Review Article

Setting intraoperative positive end expiratory pressure: how to be protective

Arianna Iachi[1], Denise Battaglini[1], Chiara Robba[2], Paolo Pelosi[1,2], Lorenzo Ball[1,2]

[1]Department of Surgical Sciences and Integrated Diagnostics, University of Genoa, Genoa, Italy; [2]Department of Anesthesia and Intensive Care, San Martino Policlinico Hospital, IRCCS for Oncology and Neurosciences, Genoa, Italy

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Correspondence to: Professor Paolo Pelosi, MD, FERS. Department of Surgical Sciences and Integrated Diagnostics, University of Genoa, Genoa, Italy; San Martino Policlinico Hospital, IRCCS for Oncology and Neurosciences, Largo Rosanna Benzi 8, 16131 Genoa, Italy.
Email: ppelosi@hotmail.com.

Abstract: General anesthesia and mechanical ventilation are required to perform most surgical procedures. Several study groups conducted observational and randomized trials to improve ventilator management and better understand how the setting of certain ventilator parameters may prevent postoperative complications. This review is focused on the role of positive end expiratory pressure (PEEP), summarizing the evidence in the general surgical population and in specific settings such as obese patients, laparoscopic procedures and thoracic surgery requiring one-lung ventilation. Several functional changes occur in the respiratory system following the induction of general anesthesia, which result in respiratory mechanics alterations, mainly airway closure and atelectasis formation. The application of a certain level of PEEP can limit the formation of atelectasis and avoid repetitive opening and closing of the alveoli, but these beneficial effects in respiratory mechanics do not necessarily translate into improved clinical outcome. On the other hand, higher levels of PEEP can impair patients' hemodynamic and require more intraoperative fluids and vasoactive drugs. Setting PEEP level can be guided by patient's characteristics and other parameters of respiratory system, in a tailored way. Several methods have been investigated, comprising setting PEEP to achieve the highest compliance of the respiratory system. However, tailored techniques so far failed to show benefits in terms of reduced incidence of postoperative complications. Applying an initial fixed minimal PEEP level of 2 to 5 cmH_2O seems to be a pragmatic approach suitable for most surgical patients, to avoid excessive atelectasis formation while avoiding the negative effects of higher PEEP levels. Higher levels might be considered in long surgical interventions, laparoscopy and extreme Trendelenburg positioning.

Keywords: Mechanical ventilation; positive end expiratory pressure (PEEP); atelectasis; post-operative pulmonary complications

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Introduction

General anesthesia is nowadays considered as a safe procedure, with a relatively low mortality due to the improvement of anesthesiology and perioperative care, even though population is becoming elderly and with more co-morbidities. Despite an increase in popularity of locoregional techniques, general anesthesia and mechanical ventilation are still necessary in many surgical procedures; therefore several observational studies and randomized controlled trials have been conducted to better understand and improve ventilator management in different populations and surgical

procedures (1-4). The role of modern anesthesiologists includes preventing postoperative complications, to improve the outcome of surgical patients, decreasing hospital length of stay and health-care systems costs.

During anesthesia, several mechanisms converge in reducing the functional residual capacity and impair gas exchange; while this mechanism has been traditionally considered the main determinant of postoperative pulmonary complications (PPCs) (5), research in the last two decades suggested that PPCs are the result of a complex interaction between patient-, anesthesia-, ventilation- and surgery-related factors (6). The occurrence of PPCs is estimated around 5–10% of patients (1), and it is associated with increased mortality and length of hospital stay (7); therefore, several scoring systems have been proposed to stratify patients' risk. Among these, the 'Assess Respiratory Risk in Surgical Patients in Catalonia risk score for PPCs' (ARISCAT) score has been developed (8) and externally validated (9). Considering the high number of surgical procedures which require invasive ventilation—more than 200 million per year—identifying strategies to reduce the incidence of PPCs can have a great impact on patient's outcomes and healthcare resources consumption. Protective mechanical ventilation strategies with low tidal volumes (Vt) set at 6 mL/kg of predicted body weight (10), and the use of positive end expiratory pressure (PEEP) are the standard of care in patients with acute respiratory distress syndrome (ARDS) (11,12). Many study groups hypothesized that low tidal volume and PEEP could be applied beneficially also in patients undergoing surgical procedures, even without pulmonary lesions. While the associations between higher plateau and driving (plateau-PEEP) pressures and PPCs have been demonstrated, the role of PEEP is still debated (13). The large observational trial LAS VEGAS (1) provided a snapshot on clinical practice in several countries, observing that two fixed levels of PEEP are typically used: 0 cmH_2O or 5 cmH_2O, also in patients with an increased risk of PPCs.

The aim of this review is to summarize the effects of PEEP in the surgical patient, to provide a review on the evidence regarding its use and to highlight gray areas warranting further research.

Pathophysiology: rationale of PEEP

Effects of general anesthesia on the respiratory system

Several functional changes occur in the respiratory system following the induction of general anesthesia, which result in respiratory mechanics alterations and gas exchange impairment; among these airway closure, atelectasis formation with formation of true shunt play a major role (14). Several mechanisms have been proposed for atelectasis formation during general anesthesia, including small airway collapse, lung structures compression, impairment of surfactant function and gas resorption. The application of PEEP can revert these effects and limit the formation of atelectasis (15). However, these advantages do not necessarily translate into improved clinical outcome (16).

Effects of PEEP in healthy lungs

Decades of research illustrated several potentially beneficial effects of PEEP during mechanical ventilation, especially in experimental studies in models of lung injury. In healthy lungs, the effects of PEEP on atelectasis reversal are mainly mediated by increased end-expiratory lung volume and improved ventilation/perfusion ratio (17). However, in patients with healthy lungs these beneficial effects seem to be more relevant in patients with major lung collapse following induction, as is the case of obese patients (18). The formation of atelectasis can persist in the post-operative period and could contribute to the development of PPCs through different mechanisms, e.g. inflammatory processes in the non-aerated lung regions (19). However, whether these theoretical advantages have a clinical impact is still debated and challenged by the findings of recent trials.

Pulmonary mechanics with PEEP application

Lung aeration starts early after induction of general anesthesia and, ideally, could be prevented by positive-pressure pre-oxygenation during the induction phase (20). This loss of aeration results in atelectasis formation and reduction of lung end-expiratory volume. The execution of a recruitment maneuver and the application of PEEP can revert this mechanism and restore lung aeration, also in patients at higher risk such as obese patients (21). However, compared to zero PEEP the application of a moderate PEEP level alone without recruitment maneuvers was sufficient to minimize atelectasis in a recent study in non-abdominal surgery (22). Therefore, PEEP and lung recruitment should maximize the lung volume available for ventilation, improving lung compliance (23). However, studies suggest that in many patients PEEP

levels as low as 2 cmH_2O can prevent lung collapse (24). Despite these theoretical advantages, an experimental study recently suggested that, in healthy lungs ventilated at low protective Vt, elevated PEEP levels increasing lung volume close to inspiratory capacity are injurious per se (25). This might explain why the advantages of protective intraoperative ventilation were observed when higher PEEP was used in conjunction with Vt reduction (26), but not when used alone at the same low Vt (3,4).

Hemodynamic effects of PEEP

After PEEP application, changes occur in the hemodynamic function. Overall, these effects are mediated by the action of airway pressure on the venous return, which according to Guyton is determined by compliance of veins, stressed volume, venous resistance and right atrial pressure (27). Lung volume change increases the difference between pleural and airway pressure, that could lead to vessels collapse and increase of pulmonary vascular resistances, reducing right ventricular injection. This phenomenon could be considered as a PEEP-induced capillary de-recruitment. On the contrary, reduction in end-expiratory lung volume determines alveolar collapse and increases vasomotor tone by pulmonary vasoconstriction (28). Patients with a low vascular reserve, as surgical patients that are often fasting before surgery, might be particularly sensitive to hypotensive effects (29). To counterbalance PEEP-induced hypotension fluids and vasoactive drugs might be required, but this might result in post-operative fluid overload.

Methods for setting PEEP in the operating room

Fixed PEEP levels

The commonest method for setting PEEP in the operating room is applying a fixed level to all patients (1), chosen by the clinician based on the characteristics of the patient and his own expertise and training. As mentioned above, in the general surgical population the most commonly used values are 0 and 5 cmH_2O (1), while only slightly higher levels are used in particular cohort of patients, e.g., obese patients (30). It must be stressed that many anesthesia machines based on the bellows-in-bottle design, for technical reasons, cannot deliver an actual PEEP of 0 cmH_2O, but a minimum level of 1–2 cmH_2O: actual zero-PEEP conditions are rarely achieved in the clinical practice. These values typically ensure acceptable gas exchange in most patients. However, in patients with stiffer chest wall, such as in obesity or intra-abdominal hypertension, higher PEEP levels could be considered.

A recent hospital-based registry retrospective study (31) suggested that a PEEP level of 5 cmH_2O was associated with a lower rate of PPCs compared with values higher or lower than 5. A large randomized multicenter trial compared two fixed PEEP strategies at the same protective Vt: 2 cmH_2O without recruitment maneuvers versus PEEP of 12 cmH_2O with recruitment maneuvers (4). The study included non-obese patients scheduled for open abdominal surgery at intermediate to high risk of developing PPCs. The higher fixed PEEP strategy allowed to maximize lung aeration, as reflected by an improvement of the dynamic compliance of the respiratory system, suggesting alveolar recruitment during mechanical ventilation for open abdominal surgery. A similar strategy was applied in another large randomized trial in patients with body mass index above 35 kg/m^2 comparing PEEP of 4 versus 12 cmH_2O, observing improved intraoperative oxygenation and compliance (2). Despite these findings concerning respiratory mechanics data, outcome of patients did not differ between the two study groups and the incidence of PPCs was similar, but hemodynamic impairment occurred more frequently in the high PEEP groups of both studies. This suggests that other mechanisms beside atelectasis could be involved in PPCs and morbidity after major surgery. Overall, the results of these two studies underline that a fixed PEEP level strategy is feasible, and that a low-moderate level is preferable in most patients.

Driving pressure (ΔP) or 'open lung' techniques

The ΔP is the difference between plateau pressure and PEEP, and has been proposed as a parameter to help anesthesiologist to set mechanical ventilation (32). It represents the dynamic strain of lung fibers and reflects the compliance of the respiratory system (33). After observing an association between high ΔP and the occurrence of PPCs (13), authors started proposing to titrate PEEP to the level corresponding to the minimum ΔP, namely to the highest respiratory system compliance. In this case, the level of PEEP can be set during a decremental PEEP test after a recruitment maneuver. PEEP increases the aerated volume both recruiting collapsed alveoli and causing hyperdistention; collapse and hyperdistention cause an increase of the ΔP, thus titrating PEEP based on this value

could theoretically help balancing between these two unwanted phenomena (32). However, a recent physiological study challenged this assumption, observing that during ventilation of healthy lungs in surgical patients ΔP reflects lung aeration status only when no hyperinflation above the physiological functional residual capacity occurs, as is often the case when high PEEP levels are used (24).

A large randomized trial compared an 'open lung' PEEP titration strategy plus postoperative CPAP (3) in non-obese abdominal surgery patients at intermediate-high risk of PPCs. In this trial, PEEP titrated according to the lowest ΔP was compared with a fixed PEEP strategy with 5 cmH_2O. The study did not find any difference in a composite of postoperative complications between the individualized strategies and standard, fixed-PEEP, lung-protective mechanical ventilation. A secondary outcome of PPCs was slightly favoring individualized intraoperative PEEP and postoperative CPAP.

The negative results of this trial do not make monitoring ΔP less important, as values above 13 cmH_2O were associated with PPCs (13). Titration of PEEP has unclear ability to reduce this risk when identified but the clinician should keep in mind that if a PEEP increase translates in ΔP it means that harmful hyperdistention occurred, and PEEP should be lowered. An elevated ΔP is a marker of increased risk of PPC, and one method to lower ΔP and potentially the injuriousness of ventilation could be further reducing Vt (32).

While no clear superiority of titrated over fixed-PEEP strategies is demonstrated so far, further larger randomized trials could explore the possibility of further improving patient outcome through personalized ventilation.

Transpulmonary pressure (P_L)

The pressure which is actually applied to alveoli during controlled positive pressure ventilation is the P_L, that represents the difference between airways pressure and the pleural pressure. P_L cannot be directly measured in the clinical practice, but it can be estimated measuring esophageal pressure (P_{ES}), a surrogate of pleural pressure (34,35). The measurement and interpretation of P_{ES} has been debated, but many physiological studies conducted in animal models and cadavers suggest that it is a reliable indicator of the absolute pleural pressures applied across the horizontal plane of the balloon. Titrating PEEP to achieve a positive end-expiratory P_L improves oxygenation and compliance of the respiratory system in patients with ARDS thus could be a way to guide mechanical ventilation (36), but failed to show mortality benefits (37). The titration of PEEP based on P_{ES} can be applied in clinical practice for setting the optimal PEEP in critically ill patients but in the operating room it is limited to research purposes and physiologic mechanical respiratory system measurements (35).

Clinical recommendations

Every of the described methods has a clear physiologic rationale. The studies conducted so far, resumed in *Table 1* (2-4,10,26,38-42), did not demonstrate the superiority of none of them. In absence of clear evidence, a fixed moderate-low PEEP between 2 and 5 cmH_2O could be a reasonable initial value for most patients, while slightly higher values could be considered in specific subgroups of patients, as described below.

Grey areas

Some clusters of patients and types of surgical procedures have unique characteristics and specific features which might influence the choice of the PEEP level. In these fields, clinical evidence is particularly scarce and more clinical trials are required.

Laparoscopic and robotic surgery

Laparoscopic procedures are widely spread since they are less invasive compared to open surgery, but they present some features that can further impair the respiratory mechanics of patients. A pneumoperitoneum has to be induced by carbon dioxide inflation, with an increased abdominal pressure and cranial shift of the diaphragm. Then, many of these procedures require Trendelenburg positioning, that may worsen atelectasis formation in the dependent lung regions (43). The recent availability of robotic surgery makes positioning even more challenging. A PEEP level of 5 cmH_2O applied to patients during laparoscopic procedures seems to be beneficial, leading to alveolar recruitment and improvement of chest wall and lung elastance (35). Higher levels could be considered in very long interventions and extreme positionings, as is the case of robotic surgery.

Duration of surgery

All the large randomized trials on intraoperative PEEP setting included procedures with an average duration

Table 1 Prospective randomized controlled trials conducted in adults

Study	Design	Surgical procedure and population	Intervention	Control	Outcome
Sundar *et al*., 2011 (38)	Single-center	Elective cardiac surgery (n=149)	VT: 6 mL/kg. PEEP/FiO_2: according to ARDS Network table	VT: 10 mL/kg. PEEP/FiO_2: according to ARDS Network table	In the Intervention group: -lower rate of reintubation -lower number of patients requiring ventilation 6 h postoperatively
Treschan *et al*., 2012 (39)	Single-center	Elective upper abdominal surgery lasting ≥3h (n=101)	VT: 6 mL/kg. PEEP: 5 cmH_2O	VT: 12 mL/kg. PEEP: 5 cmH_2O	In the Control group: -Lower rate of atelectasis -Higher PaO_2/FiO_2 -Higher PaO_2 at postoperative day 5
Maslow *et al*., 2013 (40)	Single-center	Elective pulmonary resection (n=34)	VT: 5 mL/kg both in TLV and OLV. PEEP: 5 cmH_2O both in TLV and OLV	VT: 10 mL/kg both in TLV and OLV. PEEP: 0 cmH_2O both in TLV and OLV	In the Control group: -Lower rate of atelectasis -Higher Cdyn -Lower $PaCO_2$ and alveolar dead space
Shen *et al*., 2013 (41)	Single-center	Elective thoracoscopic esophagectomy (n=101)	VT: 8 mL/kg during TLV; VT: 5 mL/kg during OLV. PEEP: 5 cmH_2O both in TLV and OLV	VT: 8 mL/kg during TLV; VT: 8 mL/kg during OLV. PEEP: 5 cmH_2O both in TLV and OLV	In the Intervention group: -Lower rate of PPCs -Higher PaO_2/FIO_2 -Higher $PaCO_2$
Futier *et al*., 2013 (26)	Multicenter	Major abdominal surgery. Patients at intermediate to high risk of PPCs (n=400)	VT: 6–8 mL/kg. PEEP: 6–8 cmH_2O	VT: 10–12 mL/kg. PEEP: 0 cmH_2O	In the Intervention group: -Lower rate of major pulmonary or extrapulmonary complications -Reduced rate of atelectasis, pneumonia, need for ventilation within 7 days and sepsis -Reduced length of hospital stay
Severgnini *et al*., 2013 (10)	Single-center	Elective open abdominal surgery ≥2 h (n=56)	VT: 7 mL/kg. PEEP: 10 cmH_2O	VT: 9 mL/kg. PEEP: 0 cmH_2O	In the Intervention group: -Improved Pulmonary function tests -Lower Modifed Clinical Pulmonary Infection Score -Higher PaO_2 at postoperative days 1, 3, and 5 -Lower rate of chest radiograph abnormalities
Ge *et al*., 2013 (42)	Single-center	Spine fusion (n=60)	VT: 6 mL/kg. PEEP: 10 cmH_2O. RM every 15 minutes	VT: 10–12 mL/kg. PEEP: 0 cmH_2O. No RM	In the Intervention group: -Lower rate of PPCs -Higher PaO_2/FIO_2
PROVE Net Investigators, 2014 (4)	Multicenter, international	Major abdominal surgery. Patients at intermediate to high risk of PPCs (n=900)	VT: 8 mL/kg. PEEP: 12 cmH_2O. RM after induction and before extubation	VT: 8 mL/kg. PEEP: 0–2 cmH_2O. No RM	No difference in incidence of PPCs In the Intervention group: -Higher rate of intraoperative hemodynamic impairment (hypotension, vasoactive drugs) -Lower rate of desaturation

Table 1 (*continued*)

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Study	Design	Surgical procedure and population	Intervention	Control	Outcome
Ferrando *et al*., 2018 (3)	Multicenter	Elective open abdominal surgery ≥2 h. Patients at intermediate to high risk of PPCs (n=1,012)	VT: 8 mL/kg PBW. PEEP according to OLARM if clinically necessary	VT: 8 mL/kg PBW. PEEP: 5 cmH_2O. No RM	No difference in incidence of PPCs In the Intervention group (OLA-iCPAP): -Lower incidence of PPCs
PROVE Net Investigators, 2019 (2)	Multicenter, international	Noncardiac, non-neurological surgery under general anesthesia. Obese patients (BMI ≥35) (n=2,013)	VT: 7 mL/kg PBW. PEEP: 12 cmH_2O. RM (stepwise increase of VT) after induction, every hour and before extubation	VT: 7 mL/kg PBW. PEEP: 4 cmH_2O. No RM	No difference in incidence of PPCs In the Intervention group: -Lower rate of intraoperative hypoxemia -Higher rate of intraoperative hypotension and bradycardia -Higher rate of pleural effusion

Cdyn, dynamic compliance of the respiratory system; FiO_2, inspired fraction of oxygen; OLV, one-lung ventilation; $PaCO_2$, partial pressure of arterial carbon dioxide; PaO_2, partial pressure of arterial oxygen; PaO_2/FiO_2, ratio of partial pressure of arterial oxygen to inspired fraction of oxygen; RM, recruitment maneuver; TLV, two-lung ventilation; VT, tidal volume.

around 3 hours. The role of PEEP in longer interventions is unclear; as the risk of lung collapse increases with the duration of invasive mechanical ventilation, higher PEEP levels might be considered in these patients to reduce atelectasis and possibly the incidence of PPCs.

Obese patients

Obese patients with an elevated body mass index present an increased intraabdominal pressure, with decreased chest wall elastance and lung volume, so they can experience a more severe gas exchange deterioration after anesthesia induction (44). Moreover, airway ΔP poorly reflects lung mechanics when chest wall compliance is reduced and intraabdominal pressure increases (45). Literature suggested how PEEP may improve respiratory mechanics in obese patients (18) and PEEP levels required to achieve lung recruitment might be proportional to the degree of obesity, as suggested by imaging-based studies (46). A large randomized trial was recently conducted, where the study group aimed to determine if this enhancement of respiratory function would also have a clinical effect on patients' outcome (2). Around 2,000 patients with BMI ≥35 kg/m^2 were randomized in two groups: higher level of PEEP (12 cmH_2O with alveolar recruitment maneuvers) and low level of PEEP (4 cmH_2O); the set tidal volume was the same in both groups. Remarkably, the data of this study demonstrate how an improvement of respiratory function due to higher levels of PEEP is not reflected by a reduction of PPCs. These findings suggest that setting a PEEP level around 12 cmH_2O in obese patients is not routinely suitable, since the reduction of intraoperative ΔP and atelectasis are not related to a clinical enhancement.

Neurosurgical patients

Patients undergoing neurosurgical procedures and neurologically ill patients undergoing surgery (e.g., trauma patients) are more sensitive to hypercapnia because it may cause cerebral vasodilation with consequent detrimental effects on cerebral perfusion pressure and intracranial pressure. Application of PEEP in neurologically ill patients was traditionally considered harmful because of the reduction of the venous outflow (47), while recent evidence demonstrate that the application of moderate PEEP levels in both pediatric and adult population undergoing neurosurgical procedures may be safe, if an adequate arterial pressure and cerebral perfusion pressure are preserved (48-51). However, there is paucity of literature concerning the intraoperative ventilatory management of these patients,

and caution should be applied when setting the PEEP level.

One lung ventilation (OLV)

During thoracic surgery, OLV is often required to allow surgeons to access the lung, chest wall or mediastinum. One lung is non-aerated and collapsed, with consequent potential alveolar inflammation and acting as shunt. The other lung must provide gas exchange for the organism during the intraoperative period. Incidence of PPCs is higher than in other surgical scenarios. A meta-analysis based on 22 studies suggests that a PEEP level ≥5 cmH_2O may have a beneficial effect in reducing PPCs during one-lung ventilation (52). A large randomized controlled trial is ongoing (53) to investigate the effects of high PEEP (10 cmH_2O plus recruitment maneuvers) and low PEEP (5 cmH_2O) on PPCs during one-lung ventilation for thoracic surgery. In this setting, it must be remembered that when the non-dependent lung is excluded from ventilation, applying elevated PEEP to the dependent lung could divert the pulmonary blood flow to the excluded lung, increasing shunt and worsening oxygenation.

Conclusions

Adjusting PEEP levels influences gas exchange, hemodynamics and lung mechanics, together with the other ventilation parameters and the mechanical properties of the lung and chest wall to which ventilation is applied. A minimal value of PEEP between 2 and 5 cmH_2O can be appropriate for most patients, to avoid atelectasis and compensate the loss of volume due to body positioning and loss of muscular tone. Since an 'open lung' approach doesn't seem to improve outcome, an approach comprising a certain degree of 'permissive atelectasis' might be considered. Level of PEEP, as well as the other ventilation parameters, has to be adapted to specific surgical settings such as laparoscopic procedures, obese patients, one-lung ventilation, neurologically ill patients and long-duration procedures. A reasoned approach to PEEP titration is warranted, based on clinical practice and scientific evidence.

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Footnote

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