Randomized clinical trial to assess the effect of maximum alveolar recruitment plus PEEP titration vs. standard strategy (ARDSNet) on the mortality of patients with ARDS

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STUDY FLOW CHART

**Patients**
Intubated, mechanically ventilated adult patients with acute respiratory distress syndrome (ARDS) of less than 72 hours’ duration.

**Informed consent form**

**Central randomization**

**ART Strategy - Maximum alveolar recruitment and PEEP titration**

**ARDSNet Strategy (PEEP adjusted for FiO₂ according to ARDSNet table)**

**28-day follow-up**
Primary outcome: 28-day survival

**6-month follow-up**
<table>
<thead>
<tr>
<th><strong>Title</strong></th>
<th>Randomized clinical trial to assess the effect of maximum alveolar recruitment plus PEEP titration vs. standard strategy (ARDSNet) on the mortality of patients with ARDS</th>
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| **Coordinating Center** | Research Institute at Hospital do Coração (IEP-HCor)  
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Phone: +55 11 3053 6611 Extension: 8203  
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| **Study design** | Randomized, multicenter, pragmatic clinical trial with allocation concealment |
| **Bias control** | Allocation concealment with Web-based randomization; intention-to-treat analysis |
| **Primary objective** | To determine if maximum stepwise alveolar recruitment associated with PEEP titration adjusted according to static compliance of the respiratory system is able to increase 28-day survival in patients with acute respiratory distress syndrome compared to conventional treatment (ARDSNet strategy) |
| **Eligibility** | **Inclusion criteria:**  
Intubated, mechanically ventilated adult patients with acute respiratory distress syndrome (ARDS) of less than 72 hours’ duration.  
**Exclusion criteria:**  
- Age < 18 years;  
- Use of vasoconstrictor drugs in increasing doses over the past 2 hours or mean arterial pressure < 65 mmHg;  
- Contraindication to hypercapnia with intracranial hypertension or acute coronary syndrome;  
- Undrained pneumothorax or subcutaneous emphysema. |
| Treatment regimen | Maximum alveolar recruitment maneuver at bedside followed by PEEP titration adjusted according to static compliance of the respiratory system.

Tidal volume will be adjusted between 4 to 6mL/kg of predicted body weight to keep plateau pressure ≤30cmH₂O. |
| Comparator regimen | ARDSNet approach: PEEP adjusted according to FiO₂. Tidal volume will be adjusted between 4 to 6mL/kg of predicted body weight to keep plateau pressure ≤30cmH₂O. |
| Follow-up | Hospital discharge, 28 days and 6 months. |
| Endpoints | Primary outcome: 28-day survival

Secondary outcomes:
- Length of hospital stay
- Pneumothorax requiring chest tube
- Barotrauma (i.e. any new pneumothorax, pneumomediastinum or subcutaneous emphysema or pneumatocele > 2 cm)
- Ventilator-free days from day 1 to day 28
- ICU survival
- In-hospital survival
- 6-month survival |
| Sample size | This study is event-guided, and will be continued until there are 520 events (deaths within 28 days). This number of events allows detection of a hazards ratio of 0.75, with 90% power and two-tailed type I error of 5%. |
| Statistical analysis | The primary outcome will be analyzed using unadjusted Cox’s proportional hazards models and Kaplan Meier curves. |
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LIST OF ACRONYMS AND ABBREVIATIONS

ALI – Acute lung injury

AMIB – Brazilian Association of Intensive Care Medicine (Associação de Medicina Intensiva Brasileira)

ARDS – Acute respiratory distress syndrome

CPAP – Continuous positive airway pressure

ICU – Intensive care unit

IL – Interleukin

MAR – Maximum alveolar recruitment

PEEP – Positive end-expiratory pressure

$P_{\text{FLEX}}$ – Lower inflection point of the pressure-volume curve

REC – Research Ethics Committee

VILI – Ventilator-induced lung injury
1 INTRODUCTION

1.1 What is ARDS?

Acute respiratory distress syndrome (ARDS) is defined as acute onset respiratory failure, according to table 1:

<table>
<thead>
<tr>
<th>Timing</th>
<th>Onset respiratory failure within 1 week of a known clinical insult or new or worsening respiratory symptoms.</th>
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<tbody>
<tr>
<td>Chest imaging*</td>
<td>Bilateral opacities—not fully explained by effusions, lobar/lung collapse, or nodules.</td>
</tr>
<tr>
<td>Origin of edema</td>
<td>Respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (eg, echocardiography) to exclude hydrostatic edema if no risk factor presente (echocardiography or pulmonar artery occlusion pressure ≤18cmH₂O).</td>
</tr>
<tr>
<td>Hypoxemia</td>
<td>PaO₂/FiO₂ ≤ 300mmHg in arterial blood gases with PEEP or CPAP 5cmH₂O</td>
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* Chest X ray or CT

1.2 Epidemiology

The incidence of ARDS is 58.7 cases per 100,000 people/year.² Among ICU patients, 10 to 15% meet the criteria for ARDS.³⁴ The frequency of ALI among patients on mechanical ventilation is up to 20%. Most of these patients have moderate-severe ARDS (PaO₂/FiO₂ ≤ 200), and more than half of patients with PaO₂/FiO₂ initially between 200 and 300mmHg will develop moderate-severe ARDS.⁵
Mechanical ventilation, sepsis, pneumonia, shock, aspiration, trauma (especially pulmonary contusion), major surgery, massive transfusion, smoke inhalation, adverse drug reactions or overdose, fat embolism, reperfusion pulmonary edema following lung transplantation, or pulmonary embolectomy can be triggers for ARDS. Pneumonia and sepsis are the most common triggers, and pneumonia is present in more than 60% of patients.²

Hospital mortality of patients with moderate-severe ARDS is high, between 41 and 58%.²³⁶ Besides the impact on survival, health-related quality of life will be reduced in ARDS survivors for at least one year, mainly because of extra-pulmonary problems such as muscle loss and weakness limiting their functional capacity.⁷

### 1.3 Pathophysiology

ARDS result from alveolar injury that produces diffuse alveolar damage. The injury causes the release of pro-inflammatory cytokines such as tumor necrosis factor, interleukin-1 (IL-1), IL-6, and IL-8.⁸⁻¹¹ These cytokines recruit neutrophils to the lungs, where they are activated and release toxic mediators (e.g., proteases and reactive oxygen species) that damage the capillary endothelium and alveolar epithelium.¹²⁻¹⁶

When the capillary endothelium and alveolar epithelium are damaged, proteins are allowed to pass from the vascular into the interstitial space and alveoli. The oncotic pressure gradient, which promotes fluid reabsorption, is lost, and the interstitium is flooded, exceeding the capacity of lymphatic drainage.¹⁷ The ability to increase alveolar fluid clearance may also be impaired.¹⁸ As a consequence, the alveolar space is filled with protein-rich fluid, blood, and cellular debris. Additionally, there is loss of alveolar surfactant, causing alveolar collapse.

Among the various consequences of ARDS, some are especially deleterious, such as impaired gas exchange, decreased compliance, and pulmonary arterial hypertension. Impairment of gas exchange results primarily from changes in the ventilation-perfusion relationship. Non-ventilated
alveoli continue to be perfused (shunt) simultaneously with the increase in physiological dead space that limits carbon dioxide release.\textsuperscript{19, 20} A high minute volume is usually required to maintain normal PaCO\textsubscript{2}, but hypercapnia is unusual.

### 1.4 Etiology

ARDS is a clinical syndrome with various etiologies. ARDS usually occurs between 24 and 48 hours after injury (trauma, burn, aspiration, massive blood transfusion, drug or alcohol abuse) or acute illness (infectious pneumonia, sepsis, acute pancreatitis) and is associated with a variety of pathologic findings, especially diffuse alveolar damage.

Distant lesions, such as abdominal sepsis, may cause the release of inflammatory mediators that will damage the lungs. In turn, pulmonary contusion produces a direct lung injury, resulting in the release of inflammatory factors similarly to what occurs in indirect lung injuries.

Although ARDS is traditionally understood as a pattern encompassing lung injury and common clinical manifestations that can be caused by various aggressive factors, there are differences in the type of injury and clinical presentation. For example, in ARDS due to primary lung processes the decrease in compliance is more marked and responsiveness to PEEP is lower than when secondary to extrapulmonary triggers, such as sepsis.\textsuperscript{21-24}

### 1.5 Ventilator-induced lung injury (VILI)

Mechanical ventilation is an essential part of the treatment of ARDS. However, mechanical ventilation itself can produce alveolar injury and cause or worsen ARDS.\textsuperscript{25} Barotrauma, volutrauma, biotrauma, and atelectrauma are mechanisms that produce ventilator-induced alveolar injury.\textsuperscript{26}

Barotrauma refers to lung injury induced by application of high pressures.\textsuperscript{27} Pneumothorax, pneumomediastinum, subcutaneous emphysema, and gas embolism are gross forms of barotrauma.
Volutrauma refers to lung injury induced by high tidal volumes.\textsuperscript{28} This concept was initially proposed in an experiment with rats submitted to high-pressure mechanical ventilation in which chest expansion was limited by binding, and which did not develop lung injury. Conversely, severe injury was noted in a group of rats submitted to lower pressures and high tidal volumes.

In normal individuals or patients with ARDS, within physiological limits, increases in transpulmonary pressure (stress) usually accompany linear increases in volume (strain).\textsuperscript{26} Therefore, in clinical practice, there are no major differences between barotrauma and volutrauma, which are just two sides of the same coin.

Non-physiological stress/strain at insufficient levels to produce gross barotrauma is associated with the release of pro-inflammatory cytokines, leukocyte recruitment, and inflammation. This phenomenon is known as biotrauma, an extension of the concept of barotrauma/volutrauma.\textsuperscript{29}

Atelectrauma is lung injury attributed to cyclic opening and closing of respiratory bronchioles and alveolar duct units.\textsuperscript{30} A mathematical model suggests that the pressures acting on the interface between open and collapsed alveoli can reach 140 cmH\textsubscript{2}O even with airway pressure of 30 cmH\textsubscript{2}O.\textsuperscript{31} The intensity of these forces reaches maximum values in alveolar duct units that open during inspiration and that are adjacent to permanently collapsed alveolar units.

Such injury mechanisms indicate that VILI occurs at two extremes:\textsuperscript{26}

- At end expiratory lung volume (beginning of inspiration), i.e., atelectrauma caused by stress/strain in lung units that open cyclically and are adjacent to closed units;
- Upon reaching total lung capacity (end of inspiration), i.e., biotrauma/barotrauma/volutrauma.

Protective ventilation strategies aim at preventing stress/strain at the end of inspiration and at the end of expiration.\textsuperscript{32, 33} Biotrauma/barotrauma/volutrauma could be prevented by means of
ventilation with low tidal volumes and low pressures; in turn, high PEEP would prevent atelectrauma and reduce the strain of less compromised units by recruiting alveolar units and keeping them open.

1.6 Lung-protective ventilation strategies in ARDS

1.6.1 Reduced stress/strain at end inspiration: low tidal volume/plateau pressure

Many experimental studies have demonstrated that both high inspiratory pressures and high tidal volumes are able to cause ARDS in healthy animals and worsen ARDS in ill animals. In general, very high tidal volumes were employed in these studies (≥ 14mL/kg).

A number of randomized clinical trials comparing low tidal volume and/or low plateau pressure vs. high volume/pressure in patients with ARDS using similar PEEP have found different results. A study by the ARDSNet including 861 patients found reduced hospital mortality in the group with tidal volume of 6mL/kg of predicted body weight compared with the group with 12mL/kg of predicted body weight. No differences in mortality were reported in most of the other studies, which were smaller.

A systematic review identified 8 randomized controlled trials comparing different levels of tidal volume and/or pressure, while using similar PEEP in different groups. In most studies, the tidal volume reached on the first day after randomization was around 7mL/kg of predicted body weight in the experimental group, vs. 6mL/kg in the ARDSNet study, which was also covered in this review. The studies also reported similar tidal volume in the control groups, around 10mL/kg of predicted body weight, except for the ARDSNet study, with 11.8mL/kg. In the meta-analysis, the relative risk for death was 0.90 (95% confidence interval [95%CI]: 0.74 to 1.09) with some heterogeneity between studies ($I^2 = 44.8\%$). There were no differences regarding risk of barotrauma; however, the strategy of low volumes/pressures resulted in greater use of neuromuscular blocking agents and respiratory acidosis. The reason for the heterogeneity of effects between the studies was not
explained. A possible explanation for the positive results obtained in the ARDSNet study is the broader difference in tidal volume between the experimental and control groups as compared to the other studies. A meta-regression was performed to test this hypothesis and the result was negative; however, this type of analysis has very limited power with a small number of studies. In turn, the benefits of using tidal volume ≤ 6mL/kg may be restricted to more severe patients with very low volume of ventilable lung ("baby lung").

Current guidelines recommend the use of low tidal volume up to 6mL/kg of predicted body weight in patients with ARDS. In turn, low tidal volumes have adverse effects such as increased need for sedatives and neuromuscular blockers, as well as acidosis. For these reasons,Gattinoni et al. consider it mandatory to titrate tidal volume according to the size of the "baby lung," although this is impractical because it would require moving critically ill patients for chest tomography.

1.6.2 Reduced stress/strain at end expiration: alveolar recruitment and maintenance of PEEP titration to keep an open lung

PEEP effect

Atelectrauma is caused by stress/strain at end expiration and at the start of subsequent inspiration. An "open lung" strategy consisting of alveolar recruitment and temporary increase in transpulmonary pressure associated with PEEP was suggested to neutralize this injury mechanism. The goal of this strategy is to open collapsed lung units using alveolar recruitment and to keep them open by adjustment of PEEP levels.

Many experimental studies have demonstrated a protective effect of PEEP. In 1974, Webb and Tierney used a rat model to show that high tidal volumes/pressures resulted in lung injury that could be prevented by adjustment of PEEP. Another group submitted rats to high tidal volumes, showing that PEEP was able to significantly reduce alveolar edema and ultrastructural alveolar lesions. Muscedere et al. demonstrated that low tidal volumes are not sufficient to
prevent alveolar and bronchial injury if PEEP is below the lower inflection point ($P_{\text{flex}}$) as determined from the pressure-volume curve.\textsuperscript{30} That suggests that atelectrauma is an independent mechanism of lung injury. Chiumello et al. demonstrated that both the use of high tidal volume and the absence of PEEP were associated with systemic release of inflammatory cytokines, possibly contributing to the development of multiple organ dysfunction syndrome.\textsuperscript{34}

The first randomized study evaluating an open lung strategy was published in 1998 by Amato et al.\textsuperscript{32} Patients with ARDS with $\text{PaO}_2/\text{FiO}_2 < 200$mmHg ($n = 58$) were randomized to receive "open lung" or conventional ventilation. The open lung strategy began with lung recruitment with CPAP from 35 to 40cmH$_2$O, followed by tidal volume ventilation $\leq 6$mL/kg and PEEP 2cmH$_2$O above $P_{\text{flex}}$. The conservative strategy used tidal volume of 12mL/kg and PEEP values that were sufficient to maintain blood oxygenation with $\text{FiO}_2 \leq 60\%$. The study was stopped early for benefit: a reduction in mortality was noted, from 71 to 38\% in the experimental group ($P < 0.001$).

Villar et al. conducted a study that was similar to that by Amato et al.\textsuperscript{45} A tidal volume between 9 and 11mL/kg of predicted body weight and PEEP $\geq 5$cmH$_2$O were used in the control group. In the intervention group, tidal volume was between 5 and 8mL/kg of predicted body weight with PEEP titration of 2cmH$_2$O above $P_{\text{flex}}$. In both groups, $\text{FiO}_2$ was set to maintain arterial oxygen saturation $> 90\%$ and $\text{PaO}_2$ 70-100 mmHg. No lung recruitment maneuver was used. This study was also stopped early for benefit, with hospital mortality reported as 55.5\% in the control group vs. 34.0\% in the experimental group ($P = 0.04$).

The benefits found by Amato et al.\textsuperscript{32} and Villar et al.\textsuperscript{45} can be attributed to: 1) differences in PEEP between the groups; and/or 2) differences in tidal volume between the groups. It was not possible to determine how much of the benefit can be attributed to either factor. Additionally, because these studies included small samples and had other limitations, including the early discontinuation (albeit resulting from a beneficial effect), which might have contributed to overestimate the treatment effect.\textsuperscript{46}
Three large randomized studies were designed to compare the isolated effects of differences in PEEP on patients with ARDS with similar tidal volumes in different groups.  

The ARDSNet ALVEOLI study used a PEEP and FiO\textsubscript{2} combination table to adjust PEEP values in both groups, with higher PEEP values in the experimental group.\textsuperscript{49} Tidal volume was 6mL/kg of predicted body weight in both groups. Five hundred and forty-nine patients with ARDS (PaO\textsubscript{2}/FiO\textsubscript{2} ≤ 300mmHg) were randomized. The mean PEEP values between day 1 and day 4 were approximately 8cmH\textsubscript{2}O in the control group and 13cmH\textsubscript{2}O in the experimental group. The study was terminated early for futility (interim analysis showing a small probability of favorable result for the experimental group). There were no statistically significant differences in hospital mortality between the groups.

The LOVS study included 985 patients with ARDS and compared different levels of PEEP adjusted according to FiO\textsubscript{2}.\textsuperscript{48} Target tidal volume was 6mL/kg predicted body weight in both groups, and the values reached were approximately 7mL/kg predicted body weight. The difference regarding the ALVEOLI study was the use of a recruitment maneuver with CPAP of 40cmH\textsubscript{2}O for 40 seconds in the experimental group. There were no differences between the groups in the primary outcome, hospital mortality (36.4% in the high PEEP group and 40.4% in the control group, P=0.19).

The third study comparing different levels of PEEP alone in patients with ALI was the EXPRESS study,\textsuperscript{47} including 767 patients. PEEP was set to a moderate level (5-9 cmH\textsubscript{2}O) or to reach a plateau pressure of 28 to 30 cm H\textsubscript{2}O. Target tidal volumes were 6mL/kg in both groups. There were no differences in mortality rates between the groups (35.4% in the high PEEP group vs. 39.0% in the low PEEP group, P=0.31).

A systematic review of the literature with individual patient data meta-analysis of three randomized studies evaluating different high PEEP approaches for ARDS did not show beneficial effects overall.\textsuperscript{50} However, treatment effects were different between the subgroups of patients with PaO\textsubscript{2}/FiO\textsubscript{2} ≤
200 mmHg compared to $\text{PaO}_2/\text{FiO}_2$ 200 mmHg and ≤ 300 mmHg ($P=0.02$ for heterogeneity). Thus, among patients with moderate-severe ARDS ($\text{PaO}_2/\text{FiO}_2 \leq 200$ mmHg), there was a decrease in hospital mortality (relative risk 0.90, 95%CI 0.81-1.00, $P=0.049$) and ICU deaths (relative risk 0.85, 95%CI 0.76-0.95, $P=0.001$), in addition to other benefits such as greater number of mechanical ventilation-free days in 28 days and less frequent use of rescue therapies for refractory hypoxemia. It is interesting to note that: 1) mean PEEP for the three studies was 15.3 cmH$_2$O in the high PEEP group vs. 9.0 cmH$_2$O in the low PEEP group; 2) recruitment maneuvers were used in only one study, the LOVS, which employed CPAP for recruitment. In that case, the CPAP pressure was lower than that achieved with a stepwise PEEP increase up to 45 cmH$_2$O and controlled pressure of 15 cmH$_2$O. A greater beneficial effect might have been achieved with maximum alveolar recruitment maneuvers followed by PEEP titration based on the static compliance of the respiratory system.

**Recruitment maneuvers**

Lung recruitment maneuvers are capable of increasing the ventilated lung volume and improving gas exchange and lung mechanics. Additionally, the ideal PEEP titration – PEEP value that is capable of keeping the lung open – is best performed during the expiratory phase of the pressure-volume curve, after alveolar recruitment.

A systematic review of alveolar recruitment maneuvers found that most studies employed sustained inflation (CPAP) recruitment maneuvers (18 studies), followed by high pressure controlled ventilation (9 studies) and incremental PEEP (8 studies). Even though alveolar recruitment resulted in improved oxygenation, this effect was lost within a few hours in most studies. Transient hypotension (12%) and desaturation (9%) were the most common problems, but severe adverse events were not frequent (1% barotrauma, 1% severe arrhythmia).

Borges et al. showed that it is possible to recruit more than 95% of collapsed lung mass in almost all patients with early ARDS. The authors evaluated 26 patients, 20 of whom had $\text{PaO}_2/\text{FiO}_2$
≤200 mmHg. A maximum recruitment strategy was applied. PEEP was initially set to 25 cmH₂O with pressure-controlled ventilation of 15 cmH₂O. This was followed by stepwise increases of 5 cmH₂O in PEEP every 2 minutes, until a PEEP of 45 cmH₂O and peak inspiratory pressure of 60 cmH₂O were reached. PEEP 25 cmH₂O was applied between the periods of PEEP increment. Next, the authors performed PEEP titration starting with 25 cmH₂O PEEP, PEEP decreases of 2 in 2 cmH₂O for 4 minutes until PaO₂+PaCO₂ <380 mmHg. The last value of PEEP associated with PaO₂+PaCO₂ ≥ 400 mmHg was considered the best PEEP. The investigators repeated the recruitment maneuver and the ideal PEEP was maintained. It was possible to achieve open lung, confirmed by blood gas test, in 24 out of 26 patients. Hemodynamic effects and hypercapnia were transient. There was no barotrauma directly associated with the maneuver. Blood gas monitoring 6 hours later showed that the effects on blood oxygenation were preserved.

The results of the study by Borges et al. were confirmed by another study including 12 patients with moderate-severe ARDS submitted to maximum recruitment guided by helical computed tomography (CT) of the lung. Recruitment was achieved by 5 cmH₂O PEEP increments starting at 10 cmH₂O until reaching 45 cmH₂O. Patients were kept on pressure-controlled ventilation set for a maximum difference of 15 cmH₂O, that is: at maximum recruitment, PEEP was 45 cmH₂O and peak pressure was 60 cmH₂O. The stepwise increase in PEEP was interrupted if lung recruitment was observed on CT at PEEP levels below 45 cmH₂O. However, only one of 12 patients achieved maximum recruitment with PEEP < 45 cmH₂O. After recruitment, PEEP was decrementally titrated starting at 25 cmH₂O to 20 cmH₂O and 10 cmH₂O. PEEP titration was guided by the tomographic images. The maximum time of recruitment including PEEP titration was 48 minutes, with each level of PEEP maintained for about 5 minutes. The level of titrated PEEP was 20 cmH₂O (3 of 12 patients) or 25 cmH₂O (9 of 12 patients). After maximum recruitment and PEEP titration, PaO₂/FiO₂ increased from 132±38 to 336±59 (P <0.01) without significant changes in PaCO₂ and arterial pH. The authors concluded that the maximum recruitment strategy followed by PEEP titration significantly reduced
the collapsed lung mass, "tidal recruitment" and "tidal stretch," with no significant increase in the amount of lung overdistension.

In a rat model of sepsis-induced ARDS, the effects of four lung recruitment strategies on the following outcomes were evaluated: gas exchange, lung mechanics, structural cell damage, markers of inflammation, fibrogenesis, and apoptosis. Study questions included: 1) Is the stepwise increase in airway pressure more efficient than an abrupt increase in pressure? and 2) Are prolonged recruitment maneuvers more efficient than short duration maneuvers? Both stepwise increase in pressure and long term high pressures resulted in smaller hyperinflated area, less cell damage (to the alveolar-capillary membrane, type II epithelial cells, and endothelial cells), and decreased activation of inflammatory, fibrogenic, and apoptotic mediators. The size of collapsed area, however, was similar with both approaches. Therefore, the beneficial mechanism of incremental and prolonged maneuvers cannot be attributed to different amounts of atelectrauma. In short, these findings suggest that the recruitment strategy used in the ART study, with incremental increase in pressure and prolonged duration, is more efficient than the most common maneuver, using high CPAP (30 to 40cmH₂O) for 30 to 40 seconds. Other studies have confirmed that lung recruitment with incremental PEEP yields better results in terms of blood oxygenation and less lung injury than the method of abrupt pressure increase with CPAP.

The effect of lung recruitment maneuvers was evaluated in a systematic review of randomized trials. However, because the studies had treatment differences, for example in tidal volumes, it was not possible to evaluate the isolated effect of recruitment maneuvers on clinical outcomes.
**PEEP titration**

Several studies have shown that PEEP titration should be performed in the deflation limb of the PV curve, and thus it is not appropriate to use the lower inflection point ($P_{\text{flex}}$) as reference to set PEEP.\textsuperscript{55, 56, 60, 61} Instead, PEEP should be titrated after the recruitment maneuver.

Several methods have been proposed for optimal PEEP titration after alveolar recruitment, including static compliance,\textsuperscript{62} dynamic compliance,\textsuperscript{63} $\text{PaO}_2+\text{PaCO}_2 \geq 400\text{mmHg}$,\textsuperscript{51} decreased levels of $\text{PaO}_2$ or $\text{SpO}_2$,\textsuperscript{64} and imaging studies such as CT\textsuperscript{51} and bioelectrical impedance.\textsuperscript{65}

A sheep model of ARDS was used to compare several methods of PEEP titration.\textsuperscript{66} However, that study inappropriately used as gold standard one of the methods being tested (dynamic compliance), while no imaging evaluations were performed. The following approaches for setting PEEP were considered to be equivalent: dynamic compliance, maximum $\text{PaO}_2+\text{PaCO}_2$, maximum $\text{PaO}_2$, minimum shunt, lower $P_{\text{flex}}$ of the inflation limb of the P-V curve, and point of maximal compliance increase on the inflation limb of the P-V curve. Static compliance was not assessed.

Static compliance is an interesting variable to be used in large-scale clinical trials because it is easily measured and does not depend on the result of laboratory tests. Respiratory system compliance stabilizes 3 to 5 minutes after each level of pressure is applied, so that total time for PEEP titration is relatively short.

Dynamic compliance can be used for PEEP titration, but it depends on the use ventilators that are capable of measuring it.\textsuperscript{63, 66} Static compliance is generally higher than dynamic compliance, but the correlation between the two is excellent, and it is reasonable to assume that they are equivalent for PEEP titration.\textsuperscript{63}

Decremental PEEP titration by stepwise decreases of 2cmH\textsubscript{2}O every four minutes beginning at 25cmH\textsubscript{2}O has drawbacks that limit the applicability and effectiveness of this approach: 1) patients
are exposed to a second recruitment maneuver, which is associated with risk and makes the procedure more complex; 2) the time required to titrate PEEP can be long (up to 32 minutes), and the entire procedure takes longer because of the second recruitment; 3) optimal PEEP value may be underestimated. Given these potential limitations, we propose to adapt PEEP titration to a decrease of 3cmH₂O starting at 23cmH₂O in order to reduce the number of steps and total titration time.

1.7 Why is a large-scale study necessary to address this research question?

ARDS is a common problem in critically ill patients, associated with high morbidity and mortality, especially moderate-severe ARDS. There are few effective interventions for these patients. In fact, observational studies have shown only a slight reduction in the mortality rate of moderate-severe ARDS over the years.

Maximum alveolar recruitment followed by PEEP titration is a relatively simple and widely available intervention with potential to improve the prognosis of patients with moderate-severe ARDS.

Large-scale pragmatic, randomized trials are needed to identify new treatments for patients with ARDS. A large sample size is critical to identify moderate benefit. As much as possible, simplification of eligibility criteria, interventions, and evaluation of the study variables is important to allow fast enrollment of patients, as well as to increase the applicability of results if the experimental intervention is beneficial.
2 OBJECTIVES

2.1 Primary objective

To determine if maximum alveolar recruitment associated with PEEP titration adjusted according to the static compliance of the respiratory system increases 28-day survival rate of patients with moderate-severe ARDS compared to conventional treatment (ARDSNet strategy).

2.2 Secondary objectives

To evaluate the effect of the maximum alveolar recruitment approach associated with PEEP titration adjusted according to the static compliance of the respiratory system compared to conventional treatment (ARDSNet strategy) on the following outcomes:

- Length of hospitalization;
- Pneumothorax requiring chest tube at 7 days;
- Barotrauma (any pneumothorax, pneumomediastinum, subcutaneous emphysema or pneumatocele > 2cm after randomization) at 7 days;
- Ventilator-free days from day 1 to day 28
- ICU survival
- In-hospital survival
- 6-month survival.
3 METHODS

3.1 Study design

Randomized, multicenter, pragmatic clinical trial with allocation concealment and intention-to-treat (ITT) analysis, comparing a strategy of maximum lung recruitment associated with PEEP titration adjusted according to static compliance of the respiratory system vs. ARDSNet approach for patients with moderate-severe ARDS.

3.2 Eligibility

3.2.1 Assess intubated patients receiving mechanical ventilation daily.

Consider including ALL patients who meet the inclusion criteria below:

3.2.2 Inclusion criteria:

- Acute onset respiratory failure;
- Bilateral pulmonary infiltrate on chest X ray compatible with pulmonary edema;
- Absence of left atrial hypertension based on the medical team’s decision (clinical or echocardiographic signs);
- Presence of a risk factor for lung injury [shock, gastric aspiration, sepsis, pneumonia, high-risk surgery (orthopedic spine, acute abdominal, cardiac, vascular aortic), head injury, smoke inhalation, near drowning, pulmonary contusion, multiple fractures, multiple transfusions, drug or alcohol abuse;
- Severe hypoxemia, defined as PaO$_2$/FiO$_2$ ≤200;
• Absence of left atrial hypertension based on the medical team's evaluation (clinical or echocardiographic signs);

• Presence of a risk factor for lung injury.

3.2.3 Exclusion criteria:

Patients with anyone of the following should be excluded:

• Age < 18 years;

• Use of vasoconstrictor drugs in increasing doses over the past 2 hours (≥0.2mcg/kg per min for norepinephrine or ≥5mcg/kg per min for dopamine) or mean arterial pressure <65 mmHg; In case a patient presents this criterion, the medical team should later reassess the possibility of including the patient, because this is a transitory exclusion criterion;

• Contraindication to hypercapnia with intracranial hypertension or acute coronary syndrome;

• Pneumothorax, subcutaneous emphysema, pneumomediastinum or pneumatocele;

• Patient with no therapeutic perspective; candidate for palliative care exclusively (eg.: patient with imminent death, in moribund state or dying cancer patient under exclusive palliative care);

• Patient previously randomized in the study.
3.2.3 Eligibility confirmation:

If the patient meets all the inclusion criteria and none of the exclusion criteria, he/she will be potentially eligible. In this case, ventilate the patient using a conventional approach (ARDS Net strategy) for 3 hours:

**Suggested ventilation of potentially eligible patients:**

- **Mode:** assisted/controlled volume
- **Tidal volume:** 4-6mL/kg of predicted body weight or less in order to ensure:
  - Plateau pressure ≤30cmH₂O
- **Keep I:E ratio = 1:1 to 1:3**
- **Inspiratory flow** 60 L/min, descending waveform. Reduce to 40 L/minute if peak pressure is >45 cmH₂O
- **Inspiratory pause** of 0.5 second. Inspiratory pause may be adjusted if the I:E ratio is not within the range between 1:1 and 1:2
- **Respiratory rate** to keep the same minute ventilation recorded before reduction of tidal volume (Respiratory rate = minute ventilation / new tidal volume)
- **Do not apply alveolar recruitment maneuvers** during this phase.
- **PEEP and FiO₂** adjusted according to the ARDSNet table to maintain SpO₂ 88%-95% and PaO₂ 55-80mmHg (table 2)

<table>
<thead>
<tr>
<th>FiO₂</th>
<th>30%</th>
<th>40%</th>
<th>50%</th>
<th>60%</th>
<th>70%</th>
<th>80%</th>
<th>90%</th>
<th>90%</th>
<th>90%</th>
<th>100%</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEEP</td>
<td>5</td>
<td>5</td>
<td>8</td>
<td>8</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>12</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>14</td>
<td>16</td>
<td>16</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>18-24</td>
</tr>
</tbody>
</table>

**Table 2.** ARDSNet table of FiO₂ and PEEP values to keep SpO₂ ≥ 88% and PaO₂ ≥ 55mmHg

Predicted body weight should be calculated for all patients according to the formula:
Men: Predicted body weight (kg) = 50 + 2.3 ((height [cm] × 0.394) – 60)

Women: Predicted body weight (kg) = 45.5 + 2.3 ((height [cm] × 0.394) – 60)

Procedures for measurement of blood gases that define eligibility:

Keep ventilation as described in the prior section and adjust:

- 100% FiO$_2$
- PEEP = 10cmH$_2$O (except for patients with PEEP≥16cmH$_2$O for whom PEEP should be maintained)

Arterial blood gases should be measured after 30 minutes on the above parameters.

Patients will be considered eligible if the PaO$_2$ measured with FiO$_2$=100% and PEEP=10cmH$_2$O (or ≥16cmH$_2$O) is 200mmHg or less, and less than 72 hours have been spent since the first time a PaO$_2$/FiO$_2$ ≤200 was determined. Then, obtain Consent Informed signed in order to randomize the patient.

3.3 Randomization method and allocation concealment

The randomization list will be generated electronically using appropriate software. Randomization will be performed in blocks with stratification by center, age (≤55 or >55 years-old) and by PaO$_2$/FiO$_2$ ratio (≤100 or >100mmHg).

Allocation concealment will be maintained by means of a web-based central, automated randomization system, available 24 hours a day (ACT-Clinic), developed by a team of programmers and investigators from the Research Institute at Hospital do Coração. The group to which the patient will be allocated will only be disclosed after the information is recorded in the electronic system. This prevents the investigator and the medical team from predicting to which treatment group the patient will be allocated. To include a patient in the study, investigators must simply
access the IEP-HCor website (https://servicos.hcor.com.br/iep/estudoclinico) and fill in a short medical record form.

### 3.4 Interventions

After the informed consent (IC) form is signed, the patient's information must be entered in the electronic system. The system will then generate an individual identification number for each in the trial. Electronic randomization will be performed after that, with disclosure of the ventilatory strategy to be adopted:

- **ART strategy**: maximum alveolar recruitment maneuver associated with PEEP titration adjusted according to static compliance of the respiratory system, or

- **ARDSNet strategy**.

#### 3.4.1 ART Strategy - Maximum alveolar recruitment maneuver associated with PEEP titration

The mechanical ventilation procedures for this group are described in detail in Appendix A. Briefly, patients will undergo alveolar recruitment with incremental PEEP levels and inspiratory pressure delta of 15cmH₂O until reaching PEEP 35cmH₂O. Next, patients will receive ventilatory support with PEEP values titrated adjusted according to the static compliance of the respiratory system. Figure 1 shows a schematic representation of the recruitment maneuver followed by PEEP titration, and table 2 summarizes the mechanical ventilation procedures in this group compared to the ARDSNet group.

After recruitment and PEEP titration, patients will be ventilated in controlled volume mode. Tidal volume will not exceed 6mL/kg of predicted weight except for special situations described in Appendix A, in which case it may reach 8mL/kg of predicted weight.
Figure 1. ART Strategy - Maximum alveolar recruitment maneuver associated with PEEP titration.
### Table 2. Summary of mechanical ventilation procedures in the ART strategy group vs. ARDSNet strategy group*

<table>
<thead>
<tr>
<th>Procedure</th>
<th>ART Strategy - Maximum alveolar recruitment maneuver associated with PEEP titration</th>
<th>ARDSNet strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alveolar recruitment maneuver</td>
<td>Yes (see figure 1)</td>
<td>No</td>
</tr>
<tr>
<td>Ventilation mode</td>
<td>Controlled volume</td>
<td>Controlled volume</td>
</tr>
<tr>
<td>Target plateau pressure and driving pressure</td>
<td>Plateau ≤30cmH₂O</td>
<td>Plateau ≤30cmH₂O</td>
</tr>
<tr>
<td>Target tidal volume</td>
<td>4 to 6mL/kg of predicted body weight</td>
<td>4 to 6mL/kg of predicted body weight</td>
</tr>
<tr>
<td>Respiratory rate and pH goal</td>
<td>6-35/min, adjusted for pH ≥ 7.30 if possible</td>
<td>6-35/min, adjusted for pH ≥ 7.30 if possible</td>
</tr>
<tr>
<td>I:E ratio</td>
<td>1:1 to 1:2; Flow 60L/min; Inspiratory pause 0.5sec</td>
<td>1:1 to 1:2; Flow 60L/min; Inspiratory pause 0.5sec</td>
</tr>
<tr>
<td>Oxygenation goals</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PaO₂</td>
<td>60-80mmHg</td>
<td>55 – 80mmHg</td>
</tr>
<tr>
<td>SpO₂</td>
<td>90-95%</td>
<td>88 – 95%</td>
</tr>
<tr>
<td>PEEP and FiO₂ adjustment</td>
<td>PEEP titration 2cmH₂O above PEEP value associated with maximum compliance. FiO₂ titration adjusted according to oxygenation goals</td>
<td>According to PEEP/FiO₂ combination table</td>
</tr>
<tr>
<td>Weaning</td>
<td>After 24 hours with PaO₂/FiO₂ (same or ascending of anterior day) start weaning from PEEP 2cmH₂O every 8 hours. Consider pressure support ventilation after PEEP≤14 cmH₂O. Spontaneous ventilation test in PS = 5cmH₂O and PEEP = 5cmH₂O. Prophylactic use of NIV immediately after extubation is encouraged.</td>
<td>Weaning from PEEP according to table of PEEP and FiO₂ combinations. Consider pressure support ventilation after PEEP≤14 cmH₂O. Spontaneous ventilation test in PS = 5cmH₂O and PEEP = 5cmH₂O. Prophylactic use of NIV immediately after extubation is encouraged.</td>
</tr>
</tbody>
</table>

* Complete instructions for mechanical ventilation are described in Appendix A for the ART strategy group (maximum alveolar recruitment associated with PEEP titration), and Appendix B for the ARDSNet strategy group.
3.4.2 ARDSNet strategy

The mechanical ventilation procedures for this group are described in detail in Appendix B. The strategy for this group is the one proposed by the ARDSNet.\textsuperscript{40, 49}

Table 2 summarizes the procedures for this group compared to the group treated with maximum lung recruitment.

3.4.3 Co-interventions – rescue therapies for refractory hypoxemia

Rescue therapies for refractory hypoxemia may be administered at the discretion of the medical team and may include:

- Prone position
- Nitric oxide inhalation
- High frequency oscillatory ventilation
- Extracorporeal membrane oxygenation

3.4.4 Blinding

Since the intervention will be administered to critically ill patients on mechanical ventilation (that is, mostly sedated), blinding of these patients is not necessary. Because this is a non-pharmacological intervention, blinding of the medical team is not feasible. There is no need of a committee to validate the study endpoint (death), and therefore outcome evaluators will not be blinded. However, the statisticians in charge of the analyses will be blinded to treatment groups throughout the study.
3.5 Endpoints

3.5.1 Primary outcome

- 28-day survival.

3.5.2 Secondary outcomes

- Length of hospital stay;
- Pneumothorax requiring chest tube at 7 days;
- Barotrauma (any pneumothorax, pneumomediastinum, subcutaneous emphysema or pneumatocele > 2cm after randomization) at 7 days;
- Mechanical ventilation-free days from day 1 to day 28;
- ICU survival
- In-hospital survival
- 6-month survival.

3.6 Study variables and visits

Study visits and the variables collected at each visit are described below. It is of utmost importance that the investigators complete the case report forms in a timely fashion. The deadline for filling baseline, treatment, 1-day, 3-day, 7-day and 28-day follow-up forms is two days after the respective date (eg. maximum two days after the day of randomization for baseline data). The deadline for filling the discharge and 6-month forms is 7 days after the respective date.

3.6.1 Screening (day 0)

- Verification of moderate-severe ARDS criteria
• Signature of informed consent form

• Respiratory variables before randomization
  o Mode
  o Tidal volume
  o Plateau pressure
  o Total respiratory rate
  o PEEP
  o FiO₂

3.6.2 Baseline data and randomization (day 0)

Randomization
• \( \text{PaO}_2 \) obtained at \( \text{FiO}_2=100\% \) and \( \text{PEEP}=10\text{cmH}_2\O \) (or \( \geq 16\text{cmH}_2\O \) if patients were receiving these levels of PEEP)
• Reason for non-randomization of eligible patients (in case decision is not to randomize)

Baseline data
• Date of birth
• Sex
• Weight (measures with a weighing scale)
• Height
• SAPS 3 (ICU admission)
• Sequential organ failure assessment (SOFA)
• Cause of ARDS
• Estimated time from onset of moderate-severe ARDS (onset of moderate-severe ARDS based on arterial blood gases until randomization)
• Time from intubation to randomization
• Presence of septic shock
• Presence of Influenza A (H1N1)
• Presence of acquired immunodeficiency syndrome (AIDS)

3.6.3 Treatment (1 hour after start of intervention)

• Alveolar recruitment (for the group treated with maximum alveolar recruitment)
  o Maximum PEEP reached
  o If maximum alveolar recruitment is interrupted, provide the reason (list of criteria for interruption)
  o PEEP titration adjusted according to static compliance
  o If recruitment maneuver is repeated after PEEP titration

• Respiratory variables of maintenance ventilation
  o Tidal volume
  o Plateau pressure
  o Total respiratory rate
  o PEEP
  o FiO₂
  o PaO₂
  o PaCO₂
  o Arterial pH

• Hemodynamic variables
  o Heart rate
  o Mean blood pressure
  o Use of noradrenaline and dopamine

• Events
  o Cardiac arrest

3.6.4 1-day follow-up
• Respiratory variables
  o Tidal volume
  o Plateau pressure
  o Respiratory rate
  o PEEP
  o FiO₂
  o PaO₂
  o PaCO₂
  o arterial pH
• Water balance and weight (weighing scale)
• Hemodynamic variables
  o Mean blood pressure
  o Use of noradrenaline and dopamine
• Events
  o Cardiac arrest

3.6.5 3-day follow-up

• Respiratory variables
  o Tidal volume
  o Plateau pressure
  o Respiratory rate
  o PEEP
  o FiO₂
  o PaO₂
  o PaCO₂
  o arterial pH
• Water balance and weight (weighing scale)

• Hemodynamic variables
  o Mean blood pressure
  o Use of noradrenaline and dopamine

3.6.6 7-day follow-up

• Respiratory variables on day 7
  o FiO₂
  o PaO₂
  o PaCO₂
  o pH

• Respiratory variables on day 7 for patients still on mechanical ventilation
  o Tidal volume
  o Plateau pressure
  o Respiratory rate
  o PEEP

• Weight (weighing scale)

• Co-interventions during the period
  o Use of/ number of days using neuromuscular blockers
  o Use of/ number of days using continuous infusion of sedatives
  o Use of/ number of days using continuous infusion of narcotics
  o Use of/ number of days using noradrenaline or dopamine
  o Rescue therapies for refractory hypoxemia
    ▪ Prone position
- Nitric oxide
- High frequency oscillatory ventilation
- Oxygenation with extracorporeal circulation

- Pneumothorax requiring chest tube drainage during the period (pneumothorax due to barotrauma only)
- Barotrauma (any pneumothorax, pneumomediastinum, subcutaneous emphysema or pneumatocele > 2cm after randomization) during the period
- Death occurred due to complications in alveolar recruitment maneuver or PEEP titration

3.6.7 Hospital discharge

- Date of ICU discharge
- Vital status at ICU discharge
- Date of hospital discharge
- Vital status at hospital discharge

3.6.8 28-day follow-up

- Days on mechanical ventilation (considering the first 28 days after randomization)
- Vital status
  - Date of death

3.6.9 6-month follow-up

- Vital status
3.6.10 Adverse Event

- Description of any non-expected serious adverse event, which the investigator believes is directly related to the assigned ventilation strategy of the ART study

3.6.11 Death related to alveolar recruitment maneuver and/or PEEP titration

- Description of the case

3.6.12 Additional hemodynamic data, if applicable

For patients who will be randomized to the study and already have any cardiac index monitoring system (e.g. pulmonary artery catheter/Swan Ganz, FLOTRAC, PICCO, LIDCO, EV1000, or others): There is an additional form that should be completed with hemodynamic data at hour 0 (very close to randomization time), 2, 6, 12, 18 and 24 hours after the randomization.

3.7 Statistical considerations

3.7.1 Sample size calculation

ART is an event driven study designed to last until 520 events (deaths within 28 days) are observed. This number of events is sufficient to detect a hazards ratio of 0.75 (i.e., relative reduction in event rate of 25%), considering a type I error of 5%, 90% power, and a similar allocation of subjects to each group.

Considering an event rate in the control group of 36% (mean proportion of deaths in randomized studies conducted after 1994, when the definition of ARDS was standardized), we expect that about 1,620 patients will be needed to achieve the number of events planned. However, since this is an event driven study, the total sample size can vary depending on the event rate in the experimental and control groups.
The advantage of using an event driven strategy is that it ensures adequate power for the study, as well as recruitment of an adequate number of patients — if the event rate turns out to be higher than that reported in the literature, the study will be completed with a smaller sample size than would be required by a method based on total sample size, i.e., there is no unnecessary inclusion of patients. If the event rate turns out to be lower than that reported in the literature, the study is not interrupted before it has adequate power, as might be the case if the total sample size method were used.

3.7.2 Statistical analysis plan

Survival within 28 days (primary outcome) in both groups will be assessed using Kaplan Meier curves and Cox proportional hazard models, without adjustment for other co-variates. The two-sided \( \alpha \)-level for the primary outcome final analysis is 0.042 to account for the two interim analysis with boundaries at one-sided alpha=0.01. For all other outcomes, statistical significance is defined as \( P<0.05 \).

Treatment effects on length of hospital stay and number of mechanical ventilation-free days at 28 days will be analyzed using Mann-Whitney tests. Occurrence of pneumothorax and barotrauma will be evaluated using chi-square tests; 6-month survival will be analyzed using Kaplan Meier curves and Cox proportional hazards models.

Treatment effect on 28-day mortality will be analyzed in the following subgroups: 1) \( \text{PaO}_2/\text{FiO}_2 \leq 100 \) vs. \( >100 \text{mmHg} \); 2) SAPS III score <50 vs. \( \geq 50 \); 3) pulmonary ARDS vs. extrapulmonary ARDS; 4) time of ARDS \( \leq 36 \) hours vs. \( >36 \) to \( <72 \) hours; 5) mechanical ventilation \( \leq 2 \) days; 3 to 4 days; \( \geq 5 \) days. Effects on subgroups will be evaluated using the chi-square test for homogeneity.

All analyses will be carried out using the statistical software R (R Development Core Team, URL http://www.R-project.org - version 2.13) or STATA SE 11 for Windows (College Station, USA).

3.7.3 Preliminary analysis
A preliminary analysis will be conducted after 100 patients are enrolled with the aim of assessing feasibility, adherence to study procedures, physiological variables, and safety outcomes. However, we will not evaluate mortality endpoints at preliminary analysis. Results obtained in the preliminary analysis will be used to consider adjustments in the study protocol and study organization.

3.8 Ethical aspects and good clinical practices

The study will be carried out in accordance with national and international resolutions described in the following documents:

- Resolution n° 196, dated October 10, 1996 and additional rulings by the National Health Council/Ministry of Health
- Helsinki Declaration and all its revisions and changes
- Document of the Americas (Documento de las Américas)

3.8.1 Study approval

Before starting the study, the investigator shall forward a copy of the protocol, a copy of the informed consent form, and other required statements to the Research Ethics Committee (CEP) of each participating institution. A covering letter and an approval letter from the CEP, if approval is obtained, shall be forwarded to the Coordinating Center. Additionally, all amendments to the protocol shall be approved by the CEP of each participating center.

3.8.2 Informed consent form

Written consent will be requested from the legal representative of eligible patients because their clinical status (mechanical ventilation, sedation) does not allow them to directly provide consent. The Principal Investigator or the Study Coordinator will be responsible for requesting consent and providing the legal representative with information about the study. The patient's legal representative and the investigator responsible for obtaining consent should date and sign two
copies of the informed consent form. One copy must be delivered to the patient's legal representative and one copy will be filed with other study documents. The investigator will clearly explain that participation is voluntary and that the patient or his/her legal representative may withdraw consent and leave the study at any time without any consequences to the quality and management of subsequent medical treatment. The informed consent form proposed by the study should be evaluated by each research center; any changes that might be required must be approved by the Coordinating Center of the Study prior to submission to the CEP.

3.8.3 Criteria for withdrawal study patients

The patient withdrawal of the study will only occur in cases of withdrawal of informed consent by the patient, or the legal representative or the patient's physician.

Treatment should be discontinued if the patient develops instability that contraindicates the continued use of high PEEP levels. The measures needed to minimize instability and adverse effects caused by the use of high PEEP levels should be implemented as considered appropriate by the medical staff assistant. However, the action in the trial should proceed normally: the patient will not be excluded from follow-up visits and analysis.

3.8.4 Confidentiality of data

Patient identification data will not be submitted to the Coordinating Center of the Study. Each patient and research center is identified in the electronic case report form by a unique number. Information obtained from medical records should be handled as confidential data by the research centers; it must be kept in restricted access locations and anonymity must be ensured on interim and final reports.

3.8.5 Progress Reports

Investigators must submit written summaries of the status of the study to their Institution's CEP every six months, as well as a final report at the end of the study.
3.8.6 Reporting serious adverse events

A study-related serious adverse event in the ART Trial is defined as 1) any event that is fatal or immediately life threatening, permanently disabling, severely incapacitating, or requires prolonged inpatient hospitalization; OR 2) any event that may jeopardize the patient and requires medical or surgical intervention to prevent one of the outcomes listed above; AND 3) which the attending physician believes to be related to enrolment in the ART Trial. Serious adverse events will be considered study-related if the event could readily have been produced by, and follows a reasonable temporal sequence from, a study procedure.

Adverse events which are primary or secondary outcomes (deaths up to six months after randomization, barotraumas) of the ART trial should not be reported as serious adverse events, except if, because of the course or severity or any other feature of such events, the investigator, according to his/her best medical judgment, considers these events as exceptional in this medical condition.

Study-related serious adverse events which are not primary or secondary outcomes should be reported within 24 hours of knowledge of the event. Investigators should fill in the appropriate electronic case report form. The Coordinating Center will immediately forward the report to the Data Monitoring Committee.

Study organization

3.8.7 Coordinating Center

The study will be managed by a team from the Research Institute at Hospital do Coração (IEP-HCor). The Coordinating Center team includes the Principal Investigator, the Project Manager, a research assistant, a data manager, a statistician and a systems analyst.

The Coordinating Center is in charge of:
• Planning and conducting the study
  o Designing the protocol
  o Designing the electronic case report forms (e-CRF)
  o Designing the operation guide
  o Managing and controlling data quality
  o Designing, testing and maintaining the electronic data capture system
  o Continuous data quality control
  o Assisting the Steering Committee

• Managing the research centers
  o Selecting and training the research centers
  o Helping the centers prepare a regulatory report to be submitted to the CEPs and assisting the centers with the submission
  o Monitoring recruitment rates and the actions to increase recruitment
  o Monitoring follow-up and implementing actions to prevent follow-up losses
  o Auditing
  o Sending study materials to the research centers
  o Producing a monthly study newsletter
  o Developing supporting material for the study

• Statistical analysis and research reporting
  o Complete statistical analysis
  o Helping to write the final manuscript

3.8.8 Institutional support from the Brazilian Association of Intensive Care Medicine (Associação de Medicina Intensiva Brasileira - AMIB)

The AMIB supports the ART study by means of the AMIB-Net. The AMIB-Net is a group of critical care physicians (intensivists) organized and coordinated by the AMIB that aims to assist in the
development and performance of collaborative clinical research to improve the outcome of critically ill children and adults.

The AMIB-Net will assist with the selection and invitation of centers to participate in the ART study, as well as it will facilitate the organization of meetings of researchers during national scientific meetings organized by the AMIB.

3.8.9 Steering Committee

The Steering Committee is responsible for the overall study supervision, assisting in developing the study protocol and preparing the final manuscript. All other study committees report to the Steering Committee. The Steering Committee members are investigators trained in designing and conducting randomized clinical trials, intensivists, and pulmonologists experienced in conducting multicenter randomized studies on ARDS.

The members of the Steering Committee are:

- Alexandre Biasi Cavalcanti, PhD. Chair of the Steering Committee. Epidemiologist, intensivist. Coordinator of Research Initiatives at the IEP-HCor, São Paulo - SP.
- Carlos Carvalho, PhD. Senior Investigator. Pulmonologist. Associate Professor at the University of São Paulo and supervising physician at the Hospital das Clínicas, FMUSP, São Paulo - SP, where he is Head of the Respiratory ICU.
- Marcelo Britto Passos Amato, PhD. Pulmonologist. Supervising physician at the Respiratory Intensive Care Unit in Hospital das Clínicas – FMUSP, Coordinator of the Medical Investigation Laboratory-09-Experimental Pulmonology (FMUSP) and Collaborating Professor at the University of São Paulo
- Otávio Berwanger, PhD. Epidemiologist. Director of the IEP-HCor, São Paulo - SP.
- Érica Aranha Suzumura. Respiratory Therapist. Research Coordinator at the IEP-HCor, São Paulo - SP.
• Ederlon Alves de Carvalho Rezende. Cardiologist. Director of the Intensive Care Medicine Service at Hospital do Servidor Público Estadual de São Paulo, São Paulo - SP. President of the Brazilian Association of Intensive Care Medicine.

• José Mário Meira Telles. Intensivist. Coordinator of the Adult ICU, Hospital Santo Amaro, Salvador, BA. President Elect of the Brazilian Association of Intensive Care Medicine (2012-2013 management).

• Edson Romano. Cardiologist and intensivist. Coordinator of the Adult ICU-HCor, São Paulo.

• Marisa de Moraes Regenga. Respiratory therapist. Manager of Rehabilitation of the HCor, São Paulo – SP.

• Luzia Noriko Takahashi. Respiratory therapist. Coordinator of Physical Therapy of the HCor, São Paulo – SP.

• Hélio Penna Guimarães. Assistant Physician, Clinical Practice Discipline at the Federal University of São Paulo (UNIFESP), and attending physician at the Medical Clinic ICU at Hospital São Paulo - UNIFESP, São Paulo - SP.

• Cassiano Teixeira, PhD. Intensivist, on-call physician at Complexo Hospitalar da Santa Casa de Porto Alegre and attending physician at Hospital Moinhos de Vento, Porto Alegre-RS. Associate professor at Universidade Federal de Ciências da Saúde de Porto Alegre (UFCSPA).

• Roselaine Pinheiro de Oliveira, PhD. Intensivist, attending physician at Central ICU at Complexo Hospitalar da Santa Casa de Porto Alegre and attending physician at Hospital Moinhos de Vento, Porto Alegre-RS. Associate professor, School of Medicine, Universidade de Santa Cruz do Sul (UNISC).

• Flávia Machado, MD, PhD. Intensivist. Professor and chair of Anesthesiology and Pain courses and ICU at Universidade Federal de São Paulo. Vice-president of Instituto Latino Americano de Sepse (ILAS). Editor-in-Chief of Revista Brasileira de Medicina Intensiva.

• Fredi Alexander Diaz-Quijano, PhD. Edipemiologist. Director of Organización Latinoamericana para el Fomento de la Investigación en Salud (OLFIS). National coordinator of Colombia in ART.
3.8.10 Study centers

Eighty centers will be invited to participate in the study. The aid of the AMIB-Net will be vital for the invitation and selection of participating centers.

In order to reach the target number of events, of 520 deaths, considering an event rate of 36% in the control group, approximately 1,620 patients will be necessary. Considering a monthly inclusion rate of 0.67 patients per center (two every three months), patient inclusion is expected to last approximately 31 months.

3.8.11 Data monitoring committee

A Data Monitoring Committee will be set up with independent epidemiologists and intensivists.

The Data Monitoring Committee is in charge of providing recommendations for the Steering Committee of continuing the study as planned or discontinuing the recruitment based on evidence that the intervention causes increased mortality in the experimental group as compared to the control group.

Interim analyses to evaluate primary and secondary endpoints will be conducted after recruitment of approximately 33% and 66% of the sample, that is, 172 and 344 deaths within 28 days have occurred. Based on these interim analyses, and, possibly, on external evidence, the Data Monitoring Committee shall decide whether there is evidence beyond a reasonable doubt that the treatment is clearly contraindicated in all patients or any subgroup.

The criterion of evidence beyond a reasonable doubt is increased mortality at 28 days with the maximum lung recruitment strategy compared with the low PEEP strategy, with \( P < 0.01 \). Otherwise, the Steering Committee and other investigators will not be informed of the results of interim analyses.
Considering previous evidence showing that: 1) early discontinuation of randomized trials due to benefits tends to produce biased estimates of effect (overestimation of the true effect), leading to erroneous medical guidelines and decisions; 2) according to the ethical principle of non-maleficence, a new treatment should not be used until there is clear, objective evidence that it is beneficial; 3) clinical practice usually does not change unless there is fairly convincing evidence of the advantages of the new treatment, which would be undermined if the study is discontinued early due to benefits; the decision of early discontinuation of the experimental treatment due to benefits may not be advantageous for future patients, or may cause contribute to misleading guidelines.

For these reasons, early discontinuation of the study due to benefits of the experimental treatment is not planned.

Every effort will be made by the Coordinating Centre to provide the data for interim analyses to the DMC without delay, in order to ensure the safety of patients. Accordingly, the Coordinating Centre should send the data for interim analysis as soon as possible, with a maximum span of 45 days after the 172th and 344th deaths have occurred.

Apart from evaluating primary and secondary outcomes interim analyses, the Data Monitoring Committee will receive periodic reports on the incidence of the following study adverse events:

1. During alveolar recruitment (for alveolar recruitment maneuver group):
   a. Need to interrupt alveolar recruitment maneuver and reasons (Heart rate > 150 bpm or < 60 bpm; Reduction of mean blood pressure to <65mmHg or systolic blood pressure <90mmHg; reduction of SpO2 <88% for >30 seconds; severe arrhythmias: acute atrial fibrillation or flutter, ventricular tachycardia)

2. One hour after randomization:
   a. Hypotension (mean blood pressure < 65mmHg)
   b. Use of vasopressors (norepinephrine or dopamine)
c. Hypotension or need of vasopressors

d. Hypoxemia (PaO2 < 55mmHg)

e. Severe acidosis (pH <7.15)

3. From randomization up to day 7:

a. Pneumothorax requiring chest tube;

b. Barotrauma (i.e. any new pneumothorax, pneumomediastinum or subcutaneous
   emphysema or pneumatocele > 2 cm);

The Coordinating Centre will also send reports of study-related serious adverse events to the DMC immediately after receiving them.

3.8.12 Responsibilities of Investigators and Co-Investigators at Participating Centers

The principal investigator at each center will lead and/or supervise the daily operation of the project at his/her participating center and may appoint a Co-investigator and a Research Coordinator. Most tasks can be delegated by the Principal Investigator to research professionals at the Participating Center, provided that the professionals are qualified for such tasks and that the delegation is clearly recorded, with the name of the professionals and their role. However, the principal investigator is legally responsible for the study. Additionally, the principal investigator is responsible for initial implementation of the protocol at each site, for maintenance and refinement of the protocol, quality assurance, and accuracy of data.

The principal investigator is responsible for:

1. Getting approval from the research ethics committee and forwarding the approval to the
   Coordinating Center of the Study; ensuring that approval is obtained before the beginning
   of recruitment;
2. Ensuring compliance with the protocol;

3. Ensuring that all ICU professionals involved in patient treatment are aware of and informed about the study;

4. Ensuring that all patients on mechanical ventilation, who are likely to remain on mechanical ventilation for more than 24 hours, are screened for study participation and that the screening data are entered into the Study Data Management System;

5. Ensuring that data are properly collected and entered into the Study Data Management System.

3.9 Managing and controlling data quality

3.9.1 Electronic data collection system

The IEP-HCor Data Management System is a web-based system developed by a team of programmers at IEP-HCor to run on a Microsoft SQL platform®. The system has the following functions: patient registration, 24-hour randomization with allocation concealment, data input, data cleaning, and data export for statistical analysis.

Data will be collected by means of electronic case report forms via the Internet using the IEP-HCor Data Management System. Data are entered into the system by each center team. All forms are electronically signed by the Principal Investigator in each center or by other appointed persons. Instructions for using the system will be made available to investigators.

3.9.2 Ensuring quality of data

The procedures to ensure data quality include:

1) All investigators will attend a training session before the start of the study to standardize procedures, including data collection;
2) The investigators may contact the Study Coordinating Center to solve issues or problems that may arise;

3) Data entry into the IEP-HCor Data Management System is subject to various checks for missing data, plausible, possible or non-permitted value ranges, and logic checks. Problems are informed by the system at the time of data entry;

4) Statistical techniques to identify inconsistencies will be applied periodically (about every two weeks). The centers will be notified of the inconsistencies and asked to correct them;

5) Statistical routines to identify fraud will be conducted periodically (every 90 days);

6) All centers will be monitored throughout the study;

7) The Coordinating Center will conduct a monthly review of detailed reports on screening, inclusion, follow-up, and data consistency and completeness. The Coordinating Center will take immediate action to solve any problems.

3.9.3 Monitoring

The Coordinating Center (IEP-HCor) is in charge of setting up a monitoring program. Trained professionals will be appointed by the Coordinating Center to monitor the centers.

The monitors will visit all participating centers to ensure compliance with the protocol and standards of good clinical practice. There will be at least one visit to each center to ensure the safety of patients and appropriateness of data collection. Monitoring visits will depend on recruitment rates and may be more frequent at centers with a larger number of patients or centers with missing data/inconsistencies identified through the central statistical monitoring. Training sessions will be provided for investigators and their teams at the start of the study and subsequently as required.

During the monitoring visits, all information will be treated as strictly confidential.

The investigator/institution should provide direct access of all data/documents, and reports for the purpose of monitoring if the coordinator center requests it.
3.10 Publication policy

The Steering Committee of the ART study is responsible for publishing the study’s findings, whatever they are. Because the ART is a large-scale, collaborative, randomized study, we intend to submit the main manuscript to high-impact journals (e.g., New England Journal of Medicine, The Lancet, or JAMA).

The success of the study will depend on the team and on a collaborative effort between investigators, research coordinators and patients. Thus:

- The primary results of the trial will be published under the name of ART Investigators.
- The names of all investigators will be listed at the end of manuscripts or as supplementary material, depending on the editorial policy of each journal. Names will be listed following the alphabetical order of center names.

Suggestions of topics for sub-studies and secondary publications must be submitted by the investigators to the Steering Committee, which will assess the proposal and may approve it, suggest improvements, or reject it. The evaluation will be conducted on the basis of scientific merit and contribution of investigators for the success of the main study.
4  POTENTIAL BENEFITS OF THE STUDY

If the study confirms that maximum alveolar recruitment associated with maintenance of PEEP titration (titration adjusted according to static compliance of the respiratory system) decreases mortality in patients with ARDS, this intervention may, and shall be, widely used in intensive care settings.

If this study finds that the intervention is not beneficial, this finding will also play a role in changing medical practice, since maximum alveolar recruitment associated with high levels of PEEP is routinely used in many institutions, despite the controversy surrounding the available evidence.
REFERENCES


36. GREENFIELD LJ, EBERT PA, BENSON DW. EFFECT OF POSITIVE PRESSURE VENTILATION ON SURFACE TENSION PROPERTIES OF LUNG EXTRACTS. Anesthesiology 1964;25:312-316.


64. Girgis K, Hamed H, Khater Y, Kacmarek RM. A decremental PEEP trial identifies the PEEP level that maintains oxygenation after lung recruitment. Respir Care 2006;51(10):1132-1139.


Appendix A

ART Strategy - Maximum alveolar recruitment maneuver associated with PEEP titration

If patients are assigned to the strategy of maximum alveolar recruitment associated with PEEP titration, the following steps should be observed:

- Maneuver preparation
- Maximum alveolar recruitment maneuver
- PEEP titration
- New recruitment

1 Preparation for performing maximum alveolar recruitment

- Sedate and curarize patient
- Keep patient in same position which the patient was before the randomization (supine or prone)
- Aspirate secretions
- Install closed tracheal suction system (Trach-Care): the ventilatory circuit cannot be disconnected after maximum lung recruitment, because this will cause alveolar collapse and the maneuver will have to be repeated with additional risk for the patient. Therefore, the use of a closed tracheal suction system is mandatory
• Minimum monitoring required during the procedure: heart rate and rhythm; SpO₂; invasive blood pressure

• Correct hypovolemia: volume expansion is important.
  
  o If possible, use the end –expiratory occlusion test or variation in arterial pulse pressure (ΔPP) as a guide. Infuse crystalloids or colloids if pulse pressure increases >5% after end-expiratory occlusion test or if respiratory variation in pulse pressure (ΔPP) is > 13%. If you choose to measure ΔPP, provisionally adjust tidal volume to 8mL/kg for 15 minutes before measuring ΔPP.

  o If end-expiratory occlusion test or ΔPP is not available the goal is a CVP >10cmH₂O

• Maintain MAP ≥75mmHg. If necessary, initiate or increase vasopressors.

• Adjust the respiratory rate to 35 rpm for at least 20 minutes before recruitment.

• Disable backup or apnea ventilation. If this is not possible, reduce activation criteria to the minimum level

2 Maximum Alveolar Recruitment Maneuver and PEEP Titration
Figure 1 shows a graphical representation of the maximum alveolar recruitment maneuver. The mechanical ventilator should be set at controlled pressure mode with 100% FiO₂. The phases of the maneuver are described below:

• Pressure control mode with FiO₂=100%;

• Start with PEEP of 25cmH₂O and delta pressure above PEEP (driving pressure) of 15cmH₂O, which will produce a peak pressure of 40cmH₂O. Respiratory rate of 15/min and I:E ratio of 1:1. These parameters are maintained for 1 minute;
• Next, PEEP should be increased to 30cmH\textsubscript{2}O with driving pressure of 15cmH\textsubscript{2}O. Keep it for 1 minute

• Increase PEEP to 35cmH\textsubscript{2}O, maintaining driving pressure of 15cmH\textsubscript{2}O for 1 minute

3 PEEP titration

• Right after completing the last phase of recruitment, set PEEP to 23cmH\textsubscript{2}O. Change ventilatory mode to controlled volume with tidal volume of 5mL/kg, flow of 30L/min (square wave flow pattern), respiratory rate = 20/min and FiO\textsubscript{2} = 100%; after 3 minutes using these parameters, calculate and record static compliance of the respiratory system (inspiratory pause ≥ 2 seconds required to reach plateau pressure)

\[
\text{Compliance}_{\text{SR}} = \frac{\text{Tidal volume}}{\text{Plateau pressure} - \text{PEEP}}
\]

• Adjust PEEP to 20 cmH\textsubscript{2}O (maintaining the other parameters); after 3 minutes, calculate and record static compliance of the respiratory system

• Adjust PEEP to 17 cmH\textsubscript{2}O (maintaining the other parameters); after 3 minutes, calculate and record static compliance of the respiratory system

• Adjust PEEP to 14 cmH\textsubscript{2}O (maintaining the other parameters); after 3 minutes, calculate and record static compliance of the respiratory system

• Adjust PEEP to 11 cmH\textsubscript{2}O (maintaining the other parameters); after 3 minutes, calculate and record static compliance of the respiratory system

• **The optimal PEEP value is the PEEP at maximum compliance plus 2cmH\textsubscript{2}O**
During PEEP titration, please note:

- If compliance is decreased when PEEP is reduced (e.g., from 23cmH\textsubscript{2}O to 20cmH\textsubscript{2}O) and the decrease in compliance is maintained after the next PEEP decrement (from 20cmH\textsubscript{2}O to 17cmH\textsubscript{2}O), no further reduction in PEEP is required.

- Values of compliance with difference <1mL/cmH\textsubscript{2}O are considered similar (e.g.: if compliance measured at two PEEP are 22.9mL/cmH\textsubscript{2}O and 22.0mL/cmH\textsubscript{2}O they are considered similar).

- In some cases, compliance increases following PEEP decrements and reaches a plateau (maximum value of compliance similar in two or more PEEP levels). In these cases, optimal PEEP = highest PEEP within the plateau range + 2cmH\textsubscript{2}O.

4 Repeat lung recruitment:

- Return to controlled pressure mode, respiratory rate of 15/min and I:E ratio of 1:1; delta pressure above PEEP (driving pressure) of 15 cmH\textsubscript{2}O and adjust PEEP to 35 cmH\textsubscript{2}O, maintaining it for 1 minute.

- After repeating Maintenance ventilation, initiate maintenance ventilation as described on item 7.

5 Criteria for terminating maximum alveolar recruitment maneuver

- Heart rate > 150 bpm or < 60 bpm

- Reduction of MAP to <65mmHg or SAP <90mmHg
• Reduction of SpO₂ <88% for >30 seconds

• Severe heart arrhythmias:
  o Acute atrial fibrillation or flutter
  o (Sustained or non-sustained) ventricular tachycardia

If recruitment is interrupted, physicians should proceed to PEEP titration, but should not repeat recruitment after titration. If a patient remains unstable while PEEP is titrated, then PEEP titration should be interrupted and the patient should be placed on the ARDS Net protocol. In this case, recruitment should be considered later if the patient’s condition stabilizes.

6 When should the maximum alveolar recruitment maneuver be repeated?
The maximum alveolar recruitment maneuver can be repeated every 24 hours if the initial recruitment maneuver was successful* and the patient presents with anyone of the following:

1) PaO₂/FiO₂ is lower than 250 AND there is decrease >50mmHg in the PaO₂/FiO₂ ratio. After the recruitment maneuver, PEEP should be set at the value it was before plus 2cmH₂O. That is, there is no need to titrate PEEP again.

2) If an accidental disconnection of the respiratory circuit occurs and PEEP is ≥12cmH₂O. As much as possible, avoid disconnecting the ventilator circuit. After the recruitment maneuver, PEEP should be set at the same level it was before disconnection. There is no need to titrate PEEP again.

*The recruitment maneuver is considered successful if:

Increase in PaO₂/FiO₂ ≥50mmHg in blood gases measured after recruitment.
**Figure 1.** ART Strategy - Maximum alveolar recruitment maneuver associated with PEEP titration.
7 Maintenance ventilation

- **PEEP:** set PEEP to the optimal value
- **Mode:** controlled volume mode
- **Plateau pressure ≤ 30cmH2O**
- **Tidal volume:** 6mL/kg of predicted body weight. If plateau pressure > 30cmH2O, reduce the tidal volume to 5 or 4 mL/kg of predicted body weight. Minimum and maximum values of tidal volume are 4 and 6mL/kg of predicted body weight, in order to maintain plateau pressure ≤ 30cmH2O. Predicted body weight to be calculated for all patients according to Devine’s formula:

**Men:** Predicted body weight (kg) = 50 + 2.3 ((height [cm] × 0.394) – 60)

**Women:** Predicted body weight (kg) = 45.5 + 2.3 ((height [cm] × 0.394) – 60)

- **Respiratory rate:** 35/min. If pH >7.5 in arterial blood gases 1 hour after randomization (or subsequent blood gas analysis), adjust the respiratory rate.
- **Flow:** 60L/min
- **Descending flow waveform**
- **Inspiratory pause:** 0.5 second
- **I:E ratio** between 1:1 and 1:2
- **FiO2** to maintain SpO2 ≥90% and ≤95%

8 Adjustments on ventilator settings

8.1 Adjustments on respiratory rate
Goals: Respiratory rate must be adjusted to achieve the arterial pH goal.

Arterial pH goals

pH between 7.30 and 7.45.

The pH is measured when clinically indicated

Management of alkalemia

**Alkalemia (pH > 7.45):** reduce respiratory rate, if possible

Management of acidemia

**Mild acidemia** (7.15 ≤ pH < 7.30):

- Control of body temperature (≤37°C);

- If PaCO₂≤40mmHg, consider sodium bicarbonate and, if possible, treat the cause of metabolic acidosis

- If PaCO₂>40mmHg:
  - Increase respiratory rate up to a maximum of 35 aiming a pH > 7.30 or PaCO₂ < 40mmHg, whichever occurs first. If there is associated metabolic acidosis, it should also be managed.
  - If the respiratory rate = 35 and pH is between 7.15 and 7.30, there is no need of additional measures.

**Severe acidemia** (pH < 7.15):

- If PaCO₂≤40mmHg, consider sodium bicarbonate and, if possible, treat the cause of metabolic acidosis

- If PaCO₂>40mmHg, following the sequential steps below:
Increase respiratory rate to 35. If there is associated metabolic acidosis, it should also be managed.

If respiratory rate = 35, pH < 7.15, and PaCO₂ >40mmHg, increase tidal volume in steps of 1mL/kg, up to 6mL/kg of predicted body weight. In this condition, the plateau pressure goal of 30 cmH₂O can be exceeded.

If respiratory rate = 35, pH < 7.15, PaCO₂ >40mmHg, and tidal volume is 6mL/kg of predicted body weight, increase tidal volume to 7mL/kg of predicted body weight.

If the situation remains unresolved (respiratory rate = 35, pH < 7.15, PaCO₂ >40mmHg, and tidal volume is 7mL/kg of predicted body weight) increase tidal volume to 8mL/kg of predicted body weight.

If the situation remains unresolved (respiratory rate = 35, pH < 7.15, PaCO₂ >40mmHg, and tidal volume is 8mL/kg of predicted body weight), consider:

- Change passive heat and moisture exchangers (HME) to active heated humidifiers;
- Nitric oxide;
- ECMO, if available.

### 8.2 Inspiratory flow and I:E ratio

- Keep I:E ratio between 1:1 to 1:2.
- Inspiratory flow of 60L/min. May be decreased up to 40L/min if peak pressure is >45cmH₂O;
- Inspiratory pause of 0.5 second. May be adjusted if I:E ratio is not between 1:1 to 1:2.

### 8.3 Adjustments in FIO₂

Adjust FiO₂ to reach the oxygenation goal.
Oxygenation goals are:

- \(60 \text{mmHg} \leq \text{PaO}_2 \leq 80 \text{mmHg}\)

  or

- \(90\% \leq \text{SpO}_2 \leq 95\%\)

**Observations:**

- When \(\text{PaO}_2\) and \(\text{SpO}_2\) are measured simultaneously, consider \(\text{PaO}_2\).

- \(\text{FiO}_2\) can be reduced to a minimum of 30%.

- Arterial oxygenation should be assessed by \(\text{SpO}_2\) or \(\text{PaO}_2\) at least every 4 hours. When \(\text{SpO}_2\) was used to assess arterial oxygenation, the following measures should be taken, if possible, to ensure accuracy: make sure that the \(\text{SpO}_2\) sensor is well positioned, clean, and providing consistent measures with satisfactory waveforms; changes in position or tracheal aspiration should not be performed in the last 10 minutes; there should not be invasive procedures or ventilator changes the for at least 30 minutes. The \(\text{SpO}_2\) value to be recorded will be based on observation of \(\text{SpO}_2\) for at least one minute.

- \(\text{FiO}_2 = 100\%\) can be used for short intervals (10 minutes) of transient decrease in \(\text{SpO}_2\) or to prevent drop in \(\text{SpO}_2\) during procedures such as tracheal aspiration or changes in position.

### 8.4 Refractory hypoxemia

Refractory hypoxemia is defined as a \(\text{PaO}_2<55\text{mmHg}\) or \(\text{SpO}_2<88\%\) with \(\text{FiO}_2=100\%\).

The following sequential actions should be taken for patients presenting with refractory hypoxemia:

- Prone position: patient should be put on prone position;

- If the patient does not improve, then start inhaled nitric oxide, if available, beginning with 5ppm and increasing in steps of 5ppm until there is improvement in oxygenation;

- Final step is to initiate ECMO (extracorporeal membrane oxygenation) if available.
8.5 Patient-ventilator dyssynchrony

If airway pressure falls below PEEP during inspiration or if ventilator performs more than 3 double-inspirations per minute because of pressure drop (or flow) below the level of sensitivity (trigger threshold) at the end of inspiration, consider increasing the level of sedation or add neuromuscular blockade.

8.6 Changes of heat-moisture exchanger and closed aspiration system

We suggest changing heat-moisture exchanger and closed-aspiration system only when there is visible filth. In order to avoid reducing airway pressures, use a Reynold nipper to occlude endotracheal tube while changing HME or closed-aspiration system. Changes should preferentially be conducted by more than one person in the minimum possible time.

9 Weaning

9.1 PEEP reduction

Start reducing PEEP only after FiO₂ ≤ 40%.

PEEP may be reduced in patients with PaO₂/FiO₂ above 300 for more than 24 hours. PEEP can be reduced by 2cmH₂O every 8 hours if PaO₂/FiO₂ remains above 300.

In patients who do not reach maximum values of PaO₂/FiO₂ above 300 after recruitment, start weaning from PEEP 24 hours after recruitment if PaO₂/FiO₂ values are similar to or greater than the values recorded the day before.

**When to stop decreasing PEEP?**

If the PaO₂/FiO₂ drops >50mmHg after decreasing PEEP return to the previous PEEP value.

If the PaO₂/FiO₂ drops >50mmHg and below 250mmHg, and the initial recruitment maneuver was successful (PaO₂/FiO₂ > 300mmHg or increase in PaO₂/FiO₂ > 100mmHg after recruitment maneuver) then alveolar
recruitment should be repeated, and PEEP should be set to the previous value (value before recruiting plus 2cmH₂O).

9.2 Pressure support ventilation
May be initiated in alert patients when PEEP is ≤ 14cmH₂O. Start with PS of 10cmH₂O or less to achieve tidal volume of 6 mL/kg of predicted body weight. PS ventilation can be reduced from 2 to 4 cmH₂O twice daily as long as respiratory frequency is <28 breaths per min (and there are no other signs of discomfort). In patients with signs of discomfort (eg, those with ≥30 breaths per minute) investigators should consider other causes (eg, pain or anxiety) before increasing PS. If PS over 14cmH₂O is needed, then volume-controlled ventilation will be resumed.

9.3 When should a "spontaneous breathing" test be performed?
Weaning should be attempted daily, preferably in the morning. The criteria shown on Table 1 must be considered to start the spontaneous breathing test. After weighing these criteria, the clinician should make a decision to perform or not the spontaneous breathing test.
Table 1. Criteria for performing a spontaneous breathing test

<table>
<thead>
<tr>
<th>Clinical assessment</th>
<th>Improvement of acute process (ARDS and associated conditions) leading to intubation and mechanical ventilation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient is alert and cooperative</td>
<td></td>
</tr>
<tr>
<td>Chest pain is controlled</td>
<td></td>
</tr>
<tr>
<td>Adequate cough (moderate to high strength)</td>
<td></td>
</tr>
<tr>
<td>Absence of excessive tracheobronchial secretion</td>
<td></td>
</tr>
<tr>
<td>No signs of respiratory distress:</td>
<td></td>
</tr>
<tr>
<td>Nostril flaring</td>
<td></td>
</tr>
<tr>
<td>Use of accessory muscles of respiration (suprasternal and/or intercostal retraction)</td>
<td></td>
</tr>
<tr>
<td>Paradoxical movements of the chest/abdomen</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Objective measurements</th>
<th>Respiratory stability: oxygenation</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEEP ≤ 8cmH₂O</td>
<td></td>
</tr>
<tr>
<td>Support pressure ≤12cmH₂O</td>
<td></td>
</tr>
<tr>
<td>PaO₂/FiO₂ ≥250 (consider weaning if ≥200)</td>
<td></td>
</tr>
<tr>
<td>SpO₂&gt;90% under FiO₂≤ 40%</td>
<td></td>
</tr>
</tbody>
</table>

Respiratory stability: function

<table>
<thead>
<tr>
<th>Respiratory rate ≤ 35 breaths/min</th>
<th>Minute volume &lt;10 L/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory rate/tidal volume (L) &lt; 105 breath/min/L</td>
<td>No significant respiratory acidosis (pH ≥ 7.25)</td>
</tr>
</tbody>
</table>

Cardiovascular stability

<table>
<thead>
<tr>
<th>Heart rate &lt; 140 bpm</th>
<th>Systolic blood pressure&gt; 90 and &lt;160mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without vasoconstrictor/inotropic drugs (or low doses)</td>
<td></td>
</tr>
</tbody>
</table>

Neurological stability


Clinicians often underestimate the patients’ ability to be successfully extubated, and none of the criteria described in Table 1 is highly sensitive or specific. Thus, these criteria serve as a guide for clinicians. Some patients who do not meet all the criteria may perform the spontaneous breathing test and be successfully extubated.
9.3.1 Spontaneous breathing test

The ability to discontinue mechanical ventilation should be evaluated formally by means of spontaneous breathing test and not during regular ventilatory support.

Settings for the spontaneous breathing test

- Mode: support pressure
- PEEP: 5cmH₂O
- Support pressure: 5cmH₂O (insufficient to provide ventilatory support, serving only to offset resistance of the circuit/tube)
- FiO₂: keep as before the test
- Duration: 30 minutes

Success/failure of the spontaneous breathing test

The criteria that determine failure of the spontaneous breathing are shown in Table 2.
**Table 2.** Criteria for failure of the spontaneous breathing test

<table>
<thead>
<tr>
<th>Clinical assessment</th>
<th>Objective measurements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agitation, excessive anxiety or depressed level of consciousness</td>
<td>Respiratory instability: oxygenation</td>
</tr>
<tr>
<td>Major sweating</td>
<td>SpO₂ &lt; 90%</td>
</tr>
<tr>
<td>Cyanosis</td>
<td>Heart instability: function</td>
</tr>
<tr>
<td>Signs of respiratory distress:</td>
<td>Respiratory rate &gt; 35 breaths/min or increase &gt; 10 breaths/min</td>
</tr>
<tr>
<td>Nostril flaring</td>
<td>Respiratory rate/tidal volume (L) &lt; 105 breath/min/L</td>
</tr>
<tr>
<td>Use of accessory muscles of respiration (suprasternal and/or intercostal retraction)</td>
<td>If arterial blood gases measured:</td>
</tr>
<tr>
<td>Paradoxical movements of the chest/abdomen</td>
<td>pH &lt; 7.25</td>
</tr>
<tr>
<td></td>
<td>PaCO₂ &gt; 50mmHg or increase &gt; 8mmHg</td>
</tr>
<tr>
<td></td>
<td>Cardiovascular instability</td>
</tr>
<tr>
<td></td>
<td>Heart rate &lt; 140 bpm</td>
</tr>
<tr>
<td></td>
<td>Systolic blood pressure &lt; 90 and &gt; 160mmHg</td>
</tr>
<tr>
<td></td>
<td>Onset of arrhythmias (e.g., frequent ventricular extrasystole)</td>
</tr>
</tbody>
</table>

If there are signs of failure:

- Terminate test immediately

- Return to pre-test mechanical ventilation settings and keep them until the next morning (for rest)

- Find and treat factors reducing the success of weaning (e.g., anxiety, delirium, bronchospasm, heart failure, hypophosphatemia/hypokalemia/hypomagnesemia, abdominal strain)

9.3.2 **Extubation**
Patients who pass the spontaneous breathing test can be extubated. Cuff leak test is optional. Consider use of systemic steroids in patients intubated for long periods to prevent upper airway obstruction after extubation.

9.3.3 Post-extubation NIV

Consider non-invasive ventilation immediately after extubation for all patients. This is strongly recommended for patients at high risk of extubation failure, such as:

- Patients who do not meet all the criteria for extubation (i.e., respiratory rate/tidal volume (L) ≥ 105 breaths/min/L)
- Patients who failed the spontaneous breathing test at least once
Appendix B

ARDSNet strategy

The mechanical ventilation procedures for this group are:

1 Mechanical ventilation settings

- Mode: controlled volume mode
- Plateau pressure ≤ 30cmH2O
- Tidal volume: 6mL/kg of predicted body weight. If plateau pressure > 30cmH2O, reduce the tidal volume to 5 or 4 mL/kg of predicted body weight. Minimum and maximum values of tidal volume are 4 and 6mL/kg of predicted body weight, in order to maintain plateau pressure ≤ 30cmH2O.

Predicted body weight to be calculated for all patients according to Devine’s formula:

Men: Predicted body weight (kg) = 50 + 2.3 ((height [cm] × 0.394) – 60)

Women: Predicted body weight (kg) = 45.5 + 2.3 ((height [cm] × 0.394) – 60)

- Respiratory rate: If possible, adjust initial frequency with the aim of maintaining the same minute volume recorded before study entry. Maximum respiratory rate will be 35/min.
- Flow: 60L/min
- Descending flow waveform
- Inspiratory pause: 0.5 second
- I:E ratio between 1:1 and 1:2
- PEEP and FiO2 adjusted according to the ARDSNet table (Table 1) to maintain SpO2 88-95% (55-80mmHg) (table1).
Table 1. ARDSNet table of FiO₂ and PEEP values to keep SpO₂ 88-95% and PaO₂ 55-80mmHg

<table>
<thead>
<tr>
<th>FiO₂</th>
<th>30%</th>
<th>40%</th>
<th>50%</th>
<th>60%</th>
<th>70%</th>
<th>80%</th>
<th>90%</th>
<th>90%</th>
<th>100%</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEEP</td>
<td>5</td>
<td>5</td>
<td>8</td>
<td>8</td>
<td>10</td>
<td>10</td>
<td>12</td>
<td>14</td>
<td>14</td>
</tr>
</tbody>
</table>

2 Adjustements on ventilator settings

2.1 Settings of tidal volume and respiratory rate

Respiratory rate and tidal volume must be adjusted to achieve arterial pH and inspiratory plateau pressure goals, respectively.

Arterial pH goals

pH between 7.30 and 7.45.

Arterial pH will be measured when clinically indicated.

Management of alkalemia

Alkalemia (pH > 7.45): reduce respiratory rate, if possible

Management of acidemia

Mild acidemia (7.15 ≤ pH < 7.30):

- If PaCO₂≤40mmHg, consider sodium bicarbonate and, if possible, treat the cause of metabolic acidosis
- If PaCO₂>40mmHg:
  - Control of body temperature (≤ 37°C)
  - Increase respiratory rate up to a maximum of 35 aiming a pH > 7.30 or PaCO₂ < 40mmHg, whichever occurs first. If there is associated metabolic acidosis, it should also be managed.
o If the respiratory rate = 35 and pH is between 7.15 and 7.30, there is no need of additional measures.

Severe acidemia (pH < 7.15):

- If PaCO$_2$$\leq$40mmHg, consider sodium bicarbonate and, if possible, treat the cause of metabolic acidosis
- If PaCO$_2$>40mmHg, following the sequential steps below:
  o Increase respiratory rate to 35. if there is associated metabolic acidosis, it should also be managed.
  o If respiratory rate = 35, pH < 7.15, and PaCO$_2$ >40mmHg, increase tidal volume in steps of 1mL/kg, up to 6mL/kg of predicted body weight. In this condition, the plateau pressure goal of 30 cmH2O can be exceeded.
  o If respiratory rate = 35, pH < 7.15, PaCO$_2$ >40mmHg, and tidal volume is 6mL/kg of predicted body weight, increase tidal volume to 7mL/kg of predicted body weight.
  o If the situation remains unresolved (respiratory rate = 35, pH < 7.15, PaCO$_2$ >40mmHg, and tidal volume is 7mL/kg of predicted body weight) increase tidal volume to 8mL/kg of predicted body weight.
  o If the situation remains unresolved (respiratory rate = 35, pH < 7.15, PaCO$_2$ >40mmHg, and tidal volume is 8mL/kg of predicted body weight, consider:
    - Change passive heat and moisture exchangers (HME) to active heated humidifiers;
    - Nitric oxide;
    - ECMO, if available.

o Goals of plateau pressure
Plateau pressure ≤ 30 cmH₂O.

- Check the plateau pressure often at least every 4 hours. Plateau pressure should also be checked 1-5 minutes after each change in PEEP or tidal volume. To verify the plateau pressure, patients should be relaxed, not coughing or moving. If plateau pressure cannot be measured because of air leaks, then peak inspiratory pressure will be replaced.

- Reduce tidal volume by 1 ml/kg of predicted body weight every 2-3 hours if necessary to maintain plateau pressure ≤ 30 cmH₂O, except if arterial pH < 7.15.

- If airway pressure falls below PEEP during inspiration or if ventilator performs more than 3 double-inspirations per minute because of pressure drop (or flow) below the level of sensitivity (trigger threshold) at the end of inspiration, consider increasing the level of sedation or add neuromuscular blockade.

### 2.2 Inspiratory flow and I:E ratio

- Keep I:E ratio between 1:1 to 1:2.

- Inspiratory flow of 60L/min. May be decreased up to 40L/min if peak pressure is >45cmH₂O;

- Inspiratory pause of 0.5 second. May be adjusted if I:E ratio is not between 1:1 to 1:2.

### 2.3 Adjustements on PEEP and FiO₂

Target ranges for oxygenation are:

\[ 55 \text{ mmHg} \leq \text{PaO}_2 \leq 80 \text{ mmHg} \]

or

\[ 88\% \leq \text{SpO}_2 \leq 95\% \]

Oxygenation will be kept within the target ranges using the following PEEP/FiO₂ on table 1.

**Observations:**

- When both PaO₂ and SpO₂ are available simultaneously, choose PaO₂.
• PEEP levels in the FiO₂/PEEP scale represent the levels set on the ventilator, rather than of total-PEEP, auto-PEEP or intrinsic-PEEP levels.

• Arterial oxygenation should be assessed by SpO₂ or PaO₂ at least every 4 hours. When SpO₂ was used to assess arterial oxygenation, the following measures should be taken, if possible, to ensure accuracy: make sure that the SpO₂ sensor is well positioned, clean, and providing consistent measures with satisfactory waveforms; changes in position or tracheal aspiration should not be performed in the last 10 minutes; there should not be invasive procedures or ventilator changes the for at least 30 minutes. The SpO₂ value to be recorded will be based on observation of SpO₂ for at least one minute.

• If arterial oxygenation is outside the target range, then FiO₂ or PEEP should be adjusted within 30 minutes. Next, oxygenation should be reevaluated within 15 minutes and subsequent adjustments should be made, if necessary.

• If PEEP/FiO₂ in a patient is not compatible with the PEEP/FiO₂ scale (i.e., immediately after randomization and after urgent changes in FiO₂ or PEEP in response to decreases in SpO₂, blood pressure, etc.), PEEP and FiO₂ (or both) should be adjusted every 5-15 minutes until achieving a combination compatible with the scale.

• If PaO₂ < 55mmHg or SpO₂ < 88% and tidal volume = 4ml/kg of predicted body weight (or minimum tidal volume required for pH control) and plateau pressure ≥ 30 30cmH₂O, then FiO₂ should be increased until PaO₂ = 55 – 80 mmHg or SpO₂ = 88-95%. If PaO₂ < 55mmHg or SpO₂ < 88% and FiO₂ = 100%, PEEP should be increased at 2 cmH₂O increments up to a maximum of 24cmH₂O. Under these conditions, plateau pressure may exceed 30 cmH₂O.

• Brief periods (5 minutes) of SpO₂ < 88% or > 95% can be tolerated without changes in FiO₂ or PEEP.

• FiO₂ = 100% can be used for short intervals (10 minutes) of transient decrease in SpO₂ or to prevent drop in SpO₂ during procedures such as tracheal aspiration or changes in position.
• Tracheal aspiration should be performed using a closed-tracheal suction system (Trach-Care). Disconnections should be avoided as much as possible.

2.4 Simultaneous changes

Changes in more than one ventilator setting based on the measures of PaO$_2$, pH and plateau pressure may be performed simultaneously, if necessary. Obtain arterial blood gases after all changes in the mechanical ventilator as clinically recommended.

2.5 Refractory hypoxemia

Refractory hypoxemia is defined as a PaO$_2$<55mmHg or SpO$_2$<88% with FiO$_2$=100%.

The following sequential actions should be taken for patients presenting with refractory hypoxemia:

• Increase PEEP level up to 24cmH$_2$O (the right end of the ARDS Net table).

• Increase PEEP by 2-5cmH$_2$O stepwise until a maximum of 34cmH$_2$O or until PaO$_2$ = 55 to 80 mmHg or SpO$_2$ = 88-95%. If there is no increase in PaO$_2$ ≥ 5 mmHg within 05-10 minutes, PEEP should be kept at 24 cmH$_2$O

• Prone position: patient should be put on prone position;

• If the patient does not improve, then start inhaled nitric oxide, if available, begining with 5ppm and increasing in steps of 5ppm until there is improvement in oxygenation;

• Final step is to initiate ECMO (extracorporeal membrane oxygenation) if available.

Alveolar recruitment maneuvers should not be conducted for patients assigned to the ARDSNet Strategy.

3 Weaning

3.1 PEEP reduction

PEEP reduction should be performed according to the ARDSNet PEEP/FiO$_2$ combination table (see above).
3.2 Pressure support ventilation

May be initiated in alert patients when PEEP is ≤ 14cmH2O. Start with PS of 10cmH2O or less to achieve tidal volume of 6 mL/kg of predicted body weight. PS ventilation can be reduced from 2 to 4 cmH2O twice daily as long as respiratory frequency is <28 breaths per min (and there are no other signs of discomfort). In patients with signs of discomfort (eg, those with ≥30 breaths per minute) investigators should consider other causes (eg, pain or anxiety) before increasing PS. If PS over 14cmH2O is needed, then volume-controlled ventilation will be resumed.

3.3 When should a "spontaneous breathing" test be performed?

Weaning should be attempted daily, preferably in the morning. The criteria shown on Table 2 must be considered to start the spontaneous breathing test. After weighing these criteria, the clinician should make a decision to perform or not the spontaneous breathing test.
**Table 2. Criteria to perform spontaneous breathing test**

<table>
<thead>
<tr>
<th>Clinical assessment</th>
<th>Improvements of acute process (ARDS and associated conditions) leading to intubation and mechanical ventilation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patient is alert and cooperative</td>
</tr>
<tr>
<td></td>
<td>Chest pain is controlled</td>
</tr>
<tr>
<td></td>
<td>Adequate cough (moderate to high strength)</td>
</tr>
<tr>
<td></td>
<td>Absence of excessive tracheobronchial secretion</td>
</tr>
<tr>
<td></td>
<td>No signs of respiratory distress:</td>
</tr>
<tr>
<td></td>
<td>Nostril flaring</td>
</tr>
<tr>
<td></td>
<td>Use of accessory muscles of respiration (suprasternal and/or intercostal retraction)</td>
</tr>
<tr>
<td></td>
<td>Paradoxical movements of the chest/abdomen</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Objective measurements</th>
<th>Respiratory stability: oxygenation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PEEP ≤ 8cmH₂O</td>
</tr>
<tr>
<td></td>
<td>Support pressure ≤12cmH₂O</td>
</tr>
<tr>
<td></td>
<td>PaO₂/FiO₂ ≥250 (consider weaning if ≥200)</td>
</tr>
<tr>
<td></td>
<td>SpO₂&gt;90% under FiO₂≤ 40%</td>
</tr>
<tr>
<td></td>
<td>Respiratory rate ≤ 35 breaths/min</td>
</tr>
<tr>
<td></td>
<td>Minute volume &lt;10 L/min</td>
</tr>
<tr>
<td></td>
<td>Respiratory rate/tidal volume (L) &lt; 105 breath/min/L</td>
</tr>
<tr>
<td></td>
<td>No significant respiratory acidosis (pH ≥ 7.25)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cardiovascular stability</th>
<th>Heart rate &lt; 140 bpm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Systolic blood pressure&gt; 90 and &lt;160mmHg</td>
</tr>
<tr>
<td></td>
<td>Without vasoconstrictor/inotropic drugs (or low doses)</td>
</tr>
</tbody>
</table>


Clinicians often underestimate the patients' ability to be successfully extubated, and none of the criteria described in Table 2 is highly sensitive or specific. Thus, these criteria serve as a guide for clinicians. Some patients who do not meet all the criteria may perform the spontaneous breathing test and be successfully extubated.
3.3.1 Spontaneous breathing test

The ability to discontinue mechanical ventilation should be evaluated formally by means of spontaneous breathing test and not during regular ventilatory support.

Settings for the spontaneous breathing test

- Mode: support pressure
- PEEP: 5cmH\textsubscript{2}O
- Support pressure: 5cmH\textsubscript{2}O (insufficient to provide ventilatory support, serving only to offset resistance of the circuit/tube)
- FiO\textsubscript{2}: keep as before the test
- Duration: 30 minutes

Success/failure of the spontaneous breathing test

The criteria that determine failure of the spontaneous breathing are shown in Table 3.
Table 3. Criteria for failure of the spontaneous breathing test

<table>
<thead>
<tr>
<th>Clinical assessment</th>
<th>Agitation, excessive anxiety or depressed level of consciousness</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Major sweating</td>
</tr>
<tr>
<td></td>
<td>Cyanosis</td>
</tr>
<tr>
<td>Signs of respiratory distress:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nostril flaring</td>
</tr>
<tr>
<td></td>
<td>Use of accessory muscles of respiration (suprasternal and/or intercostal retraction)</td>
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<td>Paradoxical movements of the chest/abdomen</td>
</tr>
<tr>
<td>Objective measurements</td>
<td>Respiratory instability: oxygenation</td>
</tr>
<tr>
<td></td>
<td>SpO$_2$ &lt; 90%</td>
</tr>
<tr>
<td>Heart instability: function</td>
<td>Respiratory rate &gt; 35 breaths/min or increase &gt; 10 breaths/min</td>
</tr>
<tr>
<td></td>
<td>Respiratory rate/tidal volume (L) &lt; 105 breath/min/L</td>
</tr>
<tr>
<td>If arterial blood gases measured:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>pH &lt; 7.25</td>
</tr>
<tr>
<td></td>
<td>PaCO$_2$ &gt; 50 mmHg or increase &gt; 8 mmHg</td>
</tr>
<tr>
<td>Cardiovascular instability</td>
<td>Heart rate &lt; 140 bpm</td>
</tr>
<tr>
<td></td>
<td>Systolic blood pressure &lt; 90 and &gt; 160 mmHg</td>
</tr>
<tr>
<td></td>
<td>Onset of arrhythmias (e.g., frequent ventricular extrasystole)</td>
</tr>
</tbody>
</table>

If there are signs of failure:

- Terminate test immediately
- Return to pre-test mechanical ventilation settings and keep them until the next morning (for rest)
- Find and treat factors reducing the success of weaning (e.g., anxiety, delirium, bronchospasm, heart failure, hypophosphatemia/hypokalemia/hypomagnesemia, abdominal strain)

3.3.2 Extubation

Patients who pass the spontaneous breathing test can be extubated. Cuff leak test is optional. Consider use of systemic steroids in patients intubated for long periods to prevent upper airway obstruction after extubation.
3.3.3 Post-extubation NIV

Consider non-invasive ventilation immediately after extubation for all patients. This is strongly recommended for patients at high risk of extubation failure, such as:

- Patients who do not meet all the criteria for extubation (i.e., respiratory rate/tidal volume (L) ≥ 105 breaths/min/L)
- Patients who failed the spontaneous breathing test at least once
Statistical Analysis Plan for the Alveolar Recruitment for ARDS Trial (ART): A Randomized Controlled Trial

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2. Pulmonary Division, Heart Institute (InCor), Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil.
1 INTRODUCTION

Alveolar collapse with reduction of functional lung size (“baby lung”) is a hallmark of acute respiratory distress syndrome (ARDS).\(^1\) Although, mechanical ventilation is needed to support life in patients with moderate-to-severe ARDS, it may damage lungs via two mechanisms 1) overdistention and 2) cyclic opening and closing of small airways and alveoli (atelectrauma).\(^2\) Mechanical ventilation with low tidal volumes and low positive end-expiratory pressure (PEEP) decreases but does not cease ventilator-induced lung injury (VILI).\(^3,4\) Cyclic opening and closing of lung units persists with this strategy.\(^5\) The aim of recruitment maneuvers and PEEP titration is to open collapsed units and keep them opened, thus minimizing atelectrauma and possibly dynamic overdistention.\(^6\) Most patients with ARDS for less than 72 hours are highly responsive to recruitment maneuvers and serious adverse events are uncommon.\(^7,8\) However, the effect of recruitment maneuvers and PEEP titration on clinical outcomes of ARDS patients is uncertain. A systematic review with meta-analysis of studies assessing recruitment maneuvers has suggested a reduction in mortality, however quality of evidence is limited due to high risk of bias in most primary studies and variable use of co-interventions such as PEEP titration.\(^9\)

The Alveolar Recruitment Trial (ART) is an international, multicenter, randomized, controlled trial comparing a strategy of maximum lung recruitment associated with PEEP titration adjusted according to static compliance of the respiratory system versus a conventional approach (ARDSNet protocol) for patients with moderate-severe ARDS.
This document outlines the statistical analysis plan for ART with the aim of preventing statistical analysis bias arising from exploratory analyses after study results are known. The statistical analysis plan has been developed before locking the trial database and starting analyses.

2 OBJECTIVE

The primary objective is to determine if alveolar recruitment associated with PEEP titration adjusted according to the static compliance of the respiratory system (ART strategy) increases 28-day survival rate of patients with moderate to severe ARDS compared to conventional treatment (ARDSNet strategy).

3 METHODS

Design

ART is an international, multicenter, randomized, pragmatic, controlled trial with allocation concealment and intention-to-treat (ITT) analysis, comparing a strategy of maximum lung recruitment associated with PEEP titration adjusted according to static compliance of the respiratory system (ART strategy) versus ARDSNet approach for patients with moderate to severe ARDS. The trial is being conducted in 120 intensive care units in Brazil, Argentina, Colombia, Italy, Poland, Portugal, Malaysia, Spain, and Uruguay. The trial protocol was previously published and is registered with ClinicalTrials.gov (NCT01374022). It was approved by the ethics committee of all participant institutions.

Patients
Eligibility is evaluated in two phases, screening phase and defining eligibility phase. In the screening phase, patients are considered for inclusion in the study if they are receiving invasive mechanical ventilation and have ARDS of less than 72 hours’ duration. All of the following criteria should be met: acute onset respiratory failure; bilateral pulmonary infiltrate on chest X ray compatible with pulmonary edema; severe hypoxemia, defined as PaO$_2$/FiO$_2$ ≤ 200 in arterial blood gases for less than 72 hours; absence of left atrial hypertension based on the medical team’s evaluation (clinical or echocardiographic signs); presence of a risk factor for lung injury.

The following are exclusion criteria (exclusion if anyone present): age < 18 years; use of vasoconstrictor drugs in increasing doses over the past 2 hours (≥ 0.2mcg/kg per min for norepinephrine or ≥ 5mcg/kg per min for dopamine) or mean arterial pressure < 65 mmHg; contraindication to hypercapnia with intracranial hypertension or acute coronary syndrome; pneumothorax, subcutaneous emphysema, pneumomediastinum or pneumatocele; patient with no therapeutic perspective; candidate for palliative care exclusively (e.g.: patient with imminent death, in moribund state or dying cancer patient under exclusive palliative care); patient previously randomized in the study.

While waiting for the consent of a legal representative we suggest to ventilate patients using a conventional approach (ARDSNet) as follows: volume-controlled mode, tidal volume of 4-6mL/kg of predicted body weight to ensure plateau pressure ≤ 30cmH$_2$O, PEEP and FiO$_2$ adjusted according to the ARDSNet table (Table 1) to maintain SpO$_2$ ≥ 88% and PaO$_2$ ≥ 55mmHg, flow of 60 L/min (may be reduced if peak pressure >45cmH$_2$O), descending waveform, inspiratory to expiratory ratio (I:E) of 1:1
to 1:2, inspiratory pause of 0.5 second (may be reduced if I:E ratio is inverted), respiratory rate to keep PaCO₂ between 35mmHg and 60mmHg. Alveolar recruitment maneuvers should be avoided. After three hours of mechanical ventilation according to the ARDSNet protocol, FIO₂ is adjusted to 100% and PEEP to 10cmH₂O (except if previous PEEP was ≥16cmH₂O; in this case PEEP is maintained) for 30 minutes, after which arterial blood gases are measured. Patients are considered eligible if the PaO₂ measured with FIO₂ = 100% and PEEP = 10cmH₂O (or ≥ 16cmH₂O) is 200 mmHg or less, and less than 72 hours have been spent since the first time a PaO₂/FIO₂ ≤ 200 was determined.

Randomization

Eligible patients are randomly allocated in a 1:1 ratio to treatment with either the ART or ARDSNet strategy. The randomization list is generated electronically using appropriate software. Randomization is performed in blocks with stratification by center, age (≤ 55 or > 55 years-old) and by PaO₂/FIO₂ ratio (≤ 100 or > 100mmHg).

Allocation concealment is maintained by means of a web-based central, automated randomization system, available 24 hours a day (ACT-Clinic), developed by a team of programmers and investigators from the Research Institute HCor. The group to which the patient is allocated is disclosed only after the patient is registered in the electronic system. This prevents the investigator and the medical team from predicting to which treatment group the patient will be allocated. To include a patient in the study, investigators must simply access the HCor Data Management System website (https://servicos.hcor.com.br/iep/estudoclinico) and fill in a short medical record form.

Treatment groups
Patients randomly assigned to the ART group undergo alveolar recruitment with incremental PEEP levels, then PEEP titration according to the static compliance of the respiratory system, followed by a new recruitment. After recruitment and PEEP titration, patients are ventilated in controlled volume mode with PEEP set at titrated value for at least 24 hours. Figure 1 shows a schematic representation of the recruitment maneuver followed by PEEP titration.

In the first version of the protocol we applied a recruitment maneuver using pressure controlled ventilation and driving pressure of 15 cmH₂O. We started with PEEP of 25 cmH₂O for 1 minute, then PEEP of 35 cmH₂O (for 1 minute) and 45 cmH₂O (for 2 minutes). After recruitment, decremental PEEP titration was started with a PEEP of 23 cmH₂O in volume controlled mode, with a tidal volume of 5 mL/kg of predicted body weight. PEEP was decreased in steps of 3 cmH₂O down to a minimum of 11 cmH₂O. After 4 minutes in each step, we measured static compliance of the respiratory system. The PEEP associated with the best static compliance of the respiratory system plus 2 cmH₂O was considered the optimal PEEP. After PEEP titration a new recruitment in pressure controlled ventilation was carried out in one step using PEEP of 45 cmH₂O for 2 minutes. Then, maintenance ventilation was started in controlled volume mode, with tidal volume of 6 mL/kg, using the optimal PEEP. Tidal volume was decreased to 5 mL/kg or 4 mL/kg if plateau pressure exceeded 30 cmH₂O.

The steering committee proposed an amendment to the protocol after 3 cases of resuscitated cardiac arrests had occurred in the experimental arm. The investigators considered that two of the adverse events were likely caused by respiratory acidosis and one case caused by hemodynamic collapse, all possibly related to study interventions (recruitment maneuver and PEEP titration). The amendment was aimed at decreasing risk of respiratory acidosis and hemodynamic impact of the recruitment
maneuver. It involved the following modifications in the experimental group protocol: 1) During recruitment PEEP starts from 25 cmH₂O, then 30 cmH₂O and finally 35 cmH₂O. Maximum airway pressure reaches 50 cmH₂O (instead of 60 cmH₂O); 2) All recruitment steps last 1 minute, totalizing 3 minutes; 3) PEEP titration steps were shortened to 3 minutes; 4) after PEEP titration, recruitment is repeated with PEEP of 35 cmH₂O for 1 minute. The steering committee consulted the Data Monitoring Committee, which agreed with the proposal. The amendment was implemented in June 18, 2015, starting with the 556th patient enrolled in ART.

Outcomes

Our primary outcome is 28-day survival.

Our secondary outcomes are: length of ICU stay and hospitalization; ventilator-free days from day 1 until day 28; pneumothorax requiring drainage within 7 days; barotrauma within 7 days; intensive care unit (ICU), in-hospital and 6-month survival.

We consider as pneumothorax requiring chest tube within 7 days any case that is possibly due to barotrauma, that is, we do not consider cases judged to be clearly caused by invasive procedures such as central venous punction or thoracocentesis. We consider as barotrauma within 7 days any pneumothorax, pneumomediastinum, subcutaneous emphysema or pneumatocele > 2cm detected on image exams between randomization and 7 days, except those judged to be clearly caused by invasive procedures.

The trial also has some exploratory outcomes: death with refractory hypoxemia within 7 days (defined as PaO₂ < 55 mmHg in the last arterial blood gas analysis with FIO₂ = 100%); death with refractory
acidosis within 7 days (defined as pH ≤ 7.10 in the last arterial blood gas analysis); death with barotrauma within 7 days; cardiorespiratory arrest (defined as unexpected cardiac arrest, not due to progressive refractory shock) on day 1; need of commencement/increase of vasopressors or hypotension (MAP<65mmHg) within 1 hour after randomization; refractory hypoxemia (PaO₂ < 55mmHg) within 1h after randomization; severe acidosis (pH <7.10) within 1h after randomization.

Data Management

The objective of our clinical data management plan is to provide high-quality data by adopting standardized procedures to ensure low number of errors and missing data and, consequently, to generate an accurate database for analysis.

Responsibilities

The principal investigator at each center leads and/or supervises the daily operation of the project at his/her participating center and may appoint a Co-investigator and a Research Coordinator. Most tasks can be delegated by the Principal Investigator to research professionals at the Participating Center, provided that the professionals are qualified for such tasks and that the delegation is clearly recorded, with the name of the professionals and their role. However, the principal investigator is legally responsible for the study. The principal investigator is responsible to ensure that data are properly collected and entered into the Study Data Management System.

The Research Institute HCor assigns a coordinating team, including a qualified data manager who is responsible to guarantee the data accuracy during the data collection, process and analysis.

Data collection
Data collection is done using electronic case report (CRF) forms via the Internet at the HCor Data Management System. The system has the following functions: patient registration, 24-hour randomization with allocation concealment, data input, data cleaning, and data export for statistical analysis. Data is entered directly into the system by each center team. All forms are electronically signed by the Principal Investigator in each center or by other appointed persons. Instructions for using the system will be made available to investigators.

Quality Assurance

Several strategies are performed to generate completeness and correctness of the clinical data. Investigators attended a training session before the start of the study to standardize procedures, including data collection. Study support material is available for all sites and the investigators may contact the Study Coordinating Center to solve issues or problems that may arise.

Several problems can be detected by the system at the time of data entry. Subsequently, data monitoring is performed by a data management team in the central office who looks for missing data and inconsistencies using routines implemented in software R. In this sense, missing, inconsistent, illogical, out of range and discrepant data will be marked and the participating sites will be notified for corrections or justifications. Weekly reports listing incomplete follow-up data and inconsistencies are referred to the sites. Resolution of queries by the investigator are updated in the database. If the investigator cannot provide a resolution, the reasons for that are collected in a spreadsheet. Finally, HCor staff contacts all patients discharge alive from hospital or their relatives to make sure that reported 6-month follow-up vital status is accurate.
The data management team is also responsible for helping to detect cases of protocol deviation. When these situations occur, we program new training sessions with the sites to revise the protocol. In addition, the data manager provides prospective reminders and protocol summaries by email about frequent queries detected.

**Database locking**

The database lock will occur as soon as all data has been entered and all discrepancy or missing data are resolved in the database, or if all efforts are employed and we consider that remaining issues cannot be fixed. At this step, our statisticians will review the data before database locking. We will fill-out a checklist for database lock before locking the database to ensure the completion of activities. After that, the study database will be locked and exported for statistical analysis. At this stage, permissions to access the study database will be removed and database archived.

**Storage and Backup**

Electronic files are archived in the HCor Server in a secure and controlled environment to maintain confidentiality. Electronic documents are controlled with password protection, according to best practices.

**Trial Organization and Funding**

The Research Institute HCor is the sponsor and coordinator of the study. The Research Institute HCor is primarily responsible for generating the randomization scheme, the study database, data quality assurance and data analysis. The trial structure includes the following groups: the coordinating center,
investigators, steering committee and data monitoring committee. The trial is endorsed by the Brazilian Research in Intensive Care Network (BRICNet).

The trial also receives institutional support from the Brazilian Association of Intensive Care Medicine (Associação de Medicina Intensiva Brasileira - AMIB) by means of its research network, the AMIBNet.

The study is conducted as part of and funded by the Program to Support Institutional Development of the Universal Health System (PROADI-SUS) from the Brazilian Ministry of Health. The funding sources have no role in the design, execution, analysis, and decision to publish the results.

**Data Monitoring Committee and Interim Analyses**

A Data Monitoring Committee (DMC) was set up with an independent epidemiologist, an intensivist, and a statistician in 2012 soon after the trial started. The responsibilities of the DMC are first to help ensure the safety of patients in the trial by protecting them from avoidable harm. Second, the DMC should provide the Steering Committee with advice about the conduct of the trial and the integrity of the data, so as to protect the validity and scientific credibility of the trial. However, the DMC has only a limited role on this issue because their detailed review of trial progress will occur only infrequently. Third, the DMC should evaluate interim analyses and judge efficacy, harm, and net clinical effect.

Interim analyses to evaluate primary and secondary endpoints were conducted by an independent statistician and sent to the DMC after recruitment of approximately 33% and 66% of the sample, that is, when 172 and 344 deaths within 28 days had occurred. Based on these interim analyses, and, possibly, on external evidence, the DMC were to decide whether there was evidence beyond a reasonable doubt that the treatment was clearly contraindicated in all patients or any subgroup. The
criterion of evidence beyond a reasonable doubt was increased mortality at 28 days with the maximum lung recruitment strategy compared with the low PEEP strategy, with \( P < 0.01 \). Otherwise, the steering committee and other investigators would not be informed of the results of interim analyses. The two interim analyses were conducted and the DMC recommended that the trial continued.

Considering previous evidence showing that: 1) early discontinuation of randomized trials due to benefits tends to produce biased estimates of effect (overestimation of the true effect), leading to erroneous medical guidelines and decisions; 2) according to the ethical principle of non-maleficence, a new treatment should not be used until there is clear, objective evidence that it is beneficial; 3) clinical practice usually does not change unless there is fairly convincing evidence of the advantages of the new treatment, which would be undermined if the study is discontinued early due to benefits; the decision of early discontinuation of the experimental treatment due to benefits may not be advantageous for future patients, or may contribute to misleading guidelines. For these reasons, early discontinuation of the study due to benefits of the experimental treatment was not planned.

Apart from evaluating interim analysis of primary and secondary outcomes, the Data Monitoring Committee has also received periodic reports (after multiples of 100 patients were enrolled) on the incidence of the following study adverse events: 1) need to interrupt alveolar recruitment maneuver and reasons (heart rate > 150 bpm or < 60 bpm; reduction of mean blood pressure to < 65mmHg or systolic blood pressure < 90mmHg; reduction of \( \text{SpO}_2 < 88\% \) for >30 seconds; severe arrhythmias: acute atrial fibrillation or flutter, ventricular tachycardia). 2) Hypotension (mean blood pressure < 65mmHg) within one hour after randomization. 3) Use of vasopressors (norepinephrine or dopamine)
within one hour. 4) Hypotension or need of vasopressors within one hour. 5) Hypoxemia (PaO$_2$ < 55mmHg) within one hour. 6) Severe acidosis (pH < 7.10) within one hour. 7) Pneumothorax requiring drainage in the first 7 days after randomization. 8) Any barotrauma in the first 7 days after randomization. The Coordinating Centre has also sent reports of study-related serious adverse events to the DMC immediately after receiving them.

**Sample size**

ART is an event driven study designed to last until 520 events (deaths within 28 days) are observed. This number of events is sufficient to detect a hazards ratio of 0.75 (i.e., relative reduction in event rate of 25%), considering a type I error of 5%, 90% power, and a similar allocation of subjects to each group.

An important advantage of using an event driven strategy is that it ensures adequate power for the study, as well as recruitment of an adequate number of patients — if the event rate turns out to be higher than that reported in the literature, the study will be completed with a smaller sample size than would be required by a method based on total sample size, consequently there is no unnecessary inclusion of patients. If the event rate turns out to be lower than that reported in the literature, the study is not interrupted before it has adequate power, as might be the case if the total sample size method were used.

**Statistical analysis**

**Principles**
All statistical analyses will be conducted according to the intention-to-treat principle. Thus, the patients will be analyzed according to the arm to which they were allocated (ART or ARDSNet).

Continuous distribution will be assessed by visual inspection of histograms and D'Agostino-Pearson's normality tests. For the experimental and control arms, baseline characteristics will be expressed as counts and percentages, mean and standard deviation (SD), or median and interquartile range (IQR), whenever appropriate as indicated in mock tables 2 to 6, which we intend to include in the main results paper.

Hypothesis tests will be two-sided, with significance level of 5%. We will not adjust P values for multiple comparisons. Analyses will be performed using the R (R Core Team, 2016, Vienna, Austria) program.

**Trial Profile**

Patients flow will be presented as a Consolidated Standards of Reporting Trials diagram (Figure 2).

**Baseline comparisons**

We will present patients’ baseline characteristics by study arm as depicted in the table 2.

**Adherence to study interventions, respiratory variables**

We will report data to assess adherence to the components of recruitment maneuver and PEEP titration procedures as shown in table 3, and respiratory variables from hour 1 to day 7 for both arms as shown in table 4. Fluid balance, weight gain and co-interventions during the first seven days of treatment will also be presented as depicted in table 5.
Effect on outcomes

We will report the number and percentage of deaths within 28 days after randomization (Table 6).

Survival within 28 days in both groups will be assessed using Kaplan-Meier curves, and hazard ratio with 95% confidence interval will be calculated with Cox proportional hazard models, without adjustment for other co-variates.

The two-sided $\alpha$-level for the primary outcome final analysis is 0.042 to account for alpha spent with the two interim analyses with boundaries at one-sided $\alpha = 0.01$.

We will extend survival analysis until 6 months follow up and presented the results using Kaplan-Meier curves and hazard ratio with 95% confidence interval will be calculated with Cox proportional hazard models. We will also test proportional hazard assumptions and propose alternatives parametric survival models if the proportionality assumption is not sustained.$^{11}$

We will assess the effect of the intervention on ICU and in-hospital mortality with risk ratios, 95% confidence intervals, calculated with Wald’s likelihood ratio approximation test, and chi-squared tests for hypothesis test. The effects of the intervention on length of hospitalization, ICU stay and ventilator-free days (until 28$^{th}$ day since randomization) will be estimated with generalized linear models considering distributions that will fit possible right heavy tailed distribution (such as gamma, or inverse Gaussian, or truncated Poisson for ventilator-free days specifically) choosing what fits better according to the model’s deviance.$^{12}$
We will also address the effect of the intervention on the following secondary safety outcomes described in mock table 6. Every comparison will be assessed by risk ratios with respective 95% CI calculated according to Wald’s likelihood ratio approximation test.

**Subgroup analyses**

Treatment effect on 28-day mortality will be analyzed in the following subgroups: 1) PaO$_2$/FiO$_2$ ≤100 vs. >100mmHg; 2) Simplified Acute Physiology Score (SAPS) 3 score <50 vs. ≥50; 3) pulmonary ARDS vs. extrapulmonary ARDS; 4) time of ARDS ≤36 hours vs. >36 to <72 hours; 5) mechanical ventilation ≤2 days; 3 to 4 days; ≥5 days 6) prone position. Subgroups will be classified with data obtained at baseline, except for prone position, which will be classified according to the position (prone or not prone) determined at 1 hour after randomization. The reasoning to consider 1-hour data for determining prone vs other position is because we have recommended to investigators that patients with indication for prone positioning should be moved to that position immediately after randomization. Effects on subgroups will be evaluated by interaction effects between subgroup and the studies arms by Cox proportional hazard models.

**Other exploratory analyses**

We will test whether the effect of the intervention on primary and secondary outcomes are similar before and after the protocol amendment of June 2015.

As a sensitivity analysis, we will estimate the effect of the study intervention on the primary outcome using Cox proportional hazard models with adjustment for the following covariates determined at baseline: age, SAPS 3 score, PaO$_2$/FiO$_2$, and pH.
It has been hypothesized that the responsiveness to PEEP in terms of improving oxygenation may predict a higher likelihood of favorable treatment effect of an open lung approach on clinical outcomes.\textsuperscript{13} We should explore this hypothesis by testing whether the treatment effect on the primary outcome differs between responders and non-responders to the recruitment maneuver and PEEP titration. We defined as responders, those patients who had and increasing in the PaO2/FIO2 ratio $\geq$ 50mmHg in arterial blood gases evaluated after recruitment.

Finally, if there is evidence that the experimental treatment decreases 28-day mortality then we should assess whether driving pressure mediates eventual effects of the randomly assigned treatment on 28-day mortality. Mediators are variables which are affected by treatment-group assignment and which subsequently affect the outcome.\textsuperscript{14} Therefore, mediators are on the causal pathway of the relation between treatment and outcome, and explain at least partly the effects of the treatment on the outcome. In a first step, we plan to assess the effect of driving pressure determined on day 1 on 28-day mortality. This exploratory analysis will be conducted using Cox proportional hazard model adjusted for treatment assignment (ART or ARDSNet), age, SAPS 3 score, baseline PaO2/FIO2, and pH. The effect of other respiratory variables determined on day 1 (tidal volume, PEEP, plateau pressure, static compliance of the respiratory system) on 28-day mortality will also be modelled by adding them to the previously described Cox proportional hazard model.

In a second step, we will use the bootstrapping technique to test mediation models, an alternative technique to the Baron and Kenny’s causal steps model to evaluate mediation.\textsuperscript{15} We will use the R package \textit{mediation}.\textsuperscript{16} These models will be adjusted for baseline tidal elastance of the respiratory system to avoid possible confounding due to differences in the severity of the underlying respiratory
illness. The outputs of the mediation models will be the average causal mediation effect (indirect effect) and the direct effect. The indirect effect expresses the proportion of treatment effect occurring via mediator and the direct effect expresses the proportion of treatment effect which is independent of the mediator.

Missing data
We anticipate no or minimal losses to follow-up for the primary or secondary outcome data. We plan to carry out complete-case analysis for primary and secondary outcomes, that is, we will exclude patients with missing data. However, if we end the trial losing primary outcome data of 1% of more of the patients, we will carry out a sensitivity analysis using multiple imputation techniques.
REFERENCES

**Figure 1.** Schematic representation of the ART strategy, with recruitment maneuver and PEEP titration according to static compliance of the respiratory system.

Recruitment maneuver and PEEP (positive end-expiratory pressure) titration are initiated only after a protocolized preparation that includes: 1) providing sedation and neuromuscular blockade; 2) keeping patient at supine or prone position; 3) aspirating lower airways secretion; 4) installing closed tracheal suctioning system and heat and moisture exchanger; 5) assuring adequate monitoring including invasive blood pressure measurement; 6) correcting hypovolemia; 7) keeping the mean arterial pressure ≥75mmHg (if needed by starting or increasing vasopressors); 8) adjusting respiratory rate to 35 breaths per minute for at least 20 minutes before recruitment; 9) disabling back-up or apnea ventilation.

Recruitment maneuver is conducted at controlled pressure mode, with respiratory rate of 15 breaths per minute, FIO₂=100%, inspiratory to expiratory (I:E) ratio of 1:1. PEEP was set at 25cmH₂O with pressure above PEEP of 15cmH₂O for 1 minute. Then PEEP is increased to 30 cmH₂O for 1 minute, and finally to 35 cmH₂O.

After recruitment, PEEP titration is started with the following settings: PEEP of 23cmH₂O, volume controlled mode, tidal volume of 5mL/kg of predicted body weight, respiratory rate of 20 breaths per minute, flow of 30L/min (square wave flow) and FIO₂=100%. After 3 minutes, static compliance of the respiratory system is calculated (with an inspiratory pause of 2 seconds). Then PEEP is reduced by 3cmH₂O, kept for 3 minutes and static compliance is measured again, and steps are repeated until reaching a PEEP of 11cmH₂O. The ideal PEEP is the PEEP with best static compliance of the respiratory system plus 2cmH₂O.
After PEEP titration a new recruitment maneuver is conducted as follows: pressure-controlled mode, respiratory rate of 15 breaths per minute, FIO₂=100%, inspiratory to expiratory (I:E) ratio of 1:1 and PEEP of 35cmH₂O with pressure above PEEP of 15cmH₂O for 1 minute. Maintenance ventilation with optimal PEEP is started soon after this last recruitment maneuver.
Figure 2. Study flow.
ARDS denotes acute respiratory distress syndrome, and PEEP positive end-expiratory pressure. MAP denotes mean arterial pressure.
Table 1. ARDSNet table of FIO₂ and PEEP values to keep SpO₂ ≥ 88% and PaO₂ ≥ 55mmHg

<table>
<thead>
<tr>
<th>FIO₂</th>
<th>30%</th>
<th>40%</th>
<th>40%</th>
<th>50%</th>
<th>50%</th>
<th>60%</th>
<th>70%</th>
<th>70%</th>
<th>80%</th>
<th>90%</th>
<th>90%</th>
<th>90%</th>
<th>100%</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEEP</td>
<td>5</td>
<td>5</td>
<td>8</td>
<td>8</td>
<td>10</td>
<td>10</td>
<td>12</td>
<td>14</td>
<td>14</td>
<td>14</td>
<td>16</td>
<td>18</td>
<td>18-24</td>
</tr>
</tbody>
</table>
Table 2. Baseline Characteristics of the Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ART</th>
<th>ARDSNet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age – years</td>
<td>xx.x±xx.x</td>
<td>xx.x±xx.x</td>
</tr>
<tr>
<td>Female sex – No. / total No. (%)</td>
<td>x/x (xx.x)</td>
<td>x/x (xx.x)</td>
</tr>
<tr>
<td>SAPS3 score</td>
<td>xx.x±xx.x</td>
<td>xx.x±xx.x</td>
</tr>
<tr>
<td>No. of non-pulmonary organ failures</td>
<td>xx.x±xx.x</td>
<td>xx.x±xx.x</td>
</tr>
<tr>
<td>Septic shock – No. / total No. (%)</td>
<td>x/x (xx.x)</td>
<td>x/x (xx.x)</td>
</tr>
<tr>
<td>Cause of ARDS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary ARDS – No. / total No. (%)</td>
<td>x/x (xx.x)</td>
<td>x/x (xx.x)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>x/x (xx.x)</td>
<td>x/x (xx.x)</td>
</tr>
<tr>
<td>Gastric Aspiration</td>
<td>x/x (xx.x)</td>
<td>x/x (xx.x)</td>
</tr>
<tr>
<td>Lung contusion</td>
<td>x/x (xx.x)</td>
<td>x/x (xx.x)</td>
</tr>
<tr>
<td>Near drowning</td>
<td>x/x (xx.x)</td>
<td>x/x (xx.x)</td>
</tr>
<tr>
<td>Extrapulmonary ARDS – No. / total No. (%)</td>
<td>x/x (xx.x)</td>
<td>x/x (xx.x)</td>
</tr>
<tr>
<td>Non-septic shock</td>
<td>x/x (xx.x)</td>
<td>x/x (xx.x)</td>
</tr>
<tr>
<td>Sepsis/septic shock</td>
<td>x/x (xx.x)</td>
<td>x/x (xx.x)</td>
</tr>
<tr>
<td>Trauma without lung contusion</td>
<td>x/x (xx.x)</td>
<td>x/x (xx.x)</td>
</tr>
<tr>
<td>Cardiac surgery</td>
<td>x/x (xx.x)</td>
<td>x/x (xx.x)</td>
</tr>
<tr>
<td>Other major surgery</td>
<td>x/x (xx.x)</td>
<td>x/x (xx.x)</td>
</tr>
<tr>
<td>Head trauma</td>
<td>x/x (xx.x)</td>
<td>x/x (xx.x)</td>
</tr>
<tr>
<td>Smoke inhalation</td>
<td>x/x (xx.x)</td>
<td>x/x (xx.x)</td>
</tr>
<tr>
<td>Multiple transfusions</td>
<td>x/x (xx.x)</td>
<td>x/x (xx.x)</td>
</tr>
<tr>
<td>Drug or alcohol abuse</td>
<td>x/x (xx.x)</td>
<td>x/x (xx.x)</td>
</tr>
<tr>
<td>Other</td>
<td>x/x (xx.x)</td>
<td>x/x (xx.x)</td>
</tr>
<tr>
<td>Prone position – No. / total No. (%)</td>
<td>x/x (xx.x)</td>
<td>x/x (xx.x)</td>
</tr>
<tr>
<td>Time since onset of ARDS – hours</td>
<td>x/x (xx.x)</td>
<td>x/x (xx.x)</td>
</tr>
<tr>
<td>Days intubated prior to randomization – median (IQR)</td>
<td>x/x (xx.x)</td>
<td>x/x (xx.x)</td>
</tr>
<tr>
<td>Respiratory measures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PaO₂ at FIO₂=1</td>
<td>xx.x±xx.x</td>
<td>xx.x±xx.x</td>
</tr>
<tr>
<td>Tidal volume – ml/kg predicted body weight</td>
<td>xx.x±xx.x</td>
<td>xx.x±xx.x</td>
</tr>
<tr>
<td>Plateau airway pressure – cmH₂O</td>
<td>xx.x±xx.x</td>
<td>xx.x±xx.x</td>
</tr>
<tr>
<td>Minute ventilation – liters/min</td>
<td>xx.x±xx.x</td>
<td>xx.x±xx.x</td>
</tr>
<tr>
<td>Respiratory rate – breaths/min</td>
<td>xx.x±xx.x</td>
<td>xx.x±xx.x</td>
</tr>
<tr>
<td>Driving pressure</td>
<td>xx.x±xx.x</td>
<td>xx.x±xx.x</td>
</tr>
<tr>
<td>Positive end-expiratory pressure – cmH₂O</td>
<td>xx.x±xx.x</td>
<td>xx.x±xx.x</td>
</tr>
<tr>
<td>Respiratory system static compliance – ml/cmH₂O</td>
<td>xx.x±xx.x</td>
<td>xx.x±xx.x</td>
</tr>
</tbody>
</table>

Plus–minus values are means ± SD. PaO₂ denotes partial pressure of arterial oxygen. FIO₂ denotes fraction of inspired oxygen. SAPS denotes Simplified Acute Physiology Score. ARDS denotes acute respiratory distress syndrome.
Table 3. Maximum alveolar recruitment maneuver and titrated PEEP levels

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ART</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum alveolar recruitment maneuver – no. (%)</td>
<td></td>
</tr>
<tr>
<td>Completed (PEEP = 45 cmH2O)</td>
<td>x/x (x.x)</td>
</tr>
<tr>
<td>Completed (PEEP = 35 cmH2O)</td>
<td>x/x (x.x)</td>
</tr>
<tr>
<td>Interrupted at PEEP = 45 cmH2O</td>
<td>x/x (x.x)</td>
</tr>
<tr>
<td>Interrupted at PEEP = 35 cmH2O</td>
<td>x/x (x.x)</td>
</tr>
<tr>
<td>Interrupted at PEEP = 30 cmH2O</td>
<td>x/x (x.x)</td>
</tr>
<tr>
<td>Interrupted at PEEP = 25 cmH2O</td>
<td>x/x (x.x)</td>
</tr>
<tr>
<td>Interrupted at other PEEP levels</td>
<td>x/x (x.x)</td>
</tr>
<tr>
<td>Not attempted</td>
<td>x/x (x.x)</td>
</tr>
<tr>
<td>Neuromuscular blocking agent immediately before alveolar recruitment maneuver – no.(%)</td>
<td></td>
</tr>
<tr>
<td>Volemia optimized before alveolar recruitment maneuver – no. (%)*</td>
<td>x/x (x.x)</td>
</tr>
<tr>
<td>Reason to interrupt alveolar recruitment maneuver – no. (%)</td>
<td></td>
</tr>
<tr>
<td>Heart rate &lt;60bpm or &gt;150bpm</td>
<td>x/x (x.x)</td>
</tr>
<tr>
<td>Mean blood pressure &lt;65mmHg or systolic blood pressure &lt;90mmHg</td>
<td>x/x (x.x)</td>
</tr>
<tr>
<td>SpO₂ &lt;88% for longer than 30s</td>
<td>x/x (x.x)</td>
</tr>
<tr>
<td>Other</td>
<td>x/x (x.x)</td>
</tr>
<tr>
<td>Titrated PEEP, cmH2O</td>
<td>xx.x±xx.x</td>
</tr>
<tr>
<td>Alveolar recruitment maneuver repeated immediately after PEEP titration – no. (%)</td>
<td></td>
</tr>
<tr>
<td>Recruitment maneuver repeated on days 1 to 7 – no. (%)</td>
<td>x/x (x.x)</td>
</tr>
<tr>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Once</td>
<td>x/x (x.x)</td>
</tr>
<tr>
<td>Twice</td>
<td>x/x (x.x)</td>
</tr>
<tr>
<td>Three or more times</td>
<td>x/x (x.x)</td>
</tr>
</tbody>
</table>

Plus-minus values are means ± SD. PEEP denotes positive end-expiratory pressure, SpO₂ peripheral oxygen saturation.

* Volemia is considered optimized when fluids are administered before recruitment maneuver if dynamic signs of fluid responsiveness are present (such as pulse pressure variation >13%) or central venous pressure <10cmH₂O.
Table 4. Respiratory variables during the first seven days of treatment

<table>
<thead>
<tr>
<th>Variable</th>
<th>1hour</th>
<th>Day 1</th>
<th>Day 3</th>
<th>Day 7</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ART</td>
<td>ARDSNet</td>
<td>P Value</td>
<td>ART</td>
</tr>
<tr>
<td>Tidal volume – mL/kg of predicted body weight</td>
<td>x.x±x.x</td>
<td>x.x±x.x</td>
<td>x.xx</td>
<td>x.x±x.x</td>
</tr>
<tr>
<td>Tidal volume &gt; 6.5 mL/kg of predicted body weight – n/total no. (%)</td>
<td>x/x (x.x)</td>
<td>x/x (x.x)</td>
<td>x.xx</td>
<td>x/x (x.x)</td>
</tr>
<tr>
<td>PEEP – cmH2O</td>
<td>x.x±x.x</td>
<td>x.x±x.x</td>
<td>x.xx</td>
<td>x.x±x.x</td>
</tr>
<tr>
<td>Plateau pressure – cmH2O</td>
<td>x.x±x.x</td>
<td>x.x±x.x</td>
<td>x.xx</td>
<td>x.x±x.x</td>
</tr>
<tr>
<td>Plateau pressure &gt; 30 cmH2O – no./total no. (%)</td>
<td>x/x (x.x)</td>
<td>x/x (x.x)</td>
<td>x.xx</td>
<td>x/x (x.x)</td>
</tr>
<tr>
<td>Driving pressure - cmH2O</td>
<td>x.x±x.x</td>
<td>x.x±x.x</td>
<td>x.xx</td>
<td>x.x±x.x</td>
</tr>
<tr>
<td>Respiratory system static compliance – ml/cmH2O</td>
<td>x.x±x.x</td>
<td>x.x±x.x</td>
<td>x.xx</td>
<td>x.x±x.x</td>
</tr>
<tr>
<td>Respiratory rate – breaths/min</td>
<td>x.x±x.x</td>
<td>x.x±x.x</td>
<td>x.xx</td>
<td>x.x±x.x</td>
</tr>
<tr>
<td>PaO2/FIO2</td>
<td>x.x±x.x</td>
<td>x.x±x.x</td>
<td>x.xx</td>
<td>x.x±x.x</td>
</tr>
<tr>
<td>PaCO2 – mmHg</td>
<td>x.x±x.x</td>
<td>x.x±x.x</td>
<td>x.xx</td>
<td>x.x±x.x</td>
</tr>
<tr>
<td>Arterial pH</td>
<td>x.x±x.x</td>
<td>x.x±x.x</td>
<td>x.xx</td>
<td>x.x±x.x</td>
</tr>
</tbody>
</table>

Plus–minus values are means ± SD. PEEP denotes positive end-expiratory pressure.
Table 5. Fluid balance, weight gain and co-interventions during the first seven days of treatment

<table>
<thead>
<tr>
<th></th>
<th>ARDSNET (n=x)</th>
<th>ART (n=x)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-h fluid balance – mL</td>
<td>xx.x±xx.x</td>
<td>xx.x±xx.x</td>
<td>x.xx</td>
</tr>
<tr>
<td>Day 1</td>
<td>xx.x±xx.x</td>
<td>xx.x±xx.x</td>
<td>x.xx</td>
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<tr>
<td>Day 3</td>
<td>xx.x±xx.x</td>
<td>xx.x±xx.x</td>
<td>x.xx</td>
</tr>
<tr>
<td>Weight gain – kg</td>
<td>xx.x±xx.x</td>
<td>xx.x±xx.x</td>
<td>x.xx</td>
</tr>
<tr>
<td>Baseline to day 1</td>
<td>xx.x±xx.x</td>
<td>xx.x±xx.x</td>
<td>x.xx</td>
</tr>
<tr>
<td>Baseline to day 3</td>
<td>xx.x±xx.x</td>
<td>xx.x±xx.x</td>
<td>x.xx</td>
</tr>
<tr>
<td>Baseline to day 7</td>
<td>xx.x±xx.x</td>
<td>xx.x±xx.x</td>
<td>x.xx</td>
</tr>
<tr>
<td>Use of vasopressors – no./total no. (%)</td>
<td>x/x (xx.x)</td>
<td>x/x (xx.x)</td>
<td>x.xx</td>
</tr>
<tr>
<td>Days of vasopressor use - median (IQR)</td>
<td>median (IQR)</td>
<td>median (IQR)</td>
<td>x.xx</td>
</tr>
<tr>
<td>Neuromuscular blockade – no./total no. (%)*</td>
<td>x/x (xx.x)</td>
<td>x/x (xx.x)</td>
<td>x.xx</td>
</tr>
<tr>
<td>Days of neuromuscular blocker use - median (IQR)</td>
<td>median (IQR)</td>
<td>median (IQR)</td>
<td>x.xx</td>
</tr>
<tr>
<td>Sedative infusion– no./total no. (%)</td>
<td>x/x (xx.x)</td>
<td>x/x (xx.x)</td>
<td>x.xx</td>
</tr>
<tr>
<td>Days of sedative infusion - median (IQR)</td>
<td>median (IQR)</td>
<td>median (IQR)</td>
<td>x.xx</td>
</tr>
<tr>
<td>Narcotic infusion– no./total no. (%)</td>
<td>x/x (xx.x)</td>
<td>x/x (xx.x)</td>
<td>x.xx</td>
</tr>
<tr>
<td>Days of narcotic infusion - median (IQR)</td>
<td>median (IQR)</td>
<td>median (IQR)</td>
<td>x.xx</td>
</tr>
<tr>
<td>Use of corticosteroid – no./total no. (%)</td>
<td>x/x (xx.x)</td>
<td>x/x (xx.x)</td>
<td>x.xx</td>
</tr>
<tr>
<td>Days of corticosteroid - median (IQR)</td>
<td>median (IQR)</td>
<td>median (IQR)</td>
<td>x.xx</td>
</tr>
<tr>
<td>Rescue therapies – no./total no. (%)</td>
<td>x/x (xx.x)</td>
<td>x/x (xx.x)</td>
<td>x.xx</td>
</tr>
<tr>
<td>Prone position – no./total no. (%)</td>
<td>x/x (xx.x)</td>
<td>x/x (xx.x)</td>
<td>x.xx</td>
</tr>
<tr>
<td>Inhaled nitric oxide – no./total no. (%)</td>
<td>x/x (xx.x)</td>
<td>x/x (xx.x)</td>
<td>x.xx</td>
</tr>
<tr>
<td>High frequency oscillation – no./total no. (%)</td>
<td>x/x (xx.x)</td>
<td>x/x (xx.x)</td>
<td>x.xx</td>
</tr>
<tr>
<td>Extracorporeal membrane oxygenation– no./total no. (%)</td>
<td>x/x (xx.x)</td>
<td>x/x (xx.x)</td>
<td>x.xx</td>
</tr>
</tbody>
</table>
## Table 6. Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>ART</th>
<th>ARDSNet</th>
<th>Hazard ratio (95% CI*)</th>
<th>( \nu_{i} )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death within 28 days – no. of events / total no. (%)</td>
<td>x/x (xx.x)</td>
<td>x/x (xx.x)</td>
<td>x.xx (xx.xx-xx.xx)</td>
<td>x</td>
</tr>
<tr>
<td><strong>Secondary outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death in hospital - no. of events / total no. (%)†</td>
<td>x/x (xx.x)</td>
<td>x/x (xx.x)</td>
<td>x.xx (xx.xx-xx.xx)</td>
<td>x</td>
</tr>
<tr>
<td>Death in intensive care unit - no. of events / total no. (%)†</td>
<td>x/x (xx.x)</td>
<td>x/x (xx.x)</td>
<td>x.xx (xx.xx-xx.xx)</td>
<td>x</td>
</tr>
<tr>
<td>Death within 6 months - no. of events / total no. (%)</td>
<td>x/x (xx.x)</td>
<td>x/x (xx.x)</td>
<td>x.xx (xx.xx-xx.xx)</td>
<td>x</td>
</tr>
<tr>
<td>Length of intensive care unit stay - days‡</td>
<td>xx.x±xx.x</td>
<td>xx.x±xx.x</td>
<td>x.xx (xx.xx-xx.xx)</td>
<td>x</td>
</tr>
<tr>
<td>Length of hospital stay - days‡</td>
<td>xx.x±xx.x</td>
<td>xx.x±xx.x</td>
<td>x.xx (xx.xx-xx.xx)</td>
<td>x</td>
</tr>
<tr>
<td>No. of ventilator-free days from day 1 to day 28‡</td>
<td>xx.x±xx.x</td>
<td>xx.x±xx.x</td>
<td>x.xx (xx.xx-xx.xx)</td>
<td>x</td>
</tr>
<tr>
<td>Pneumothorax requiring drainage within 7 days - no. of events / total no. (%)†</td>
<td>x/x (xx.x)</td>
<td>x/x (xx.x)</td>
<td>x.xx (xx.xx-xx.xx)</td>
<td>x</td>
</tr>
<tr>
<td>Barotrauma within 7 days - no. of events / total no. (%)†</td>
<td>x/x (xx.x)</td>
<td>x/x (xx.x)</td>
<td>x.xx (xx.xx-xx.xx)</td>
<td>x</td>
</tr>
<tr>
<td><strong>Exploratory outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death with refractory hypoxemia within 7 days - no. of events / total no. (%)†</td>
<td>x/x (xx.x)</td>
<td>x/x (xx.x)</td>
<td>x.xx (xx.xx-xx.xx)</td>
<td>x</td>
</tr>
<tr>
<td>Death with refractory acidosis within 7 days - no. of events / total no. (%)†</td>
<td>x/x (xx.x)</td>
<td>x/x (xx.x)</td>
<td>x.xx (xx.xx-xx.xx)</td>
<td>x</td>
</tr>
<tr>
<td>Death with barotrauma within 7 days - no. of events / total no. (%)†</td>
<td>x/x (xx.x)</td>
<td>x/x (xx.x)</td>
<td>x.xx (xx.xx-xx.xx)</td>
<td>x</td>
</tr>
<tr>
<td>Cardiorespiratory arrest on day 1 - no. of events / total no. (%)†</td>
<td>x/x (xx.x)</td>
<td>x/x (xx.x)</td>
<td>x.xx (xx.xx-xx.xx)</td>
<td>x</td>
</tr>
<tr>
<td>Need of commencement/increase of vasopressors or hypotension (MAP&lt;65mmHg) within 1 hour†</td>
<td>x/x (xx.x)</td>
<td>x/x (xx.x)</td>
<td>x.xx (xx.xx-xx.xx)</td>
<td>x</td>
</tr>
<tr>
<td>Refractory hypoxemia (PaO(_2) &lt; 55mmHg) within 1 hour – no. (%)†</td>
<td>x/x (xx.x)</td>
<td>x/x (xx.x)</td>
<td>x.xx (xx.xx-xx.xx)</td>
<td>x</td>
</tr>
<tr>
<td>Severe acidosis (pH &lt; 7.10) within 1 hour— no. (%)†</td>
<td>x/x (xx.x)</td>
<td>x/x (xx.x)</td>
<td>x.xx (xx.xx-xx.xx)</td>
<td>x</td>
</tr>
</tbody>
</table>
* CI denotes confidence interval.
† Effect estimates are risk ratios.
‡ Effect estimates are mean difference