Prone Position in Intubated, Mechanically Ventilated Patients with Coronavirus Disease-19.

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Research

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Abstract

Background: Limited data are available on the use of prone position in intubated, invasively ventilated patients with Coronavirus disease-19 (COVID-19). Aim of this study is to investigate the use and effect of prone position in this population during the first 2020 pandemic wave.

Methods: Retrospective, multicentre, national cohort study conducted between February 24 and June 14, 2020 in 24 Italian Intensive Care Units (ICU) on adult patients needing invasive mechanical ventilation for respiratory failure caused by COVID-19.

Clinical data were collected on the day of ICU admission. Information regarding the use of prone position were collected daily. Follow-up for patient outcomes was performed on July 15, 2020. The respiratory effects of the *first* prone position were studied in a subset of 78 patients. Patients were classified as *Responders* if the PaO_2/FiO_2 ratio increased ≥ 20 mmHg during prone position.

Results: Of 1057 included patients, mild, moderate and severe ARDS was present in 15, 50 and 35% of patients, respectively and had a resulting mortality of 25, 33 and 41%. Prone position was applied in 61% of the patients. Patients placed prone had a more severe disease and died significantly more (45% vs 33%, $p<0.001$). Overall, prone position induced a significant increase in PaO_2/FiO_2 ratio, while no change in respiratory system compliance was observed. Seventy-eight % of patients were *Responders* to prone position. Non-Responders had a more severe respiratory failure and died more often in the ICU (65% *vs.* 38%, $p=0.047$).

Conclusions: During the COVID-19 pandemic, prone position has been widely adopted to treat mechanically ventilated patients with respiratory failure. The majority of patients improved their oxygenation during prone position, most likely due to a better ventilation perfusion matching.

Trial registration: clinicaltrials.gov number: NCT04388670

Background

An outbreak of pneumonia of unknown origin started from Wuhan, Hubei, China at the end of 2019 and subsequently spread worldwide. Italy was hit at the end of February 2020 and, as of the end of July 2020, more than 250000 infections and more than 35000 deaths had been reported(1). Approximately 40% of the cases of the first wave have been concentrated in Lombardy, a region in the north of the Country(2–4).

A novel beta-coronavirus, named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-COV–2), was identified as the cause of the epidemic(5) and the resulting disease was called Coronavirus Disease 2019 (COVID–19). COVID–19 has a broad spectrum of clinical presentations, ranging from asymptomatic to extremely severe forms. Approximately 5–15% of infected subjects develop a severe form of acute respiratory distress syndrome (ARDS)(6) and therefore require mechanical ventilation and admission to an intensive care unit (ICU)(7).

In patients developing refractory hypoxemia despite invasive mechanical ventilation, the application of rescue therapies such as extracorporeal gas exchange, inhaled nitric oxide and prone positioning is frequently required(8). Previous experience in patients with moderate-to-severe ARDS from different causes showed that early application of prone position is associated with a significant survival benefit(9–11).

Given the high number of COVID–19 patients with respiratory failure treated outside the ICU, there has been an increasing interest in the use of prone position in awake, spontaneously breathing patients(12–16). On the contrary, limited data are available on the use of prone position in intubated, invasively ventilated patients(17).

Aims of the present study are: (i) to describe the frequency of use of prone positioning and the clinical characteristics and outcomes of patients undergoing prone positioning in a large cohort of critically ill, mechanically ventilated patients with COVID–19; and (ii) to describe, in a subgroup of patients, the pathophysiological effects of prone positioning.

Methods

Study design

This Italian multicentre, retrospective study of prospectively collected data was approved by the Ethical Committees of all participating centres (Promoting Centre's Ethical Committee: Comitato Etico Milano Area 2; protocol: 0008489; date of approval: March 20, 2020) and registered at clinicaltrials.gov (NCT04388670). The need for informed consent from individual patients was waived owing to the retrospective nature of the study.

All patients admitted between February 22, 2020 and June 14, 2020, inclusive for those days, to the COVID–19 ICUs of 24 Italian hospitals (see Additional File for the complete list) were screened for eligibility. Laboratory-confirmed SARS-CoV–2 infection, (*i.e.* positive result of real-time reverse transcriptase–polymerase chain reaction assay of nasal and pharyngeal swabs), and ICU admission for acute respiratory failure constituted the inclusion criteria. Exclusion criteria were: age < 18 years; patients treated exclusively with non-invasive respiratory support; missing clinical data regarding the use of prone position. Clinical management (including mechanical ventilation setting and pharmacological therapies) followed the local treatment guidelines of each center. The choice to position patients prone was at discretion of the attending physician.

The population of patients included in the analysis was subdivided in two groups according to the use of prone positioning: 1) *PP group:* patients who were turned prone at least once during their ICU stay; and 2) *SP group:* patients always treated in the supine position.

Data collection

An electronic case report form (REDCap electronic data capture tools) hosted at IRCCS Ca' Granda Ospedale Maggiore Policlinico was used for data collection. An extensive set of information regarding demographic and anthropometric data, comorbidities(18) and clinical data (severity scores(19–21), vital signs, type of respiratory support, use of prone positioning, respiratory parameters, laboratory tests including blood gas analysis) was collected on the day of admission to the ICU. Relevant clinical and laboratory data, including information regarding the use of prone positioning in the prior 24 hours, were then collected daily until ICU discharge or patient death (See Additional File).

Finally, the following patient outcomes were recorded: ICU and hospital survival, ICU and hospital length of stay (LOS), duration of invasive mechanical ventilation. The final date of follow-up for patient outcomes was July 15, 2020.

Effect of prone positioning on respiratory mechanics and gas exchange

To assess the physiologic effects of pronation, a subgroup of 78 patients who underwent prone positioning in two of the participating hospitals (Grande Ospedale Metropolitano Niguarda and Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, both in Milan) was investigated at three different time points: 1) prior to the first pronation (Baseline); 2) during the last hour of the first session of prone ventilation (Prone); and 3) within 4 hours after turning the patients back to supine position (Supine). At each time-point, end-inspiratory and end-expiratory airway occlusion manoeuvres were performed and arterial blood gases analyzed to obtain the following variables: compliance of the respiratory system (Crs, calculated as the ratio between tidal volume and airway driving pressure); ratio between partial pressure of oxygen (PaO_2) and inspired fraction of oxygen (FiO_2), - PaO_2/FiO_2 ratio; corrected minute ventilation(22) and ventilatory ratio(23). Patients were defined as *Responders* to prone position if they had an increase of the PaO_2/FiO_2 ratio of $\geq$ 20 mmHg during prone ventilation as compared to baseline values in supine position(24,25).

Statistical Analysis

Continuous variables are presented as mean with standard deviation (SD) or median and interquartile range (IQR). Categorical variables are expressed as frequencies (percentages).

Mann-Whitney rank sum test was used to compare nonparametric continuous variables between study groups. $\chi 2$ or Fisher exact test was used for categorical variables, as appropriate.

Differences among time-points were tested by one-way ANOVA for repeated measures. Pairwise multiple comparisons were tested using Tukey's test. All statistical tests were 2-tailed, and statistical significance was defined as a P value below 0.05. Analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA), STATA computer software, version 16.0 (StataCorp LLC) and SigmaPlot 12.0 (Systat Software Inc., San Jose, CA).

Results

One thousand three hundred twenty-six patients fulfilled the inclusion criteria. After exclusions (one patient aged < 18 years, 123 patients with missing medical records and 145 patients who were never intubated), 1057 patients were analyzed (Flowchart reported in eFigure 1 of the Additional File).

Table 1 summarizes the patients' demographic and clinical characteristics at ICU admission and their clinical outcomes. Additional information is reported in eTable 2 of the Additional File. Most patients were male (79%), median age was 63 [55—69] years and median body mass index was 28 [25 –31] kg/m^2. Median SAPS II and SOFA score at ICU admission were 36 [30—44] and 4 [3—4], respectively. Eighty-four % of patients were intubated and mechanically ventilated at ICU admission or during the first day in ICU. ARDS severity was mild in 15%, moderate in 50% and severe in 35% of the cases. Median PaO_2/FiO_2 ratio, respiratory rate, tidal volume/predicted body weight, and plateau airway pressure of mechanically ventilated patients were 120 mmHg [88—173], 20 [18—25] breaths/min, 7.0 [6.3—7.8] mL/kg and 24 [22–27] cmH_2O, respectively. As of July 15, 2020, 677 (64%) patients had been discharged from the ICU and 374 (33%) had died (6 missing data). Mortality increased significantly with increasing severity of ARDS (25, 33, 41%, p = 0.004, for mild, moderate and severe ARDS respectively). The median ICU length of stay was 16 [10—28] days for patients discharged from the ICU, and 12 [6–20] days for those who died in the ICU.

Use of prone positioning and differences between Pronated and Non-Pronated patients

Six-hundred and forty-eight patients (61% of the overall population) were placed in prone position at least once during their stay in the ICU (PP Group), while 409 patients (39% of the overall population) were always treated in the supine position (SP Group). The frequency of use of prone positioning increased with ARDS severity (52/128 (44%), 243/426 (57%) and 229/298 (77%), p <0.001, in mild, moderate and severe ARDS respectively). Prone positioning was first applied 2 [1 —4] days after ICU admission and a median of 3 [1 —4] pronation sessions per patient were performed.

Table 1 outlines the principal differences between the two groups (see eTable 2 in the Additional File). No difference in comorbidities was observed (Charlson Comorbidity Index 2 [1—3] *vs.* 2 [1—3], p = 0.165). Patients in the PP group had significantly more severe respiratory disease, as suggested by a higher percentage of severe ARDS (44% vs. 21%, p <0.001) and a lower percentage of mild ARDS (10 vs. 23%, p < 0.001). Respiratory rate, positive end-expiratory pressure (PEEP), FiO_2 and Plateau pressure were significantly higher, while respiratory system compliance, PaO_2/FiO_2 ratio and arterial pH at ICU admission were significantly lower in the PP group. In addition, biochemical markers of inflammation and disease severity, such as LDH, D-dimers and ferritin were consistently higher in patients of the PP Group. Patients of the PP group had higher severity scores: SOFA (4 [3 –5] *vs.* 4 [3–4], p<0.001) and APACHE II scores (10 [8–13] *vs.* 9 [7–13], p<0.001). Finally, ICU mortality and length of stay, length of mechanical ventilation and hospital mortality and length of stay were all significantly worse in patients in the PP group.

Physiological effects of prone position

In the subgroup of 78 patients, median duration of the first pronation was 18.5 [16—22] hours. Respiratory system compliance did not change significantly with the change in body position (Figure 1, Panel A). Similarly, prone positioning had no significant effect on ventilatory ratio (Figure 1, Panel C). Overall, prone positioning led to a significant increase in PaO_2/FiO_2 ratio, which was followed by a subsequent significant decrease with re-supination (Figure 1, Panel B). On average, PaO_2/FiO_2 ratio after re-supination remained significantly higher as compared to baseline values. Table 2 summarizes the physiologic variables at the three different time points selected for the analysis.

Responders vs. Non-responders to prone positioning

Sixty-one out of 78 patients (78%) had an increase in PaO_2/FiO_2 ratio ≥ 20 mmHg (median increase 68 [42—117] mmHg) and where therefore defined as *Responders.* Seventeen (22%) patients had an increase in PaO_2/FiO_2 ratio < 20 mmHg (median variation 3 [1—12] mmHg) and were therefore classified as *Non-Responders.* Individual variations in PaO_2/FiO_2 ratio due to the change in body position in *Responders* and *Non-Responders* are reported in Figure 2, Panel A and B, respectively. Table 3 summarizes the differences between *Responders* and *Non-Responders (*see eTable 3, in the Additional File). Demographics, comorbidities and admission severity scores were similar between *Responders* and *Non-Responders.*

Notably, at ICU admission, driving pressure (14 [12 - 15] *vs.* 12 [8 - 13] cmH_2O, p = 0.022), plateau pressure (27 [24 - 28] *vs.* 24 [22 - 27] cmH_2O, p = 0.043) and respiratory system compliance (34 [30 - 45] *vs.* 45 [34 - 56] mL/cmH_2O, p = 0.018) were significantly different between *Non-Responders* and *Responders.* Prior to first pronation, baselinedriving pressure (14 [11 - 16]*vs.* 11 [10 - 13] cmH_2O, p = 0.036), respiratory rate (22 [20 - 24] *vs.* 20 [18 - 22] breaths per minute, p = 0.014), $PaCO_2$ (58 [50 - 67] *vs.* 52 [45 - 60] mmHg, p = 0.092) and ventilatory ratio (2.2 [1.9 - 2.7] *vs.* 1.9 [1.6 - 2.2], p = 0.014) were higher in *Non-Responders* while Respiratory System Compliance (33 [26 - 45] vs. 44 [33 - 51] mL/cmH_2O, p = 0.029), and pH (7.33 [7.31—7.38] *vs.* 7.37 [7.34—7.40], p = 0.041) were lower in *Non-Responders.* ICU mortality (11/17, 65% vs 23/61, 38%, p = 0.047) was higher in *Non-Responders.*

Discussion

In this national, multicentre, retrospective observational study performed in the ICUs of 24 Italian hospitals during the first peak of the 2020 COVID–19 pandemic, we investigated the use of prone positioning in a cohort of 1057 critically ill, invasively ventilated patients with respiratory failure due to COVID–19. We also analyzed the pathophysiologic respiratory effects of this manoeuvre in a subset of 78 patients. A major finding of our study is that prone positioning was applied very frequently, significantly more often than previously reported in other populations of ARDS patients(8,26). Indeed, 61% of our patients underwent at least one pronation session during their ICU stay, as compared to 8% of the patients enrolled in the LUNG SAFE study. The frequency of use of prone positioning increased with increasing ARDS severity. Notably, 77% of COVID–19 patients with severe ARDS underwent prone positioning, as compared to the 16% of those with severe ARDS in the LUNG SAFE cohort.

Changing body position from supine to prone (or vice versa) requires dedicated and experienced personnel. Moreover, the manoeuvre frequently requires incremental dosages of sedatives and muscle relaxants(27) and may lead to hemodynamic instability. In addition, it is associated with an increased risk of device displacement and pressure ulcers(28). It is important to underline that in our study, the decision to turn the patients in prone position was at the discretion of the ICU team, *i.e.* there were no pre-specified criteria for the application of this rescue manoeuvre. Due the overwhelming number of critically ill patients requiring ICU admission, the ICU bed capacity of our hospitals had to be rapidly increased(29). Therefore, many physicians and nurses usually working outside the ICU environment and even doctors from other specialities were recruited to allow the surge in ICU capacity. This of course reduced the expertise of the whole ICU staff. Our data clearly show that prone positioning was applied to patients with more severe disease, mainly as a rescue therapy (Table 1). Consequently, the worse clinical outcomes of patients undergoing prone positioning can be explained by the higher disease severity. However, given the retrospective nature of the study, we cannot draw any conclusions on the efficacy of prone position in terms of outcome.

Another important finding, resulting from the physiological sub-study, is that, on average, the PaO_2/FiO_2 ratio increased significantly from 98 [72 –212] to 158 [112 –220] mmHg, p <0.001 (Figure 1, Panel B) during the first pronation session. Moreover, while the PaO_2/FiO_2 ratio dropped with re-supination, as previously observed(30,31), values after re-supination remained significantly higher than baseline values (128 [87 - 174] vs. 98 [72 –212], p <0.05).

The findings of the physiologic sub-study (Table 2) thus suggest that the main mechanism inducing an improvement in oxygenation during the first pronation of COVID–19 patients with ARDS, is the improvement of the ventilation-perfusion matching due to a redistribution of flow from dorsal to ventral lung areas. Indeed, the lack of improvement of respiratory system compliance with the change in body position (Figure 1, Panel A) suggests that lung recruitment was not the major mechanism. We observed a modest, though significant increase in set respiratory rate and a resulting trend toward higher minute ventilations during prone positioning (Table 2). However, we did not observe a significant variation of the ventilatory ratio, a proxy of dead space and efficiency in CO_2 removal (Figure 1, Panel C). Taken together these results suggest that CO_2 production somehow increased during prone position, requiring an increase in minute ventilation to maintain stable $PaCO_2$ values.

We used an increase in PaO_2/FiO_2 ratio during pronation of at least 20 mmHg as cut-off to define the response to prone position in terms of oxygenation. Using this definition, 78% of the studied patients were considered *Responders.* There is no universally applied criteria to define the response to prone position, however, when looking at literature using the same cut-off(24,25), the percentage of patients with COVID–19-induced ARDS that responded to prone position seems similar to the percentage of the "general" ARDS population(25).

When analyzing the differences between *Responders* and *Non-Responders,* we observed that, despite similar comorbidities and baseline severity scores, respiratory failure was on average more severe in *Non-Responders (*Table 3). Indeed, *Non-Responders* had higher driving pressure and ventilatory ratio, suggesting a higher extension of lung dysfunction and a lower efficiency of gas exchange. In the ARDS literature, several studies did not find a different mortality between *Responders* and *Non-Responders(*24,25), while a recent study performed on ARDS, non-COVID patients, suggested that improved oxygenation after prone positioning might be a predictor of survival(32). Also in our study performed in COVID–19 ARDS patients, we found that the mortality of *Non-Responders* was significantly higher as compared to *Responders (*65% *vs.* 38%, p = 0.039).

The retrospective observational nature of the study is a clear limitation of our study. As already discussed, the decision to place the patient in prone position was at discretion of the attending physicians and the general clinical patient management was not standardized among centers. The comparison between the two groups gives therefore useful information about the decision-making process of Italian doctors caring for severely ill COVID-patients during the first wave of the 2020 COVID pandemic. On the contrary, the comparison does not provide information about the efficacy of pronation in terms of outcome. In addition, we have not collected information regarding complications related to prone positioning. A certain rate of complications usually occurs during prone position. It is conceivable that the rate might be higher in the specific context of a pandemic surge. Regarding the physiologic sub-study, the absence of information of partitioned respiratory mechanics is certainly a limitation. Nevertheless, the fact that the respiratory system compliance did not change in the 3 time-points suggests that lung recruitment did not play a significant role during the first pronation.

Conclusions

During the most intense months of the first wave of 2020 COVID–19 pandemic in Italy, critically ill, intubated and mechanically ventilated patients with ARDS were frequently placed in prone position. The more severe the respiratory failure, the more frequent the use of this rescue therapy. Placing the patients prone is a cheap and effective manoeuvre, able to improve oxygenation in the vast majority of patients with respiratory failure due to COVID–19. The main mechanisms responsible for the improved oxygenation seems to be the improvement of the ventilation/perfusion matching.

Abbreviations

APACHE II: Acute Physiology and Chronic Health Disease Classification System II

ARDS: acute respiratory distress syndrome

COVID–19: Coronavirus Disease 2019

FiO_2: inspired fraction of oxygen

ICU: Intensive Care Unit

IQR: Interquartile Range

LDH: Lactate Dehydrogenase

LOS: Length of Stay

PaO_2 : partial pressure of oxygen

PP: Prone Position

SAPS II: Simplified Acute Physiology Score II

SARS-COV–2: Severe Acute Respiratory Syndrome Coronavirus 2

SOFA: Sequential Organ Failure Assessment

SP: Supine Position

SD: Standard Deviation

Declarations

Ethics approval and consent to partecipate: This study was approved by the Ethical Committees of all participating centres (Promoting Centre's Ethical Committee: Comitato Etico Milano Area 2; protocol: 0008489; date of approval: March 20, 2020). The need for informed consent from individual patients was waived owing to the retrospective nature of the study.

Availability of data and materials: The dataset used and/or analysed during the current study are available from corresponding author on reasonable request.

Consent for publication: Not applicable.

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Authors' contributions: TL, AG, MB and GG conceived and designed the analysis; TL, EC and AG contributed in data management and performed statistical analyses; LC, GC, FDC, EDR, MF, AF, CF, DLG, LM, VN, PP, AP, RR, FT, TT, FZ collected and analyzed the data; TL, AG, MB, EC, GF, MG, MA, MR, AP, RF, GG contributed in data analysis, interpretation of the data and drafting the manuscript. All authors: reviewed and approved the manuscript for submission.

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Tables

Table 1. Patients' characteristics at admission in ICU and outcome

Variables	Overall (n = 1057)	Non-proned (n = 409, 39%)	Proned (n = 648, 61%)	p-value
Males, no. (%)	831 (79)	317 (78)	514 (79)	0.483
Age (years)	63 [55 - 69]	63 [55 - 69]	63 [55 - 69]	0.773
BMI (kg/m^2)	28 [25 - 31]	27 [25 - 31]	28 [25 - 31]	0.023
SOFA Score	4 [3 - 5]	4 [3 - 4]	4 [3 - 5]	<0.001
APACHE II Score	10 [7 - 13]	9 [7 - 13]	10 [8 - 13]	0.013
Intubated, no. (%) [a]	892 (84)	351 (86)	541 (84)	0.309
Respiratory Rate (breaths/min) [b]	20 [18 - 25]	20 [16 - 24]	20 [18 - 25]	<0.001
FiO_2 (%) [b]	70 [60 - 90]	60 [50 - 80]	80 [60 - 90]	<0.001
PEEP (cmH_2O) [b]	12 [10 - 14]	12 [10 - 14]	12 [10 - 14]	<0.001
PaO_2/F_IO_2 ratio [b]	120 [88 - 173]	145 [107 - 197]	108 [81 - 148]	<0.001
ARDS severity, no. (%) [b]				
Mild	128 (15)	76 (23)	52 (10)	<0.001
Moderate	426 (50)	183 (56)	243 (46)	
Severe	298 (35)	69 (21)	229 (44)	
Tidal Volume/PBW (mL/kg) [b]	7.0 [6.3 - 7.8]	7.1 [6.3 - 7.9]	7.0 [6.2 - 7.8]	0.140
Plateau Pressure (cmH_2O) [b]	24 [22 - 27]	24 [21 - 26]	25 [22 - 28]	<0.001
Driving Pressure (cmH_2O) [b]	12 [9 - 14]	12 [9 - 13]	12 [9 - 14]	0.120
Respiratory System Compliance (mL/cmH_2O) [b]	40 [33 - 50]	42 [35 - 50]	38 [32 - 50]	0.035
pH	7.39 [7.32 - 7.46]	7.40 [7.33 - 7.46]	7.39 [7.31 - 7.45]	0.220
PaO_2 (mmHg)	80 [67 - 101]	86 [70 - 108]	77 [65 - 97]	<0.001
$PaCO_2$ (mmHg)	43 [36 - 52]	43 [37 - 51]	43 [36 - 53]	0.710
LDH (units/L)	479 [359 - 640]	424 [324 - 593]	507 [392 - 667]	<0.001
D-dimer (ng/mL)	1492 [608 - 4602]	1190 [520 - 3470]	1730 [690 - 6576]	0.001
Ferritine (ng/mL)	1408 [811 - 2399]	1214 [668 - 1903]	1552 [1031 - 2491]	0.003
ICU Mortality, no. (%)	374 (36)	112 (28)	262 (41)	<0.001

Hospital Mortality, no. (%)	405 (41)	127 (33)	278 (45)	<0.001
ICU LOS (days)	15 [9 – 25]	12 [7 - 21]	16 [10.5 – 28]	<0.001
Hospital LOS (days)	29 [17 – 46]	26 [16 – 40]	30 [17 – 49]	0.008
Mechanical ventilation (days)	14 [8 – 26]	10 [5.5 – 19]	16 [10 – 30]	<0.001

Data are expressed either as median [interquartile range] or as frequency (percentage). BMI = Body Mass Index; SOFA = Sequential Organ Failure Assessment; APACHE II = Acute Physiologic Assessment and Chronic Health Evaluation II; FiO_2 = Inspired fraction of oxygen; PEEP = Positive End-Expiratory Pressure; PBW: Predicted Body Weight; PaO_2: partial pressure of oxygen in arterial blood; $PaCO_2$: partial pressure of carbon dioxide in arterial blood; LDH: lactate dehydrogenase; LOS = Length of stay; [a] Patients intubated same day of ICU admission; [b] values refer to patients intubated on the same day of ICU admission.

Table 2. Physiologic variables before, during and after prone positioning (n = 78).

Variables	Baseline	Prone	Supine	p-value
PEEP (cmH_2O)	14 [12 - 15]	14 [12 - 15]	14 [12 - 15]	0.679
FiO_2 (%)	70 [60 - 90]	60 [50 - 70]*	60 [45 - 80]*	< 0.001
Tidal Volume/PBW (mL/kg)	6.8 [6.1 - 7.6]	6.7 [6.2 - 7.3]	6.8 [6.2 - 7.4]	0.619
Driving Pressure (cmH_2O)	11 [10 - 14]	11 [10 - 14]	11 [9 - 14]	0.147
Plateau Pressure (cmH_2O)	25 [22 - 28]	24 [23 - 27]	24 [23 - 28]	0.324
Respiratory Rate (breaths/min)	20 [18 - 22]	22 [20 - 24]*	22 [20 - 24]*	< 0.001
Minute Ventilation (L/min)	9.4 [7.7 - 11.0]	9.6 [8.3 - 11.2]	9.9 [8.2 - 11.2]	0.052
Corrected Minute Ventilation (L/min)	12.6 [9.8 - 15.2]	12.6 [9.5 - 15.7]	12.2 [10.3 - 14.9]	0.881
$PaCO_2$ (mmHg)	53 [45 - 60]	53 [43 - 59]	52 [46 - 60]	0.302
Respiratory System Compliance (mL/cmH_2O)	43 [31 - 50]	42 [35 - 48]	41 [34 - 48]	0.943
PaO_2/FiO_2 ratio	98 [72 - 121]	158 [112 - 220]*	128 [87 - 174]*§	< 0.001
Ventilatory Ratio	2.0 [1.6 - 2.4]	2.0 [1.5 - 2.5]	1.9 [1.6 - 2.5]	0.881

Data are expressed as median [interquartile range]. PEEP = Positive End-Expiratory Pressure; FiO_2 = fraction of inspired oxygen; PBW = Predicted Body Weight; $PaCO_2$ = partial pressure of carbon dioxide in arterial blood. * $p < 0.05$ *vs.* Baseline; § $p < 0.05$ *vs.* Prone.

Table 3. Patients' characteristics at admission in ICU and outcome divided by Responders vs Non-Responders

Variables	Overall (n = 78)	Non responders (n = 17, 22%)	Responders (n = 61, 78%)	p-value
Males, no. (%)	61 (78)	13 (77)	48 (79)	0.845
Age (years)	62 [51 - 68]	56 [51 - 66]	62 [52 - 68]	0.389
BMI (kg/m^2)	27 [25 - 31]	26 [24 - 31]	27 [26 - 31]	0.670
SOFA Score	4 [3 - 5]	4 [3 - 5]	4 [4 - 5]	0.294
APACHE II Score	10 [8 - 12]	11 [8 - 14]	10 [8 - 12]	0.620
Intubated, no. (%) [a]	75 (96)	16 (94)	59 (97)	0.622
Respiratory Rate (breaths/min) [b]	20 [18 - 22]	19 [18 - 22]	20 [17 - 22]	0.813
FiO_2 (%) [b]	75 [60 - 90]	80 [60 - 88]	70 [60 - 90]	0.839
PEEP (cmH_2O) [b]	14 [12 - 15]	14 [11 - 14]	14 [12 - 15]	0.662
PaO_2/F_IO_2 ratio [b]	111 [83 - 164]	99 [72 - 150]	114 [85 - 168]	0.419
ARDS severity, no. (%) [b]				
Mild	10 (13)	2 (13)	8 (14)	0.721
Moderate	34 (45)	6 (38)	28 (48)	
Severe	31 (41)	8 (50)	23 (39)	
Tidal Volume/PBW (mL/kg) [b]	7.0 [6.4 - 7.8]	7.2 [6.2 - 7.9]	7.0 [6.4 - 7.8]	0.707
Plateau Pressure (cmH_2O) [b]	25 [22 - 27]	27 [24 - 28]	24 [22 - 27]	0.043
Driving Pressure (cmH_2O) [b]	12 [9 - 14]	14 [12 - 15]	12 [8 - 13]	0.022
Respiratory System Compliance (mL/cmH_2O) [b]	42 [32 - 53]	34 [30 - 45]	45 [34 - 56]	0.018
pH	7.36 [7.31 - 7.41]	7.33 [7.29 - 7.42]	7.37 [7.32 - 7.41]	0.244
PaO_2 (mmHg)	78 [70 - 95]	76 [68 - 90]	80 [70 - 99]	0.443
$PaCO_2$ (mmHg)	47 [40 - 56]	50 [39 - 58]	47 [41 - 55]	0.417
LDH (units/L)	414 [307 - 490]	418 [329 - 485]	400 [301 - 490]	0.620
ICU mortality, no. (%)	34 (44)	11 (65)	23 (38)	0.047
Hospital mortality, no. (%)	34 (44)	11 (65)	23 (38)	0.047
ICU LOS (days)	18 [11 – 34]	18 [12 – 47]	19 [11 – 33]	0.981
Hospital LOS (days)	36 [17 – 58]	32 [14 – 47]	39 [21 – 61]	0.295

Mechanical Ventilation (days)	19 [11 – 35]	16 [11 – 35]	19 [11 – 35]	0.832

Data are expressed either as median [interquartile range] or as frequency (percentage). BMI = Body Mass Index; SOFA = Sequential Organ Failure Assessment; APACHE II = Acute Physiologic Assessment and Chronic Health Evaluation II; FiO_2 = Inspired fraction of oxygen; PEEP = Positive End-Expiratory Pressure; PBW: Predicted Body Weight; PaO_2: partial pressure of oxygen in arterial blood; $PaCO_2$: partial pressure of carbon dioxide in arterial blood; LDH: lactate dehydrogenase; LOS = Length of stay; [a] Patients intubated same day of ICU admission; [b] values refer to patients intubated on the same day of ICU admission

Figures

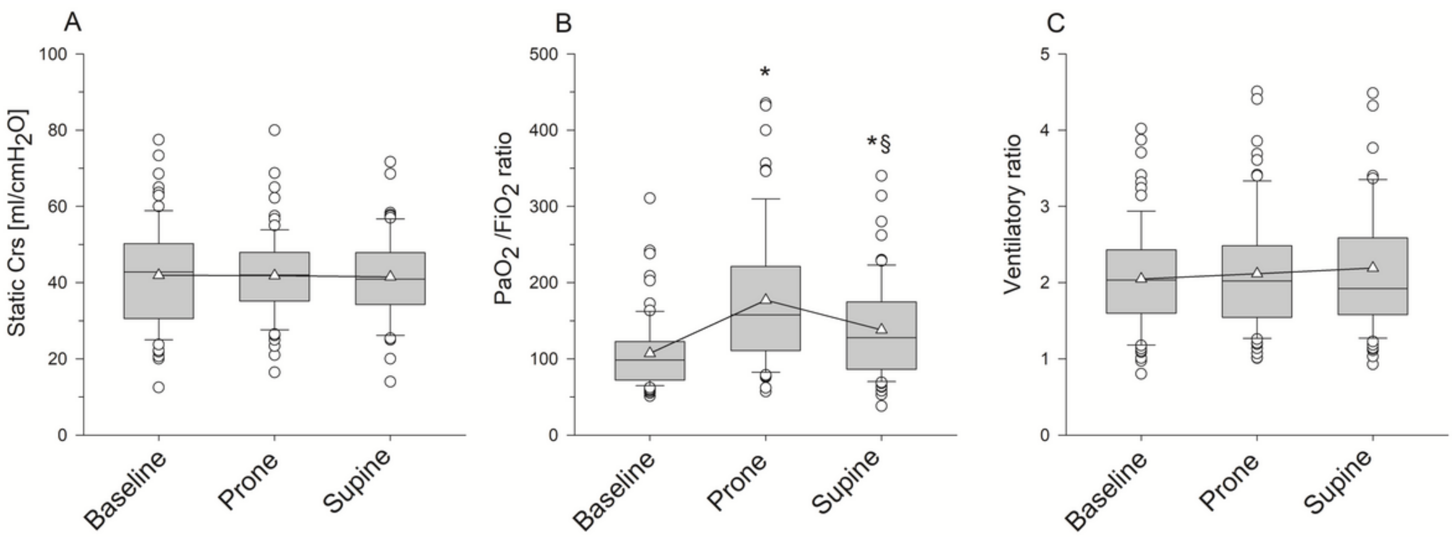

Figure 1

Physiological parameters’ changes during the first session of prone positioning.

resp_no_resp_PF_20>=20 mmHg

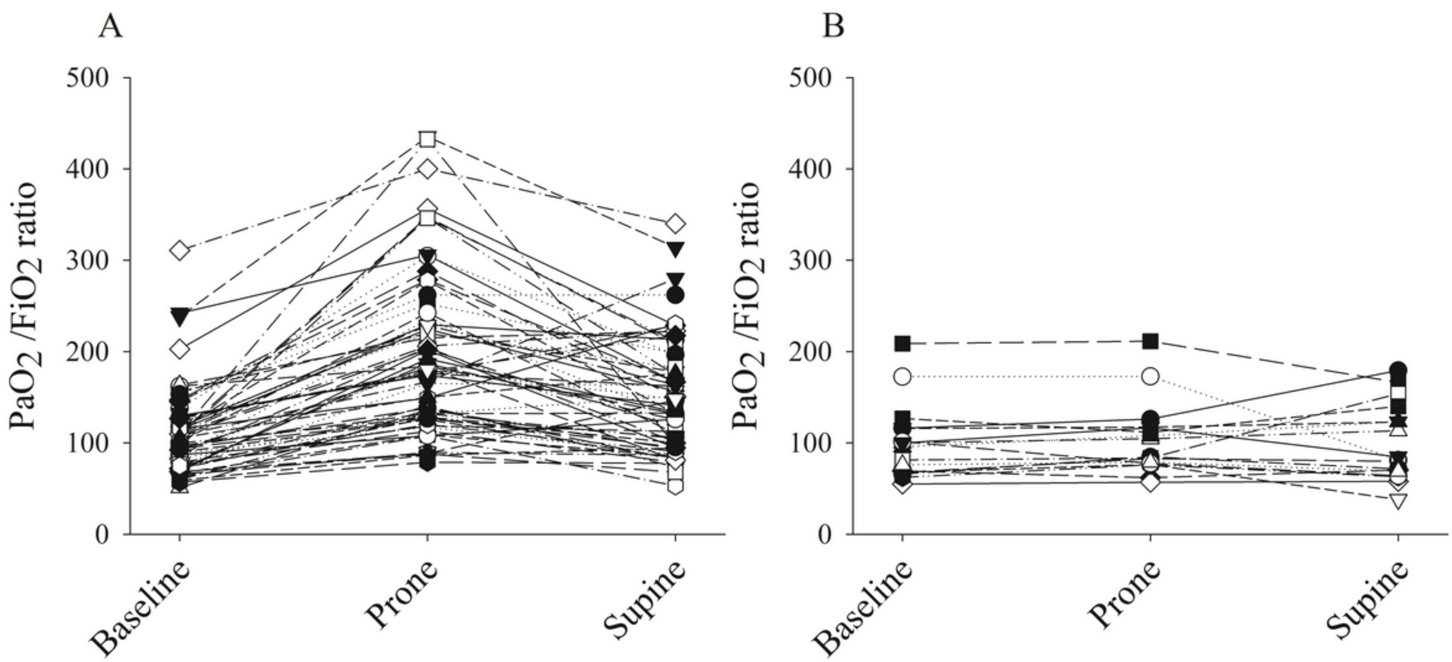

Figure 2

Individual variations in PaO2/FiO2 ratio in Responders and Non-Responders during the first session of prone positioning.

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