



UNIVERSITÀ DEGLI STUDI DI PADOVA

School of Medicine

Single-Cycle Master's Degree Course in Medicine and Surgery

Dipartimento di Medicina

Director: Prof. Paolo Simioni

Istituto di Anestesia e Rianimazione

Director: Prof.ssa Annalisa Boscolo Bozza

THESIS

**EVALUATION OF POSITIVE END-EXPIRATORY PRESSURE
USING TRANSPULMONARY COMPLIANCE AND
ELECTRICAL IMPEDANCE TOMOGRAPHY IN PATIENTS
WITH ACUTE HYPOXEMIC RESPIRATORY FAILURE**

Supervisor: **Prof.ssa Annalisa Boscolo Bozza**

Co-Supervisor: **Prof. Tommaso Pettenuzzo**

Graduand: **Rossana Locati**

Academic Year 2025/2026

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ABSTRACT

Background: Simultaneous optimization of alveolar distension and collapse, estimated by electrical impedance tomography (EIT), is increasingly used to guide positive end-expiratory pressure (PEEP) titration in critically ill patients. This approach conventionally determines regional compliance changes from airway pressure (P_{AW}), implicitly assuming that chest wall compliance (C_{CW}) remains constant across the explored PEEP range, making respiratory system compliance (C_{AW}) a reliable surrogate for transpulmonary compliance (C_L). Whether this assumption holds, and whether using transpulmonary rather than respiratory system pressure meaningfully changes the PEEP selected by EIT-based titration, has not been formally tested yet. So far, this has been validated only in patients receiving partial ventilatory support.

Aims: To investigate whether the use of transpulmonary pressure (P_L), compared with respiratory system pressure (P_{AW}), influenced the selection of optimal PEEP identified by EIT-based titration in patients with acute hypoxemic respiratory failure (AHRF) receiving fully ventilatory support, and to characterize the physiological factors associated with any divergence between the two practices. As secondary aims, the study compares overdistension, collapse, lung recruitability, and respiratory mechanics between the two techniques throughout the decremental PEEP trial. It examines whether recruitability or overdistension risk influence the optimal PEEP identified by each method; and assesses how chest wall compliance varies with PEEP.

Methods: We performed a multicenter physiological analysis of 36 intubated patients with acute hypoxemic respiratory failure. During decremental PEEP trials conducted under concurrent EIT and esophageal pressure monitoring,

overdistension and collapse were calculated using either the change in airway pressure (ΔP_{AW}) or in transpulmonary pressure (ΔP_L). For both approaches, optimal PEEP was determined in two ways: as the crossing point between the cumulative overdistension and collapse curves, and as the PEEP level minimizing the absolute difference between overdistension and collapse.

Results: Median optimal PEEP was 12 cmH₂O (8-14) with both methods. At the individual level, the P_L -based method selected a slightly higher optimal PEEP than the P_{AW} -based method, with a mean paired difference of 0.44 cmH₂O; Bland-Altman analysis showed 95% limits of agreements of -2.94 to +2.05 cmH₂O. The two techniques identified the same optimal PEEP in 23 patients (64%); P_L selected a higher PEEP in 10 patients (28%) and a lower PEEP in 3 (8%). This divergence demonstrated that P_L -based method assigned a higher PEEP specifically to patients with greater lung recruitability and more severe hypoxemia, without a corresponding increase in overdistension and end-inspiratory P_L . At the P_L -based optimal PEEP, alveolar collapse was lower than at the P_{AW} -optimal PEEP. Despite considerable inter-individual variability, increasing PEEP was associated with a significant decrease in C_{CW} across the cohort, and patients with more impaired baseline compliance often showed the opposite pattern. A sensitivity analysis restricted to a narrower PEEP range demonstrated improved agreement between the two techniques.

Conclusions: P_{AW} - and P_L -based EIT methods for optimal PEEP titration were broadly concordant at the population level, supporting the clinical robustness of the conventional, P_{AW} -based approach to EIT-guided PEEP selection in AHRF. However, in a clinically relevant subgroup of more hypoxemic and more recruitable patients, the P_{AW} -based technique may underestimate the optimal PEEP, as a PEEP-dependent decrease in chest wall compliance can lead to overestimation of lung overdistension when P_{AW} , rather than P_L , is used in PEEP titration.

1. INTRODUCTION

1.1 Acute Respiratory Failure (ARF)

Acute respiratory failure (ARF) is a devastating condition for patients that results from impaired function of one or both components of lung gas exchange ¹², meaning oxygenation of and/or elimination of carbon dioxide from mixed venous blood, causing a sudden inability to maintain adequate gas exchange between the atmosphere and the blood ¹. It represents a challenging, heterogeneous condition associated with a high hospital morbidity and mortality rate, ethical issues in managing end of life decisions and increased consumption of healthcare resources. The mortality rate for ARF in hospital settings ranges from 20% to 40%, depending on the severity of the condition, the underlying etiology, and the presence of comorbidities, such as chronic respiratory, cardiovascular and neurovascular diseases, sepsis, trauma and post-surgical complications ². Survivors of ARF often experience long-term sequelae, including reduced quality of life, persistent respiratory symptoms, and functional impairments, underscoring the need for comprehensive post-acute care and rehabilitation ².

The etiology of ARF is multifactorial, encompassing a wide array of pulmonary and extrapulmonary disorders.

Just like etiology, also pathophysiology is determined by complex interactions between pulmonary and systemic factors affecting the respiratory system. The respiratory system can be said to consist of two parts: the lung, i.e. the gas-exchanging organ, and the pump that ventilates the lungs. The pump consists of the chest wall, including the respiratory muscles, the respiratory controllers in the central nervous system (CNS) and the pathways that connect the central controllers with the respiratory muscles (spinal and peripheral nerves). Failure of each part of the system leads to distinct entities ¹².

ARF symptoms can be broadly divided into respiratory, hypoxemia-related and hypercapnia-related symptoms. Respiratory distress is the hallmark of ARF and it can present with dyspnea, tachypnea, use of accessory muscles or increased work of breathing, orthopnea and paroxysmal nocturnal dyspnea. Hypoxemia-related symptoms can be cyanosis, confusion and altered mental status, and cardiovascular effects, namely tachycardia, arrhythmias, hypotension and signs of cardiac ischemia. Hypercapnia can manifest with headaches, flushed skin, confusion and lethargy, and asterixis. Additionally, the clinical manifestation of ARF is influenced by the underlying cause that might present with disease-specific symptoms and signs. Understanding of the wide range of clinical manifestations is essential for a prompt diagnosis and intervention ².

The diagnosis of respiratory failure is a laboratory one, but the cut-off values are not rigid as they represent a general guide that must be completed with the history and clinical assessment of the patient ¹². Diagnostic tests provide insight on the possible etiology, the condition severity and guide management decisions. The essential test to diagnose and characterize ARF is the arterial blood gas (ABG) analysis, which yields information about oxygenation and ventilation. ARF is conventionally defined by an arterial oxygen tension PaO_2 of <8.0 kPa (60 mmHg), an arterial carbon dioxide tension PaCO_2 of >6.0 kPa (45 mmHg) or both. Based on its results, we can categorize ARF into two main types ^{2; 12}.

- Hypoxemic respiratory failure (Type 1): Represents the failure of the lungs and it arises from defective oxygen transfer within the alveolar units. It is caused by multiple conditions leading to lung damage including acute cardiogenic pulmonary oedema, pneumonia and trauma.
- Hypercapnic respiratory failure (Type 2): Represents the failure of the pump, resulting from an imbalance between the load imposed on the respiratory muscles and the capacity of the muscle pump, leading to carbon dioxide retention. Hypercapnia is defined as a partial pressure of carbon dioxide $\text{PaCO}_2 > 45$ mmHg at ABG. This category mainly includes patients with acute exacerbation of chronic obstructive pulmonary disease

(COPD), as well as patients with neuro-myopathies, chest wall deformities, drug overdose and obesity¹.

Defining the type of ARF is critical in the decision of the therapeutic plan and management. The aim in the management of ARF is stabilizing the patient's respiratory status, addressing the underlying cause, and preventing complications. The initial approach starts with supportive measures and pharmacological therapies, however ventilation (both non-invasive and invasive mechanical ventilation) and advanced therapies, such as extracorporeal membrane oxygenation (ECMO), can be adopted based on patient characteristics². In particular, oxygen therapy and ventilation are cornerstones in the treatment of ARF: non-invasive ventilation (NIV) has revolutionized management approaches by providing effective support and reducing the need for intubation and its associated complications. This interplay of multiple measures affords time for etiological therapy to reverse the cause of the acute decompensation of the respiratory system and improve patient outcomes, while minimizing the potential lung injuring effects of therapeutic interventions, such as ventilator-induced lung injury^{1;2}.

1.2 Acute Hypoxemic Respiratory Failure (AHRF)

Acute hypoxemic respiratory failure (AHRF), also named Type 1 acute respiratory failure, is described by the inability of the respiratory system to maintain an adequate blood oxygen level to preserve normal organ function. Hypoxemia is defined by a $\text{PaO}_2 < 60$ mmHg or $\text{SaO}_2 < 88\%$, which indicate the impairment of gas exchange⁴. AHRF is the leading cause of intensive care unit ICU admissions⁵, 40 %–50 % of these patients will require intubation during their stay in the ICU⁶ and 30%-80% will meet the Berlin criteria for Acute Respiratory Distress Syndrome (ARDS).

2012 Berlin criteria diagnose ARDS when all four parameters are met:

- Timing: The onset of symptoms must occur within one week of a known clinical insult or worsening respiratory symptoms.
- Chest Imaging: Bilateral opacities on chest x-ray or CT scan. These opacities are not fully explained by effusions, lung collapse, or pulmonary nodules.
- Origin of Edema: Respiratory failure not fully explained by heart failure or fluid overload.
- Hypoxemia: $\text{SpO}_2/\text{FiO}_2 \leq 300$ with $\text{SpO}_2 \leq 97\%$ and $\text{PEEP} \geq 5 \text{ cmH}_2\text{O}$ ¹⁶.

There are multiple mechanisms leading to hypoxemia: V/Q mismatch is the most common and the most extreme example of reduced V/Q ratio is anatomic shunt, which is the complete impairment in ventilation despite adequate blood flow. Other possible mechanisms are diffusion limitation, in which oxygen is unable to move across the alveolus into the capillary blood despite an unchanged V/Q ratio, hypoventilation which is a reduction in the partial pressure of oxygen in the alveolus PaO_2 without concomitant changes in the ability of the capillary blood to extract oxygen, and lastly low inspired FiO_2 or oxygen delivery-consumption imbalance (hypermetabolism, low cardiac output, low oxygen carrying capacity) ⁴.

AHRF evaluation begins with the peripheral oxygen saturation SpO_2 or arterial oxygen saturation SaO_2 (obtained with an arterial blood gas analysis) to determine if hypoxia is present. The A-a gradient, that is the difference between PAO_2 from the alveolar gas equation and PaO_2 from arterial blood, allows for identification of abnormalities in oxygen absorption in the lung. If the A-a gradient is wider than expected, the etiology of hypoxemia is related to V/Q mismatch, shunt or diffusion limitation ⁴.

Rapid identification of AHRF and its underlying cause is necessary to tailor the management to each case and reach a better outcome. The most common causes of AHRF reported in the FLORALI trial are community-acquired pneumonia (present in 64% of cases), hospital-acquired pneumonia (11.9%), extrapulmonary sepsis (5.2%), and aspiration and near drowning (1.9%) ¹³. AHRF is less commonly associated with non-cardiogenic shock and trauma. These conditions must be kept in mind when searching for the etiology of AHRF as they can be identified in the

majority of patients. However, the cause remains undiagnosed after the initial approach in rare cases, particularly among immunosuppressed patients, in whom up to 15% of cases remain undiagnosed after beginning work-up ¹⁴, representing a challenge for the management of these patients. A comprehensive diagnostic work-up is imperative to cure conditions in a timely manner and to prevent unfavorable outcomes.

The diagnostic approach begins by excluding cardiogenic pulmonary edema or fluid overload, atelectasis or lung collapse, pleural effusion, and pulmonary embolism. This step is carried out with medical history, physical examination, chest x-ray, cardiac and pleuropulmonary ultrasound. The second step is to check for the common causes of AHRF: recent and past medical history, physical examination and laboratory tests (microbiological investigations) help in the diagnosis of pneumonia, non-pulmonary infection, trauma, aspiration and shock ⁵. If these tests are inconclusive, the diagnostic work-up focuses on the identification of rare causes of AHRF.

The management of AHRF concentrates on the treatment and resolution of the underlying cause, but all hypoxemic patients are supported with oxygen therapy to maintain adequate oxygen delivery to tissues ⁴. Monitoring for hypoxemia is essential, but non-invasive monitoring has some limitations, especially the inaccuracy and systematic bias based on skin tone of pulse oximetry ¹⁵.

1.3 Mechanical Ventilation

There are numerous techniques employed to support ventilation and oxygenation and are generally divided into invasive mechanical ventilation (IMV) or non-invasive ventilation (NIV). The latter represents a clinical approach that bypasses the requirement for an artificial airway, avoiding the use of endotracheal tubes or tracheostomy. Instead, this supportive technique utilizes external interfaces, such as masks, nasal cannulas or specialized helmets, to deliver ventilatory support.

These techniques can deliver oxygen at flow rate up to six liters per minute and for each liter per minute the expected delivered FiO_2 increases by approximately 4% above the room air FiO_2 . Critically ill patients sometimes require oxygen delivery above the rates achieved by traditional non-invasive ventilation methods because of their increased minute ventilation, resulting in a dilution of the administered oxygen with room air. To solve this problem in AHRF patients, the American College of Physicians published a practice guideline in 2021, recommending the use of HFNC over conventional oxygen therapies¹⁷. HFNC is a technique able to provide oxygen up to 60 liters per minute, addressing the increased work of breathing of the patient. Therefore, conventional non-invasive ventilation is employed in patients with hypoxemia and normal work of breathing, while HFNC is the technique of choice in patients with persistent hypoxemia requiring more than 6 liters per minute of supplemental oxygen. If elevated work of breathing, hypoxemia and dyspnea persist despite the use of HFNC, intubation and invasive mechanical ventilation might be unavoidable. There is not a defined threshold at which to intubate a patient with AHRF and a 2021 meta-analysis revealed no significant statistical difference in all-cause mortality between early and late intubation groups¹⁸. The decision to move to invasive mechanical ventilation is therefore tailored based on each case and its evidence of tissue hypoperfusion despite maximal non-invasive oxygen therapy.

1.4 Invasive Mechanical Ventilation (IMV)

Mechanical ventilation is a form of support necessary to guarantee the survival of patients with acute hypoxemic respiratory failure while they are treated for the etiological condition. Safe and effective ventilation strategies are based on solid understanding of human physiology and airway mechanics to select the appropriate ventilation modes, initial settings and supportive care for intubated patients. During spontaneous inspiration, the lung expands as transpulmonary pressure results from the negative pleural pressure generated by the inspiratory

muscles. In contrast, controlled mechanical ventilation relies on positive inspiratory pressure to drive gas into the lungs, creating a positive pressure environment.

Invasive ventilation modes are categorized based on the breath initiation and breath delivery. Breaths can be initiated by the ventilator, the patient, or a combination of the two. A key dichotomy is whether breaths are delivered with a set amount of volume or a set amount of pressure¹⁹. In either case, the opposing variable reflects the compliance of the respiratory system (C_{AW}), calculated as the ratio between the change in volume over the change in pressure.

$$C_{AW} = \frac{\Delta V}{\Delta P}$$

Consequently, if volume is set on the ventilator, pressure is the dependent variable monitored to understand compliance. If pressure is set on the ventilator, volume is the dependent variable monitored to understand compliance.

When initiating controlled mechanical ventilation, the clinician must configure core input variables: tidal volume (V_T), positive end-expiratory pressure (PEEP), respiratory rate (RR), inspiratory airflow (V'), and the fraction of inspired oxygen (FiO_2).

Among these, tidal volume (V_T) is an essential clinical parameter: it represents the volume of inspired and expired air that helps keep oxygen and carbon dioxide levels stable in the blood. It is vital when setting the ventilator in critical patients as the goal is to deliver a tidal volume small enough to prevent lung trauma while maintaining adequate ventilation. Rather than being arbitrary, it must be scaled to the patient's ideal or predicted body weight, aiming to optimize gas exchange while preventing airway closure and maximizing functional residual capacity.

Managing the core input variables creates a delicate mechanical balance and, once these inputs have been adjusted, the clinician has to monitor closely critical output variables such as intrinsic PEEP, peak (P_{peak}) and plateau (P_{plat}) pressures, driving pressure (ΔP), transpulmonary pressure (P_L), mechanical energy, mechanical power, and intensity.

In patients with AHRF, whose functional lung size is drastically reduced, delivery of unadjusted or excessive V_T generates dangerous spikes in these pressures. The result of ventilation with large tidal volumes can be volutrauma, due to alveolar overdistension and repetitive opening of collapsed alveoli, or barotrauma, characterized by alveolar rupture followed by air accumulation in the pleural cavity or mediastinum. Patients with AHRF already have injured lungs, and mechanical ventilation should follow a lung-protective strategy to avoid the development of ventilator-induced lung trauma (VILI) ²⁰.

1.5 Ventilator-Induced Lung Injury (VILI)

Even though mechanical ventilation is necessary to guarantee survival of patients with AHRF, it is not a cure and, as demonstrated by preclinical and clinical studies, it can cause or aggravate the pulmonary pathology, leading to ventilatory-induced lung injury (VILI). Any patient with either acute respiratory distress syndrome (ARDS) or other forms of respiratory insufficiency are at risk of developing this complication since mechanical ventilation can exacerbate lung injury in an already diseased organ.

The concept of VILI is not new as it has been described in literature from 1745 by John Fothergill when discussing mouth-to-mouth resuscitation ("Observations on the Recovery of a Man Dead in Appearance by Distending the Lungs with Air," London, 1745): he deemed it the preferred method of ventilation since he understood that the mechanical force exerted by a man could be borne by the lung without injury ²¹.

The pathogenesis of VILI has not yet been completely understood, but VILI is the result of repeated application of high mechanical forces that either tear fragile tissue directly or initiate signaling that culminates in inflammatory changes.

Multiple types of VILI exist and they are related to two main mechanisms: one is the excessive alveolar distension resulting from elevated transpulmonary pressure

(barotrauma) and current volumes (volutrauma), the other is the repetitive opening and closure of alveolar units (atelectrauma).

Particularly sensitive to ventilatory-induced injury are the regions of pulmonary parenchyma inhomogeneity where the mechanical distension is exacerbated by the decreased gas/tissue ratio compared to surrounding zones, and the parenchymal areas of the superior lobes which are still ventilated.

1.5.1 Baby Lung

In ARDS, the entire lung parenchyma is involved in the disease process, and the edema is distributed evenly from vertebra to the sternum, not following gravity. The accumulated edema increases the lung weight, raising the hydrostatic pressures transmitted throughout the lung, which is called superimposed pressure²². This pressure drives the gas out from the underlying dependent lung regions, forming areas of density caused by the compressive gravitational forces of both the weight of the edema and of the heart.

The fraction of the lung that still maintains normal inflation is defined as baby lung. The concept of baby lung is not anatomical, but functional as it represents the primary site of CO₂ clearance and blood oxygenation. It is mainly located in the nondependent lung regions which are not compressed by the edema.

Its size depends on ARDS severity and it relates to the compliance of the respiratory system. Additionally, its size depends on the site since it can change following the body position: when the patient is prone, the baby lung shifts from ventral to dorsal lung regions, increasing its size. The size of the baby lung can also increase in relation with positive end expiratory pressure (PEEP), allowing better inflation of patent alveoli and adding new pulmonary units.

The baby lung concept is critical for managing VILI. Proning recruits additional lung units, therefore increasing the size of the baby lung, minimizing high-stress junctions between open and closed units. This decreases alveolar driving pressure,

a key indirect measure of lung compliance and respiratory strain. In other words, compliance appears to gauge the dimension of the baby lung ²².

The heterogeneity and fragility of the baby lung highlight the urgent need of reliable ways to monitor and quantify ongoing mechanical stress. However, the methods and clinical markers historically and currently applied for VILI evaluation have profound limitations in capturing regional heterogeneity typical of the baby lung.

1.5.2 VILI Evaluation

In order to prevent VILI, the evaluation of the risk of lung injury comes first. Lung injury results from excess mechanical stress, the internal distending force evaluated by the transpulmonary pressure, and strain, which is the deformation in lung volume relative to its resting functional residual capacity.

Transpulmonary pressure is evaluated and measured as the airway opening pressure minus the pleural pressure estimated with esophageal manometry.

$$P_L = P_{AW} - P_{ES}$$

High transpulmonary pressure is caused by the delivery of large tidal volumes (V_T), leading to lung stress and subsequent lung injury and inflammation. When the mechanical forces are unmanaged, they disrupt the alveolar-capillary barrier, triggering biotrauma.

Biotrauma is a severe inflammatory response triggered in the lungs when mechanical ventilation overdistends alveolar epithelial and endothelial cells, releasing immune system mediators, causing damage to both the lungs and other organs. The immune response is not localized in the lungs, but it becomes systemic, driving multi-organ failure (MODS). VILI represents not only a structural lung injury, but it is a systemic inflammatory disease with critical consequences ²⁴.

In addition to static stretch, atelectrauma is the damage caused by repetitive collapse of the lung at end-expiration, highlighting how incorrect or inadequate PEEP titrations contribute to damage ²³.

To combine these insults, the risk assessment involves the driving pressure of the respiratory system (ΔP_{AW}): it is defined as the distending pressure above the applied positive end-expiratory pressure (PEEP) required to generate tidal volume (V_T). It is obtained by the difference between the plateau pressure, so the pressure measured in the airways during the end expiratory pause, and total PEEP in the absence of spontaneous breathing.

$$\Delta P = P_{Plat} - PEEP$$

It derives from the ventilator and it reflects the combined effects of the tidal volume and the respiratory compliance ²⁵. Driving pressure is currently considered the best predictor of VILI, but the evidence is indirect and derived from statistical models of retrospective studies²⁶.

These parameters are traditionally used as predictors for the risk of VILI, although they share a major physiological blind spot: they measure the mechanics of the total respiratory system, combining lungs and chest wall. Both driving pressure and plateau pressure comprise these two components, one related to pulmonary expansion and the other associated with the expansion of the chest wall. Plateau pressure, which reflects the total respiratory system pressure, does not allow these two components to be distinguished. Consequently, it cannot isolate the pressure component associated with the pulmonary expansion, which is more directly related with the risk of VILI.

To evaluate VILI strictly at the pulmonary level, clinicians must isolate the true pressure distending the alveoli. This is achieved by using the transpulmonary pressure (P_L), calculated via esophageal manometry as the difference between airway pressure and pleural pressure. This mathematically removes the influence of the chest wall, allowing the quantification of the true lung stress.

1.6 Protective Ventilation Paradigm

The evaluation of VILI, its pathophysiological mechanisms and consequences highlight the utter importance of the optimization of mechanical ventilation settings to proactively prevent VILI and protect systemic organ function. Precautions to avoid VILI can be taken and it is carried out with protective ventilation, which is the current standard for mechanical ventilation in patients with and without ARDS. The paradigm is based on the proposal that airway pressure and tidal volume should be limited in managing ventilation ²⁷. The reduction of the driving pressure has been associated with better outcomes and decreased mortality in both patients with and without ARDS. The use of lower tidal volumes was found to be efficacious in decreasing mortality and was associated with better outcomes in multiple studies comparing it with the use of traditional tidal volumes.

Lowering tidal volume and plateau pressure are not the sole core principles of protective ventilation as this paradigm relies heavily on the prevention of end-expiratory alveolar collapse and atelectrauma by optimizing PEEP ²⁸.

1.7 PEEP

Positive end-expiratory pressure (PEEP) is a fundamental component of mechanical ventilation used to maintain alveolar patency and to prevent alveolar collapse at the end of expiration. PEEP is widely used in invasive and noninvasive ventilation strategies in emergency, critical care and perioperative settings as it improves oxygenation and reduces the risk of atelectrauma. By maintaining a positive pressure in the lungs, PEEP enhances functional residual lung capacity, decreasing intrapulmonary shunting and ventilation-perfusion mismatch. It has a direct impact on oxygenation and an indirect impact on ventilation. PEEP is also able to decrease breathing work, aiding intubated patients with low lung

compliance. In these patients, breathing can represent up to 30% of total energy expenditure, leading to higher CO₂ and lactate production, causing acid-base abnormalities²⁹.

However, the application of PEEP is a delicate balance: while higher PEEP recruits collapsed alveolar units, excessive PEEP can simultaneously overdistend already patent regions, contributing to volutrauma. In addition to VILI, high PEEP may also be responsible for the compression of the pulmonary vasculature, impairing venous return and reducing cardiac output. Because the optimal PEEP level varies individually, finding the exact pressure that maximizes recruitment while minimizing overdistension remains one of the greatest challenges in critical care.

1.7.1 Limitations of Current PEEP Titration Methods

PEEP is considered a core pillar in the protective ventilation paradigm even though incorrect PEEP titration may induce alveolar overdistension and compromised hemodynamic due to increased intrathoracic pressure. Optimal PEEP levels vary depending on the patient's clinical condition and require careful titration. PEEP selection should be individualized based on lung mechanics, oxygenation targets, and patient-specific factors. In ARDS, current strategies suggest higher PEEP values, but emphasize individualization using driving pressure, compliance and electrical impedance tomography (EIT). Even though the need of personalized PEEP selection methods has been recognized, the easiest and most diffused approach remains targeting PEEP titration on arterial oxygenation through the PEEP/inspired fraction of oxygen FiO₂ tables³⁶.

Moreover, the injured lung is deeply heterogeneous, as it is explained in the previous chapter when explaining the baby lung, and current methods do not take into consideration regional mechanics. Lung recruitability, defined as the ability of closed lung units to become aerated again, must be assessed for a safe PEEP selection in mechanically ventilated patients.

Numerous titration methods have been proposed and recent studies suggest the use of electrical impedance tomography (EIT) in the selection of the most beneficial PEEP.

1.8 Electrical Impedance Tomography (EIT)

Electrical impedance tomography (EIT) is a validated, non-invasive, radiation-free, functional diagnostic tool that enables real-time evaluation of pulmonary function at the patient's bedside, allowing the monitoring of regional distribution of ventilation and pulmonary perfusion ³⁰. Image reconstruction in EIT is based on estimating impedance variations that occur during respiration. The main determinants of impedance variations are movements of air and blood within the thorax: reduced conductivity can result from both an increase in intrapulmonary gas volume and a decrease in blood volume. The increase in impedance during inspiration correlates with greater resistance that electrical current encounters due to the thinning and elongation of alveolar septa.

The EIT system consists of three fundamental components: a thoracic belt fitted with equidistant electrodes, a software package that processes the signals from the electrodes, and a display that represents analysis results (Figure 1). During the examination, EIT detects the thorax impedance to the passage of low-intensity alternating electrical currents applied through a pair of electrodes while the other electrodes measure the resulting voltage. All voltage values collected during the alternating current cycle are processed by an algorithm that, starting from impedance variation signal, reconstructs a two-dimensional, cross-sectional scan image of the portion of the lung surrounded by the electrodes ³⁰. Therefore, the reconstruction of the EIT image describes the regional variations in ventilation (air movement) and perfusion (blood movement).

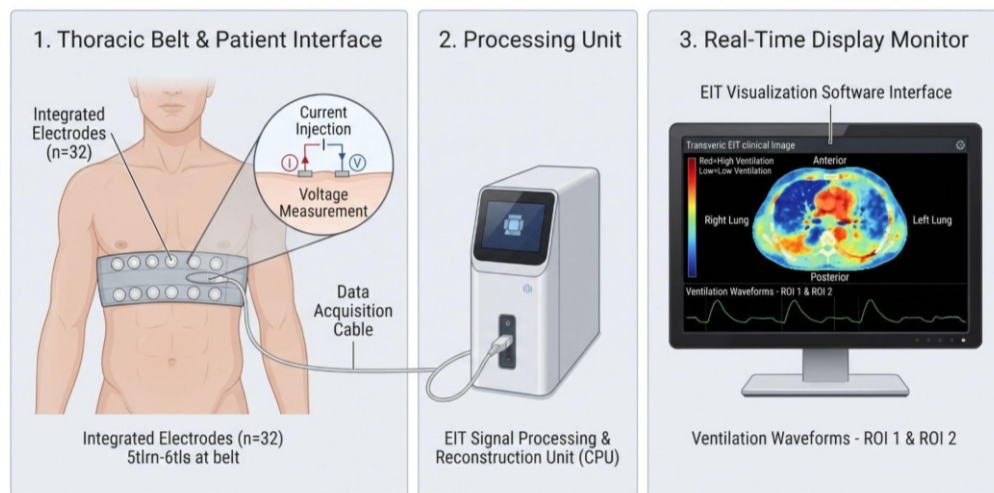


Figure 1. Electrical Impedance Tomography System Component Overview. Schematic representation of the three main elements of EIT. From left to right: thoracic belt, processing unit with the software, and monitor for the result evaluation.

EIT allows patient-specific and regional (dependent vs non-dependent lung) assessment of PEEP effects on overdistension and collapse of the alveoli, as well as interaction with position changes ³¹. For this reason, EIT has a valuable role in setting the ideal PEEP in critically ill patients and has been included in PEEP titration methods, given its ability to define lung recruitability.

1.9 The “Costa” Method

The first and most commonly used EIT-based PEEP titration in patients with ARDS is the “Costa” method, also called overdistension and collapse (OD-CL) method, that was proposed for the first time in 2009. It assesses relative changes of regional lung compliance on a pixel-level during an initial decremental PEEP trial after maximal lung recruitment, requiring the measurement of driving pressure (ΔP).

The method is based on the assumption that each pixel has its optimal compliance at some pressure within the applied PEEP range. Because local tidal volume is correlated with local thoracic impedance variations, the optimal compliance in the system is estimated as the ratio between tidal impedance variation (TIV) and ΔP . Relative compliance loss is interpreted as either overdistention, associated at higher PEEP, or collapse at lower PEEP. Consequently, the decremental PEEP trial uses the highest and lowest PEEP as a reference for 0% collapse and 0% overdistention, respectively³¹.

After the PEEP trial, the curves representing the cumulative percentage of compliance loss due to either collapse or overdistention are plotted in the same graph against varying PEEP levels³². The PEEP value identified by the crossing point of the curves is defined as the optimal PEEP for the individual patient (Figure 2). At the intersection of the curves, the difference between the percentages of overdistention and collapse is minimal, achieving the best compromise between the two.

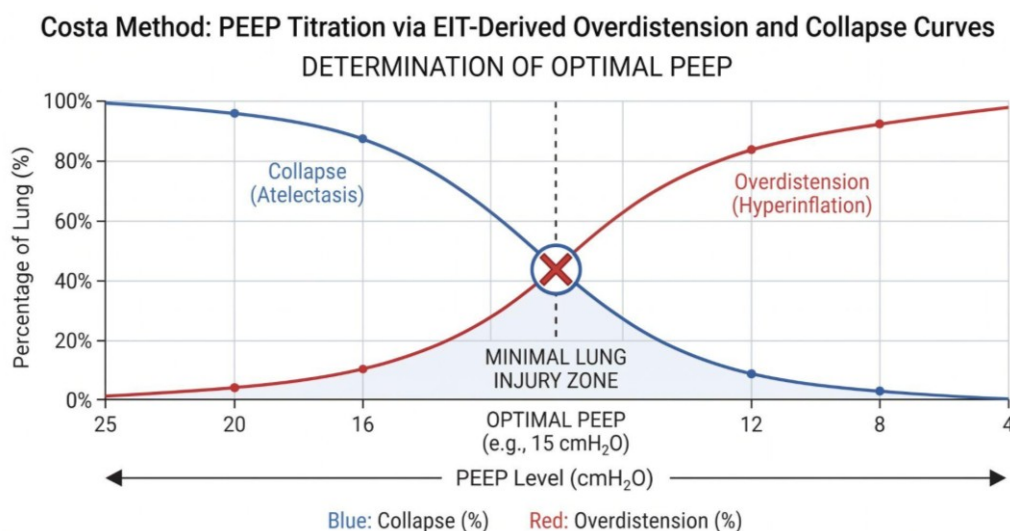


Figure 2. Crossing Point Method for Optimal PEEP Determination.

Graph representing the plotting of the percentage of collapse (blue) and overdistension (red) at different PEEP levels. The crossing point determines the optimal PEEP in order to minimize VILI.

This method of PEEP titration has been used in various contexts and, as demonstrated in some clinical studies, it has been associated with improvements in respiratory mechanics and clinical outcomes^{33, 34}. The “Costa” method has been validated in patients receiving invasive mechanical ventilation under anesthesia, after surgery, for ARDS, including in severe forms requiring extracorporeal membrane oxygenation ECMO (Figure 3).

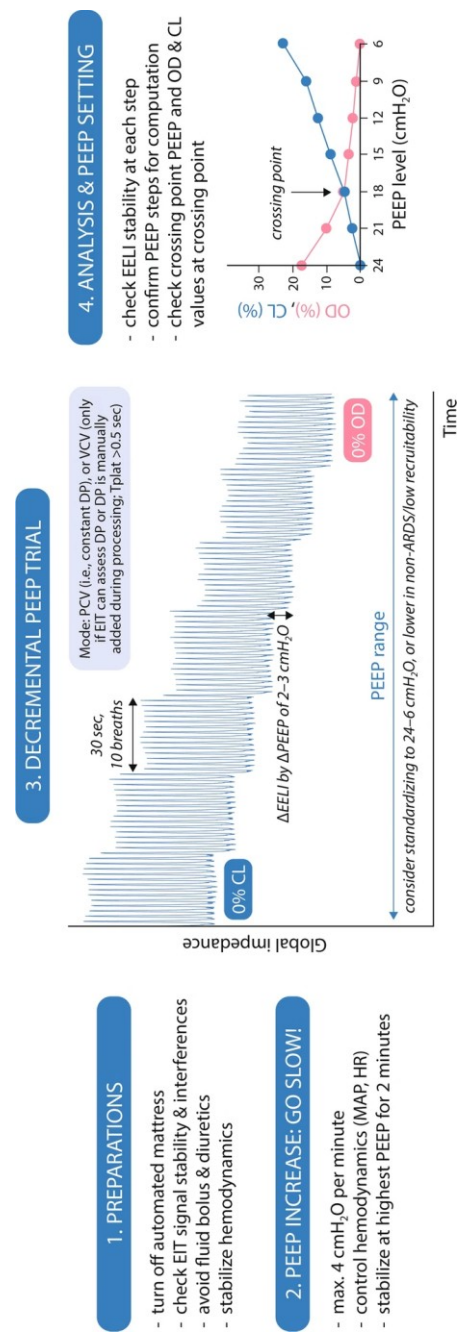


Figure 3. EIT-Based PEEP Titration: Step-by-Step Recommendations.

Optimal PEEP is selected at the crossing point of the OD and CL curves; if the crossing point is between two PEEP levels, values are usually rounded up to the nearest integer. From: Scaramuzzo et al., Crit Care. 2024).

1.9.1 “Costa” Method Limitations

However, this method has some profound limitations. Firstly, it assumes that alveolar collapse and overdistensions are equally damaging to the lung, therefore contributing equivalently to VILI. Secondly, the estimations and calculations are based on the compliance of the respiratory system (C_{AW}), rather than the transpulmonary compliance (C_L). In addition, it rests on the premise that the chest wall compliance (C_{CW}) remains constant over the explored PEEP range, and that changes in regional compliance are relative only to the lung. If C_{CW} is PEEP-dependent, compliance alterations misattributed to pulmonary overdistention or alveolar collapse would actually arise from chest wall mechanics, systematically biasing the estimation of optimal PEEP by “Costa” method.

The physiological efficacy of the “Costa” method was assessed by Mauri et al.³⁵, who compared PEEP derived from the conventional low PEEP/ FiO_2 table with PEEP identified via the intersection of curves representing the cumulative percentage loss of transpulmonary compliance at high and low PEEP levels, thereby utilizing transpulmonary rather than overall respiratory system compliance. The modification of the original “Costa” method with the use of transpulmonary compliance selected a PEEP associated with a reduction in lung stress and work of breathing compared to the method based on the low PEEP/ FiO_2 tables. This study demonstrated that this method of PEEP selection is feasible and safe, but the study was done only in patients with partial ventilation support.

1.9.2 Chest Wall Compliance (C_{CW})

The respiratory system compliance (C_{AW}) reflects the combined mechanical behavior of two structurally and functionally different components: the lung and the chest wall. While pulmonary compliance (C_L) depends on alveolar surface tension, tissue elastic recoil, and degree of ventilation, chest wall compliance (C_{CW})

reflects the mechanical properties of the rib cage, respiratory muscles, diaphragm, and abdominal compartment⁵⁰. C_{CW} is calculated as the change in thoracic volume relative to the change of pleural pressure estimated by esophageal manometry.

$$C_{CW} = \frac{\Delta V}{\Delta P_{es}}$$

Because standard measurements capture only the combined behavior of the two compartments, C_{CW} cannot be isolated without the estimation of pleural pressure, which is why esophageal pressure (P_{ES}) monitoring remains the only bedside method available to isolate the two components of C_{AW} ⁵¹.

C_{CW} is influenced by conditions that increase the mechanical load external to the lung, including obesity, elevated intra-abdominal pressure, thoracic and abdominal edema, pleural effusion, and altered chest wall configurations. It also changes with patient positioning. Some of these conditions lower C_{AW} independently from any change in the lung, so that both P_{plat} and driving pressure, which are measured from C_{AW} , may overestimate the mechanical stress applied to the lung.

The conventional “Costa” method is based on the assumption that C_{CW} remains stable across the initial decremental PEEP trial, so that changes in C_{AW} observed during the different PEEP levels can be attributed only to the lung. However, this stability has not been confirmed, since the determinants of chest wall behavior during the decremental PEEP trial have not been completely defined. If C_{CW} were to change meaningfully within the explored PEEP range, compliance losses attributed to pulmonary overdistension or alveolar collapse could in part reflect chest wall mechanics rather than lung behavior alone.

1.10 Transpulmonary Pressure

Transpulmonary pressure is calculated as the difference between airway pressure (P_{AW}) and pleural pressure, estimated via esophageal pressure (P_{ES}).

Pleural pressure is challenging to directly measure in clinical settings, and esophageal manometry using esophageal balloon catheters was suggested for estimation. The catheter has pressure sensors and transmits intraluminal pressure data that are subsequently converted into dynamic esophageal pressure topography plots. Pes measurement has some limitations, as it is influenced by the ventrodorsal gradient of pleural pressure and mechanical differences across various lung regions. Furthermore, several factors interfere with the accuracy of the measurement, which also requires a precise insertion technique and careful calibration. Monitoring of P_{ES} for adjustment of mechanical ventilation to prevent or reduce VILI is still debated as it has controversial results in clinical studies ³⁷.

The “Costa” method estimates overdistension and collapse as a function of the respiratory system driving pressure (ΔP_{AW}), rather than transpulmonary driving pressure (ΔP_L). ΔP_L represents the distending pressure applied on the lung associated with tidal volume delivery and it allows removal of the contributions of the chest wall to ΔP_{AW} ³⁵, which is not relevant in VILI risk assessment. Therefore, ΔP_L is considered a better denominator for regional compliance to assess the risk of VILI, which depends on the severity of lung stress and strain ³⁴. The superiority of ΔP_L over ΔP_{AW} is being studied, as chest wall compliance seems stable in different patients at different levels of PEEP ³⁸. Regardless, chest wall mechanics estimations require P_{ES} measurement, which requires an accurate calibration and is subjected to the aforementioned limitations.

2. AIMS OF THE STUDY

This is a retrospective multicentric physiological study conducted to verify whether using transpulmonary pressure, compared to the pressure of the entire respiratory system, yields different results of optimal PEEP in the application of the overdistention-collapse crossing point method for EIT-based PEEP titration in patients with acute hypoxemic respiratory failure (AHRF) receiving invasive mechanical ventilation.

These two methods were first proposed by Mauri et al. in patients with partial ventilation support. The objective of the study is to apply the two techniques in patients with total support ventilation with the intention of comparing the resulting optimal PEEP and some additional characteristics.

As a secondary aim, this study undertakes a comparative analysis between the two methodologies by evaluating overdistension and alveolar collapse, as well as lung recruitability, and overall respiratory mechanics. Throughout the decremental PEEP trial performed in each technique, the relative proportions of overdistension and collapse are monitored and compared at each PEEP level. Moreover, this study aims to verify whether patients exhibiting higher pulmonary recruitability or a greater tendency toward overdistension estimated by EIT demonstrate different optimal PEEP values when evaluated in the two methods. This research also assesses dynamic variations in chest wall compliance (C_{CW}) in correlation with incremental modifications in PEEP titration.

3. MATERIALS AND METHODS

3.1 Patients

A novel analysis has been conducted with data collected in patients with acute hypoxemic respiratory failure (AHRF) under invasive controlled mechanical ventilation. These patients were enrolled in three prospective physiological studies with similar inclusion and exclusion criteria, making the comparison possible. The common eligibility criteria are:

- Age ≥ 18 years old;
- Acute hypoxemic respiratory failure: the partial pressure of oxygen (PaO_2) to fraction of inspired oxygen (FiO_2) ratio varies depending on the study. LOVE BEER includes patients with a $\text{PaO}_2/\text{FiO}_2$ ratio < 300 mmHg, while RECRUIT < 200 mmHg.
- Invasive controlled mechanical ventilation.

Exclusion criteria have some overlapping in the three studies. The common criteria are:

- Contraindications to electrical impedance tomography monitoring: they are represented by the presence of pacemakers, wounds, thoracic medications or burns;
- Hemodynamic instability.

All the studies were approved by the local ethical committee (protocols 5756/AO/23, 1096_2020, and 827/2022 for the LOVE BEER, RECRUIT, and CHESTOMY studies, respectively). All the patients included in the studies gave informed consent, following local regulations.

3.2 LOVE BEER

The LOVE BEER study (NCT06174636) is a monocentric interventional study conducted at the University of Padua. It is a study done to assess the effects on the respiratory system of the positioning of abdominal weight in order to increase the intra-abdominal pressure by 5 mmHg. It enrolled 20 patients receiving invasive mechanical ventilation for AHRF, defined in this study by $\text{PaO}_2/\text{FiO}_2 < 300$ mmHg. These patients underwent a decremental PEEP trial from 20 to 8 cmH₂O, with 2 cmH₂O decreases, in a volume-controlled ventilation (VCV), while monitored with EIT and P_{ES} .

For the present study, only data without the abdominal weight are considered.

3.3 RECRUIT Study

RECRUIT (NCT04460859) is a multicentric, prospective study including 108 patients with moderate-to-severe AHRF, defined by a $\text{PaO}_2/\text{FiO}_2 < 200$ mmHg, secondary to coronavirus COVID-19 infection. The protocol includes a decremental PEEP trial from 24 to 6 cmH₂O, with 2 cmH₂O decreases. The patients were in volume-controlled ventilation (VCV), under EIT and P_{ES} monitoring.

For the present study, only patients from ICUs of Milan Policlinico Hospital are considered.

3.4. CHEMOSTOMY Study

The last study taken into consideration is the CHEMOSTOMY study (NCT05726500): it is an on-going, single-center study conducted in Ferrara. It evaluates regional ventilation distribution in patients affected by abdominal sepsis

after emergent laparotomy. These patients have acute respiratory failure and undergo a decremental PEEP trial from 16 to 6 cmH₂O.

3.5 Method

For the present study, continuous EIT monitoring was performed with a thoracic belt placed between the fourth and the fifth intercostal space, while connected to the PulmoVista 500 device (Dräger, Lübeck, Germany).

Before the start of the study, the Cooper Surgical (Trumbull, Connecticut, USA) or Nutrivent (Sidam, Mirandola, Italy) adult esophageal balloon catheters were positioned, inflated, and calibrated to obtain P_{ES}, following the procedure of Mauri et al. Critical placement of the esophageal catheter and balloon is critical for ensuring accurate transpulmonary pressure monitoring. The insertion procedure is the same for both types of catheters, but filling volumes for the balloons differ: 1.0-2.0 ml for Cooper Surgical and 4.0 ml for Nutrivent.

Prior to procedural initiation, the catheter is prepared and the balloon integrity is verified to exclude manufactory defects. The required insertion length of the catheter is calculated with external anatomical landmarks, measuring the distance from the xiphoid, to the earlobe and then to the tip of the nose. to avoid potential technical artifacts, the P_{ES} waveform shown by the ventilator display has to be equal to 0 ± 0.5 cmH₂O before inserting the catheter.

The guide wire is lubricated and inserted in the catheter before lubricating the tip of the catheter and positioning the patient in a semi-recumbent position to facilitate the procedure. The catheter is carefully introduced either transnasally or transorally to an approximate depth of 50 to 60 cm to ensure initial gastric positioning of the balloon. The balloon is deflated with a syringe to ensure it is completely empty of air before inflating it with the required filling volume.

The catheter is gently withdrawn until cardiac oscillations appear on the P_{ES} waveform on the ventilator interface, which is connected to the catheter through

the P_{ES} port. A significant variance in the baseline pressure indicates the balloon has moved from abdomen to chest (Figure 4).

To validate the measurement, a dynamic occlusion test is performed during an expiratory hold maneuver by applying gentle manual chest compression and positive deflections of airways and esophageal pressure are compared. If the catheter is positioned correctly, P_{ES} and P_{AW} waveforms display similar changes, with acceptable deviation from 1:1 $\frac{\Delta P_{ES}}{\Delta P_{AW}}$ ratio during the occlusion of 20%. The catheter is finally secured and the guide wire extracted.

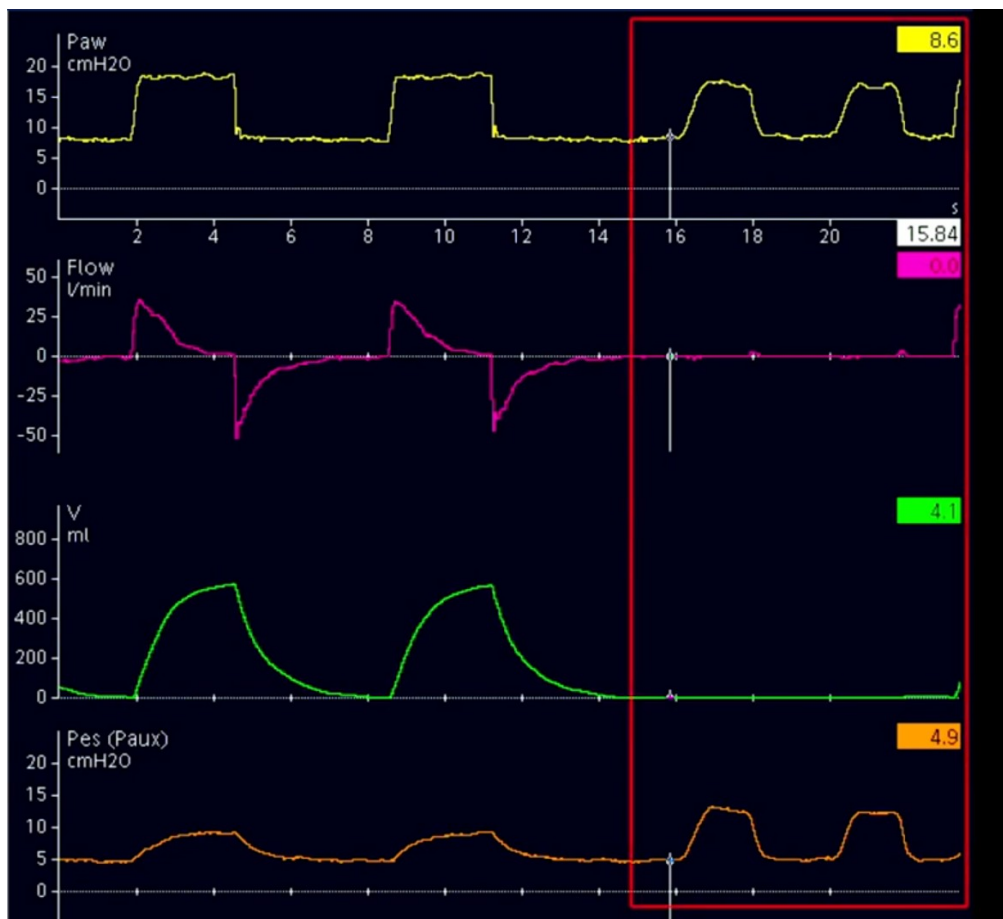


Figure 4. Representative Waveforms for Respiratory System Pressure (P_{AW}) and Esophageal Pressure (P_{ES}).

Example of waveform displayed by the ventilator interface before and during a dynamic occlusion test (red box). When the gentle pressure is applied on the chest, the waveforms (yellow for P_{AW} and orange for P_{ES}) follow a similar pattern, validating the measurement of P_{ES} and the correct positioning of the balloon in the distal esophagus.

3.6 Data Analysis

In this study, original recordings of EIT, P_{AW} and P_{ES} tracing were captured online and subsequently evaluated offline utilizing PulmoVista EIT Diag (Dräger Medical, Lübeck, Germany) software with the 1.6 version. Pulmovista is the EIT system by Dräger that allows continuous bedside visualization of respiratory functions and regional ventilatory distribution.

Calculations for pulmonary overdistension and alveolar collapse at each incremental step were performed using either the change in airway pressure (ΔP_{AW}) or the change in transpulmonary pressure (ΔP_L), following previously described methodologies.

For both P_{AW} and P_L -based techniques, optimal PEEP was calculated following two criteria:

- Graphical method: crossing point of the curves representing the cumulative percentage of compliance loss at higher and lower PEEP levels;
- Mathematical method: the PEEP level minimizing the difference between compliance losses at higher and lower PEEP titrations.

As part of the secondary aims of the study, recruitability, which is defined as the lung's ability to reopen previously collapsed alveoli when air pressure is increased, was calculated as the percentage decrease in P_{ES} -based collapse when comparing the lowest PEEP with the highest ³⁹. This evaluation led to the classification of patients: they were classified as having higher or lower recruitability and as having higher or lower risk of overdistension according to median values.

Additionally, respiratory system (C_{AW}) and lung compliance (C_L) losses were evaluated at different levels: they were assessed at ventral, mid-ventral, mid-dorsal, and dorsal regions of interest (ROIs) and for the whole lung. ROI represents a subset of pixels and its definition is fundamental for regional analysis of lung behavior. It allows inter-regional comparison within the lung area. It characterizes spatial ventilation heterogeneity using horizontal, vertical layers or quadrants ⁴⁰.

ROI analysis can be implemented to whole EIT images (ventilated and non-ventilated areas) or to functional EIT images. C_{CW} was calculated as the ratio of tidal volume to the tidal swing in P_{ES} , meaning the fluctuation in esophageal pressure during the breath, at each PEEP level. Traditional methods for calculating lung mechanics using P_{AW} assume that chest wall compliance (C_{CW}) stays constant and is PEEP-independent. This study tests this assumption by calculating C_{CW} directly using P_L .

Finally, the recruitment-to-inflation ratio was calculated between the highest PEEP level and after a decrease of 10 cmH₂O from that level, using C_{AW} at the lowest PEEP as indicated by Rosà et al (2025) ⁴¹.

3.7 Statistical Analysis

Continuous quantitative variables, such as PEEP, compliance, and pressures, were reported as medians with first-third range quartiles. The use of mean and standard deviation was not possible because the data did not follow a normal bell-curved distribution. Qualitative variables were expressed as percentages, so an absolute number.

Paired comparison between P_{AW} and P_L -based techniques was performed using Wilcoxon signed-rank test. It is a non-parametric, statistical test used to compare two related or paired data (within-subject) when data do not follow a normal distribution. For each patient, the difference between two paired measurements is calculated, the differences are ranked by absolute magnitude, and the signs of the ranks are used to test whether the median difference departs significantly from zero. Since it relies on ranks rather than raw values, it does not assume normally distributed differences, making it appropriate in this study where the distribution is not bell-curved. This test was selected because each patients provides two related measurements, one per technique, and because the sample size is small.

The number and proportion of patients in whom the two techniques identified the same optimal PEEP, a higher P_L -based optimal PEEP, or a lower P_L -based optimal PEEP were reported. Agreement between P_{AW} -based and P_L -based optimal PEEP, both identified using mathematical method, was further assessed using Bland-Altman analysis. This approach quantifies agreement between two measurements by plotting the difference between paired measurements against their mean, allowing estimation of the mean bias and the 95% limits of agreement, so the range within which most differences between methods are expected to be found, calculated as the mean bias ± 1.96 standard deviations of the differences. This test specifically evaluates the magnitude and consistency of disagreement, making it the standard approach for comparing two techniques intended to measure the same underlying parameter. Patients were classified according to the direction of disagreement between the two EIT-based PEEP titration methods: P_{AW} -based optimal PEEP higher than P_L -based optimal PEEP, identical optimal PEEP, or P_L -based optimal PEEP higher than P_{AW} -based optimal PEEP. Patients with agreement versus disagreement in optimal PEEP levels were compared with respect to baseline characteristics and physiological variables (respiratory system and lung mechanics, recruitment-to-inflation ratio, recruitability, and overdistention risk) using Wilcoxon rank-sum tests, Kruskal-Wallis tests, or Fisher's exact tests, as appropriate to the number of groups and the nature of the variable. The Wilcoxon rank-sum test is a non-parametric equivalent of the unpaired t-test, comparing the distribution of a continuous variable between two independent groups by ranking all observations together and testing whether ranks are systematically higher in one group. The Kruskal-Wallis test extends the same logic to comparisons among three or more independent groups, testing whether at least one group differs in rank distribution from the others. Fisher's exact test was used for categorical variables, particularly when expected cell counts in a contingency table were small. It calculates the exact probability of observing a distribution of categorical outcomes under the null hypothesis of independence, without relying on the large-sample approximation used in the chi-squared test.

Relative overdistension and collapse were calculated at each PEEP level during the decremental PEEP trial and compared between techniques using paired Wilcoxon signed-rank tests, applying the same rationale explained before to the two titration methods. Since multiple comparisons were performed across PEEP levels and variables, the Benjamini-Hochberg procedure was applied to control the false discovery rate (FDR). This method adjusts p-values from multiple hypothesis tests to limit the expected proportion of false positives among all rejected null hypotheses.

For subgroup analyses, patients were further stratified according to the median value of P_L -defined recruitability and P_L -defined overdistension risk. Regional and global indices of collapse and overdistension, end-inspiratory elastance-derived P_L , and end-expiratory directly measured P_L were compared at the two technique-specific optimal PEEP levels, both in the overall cohort and within P_L -defined subgroups, using Wilcoxon signed-rank tests, consistent with the paired within-patient design of these comparisons.

The association between PEEP and C_{CW} was analyzed using linear mixed-effects models, with PEEP included as a fixed effect and patient included as a random intercept. This modeling approach accounts for repeated measurements within the same patient across multiple PEEP levels, separating fixed, population-level relationship between PEEP and C_{CW} from patient-specific baseline variability, thereby avoiding the loss of statistical power and violation of independence assumptions that would occur if repeated measures were treated as independent observations. The within-patient variation in C_{CW} was calculated as the difference between values at the highest and lowest available PEEP levels and correlated with physiological variables (respiratory system and lung mechanics, recruitment-to-inflation ratio, recruitability, and overdistention risk) using Spearman correlation. Spearman's rank correlation coefficient assesses the strength and direction of a monotonic association between two variables by correlating their ranks rather than their raw values, making it suitable for non-normally distributed data or non-linear but monotonic relationships. Patients showing increasing versus decreasing C_{CW} with increasing PEEP were compared with respect to the baseline

characteristics and physiological variables using Wilcoxon rank-sum tests, Kruskal-Wallis tests, or Fisher's exact tests, as appropriate, following the same rationale outlined above.

A two-tailed p-value < 0.05 was considered statistically significant. All statistical analyses were performed using R software, version 4.5.2 (R Foundation for Statistical Computing, Vienna, Austria).

4. RESULTS

4.1 Baseline Characteristics

Thirty-six patients were included from three centers: 20 patients from the LOVE BEER study, 7 from the RECRUIT study, and 9 from the CHEMOSTOMY study.

Table I. Baseline Patient Characteristics	
Variable	N= 36
Age (years)	68 (52; 76)
Gender n (%)	
• Female	7 (19%)
• Male	29 (81%)
Height (cm)	1.73 (1.70; 180)
Weight (kg)	83 (75; 99)
Predicted body weight PBW (kg)	69 (65; 75)
Body mass index BMI (kg/m ²)	27 (25;31)
Etiology	
• ARDS	12 (33%)
• Unilateral pneumonia	11 (31%)
• Postoperative AHRF	10 (28%)
• Other	3(8%)
○ Septic shock	2 (5.3%)
○ Chemical pneumonitis	1 (2.6%)
PaO ₂ /FiO ₂ (mmHg)	190 (152; 235)

Vt (mL)	440 (380; 450)
Vt/ kg of PBW (mL/kg)	6.0 (5.8; 6.2)
Respiratory rate (breaths/min)	20 (16; 22)
Clinical PEEP (cmH ₂ O)	10 (6; 12)
C _{AW} at clinical PEEP (mL/cmH ₂ O)	43 (39; 50)
ΔP_{AW} at clinical PEEP (cmH ₂ O)	10 (8; 11)
<i>Quantitative variables are expressed as median (first quartile; third quartile). Qualitative variables are expressed as absolute number (percentage).</i> <i>Abbreviations: ARDS = acute respiratory distress syndrome; PaO₂/FiO₂ = arterial partial pressure of oxygen to fraction of inspired oxygen ratio; Vt = tidal volume; PEEP = positive end-expiratory pressure; C_{AW} = respiratory system compliance; ΔP_{AW} = respiratory system driving pressure.</i>	

4.2 Graphical Method

When the analysis was performed across the entire study cohort, the intersection point between the two EIT-derived curves, representing the cumulative percentage of overdistension and collapse, meaning the loss of compliance at high and low PEEP, was located between 10 and 12 cmH₂O. This crossing point fell within the same range regardless of whether the pressure values used were derived from P_{AW} or P_L-based methods (Figure 5).

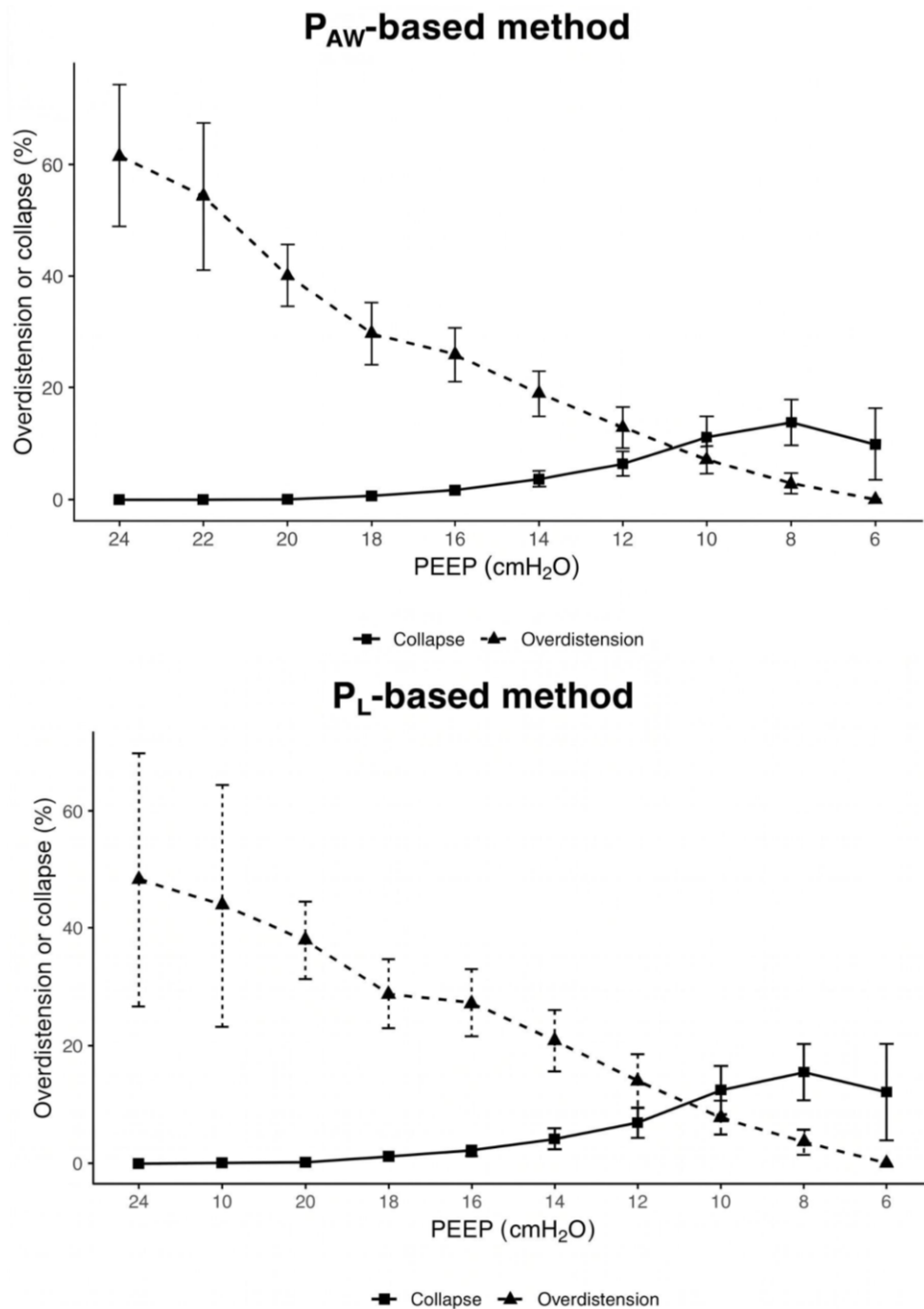


Figure 5. Global Compliance Losses estimated using P_{AW} and P_L .

Global compliance losses estimated across positive end-expiratory pressure PEEP levels, using airway pressure approach (upper graph), and the transpulmonary- based EIT method (lower graph). At elevated PEEP titers, the cumulative compliance loss curve denotes the approximated relative overdistension (dashed line with triangles). At reduced PEEP levels, the curve indicates the approximate relative collapse (solid line with squares). Points and error bars represent mean values with 95% confidence intervals at each PEEP level.

4.3 Mathematical Method

Using the mathematical method, the median optimal PEEP level minimizing the difference between loss of compliance at high and low PEEP was 12 (8-14) cmH₂O, and this value was identical for both P_{AW}-based and P_L-based approaches when considering the overall cohort's central tendency.

However, when optimal PEEP values were compared within each patient, the P_L-based method identified a slightly higher optimal PEEP than the P_{AW}-based method, with a mean paired difference of 0.44 cmH₂O ($p = 0.049$ by Wilcoxon signed-rank test).

To further characterize the degree of concordance between the two approaches, Bland-Altman analysis was applied to the optimal PEEP values obtained using the mathematical method. This analysis demonstrated a standard deviation of the differences of 1.27, yielding 95% limits of agreement of -2.94 to +2.05 cmH₂O calculated as the mean bias ± 1.96 standard deviations. This indicates that for most patients, the difference in optimal PEEP identified by the two techniques is expected to fall within -2.94 to +2.05 cmH₂O. The Bland-Altman analysis did not reveal any systematic proportional bias across the range of mean PEEP values: the two techniques agreed similarly regardless of whether the optimal PEEP was low or high, supporting the consistency of their relationship across the studied range (Figure 6).

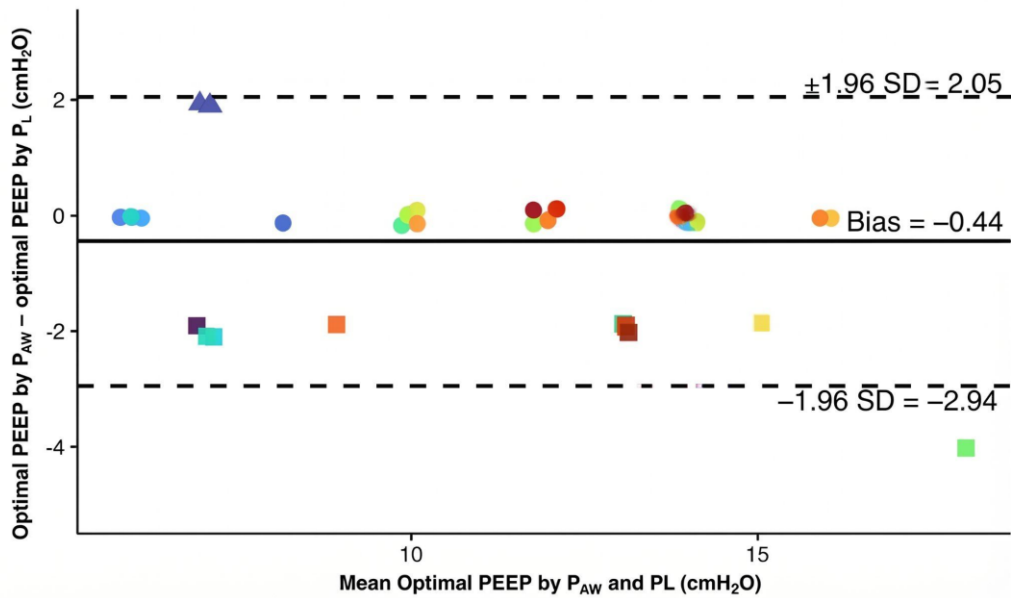


Figure 6. Bland-Altman Plot.

This plot assesses the agreement between optimal positive end-expiratory pressure PEEP values determined via airway pressure (P_{AW}) versus transpulmonary pressure (P_L) methods. The abscissa displays the average optimal PEEP across both techniques; the ordinate indicates the paired difference between techniques, calculated as the P_{AW} -derived optimal PEEP minus the P_L -derived optimal PEEP. The solid horizontal line represents the average bias, while dashed lines represent the 95% limits of agreement. Individual data points are color-coded by patient and jittered for visualization of overlapping values. Patients with higher, equal, and lower optimal PEEP with P_{AW} , compared with P_L , are depicted by triangles, circles, and squares, respectively.

The two techniques identified the same optimal PEEP value in 23 patients, corresponding to 64% of the cohort. Among the remaining patients, for whom the two methods yielded discordant results, the direction of disagreement was not symmetric: the P_L -based technique identified a higher optimal PEEP than the P_{AW} -based method in 10 patients (28% of the cohort), while P_{AW} -based assigned a higher PEEP level only in 3 patients (8% of the cohort) (Figure 7). This suggests that when the two techniques diverge, the P_L -based method favors a higher PEEP than the P_{AW} -based method.

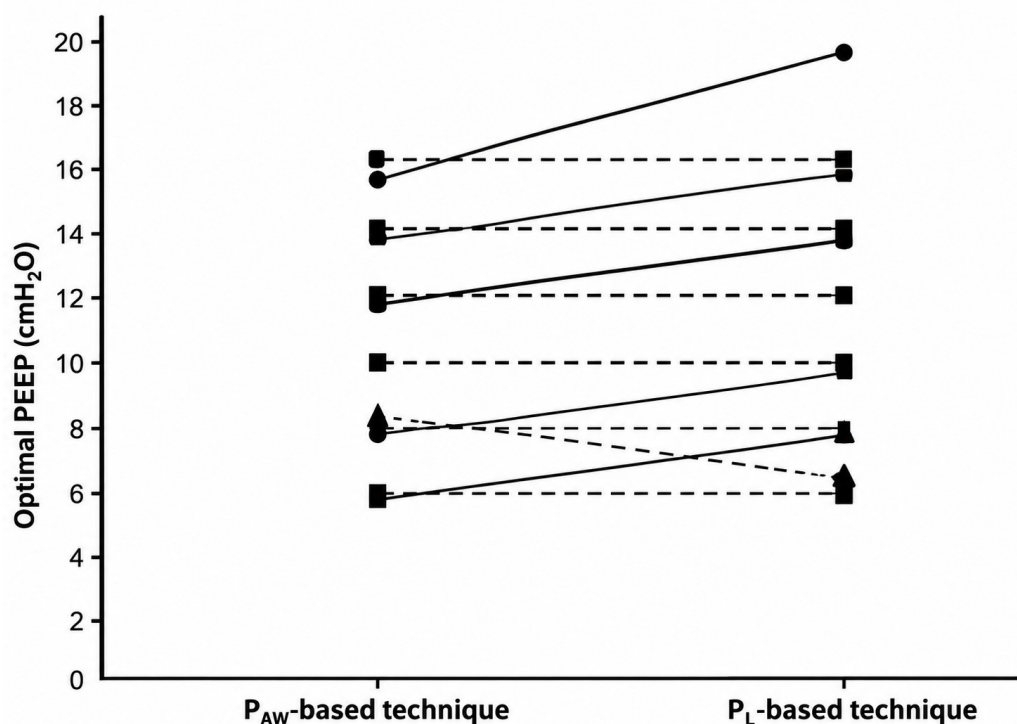


Figure 7. Individual comparison of optimal positive end-expiratory pressure PEEP identified by airway pressure and transpulmonary pressure-based techniques.

Each line represents an individual patient and connects the optimal PEEP determined by P_{AW} -based technique (on the left) with the value determined by P_L -based technique (on the right). Points and connecting lines are slightly offset for graphical clarity to facilitate visualization of overlapping patients. Patients are categorized according to the relationship between the two techniques: identical optimal PEEP (squares), higher optimal PEEP identified by P_L -based technique (circles), or higher optimal PEEP identified by P_{AW} -based technique (triangles).

4.4 Physiological Determinants of Discordance Between P_L and P_{AW} -based Optimal PEEP

P_L -defined recruitability differs significantly across the three subgroups of patients classified according to the direction of disagreement between P_L -based and P_{AW} -Based techniques. Specifically, patients in whom the P_L -based method selected a higher optimal PEEP than P_{AW} -based technique showed a median recruitability of

22.4% (8.7; 30.5), which was higher than that observed in patients with no difference between the two methods' optimal PEEP values (16.2%, interquartile range 9.2-25.2), and than that observed in patients in whom P_{AW} -based technique selected a higher PEEP than the P_L -based method (1.1, interquartile range 0.8-1.9). The difference between these subgroups reached statistical significance with $p=0.030$. Higher recruitability did not correspond to a higher risk of P_L -based overdistension (Figure 8).

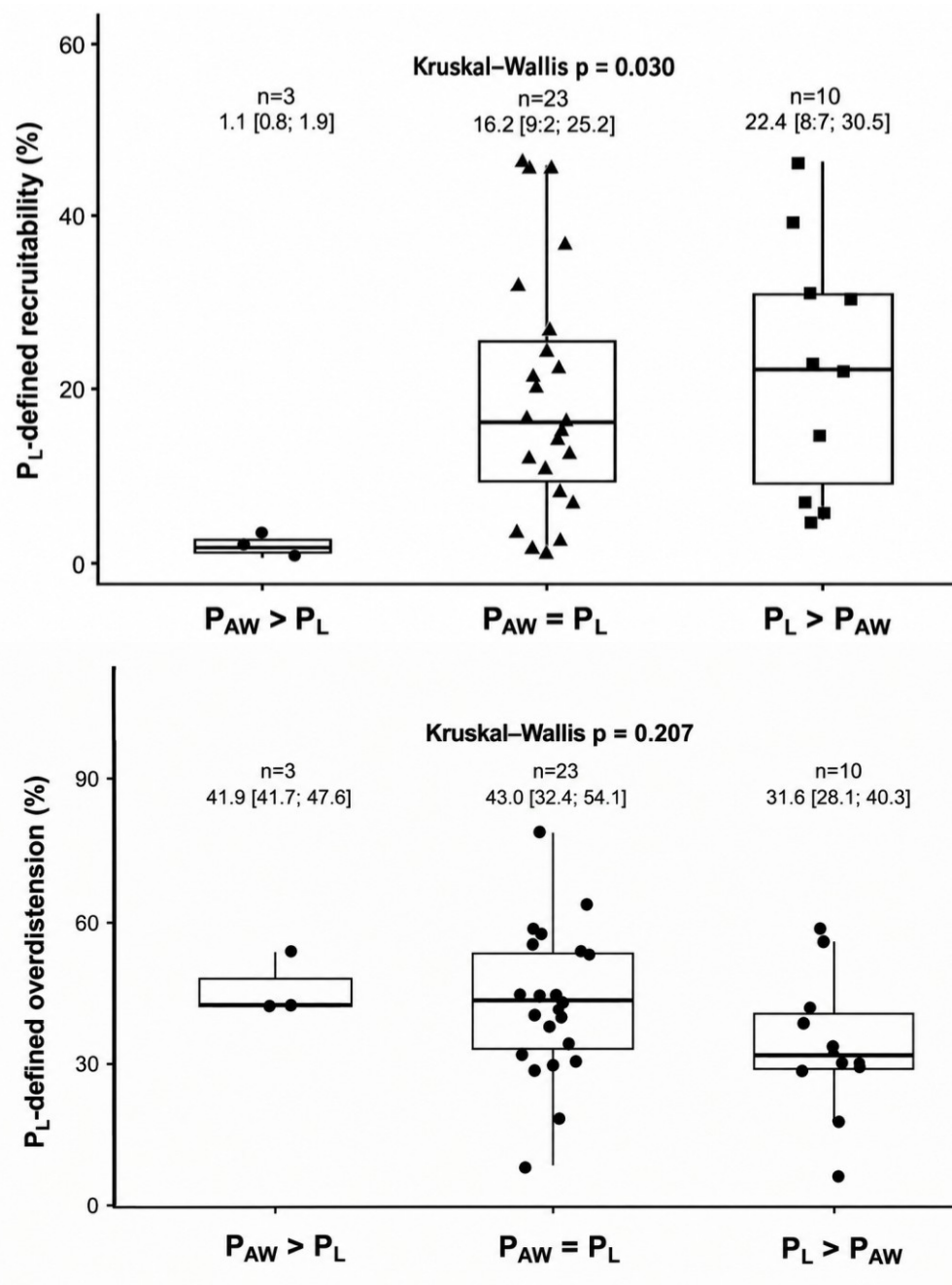


Figure 8. Direction of Optimal PEEP Disagreement Between the P_{AW}- and P_L-based techniques.

Transpulmonary pressure-based recruitability and overdistension were compared among patients according to the relationship between the optimal PEEP defined by P_L- and P_{AW}-based techniques: patients with higher optimal PEEP identified by P_{AW}-based method (circles), patients in whom both techniques identified the same optimal PEEP (triangles), and patients with higher PEEP defined by P_L-based method (squares). Boxes indicate the median and interquartile range, whiskers represent data dispersion, and points represent individual patients.

Baseline $\text{PaO}_2/\text{FiO}_2$ at clinical PEEP also differed across groups and the lowest value (147 mmHg, interquartile range 128-160) was identified in patients in whom the P_L -based technique selected a higher PEEP. In patients with no difference in optimal PEEP levels the clinical PEEP was 194 mmHg (179; 220), while in patients in whom the P_{AW} -based method selected a higher optimal PEEP the clinical value was 291 mmHg (288; 293). Also, this analysis reached the statistical significance with a p value of 0.008 (Figure 9).

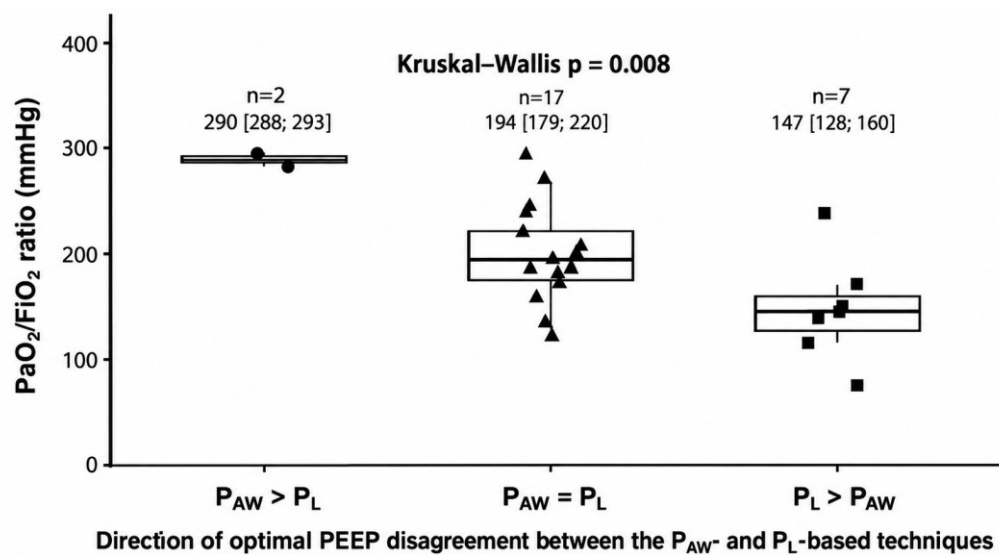


Figure 9. Direction of Optimal PEEP Disagreement Between the P_{AW} - and P_L -based techniques.

$\text{PaO}_2/\text{FiO}_2$ ratio was compared among patients according to the relationship between the optimal PEEP defined by P_{AW} - and P_L -based techniques: patients with higher optimal PEEP identified by P_{AW} -based technique (circles), patients in whom both techniques yielded the same optimal PEEP (triangles), and patients with higher optimal PEEP defined by P_L -based method (squares). Boxes represent median and interquartile range, whiskers represent data dispersion, and points represent individual patients.

No additional significant differences were observed among the three patient subgroups in any baseline variable, in respiratory system or lung mechanics, in the recruitment-to-inflation ratio, or in overdistension risk indices.

4.5 Overdistension and Collapse Across PEEP Levels

Differences between P_{AW} - and P_L -based estimates were generally small and consistent across the range of PEEP levels examined. Overall, the P_{AW} -based technique tended to overestimate the degree of overdistension relative to P_L -based technique.

Specifically, for overdistension, the median P_{AW} - P_L difference ranged from -1.59% to +0.15% between PEEP levels of 8 and 20 cmH₂O, indicating close agreement between the two methods across this interval. However, at the highest PEEP levels examined, this discrepancy increased, reaching +9.20% at PEEP 22cmH₂O and +11.54% at PEEP 24 cmH₂O. These larger differences should be interpreted with caution since only six patients contributed data to these upper PEEP levels, resulting in wide confidence intervals and limited statistical precision.

In contrast, differences in collapse were predominantly small and negative, and progressively approached zero as PEEP increased (Figure 10).

After applying the Benjamini-Hochberg correction for multiple comparisons, none of the PEEP-specific differences in overdistension or collapse between the two techniques remained statistically significant.

At the highest patient-specific PEEP level, P_L -defined recruitability was not significantly associated with overdistension difference between P_{AW} -based and P_L -based estimates. This suggests that the degree of lung recruitability alone did not explain the differences observed between the two methods. By contrast, two other physiological variables did show a significant relationship with this difference. Higher PaO_2/FiO_2 ratio was associated with a more negative overdistension difference, meaning that patients with a better baseline

oxygenation (higher $\text{PaO}_2/\text{FiO}_2$ ratio) tended to show progressively larger underestimation of overdistension by P_L -based method relative to the P_{AW} -based method (slope -0.087 per mmHg; 95% CI is -0.130 to -0.044; $p < 0.001$; $R^2=0.42$). Similarly, higher lung compliance (C_L) measured at the lowest PEEP level was also associated with a more negative overdistension difference, indicating that patients with more compliant lungs at baseline showed greater divergence between the two techniques as PEEP increased (slope -0.062 per mL/cmH₂O; 95% CI is -0.108 to -0.016; $p=0.010$; $R^2=0.22$).

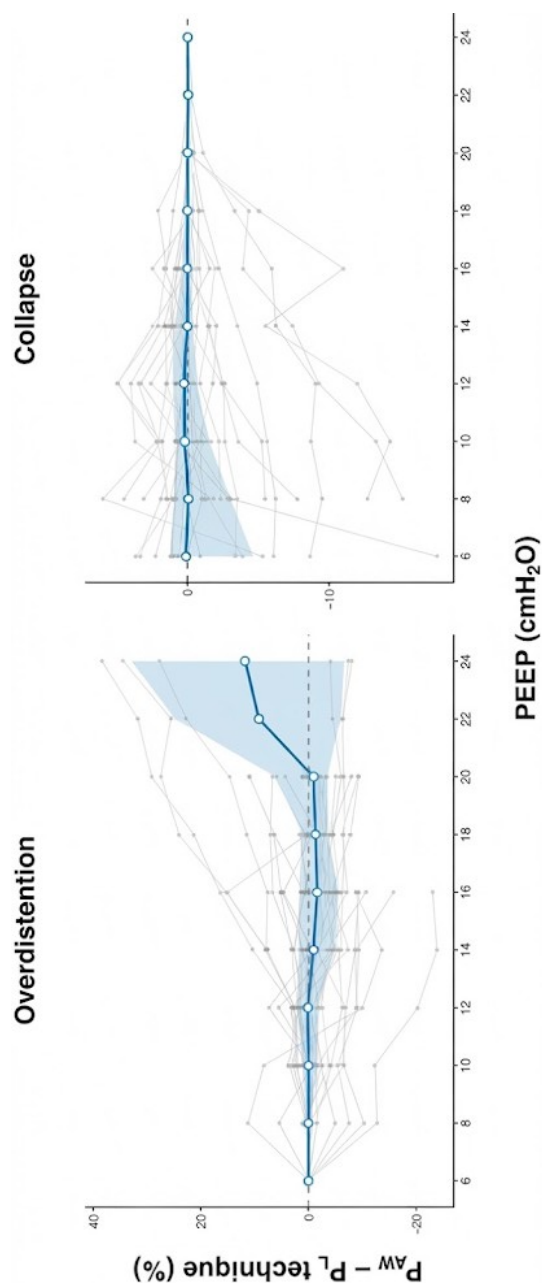


Figure 10. Difference Between P_{AW} - and P_L -based Estimates of Overdistension and Collapse Across PEEP.

The within-patient difference was calculated at each PEEP level as P_{AW} -based minus P_L -based overdistension (left) or collapse (right). Positive values indicate greater estimated overdistension or collapse with the P_{AW} -based technique; negative values indicate greater estimated overdistension or collapse with P_L -based technique. Thin grey lines and points represent individual patients; blue points and solid blue lines represent median differences, and the shared area represents the interquartile range. The horizontal dashed line indicates no difference between techniques.

4.6 Chest Wall Compliance

When considering the entire cohort, PEEP was found to be significantly and inversely associated with chest wall compliance C_{CW} : for each 1 cmH₂O increase in PEEP, C_{CW} decreased by an estimated 4.52 mL/cmH₂O, (estimate -4.52, standard error 2.26; $p=0.048$) (Figure 11). This finding indicates that, as PEEP was progressively increased, the chest wall became less compliant, a pattern consistent across the majority of patients despite individual variability based on the resulting standard error and p value.

When patients were classified according to direction of change in C_{CW} with increasing PEEP, distinct physiological profiles emerged between the two groups. Patients who exhibited increasing C_{CW} at higher PEEP levels ($n=7$, corresponding to 19% of the cohort) had lower lung compliance C_L at the lowest PEEP level compared with patients who showed decreasing C_{CW} as PEEP increased ($n=21$, 58% of the cohort). Median C_L was 41 mL/cmH₂O (interquartile range 34-46) in the former group versus 85 mL/cmH₂O (interquartile range 57-102) in the latter. This difference reached statistical significance with a p value of 0.018. This suggests that patients with lower compliance at baseline were more likely to show an increase in C_{CW} as PEEP was set higher.

Additionally, patients with decreasing C_{CW} tended to show greater P_L -defined recruitability than those with increasing C_{CW} , with median values of 16.3% (interquartile range 6.5-30.1) versus 7.8% (4.1-18.1), respectively. However, this difference did not reach statistical significance ($p=0.313$).

No other statistically significant differences were observed between the two groups with respect to the remaining baseline characteristics examined. This suggests that, other than baseline C_L , the direction of C_{CW} change with PEEP was not strongly explained by other physiological parameters assessed in the present study.

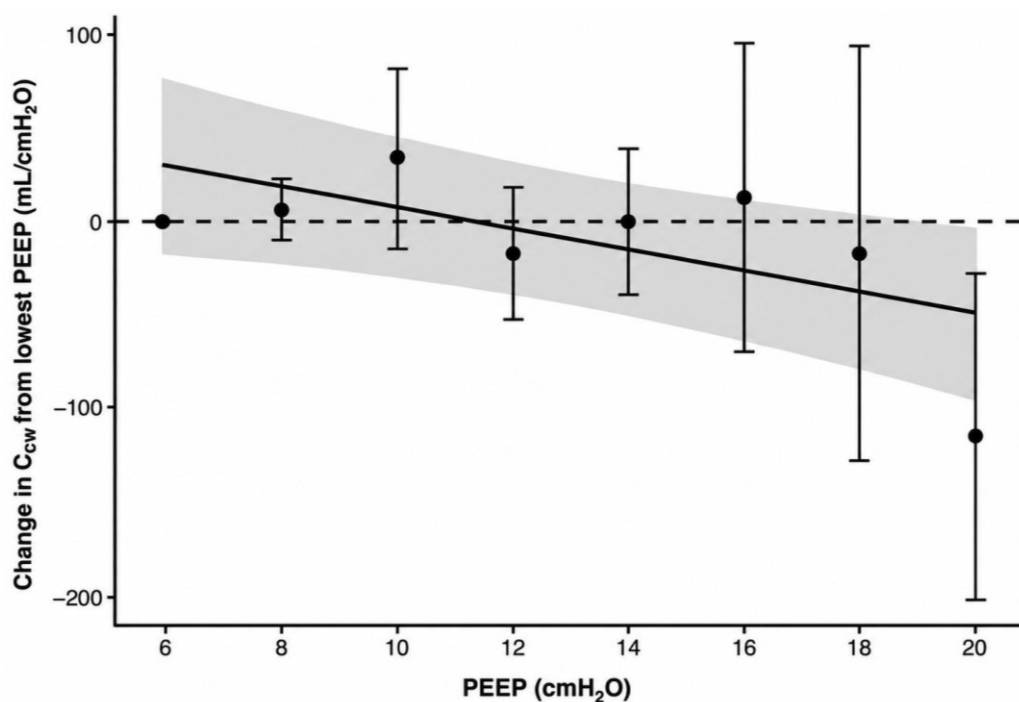


Figure 11. Within-Patient Change In Chest Wall Compliance Across PEEP.

Chest wall compliance (C_{CW}) is expressed as the within-patient change from each patient's lowest available PEEP value. Values below zero indicate C_{CW} reduction compared with the reference PEEP. Points and error bars represent mean change with 95% CI at each PEEP level. The solid line and shared band represent popular-level prediction and 95% CI from a linear mixed-effect model including PEEP as fixed effect and patient as random intercept. Observations at higher PEEP (22-24 cmH₂O) were not available.

Since C_{CW} remained relatively stable at lower PEEP values, a post-hoc sensitivity analysis was performed, restricting the range of analyzed PEEP levels to between 6 and 16 cmH₂O, and optimal PEEP was recalculated for each patient within this narrow range. Median optimal PEEP remained 12 (interquartile range 8-14) cmH₂O with both techniques, with a mean paired difference of -0.33 cmH₂O between P_L -based and P_{AW} -based methods. This difference did not reach statistical significance: with the Wilcoxon signed-rank test the p value was 0.091 (higher than 0.05, cutoff for significance). The two techniques identified the same optimal PEEP in 24 patients (67% of the cohort); P_L -based technique selected a higher optimal PEEP in 9 patients (25%), while P_{AW} -based method identified a higher optimal PEEP in 3 patients (8%).

4.7 Physiological Comparison Between P_L - and P_{AW} -based Optimal PEEP Levels

Both P_{AW} - and P_L -derived measures of collapse were found to be lower when assessed at the P_L -based optimal PEEP (4.9%, interquartile range of 2.7-6.7, and 4.6%, range of 2.4-7.3, respectively), compared with the corresponding values measured at the P_{AW} -based optimal PEEP (6.0%, interquartile range 2.7-8.1, $p=0.025$, and 6.4%, range 3.1-8.3, $p=0.003$, respectively). No significant difference in regional overdistension or collapse was observed between the P_{AW} - and P_L -defined optimal PEEP levels.

While the elastance-derived end-inspiratory P_L did not differ between the two optimal PEEP levels, the end-expiratory P_L , measured with the direct method, was higher at the P_L -optimal PEEP (1.9 cmH₂O, interquartile range 0.0-4.1) than the P_{AW} -optimal PEEP (1.0 cmH₂O, range 0.0-3.2; p value was 0.035).

When patients were categorized by P_L -defined recruitability and overdistension risk, optimal PEEP was higher with the P_L -based technique than with the P_{AW} -based method among patients with higher P_L -defined recruitability (14.0, interquartile range 12.0-14.0, versus 12.0, range 12.0-14.0) and lower P_L -defined overdistension risk (14.0, range 12.0-14.0, versus 12.0, range 12.0-14.0 cmH₂O, with a p value of 0.008).

5. DISCUSSION

In this study, the cohort consisted of 36 patients with acute hypoxemic respiratory failure (AHRF) receiving invasive controlled mechanical ventilation. Among these patients, 12 met criteria for acute respiratory distress syndrome (ARDS). In this cohort, the use of transpulmonary pressure (P_L) rather than respiratory system pressure (P_{AW}) for EIT-based PEEP titration according to the overdistension-collapse crossing-point method was associated with only a minimal difference in optimal PEEP at population level. Despite this overall similarity, a more detailed analysis revealed that P_L -based method tended to assign higher optimal PEEP specifically to patients who had more recruitability and had more severe hypoxemia, without the cost of increased overdistension risk. Overall, chest wall compliance (C_{CW}) was found to decrease progressively as PEEP increases across the cohort; patients with increasing C_{CW} at higher PEEP values demonstrated to have lower baseline lung compliance (C_L) and greater lung recruitability than those in whom C_{CW} decreased.

The conventional implementation of the overdistension-collapse method for EIT-based PEEP titration, which relies on changes in respiratory system pressure (ΔP_{RS}) to estimate regional compliance changes, was supported by the finding of this study as a clinically robust approach. The average difference in optimal PEEP between the two techniques was small and generally corresponded to no more than one or two standard PEEP increments. This observation aligns with earlier work suggesting that respiratory system mechanics often serve as a reasonable proxy for lung mechanical behavior, particularly in situations where chest wall mechanics remain relatively stable across the studied PEEP range^{42; 43}. Taken together, these findings reinforce the practical value of the conventional, P_{AW} -based overdistension-collapse method in clinical settings where esophageal pressure monitoring is not feasible: it is either unavailable, technically difficult to perform, or not part of routine practice.

At the same time, the present study advances previous work by directly testing whether replacing ΔP_{RS} with ΔP_L results in a meaningful change in EIT-derived optimal PEEP. Previous investigations have highlighted the theoretical advantage of using P_L , since it reflects more directly the pressure actually distending the lung and separates this from the mechanical contribution of the chest wall ⁴⁴. Consistent with this reasoning, this study results show that in patients with more recruitable lungs or more severe impaired oxygenation, the P_L -based method more frequently favored a higher optimal PEEP, and this was accompanied by lower alveolar collapse without any corresponding increase in overdistension or in end-inspiratory P_L . Furthermore, was observed that the P_{AW} -based technique tended to overestimate the degree of overdistension at the highest PEEP levels tested compared to the P_L -based technique; this effect was particularly pronounced among patients with higher PaO_2/FiO_2 ratios and higher C_L measured at the lowest PEEP level. These findings support the physiological concept that explicitly accounting for the chest wall's mechanical contribution may shift the balance between collapse and overdistension toward higher PEEP values in patients with more recruitable lungs. This may be clinically relevant in situations where recruitment-overdistension balance is difficult to judge, such as in patients with altered chest wall mechanics, obesity, elevated intra-abdominal pressure, or pronounced abnormalities in pleural pressure. However, because the subgroup of patients in whom P_{AW} -based optimal PEEP exceeded P_L -based optimal PEEP was very small, these observations should be regarded as exploratory rather than confirmatory. Future prospective research should examine whether combining EIT, esophageal pressure monitoring, and recruitability indices leads to improved patient-centered outcome, and should work toward identifying specific threshold or clinical phenotypes in which P_{AW} -based and P_L -based PEEP titration diverge enough to meaningfully aid clinical decision-making.

The progressive decline in C_{CW} observed with increasing PEEP suggests that higher PEEP levels may increase the elastic load of the chest wall. Although the difference did not reach statistical significance, patients whose C_{CW} declined as PEEP increased displayed approximately twice the lung recruitability of those whose C_{CW}

increased. Based on this pattern, this study proposes the hypothesis that the P_L -based crossing-point method yields a higher optimal PEEP in recruitable patients precisely because it corrects for the bias toward lower PEEP resulting from PEEP-related changes in C_{CW} during P_{AW} -guided PEEP trials. This raises the possibility that shifts in chest wall mechanics during PEEP titration may partly explain the divergence observed between P_{AW} -based and P_L -based assessments during PEEP titration. In the post-hoc sensitivity analysis restricting the decremental PEEP trial to a narrower range of 6 to 16 cmH₂O, agreement between the two techniques improved slightly, suggesting that limiting the maximum PEEP explored during the trial may reduce the confounding influence of PEEP-dependent C_{CW} changes. However, this possibility should be confirmed in future prospective studies designed specifically to test whether collapse and recruitability can be reliably characterized using a lower maximum PEEP during the initial decremental trial, effectively reducing the potential influence of PEEP-related changes in C_{CW} .

This finding diverges from earlier studies conducted on anesthetized subjects with healthy lungs, as well as in patients with ARDS (including those with obesity and COVID-19-related disease) and chronic obstructive pulmonary disease, which generally reported that C_{CW} values have low variability and remains relatively stable across typical PEEP ranges. Multiple studies indicate that most PEEP-related mechanical effects arise from the lung rather than the chest wall ^{38; 45; 46; 47; 48}. The absence of a significant interaction between C_{CW} changes and either the recruitment-to-inflation ratio or EIT-derived recruitability suggests that the PEEP-related shift in chest wall mechanics observed in the present cohort was not primarily driven by lung recruitability itself as estimated by EIT. However, the observation that patients with increasing (rather than decreasing) C_{CW} had lower lung compliance at the lowest PEEP level suggests that more severely impaired lung mechanics, potentially reflecting more advanced lung injury, may be linked to a distinct chest wall response during PEEP titration. Given the considerable inter-individual variability, this effect should be considered exploratory and hypothesis-generating rather than definitive.

5.1 Limitations and Future Works

Several limitations of this study should be acknowledged. First, the sample size was relatively modest, a drawback that became particularly limiting when performing subgroup analyses.

Second, EIT captures regional ventilation and compliance changes within the specific PEEP range examined and within the thoracic cross-section covered by the electrode belt, risking of not fully capture the whole-lung behavior.

Third, although P_{ES} allows estimation of P_L , this measurement is technically demanding and susceptible to influence from catheter positioning, calibration procedures, and mediastinal artifacts ³⁹. Because the sensitivity of an air-filled esophageal balloon depends on the volume of gas it contains relative to the surrounding pressure, both of which change as PEEP is adjusted, a PEEP-dependent shift in balloon sensitivity could produce an apparent change in C_{CW} , even in the absence of any true changes in chest wall properties. Since balloons in this study were calibrated only once, at the start of the trial, the reported data cannot distinguish a true change in the chest wall elastance from this type of measurement artifact. Future works using solid-state esophageal catheters ⁴⁹ or repeated balloon calibration at each PEEP step will be necessary to resolve this uncertainty.

Fourth, because the study population was obtained from multiple physiological studies conducted at different centers, with heterogeneous underlying causes of acute hypoxemic respiratory failure, different PEEP trial ranges, and varying study protocols, including the use of abdominal loading in one of the contributing studies (LOVE BEER study), the results should be interpreted as hypothesis-generating rather than conclusive. This residual heterogeneity may also have influenced the degree of agreement observed between techniques, and the generalizability of the findings of this study is likely further limited by a study population selected for relatively high baseline compliance, limited collapse, and greater overdistension.

Finally, the present study was designed around physiological endpoints observed during decremental PEEP trials and was not intended to determine whether P_{AW} -based or P_L -based PEEP trial leads to improved clinical outcomes.

6. CONCLUSIONS

In conclusion, this multicenter physiological study indicates that EIT-based optimal PEEP derived using respiratory system pressure (P_{AW}) is broadly concordant with the one obtained using transpulmonary pressure (P_L) in patients with acute hypoxemic respiratory failure (AHRF).

However, the P_L -based method identified a higher optimal PEEP in clinically meaningful subset of patients, particularly those with greater lung recruitability and more severe hypoxemia.

From this study emerges the hypothesis that this divergence reflects the PEEP-related decline in C_{CW} , which may lead the P_{AW} -based technique to overestimate the degree of overdistension at higher PEEP levels. However, this explanation remains exploratory, given that no single PEEP-specific difference between the two techniques had statistical significance after correction for multiple comparisons.

Prospective studies will be required to determine whether adopting this more individualized, P_L -based approach improves clinical outcomes.

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