1. Article Title:

Effectiveness of prone positioning in non-intubated ICU patients with moderate to severe ARDS by COVID-19

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4.Short title: Prone positioning in non-intubated ICU patients with ARDS by COVID-19

5. Prior Presentations: No

6. Acknowledgments: The authors thank all physicians and residents of the Department of Anesthesiology and Intensive Care Medicine, Hospital Clínico Universitario Santiago de Compostela. Spain.

8. Summary Statement: PP improves oxygenation and may avoid intubation in awake ICU patients with ARDS by COVID-19.

9. Funding Statement: No funding provided.

10.Support: Support was provided solely from institutional and departmental sources.

11. Conflicts of Interest: The authors declare the absence of conflict of interests.

12. Keywords: COVID-19, Prone positioning (PP), severe respiratory distress, acute respiratory distress syndrome (ARDS).

13. Word Count: Abstract: 406, Introduction: 171, Discussion: 469, Overall: 1537

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Effectiveness of prone positioning in non-intubated ICU patients with moderate to severe ARDS by COVID-19

ABSTRACT:

Background: In the treatment for severe acute respiratory distress syndrome (ARDS) from Coronavirus Disease 2019 (COVID-19), the World Health Organization (WHO) recommends prone positioning (PP) during mechanical ventilation for periods of 12-16 hours per day to potentially improve oxygenation and survival. In this prospective observational study, we evaluated the ability of long PP sessions to improve oxygenation in awake ICU patients with moderate or severe ARDS due to COVID-19.

Methods: The study was approved by the ethics committee of Galicia (code No. 2020-188), and all patients provided informed consent. In this case series, awake patients with moderate or severe ARDS by COVID-19 admitted to the Intensive Care Unit (ICU) at University Hospital of Santiago from March 21 to April 5, 2020 were prospectively analyzed. Patients were instructed to remain in PP as long as possible, until the patient felt too tired to maintain that position. Light sedation was administered with dexmedetomidine. The following information were collected: number and duration of PP sessions, StO2 and blood gases before, during and following a PP session, need of mechanical ventilation, duration of ICU admission and ICU outcome. Linear mixed effects models (LMM) were adjusted to estimate changes from baseline with a random effect for patient.

Results: Seven patients with moderate or severe ARDS by COVID 19 were included. All patients received at least one PP session. A total of 16 PP sessions were performed in the 7 patients during the period study. The median duration of PP sessions was 10 hours. Dexmedetomidine was used in all PP sessions. Oxygenation increased in all sixteen sessions performed in the seven patients. The ratio of arterial oxygen partial pressure to fractional inspired oxygen (PaO2/FiO2) significantly increased during PP (change from baseline and CI 95%: 110.42 [28.173 – 192.67]) and after PP, albeit not significantly (change from baseline, CI 95%: 37.7 [-1.57 – 77.07]) compared with previous supine position. Similarly, tissue oxygenation underwent a small improvement during PP (change from baseline 2.63% [CI 95% 1.396 – 3.87]) without significant changes after PP. Two patients required intubation. All patients were discharged from the ICU.

Conclusions: We found that PP improved oxygenation in ICU patients with COVID-19 and moderate or severe ARDS. PP was relatively well tolerated in our patients and may be a simple strategy to improve oxygenation trying to reduce patients in mechanical ventilation and the length of stay in the ICU, especially in COVID-19 pandemic.

KEY POINTS

Question: Can prone positioning improve oxygenation and avoid intubation in non-intubated ICU patients with moderate or severe ARDS by COVID-19?

Findings: In this prospective observational study including seven non-intubated patients admitted to the ICU with COVID-19 and moderate or severe ARDS, prone positioning improved oxygenation in all patients and intubation was avoided in 5 of them.

Meaning: PP may be possible, economic and simple strategy to improve oxygenation trying to reduce patients in mechanical ventilation and the length of stay in the ICU, especially in COVID-19 pandemic.

GLOSSARY

COVID-19 = Coronavirus Disease 2019

ICU = intensive care unit

WHO = World Health Organization

PP = prone positioning

ARDS = acute respiratory distress syndrome

StO2 = tissue O2 saturation

PaO2/FiO2 = ratio arterial partial pressure of oxygen/fraction of inspired oxygen

PaO2 = arterial partial pressure of oxygen

PaCO2 = partial pressure of carbon dioxide

FFP3 = filtering face pieces

IQR = interquartile range

LMM = Linear mixed effects models

CI = confidence intervals

SE = standard error

SAOS = sleep apnea obstructive syndrome

APACHE II = Acute Physiology and Chronic Health Evaluation II score

Introduction

Since the emergence of the 2019 novel coronavirus (SARS-CoV-2) infection in December 2019, the Coronavirus Disease 2019 (COVID-19) has rapidly spread across the globe. The clinical spectrum of patients with COVID-19 ranges from asymptomatic or mild symptoms to critical disease with a high risk of mortality. In particular, of the incidence of acute respiratory distress syndrome (ARDS) in patients hospitalized with COVID-19 can range from 17-30% (1-2). Some of these patients with ARDS (20-30%) may develop respiratory failure 10-11 days after the onset of symptoms requiring ICU admission and mechanical ventilation.[1-2]

In treatment for severe acute respiratory distress syndrome (ARDS) associated with COVID-19 one option is prone positioning (PP) during mechanical ventilation. The World Health Organization (WHO) recommends its use for periods of 12-16 hours per day because may improve oxygenation and survival.[3-4]

The objective of this prospective observational study was to evaluate the effectiveness of the PP sessions to improve oxygenation and assess the incidence of tracheal intubation and mechanical ventilation in patients with moderate or severe ARDS by COVID-19.

Methods

We prospectively evaluated patients admitted to the Intensive Care Unit (ICU) at Clinical University Hospital Santiago of Compostela from March 21 to April 5, with laboratory-confirmed COVID-19 disease who had moderate or severe ARDS. The study protocol was approved by the ethics committee of Galicia (code No. 2020-188), and all participating subjects provided informed consent.

Patients were enrolled if they met the following criteria: 18 years of age or older, ability to self-prone, and moderate or severe ARDS as defined the World Health Organization (moderate ARDS: 100 mmHg < PaO2/FiO2 ≤ 200 mmHg; severe ARDS: PaO2/FiO2 ≤ 100 mmHg).

Exclusion criteria were inability to collaborate with PP or refusal, unstable hemodynamic status, patients with moderate or severe ARDS needing intubation and mechanical ventilation. We considered that patients needed intubation when they had signs of respiratory fatigue (respiratory rate > 30, PaCO2 > 60 mmHg, pH < 7.3, and obvious accessory respiratory muscle use), unstable hemodynamic status, lethargy, or unconsciousness.

All patients were monitored with continuous electrocardiogram, oxygen saturation, and invasive arterial blood pressure. All physicians caring for patients wore standard personal protective equipment (filtering face pieces (FFP3) mask, surgical cap, goggles, surgical gown, and double gloves). Patients were instructed to remain in PP until they felt too tired to maintain that position. If the patient needed it, light sedation with dexmedetomidine 0.2–0.8 mcg/kg/hour was administered. The following information were collected: age, sex, coexisting disorders, Acute Physiology and Chronic Health Evaluation II score (APACHE II), treatments (oxygen therapy, antibiotics, antivirals, corticosteroids, others), tissue O2 saturation (StO2) and blood gases (PaO2, PaO2/FiO2, PaCO2) in ICU admission, number and duration of PP sessions, StO2 and blood gases before, during and following a PP session, need of mechanical ventilation, duration of ICU admission and ICU outcome.

Data consisted on several 1-4 prone procedures per patient and several measurements per procedure. Linear mixed effects models (LMM) were adjusted to estimate changes from baseline to account for the inherent within-patient correlation across the multiple measurements of the outcome. The outcome

variables for the six models were PaO2, PaO2/FiO2 and StO2. The fixed effects for each outcome were either pre-prone versus prone status, or pre-prone versus post-prone status. We included a random effect for patient. No other covariables were added. The variables reported for the LMM were the intercept (baseline estimate) and change from baseline estimates and 95% confidence intervals (CI 95%) as well as the intercept standard error (SE). The statistical significance criterion was based on the CI values, depending on whether the values of the CI 95% crossed zero (non-significant), were both positive (significant increase) or both negative (significant decrease). Descriptive results were presented as median and interquartile range (IQR).

To assess study viability in a setting of high workload during the pandemic peak, sample size was estimated beforehand of the study for a simple, binary outcome of improvement versus non-improvement in PaO2/FiO2. We estimated that 12 pairs of measurements would be needed to detect a 70% minimum increase and a 5% maximum decrease (up to 5% of all patients) in PaO2/FiO2 from pre-prone to prone positioning, of at least 30 mmHg, with an error alpha of 5%, and a 80% power (two-tailed), using a McNemar Chi-squared test. After data collection, the main outcome measure was later modified as the change in PaO2/FiO2 from baseline to prone-positioning, to account for within-patient correlation in a mixed model with random effects.

All analyses were conducted in Rv.3.6 6 (R Core Team, Vienna, Austria)) using the longpower (Donohue 2020), lme4 (Bates 2015) and dplyr (Wickham 2020) packages

Results

Seven awake patients with moderate or severe ARDS by COVID-19 were included during the period study. Four were female, and the mean age was 64.8 years. Patients´ characteristics and clinical ICU course of the seven patients are summarized in table 1 and Figure 1.

All patients were treated with lopinavir/ritonavir, hydroxychloroquine, azithromycin, and supportive therapies. Four patients received tocilizumab and four patients received corticosteroids. All patients received at least one PP session. A total of 16 awake PP sessions were performed in the 7 patients during the period study (table S1 in the Supplementary Appendix, Fig 1). The median duration of PP sessions was 10 hours. Sedation with dexmedetomidine (0.2–0.8 mcg/kg/hour) was used in all patients.

PP improved oxygenation during all sixteen sessions performed in the seven patients (table 2, table S1 in the Supplementary Appendix). PaO2/FiO2 increased during PP (206.8 [181 – 226.2] compared with previous supine position (114 [89.3 – 165.3]); mean difference and CI 95%: 110 [15.1 - 205.75]; change from pre-PP 110.42 mmHg with CI 95%: [28.173 – 192.67]). PaO2/FiO2 also increased after PP (160 [101.4 – 204.3]) compared with previous supine position (114 [89.3 – 165.3]; mean difference and CI 95%: 37.8 [5.46 – 70.03]). However, the change from pre-PP 37.75 with CI 95% [-1.57 – 77.07] was not significant. Similarly, tissue oxygenation underwent a small improvement after prone positioning (change from baseline 2.63% [CI 95% 1.396 – 3.87]) without significant changes in pre-PP versus post-PP (change from baseline 0.59% [-1.51 - 265.18]).

Two patients required intubation two hours after a PP session due to respiratory fatigue, tachypnea, and accessory respiratory muscle use. After intubation, PP for long periods of time (>16 hours) was used in these two patients (Figure 1). Figure 1 provides representative information of outcomes for individual patients included in the study. All seven patients were discharged from the ICU.

Discussion:

The WHO recommends the use of prone ventilation for 12-16 hours per day in the management of intubated patients with severe ARDS due to COVID-19.[3] PP is an adjunct strategy in patients with ARDS and may improving oxygenation and survival.[4] Potential explications for this improved oxygenation are reduction of ventilation/perfusion mismatch, a more homogeneous distribution of transpulmonary pressure along the ventral-to-dorsal axis in PP compared with supine position and recruitment of non-aerated dorsal lung regions of the lung.[4-8] In theory, many of the mechanisms that would explain an improve of oxygenation with PP in intubated patients would also apply to awake patients with ARDS.[9-11] Ding et al.[11] observed that early application of PP combined with non-invasive ventilation or high-flow nasal cannula in non-intubated patients with moderate to severe ARDS and StO2 >95% may avoid the need for intubation. Similarly, Scaravilli et al.[9] observed, in a retrospective study of fifteen non-intubated ICU patients with hypoxemic acute respiratory failure, that PP improved oxygenation. The duration of PP in these two studies lasted between 2-3 hours. In the present investigation, we observed that PP improved oxygenation in awake ICU patients with COVID-19 and moderate to severe ARDS. Patients tolerated long periods of PP (10 hours) relatively well with only light sedation with dexmedetomidine. Such an approach would be particularly useful in COVID-19 due to concern regarding ventilator adequacy.[12] PP in awake ICU patients with ARDS may be a potential strategy to improve oxygenation and allow patients time to recover lung function. Unlike PP in intubated patients with mechanical ventilation which is complex and requires several operators to perform it safely, the PP in awake ICU patients is easier. The patient may turn themselves prone or with the help of one operator. Recently, Sun et al.[13] described their experience in managing COVID-19. They also attempted awake prone positioning observing significant effects in improving oxygenation. According to our experience, we recommend it if the patient has no signs of respiratory fatigue or was not hemodynamically stable.

The present study has some limitations. First, the study was performed in a single center, however, it is easily deployed in other centers. Second, although we observed an improvement in oxygenation during the PP sessions, we were not able to determine the optimal duration and frequency of PP. We assume that similarly to mechanically ventilated patients with severe ARDS from COVID-19 where 12-16 hours of prone positioning are suggested, in an awake patient with moderate or severe ARDS, a longer duration, may likewise improve oxygenation. Third, the small sample size does not permit the evaluation of the effect of PP on important clinical outcomes such as intubation or mortality. We hope that our results can contribute meaningful information to clinical teams, to design and conduct further randomized assessment of this intervention, facilitating its routine use if proven beneficial.

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FIGURA 1 LEGEND: Outcomes for individual patients included in the Case Series

Table 1: Clinical Characteristics of 7 ICU patients with moderate or severe distress by COVID-19 where PP awake sessions were used.

Table 1: Clinical Characteristics of 7 ICU patients with moderate or severe ARDS by COVID-19 where PP awake sessions were used							
Characteristics	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Age (yr)	53	70	49	67	73	77	58
Sex	Female	Male	Male	Female	Female	Male	Female
APACHE II score	12	10	11	19	21	16	10
PaO2/FiO2 in ICU admission (mmHg)	73	158	155	110	120	185	167
PaO2 in ICU admission (mmHg)	65	63	62	55	61	65	53
StO2 in ICU admission (%)	93	93	92	90	85	85	84
Chronic medical illness	hypothyroidism dyslipidemia	Hypertension Obesity SAOS	Hypertension Obesity	Obesity	No	Hypertension Diabetes	Asthma
Additional therapy							
Tocilizumab	Yes	Yes	Yes	Yes	No	No	No
Glucocorticoids	Yes	Yes	No	No	No	Yes	Yes
Clinical ICU course							
Number of PP sessions	3	4	2	2	1	2	2
Median duration of PP sessions (hours)	13	6	12	9	12	12	4
Longest duration of PP session	15	9	15	13	12	12	4
Need of mechanical ventilation (days)	Yes (8 days)	No	No	No	Yes (6 days)	No	No
Duration of ICU admission (days)	13	10	7	6	10	6	4
ICU outcome	Discharge	Discharge	Discharge	Discharge	Discharge	Discharge	Discharge

PP = prone position. SAOS: sleep apnea obstructive syndrome; APACHE II: Acute Physiology and Chronic Health Evaluation II score, ICU: intensive care unit

Table 2: Arterial blood gas analyses during the different study periods.

Variable	PRE (n=16)	PRONE (n=16)	POST (n=16)	Mean difference [95% CI]	LMM Intercept (SE) [95%CI]	LMM change [95%CI]
StO2	96 [94.3 – 96.3]	97.8 [97.2 – 99.4]		2.63 [1.24, 4.03]	95.15 (0.88) [93.347; 96.93]	2.63 [1.396; 3.87]
StO2	96 [94.3 – 96.3]		96.4 [95.3 – 97.8]	0.59 [-2.03, 3.21]	95.24 (0.79) [93.652; 96.77]	0.59 [-1.51; 265.18]
PaO2 (mmHg)	81.4 [66.7 – 84]	115 [104.1 – 185]		68.3 [16.35, 120.28]	80.96 (13.83) [53.922; 108]	65.18 [26.27; 104.1]
PaO2 (mmHg)	81.4 [66.7 – 84]		84.4 [80 – 92.6]	7.36 [-1.52, 16.25]	82.27 (9.26) [63.265; 101.31]	7.30 [-0.44; 15.04]
PaO2/FiO2	114 [89.3 – 165.3]	206.8 [181 – 226.2]		110 [15.1, 205.75]	138.19 (38.88) [61.315; 218.43]	110.42 [28.17; 192.67]
PaO2/FiO2	114 [89.3 – 165.3]		160 [101.4 – 204.3]	37.8 [5.46, 70.03]	129.55 (19.79) [89.948; 168.76]	37.75 [-1.57; 77.07]

Table 2: Data in columns 2-4 presented as median and [interquartile range].

PRE: previous to prone positioning. PRONE: during prone positioning. POST: post-prone positioning. LMM: linear mixed model. SE: standard error. 95% CI: 95% confidence interval.

Mean difference [95% CI]: mean of the differences between the baseline status, and either prone positioning or post-prone.

LMM Intercept (SE) [95%CI]: baseline mean values after linear mixed modeling with random effects, to account for within-patient correlation.

LMM change [95%CI]: change from baseline after linear mixed modeling with random effects, to account for within-patient correlation.

StO2: the median StO2 was 96% pre-prone, and the mean of the differences between pre-prone and prone was 2.63. After adjusting for within-patient correlation, the increase in StO2% ranged from 1.396 to 3.87%, with a point estimate of 2.63%.

Figure 1

Click here to access/download;Figure;grafico PP.pptx

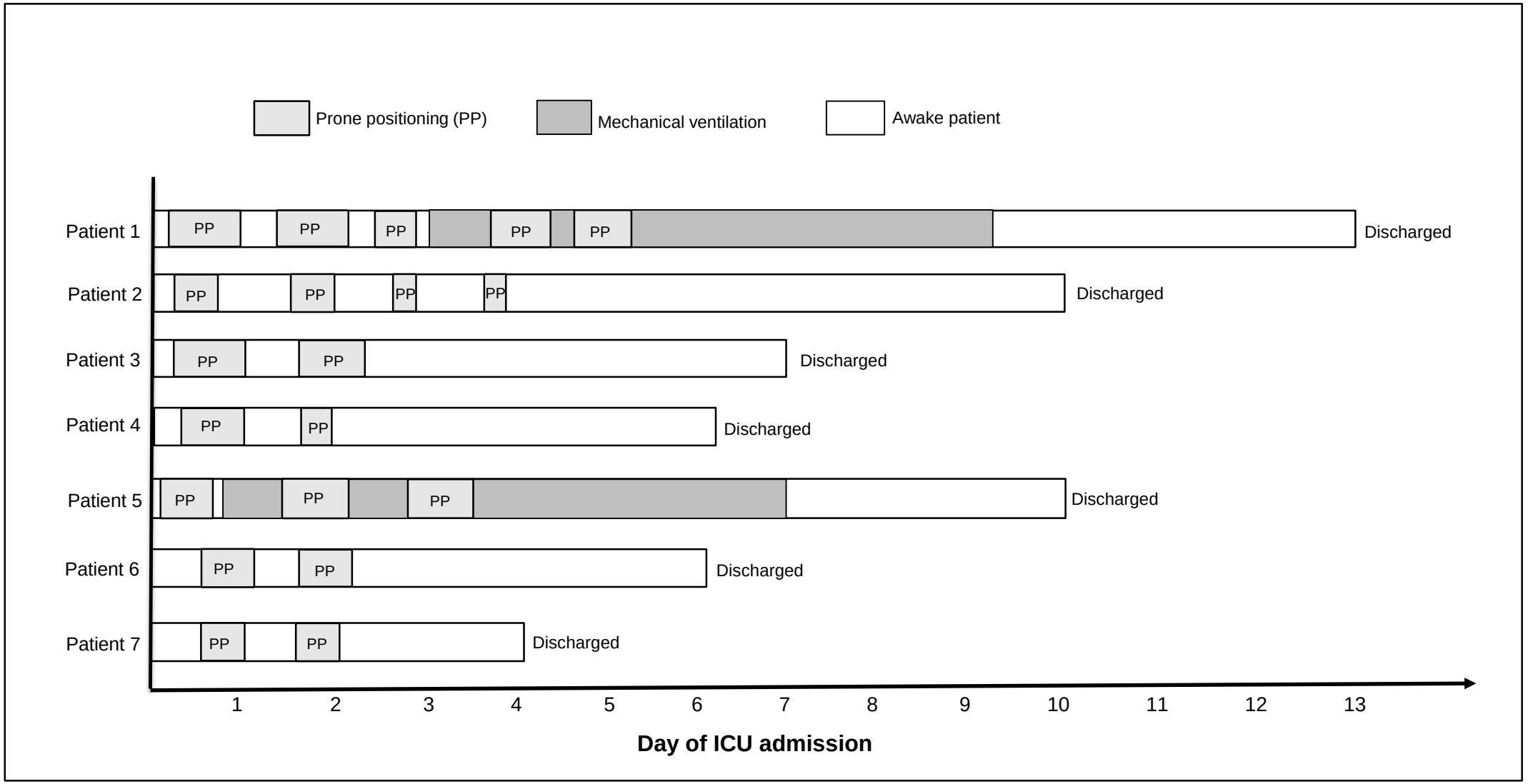

Table S1

Table S1: Oxygenation, hours, FiO2, PaO2/FiO2, PaO2, PaCO2 during all sixteen sessions performed in the seven patients

	Session PP	**Hours**	FiO2 pre	pO2 pre	pCO2 pre	**pO2/FiO2 pre**	**StO2 pre**	**FiO2 prono**	**pO2 prono**	**pCO2 prono**	**pO2/FiO2 prono**	**StO2 prono**	FiO2 post	pO2 post	pCO2 post	**pO2/FiO2 post**	**StO2 post**
Patient 1	1	**15**	0,9	65,4	35,5	**72,67**	**93,4**	0,9	200	34,5	**222,2**	**99,3**	0,9	63,3	35,1	**70,33**	**93,4**
Patient 1	2	**14**	0,9	63,3	35,1	**70,33**	**93,4**	0,9	185	35,4	**205,55**	**99,4**	0,9	82,9	38,7	**92,11**	**96,2**
Patient 1	3	**9**	0,9	78,6	38,7	**87,33**	**95,2**	0,9	204	33,4	**226,66**	**99,4**	0,8	92,9	59,8	**116,12**	**93,7**
Patient 2	4	**8**	0,5	54	41	**108**	**86**	0,5	68,2	45,5	**136**	**93,9**	0,9	88	45	**98**	**98**
Patient 2	5	**9**	0,4	92,2	46,9	**225**	**96,3**	0,4	79,2	45,5	**198**	**95,4**	0,36	84,4	40,6	**266**	**96,6**
Patient 2	6	**3**	0,9	91,8	29,4	**102**	**97,5**	0,9	98	45	**108,88**	**97,2**	0,9	92,3	36,5	**102,55**	**97,3**
Patient 2	7	**3**	0,9	81,6	41,6	**90**	**96,2**	0,5	98	38	**196**	**98**	0,4	90,2	46,9	**225**	**96,3**
Patient 3	8	**9**	0,5	82,2	41,5	**164,4**	**96,1**	0,5	185	35,4	**205**	**99,4**	0,5	80	41,2	**160**	**95,5**
Patient 3	9	**15**	0,5	67,9	34,8	**135,8**	**94,4**	0,5	101,4	45,2	**208**	**97,7**	0,5	102,7	41,4	**205,4**	**97,8**
Patient 4	10	**5**	0,9	151,6	26,9	**152**	**98,9**	0,4	112,2	28,8	**280**	**98,2**	0,5		28	**196**	**98**
Patient 4	11	**13**	0,4	96	43	**240**	**96**	0,4	116,9	47,6	**292**	**96,4**	0,4	158	33	**395**	**99,2**
Patient 5	12	**12**	0,5	61	40,6	**120**	**99,6**	0,4	349,5	39,9	**873**	**99,8**	0,3	49,3	40	**176**	**86**
Patient 6	13	**12**	0,5	84,1	28	**168**	**94,1**	0,5	113	35	**226**	**97,6**	0,9	75	37	**83**	**95,2**
Patient 6	14	**12**	0,9	81,4	28	**90**	**96,3**	0,9	99,9	35,4	**110**	**97,1**	0,5	102,7	36,4	**204**	**97,2**
Patient 7	15	**4**	0,9	75,3	37,6	**83**	**94,9**	0,9	118,7	39,8	**130**	**97,6**	0,9	82,2	42,5	**131**	**95,3**
Patient 7	16	**4**	0,5	84	28	**168**	**96**	0,5	113	35	**226**	**100**	0,5	80	37	**160**	**98**