Hypoxemia is a commonly encountered problem in mechanically ventilated patients. Treatment of hypoxemia relies on the titration of FiO₂ and positive end-expiratory pressure (PEEP) to optimize PaO₂. Modern ventilation strategies aimed at minimizing lung injury while simultaneously managing hypoxemia have improved mortality in respiratory failure, but the ideal strategy for lung-protective ventilation remains controversial. PEEP has a variety of positive effects, including improved oxygenation, decreased ventilator-induced lung injury, and decreased ventilator-associated pneumonia. However, its routine use, and the most appropriate value, continues to be debated. Furthermore, PEEP titration can be challenging in an individual patient, and data on how to best titrate PEEP to improve outcomes are lacking. Use of an esophageal balloon can facilitate a physiologic approach to PEEP titration based on respiratory mechanics. Esophageal pressure can be used to estimate pleural pressure and assist in titrating PEEP to a positive end-exhalation transalveolar pressure.

We describe an obese patient with intracerebral hemorrhages and persistent hypoxemia in the neuroscience intensive care unit whose hypoxemia improved with increased PEEP, titrated using esophageal manometry. We provide a discussion of the rationale and process for the titration of PEEP in mechanically ventilated patients using esophageal manometry.

Case Report

A 50-yr-old obese man (180 cm, 154.8 kg, and body mass index of 50.4) was brought to the emergency department by ambulance after collapsing. On arrival, he had a systolic blood pressure of 250 mmHg, heart rate of 101 beats/min, respiratory rate of 8 breaths/min, and SpO₂ of 89% on 15 l O₂ by face mask. On neurologic examination, his Glasgow Coma Score was 3. He was intubated with a 7.5-mm endotracheal tube. A brain computed tomography scan revealed a large left basal ganglia bleed and a left pontine bleed. He was started on a nicardipine drip to treat hypertension and was admitted to the neuroscience intensive care unit.

Upon arrival to the neuroscience intensive care unit, his initial ventilator settings were pressure control ventilation of 14 cm H₂O with PEEP 12 cm H₂O, FiO₂ 0.7, and an inspiratory time of 1.2 s. On these settings, he had a respiratory rate of 26 breaths/min, tidal volume of 480 ml (6.8 ml/kg ideal body weight), and minute ventilation of 11.4 l/min with an arterial blood gas of pH 7.37, PaCO₂ 50 mmHg, and PaO₂ 116 mmHg. The alveolar–arterial P O₂ gradient was felt to be out of proportion to his clinical presentation. PEEP was increased to 15 cm H₂O with no significant improvement in his oxygenation. A chest radiograph showed small bilateral pleural effusions, low lung volumes, and bibasilar airspace opacities.

Given his obesity, the airspace opacities were felt to primarily represent atelectasis due to a heavy chest wall. We reasoned that the cause of atelectasis was a high pleural pressure that was compressing lung tissue. Thus, a PEEP trial was performed using esophageal manometry. A balloon-tipped 8-French catheter was placed orally into the lower esophagus (35 cm from the lips). The balloon was inflated with 0.5 ml of air and its position was confirmed by the presence of cardiac oscillations and transmitted abdominal compression.
as described by Talmor et al.\textsuperscript{10} The ventilator was set to volume control with a tidal volume of 6 ml/kg ideal body weight, respiratory rate of 26 breaths/min, and an inspiratory time of 0.8 s. At a PEEP of 15 cm H\textsubscript{2}O (fig. 1), the corresponding end-exhalation esophageal pressure (P\textsubscript{es}) was 22 cm H\textsubscript{2}O, resulting in a transalveolar pressure of \textasciitilde{7} cm H\textsubscript{2}O (fig. 1, A, C, and E). P\textsubscript{a} during an inspiratory hold was 24 cm H\textsubscript{2}O, whereas plateau pressure was 25 cm H\textsubscript{2}O, leading to a transalveolar pressure of 1 cm H\textsubscript{2}O (fig. 1, A, C, and E). At these ventilator settings, his blood pressure was 147/77 mmHg with a heart rate of 75 beats/min. Increasing the PEEP to 22 cm H\textsubscript{2}O resulted in an end-exhalation P\textsubscript{es} of 22 cm H\textsubscript{2}O and a transalveolar pressure of 0 cm H\textsubscript{2}O (fig. 1, B, D, and F). During an inspiratory hold, the plateau pressure was 35 cm H\textsubscript{2}O with a corresponding esophageal pressure of 24 cm H\textsubscript{2}O, translating to an end-inspiratory transalveolar pressure of 11 cm H\textsubscript{2}O (fig. 1, B, D, and F). At a PEEP of 22 cm H\textsubscript{2}O, his blood pressure was 158/77 mmHg with a heart rate of 86 beats/min. His PEEP was maintained, and during the next 18 h the Fi\textsubscript{O\textsubscript{2}} was decreased to 0.4 with a Pa\textsubscript{O\textsubscript{2}} of 101 mmHg in the absence of any other interventions. During the subsequent 48 h, atelectasis improved on chest radiograph, and we were able to decrease PEEP to 10 cm H\textsubscript{2}O.

Although his respiratory status improved, his neurologic status remained poor. After discussion with the family, he was extubated and transitioned to comfort care; he died on hospital day 8.

**Discussion**

**PEEP Titration Using Esophageal Manometry**

Various methods have been described to guide PEEP titration in mechanically ventilated patients.\textsuperscript{3,10–17} Esophageal balloon manometry allows for the estimation of pleural pressure and calculation of transalveolar pressure, thereby providing guidance by which PEEP can be increased to minimize both atelectrauma and volutrauma.\textsuperscript{10} This approach may be particularly useful in certain unique patients, such as those with obesity.

As demonstrated by our case, high levels of PEEP are sometimes both necessary and safe, particularly if supported by transalveolar pressure calculations guided by esophageal manometry. To make these calculations, an esophageal balloon is placed and the esophageal pressure is transduced in real-time. The esophageal pressure is measured as a surrogate for pleural pressure. End-exhalation and end-inspiratory transalveolar pressures are then calculated. Transalveolar pressures of 0 to 10 cm H\textsubscript{2}O at end-exhalation are accepted as distending pressures that counterbalance the collapsing effect of the chest wall to prevent atelectasis. At the same time, end-inspiratory transalveolar pressure is measured to monitor for overdistension. These measurements are made during full ventilator support. Although paralysis is not mandatory, patient breathing efforts affect chest wall tone and confound the interpretation of the measurement.\textsuperscript{18}

In a single-center study, Talmor et al.\textsuperscript{10} reported improved oxygenation and respiratory system compliance using this approach, and a phase II study designed to further clarify the association between esophageal balloon management of PEEP titration, mortality, and ventilator-free days is underway (EPVent; ClinicalTrials.gov NCT01681225).

Implicit in using esophageal pressure as a surrogate for pleural pressure is that the two are similar. The esophagus sits within the pleural space, and pleural pressures are thought to transmit proportionally to the luminal surface of the esophagus. As such, although the absolute value of the esophageal pressure may not be identical to the pleural pressure, it provides a guide to pleural pressure in an individual patient. When the esophageal balloon is properly positioned, esophageal pressure and airway pressure will change proportionately during an inspiratory effort or Valsalva maneuver against a closed airway.\textsuperscript{19,20} This provides evidence that esophageal manometry produces a valid representation of changing pleural pressures.\textsuperscript{19,21} Similar correlations have been demonstrated in critically ill, mechanically ventilated patients with acute respiratory failure.\textsuperscript{21} The main limitation of esophageal balloon-guided PEEP titration is that esophageal pressure is measured at a single point in the thorax as a global estimate of pleural pressure; the pleural pressure will be more positive in the dependent regions and more negative in the nondependent regions.\textsuperscript{22,23} The weight of the heart and mediastinum will also increase the measured esophageal pressure above the mid-lung pleural pressure in the supine-positioned patient.\textsuperscript{20,23} Thus, there still exist some risks of atelectrauma in dependent regions of lung and overdistension in nondependent regions. However, in patients with suspected high pleural pressure (e.g., obesity), the additional data from esophageal manometry may allow for improved clinical decision making.

Alternatives to esophageal manometry are occasionally used to titrate PEEP. We selected esophageal manometry rather than another approach such as the Acute Respiratory Distress Syndrome Network tables or pressure-volume curves because esophageal manometry enabled us to identify increased pleural pressures and select PEEP to counterbalance the collapsing effects of these pleural pressures and estimate the risk for alveolar overdistention. In this case, we did not measure pressure-volume curves because the ventilator used does not allow a constant slow flow maneuver to correctly make this measurement. Furthermore, previous work from our center has identified issues related to the use of the pressure-volume curve for PEEP titration and we have abandoned its use for PEEP titration.\textsuperscript{24}

Although we have clinical evidence that the patient’s atelectasis improved with the increase in PEEP, we did not measure functional residual capacity (end-expiratory lung volume) because the ventilator we used could not make that measurement. Moreover, after an increase in PEEP, it is difficult to know whether an increase in end-exhalation lung volume is the result of alveolar recruitment or overdistention of already open alveoli.\textsuperscript{25}
Esophageal Manometry-guided Titration of PEEP

PEEP and Transalveolar Pressure

Obesity is associated with a heavy chest wall and increased pleural pressure due to impaired chest wall outward recoil. Inadequate PEEP leads to alveolar collapse, derecruitment, and hypoxemia even in the absence of pulmonary pathology. To understand PEEP as it relates to obesity, one must first understand transalveolar pressures. Figure 2 illustrates the respiratory pressures at the time of esophageal balloon insertion in our patient. Transalveolar pressure (ΔPₘₐ) is the difference between alveolar (Pₐ) and pleural (Pₚₗ) pressure:

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\Delta P_m = P_a - P_{pl}
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where pleural (Pₚₗ) pressure is the esophageal (Pₑₙₑ) pressure, and Pₐ is equal to PEEP at end-expiration and plateau pressure during an inspiratory hold. Transalveolar pressure (ΔPₘₐ) is the distending pressure of the lung. Positive values lead to lung volume increase and negative values lead to alveolar collapse. At a PEEP of 15 cm H₂O, the transalveolar pressure in our patient was −7 cm H₂O at end-expiration (fig. 2A) and 1 cm H₂O during an inspiratory hold (fig. 2B), demonstrating significant end-expiratory alveolar collapse during tidal breathing.

When PEEP was increased to 22 cm H₂O, the transalveolar pressure increased to 0 cm H₂O at end-expiration (fig. 2C) and 11 cm H₂O during an inspiratory hold (fig. 2D). By matching PEEP to pleural pressure, the collapsing transalveolar forces at end-expiration are removed. As such, minimal atelectasis should occur, leading to an improved oxygenation. Despite unusually high PEEP, he remained hemodynamically stable because the transalveolar pressures remained within the acceptable range and did not significantly increase pleural pressure. Venous return is decreased by high PEEP only when it causes an increase in pleural pressure. When PEEP does not result in an increase in pleural pressure, as in our patient, it should have minimal hemodynamic effects. Similarly, although the plateau pressure (35 cm H₂O) at a PEEP of 22 cm H₂O exceeded existing guidelines for ventilator management, the corresponding transalveolar pressure (a clinical correlate of stress) in our patient (11 cm H₂O) was significantly less than the limit of 27 cm H₂O suggested as safe by Chiumello et al.²⁶ By using esophageal manometry, we were able to directly calculate the

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Fig. 1. (A, C, E) Airway, esophageal, and transalveolar pressure tracings during the respiratory cycle at a positive end-expiratory pressure (PEEP) of 15 cm H₂O. Airway pressure (A) starting at end-exhalation with a PEEP of 15 cm H₂O, followed by a tidal volume breath (6 ml/kg ideal body weight) with an inspiratory hold demonstrates a plateau pressure of 25 cm H₂O. Corresponding esophageal pressure (C) displays an esophageal pressure of 24 cm H₂O during an inspiratory hold with an end-exhalation esophageal pressure of 22 cm H₂O. The transalveolar pressure (E) is calculated by subtracting the esophageal pressure (C) from the airway pressure (A) and establishes an inspiratory hold transalveolar pressure of 1 cm H₂O and an end-exhalation transalveolar pressure of −7 cm H₂O. (B, D, F) Airway, esophageal, and transalveolar pressure tracings during the respiratory cycle at a PEEP of 22 cm H₂O. Airway pressure (B) starting at end-exhalation with a PEEP of 22 cm H₂O shows a tidal volume breath (6 ml/kg ideal body weight), followed by a second tidal volume breath with an inspiratory hold that demonstrates a plateau pressure of 35 cm H₂O. Corresponding esophageal pressure (D) displays an end-exhalation esophageal pressure of 22 cm H₂O with an esophageal pressure of 24 cm H₂O during an inspiratory hold. The transalveolar pressure (F) is calculated by subtracting the esophageal pressure (D) from the airway pressure (B) and establishes an end-exhalation transalveolar pressure of 0 cm H₂O and an inspiratory hold transalveolar pressure of 11 cm H₂O.

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Fig. 2. Intrathoracic pressures at various levels of positive end-expiratory pressure (PEEP). $P_{\text{plat}}$ = plateau pressure, $P_{\text{pl}}$ = pleural pressure which is the esophageal pressure ($P_{\text{eso}}$), $\Delta P_A$ = transalveolar pressure. (A, B) PEEP = 15 cm H$_2$O. At end-exhalation (A), the PEEP of 15 cm H$_2$O is insufficient to counterbalance the pleural pressure of 22 cm H$_2$O leading to a transalveolar pressure of $-7$ cm H$_2$O which exerts a collapsing force on the lung and results in atelectasis. During an inspiratory hold (B), the plateau pressure of 25 cm H$_2$O offsets the pleural pressure of 24 cm H$_2$O and results in a transalveolar pressure of $1$ cm H$_2$O just overcoming the collapsing force of the high pleural pressure during tidal breathing. At this level of PEEP, the low transalveolar...
transalveolar pressure during an inspiratory hold, to minimize overdistension during PEEP titration.

In summary, using higher PEEP prevents alveolar collapse in obese patients by counterbalancing higher pleural pressures. Without a measure of pleural pressure, that is, esophageal pressure, it is difficult to determine an appropriate balance between preventing atelectasis and causing overdistension in an obese patient.

**Pulmonary Effects of PEEP**

The goal of mechanical ventilation is to provide oxygenation and ventilation until spontaneous ventilation resumes. Unfortunately, decades of research have shown that harm can be done by mechanical ventilation. The term ventilator-induced lung injury refers to the various pulmonary insults and systemic effects caused by mechanical ventilation including atelectrauma, volutrauma, and biotrauma.5,27 Atelectrauma is defined as the structural damage resulting from repeated collapse and reopening of individual alveoli.5,28–30 PEEP decreases atelectrauma by preventing end-exhalation alveolar collapse, but studies evaluating higher versus lower PEEP strategies have not reported decreased mortality.5 Volutrauma is the pulmonary injury secondary to increased transalveolar pressures, which can be due to both high tidal volumes and increased PEEP. Limiting tidal volumes and plateau pressures decrease mortality and provides the cornerstone of the low inflation strategy.11 Knowledge of the physiologic mechanisms by which PEEP can both prevent and cause atelectrauma and volutrauma is necessary to balance the risks against the clinical necessity of a given level of PEEP.

**Extrapulmonary Effects PEEP**

Biotrauma refers to the combined effects of atelectrauma and volutrauma; it describes the systemic effects of ventilator-induced lung injury that can lead to multisystem organ failure.27 This inflammatory cascade is not well understood, and research is ongoing to further understand the effects of lung inflammation.

The application of PEEP has other extrapulmonary effects as well, most prominently on hemodynamics. PEEP may cause increased intrathoracic pressure when it exceeds pleural pressure. High intrathoracic pressure may lead to impaired venous return, which in turn can result in hemodynamic compromise, increased intracranial pressure (ICP), and decreased cerebral perfusion pressure. Figure 2, E and F, is a hypothetical scenario in which PEEP is further increased beyond the patient’s baseline pleural pressure. In such a case, the increasing alveolar pressure leads to an increased intrapleural pressure, which may directly compromise cardiac output and cerebral perfusion pressure. Some clinicians suggest that intravascular pressures measured in the thorax (i.e., from a pulmonary arterial catheter or central venous catheter) should be corrected for pleural pressure to establish the true transmural pressure, as increasing pleural pressures will directly increase measured intravascular pressures. This becomes especially clinically relevant in patients with abnormal chest wall mechanics (i.e., obesity, abdominal compartment syndrome, bony abnormalities, etc.). In these cases, pulmonary vascular resistance may decrease as PEEP is applied to counteract collapsing alveolar pressures because pulmonary vascular resistance increases at lower lung volumes. Alternatively, PEEP levels that lead to overdistension will increase pulmonary vascular resistance through extrinsic pressure on the pulmonary vasculature. Clinical decision making may be improved through indirect measurements of pleural pressures (e.g., esophageal manometry) when the hemodynamic effects of PEEP titration are of particular concern.

The effect of high PEEP on ICP is often a topic of interest in patients with neurologic injuries who require mechanical ventilation. It has been hypothesized that increased PEEP may increase ICP due to (1) reduced cerebrospinal fluid outflow secondary to increased spinal pressure, (2) reduced cerebral venous outflow secondary to increased intrathoracic pressure, and (3) cerebral vasodilation secondary to decreased mean arterial pressure.31 However, studies involving progressive PEEP increase to a maximum of 21 cm H2O in patients with intracranial hemorrhage,32 traumatic brain injury,33 ischemic stroke,31 intracranial tumor,34 and subarachnoid hemorrhage35 showed no significant increase in ICP. The relation between PEEP and ICP is highly variable, with some patients demonstrating increased ICP as PEEP is increased, some patients demonstrating decreased ICP as PEEP is increased, and others showing no change in ICP.31,32,35,36 The varied responses to increased PEEP are hypothesized to be multifactorial and thought to be related to factors such as patient age, degree of hypoxemia and hypercarbia, and respiratory system compliance.32 For example, some studies have demonstrated increased PEEP had no effect on cerebral perfusion pressure or ICP in mechanically ventilated patients with decreased...
respiratory system compliance, whereas it decreased cerebral perfusion pressure in patients with normal compliance. We assert that the relation between PEEP and pleural pressure dictates the effect of PEEP on ICP rather than the absolute value of PEEP. An ICP monitor was not indicated in this patient, but the combination of data from an ICP monitor and esophageal manometry deserves future evaluation.

Conclusions and Knowledge Gap

It can be difficult to find a level of PEEP that safely balances the risks of atelectrauma and volutrauma in clinical scenarios that deviate from physiologic norms. In the setting of high intrapleural pressure caused by abnormal chest wall mechanics, increased PEEP is necessary to counterbalance the collapsing effect of the chest wall. In certain patients, using esophageal manometry to estimate transalveolar pressure, PEEP can be safely titrated to a level that does not significantly exceed pleural pressure. In this way, increased PEEP will improve hypoxemia and respiratory system compliance without adversely affecting hemodynamics or ICP.

In this case, we used an esophageal balloon catheter to estimate transalveolar pressure as a guide for PEEP titration in a morbidly obese adult man with hypoxemia. Whether the use of esophageal manometry can also be used to titrate PEEP in pediatric patients is unknown and deserves further study.

To our knowledge, no data yet exist that clearly demonstrate improved mortality with this approach, but a multicenter trial is ongoing (EPVent; ClinicalTrials.gov NCT01681225). Although existing data are conflicting with regard to the effect of PEEP on ICP and other neurologic parameters, it is reasonable to anticipate that when PEEP is titrated to match pleural pressure there should be minimal effect on ICP. Further well-designed studies are needed to clinically confirm this physiologic assumption.

The results of a recent study suggest that bedside PEEP selection methods based on lung mechanics or absolute esophageal pressures provide PEEP unrelated to lung recruitability, whereas an oxygenation-based method (e.g., one similar to that used by the Acute Respiratory Distress Syndrome Network) provided PEEP levels correlated with lung recruitability. In other words, the oxygenation approach provided PEEP better matched to recruitment. However, these data do not directly apply to our patient due to the altered chest wall mechanics related to obesity, which is likely a different phenotype than the typical patient with acute respiratory distress syndrome.

Positive end-expiratory pressure titration is based on the balanced risks of alveolar collapse and overdistension, with the ideal point on this continuum remaining elusive. Until further data emerge, current practice is informed by applying the best evidence to the unique physiology of the individual patient.

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Competing Interests

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References


