 ± 0.18	0.12 ± 0.15	0.15 ± 0.4	0.34
Midazolam (mg/kg/h)	0.008 ± 0.02	0.007 ± 0.02	0.1 ± 0.03	0.47
Sufentanil (mcg/kg/h)	0.06 ± 0.07	0.06 ± 0.07	0.07 ± 0.07	0.41
RASS, mean ± SD	-4 ± 1	-4 ± 1	-5 ± 1	0.09
NMBA use, n (%)	23 (20)	3 (4)	20 (69)	<0.0001
Premature termination of PP, n (%)	4 (3.5)	4 (5)	0	0.3
Cardiac arrest, n (%)	1 (0.9)	1 (1)	0	0.74
Unplanned extubation, n (%)	2 (1.8)	2 (2)	0	0.55
Mainstem bronchus intubation, n (%)	1 (0.9)	1 (1)	0	0.74
Hemodynamic instability, n (%)	30 (26.5)	21 (25)	9 (31)	0.34

SD: Standard Deviation; NMBA: Neuromuscular Blocking Agent; RASS: Richmond Agitation and Sedation Scale



Flow chart of the study population in the two cohorts.

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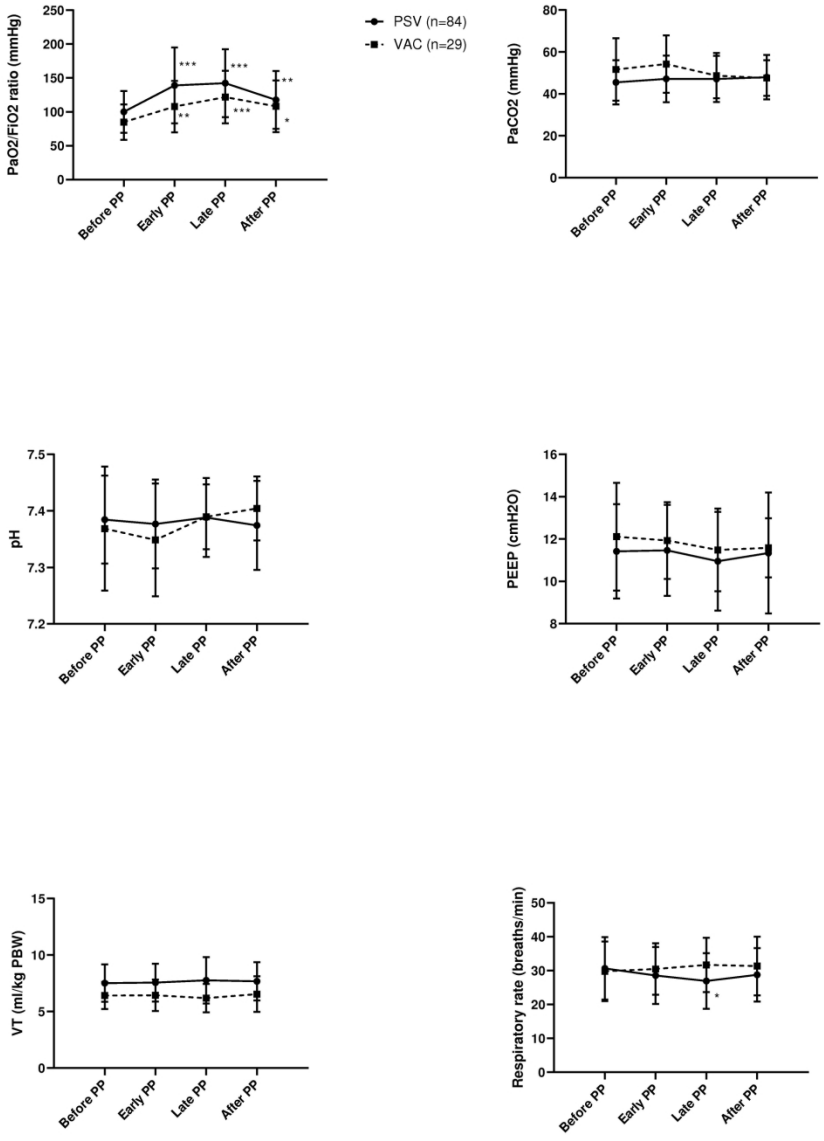

Evolution of respiratory parameters throughout prone position sessions in pressure support ventilation (PSV, continuous line) and in Volume assist-control ventilation (VAC, dashed line).

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STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5-6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	7-8
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	8
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	8-9
Outcome data	15*	Report numbers of outcome events or summary measures over time	8-9

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	8-9
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8-9
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9-13
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	2

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.