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REVIEW

Positive end-expiratory pressure in acute respiratory distress syndrome; where have we been, where are we going?

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ABSTRACT:

ARDS is a heterogenous syndrome with a high mortality rate and limited therapeutic strategies. PEEP is routinely applied to these patients as a part of a protective lung ventilation strategy because getting it right helps optimize respiratory system compliance and improve oxygenation. However, if the PEEP is too low or too high, it may cause harm. Large clinical trials, focusing on patients with ARDS, have generally compared strategies designed to deliver low PEEP with those designed to deliver higher PEEP. No superior strategy has emerged, perhaps because these studies did not stratify patients based on their likely response to high or low PEEP. Nevertheless, the best strategy to identify optimal PEEP remains controversial, despite many large studies over the past 50 years. In the modern era of personalized medicine, perhaps our PEEP strategy should not be high PEEP or low PEEP but individualized PEEP. In this manuscript, we review the physiological effects of PEEP and the various methods studied and available to determine optimal PEEP at the bedside, providing a guide for physicians who regularly manage mechanically ventilated patients and highlighting new avenues for research.

Keywords: ARDS, Lung compliance, Oxygenation, PEEP, Recruitment, Respiratory system compliance

INTRODUCTION

In the modern intensive care unit (ICU), positive end-expiratory pressure (PEEP) is applied to almost all patients receiving mechanical ventilation. Although its earliest use precedes the modern ICU by several decades, the therapeutic potential of PEEP did not gain much attention until the description of acute respiratory distress syndrome (ARDS) by Ashbaugh and colleagues [1] in 1968. They observed that PEEP improved oxygenation in hypoxemic patients with ARDS, and subsequent animal studies demonstrated that PEEP reduced the pathological changes present in ARDS [2,3].

Inspired by these observations, clinical studies in surgical patients receiving mechanical ventilation showed some PEEP was more effective than no PEEP at preventing ARDS and other pulmonary complications [4]. However, despite over 50 years of experience, the best method for optimizing PEEP in an individual patient remains undetermined and widely debated [5–7]. PEEP studies in ARDS patients over the last 20 years have perhaps contributed to this uncertainty by not identifying a superior strategy [8–13]. In this paper, we review the effects of PEEP

and the different strategies studied for optimizing PEEP levels, aiming to inform today's clinicians on the safe use of PEEP at the bedside and highlight new avenues for research.

PHYSIOLOGICAL EFFECTS OF PEEP

In all conditions, PEEP increases end-expiratory alveolar pressure in aerated lung units by increasing end-expiratory transpulmonary pressure. However, this simple physical principle is more complex because lung compliance, alveolar integrity, chest wall mechanics, and pulmonary vascular pathology are inhomogeneous, so a common end-expiratory pressure can have different effects across different lung regions. Thus, the application of PEEP has many physiological effects, and whether they are beneficial or harmful depends on the PEEP applied, the patient, lung morphology, and the clinical circumstances.

Beneficial effects of PEEP

PEEP can have the therapeutic effect of increasing oxygenation, and may improve cardiac function in the failing heart. It modifies oxygenation through several important mechanisms. First, increasing PEEP increases mean airway pressure, which will increase oxygenation [14] as predicted by Henry's law, provided that mean airway pressure does not negatively affect cardiac output [15]. Therefore, more oxygen will enter alveolar capillary blood if mean airway pressure is increased for a given fraction of inspired oxygen (FiO_2).

Second, the application of PEEP can prevent the cyclic collapse of functional lung units at end-expiration, allowing more functional lung units to participate in gas exchange throughout the breath cycle, reducing shunting, and improving ventilation-perfusion (V-Q) matching [16,17]. This is important because end-expiratory lung volume is reduced in supine, mechanically ventilated patients, an effect that is attributed to the end-expiratory collapse of functional lung units from abdominal compression on the lung bases with the cephalic displacement of the diaphragm and reduced muscle tone from sedation and neuromuscular blockers. However, this desirable effect depends on the degree of recruitment relative to the amount of regional overdistension induced by PEEP [18,19].

Maintaining recruitment of functional lung units at the end of expiration also improves overall respiratory system compliance (C_{RS}) [19,20]. C_{RS} at very small lung volumes is low as higher pressure is required to open lung units than to fill normally inflated lungs; this contributes to the classic sigmoidal shape of the respiratory system pressure-volume (P/V) curve [21]. On the P/V curve, the classical "lower inflection point" (LIP) correlates to the beginning of lung recruitment. Once recruitment is complete, additional pressure risks lung overdistension and decreased compliance; this leads to a flattening of the curve and is represented by the upper inflection point (UIP). The two inflection points are connected by a steep segment representing maximal C_{RS}. Setting PEEP and tidal volume (V_T) to ensure breath delivery is within the steep portion of the curve, as illustrated in Figure 1, is thought to prevent both atelectrauma and barotrauma [22,23]. However, this approach does not take into account the heterogeneity of different lung regions [24].

KEY MESSAGES:

- PEEP is routinely applied in critically ill patients, and if properly applied, it facilitates lung protective ventilation by reducing driving pressure and optimizing respiratory system compliance for a given tidal volume.
- PEEP titration strategies based on oxygenation targets will help some patients while potentially harming others.
- Setting PEEP using readily available bedside physiological measures may help avoid potential harm, and these strategies need to be investigated in sizable clinical trials.

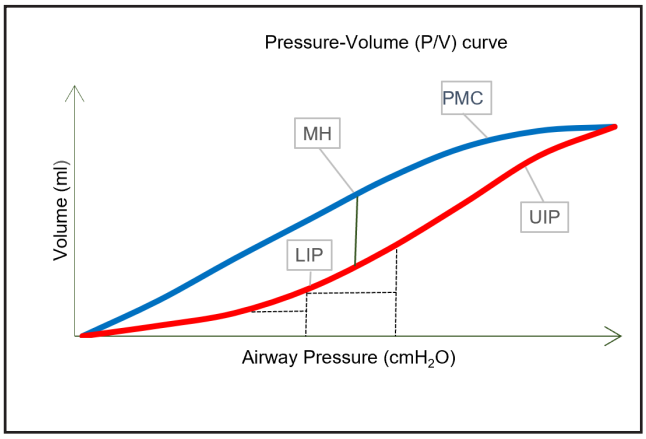


Figure 1. Pressure-Volume (P/V) curve: Below the LIP, increasing the pressure will have little effect on volume; however, increasing the pressure in the steeper portion of the curve between the LIP and UIP will result in more volume rise. Abbreviations: LIP: lower inflection point; UIP: Upper inflection point; PMC: Point of maximum curvature; MH: Maximum hysteresis

Classical teaching explains the higher opening pressure of functional lung units using Laplace's law, which states that the pressure inside an inflated elastic container with a curved surface is proportional to the surface tension and inversely proportional to the radius (Figure 2). However, Laplace's Law only applies to spherical structures, and in reality, individual alveoli do not behave like individual spherical elastic balloons but rather share common walls, interconnected by interalveolar pores, and have a multifaceted polygonal shape [25]. It is likely that the small airways adjacent to the alveoli contribute to the opening pressure phenomenon; when the diameter of these airways becomes very small, the fluid lining over their folds forms a continuous layer, increasing surface tension and drawing the airway to close further. As a result, the pressure required to keep it open increases. Although surfactant reduces fluid surface tension, it is often

depleted in acute lung injury, and PEEP helps prevent cyclical collapse by counterbalancing increased surface tension from surfactant breakdown [19,26]. PEEP, therefore, reduces the pressure required to deliver a given volume of air, provided V_T is not too large and overdistension is not induced, as well as mitigating dynamic stress and strain shear forces from repetitive closure and opening [27].

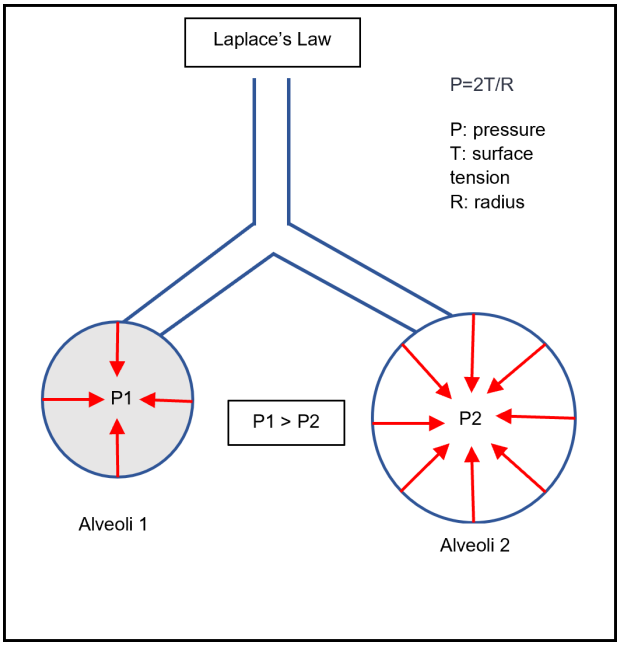


Figure 2. Laplace's law and alveoli: According to Laplace's law, if the two alveoli have the same surface tension, the smaller alveoli will have higher pressure.

The potential benefits of PEEP are not confined to the pulmonary system. PEEP has important hemodynamic effects in patients with left-sided heart failure. It increases intrathoracic pressure, causing a proportional increase in right atrial (RA) pressure, which reduces venous return and therefore reduces preload. Since both ventricles work in series, any reduction in right ventricular (RV) preload will reduce left ventricular (LV) filling and help to unload the congested heart. Increased intrathoracic pressure also externally compresses cardiac structures, resulting in reduced transmural pressure and LV afterload, thus reducing the work required by the LV to eject blood. Consequently, ventricular wall tension and myocardial oxygen consumption will decrease. Moreover, reducing the work of breathing will help redistribute the blood flow from the respiratory muscle to vital organs. Combined, these factors will benefit the patient with heart failure [28,29] (Figure 3).

Negative effects of PEEP

Excessive PEEP is always detrimental; the clinical challenge is identifying when further PEEP increases progress from being beneficial to harmful. When cardiac function is normal, PEEP will reduce cardiac output by raising intrathoracic pressure and restricting venous return while simultaneously increasing pulmonary vascular resistance and RV afterload, ultimately reducing RV output, alveolar perfusion, and LV filling. Decreasing cardiac output delivers less oxygenated blood to the tissues (Figure 3). However, the true effect of any given PEEP is complex because these detrimental effects are balanced by a PEEP-induced reduction in pulmonary vasomotor tone

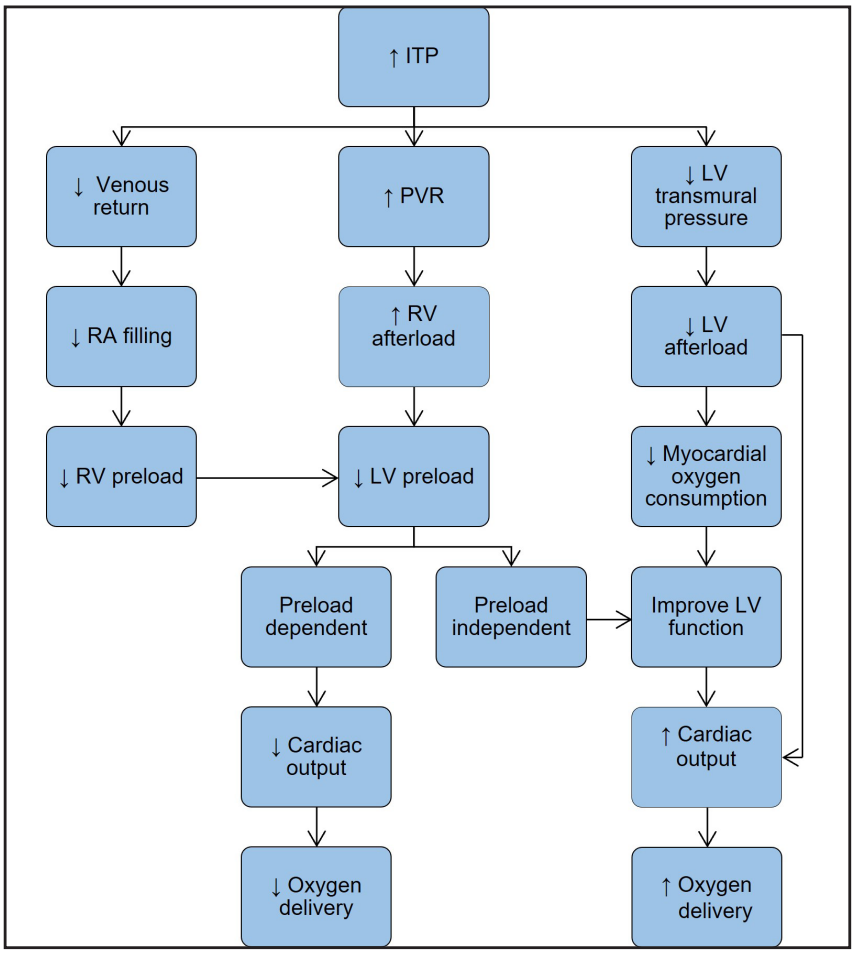


Figure 3. Cardiovascular effect of PEEP: The hemodynamic effect of PEEP is mediated through increased ITP, leading to a decrease in RV preload, increased RV afterload, and decrease LV afterload. The impact of these changes differs between patients according to their cardiac and overall fluid status. In patients with normal cardiac function or hypovolemia who are preload dependent, this would decrease the cardiac output. Yet, in patients with LV failure who are hypervolemic and preload independent, these changes would improve the cardiac output. Abbreviations: ITP: intrathoracic pressure; PVR: pulmonary vascular resistance; RA: right atrium; RV: right ventricle; LV: left ventricle

if hypoxemic alveoli are recruited and hypoxic pulmonary vasoconstriction is reversed [28,30].

Excessive PEEP may reduce blood flow through small pulmonary capillaries within the interalveolar septa by direct compression, further increasing pulmonary vascular resistance and causing more dead space ventilation [28,31]. In ARDS patients or other patients with pathologies with regional variation in patterns of involvement, PEEP may cause overdistension of complaint lung units, increasing capillary resistance in those units, and redistributing blood flow to poorly ventilated units, potentially worsening the V-Q mismatch [28,32]. Alveolar overdistension also increases tissue stress and strain and the mechanical power delivered to the lung, contributing to ventilator-induced lung injury [33,34].

Given these complex effects, bedside clinicians face a "Goldilocks" challenge when seeking the optimal PEEP. Correctly titrated PEEP can optimize the recruitment of functional lung units and improve C_{RS}, which, combined with lower V_T, enhances lung protection, improves oxygenation, and increases cardiac output in a failing heart. However, despite several large studies over the last 25 years, a universally accepted strategy to optimize PEEP remains elusive.

OPTIMIZING PEEP IN ARDS

Most of the large PEEP clinical trials have been conducted in patients presenting with ARDS, with the goal of determining the optimal PEEP strategy to accompany lower V_T, following the landmark Acute Respiratory Distress Syndrome Clinical Trials Network Low-Tidal-Volume (ARMA) trial [35]. Several strategies have been investigated, from PEEP/FiO_2 tables to invasive esophageal pressure-guided approaches.

Setting PEEP using standardized tables

In the ARMA study [35], PEEP was set using a predetermined table instructing clinicians to increase PEEP based on the FiO_2 required to keep arterial partial pressure of oxygen (PaO_2) within a specified range. The table's simplicity and reproducibility ensured PEEP was selected in the same way in both arms. After determining that lower V_T ventilation lowered mortality, the Assessment of Low Tidal Volume and Elevated End-Expiratory Pressure to Obviate Lung Injury "ALVEOLI" trial [8] was conducted to determine whether a high or low PEEP strategy should be used in conjunction with lower V_T. They compared a higher PEEP, also determined by a table, to the PEEP/FiO_2 table used in ARMA and reported no differences in mortality. Similarly, the Lung Open Ventilation Study (LOVS) [9] used tables to set PEEP based on FiO_2, but the intervention arm also received recruitment maneuvers. Again, there was no difference in mortality (Table 1).

This approach assumes that increased PEEP is always beneficial when FiO_2 must be increased to maintain PaO_2, and is based on the understanding that the primary mechanism of hypoxemia is the collapse of recruitable functional lung units. However, this assumption is not always correct. In a small physiology study, Grasso et al. [36] showed that only 10 of 19 patients with ARDS experienced an increase in lung volume when transitioning from the AVEOLI low PEEP protocol to the high PEEP protocol, and those not experiencing lung recruitment with higher PEEP experienced a reduction in C_{RS} and oxygenation. Subsequently, a re-analysis of the ALVEOLI population found two subphenotypes, based on inflammatory markers, that respond differently to PEEP. The "hyperinflammatory" subphenotype showed lower mortality with high PEEP, whereas the opposite was seen for the "hypoinflammatory" subphenotype [37].

In an attempt to investigate the role of higher PEEP levels without harming the lungs, the Expiratory Pressure (Express) study group [10] designed a strategy where PEEP is titrated upwards to achieve a plateau pressure of 28 to 30 cmH_2O in patients receiving low V_T at 6 ml/kg IBW. The aim was to maximize alveolar recruitment while simultaneously limiting plateau pressure. In the control arm, PEEP was titrated within the range of 5 to 9 cmH_2O. Again, no difference in mortality was found (Table 1).

Despite attempting to account for individual pulmonary physiology, plateau pressure is a poor indicator of tidal hyperinflation [38], and this strategy risks delivering lower PEEP in patients with reduced C_{RS} due to collapse of functional lung units and higher PEEP in those with preserved C_{RS}. Subsequent studies attempted to match PEEP to the physiology of individual patients by pairing recruitment maneuvers with decremental PEEP titrations [11,12] or by measuring transpulmonary pressure [13].

Staircase lung recruitment strategies paired with decremental PEEP titrations

Staircase recruitment protocols incrementally increase PEEP, with the patient receiving pressure-controlled ventilation, until a predefined target PEEP is reached. Then PEEP is reduced in a stepwise manner until the "point of derecruitment" is reached, determined by measuring static C_{RS} or oxygenation.

An early feasibility study demonstrated this approach increased C_{RS}, improved oxygenation, and reduced inflammatory biomarkers [39]. However, the large Alveolar Recruitment for Acute Respiratory Distress Syndrome "ART" trial [11] demonstrated harm. In this study, the intervention arm received the lung recruitment maneuver, which involved stepwise increases in PEEP up to 45 cmH_2O. However, three patients experienced cardiac arrest at this high PEEP level; therefore, the study protocol was altered to limit maximal PEEP to 35 cmH_2O. The recruitment maneuver was followed by a stepwise decrease in PEEP, with C_{RS} measured at each step. Following a second recruitment maneuver, PEEP was set at the level corresponding to the maximum measured C_{RS} + 2 cmH_2O. Compared to the control arm, where PEEP was set using the original ARMA study tables, the intervention arm demonstrated increased barotrauma and all-cause mortality (Table 1).

The publication of these findings resulted in the early termination of a similar study, the Permissive Hypercapnia, Alveolar Recruitment, Low Airway Pressures (PHARLAP) study [12]. In this study, a similar recruit-

ment maneuver was performed, and the optimal PEEP was set at 2.5 cmH_2O above the PEEP where a drop in oxygen saturation was observed. At the time of stopping, the intervention had not improved mortality (Table 1) and caused more cardiac arrhythmias. Given the expected cardiac effects of prolonged, extremely high PEEP levels, it is not surprising that both studies demonstrated increased cardiac complications during recruitment maneuvers, which would be magnified if functional lung units were not recruitable. An alternative approach to matching PEEP to the individual patient is to measure end-expiratory transpulmonary pressure.

Setting PEEP to optimize end-expiratory transpulmonary pressure

Transpulmonary pressure is the difference between airway pressure and pleural pressure, and it reflects the pressure applied to the lung from the airways and the chest wall, therefore separating the chest wall from lung mechanics in the absence of spontaneous respiratory effort. At the end of expiration, if the pressure from the chest wall exceeds PEEP, the transpulmonary pressure is negative, favoring atelectasis and the collapse of functional lung units. If PEEP is increased until end-expiratory transpulmonary pressure is close to zero, the collapse of lung units should be prevented [40,41]. Esophageal manometry is a convenient method to estimate pleural pressure and ensure optimal recruitment at the end of expiration. Additionally, it can be used to monitor end-inspiratory transpulmonary pressure, therefore ensuring V_T is set such that end-inspiratory transpulmonary pressure does not exceed limits associated with worsening ventilator-induced lung injury [42].

This approach was studied in the large Esophageal Pressure-Guided Ventilation (EPVent2) trial [13]. In the intervention arm, PEEP was titrated to target end-expiratory pleural pressure between 0 and 6 cmH_2O according to a pleural pressure/FiO_2 table. In the control arm, a standardized PEEP/FiO_2 table was used. Neither arm differed in mortality, but interestingly, the esophageal pressure-guided strategy resulted in mean PEEP values that did not significantly differ from the empirical PEEP-FiO_2 protocol (Table 1).

One reason for this finding may be that increasingly positive end-expiratory transpulmonary pressures were targeted in patients receiving higher FiO_2. In practice, the original authors target a transpulmonary pressure of 0 cmH_2O, regardless of the FiO_2 requirement, and outcomes were apparently better in the EPVent2 patients whose transpulmonary pressure was kept in the range of -2 to +2 cmH_2O [43]. Although esophageal pressure monitoring may provide insight into an individual patient's physiology for PEEP titration, this technique is not commonly used due to limited equipment availability and the associated learning curve with balloon placement and data interpretation. However, several small studies have examined the role of other physiological variables in optimizing PEEP that do not require extra equipment or training.

Optimizing PEEP using pressure/volume (P/V) curve

The P/V curve has been proposed as a bedside tool to individualize PEEP selection. It can be acquired by three different methods: the super syringe method, the multiple occlusion technique, and the constant low-flow technique. The last is easy to implement at the bedside, as many modern ventilators have built-in software to record and interpret the constant flow curves without the need to disconnect or paralyze the patient [23]. As described above, the LIP of the inspiratory limb is believed to represent the overcoming of an "opening" pressure, but using it as a PEEP target assumes the LIP represents optimal recruitment. This is probably not the case; instead, it likely reflects the pressure at which recruitment of functional lung units begins, with recruitment continuing until the UIP is reached [22]. Thus, LIP may represent the undesirable pressure at which minimal lung units are recruited. Since PEEP is an expiratory phenomenon, some authors have logically suggested using the expiratory limb of the P/V curve and "point of maximum curvature" (PMC) (Figure 1) to find the optimal PEEP, as it correlates with derecruitment and loss of aeration [44].

An approach that might overcome these challenges is to use the volume hysteresis of the P/V curve. From a physiological perspective, the inspiratory limb of the

Table 1. Summary table of key clinical trials.

	Trial	Year	Patients number	Mean PEEP		Mortality*	
				Control	Inter.	Control	Intervention
Standardized tables	*ALVEOLI*	2004	549	8.3	13.2	27.5%	25.1%
	LOVS	2008	983	9.8	14.6	32.3%	28.4%
Limiting Pplat to 28-30	*Express*	2008	767	8.4	15.8	31.2%	27.8%
Lung recruitment paired with decremental PEEP titration	*ART*	2017	1013	12.0	16.2	49.3%	55.3%
	PHARLAP	2019	115	11.3	16.1	26.8%	24.6%
Optimizing transpulmonary pressure	*EPVent2*	2019	200	16	17	30.6%	32.4%

*:All trials reported 28-day mortality rates, with the exception of the ALVEOLI study, which reported in-hospital mortality.

curve represents recruitment, whereas the expiratory limb represents derecruitment. Therefore, the difference between these limbs at any given point, the hysteresis, might represent the lung units recruited at this pressure [45]. Koefoed-Nielsen et al. [46] found PEEP set at the pressure where 90% of maximal hysteresis is observed resulted in similar oxygenation, better C_{RS}, and less hemodynamic instability than PEEP set based on LIP or PMC.

Optimizing PEEP based on stress index (SI) index

An alternative method to select PEEP is the stress index (SI), which is derived from analyzing the shape of the pressure-time curve during constant inspiratory flow. During PEEP titration, alveolar hyperinflation and reduced C_{RS} are indicated by an upward concavity (SI>1), while tidal recruitment and increased C_{RS} are indicated by a downward concavity (SI<1). When the curve's shape follows a straight line (SI=1), optimal PEEP can be assumed because there is neither tidal recruitment nor hyperinflation [47,48]. Several studies showed that using SI to optimize PEEP was associated with lower inflammatory mediators and less lung injury [49–51]. SI assessment is available on modern ventilators, but the technique is limited because it requires deep sedation and has not been validated in large trials.

Optimizing PEEP based on dead space fraction or efficiency of ventilation

Over 45 years ago, it was recognized that the PEEP associated with the highest C_{RS} and best oxygen delivery produced the lowest dead space fraction; the ratio of dead space volume to tidal volume (V_D/V_T) [52]. Unlike oxygenation measures, dead space fraction is increased if PEEP is either too low or too high, depending on its effect on V-Q heterogeneity, shunt fraction, and anatomical dead space [53]. Subsequent studies showed that the lowest dead space fraction could be a useful target for optimizing PEEP [54,55]. But, unfortunately, it requires volumetric capnography, which is not available on all ventilators. On the other hand, monitoring the end-tidal to arterial carbon dioxide ratio ($P_{ET}CO_2/PaCO_2$) using simple capnography available at the bedside can be used to assess the response to different PEEP levels and effective gas exchange [56,57]. Alternatively, the ventilatory ratio is simple to calculate from bedside data using the following formula:

$$\text{Ventilatory ratio} = \text{minute ventilation (ml/min)} \times \text{PaCO}_2\text{(kPa)}/100 \times \text{PBW} \times 5. \text{ [58]}$$

A correlation was found between the ventilatory ratio, as well as $P_{ET}CO_2/PaCO_2$, and the dead space fraction [57,59]. Although there is evidence that dead-space indices can predict survival in ARDS [57,60,61], they need to be validated in sizable clinical studies before being routinely used in clinical practice.

Optimizing PEEP to achieve the best compliance

Although the ART trial [11] failed to demonstrate improved mortality despite adjusting PEEP based on C_{RS} and limiting driving pressure, the study design perhaps did not benefit all patients. PEEP responsiveness was not assessed at baseline before the recruitment maneuver, and afterward, PEEP was actually set 2 cmH_2O above the level that resulted in the highest C_{RS}, which may have led to regional overdistension of non-dependent lung.

In other studies, PEEP titration based on the best C_{RS} was associated with less organ dysfunction, improved oxygenation, and a trend toward better mortality [62–64]. But measurement of static C_{RS}, i.e., under no gas flow conditions, requires two airway occlusion maneuvers: an end-inspiratory hold to obtain the plateau pressure and an end-expiratory hold to determine total PEEP, and it should be performed on patients with zero respiratory effort [65]. However, many modern ventilators use the least-squares fit method to measure dynamic C_{RS} without performing breath-hold maneuvers [66] and can be used in patients with respiratory effort, provided they are relaxed [67]. But dynamic C_{RS} may underestimate total compliance because it depends on airway resistance and can be misleading in some clinical situations.

Optimizing PEEP to target the best C_{RS} also ensures optimal (lower) driving pressure for a given V_T, which is associated with better survival in patients with ARDS [68]. Because of this alliance and its simplicity, PEEP titration to achieve optimal driving pressure has gained more interest in recent years [69,70]. The challenge, however, especially in ARDS, is regional variation in lung involvement, which neither driving pressure nor C_{RS} can account for. Thus, clinical trials are still needed to validate whether this strategy for PEEP optimization is effective in clinical practice.

Optimizing PEEP based on recruitment-to-inflation (R/I) ratio

The recruitment-to-inflation (R/I) ratio has been proposed as a bedside tool for assessing lung recruitability, allowing the identification of patients that may respond to higher levels of PEEP [71,72]. It is the ratio between the compliance of the recruited lung after application of high PEEP to that of the C_{RS} at low PEEP and can be determined with the single breath method. The lungs are ventilated at a fixed V_T at a high PEEP (15 cmH_2O in patients with no airway opening pressure) for 30 minutes, and C_{RS} is measured. The PEEP is then reduced to 5 cmH_2O, and the volume expired during the first breath at the new PEEP, i.e., when the PEEP is released, determines the volume recruited at the higher PEEP. In the presence of complete airway closure, the airway opening pressure is considered the low PEEP level, and the high PEEP will be set + 10 H_2Ocm above it. The compliance of this recruited volume can be estimated from the change in PEEP.

Chen et al. [71] determined that a R/I ratio of 0.5 distinguished low recruiters from high recruiters, who had a R/I ≥ 0.5. They found it correlates with oxygenation and dead space ventilation, suggesting it may be used to identify those patients who may benefit from higher PEEP. However, a recent study has highlighted that the R/I ratio may be underestimated or overestimated with different ventilators, and the procedure assumes that compliance changes in a linear fashion between the two PEEP levels [73,74].

Optimizing PEEP by imaging

Computed tomography (CT) scanning provides good spatial resolution in assessing regional lung aeration [75,76], but its widespread use is limited by cost, radiation exposure risk, and the burden of patient transfer to imaging suites. Lung ultrasound is a widely accessible bedside tool that can detect ARDS morphology (focal and non-focal) [77] and assess lung recruitment after PEEP titration based on a change in aeration score [78–81]. However, it is operator-dependent and cannot detect hyperinflation in non-dependent areas.

Electrical impedance tomography (EIT) is a non-invasive and radiation-free bedside imaging tool that has been used to detect regional collapse and overdistension [82,83]. It uses multiple chest electrodes and low-frequency electrical currents to detect the electrical resistivity of lung tissue, which corresponds to the regional variation of ventilation [83]. It has been proposed as a method for PEEP individualization, and small studies suggest that EIT-guided ventilation resulted in improved lung mechanics and gas exchange [84,85], thus improving patient outcomes [86]. So far, neither lung ultrasound nor EIT-guided ventilation have been evaluated in large-scale randomized controlled trials.

CONCLUSION

Many methods are available for optimizing PEEP; they can be broadly divided into those targeting measures of oxygenation and those targeting measures of pulmonary physiology. The largest studies have set PEEP using oxygenation targets in at least one arm, an approach that assumes impaired oxygenation can be improved by increasing PEEP. This assumption is not always accurate, and an individualized approach based on physiological measures may overcome the pitfalls of this assumption. Transpulmonary pressure shows promise but requires equipment not routinely present at the bedside and careful provider training. In contrast, C_{RS} is a measurement familiar to most clinicians, and is increasingly available as a robust real-time measure. Titrating PEEP to optimal C_{RS} while monitoring driving pressure, oxygenation, and the patient's hemodynamics might be the key to unlocking uncertainty in PEEP selection [5,7,70]. This can be combined with confirmatory measures such as EIT, stress index, ventilatory ratio, lung ultrasound, and, in certain patients, transpulmonary pressure to help avoid harmful PEEP levels, especially in obese patients and those with reduced chest wall compliance. Nevertheless, there is a continued pressing need to investigate these approaches in multicenter clinical trials.

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AUTHORS' CONTRIBUTIONS

All authors conceived the idea and edited the manuscript. SSR and MEC wrote the first draft and designed the article's tables and figures. MEC, RF, YSC, and JGC critically revised the draft. All authors approved the final version to be published.

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