Extended Prone Position Trial

Effect of Continuous Prolonged Prone Position versus Intermittent Daily Prone Position on Mortality in ARDS Patients: A Multicenter Randomized Controlled Trial

Table of Contents

I. Rationale

A landmark epidemiological study performed in 50 countries in 2015 revealed that the Acute Respiratory Distress Syndrome (ARDS) accounted for 10% of all ICU admissions with an associated mortality of 40% [1]. During the Covid-19 pandemics these numbers rose to unprecedented levels as most patients admitted to ICU and connected to mechanical ventilation had Covid-19 associated ARDS with an associated mortality that ranged between 37 and 58% [2]. Although the Covid-19 pandemic is waning, ARDS is expected to remain a major challenge for the health system given the continuing threats posed by respiratory viruses.

The management of ARDS still relies largely on supportive therapy such as invasive mechanical ventilation [3]. Through decades of research, delivery of mechanical ventilation has been refined and clinical outcomes consistently improved. The current concept of protective mechanical ventilation aims to prevent ventilator-induced lung injury (VILI). For patients with moderate-severe ARDS[4], defined as PaO2/FiO2 ratios below 150, the use of prone position has shown to be a fundamental intervention [5], and it became one of the most relevant pillars of the ICU management during the recent Covid-19 pandemics [6, 7]. Two relevant trends were observed during the Covid-19 pandemics related to prone position: first its use expanded remarkably, and second, there were several centers which reported extending prone sessions beyond 24 hours.

In the following sections we will analyze first the effects of prone position on ARDS pathophysiology and their potential relation to the extension of prone sessions. Second, we will discuss the clinical evidence for the use of prone position in ARDS with particular emphasis on the role of prone session duration in the historic development of this intervention. Third, we will review the experience reported up to now with the use of extended prone sessions, highlighting the Chilean experience

during the recent Covid-19 pandemics, which constitutes the basis for the present study.

Effects of prone position on the pathophysiology of ARDS

One of the most obvious and consistent effects of prone position is an improvement in oxygen exchange which is observed in most ARDS patients subjected to prone position [8, 9]. The increase in oxygenation induced by prone position is mainly explained by an improved ventilation-perfusion matching because of recruitment of dorsal lung regions and redistribution of ventilation from the less perfused ventral lung regions, towards the better perfused dorsal regions [10-13].

The increase in oxygenation after placing patients in prone position is progressive and can continue to improve well after the first 24 hours [14, 15]. However, after turning patients back to supine position the improvement in oxygenation is partially lost in most patients [5, 16, 17]. Interestingly, it has been shown that the more prolonged the prone session, the more persistent is the improvement in oxygenation when returning patients to supine [18]. These complex temporal dynamics of the physiologic changes induced by prone position may be explained by recent findings of studies that compared early and late effects of prone position [13, 19]. These studies revealed that recruitment of dorsal regions induced by prone position occurs slowly throughout the prone session and that ventilation-perfusion matching continues to improve towards the end of a one-day prone session. Although the effects of prone position on gas exchange are evident at the bedside and are the most appealing for clinicians, a post-hoc analysis of the PROSEVA trial found no relation between changes in gas exchange induced by prone position and survival [9]. Experts agree that the favorable impact of prone position on survival is due to its ability to prevent VILI, rather than its effect on oxygenation [3, 20-22].

Several physiologic studies have shown through advanced imaging and physiologic techniques, that prone position can attenuate the mechanisms leading to VILI. First, prone position may induce recruitment of previously collapsed lung regions, mainly at the dorsal areas, which we demonstrated by studying the effect of prone position with computed tomography in 24 ARDS patients [23], which may result in decreased global lung strain because tidal volume can be distributed among a larger number of alveolar units, with less deformation of each alveoli. Dilken et al. recently showed in 40 Covid-19 ARDS patients treated with prone position that end-expiratory lung volume (EELV) increases progressively, while global strain decreases, throughout a 16-hour prone session [16]. Interestingly, these effects were almost completely lost within the first minutes after turning the patient back to supine position. Second, the distribution of ventilation in ARDS patients on supine is markedly heterogeneous. The dorsal regions tend to be non-aerated and most of the ventilation is directed towards the ventral regions which may be overdistended and concentrate a significant strain [24]. After turning patients to prone position, it has been consistently shown in ARDS patients with classic ARDS and with Covid-19 related ARDS that a redistribution of ventilation occurs with less overdistension of ventral areas, and an improved ventilation of the dorsal areas, all of which result in a more homogenous distribution of ventilation and less concentration of strain [13, 25, 26]. Studies with animal models of acute lung injury have confirmed that prone position, by inducing a more homogeneous distribution of ventilation, results in substantially lower lung injury and a more homogeneous distribution of the lesions, compared to supine position [27, 28]. Third, we and others have shown that prone position can decrease the repeated opening and closing of lung units [11, 23].

Although the evidence about the protective role of prone position in ARDS is compelling [22], it is usually applied in an intermittent way, with repeated daily cycles of 16 to 18 hours, alternated with variable periods of supine position which may last several hours [7], during which most of the lung protective mechanisms previously described are lost. This reflects a lack of coherence between the theoretical notion of prone position as a lung protective intervention, and the way in which it is applied in clinical practice.

Clinical trials on prone position in ARDS

The first reports of prone position in ARDS patients were published in the 70s highlighting its impressive impact on oxygenation when applied for a few hours [29]. Its use became more popular in the 90s and the first two randomized clinical trials (RCT) that evaluated the impact of prone position on mortality in ARDS were published in 2001 (Prone-Supine I) and 2004 (French multicenter 1), respectively [17, 30]. These trials were planned based on the rationale that an improved oxygenation in response to prone position should lead to an improved survival. Prone sessions were limited to 7 to 8 hours per day. The rather short duration of prone sessions was due in part to the perception of fear in the face of complications derived from keeping the patients in prone position. Both trials confirmed that prone position improved oxygenation, but they found no evidence of benefit on mortality. However, a post hoc analysis suggested a favorable trend with prone position in the most severe patients [17]. Soon later, other two trials of prone position were launched (Spanish trial and Prone-Supine II trial) but now prone sessions were extended to 17 and 20 hours per day, respectively, with a renewed rationale that prone position might prevent VILI. Although both studies showed a favorable trend in favor of prone position, there was no statistically significant difference in mortality [31, 32]. In these trials patients received an average of 7 and 10 daily sessions, respectively. Finally, the PROSEVA trial, a French RCT published in 2013 which included 466 ARDS patients, was the first trial to demonstrate a survival benefit of prone position in ARDS (16% mortality for prone at 28 days vs 32.8 % for supine, $p<0.001$) [5]. Patients randomized to prone position received daily sessions of at least 16 hours, but they were turned back to supine position every day. Sessions were repeated if the patient had a PaO2/FiO2 < 150 after returning to supine position. Patients required 4 ± 4 sessions and remained in prone 73% of the time elapsed until they no longer required prone position. Therefore, we define this strategy as intermittent daily prone position. Compared to previous trials, PROSEVA selected a more severe population (ARDS with PaO2/FiO2 persistently below 150 after 12 hours of stabilization on mechanical ventilation), at an earlier phase (< 36 hours of mechanical ventilation at inclusion), it applied a more protective ventilation with tidal volumes of 6 ml/kg, and established a more strict criteria for repeated prone sessions (PaO2/FiO2 had to fall below 150 after returning to supine) which resulted in less sessions/patient compared to the Spanish and Prone-Spine II trials. After the PROSEVA trial, a metanalysis was published which confirmed that prone position was an effective intervention to decrease mortality in ARDS, but this effect was evident only in trials which applied prone for sessions of at least 12 hours per day [33].

Regarding safety, the main adverse event related to prone position reported in most clinical trials are pressure sores, with an increased risk compared to supine position ranging from 22 to 41% [17, 30, 33-35]. Pressure sores related to prone position are generally minor (grade I or II) and occur more frequently in the face, and in the ventral surface of the thorax [36]. The other complication that has been significantly associated to prone position is tracheal tube obstruction, although this adverse event is more unfrequent [33]. In relation to other usually feared complications of prone position such as unplanned extubations, removal of central venous catheters, ventilator-associated pneumonia, or barotrauma, the analysis of clinical trials has shown no differences between patients randomized to prone or supine position [33].

Despite the compelling evidence provided by the PROSEVA trial, observational studies performed before the Covid-19 pandemic described a low use of prone position in ARDS [1, 37]. However, during the recent pandemic the use of prone position in mechanically ventilated patients who developed Covid-19 related ARDS increased to 50-76% [14, 38-41]. Although the standard duration of prone sessions continued to be 16 to 24 hours [6-8, 39, 42], due to the increased workload, many centers decided to extend prone sessions beyond 24 hours, and even for several days [14, 15, 43].

Experience with extending prone position sessions beyond 24 hours

One of the first reports of prolonged prone position in ARDS patients was from the Hospital Clínico

Universidad de Chile in 2009, which described 15 ARDS patients treated with prone position for a continuous session of 55±7 hours, with a low rate of adverse events [44]. The approach was also applied during the H1N1 pandemics at that center reporting 10 patients who received prone position for 82±49 hours with an 80% survival [45]. After the H1N1 pandemics in 2009, the use of prolonged prone position was adopted by other centers in Chile, but not in the rest of the world. Until 2019 there were only 3 other monocentric studies which reported the use of prolonged prone position: one from Korea, one from Taiwan and other from Mexico [46-48].

Since the emergence of Covid-19 a few centers decided to extend prone sessions to decrease the frequency of patient repositioning, due to the intensive workload generated by caring for an overwhelming number of patients [15, 18]. Most of the reports published up to now correspond to retrospective series of cases from single centers including between 10 and 81 Covid-19 patients, with a mean prone session duration which ranged from 29 hours to 3 days, and which focused on the feasibility and safety of prolonged prone position (Table 1). One of these studies, although retrospective, was based on a prospectively annotated registry with detailed information about prone related adverse events. In 61 patients who underwent a first prolonged prone session of 3 (2-5) days, the main adverse event was grade I to III ventral pressure sores in the chest, abdomen, or groin, which were observed in 40 patients, and were independently associated to the total time in prone position, but not to the session duration [43].

During the Covid-19 pandemics in Chile, based on the previous experience of national academic centers, prolonged prone position was recommended as a nationwide strategy for mechanically ventilated ARDS patients with PaO2/FiO2 < 150 mmHg. The protocol indicated that patients should remain in prone position for at least 48 hours and that prone sessions should be further extended, if necessary, until PaO2/FiO2 was above 200 mmHg in prone position. The rationale to set a minimal duration of 48 hours of prone position was to ensure a significant period of continuous lung protection, while the threshold for PaO2/FiO2 of 200 mmHg in prone position was established to have a reserve margin so that the patient would be turned back to supine position only after there was a high probability that no new prone sessions would be required. It is well known that most patients exhibit a decrease in oxygenation after returning to supine position. Therefore, we defined this strategy as continuous prolonged prone position, in contrast with the intermittent daily prone position applied in the PROSEVA trial. We reported this experience in the largest patient series of prolonged prone position published up to now [14]. It was a retrospective cohort study of 417 patients from 15 ICUs of Chile, who were treated with a first prone position session of 4 (3-5) days, of whom 318 (76.3%) received only one session. The main adverse event was minor pressures sores (grade I-II) in 23.9% of patients, while the most severe adverse event was unplanned extubations which occurred in 17 patients (4.2%). Even though these patients were treated in the context of a pandemics with highly strained nursing staff, the rate of adverse events observed was lower than reported in RCTs of prone position which applied the intermittent daily strategy [33]. Mortality at 90 days was 36.2% which is also lower than reported during the Covid-19 pandemics [2]. Twenty-four percent of patients received a prone session > 5 days. These patients had a higher severity at baseline, and they exhibited a higher rate of pressure sores and mortality. Although prone session duration was not independently associated to mortality or to pressure sores, for the present trial we decided to set a maximum duration of 5 days for prone sessions in the continuous prolonged prone group.

Only two observational studies of prolonged prone position have included a control group treated with conventional prone sessions (< 24 hours). One was a retrospective multicenter cohort study from the Mass General Hospitals (Boston, USA) in which prone position was applied without a protocol during the Covid-19 pandemics and the duration of sessions for each patient was defined according to the clinicians' criteria [49]. They analyzed 263 consecutive patients treated with prone position and separated them in 2 groups according to whether the duration of the first prone session was < or > than 24 hours (intermittent or prolonged). 110 patients were classified in the

intermittent prone group and received sessions of 17 (14-20) hours, while 157 were classified as prolonged prone and received sessions of 40 (17-55) hours. Mortality at 30 days was 25.5% and 34.9% in the prolonged and intermittent groups, respectively. Inverse probability treatment weights (IPTW) were used to control for potential treatment selection bias and after applying multivariable survival models, prolonged prone was associated with reduced 30-day mortality (aHR 0.47; 95% CI 0.33-0.67, P<0.001). No differences were observed in relevant complications related to prone position, including pressure sores or accidental extubations. The other was a single center prospective study from a referral center in Greece in which the decision about the duration of prone sessions was left at the criterion of the attending physician [50]. They analyzed 63 C-ARDS patients treated with prone position of whom 26 received a standard session (20 [20–22] hours) and 37 received a prolonged session (46 [40–48] hours). The mortality at day 28 was 34.6% in the standard group and 21.6% in the prolonged group (p=0.25). No differences were observed in the rate of complications. No method was applied to correct for potential treatment selection bias.

The experience reported up to now with prolonged prone position indicates that it is a feasible approach, that it allows to decrease the number of sessions and therefore the need for turning the patient repeatedly. It appears to be safe with a rate of adverse events similar to those known for daily intermittent prone positioning, and there are a couple of observational studies which suggest that it may be associated to improved survival. In addition, as discussed in previous sections, there is physiologic and clinical rationale to propose that a prolonged continuous prone positioning may be superior to the daily intermittent approach: it is a lung protective intervention, and it has been shown to be effective to decrease mortality depending on the duration of sessions. However, the quality of the evidence is still low to make any recommendation. The last Clinical Practice Guidelines issued by the European Society of Intensive Care Medicine in June 2023 recommended using prone position in patients with moderate-severe ARDS and to apply sessions ≥ 16 hours, but concerning on the impact of different durations of prone sessions above that minimum, they acknowledge it as a research gap [20]. Therefore, a prospective randomized controlled trial appears to be justified.

Table 1. Cohort studies of prolonged prone position (> 24 hours) in ARDS

Study (1st author, year)	Diagnosis	Design	Patients (n)	Session duration	Number of Sessions	Pressure sores (%)	Survival %
Chan[46], 2007	ARDS	S-P	11	> 72 hours	1 (1-1)	18.2	63.6
Romero[44], 2009	ARDS	S-P	15	55±7 hours	1 (1-1)	13.3	60
Lee K[47], 2010	ARDS	S-R	96	79±61 hours	NR	20	44
Cornejo[45], 2011	H1N1	S-R	10	82±49 hours	1 (1-2)	50	80
Hernandez[48], 2019	ARDS	S-R	7	57±17 hours	1 (1-1)	57.1	100
Carsetti[18], 2020	COVID-19	S-R	10	36 (33-39) hours	NR	NR	NR
Rezoagli[51], 2021	COVID-19	S-R	15	39±6 hours	2 (2-4)	67	67
Parker[52], 2021	COVID-19	S-R	12	57 (45-66) hours	NR	0	67
Douglas[43], 2021	COVID-19	S-R	61	3 (2-5) days	1 (1-1.5)	65.6	68.9
Lucchini[53], 2021	COVID-19	S-R	37	34 (30-41) hours	3 (2-4)	51	84
Concha[54], 2022	COVID-19	S-R	17	48±18 hours	3±1	52.9	82
Garg[55], 2022	COVID-19	S-R	10	60 (66-71) hours	2 (2-2)	10	100
Cornejo[14], 2022	COVID-19	M-R	417	4 (3-5) days	1 (1-1)	36.2	66.7
Walter[15], 2022	COVID-19	S-R	81	29 (34-42) hours	2 (1-4)	26	70
Okin[49], 2023	COVID-19	M-R-C	157	40 (27-55) hours	1 (1-2)	29.2	70.7
Karlis[50], 2023	COVID-19	S-P-C	37	46 (40-48) hours	1 (1-2)	22.2	78.4

Abbreviations: S=Single center, M=Multicenter, R=retrospective, P=prospective, C=controlled;

NR=not reported

II. Scientific and clinical relevance of the proposal

From a scientific perspective, a continuous prolonged prone position not only represents a different way of dosing the intervention, but also reflects a more comprehensive understanding of the underlying physiological mechanisms through which prone position can improve outcomes. A continuous prolonged approach appears theoretically as more appropriate if we assume that prone position is a lung protective strategy, and that interrupting a protective strategy in a period in which the patient is highly vulnerable to VILI may be detrimental.

The history of prone position in ARDS is an outstanding model for the development of clinical science in which observational studies, physiological studies and clinical trials have informed each other back and forward, with a progressive refinement of our understanding. The first studies tested prone sessions of 6 to 8 hours and failed. Later the PROSEVA trial was able to confirm the favorable effect of prone position on mortality by applying daily prone sessions of 16 hours which became the new standard. However, the recent Covid-19 pandemics proved to be a unique opportunity to challenge our limits and now the option of further extending prone sessions for several days has shown to be feasible, potentially superior, and without evident safety concerns. Several investigators have proposed that a randomized trial is now required to move forward. We plan to compare the standard approach to prone position established 10 years ago by the PROSEVA trial (which we define as intermittent daily in this proposal) versus a continuous prolonged prone position. This study represents a new opportunity to continue refining the way in which we apply this fundamental intervention.

III. Hypothesis

In patients with moderate-to-severe ARDS connected to mechanical ventilation, a continuous prolonged prone position decreases the risk of mortality compared to an intermittent daily prone position, and it is not associated to an increase in adverse events potentially related to prone position.

IV. Objectives

Primary Objective
To compare the effects of a continuous prolonged prone position versus an intermittent daily prone position on 28-day mortality, in mechanically ventilated patients with moderate-to-severe ARDS.

Secondary Objectives
To compare the effects of a continuous prolonged prone position versus an intermittent daily prone position, in mechanically ventilated patients with moderate-to-severe ARDS, on the following outcomes:

- All-cause mortality at day 90, ICU mortality and hospital mortality
- Ventilator Free Days at day 28 (VFD28). The number of VFD is defined as the number of days from the time of initiating unassisted breathing to day 28 after randomization.
- ICU-free days at day 28
- Hospital-free days at day 28 and day 90
- Use of rescue procedures such as extracorporeal membrane oxygenation (ECMO), extracorporeal CO2 removal (ECCO2R)
- Daily physiologic measurements including PaO2/FiO2, oxygenation index, ventilatory ratio, and ventilatory parameters (tidal volume, respiratory rate, total PEEP, plateau pressure,

compliance of the respiratory system) up to day 7
- Occurrence of pneumothorax through day 7
- Pressure sores at days 3 and 7, by degree and location
- Adverse events potentially related to prone positioning (displacement of endotracheal tube, vascular catheters, or gastric tube; endotracheal tube obstruction, unplanned extubation, arterial oxygen desaturation, arterial hypotension, bradychardia, cardiac arrest)

V. Methods

V.1 Study design
Randomized, multicenter, two-arm parallel-group, investigator-led clinical trial with allocation concealment and intention-to-treat analysis, comparing a strategy of continuous prolonged prone position vs. intermittent daily prone position in patients with moderate-to-severe ARDS connected to invasive mechanical ventilation. The intervention is not compatible with blinding clinicians or research personnel, but blinding to treatment assignment will be maintained for investigators conducting analysis. The study will be prospectively registered in www.clinicaltrials.gov.

V.2 Setting
The study will be conducted in 35-45 Latin American ICUs.

V.3 Trial organization and management
*Steering Committee***:** This committee will be responsible for the overall study supervision, assisting in developing the study protocol and preparing the final manuscript.

*Advisory Board***:** a committee of international experts in the field will be established that will advise the Steering Committee on different requested aspects.

*Study Coordinating committee***:** this will be the executive committee, conducting the trial in all organizational, logistic, and procedural aspects, as well as controlling the data quality.

*Data Safety Monitoring Board (DSMB)***:** The DSMB will be set up with independent epidemiologists and intensivists that will supervise the trial and provide recommendations to the Steering Committee in order to continue the trial as planned, or stop the trial based on evidence of increased mortality in the continuous prolonged prone position group compared to the daily intermittent prone position group. Interim analysis will be performed after including 33% and 66% of the planned study sample.

V.4 Ethics
The use of prone position is well validated in ARDS and both groups will receive the intervention within the terms proposed by recent guidelines [20]. Many reports have suggested that the novel approach proposed (continuous prolonged prone position) appears to be reasonably safe [14, 15, 43, 49]. Up to now there is equipoise regarding the superiority of one approach versus the other in terms of safety and efficacy [20, 49, 50].
The Institutional Review Board of each participating center must approve the study. Informed consent will be obtained from the legal authorized representative of the patient.

V.5 Eligibility criteria
Inclusion criteria:
1) Age ≥ 18 years
2) Endotracheal intubation and mechanical ventilation for less than 72 hours
3) Moderate-severe ARDS defined as:
- Within 1 week of a known clinical insult or new or worsening respiratory symptoms

- Bilateral infiltrates not fully explained by effusions, lobar/lung collapse, or nodules
- Respiratory failure not fully explained by cardiac failure or fluid overload
- PaO2/FiO2 < 150 mmHg assessed in supine position *

4) Prone positioning has been indicated by the attending physician, OR has already been initiated within the last 16 hours

**This criterion must be present in the last arterial blood gas assessment made in supine position before starting prone positioning, and obtained after a period of stabilization on invasive mechanical ventilation with PEEP ≥ 5 cmH2O and tidal volume 5 to 7 ml/kg (ideal body weight). PaO2/FiO2 assessments obtained after the patient has been turned to prone position are not considered for eligibility.*

Exclusion criteria:

1) Contraindications for prone positioning such as intracranial pressure > 20 mmHg, massive hemoptysis, recent tracheal surgery or sternotomy or abdominal surgery with an open wound, recent facial trauma or facial surgery, unstable spine, femur, or pelvic fractures, or a single anterior chest tube with air leaks
2) Patient on extracorporeal membrane oxygenation (ECMO) before randomization
3) Chronic respiratory failure requiring oxygen therapy or non-invasive ventilation (NIV)
4) Known pregnancy
5) Anticipating withdrawal of life support or shift to palliative care

Use of awake prone positioning before intubation is not an exclusion criterion.

All patients connected to invasive mechanical ventilation who have the diagnosis of ARDS, and/or have been placed in prone positioning, will be screened for eligibility. If the patient is potentially eligible (all inclusion criteria present, and none of the exclusion criteria), informed consent will be asked to the patients' legal representative.

V.6 Study endpoints

Primary outcome

The primary efficacy endpoint is all-cause mortality before or at day 28.

Secondary outcomes

- All-cause mortality at day 90, ICU mortality and hospital mortality
- Ventilator Free Days at day 28 (VFD28). The number of VFD is defined as the number of days from the time of initiating unassisted breathing to day 28 after randomization.
- ICU-free days at day 28
- Hospital-free days at day 28 and day 90
- Use of rescue procedures such as extracorporeal membrane oxygenation (ECMO), extracorporeal CO2 removal (ECCO2R)
- Physiologic measurements including PaO2/FiO2, oxygenation index, ventilatory ratio, and ventilatory parameters (tidal volume, respiratory rate, total PEEP, plateau pressure, compliance of the respiratory system) at days 1,2 ,3, 7 and 14
- Occurrence of pneumothorax through day 7
- Pressure sores at days 3 and 7 by degree and location
- Adverse events potentially related to prone positioning (displacement of endotracheal tube, vascular catheters, or gastric tube; endotracheal tube obstruction, unplanned extubation, arterial oxygen desaturation, arterial hypotension, bradycardia, cardiac arrest)

V.7 Interventions

Once recruited, all patients will be randomized to be allocated in one of two groups:

1) Continuous prolonged prone positioning: The first prone session will be extended for at least 48

hours. The patient will be turned back to supine position at 48 hours if PaO2/FiO2 ≥ 200 mmHg in prone position. If PaO2/FiO2 < 200 mmHg, the prone session will be further extended until reaching this threshold, or up to a maximum of 5 days (120 hours), after which the patient will return to supine position irrespective of PaO2/FiO2 ratio. If PaO2/FiO2 worsens and decreases < 150 mmHg after turning the patient back to supine position during the treatment period, prone positioning will be re-started with a new prone session at any time (up to day 7). The duration of repeated sessions must follow the same criteria of the first session (> 48 hours + PaO2/FiO2 ≥ 200 OR maximum of 120 hours).

2) Intermittent daily prone positioning: The first prone session will be extended until completing at least 16 hours, but then the patient will be turned back to supine position before completing 24 hours. If PaO2/FiO2 worsens and decreases < 150 mmHg after turning the patient back to supine position during the treatment period, prone positioning will be re-started with a new prone session at any time (up to day 7). The duration of repeated sessions must be ≥ 16 hours and ≤ 24 hours.

V.8 Principles of general management

Recommendations for the management of patients in both groups include:
-Prone position protocol: all participating centers must adapt the general nursing protocol for the care of patients in prone position that will be provided by the study and will be applied for both study arms. Each participating center can decide to apply prone position either by the "swimmer position", or by the complete prone position (both arms on the sides). The head rotation (and change of upper arm for swimmer position) will be scheduled every 2-4 hours. In addition, a checklist should be followed with detailed recommendations about the actions to be performed before, during and after turning patients from supine to prone position, and the preventive actions to be performed while the patient stays in prone position.
-Mechanical ventilation should initially be set in volume-controlled mode with a tidal volume of 5-7 ml/kg ideal body weight.
-Ensure adequate sedation while the patient remains in prone positioning
-Neuromuscular blockers (NMB) in continuous infusion for the first 48 hours. After the first 48 hours NMB may be prolonged if the patient remains in prone positioning.
-No specific guide for PEEP and FiO2 combinations are provided, but plateau pressures should be kept < 30 cmH2O if possible.

V.9 Safety measures

Prone positioning sessions may be interrupted at any time in case of:
-life threatening complications such as: cardiac arrest, unplanned extubation, severe hypotension or bradycardia, severe and persistent hypoxemia (SpO2 < 85%), hemoptysis.
-in case of any urgent procedure indicated by the attending team (e.g. need to place a central venous line)
-in case the patient is connected to ECMO the treatment period is concluded, but the follow-up will keep on. The use of prone position during ECMO is left at the criteria of the attending team but this indication is not part of the study protocol.
-decrease in PaO2/FiO2 > 20% relative to supine position, during two consecutive prone sessions

Prone positioning sessions may be prolonged beyond the maximal extension for each group (24 hours for intermittent daily prone position group, and 120 hours for continuous prolonged prone position group) if the PaO2/FiO2 remains below 80 mmHg despite FiO2 ≥ 0.9 and optimized PEEP. In these cases, the prone session must be interrupted and the patient turned back to supine as soon as the patients' oxygenation increases above that threshold. However, prone positioning will be resumed with a new prone session at any time if PaO2/FiO2 < 150 mmHg after turning the patient back to supine position during the treatment period (up to day 14), but the duration of repeated sessions must follow the same criteria of the first session (> 48 hours + PaO2/FiO2 ≥ 200 OR maximum of 120 hours).

V.10 Randomization
Randomization will be centralized and web-based, in a 1:1 ratio in randomly variable block sizes to conceal allocation. The allocation sequence will be computer generated, stratified by center, and stratified by COVID-19 pneumonia being responsible for ARDS or not.

V.11 Sample size
Based on the two-sided Z-test with unpooled variance, a sample size of 376 patients in each randomized group achieves a power of 80% to detect a difference between the group proportions of 28-day mortality of -10%. The 28-day mortality rate is assumed to be 45% in the *Intermittent daily prone positioning* group, and 35% in the *Continuous prolonged prone positioning* group. The significance level of the test is 0.05. Considering potential dropouts due to revocation of consent or lost to follow up, we will enroll 780 patients.

V.12 Duration of treatment period
Duration of treatment period will be limited to 7 days after randomization. If the attending physician decides to extend or initiate a new prone session after day 14 the duration of sessions will rely on clinical criteria.

V.13 Duration of follow up
Patient's status will be checked daily until day 28 or until they are discharged from the ICU if it occurs before day 28. We will also check status at day 28, day 60, day 90, and at ICU and hospital discharge. A table with the detail of the patient assessments throughout the study is provided in Appendix 1.

V.14 Main statistical analysis
Statistical analyses will be conducted blinded to treatment assignment, with treatment arms denoted by letters instead of explicit labelling of intervention arms. The statistical analyses will be performed by the statistical team of HCor, Sao Paulo. The R software (https://www.R-project.org/) will be used. A detailed analysis plan will be a priori defined. Later modifications may occur before unblinding the database. A statistical analysis plan will be written in agreement with the standards as specified in the CONSORT Statement (http://www.consort-statement.org/).
All analyses will be based on the intent-to-treat (ITT) basis. The primary outcome, 28-day all-cause mortality will be compared by a chi-square test. The unadjusted treatment effect will be expressed as an absolute risk difference with 95% confidence interval. The odds ratio and 95% confidence interval will also be computed. Logistic regression will be used for an adjusted analysis where the following variables will be adjusted for: age, baseline PaO2/FiO2 ratio, severity scores.
The analyses of the durations of mechanical ventilation, ICU and hospital stay are complicated by the competing risk of mortality. Time to successful weaning from mechanical ventilation, ICU discharge and hospital discharge will each be summarized with cumulative incidence curves which account for the competing risk of death. Cause-specific Cox models will be used to test and estimate treatment effects. Other secondary outcomes which are binary will be compared with chi-square tests and summarized with risk differences and odds ratios with their associated 95% confidence intervals.

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VIII. Appendix 1. Assessments

	Eligibility	D0 Inclusion baseline	D1	D2	D3	D4	D5	D6	D7	D28	ICU discharge	Hospital discharge	Day 90
Inclusion/exclusion criteria	X												
Written informed consent (proxy)	X										X		
Intubation date	X												
ARDS onset date	X												
ARDS risk factors	X												
Randomization	X												
Charlson score		X											
APACHE II score		X											
SOFA score		X											
Height		X											
Weight		X											
Sedation assessment (RASS)		X	X	X	X	X	X	X	X				
Arterial blood gas analysis	X	X	X	X	X	X	X	X	X				
Ventilatory parameters	X	X	X	X	X	X	X	X	X		X		
Rescue therapies	X	X	X	X	X	X	X	X	X	X			
Prone position	X	X	X	X	X	X	X	X	X	X			
Pressure sore assessment					X				X				
Neuromuscular blocking agents	X	X	X	X	X	X	X	X	X	X			
Vital status	X	X	X	X	X	X	X	X	X	X	X	X	X
Ventilator-free days										X			
Steroids	X	X	X	X	X	X	X	X	X	X			
Frontal Chest X-ray	X	X											
Pneumothorax assessment		X	X	X	X	X	X	X	X				
Sedatives, analgesics	X	X	X	X	X	X	X	X	X				
Adverse events	X	X	X	X	X	X	X	X	X		X	X	