STUDY PROTOCOL

Influence of the Lung Recruitment Potential on the Response to Two Positive End-Expiratory Pressure (PEEP) Titration Strategies in Patients With Acute Respiratory Distress Syndrome (ARDS)

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STUDY PROTOCOL

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1. Study Title:

"PEEP Titration Guided by Pulmonary Recruitability in Patients with ARDS: A Randomized Pilot Study"

2. Study Summary

Acute respiratory distress syndrome (ARDS) is characterized by a severe decrease in pulmonary compliance, refractory hypoxemia, and diffuse alveolar collapse, requiring invasive mechanical ventilation (IMV) to ensure gas exchange. However, inappropriate ventilation can generate ventilator-induced lung injury (VILI), defined as acute lung damage caused or aggravated by mechanical ventilation, including alveolar overdistension, cyclic opening and closing of collapsed units, and the resulting inflammatory responses. Positive end-expiratory pressure (PEEP) is a key tool to prevent alveolar collapse and promote recruitment, although its effect is highly variable among patients. Personalized PEEP titration based on physiological parameters, such as transpulmonary pressure and the recruitment-to-inflation (R/I) ratio, could optimize ventilation and reduce the risk of collapse and pulmonary overdistension.

This study aims to compare a personalized ventilatory strategy — based on the determination of recruitment potential using the R/I ratio followed by PEEP titration guided by transpulmonary pressure — against titration guided by the best static pulmonary compliance. Patients on IMV with moderate-to-severe ARDS and high recruitment potential (R/I ratio > 0.5) will be included. The primary outcome will be the change in ventilator-free days (VFD) at 28 days, while secondary outcomes will include oxygenation parameters, respiratory mechanics, and adverse events.

This study focuses on patients with high alveolar recruitment potential, with the objective of generating evidence on the utility of personalized PEEP strategies in a subpopulation where the probability of benefit is greatest. The results could contribute to the development of more individualized ventilation guidelines aimed at reducing VILI and improving clinical outcomes in ARDS.

3. Introduction and Theoretical Framework

Acute respiratory distress syndrome (ARDS) is one of the main causes of respiratory failure in critically ill patients, associated with high morbidity and mortality and great heterogeneity in its clinical presentation. It is characterized by diffuse inflammation, increased alveolocapillary permeability, alveolar collapse, and a marked decrease in pulmonary compliance, leading to severe hypoxemia and difficulty maintaining adequate gas exchange. According to the Berlin consensus definition, the diagnosis of ARDS requires that respiratory failure appear in the context of an identifiable clinical cause and within the first week of the triggering event; that bilateral opacities on chest X-ray or CT scan not be fully explained by effusions, lobar atelectasis, or nodules; and that pulmonary edema not be primarily related to cardiac failure or volume overload. Severity is stratified according to the ratio of arterial oxygen pressure to the inspired oxygen fraction (PaO_2/FiO_2), with values ≤300 mmHg classified as mild ARDS, ≤200 mmHg as moderate, and ≤100 mmHg as severe, all under application of a minimum PEEP of 5 cmH_2O.

In this context, mechanical ventilation support is essential but can induce VILI in 10–40% of cases if not properly adjusted. Among protective strategies, the use of PEEP aims to prevent cyclic alveolar collapse and keep the lung in aerated conditions. However, the response to PEEP is highly variable: in some patients, increased pressure allows recruitment of collapsed lung tissue and improves oxygenation, while in others it may induce overdistension and compromise hemodynamics. PEEP can be decomposed into extrinsic PEEP (generated by the mechanical ventilator) and intrinsic or auto-PEEP, which corresponds to the residual positive pressure in the airway at the end of expiration, produced by incomplete exhalation. This may occur in patients with airflow obstruction, insufficient expiratory times, or high minute ventilation levels, and is relevant because it can be added to the externally applied PEEP, affecting both respiratory mechanics and the interpretation of physiological parameters.

Alveolar recruitment — understood as the reopening of previously collapsed lung units through the use of positive pressures — is a central goal in the management of ARDS. Traditionally, computed tomography (CT) has been considered the reference standard for quantifying recruitable tissue, differentiating aerated, collapsed, and overdistended zones. Gattinoni et al. demonstrated that CT allows precise estimation of recruitment potential and its regional distribution. However, logistical limitations, cost, the need for patient transport, and radiation exposure have driven the search for alternative methods to assess recruitment potential safely, repeatably, and at the bedside.

In this setting, the recruitment-to-inflation (R/I) ratio emerges as an accessible physiological tool. Chen et al. proposed its calculation using decremental PEEP maneuvers and volume and compliance measurements, determining that R/I ratio values greater than 0.5 identify high recruitment potential, while values ≤ 0.5 suggest low recruitment potential. This index offers the advantage of requiring no additional equipment beyond the mechanical ventilator and a trained operator.

In approximately 25 to 50% of patients with moderate or severe ARDS receiving controlled ventilation, complete airway closure occurs at a certain pressure level. Above this pressure level, the airway opening pressure (AOP) allows communication between the alveoli and the rest of the proximal respiratory system. Without this communication, estimation of alveolar pressure through airway pressure will be imprecise, making it a prerequisite when assessing recruitment potential via R/I ratio and PEEP titration. When a PEEP level is set below the AOP, there is a risk of VILI and bronchiolar damage from repeated opening and closing of distal airways.

PEEP titration guided by transpulmonary pressure, measured using an esophageal balloon, represents another individualized approach whose goal is to maintain a slightly positive end-expiratory transpulmonary pressure to prevent both alveolar collapse and overdistension. In a randomized trial, Talmor et al. demonstrated that this strategy improves physiological parameters in ARDS patients compared to conventional ARDSNet tables. These tables appear in the context of the ARDSNet trial published in 2000, which demonstrated that the use of lower tidal volume ventilation reduced mortality. The rationale was to provide a practical guide for the clinical team to systematically adjust ventilatory support: as FiO_2 was increased to improve oxygenation, PEEP was also raised according to the table to optimize alveolar recruitment and avoid collapse and overdistension. These tables have become a standard of practice in ARDS ventilation, although more recent studies have questioned their universal applicability due to the heterogeneity of the injured lung.

In addition to classic oxygenation indices, the *Ventilatory Ratio* (VR) has been proposed as a simple and accessible marker of ventilatory inefficiency, closely related to physiological dead space and the minute ventilation needed to maintain a stable $PaCO_2$. This index can be easily calculated from routine ventilatory parameters and has demonstrated a correlation with mortality in ARDS patients, becoming a useful tool for both physiological monitoring and the comparative evaluation of ventilatory strategies.

Along the same lines, *driving pressure* (ΔP) — the difference between plateau pressure and PEEP — has established itself as a powerful predictor of mortality. An analysis by Amato et al. demonstrated that *driving pressure* (ΔP) is more closely associated with survival in ARDS than tidal volume or PEEP individually. ΔP reflects the actual mechanical stress applied to the functional lung or *baby*

lung; the greater the ΔP, the greater the risk of VILI from cyclic deformation of lung tissue. Therefore, reducing ΔP through strategies such as personalized PEEP titration represents a promising avenue to reduce pulmonary injury.

Although the PEEP-FiO_2 table proposed by ARDSNet in 2000 remains widely used for its simplicity, its standardized nature does not account for the interindividual heterogeneity of ARDS. In recent years, other strategies have been evaluated, such as PEEP adjustment based on maximum pulmonary compliance, thoracic ultrasound (US) monitoring, or electrical impedance tomography (EIT) to estimate regional recruitment, as well as the application of recruitment maneuvers followed by PEEP titration. The available evidence suggests that a high PEEP without prolonged recruitment maneuvers could be associated with better outcomes in selected patients, whereas prolonged recruitment maneuvers combined with high PEEP may increase mortality.

PEEP titration guided by the best static pulmonary compliance is one of the most widely used strategies to individualize mechanical ventilation in ARDS patients. Initially described by Suter et al. in 1978, this approach identifies the PEEP level that maximizes respiratory system compliance after a recruitment maneuver, interpreting this point as the most favorable balance between recruitment and alveolar overdistension. Since then, multiple studies and contemporary analyses have revisited this criterion as a tool to individualize ventilatory strategy, both in protocols oriented toward lung protection and in direct comparisons between PEEP selection strategies. Although not without limitations — especially regarding regional heterogeneity of ARDS — compliance-based titration persists as one of the most widely used strategies in clinical practice.

Despite these advances, selecting the optimal strategy for each patient remains a challenge. The absence of randomized clinical trials specifically evaluating subpopulations with high recruitment potential limits the ability to personalize therapy based on solid evidence.

Enriching randomized trials by exclusively including participants who have shown a positive physiological response to an initial test dose — a response directly related to the mechanism of action of the therapy — can increase the treatment effect size and significantly improve statistical power. Following this hypothesis, the combination of a bedside physiological evaluation identifying high recruiters with individualized PEEP adjustment guided by transpulmonary pressure could represent a significant step toward truly personalized ventilation, with the potential to improve clinical outcomes and reduce VILI. The individual effect of different PEEP levels may require studies that incorporate a pre-randomization recruitment capacity test to examine the effect of PEEP in patients with greater pulmonary recruitment potential.

4. Research Question and/or Hypothesis

What is the impact of an individualized PEEP titration strategy guided by transpulmonary pressure in patients with ARDS and high recruitment potential, compared to a titration strategy guided by the best pulmonary compliance?

In patients with ARDS and high recruitment potential (R/I > 0.5), does PEEP titration guided by transpulmonary pressure increase ventilator-free days at 28 days compared to titration guided by the best pulmonary compliance?

Null Hypothesis (H_0): There is no difference in ventilator-free days at 28 days between groups.

Alternative Hypothesis (H_1): There is a difference in ventilator-free days at 28 days between groups.

5. Research Relevance

Optimal management of ARDS continues to be a major clinical challenge in intensive care units (ICU). Despite the implementation of protective ventilatory measures, morbidity and mortality associated with ARDS remains high and VILI persists as a frequent complication. In this context, individualization of the ventilatory strategy — particularly regarding PEEP titration — is emerging as one of the most promising interventions to reduce VILI. However, its application in clinical practice is limited by the heterogeneity of lung injury and the scarcity of simple and reliable bedside tools.

The clinical relevance of this study — evaluating a PEEP titration strategy guided by transpulmonary pressure in patients with high alveolar recruitment potential (identified using the R/I index) — aims to demonstrate an increase in ventilator-free days at 28 days. Early improvements in physiological parameters, such as PaO_2/FiO_2 ratio, driving pressure, and static compliance, tend to anticipate reductions in ventilation duration, incidence of barotrauma, and the need for prolonged ICU stays.

In resource-limited hospital settings, incorporating the R/I index as a stratification tool and using the esophageal balloon as a relatively accessible method represent practical alternatives to dependence on higher-cost or less-available technologies such as CT or EIT. If the strategy proves effective and safe, it could be feasibly implemented at HFRZ, avoiding unnecessary patient transfers, radiation exposure, and inefficient resource use.

In scientific terms, the study will provide evidence on the clinical validation of the R/I ratio as a selector for patients who are candidates for higher PEEP strategies, as well as on the utility of transpulmonary pressure to guide titration. It will also allow the collection of relevant physiological information (driving pressure, PaO_2/FiO_2, ventilatory ratio, static compliance) and safety data (barotrauma, pneumothorax, hemodynamic instability, need for vasoactive agents), which will enrich understanding of the mechanisms by which personalized PEEP can reduce VILI.

The potential impact of the findings also extends to institutional practice and the integrated health network, as the results could support the inclusion of R/I- and transpulmonary pressure-based stratification algorithms in local and national ventilation protocols. This would contribute to personalizing care and improving the quality of care provided to critically ill patients in the HFRZ ICU and in hospitals throughout the country.

Finally, this study will serve as a pilot trial that, in addition to generating early physiological evidence, will evaluate the impact of a personalized ventilatory strategy on the reduction of VM days within the first 28 days (VFD-28), a widely validated clinical outcome sensitive to the effects of interventions that modulate ventilator-induced lung damage. It will also allow identification of key parameters such as the variance of this outcome, the prevalence of patients with high recruitment potential, and the incidence of adverse events associated with ventilatory management — essential information for the design of future multicenter clinical trials with greater statistical power.

In summary, the relevance of this study lies in its ability to provide early physiological and clinical evidence on individualized PEEP titration strategies guided by transpulmonary pressure, with the potential to improve the efficiency of ventilatory support, shorten the duration of mechanical ventilation, and optimize patient safety. Beyond the immediate results, the findings of this study will contribute to the methodological and conceptual foundations for larger research endeavors aimed at personalizing mechanical ventilation in ARDS.

6. General and Specific Objectives

GENERAL OBJECTIVE

To evaluate whether PEEP titration guided by transpulmonary pressure in patients with ARDS and high recruitment potential — identified using the R/I ratio — in the HFRZ ICU increases ventilator-free days at 28 days compared to PEEP titration guided by the best pulmonary compliance.

SPECIFIC OBJECTIVES

- Compare ventilator-free days at 28 days (VFD-28) between patients with ARDS managed with a PEEP titration strategy guided by transpulmonary pressure and those with PEEP titration guided by the best compliance.
- Compare the evolution of physiological parameters: PaO_2/FiO_2 ratio, static compliance (Cest), driving pressure (ΔP), and ventilatory ratio (VR) — during the first 72 hours following PEEP titration in both groups.
- Compare the assessment of recruitment potential evaluated by R/I ratio during the first three days post-randomization.

- Compare the need for rescue therapies (prone positioning, ECMO) or out-of-protocol ventilation adjustments for refractory hypoxemia.
- Record and compare the incidence of adverse events related to mechanical ventilation, including barotrauma, clinically significant hypotension, and increased vasopressor requirements.
- Determine the prevalence of high AOP (greater than 5 cmH_2O) in the cohort.
- Evaluate and compare pulmonary recruitment potential using the R/I ratio.
- Evaluate transpulmonary pressure using an esophageal balloon in the intervention group.

7. Protocol or Methodology

7.1 Experimental Design

Pilot study with an analytical, longitudinal, and interventional design comprising 2 parallel randomized groups (single-blind), with an additional observational group.

7.2 Participants

Adult ICU patients at HFRZ with an ARDS diagnosis on IMV who meet the inclusion criteria.

7.3 Inclusion Criteria

A. **A. Initial eligibility criteria:**

1. Age $\geq$ 18 years.
2. Diagnosis of moderate or severe ARDS according to Berlin criteria: acute onset, bilateral opacities, respiratory failure not explained by cardiac failure, and $PaO_2/FiO_2 \leq 200$ mmHg with PEEP $\geq$ 5 cmH_2O.
3. ARDS duration < 36 hours since meeting Berlin consensus criteria.

B. **B. Randomization criteria:**

4. R/I ratio > 0.5 calculated by standardized bedside maneuver.
5. Relative hemodynamic stability: no refractory shock (norepinephrine $\leq$ 0.5 µg/kg/min).

7.4 Exclusion Criteria

6. Evidence of active air leak from the lung (bronchopleural fistula, pneumothorax, pneumomediastinum).
7. Severe uncorrectable hemodynamic instability (norepinephrine > 0.5 µg/kg/min).
8. Contraindication to esophageal balloon placement: esophageal obstruction, known perforation, recent esophageal surgery, severe esophagitis.
9. Elevated intracranial pressure or conditions in which hypercapnia-induced elevations in intracranial pressure should be avoided, including intracranial hemorrhage, cerebral contusion, cerebral edema, and mass effect (midline shift on CT).
10. Known pregnancy.
11. Severe coagulopathy (platelet count < 5,000/µL or INR > 3).
12. Terminal illness or expected death within < 24 hours according to clinical judgment.
13. Airway opening pressure greater than 15 cmH_2O (AOP > 15 cmH_2O).
14. History of severe neuromuscular disease or chronic respiratory disease.
15. Having received IMV for more than 96 hours.
16. Impossibility of obtaining consent or refusal by the legal representative.
17. Contained laparotomy (open abdomen patients).

7.5 Instruments / Variables

No.	Variable	Type	Collection Method / Source
1	Ventilator-free days at 28 days (VFD-28)	Continuous quantitative	VFD=0 if subject dies within 28 days; VFD=28−x if successfully liberated x days after start; VFD=0 if still on MV at >28 days.
2	ICU Mortality	Dichotomous qualitative	Patient discharge record (alive or deceased).
3	R/I ratio (Recruitment-to-Inflation index)	Continuous quantitative	Calculated at bedside using ventilator data during controlled maneuvers (high/low PEEP).
4	Age	Continuous quantitative	Electronic medical record (admission).
5	Sex	Dichotomous qualitative	Electronic medical record.
6	Body mass index (BMI)	Continuous quantitative	Calculated from patient weight and height.
7	ARDS etiology	Nominal qualitative	Clinical diagnosis recorded by attending physician.
8	ARDS severity (Berlin criteria)	Ordinal qualitative	Classification based on arterial blood gas (PaO_2/FiO_2).
9	PaO_2/FiO_2 at admission	Continuous quantitative	Arterial blood gas and inspired oxygen fraction (FiO_2) at inclusion.
10	Arterial oxygen pressure (PaO_2)	Continuous quantitative	Obtained from arterial blood gas.
11	Total PEEP	Continuous quantitative	Read directly from the mechanical ventilator.
12	Intrinsic PEEP	Continuous quantitative	Obtained via expiratory pause on the mechanical ventilator.
13	Static respiratory system compliance (Cst)	Continuous quantitative	Calculated using formula: VT / (Pplat − PEEP).
14	Tidal volume (VT)	Continuous quantitative	Direct ventilator reading (mL/kg ideal body weight).
15	Minute volume	Continuous quantitative	Direct ventilator reading (L/min).
16	Time on MV before study	Continuous quantitative	Hourly record of MV start in clinical history.

17	Plateau pressure (Pplat)	Continuous quantitative	Measured during inspiratory pause (ventilator reading).
19	Days on MV	Discrete quantitative	Count from MV start to extubation or death.
20	Driving pressure (ΔP)	Continuous quantitative	Calculated using mechanical ventilator data.
21	Ventilatory Ratio (VR)	Continuous quantitative	Calculated from ventilator and arterial blood gas parameters.
22	Airway Opening Pressure (AOP)	Continuous quantitative	Calculated at bedside using ventilator data.
23	APACHE and SOFA	Continuous quantitative	Calculated at patient admission by the resident physician.
24	Barthel Index	Continuous quantitative	Obtained via Barthel Index survey.
25	Patient position	Dichotomous qualitative	Supine or prone.
26	pH	Continuous quantitative	Obtained from arterial blood gas.
27	Arterial CO_2 pressure ($PaCO_2$)	Continuous quantitative	Obtained from arterial blood gas.
28	Oxygen saturation (SpO_2)	Continuous quantitative	Obtained from continuous monitoring.
29	Comorbidities / Chronic diseases	Qualitative	Obtained from clinical record.
30	Heart rate	Continuous quantitative	Obtained from continuous monitoring.
31	Systolic blood pressure	Continuous quantitative	Obtained from continuous monitoring.
32	Diastolic blood pressure	Continuous quantitative	Obtained from continuous monitoring.
33	Mean arterial pressure	Continuous quantitative	Obtained from continuous monitoring.
34	Vasopressor dose (norepinephrine)	Continuous quantitative	Obtained from nursing clinical record.

7.6 Procedures

Patient Selection and Consent

The research team will daily identify patients with an ARDS diagnosis on IMV who meet the inclusion criteria. The study will be explained to the patient or their legal representative, and signed informed consent will be obtained before any procedure.

Eligible patients will be identified in the HFRZ ICU. The research team will perform a daily review of admitted patients who meet the preliminary clinical criteria for ARDS or have an ARDS diagnosis according to Berlin criteria.

Each patient will be evaluated to confirm they are on IMV and are clinically stable for the R/I index measurement maneuver. The inclusion criteria established in the protocol will be verified.

Once a potential patient is identified, the patient or their legal representative will be informed about the study, and signed informed consent will be requested. Only after obtaining authorization will the maneuver to measure the R/I index be performed to determine final eligibility for randomization or inclusion in the observational cohort.

To ensure correct traceability and registration, each patient will receive a unique code (first letters of name and surnames plus the first 4 digits of the national ID) in the study data identification, preserving anonymity in subsequent analyses.

Daily identification:

- Each day, a team investigator will review the list of patients admitted to the HFRZ ICU with a diagnosis of ARDS, according to Berlin criteria.
- Patient eligibility will be verified based on the inclusion and exclusion criteria defined in the protocol.

Clinical stability assessment:

- It will be confirmed that the patient is hemodynamically stable, on controlled MV, with no contraindication to performing positive pressure maneuvers.
- This assessment will be carried out in conjunction with the resident physician in charge of the patient.

Consultation with the treating team:

- Before contacting the family or legal representative, verbal authorization from the physician responsible for the patient will be requested to evaluate their participation in the study.

Obtaining informed consent:

- The legal representative or responsible family member will be contacted and will receive 3 copies of the document to sign: one signed copy will be kept in the patient's file, one signed copy in an exclusive informed consent folder (in a locked cabinet in the ICU Physiotherapist Office, with restricted access), and one final copy for the patient or their representative.

Standard Procedures for Any Patient Hospitalized in the Adult ICU

Patients will be positioned supine with the head of the bed at 30–45°, connected to volume-controlled mechanical ventilation (CMV) with a tidal volume of 6–8 mL/kg ideal body weight, respiratory rate 12 to 34 rpm to maintain pH between 7.25 and 7.45 (per the pH-CO_2 regulation table), and Pplat < 28 cmH_2O, DP < 14 cmH_2O, FiO_2 to maintain SpO_2 88–98% or PaO_2 between 55 and 80 mmHg. Hamilton G5 or C6 mechanical ventilators (Hamilton Medical AG, Switzerland) will be used for mechanical ventilation, evaluations, and ventilatory therapy.

Alveolar recruitment maneuvers — both prolonged and brief — will not be performed, in accordance with the ESICM 2023 guidelines, which advise against their routine application due to lack of benefit and potential risk of complications.

The use of sedation, neuromuscular blockade, and vasoactive agents will be applied following the institutional protocol. In cases where respiratory efforts occur during evaluations, sedation/blockade/medications will be deepened or increased per the institutional protocol. The elimination of spontaneous effort and relaxation of respiratory muscles will be confirmed by the absence of patient-triggered breaths, absence of negative oscillations in airway pressure (Paw) during an expiratory pause longer than 8 seconds, and negative oscillations during inspirations on the Pes tracing, when available.

R/I Index Measurement

Assessment of AOP and R/I will be performed according to the methodology used by Chen et al. (2020): The AOP will be identified as the pressure at which an abrupt change in the slope of the pressure-time curve is produced on the ventilator screen, following an initial ultra-low compliance phase corresponding to the compliance of the respiratory circuit. The R/I ratio will be calculated from the relationship between the recruitaable lung volume and the compliance of the already-aerated lung.

R/I ratio procedure: After or following 5 minutes at a PEEP of 15 cmH_2O, the respiratory rate will be reduced to 10/min to eliminate possible intrinsic PEEP, and the expired tidal volume shown by the ventilator will be recorded. PEEP will then be abruptly reduced to 5 cmH_2O and the expired volume shown by the ventilator will be recorded immediately after the maneuver. The previous respiratory rate and PEEP will then be restored.

The recruited lung volume (Vrec) will be calculated as: the expired volume from PEEP 15 to 5 cmH_2O (DeltaVrec) minus the previous expired tidal volume and minus the lung volume calculated by compliance at low PEEP.

R/I = Crec / Crs at PEEP 5 cmH_2O

Crec = Vrec / (PEEP high − PEEP low)

Vrec = Delta Vrec − Delta V calculated

Delta Vrec = Delta expiratory lung volume between PEEP high and PEEP low − the Delta of end-expiratory calculated volume

Delta of calculated end-expiratory volume = Crs at PEEP 5 × (PEEP high − PEEP low)

PEEP high − PEEP low = PEEP 15 − PEEP 5 = 10

Crs at PEEP 5 cmH_2O = Static respiratory system compliance at PEEP 5 cmH_2O

When AOP > 5 cmH_2O, that value will replace the low PEEP, and PEEP high will be that value plus 10.

Stratification and Randomization

Patients with R/I ratio > 0.5 will be considered to have high recruitment potential and will be randomized 1:1 to the groups:

- **Intervention Group:** PEEP guided by transpulmonary pressure measured with an esophageal balloon.
- **Control Group:** PEEP guided by the best pulmonary compliance.

Patients with R/I ratio ≤ 0.5 will be assigned to an **Observational Group** and their PEEP titrated according to the ARDSNet low PEEP-FiO_2 table.

Initial Alveolar Recruitment Maneuver

An initial alveolar recruitment maneuver (ARM) will be performed in patients from the randomized groups. This maneuver will be performed in pressure-controlled ventilatory mode, with a control pressure of 15 cmH_2O, I:E ratio 1:1, FiO_2 at 1, starting at PEEP 5 and increasing by 5 cmH_2O every 10 seconds until reaching PEEP 25 cmH_2O, maintaining a maximum airway pressure limit of 40 cmH_2O for 1 minute.

PEEP Titration in the Intervention Group

In the intervention group, after the initial ARM, PEEP titration will be based on transpulmonary pressure measurements obtained using an esophageal balloon catheter (Nutrivent®, Sidam, Mirandola, Italy), which allows indirect estimation of pleural pressure. Correct positioning of the esophageal balloon will be verified using the occlusion test, which consists of applying slow and gentle bilateral thoracic compression to the patient during an end-expiratory occlusion. Positioning

will be considered adequate when the ratio between changes in airway pressure and esophageal pressure falls within the range of 0.8–1.2. Additionally, the presence of a flat transpulmonary pressure (PL) tracing during the maneuver will confirm the reliability of the measurement.

Once the position is validated, PEEP titration will be adjusted with the goal of maintaining an end-expiratory transpulmonary pressure (PLexp) between −1 and +1 cmH_2O, aiming to prevent both alveolar collapse and overdistension. Additionally, the inspiratory transpulmonary pressure (PLinsp) will be monitored to remain < 20 cmH_2O as a safety criterion, to minimize the risk of alveolar overdistension and VILI.

Monitoring will be continuous, and values of Paw, Pes (esophageal pressure), PL (transpulmonary pressure), tidal volume, plateau pressure, and driving pressure will be systematically recorded during the procedure.

PEEP Titration in the Control Group

In the control group, PEEP titration will be performed immediately after the initial ARM. After reaching PEEP 25 cmH_2O for 1 minute, the ventilatory mode will be changed to Volume Control, VT 6 mL/kg ideal body weight, maintaining PEEP, and a seven-step decremental maneuver will be performed, decreasing PEEP by 2 cmH_2O every 20 seconds down to 5 cmH_2O. At each step, plateau pressure, driving pressure, total PEEP, and compliance will be evaluated, applying inspiratory and expiratory pauses. PEEP will be titrated according to the highest compliance obtained during the decremental steps. If the same compliance is obtained at two different PEEP levels, the level with the lower plateau pressure will be selected.

Weaning Process

The ventilatory weaning process will be carried out in accordance with the HFRZ Adult ICU MV Weaning Protocol (Annex 2) for both groups, which provides a standardized daily checklist to evaluate patient readiness to begin a Spontaneous Breathing Trial (SBT), along with a structured recording form to document the development and results thereof.

The readiness checklist for SBT includes clinical, respiratory, and hemodynamic criteria to ensure the patient is in safe conditions to begin weaning.

Once these criteria are met, the SBT will be performed using the parameters defined by the institutional protocol (standardized pressure support and PEEP, minimum duration of 30 to 60 minutes, and suspension criteria). During the trial, respiratory, neurological, and hemodynamic variables will be recorded, as well as signs of fatigue or intolerance.

Ventilator-free days at 28 days (VFD-28), defined as the number of days the patient remains without IMV from successful extubation (extubation without reintubation or death within 7 days, with or without non-invasive ventilation use, or ICU discharge without MV within 7 days, whichever comes first), constitute the primary outcome of the study.

Rescue Interventions

In the event of persistent refractory hypoxemia despite ventilation optimization, increased FiO_2 and/or prone positioning, the use of ECMO may be considered, in accordance with institutional criteria and the availability of specialized resources. All such co-interventions will be applied uniformly in both study groups, except for differences inherent to the PEEP strategy defined by the protocol.

Prone positioning will be mandatory when PaO_2/FiO_2 < 100 mmHg, with sessions of at least 16 hours, which may be extended based on clinical response and the clinical team's judgment.

Safety Monitoring and Suspension Criteria

Throughout the study, continuous monitoring of clinical, hemodynamic, and ventilatory parameters will be carried out to safeguard patient safety. The team in charge will daily record variables such as SpO_2, blood pressure, heart rate, arterial blood gas, plateau pressure, and driving pressure, as well as the presence of MV-associated complications.

The study includes criteria for immediate suspension of recruitment maneuvers in the event of major adverse events during the evaluation procedures, including:

- Severe hemodynamic instability, defined as persistent hypotension (drop in mean arterial pressure > 15 mmHg) not reversible with vasopressor support adjustment.
- Refractory hypoxemia, with SpO_2 < 85% for more than 5 minutes.
- Clinically significant barotrauma, such as newly appearing pneumothorax, pneumomediastinum, or subcutaneous emphysema.
- Sustained ventricular arrhythmias or cardiorespiratory arrest attributable to the procedure.

In any of these circumstances, the recruitment maneuver or the assigned strategy will be interrupted and the patient will receive treatment as determined by the attending medical team. Adverse events will be reported and documented following institutional patient safety procedures and notified to the HFRZ Ethics Committee.

Follow-up and Registration

Blood gas and ventilatory parameter evaluations will be performed in a standardized manner for both study groups. A baseline ABG will be obtained before PEEP titration and a second measurement 15 minutes after completion of PEEP adjustment, with the patient in stable conditions and without changes in sedation or ventilatory mode. Subsequently, at 24, 48, and 72 hours after initial titration (coinciding with daily routine clinical blood gas measurements), the following will be performed and recorded: blood gas controls, ventilatory parameters, hemodynamic status, pulmonary mechanics evaluation, vasopressor doses, patient positioning. At each time point, recruitment potential will be re-evaluated using the R/I ratio and a new recruitment maneuver will be performed prior to PEEP titration. R/I ratio, PaO_2, $PaCO_2$, pH, FiO_2, total PEEP, intrinsic PEEP, plateau pressure, driving pressure, Cest, and VR will be recorded.

This strategy seeks to minimize the number of additional blood draws by integrating protocol measurements with routine clinical care controls, ensuring patient safety and reducing interference with daily clinical practice. It will also allow analysis of the temporal evolution of relevant physiological variables during the first 72 hours post-intervention, the period during which the greatest changes associated with the PEEP adjustment response are concentrated.

Clinical variables, ventilatory parameters, adverse events, and outcomes will be recorded in an electronic form using REDCap software for data storage.

7.7 Data Custody Mechanisms

All data collected during the study will be stored securely in a digital database on a password-protected computer, accessible only to the principal investigator and authorized co-investigators. To anonymize personal data (name, medical file number, etc.), they will be separated from the analytical database and replaced by a unique alphanumeric code assigned to each participant. Physical files, if any (paper collection forms), will be kept under lock in a restricted file within the HFRZ ICU.

7.8 Data Retention Period

Data will be retained for 5 years and then securely destroyed.

7.9 Data Analysis

Collected data will be analyzed following the intention-to-treat (ITT) principle, considering all randomized patients in the assigned group, regardless of subsequent compliance or withdrawal. Continuous variables will be presented as mean ± standard deviation or median and interquartile range, according to their distribution. Categorical variables will be expressed as frequencies and percentages.

For comparison of the primary outcome — ventilator-free days at 28 days — an independent samples Student's t-test will be used if data meet normality (Shapiro-Wilk), or a non-parametric test (Mann-Whitney U) otherwise.

An exploratory analysis will be performed to compare characteristics and evolution of the non-randomized group ($R/I \leq 0.5$) with the randomized groups, although this is not the primary objective of the study.

The significance level will be set at $p < 0.05$. In the event of interim analyses, appropriate statistical limits for type I error control will be adopted. All statistical analyses will be performed using JASP statistical software.

8. Ethical Considerations

This study will be conducted in accordance with universal ethical principles in clinical research, including the Declaration of Helsinki, Good Clinical Practice (GCP), and current national regulations on research in human subjects. The respect, dignity, and rights of all participants will be ensured.

Prior to inclusion, written informed consent will be requested, freely given by the patient or their legal representative, following a clear and understandable explanation of the study's objectives, procedures, potential benefits, and risks associated with participation. It will be emphasized that participation is entirely voluntary and that the patient may withdraw at any time without affecting the quality of medical care received.

To safeguard privacy and confidentiality, all personal data will be coded and stored in secure databases, with access restricted exclusively to the authorized research team. Measures will be adopted to prevent unauthorized disclosure of patient-identifying information.

Participant safety will be rigorously monitored throughout the study. A protocol will be established for the early detection and immediate management of adverse events, including the possibility of withdrawing the patient from the study in the event of unacceptable complications or risks. A detailed record of any adverse event or side effect related to the intervention will be maintained.

Ethical oversight and study surveillance will be the responsibility of the HFRZ Ethics and Safety Committee, the entity responsible for approving the protocol and conducting periodic reviews to ensure scientific and ethical integrity and the protection of participants' rights and well-being.

Finally, it will be ensured that the experimental intervention does not pose a greater risk than standard therapies used in current clinical practice, respecting the principles of beneficence and non-maleficence, with the ultimate aim of contributing knowledge that may improve the management and outcomes of ARDS patients.

Benefits

Patients included in this study may benefit from a more personalized ventilatory strategy based on the individual assessment of pulmonary recruitment potential using the R/I index and transpulmonary pressure-guided titration. This individualization could translate into optimization of ventilatory mechanics with reduced driving pressure, which is associated with lower risk of VILI and better oxygenation. At a collective level, the study will provide clinical evidence that can guide future recommendations and guidelines for ventilatory management in ARDS, contributing to improving the quality of care and clinical outcomes of this critically ill population.

Risks

Although the interventions proposed in this study are based on established clinical techniques and protocols, the manipulation of ventilatory parameters — especially PEEP titration guided by transpulmonary pressure via esophageal balloon — may entail certain risks. These include the occurrence of barotrauma, hemodynamic instability due to changes in intrathoracic pressure, esophageal injuries associated with placement and use of the esophageal catheter, and possible adverse effects related to alveolar recruitment maneuvers. Additionally, ventilatory maneuvers and adjustments may cause transient episodes of hypoxemia or hypercapnia.

Costs to the patient

Participation in this study will not imply any additional cost for the patient or their families. All procedures involved in the study will be covered by competitive funding or will be within the hospital's available resources for the care of ARDS patients.

Confidentiality of information

Collected clinical data will be anonymously coded using a unique identification number per patient. No personal data that could identify participants will be stored. Information will be kept in secure databases, accessible only to authorized investigators.

Voluntariness and revocation

Participation in this study is entirely voluntary. Neither the patient nor their family is obligated to accept inclusion, and their decision will in no way affect the quality or continuity of their usual medical care. At any time, the patient or their legal representative may revoke the previously granted consent without needing to justify their decision. If consent is revoked before completing data collection, study procedures will be immediately halted and no new information will be collected. Data already obtained may be used in anonymized form, unless the patient or their representative expressly states otherwise.

9. Work Plan

Data collection: February 2026 – December 2026

Recruitment end: December 2026

Data analysis: January–February 2027

Article writing: March 2027

10. Dissemination Activities

Study findings will be disseminated through:

- Scientific publications in national and international indexed journals.
- Presentations at conferences (SOCHIMI, Chilean Society of Respiratory Diseases, etc.).
- Academic and clinical sessions at Hospital Dr. Franco Ravera Zunino and the healthcare network.
- Delivery of a plain-language summary to patients and families, along with an informational activity at the hospital.

11. Funding

This project currently has no funding sources.

12. References

18. Ranieri VM, Rubenfeld GD, Thompson BT, et al. Acute respiratory distress syndrome: The Berlin definition. JAMA. 2012;307(23):2526-2533.
19. The ARDS Definition Task Force. Acute Respiratory Distress Syndrome: The Berlin Definition. JAMA. 2012;307(23):2526–2533. doi:10.1001/jama.2012.5669
20. Slutsky AS, Ranieri VM. Ventilator-induced lung injury. N Engl J Med. 2013;369(22):2126-2136.
21. Gattinoni L, Caironi P, Cressoni M, et al. Lung recruitment in patients with acute respiratory distress syndrome. N Engl J Med. 2006;354(17):1775-1786.
22. Ranieri VM, et al. Intrinsic positive end-expiratory pressure and cardiopulmonary interaction in patients with COPD. Am J Respir Crit Care Med. 1993;148(3):665–73.

23. Talmor D, Sarge T, Malhotra A, et al. Mechanical ventilation guided by esophageal pressure in acute lung injury. N Engl J Med. 2008;359(20):2095-2104.
24. Chen L, Del Sorbo L, Grieco DL, et al. Potential for lung recruitment estimated by the recruitment-to-inflation ratio in acute respiratory distress syndrome. Am J Respir Crit Care Med. 2020;201(5):178-185.
25. Chen L. Closure in Acute Respiratory Distress Syndrome: An Underestimated and Misinterpreted Phenomenon. American Journal of Respiratory and Critical Care Medicine. 2018.
26. Tsuchida S, Engelberts D, Peltekova V, et al. Atelectasis causes alveolar injury in nonatelectatic lung regions. Am J Respir Crit Care Med. 2006.
27. Somhorst P, van der Zee P, Endeman H, Gommers D. PEEP-FiO_2 table versus EIT to titrate PEEP in mechanically ventilated patients with COVID-19-related ARDS. Crit Care. 2022;26(1):272.
28. Sinha P, Calfee CS, Beitler JR, et al. Physiologic analysis and clinical performance of the ventilatory ratio in acute respiratory distress syndrome. Am J Respir Crit Care Med. 2019;199:333–41.
29. Amato MBP, Meade MO, Slutsky AS, et al. Driving pressure and survival in the Acute Respiratory Distress Syndrome. N Engl J Med. 2015;372(8):747–755.
30. Bugedo G, Retamal J, Bruhn A. Driving pressure: A marker of severity, a safety limit, or a goal for mechanical ventilation? Crit Care. 2017;21:199.
31. ARDS Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med. 2000;342(18):1301-1308.
32. Dianti J, et al. Association of PEEP and lung recruitment selection strategies with mortality in ARDS: a network meta-analysis. Am J Respir Crit Care Med. 2022.
33. Suter PM, Fairley HB, Isenberg MD. Effect of tidal volume and positive end-expiratory pressure on compliance during mechanical ventilation. Chest. 1978;73(2):158-62.
34. Amato MBP, Barbas CSV, Medeiros DM, et al. Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. N Engl J Med. 1998;338:347-54.
35. Pintado MC, de Pablo R, Trascasa M, et al. Individualized PEEP setting in subjects with ARDS: a randomized controlled pilot study. Respir Care. 2013;58(9):1416-23.
36. Sutherasan Y, Songsomboon C, Gulapa K, et al. The potential risk of ventilator-induced lung injury from five different PEEP titration techniques in ARDS. Front Med (Lausanne). 2025;12:1642064.
37. Goligher EC, Kavanagh BP, Rubenfeld GD, Ferguson ND. Physiologic responsiveness should guide entry into randomized controlled trials. Am J Respir Crit Care Med. 2015;192(12):1416–9.
38. Grasselli G, Calfee CS, Camporota L, et al. ESICM guidelines on acute respiratory distress syndrome: definition, phenotyping and respiratory support strategies. Intensive Care Med. 2023;49:727–759.
39. Brault C, Zerbib Y, Kontar L, et al. Positive end-expiratory pressure in COVID-19-related ARDS: do not forget the airway closure. J Crit Care. 2021;64:141–3.
40. Chiumello D, Marino A, Brioni M, et al. Lung recruitment assessed by respiratory mechanics and computed tomography in patients with acute respiratory distress syndrome: what is the relationship? Am J Respir Crit Care Med. 2016;193:1254–63.
41. Beduneau G, Pham T, Schortgen F, et al. Epidemiology of Weaning Outcome according to a New Definition. The WIND Study. Am J Respir Crit Care Med. 2017.

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