Lung-protective perioperative mechanical ventilation

Hemmes, S.N.T.

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Chapter 3

Intraoperative Protective Mechanical Ventilation for Prevention of Postoperative Pulmonary Complications

A Comprehensive Review of the Role of Tidal Volume, Positive End-Expiratory Pressure and Lung Recruitment Manoeuvres

Abstract

Postoperative pulmonary complications are associated with increased morbidity, length of hospital stay, and mortality following major surgery. Intraoperative lung-protective mechanical ventilation has the potential to reduce the incidence of postoperative pulmonary complications. This review discusses the relevant literature on definition of and methods to predict occurrence of postoperative pulmonary complication, the pathophysiology of ventilator-induced lung injury with emphasis to the non-injured lung, and protective ventilation strategies, including the respective roles of tidal volumes, positive end-expiratory pressure and recruitment manoeuvres. The authors propose an algorithm for protective intraoperative mechanical ventilation based upon evidence from recent randomized clinical trials.
Introduction

Postoperative pulmonary complications (PPCs) can have an important impact on the morbidity and mortality of patients who need major surgery.\(^1\) Approximately 5% of patients undergoing general surgery will develop a PPC and one of five patients who developed a PPC die within 30 days of surgery.\(^1\) Furthermore, the number of PPCs is strongly associated with postoperative length of stay and short-term and long-term mortality.\(^1,2\)

There is growing evidence that intraoperative lung-protective mechanical ventilation using low tidal volumes, with or without high levels of positive end–expiratory pressure (PEEP) and recruitment manoeuvres, prevents PPCs compared to mechanical ventilation with high tidal volumes and low levels of PEEP without recruitment maneuvers.\(^3-6\)

In the present article, we review the definition of and methods to predict PPCs, the pathophysiology of ventilator-induced lung injury (VILI) with emphasis on the non-injured lung, and ventilation strategies to minimize PPCs. To identify the most recent evidence from the literature on randomized clinical trials (RCTs) addressing intraoperative mechanical ventilation and non-clinical as well as clinical postoperative outcome measures, we conducted a MEDLINE review using the following search terms: (‘lower tidal volume’ OR ‘low tidal volume’ OR ‘protective ventilation’ OR ‘recruitment manoeuvres’ OR ‘PEEP’ OR ‘positive end expiratory pressure’). Retrieved articles, and cross-referenced studies from those articles, were screened for pertinent information.

Definition and prediction of postoperative pulmonary complications

Summary of current definitions

PPCs are usually presented as a composite, which then includes possible fatal and non-fatal respiratory events of new onset occurring in the postoperative period. Currently, there is no agreement about which of these events should be considered as PPC, for example respiratory failure, lung injury, pneumonia, prolonged or unplanned mechanical ventilation or intubation, hypoxemia, atelectasis, bronchospasm, pleural effusion, pneumothorax, ventilatory depression, and aspiration pneumonitis.\(^7,8\) From a clinical standpoint, it is worthwhile to present PPCs as a composite, because any of these events alone or their associations has a significant impact on the postoperative outcome,\(^1\) using different definitions. However, it is clear that these events can have different pathophysiologic mechanisms. For this reason, some studies have focused on single events, mainly respiratory failure\(^9\) and pneumonia.\(^10\)

PPCs, to be considered as such, must be related to anesthesia and/or surgery. Furthermore, the time frame must be well defined. Usually, an event is only considered as PPC if it develops within 5 to 7 days after surgery.\(^8,11\)
**Prediction of Postoperative Pulmonary Complications**

Prediction of PPCs, or any of the single postoperative respiratory events that is part of that composite, can be useful to plan perioperative strategies aiming at their prevention, and also to reduce health system costs. First, the risk factors associated with the development of PPCs must be identified. In 2006, the American College of Physicians published a systematic review of the literature listing a number of risk factors for PPCs according to their respective levels of evidence. In recent years, that list has been expanded to include other factors found to increase the risk of PPCs. Table 1 depicts risk factors associated with PPCs according to the current literature. Approximately 50% of the risk for PPCs are attributable to the patient’s health conditions, while the other 50% are related to the surgical procedure and the anaesthetic management itself.

Table 1. Risk factors for postoperative pulmonary complications

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Preoperative testing</th>
<th>Surgery</th>
<th>Anaesthetic management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Low albumin</td>
<td>Open thoracic surgery</td>
<td>General anesthesia</td>
</tr>
<tr>
<td>Male sex</td>
<td>Low SpO2 (&lt; 95%)</td>
<td>Cardiac surgery</td>
<td>High respiratory driving pressure (≥ 13 cmH2O)</td>
</tr>
<tr>
<td>ASA class ≥ 3</td>
<td>Anaemia (Hb &lt; 10 g/dL)</td>
<td>Open upper abdominal surgery</td>
<td>High inspiratory oxygen fraction</td>
</tr>
<tr>
<td>Previous respiratory infection</td>
<td>Major vascular surgery</td>
<td>Cardiac surgery</td>
<td>High volume of crystalloid administration</td>
</tr>
<tr>
<td>Functional dependency</td>
<td>Neurosurgery</td>
<td>Urology</td>
<td>Residual neuromuscular blockade</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td></td>
<td></td>
<td>Nasogastric tube use</td>
</tr>
<tr>
<td>COPD</td>
<td>Duration of surgery &gt; 2h</td>
<td>Emergent surgery</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
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<tr>
<td>Renal failure</td>
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<tr>
<td>Gastroesophageal reflux disease</td>
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<tr>
<td>Weight loss</td>
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</tbody>
</table>

ASA, American Society of Anesthesiologists; COPD, chronic obstructive pulmonary disease; Hb, haemoglobin concentration; PPCs, postoperative pulmonary complications; SpO2, oxygen saturation as measured by pulse oximetry. Respiratory driving pressure, defined as inspiratory plateau airway pressure minus positive end-expiratory pressure.

Based on risk factors, different scores have been developed that have the potential to predict the occurrence of PPCs, as shown in table 2. However, their applicability may be limited since they were derived from restricted settings, retrospective databases, or only validated for specific PPCs. The Assess Respiratory Risk in Surgical Patients in CATalonia (ARISCAT) study was conducted in a general surgical population of Catalonia, Spain. After a multivariate analysis, a score based on seven risk factors was developed and underwent internal validation, showing...
a clinically relevant predictive capability (c-statistic, 0.90). Recently, the ARISCAT score was externally validated in a large European surgical sample (the Prospective Evaluation of a Risk Score for Postoperative Pulmonary ComPlications in Europe, PERISCOPE study). Although differences in the performance of the ARISCAT score have been observed between European geographic areas, the score was able to discriminate three levels of PPCs risk (low, intermediate and high). Thus, at present, the ARISCAT score may represent the most valuable tool for predicting PPCs across different countries and surgical populations.

Putative mechanisms of ventilator-induced lung injury

The coexistence of closed, recruitable and already overdistended alveolar regions makes the lung vulnerable to detrimental effects of mechanical stress and strain induced by mechanical ventilation. The physical forces in some alveolar regions may exceed the elastic properties of the lungs although gross measurements of airway pressures or lung mechanics as usually monitored under anesthesia still suggest mechanical ventilation is in a “safe” zone. Several mechanisms have been postulated to describe the development of VILI. Increased airway pressure (barotrauma) or the application of high tidal volumes (volutrauma) may cause damage or disruption of alveolar epithelial cells, by generating transpulmonary pressures (stress) that exceed the elastic properties of the lung parenchyma above its resting volume (strain). It has been demonstrated that the duration of mechanical stress defined as the stress versus time product affects the development of pulmonary inflammatory response. While high stress versus time product increased the gene expression of biological markers associated with inflammation and alveolar epithelial cell injury and low stress versus time product increased the molecular markers of endothelial cell damage, balanced stress versus time product as defined by an inspiratory to expiratory time ratio of 1:1 was associated with attenuated lung damage. Especially in the presence of atelectasis, mechanical ventilation may cause damage by repetitive collapse and reopening of alveolar units, a phenomenon known as atelectrauma. All three mechanisms, namely barotrauma, volutrauma and atelectrauma may affect alveolar as well as vascular epithelial and endothelial cells as well as promote extracellular matrix fragmentation.

The extracellular matrix of the lung parenchyma seems to be particularly sensitive to stress from mechanical ventilation, as illustrated in figure 1. Initially, the proteoglycans on the endothelial side and between the endothelial and epithelial lines undergo damage dependent on tidal volume, as well as breathing pattern. The mechanical fragmentation of the extracellular matrix promotes interstitial oedema and activation of metalloproteinases, further damaging the extracellular matrix itself. In a second step, fragments of the extracellular matrix can promote activation of inflammatory mediators. Furthermore, the damage of the extracellular matrix induced by mechanical ventilation might be exacerbated by fluid load, which is not uncommon during general anesthesia. However, fluid overload seems to minimize the inflammatory response, likely by dilution of extracellular matrix fragments or changes in their structure, thereby down regulating the local inflammatory response. This suggests that: 1) injurious mechanical ventilation makes the lung more susceptible to further insults; 2) in previously healthy lungs, VILI can be induced without early increase in inflammatory mediators.
Table 2. Scores for prediction of postoperative pulmonary complications

<table>
<thead>
<tr>
<th>Reference/Year published</th>
<th>Study design</th>
<th>Patient population</th>
<th>Number of patients</th>
<th>Score acronym</th>
<th>Scoring system</th>
<th>Cut-off</th>
<th>Quality of prediction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prediction of general postoperative pulmonary complications</strong></td>
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<tr>
<td>Canet et. al., 2010 (^1)</td>
<td>Prospective, multicenter, observational cohort study</td>
<td>Adult patients undergoing nonobstetric surgical procedures under general, neuraxial, or regional anesthesia</td>
<td>2,464 overall 1,624 derivation 837 validation 3 patients with missing data for two parameters relevant for the score (SpO(_2)+respiratory infection during last month)</td>
<td>ARISCAT Assess Respiratory Risk in Surgical Patients in Catalonia</td>
<td>Age 51–80 &gt;80 SpO(_2)% 91–95 &lt;90 Respiratory infection &lt;30 days Preoperative anaemia (Hb &lt;10 g/dl) Surgical incision: Peripheral Upper abdominal Intrathoracic Duration of surgery: ≤2h &gt;2-3 &gt;3 Emergency procedure</td>
<td>low/&lt;26/1.6%; medium/26-44/ 13.3% high/≥45/42.1%</td>
<td>Derivation cohort AUC: 0.89 Validation cohort AUC: 0.84</td>
</tr>
<tr>
<td>Mazo et. al. 2014 (^2) (Validation of ARISCAT score from Canet et. al., 2010 (^1) in a larger, international, multicenter cohort)</td>
<td>Prospective, multicenter, observational cohort study</td>
<td>Adult patients undergoing nonobstetric surgical procedures under general, neuraxial, or plexus block anesthesia</td>
<td>5,099</td>
<td>ARISCAT Assess Respiratory Risk in Surgical Patients in Catalonia</td>
<td>see above</td>
<td>low/&lt;26/0.87%/3.39% medium/26-44/ 7.82%/12.96% high/≥45/38.13%/ 38.01%</td>
<td>AUC: 0.80</td>
</tr>
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</table>
### Prediction of selected postoperative pulmonary complications

<table>
<thead>
<tr>
<th>Study Authors</th>
<th>Study Design</th>
<th>Patient Population</th>
<th>Number of Patients</th>
<th>Score Acronym</th>
<th>Scoring System</th>
<th>Cut-off</th>
<th>Quality of Prediction</th>
<th>Level/Point/Predicted/ Observed Rate of PPC</th>
<th>AUC (Validation)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ARISCAT</strong></td>
<td>Prospective, multicenter, observational cohort study</td>
<td>Adult patients undergoing major general or vascular procedures performed under general, spinal, or epidural anesthesia</td>
<td>90,055 derivation 89,948 validation</td>
<td>RRI (Respiratory failure Risk Index)</td>
<td>Type of surgery: Integumentary, Respiratory and hemic, Heart, Aneurysm, Mouth, palate, Stomach, intestines, Endocrine</td>
<td></td>
<td></td>
<td>Low/Point/Predicted/Observed Rate of PPC:</td>
<td>Derivation cohort AUC: 0.856 Validation cohort AUC: 0.863</td>
</tr>
<tr>
<td><strong>Johnson et al. 2007</strong></td>
<td>Prospective, multicenter, observational cohort study</td>
<td>Adult patients undergoing major general or vascular procedures performed under general, spinal, or epidural anesthesia</td>
<td>90,055 derivation 89,948 validation</td>
<td>RRI (Respiratory failure Risk Index)</td>
<td>Type of surgery: Integumentary, Respiratory and hemic, Heart, Aneurysm, Mouth, palate, Stomach, intestines, Endocrine</td>
<td></td>
<td></td>
<td>Low/Point/Predicted/Observed Rate of PPC:</td>
<td>Derivation cohort AUC: 0.856 Validation cohort AUC: 0.863</td>
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<tr>
<td>Reference/Year published</td>
<td>Study design</td>
<td>Patient population</td>
<td>Number of patients</td>
<td>Score acronym</td>
<td>Scoring system</td>
<td>Cut-off</td>
<td>Quality of prediction</td>
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<tr>
<td>Brueckmann et al. 2013&lt;sup&gt;15&lt;/sup&gt;</td>
<td>Retrospective single-centre, observational cohort study</td>
<td>Cases with a surgical procedure if the adult patient was intubated at the beginning and extubated at the end of the procedure</td>
<td>33,769 overall 16,885 derivation 16,884 validation</td>
<td>SPORC</td>
<td>Score for Prediction of Postoperative Respiratory Complications</td>
<td>ASA score ≥3</td>
<td>Derivation cohort AUC: 0.81, Validation cohort AUC: 0.81</td>
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<td>Emergency procedure</td>
<td>3</td>
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<td>High-risk service</td>
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<td></td>
<td></td>
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<td>Congestive heart failure</td>
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<td></td>
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<td>Chronic pulmonary disease</td>
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<tr>
<td>Gajic et al. 2011&lt;sup&gt;6&lt;/sup&gt; (similar to Trillo-Alvarez et al. 2011&lt;sup&gt;126&lt;/sup&gt;, but used a larger, multicenter cohort)</td>
<td>Prospective, multicenter, observational cohort study</td>
<td>Adult patients with one or more ALI risk factors, including sepsis, shock, pancreatitis, pneumonia, aspiration, high-risk trauma, or high-risk surgery</td>
<td>5,584 overall 2,500 derivation 3,084 validation</td>
<td>LIPS</td>
<td>Lung Injury Prediction Score</td>
<td>Predisposing Conditions</td>
<td>Combined AUC: 0.80, Sensitivity: 0.69, Specificity: 0.78</td>
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<td>Shock</td>
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<td>Aspiration</td>
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<td>Sepsis</td>
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<td>Pneumonia</td>
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<td>High-risk surgery</td>
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<td>Orthopaedic spine</td>
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<td></td>
<td>Acute abdomen</td>
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<td></td>
<td></td>
<td>Cardiac</td>
<td>2.5</td>
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<td></td>
<td>Aortic vascular if emergency surgery</td>
<td>3.5</td>
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<td></td>
<td></td>
<td>High risk trauma</td>
<td>+1.5</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Traumatic brain injury</td>
<td>2</td>
<td></td>
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</tr>
</tbody>
</table>
Review: Intraoperative Protective Ventilation

Chapter 3

### Reference/Year Published
- **Brueckmann et al. 2013**

#### Study Design
- Retrospective single-centre, observational cohort study

#### Patient Population
- Cases with a surgical procedure if the adult patient was intubated at the beginning and extubated at the end of the procedure

#### Number of Patients
- Overall: 33,769
- Derivation: 16,885
- Validation: 16,884

#### Score Acronym
- **SPORC** Score for Prediction of Postoperative Respiratory Complications

#### Scoring System
- ASA score ≥3

#### Cut-off for Development of ALI/ARDS
- Emergency procedure
- High-risk service
- Congestive heart failure
- Chronic pulmonary disease

#### Score Values/Probability of Reintubation
- 0/0.12%
- 1-3/0.45%
- 4-6/1.64%
- 7-11/5.86%

#### Derivation Cohort
- AUC: 0.81

#### Validation Cohort
- AUC: 0.81

### Gajic et al. 2011

- (similar to Trillo-Alvarez et al. 2011, but used a larger, multicenter cohort)

#### Study Design
- Prospective, multicenter, observational cohort study

#### Patient Population
- Adult patients with one or more ALI risk factors, including sepsis, shock, pancreatitis, pneumonia, aspiration, high-risk trauma, or high-risk surgery

#### Number of Patients
- Overall: 5,584
- Derivation: 2,500
- Validation: 3,084

#### Score Acronym
- **LIPS** Lung Injury Prediction Score

#### Predisposing Conditions
- Shock
- Aspiration
- Sepsis
- Pneumonia
- High-risk surgery
  - Orthopaedic spine
  - Acute abdomen
  - Cardiac
  - Aortic vascular
  - if emergency surgery
  - High risk trauma
  - Traumatic brain injury
  - Smoke inhalation
  - Near drowning
  - Lung contusion
  - Multiple fractures
  - Risk modifiers
  - Alcohol abuse
  - Obesity (BMI >30)
  - Hypoalbuminemia
  - Chemotherapy
  - FiO2>0.35 (>4 L/min)
  - Tachypnea (RR>30)
  - SpO2<95%
  - Acidosis (pH<7.35)
  - Diabetes mellitus, if septic

#### Score Values/Probability of Reintubation
- 0/0.12%
- 1-3/0.45%
- 4-6/1.64%
- 7-11/5.86%

#### Derivation Subsample
- AUC: 0.80
- Sensitivity: 0.69
- Specificity: 0.78

#### Validation Subsample
- AUC: 0.84
- Sensitivity: 0.82
- Specificity: 0.75

### Kor et al. 2014

- (similar to Kor et al. 2011, but used a larger, multicenter cohort; secondary analysis of Gajic et al. 2011)

#### Study Design
- Secondary analysis of a prospective, multicenter cohort study

#### Patient Population
- Adult patients presenting with one or more ALI risk factors, including sepsis, shock, pancreatitis, pneumonia, aspiration, high-risk trauma, or high-risk surgery and undergoing a surgical procedure

#### Number of Patients
- 1,562

#### Score Acronym
- **SLIP 2** Surgical Lung Injury Prediction 2

#### Surgical Procedure
- High-risk cardiac surgery
- High-risk aortic vascular surgery
- Emergency surgery
- Baseline health status
- Sepsis
- Cirrhosis
- Admission source
- Physiologic markers of acute illness
- Respiratory rate 20–29
- Respiratory rate ≥30
- FiO2 >35%
- SpO2 <95%

#### Cut-off for Development of ARDS
- ≥19

#### AUC
- 0.84

### ALI, acute lung injury; ARDS, acute respiratory distress syndrome; ASA, American Society of Anesthesiologists classification; AUC, area under the curve; BMI, body mass index; COPD, chronic obstructive pulmonary disease; FiO2, fraction of inspired oxygen; Hb, haemoglobin; PPC, postoperative pulmonary complication; PRF, postoperative respiratory failure, RVU, relative value units (a measure of surgical complexity); SGOT, serum glutamic-oxaloacetic transaminase; SpO2, oxygen saturation as measured by pulse oximetry
At the cellular level, physical stimuli are transformed into chemical signals, e.g. pro- and anti-inflammatory mediators by means of direct cell injury or indirect activation of cellular signalling pathways. This process is known as “mechanotransduction”. Some mediators may promote local effects such as pro-apoptotic or pro-fibrotic actions, while others act as homing molecules recruiting local and remote immune cell populations (e.g. neutrophils and macrophages). These local effects as well as their immunological consequences are summarized by the term “biotrauma”.

Besides the extracellular matrix, both the endothelial and the epithelial compartment of the alveolar-capillary unit are affected by stress and strain originating from mechanical ventilation. In the endothelium, high stress can lead to direct cell breaks, resulting in capillary stress failure. Furthermore, mechanical stress as well as inflammatory stimuli (i.e. TNF alpha) may trigger contractions of the cytoskeleton resulting in disruption of adherence junctions, which increase endothelial permeability and contribute to oedema formation. Similar to the pulmonary endothelium, mechanical stress and strain increase the permeability of the alveolar epithelium, a phenomenon found during ventilation at high, as well as low lung volumes. Additionally, low lung volume ventilation can lead to repetitive collapse and reopening of lung, affecting the epithelium of small airways, yielding plasma membrane disruption, as well as epithelial necrosis and sloughing.

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**Figure 1. Alterations of the extracellular matrix in lungs during mechanical ventilation and fluid administration**

Besides the extracellular matrix, both the endothelial and the epithelial compartment of the alveolar-capillary unit are affected by stress and strain originating from mechanical ventilation. In the endothelium, high stress can lead to direct cell breaks, resulting in capillary stress failure. Furthermore, mechanical stress as well as inflammatory stimuli (i.e. TNF alpha) may trigger contractions of the cytoskeleton resulting in disruption of adherence junctions, which increase endothelial permeability and contribute to oedema formation. Similar to the pulmonary endothelium, mechanical stress and strain increase the permeability of the alveolar epithelium, a phenomenon found during ventilation at high, as well as low lung volumes. Additionally, low lung volume ventilation can lead to repetitive collapse and reopening of lung, affecting the epithelium of small airways, yielding plasma membrane disruption, as well as epithelial necrosis and sloughing.
Alveolar fluid clearance is essential to maintain intra-alveolar fluid homeostasis, which is usually compromised during VILI. Whereas ventilation with high tidal volumes directly decreases Na,K-adenosintriphosphatase activity, ventilation at low lung volumes may indirectly impair fluid clearance due to hypoxia following increased alveolar collapse.

Impairment of barrier function of the endothelium and epithelium, as well as of fluid clearance leads to the development of interstitial and alveolar oedema, which subsequently causes surfactant dysfunction, and impairs lungs elastic and resistive properties. Dysfunction of the surfactant system makes the lung susceptible to alveolar collapse contributing to deterioration of lung mechanics and impairing pulmonary host defense.

Although most evidence of gross structural alterations of endothelium and epithelium induced by mechanical ventilation originates from in vitro investigations of cultured cells or in vivo investigations in acute lung injury models, ventilation applying clinically relevant settings in non-injured lungs can affect the alveolar-capillary barrier function, especially in the presence of independent inflammatory triggers, making mechanical ventilation a powerful hit in presence of systemic inflammation.

Due to the disturbed integrity of the alveolar-capillary barrier function and consecutive systemic translocation of pathogens or inflammatory mediators, VILI may lead to a systemic inflammatory response affecting not only the lungs, but distal organs as well.

Lung inhomogeneity, e.g. due to atelectasis formation, is a major contributing factor to the development of VILI. However, most experimental evidence is derived from acute lung injury models. Although their basic pathogenic mechanisms may be similar, the magnitude and time course of atelectasis formation in acute lung injury may be very different from those of atelectasis occurring during anesthesia and relatively short-term intraoperative mechanical ventilation. Resorption of alveolar gas and compression of lung structures may lead to atelectasis during short-term mechanical ventilation in non-injured lungs, whereby the former might play a more important role.

In a porcine model of experimental pneumonia, both exogenous surfactant administration and ventilation according to the open lung approach attenuated bacterial growth and systemic translocation by minimizing alveolar collapse and atelectasis formation. In a similar model of experimental pneumonia in mechanically ventilated piglets, bacterial translocation was lowest with individually tailored PEEP levels, whereas low and high PEEP promoted bacterial translocation.

In isolated non-perfused mouse lungs, both an “open lung approach” (tidal volume 6 mL/kg, recruitment manoeuvres and PEEP of 14 - 16 cmH₂O) as well as a “lung rest strategy” (tidal volume of 6 mL/kg, PEEP of 8 - 10 cmH₂O, no recruitment manoeuvres) were associated with reduced pulmonary inflammatory response and improved respiratory mechanics compared to injurious mechanical ventilation (tidal volume of 20 mL/kg, PEEP of 0 cmH₂O). Interestingly, the “lung rest strategy” was associated with less apoptosis but more ultrastructural cell damage, most likely due to increased activation of mitogen-activated protein kinase pathways as compared to the “open lung strategy.”
In healthy mice, mechanical ventilation with a tidal volume of 8 ml/kg and PEEP of 4 cmH2O induced a reversible increase in plasma and lung tissue cytokines as well as increased leukocyte influx, but the integrity of the lung tissue was preserved. In another investigation, even least-injurious ventilator settings were able to induce VILI in the absence of a previous pulmonary insult in mice. Of note, the deleterious effects of mechanical ventilation in non-injured lungs are partly dependent on its duration. However, an experimental study demonstrated that large tidal volumes had only minor if any deleterious effects on lungs, despite prolonged mechanical ventilation. Possibly, this is explained by the lack of a previous inflammatory insult, as for example surgery. In fact, systemic inflammation may prime the lungs to injury by mechanical ventilation.

Mechanical ventilation strategies to protect lungs during surgery

Atelectasis and intraoperative mechanical ventilation
Atelectasis develops in as much as 90% of patients undergoing general anesthesia, and can persist to different degrees after surgery, also surrounding pleura effusion, as illustrated in figure 2. The area of non-aerated lung tissue near to the diaphragm varies depending on the surgical procedure and patient characteristics, but has been estimated in the range of 3-6 % to 20-25%, and even higher if calculated as amount of tissue.

Different mechanisms have been postulated to favour atelectasis formation during anesthesia, including: 1) collapse of small airways; 2) compression of lung structures; 3) absorption

Figure 2. Magnetic resonance imaging (MRI) scans of lungs of three patients before and on the first day after open abdominal surgery
of intra-alveolar gas content; and 4) impairment of lung surfactant function. Mechanical ventilation strategies for general anesthesia have been importantly influenced by the progressive decrease in oxygenation and compliance. Tidal volumes up to 15 mL/kg of predicted body weight were advocated to increase the end-expiratory lung volume (EELV) and counteract atelectasis in the intraoperative period. Provided there is no contraindication, PEEP and lung recruitment manoeuvres may also contribute to revert or prevent the loss of EELV and closure of small airways during anesthesia.

**Tidal volumes for intraoperative protective ventilation**

Driven by clinical and experimental studies, tidal volumes during mechanical ventilation have been importantly reduced in patients suffering from the acute respiratory distress syndrome (ARDS) in order to limit lung overdistension. Influenced by this practice in intensive care unit patients, a similar trend was observed in the operation room. As reported by different investigators, average tidal volumes in the range of 6 to 9 mL/kg of predicted body weight have gained broad acceptance for non-injured lungs, in spite of experimental and clinical data suggest that higher values are not associated with increased lung damage or inflammation. Furthermore, anaesthesiologists have consistently reduced tidal volumes also during one-lung ventilation. Whereas values as high as 10 mL/kg have been used in the past, experimental and clinical studies have suggested that tidal volumes of approximately 4 to 5 mL/kg may be more appropriate for lung protection, while still allowing adequate gas exchange. Furthermore, a small RCT showed that atelectasis did not increase significantly with low tidal volume without PEEP from induction of anesthesia until the end of surgery. This is also supported by the fact that mechanical ventilation with low tidal volume and PEEP did not result in a progressive deterioration of the respiratory system compliance and gas exchange during open abdominal surgery in a larger RCT. It must be kept in mind that “set” and “actual” (i.e. delivered) tidal volumes can differ substantially, and that settings should be adjusted judiciously.

**Positive end-expiratory pressure for intraoperative protective ventilation**

Clinical studies have shown that a PEEP of 10 cmH₂O is required to reduce or eliminate atelectasis, improve compliance without increasing deadspace, and maintain end-expiratory lung volume during general anesthesia in both non-obese and obese patients. Another study in normal subjects showed that PEEP of 10 cmH₂O increased lung volume, but did not improve the respiratory function compared to PEEP of 0 cmH₂O. Certainly, the level of PEEP should be chosen according to the patient’s particular characteristics, the particularities of the surgical approach, and patient positioning. Several targets have been proposed for a more individual titration of PEEP during general anesthesia, including the following: 1) oxygenation, also combined with dead space, or EELV; 2) mechanical properties of the respiratory system; and 3) distribution of ventilation using electric impedance tomography. However, none of these has been shown to improve patient outcome.

Although controversial, an alternative approach for PEEP during general anesthesia is the so-called “intraoperative permissive atelectasis”, when PEEP is kept relatively low and recruitment manoeuvres are waived. This concept aims at reducing the static stress in lungs, which is closely related to the mean airway pressure, assuming that collapsed lung tissue is protected against injury from mechanical ventilation (figure 3). Intraoperative permissive atelectasis may be limited
by deterioration in oxygenation, which could require higher inspiratory oxygen fractions. Also, shear stress may occur at the interface between collapsed and open tissue,\textsuperscript{18} likely resulting in lung damage and inflammation, even in presence of low global stress.\textsuperscript{97} Theoretically, intraoperative low PEEP could increase the incidence and the amount of atelectasis even in the postoperative period, resulting in further PPCs. A recent large retrospective study investigating the association between intraoperative mechanical ventilator settings and outcomes suggested that the use of “minimal” PEEP (2.2 to 5 cmH\textsubscript{2}O) combined with low tidal volumes (6 to 8 mL/kg) is associated with increased risk of 30-day mortality.\textsuperscript{77} However, a large international multicenter RCT challenged the concept that “minimal” PEEP combined with low tidal volumes in the intraoperative period is harmful.\textsuperscript{86} Also in elderly patients undergoing major open abdominal surgery, a strategy consisting of low tidal volume, PEEP 12 cmH\textsubscript{2}O and recruitment manoeuvres increased the PaO\textsubscript{2} intraoperatively compared to a strategy with high tidal volume without PEEP, but this effect was not maintained in the postoperative period.\textsuperscript{98} Even without recruitment manoeuvres PEEP improved oxygenation during upper abdominal surgery compared to zero end-expiratory pressure, but again such effects were limited to the intraoperative period and did not prevent postoperative complications.\textsuperscript{99}

\textit{Lung recruitment manoeuvres for intraoperative protective ventilation}

PEEP is most effective for preserving respiratory function if preceded by a recruitment manoeuvre, which must overcome the opening pressures of up to 40 cmH\textsubscript{2}O in non-obese,\textsuperscript{100} and 40-50 cmH\textsubscript{2}O in obese patients,\textsuperscript{101} in the absence of lung injury. Recruitment manoeuvres can be performed in different ways using the anesthesia ventilator, as illustrated in figure 4.
Most commonly, such manoeuvres are performed by “bag squeezing” using the airway pressure-limiting valve of the anesthesia machine (figure 4A). However, recruitment manoeuvres are better controlled if performed during tidal ventilation, for example using a stepwise increase of PEEP, tidal volumes, or a combination of these (figure 4B). Provided there are no contraindications, the inspiratory plateau pressure as high as 40 cmH₂O, are more likely to result in full recruitment.\textsuperscript{102}

In anesthesia devices that allow pressure-controlled ventilation, recruitment manoeuvres can be conducted with a constant driving pressure of 15-20 cmH₂O, and by increasing PEEP up to 20 cmH₂O in steps of 5 cmH₂O (30 to 60 s per step). After three to five breaths at a PEEP level that allows achieving the target inspiratory pressure, PEEP and tidal volume are adjusted to the respective desired levels (figure 4C).

\textbf{Figure 4.} Illustrative fluctuation of airway pressure during three types of lung recruitment manoeuvres for intraoperative mechanical ventilation
<table>
<thead>
<tr>
<th>Reference/Year published</th>
<th>Study design</th>
<th>Patient population/Number</th>
<th>Intervention group(s)</th>
<th>Control group</th>
<th>Nonclinical primary outcomes</th>
<th>Secondary outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wrigge et al. 2004</td>
<td>Prospective, single-centre, randomized controlled trial</td>
<td>Adult patients undergoing major thoracic surgery n=34 (2 excluded)</td>
<td>PV V̇e: 6 mL/kg PEEP: 10 cmH₂O P_w Limit 35 cmH₂O during TLV and OLV n=15</td>
<td>CV V̇e: 12-15 mL/kg ZEEP P_w Limit 35 cmH₂O during TLV and OLV n=17</td>
<td>Inflammatory mediators in plasma: no differences between groups for TNFα, IL-1, IL-6, IL-8, IL-10, IL-12</td>
<td>Gas exchange: no differences between groups</td>
</tr>
<tr>
<td>Schilling et al. 2005</td>
<td>Prospective, single-centre, randomized controlled trial</td>
<td>Adult patients undergoing elective open thoracic surgery n=32</td>
<td>PV V̇e: 5 mL/kg during TLV and OLV PEEP: 3 cmH₂O, TLV PEEP: 0-2 cmH₂O, OLV P_w Limit 30 cmH₂O n=16</td>
<td>CV V̇e: 10 mL/kg during TLV and OLV PEEP: 3 cmH₂O, TLV PEEP: 0-2 cmH₂O, OLV P_w Limit 30 cmH₂O n=16</td>
<td>Inflammatory mediators in BAL: TNFα and sICAM lower during PV No differences between groups for cell count, PMN elastase, total protein, albumin, IL-8, IL-10</td>
<td>PaO₂/FIO₂: no differences between groups PaCO₂: higher during PV</td>
</tr>
<tr>
<td>Michelet et al. 2006</td>
<td>Prospective, single-centre, randomized controlled trial</td>
<td>Adult patients undergoing planned esophagectomy n=52</td>
<td>PV V̇e: 9 mL/kg, TLV V̇e: 5 mL/kg OLV PEEP: 5 cmH₂O, TLV and OLV n=26</td>
<td>CV V̇e: 9 mL/kg, TLV and OLV ZEEP, TLV and OLV n=26</td>
<td>Inflammatory mediators in plasma: IL-1ß, IL-6, IL-8 lower during PV No differences between groups for TNFα</td>
<td>PaO₂/FIO₂ and PaCO₂: higher during PV EVLWI: lower during PV Time to extubation: shorter during PV</td>
</tr>
<tr>
<td>Lin et al. 2008</td>
<td>Prospective, single-centre, randomized controlled trial</td>
<td>Adult patients undergoing esophagectomy n=40</td>
<td>PV V̇e: 10 mL/kg, TLV V̇e: 5-6 mL/kg OLV PEEP: 3-5 cmH₂O, OLV n=20</td>
<td>CV V̇e: 10 mL/kg, TLV and OLV ZEEP, TLV and OLV n=20</td>
<td>Inflammatory mediators in plasma: IL-6, IL-8, lower during PV</td>
<td>P_plat, P_\text{raw}, and Raw: lower during PV</td>
</tr>
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</table>
### Review Intraoperative Protective Ventilation

<table>
<thead>
<tr>
<th>Unzueta et al. 2012</th>
<th>Prospective, single-centre, randomized controlled trial</th>
<th>Adult patients undergoing elective open thoracotomy n=40</th>
</tr>
</thead>
</table>
| **PV** | Vr: 8 mL/kg, TLV  
Vt: 6 mL/kg OLV  
PEEP: 8 cmH2O, TLV and OLV  
RM with stepwise PEEP/Paw increase until 20/40 cmH2O before start of OLV n=20 | Dead space: lower during PV  
PaO2/FIO2: higher  
PaCO2: lower during PV |
| **CV** | Vr: 8 mL/kg, TLV  
Vt: 6 mL/kg OLV  
PEEP: 8 cmH2O, TLV and OLV  
no RM before start of OLV n=20 |  |

### Cardiac surgery

<table>
<thead>
<tr>
<th>Koner et al. 2004</th>
<th>Prospective, single-centre, randomized controlled trial</th>
<th>Adult patients undergoing elective on-pump coronary artery bypass grafting surgery n=44</th>
</tr>
</thead>
</table>
| **PV** | Vr: 6 mL/kg  
PEEP: 5 cmH2O n=15 | Inflammatory mediators in plasma: no differences between groups for TNFα and IL-6  
Pplat: lower during PV compared to both CV groups  
Shunt fraction: lower during PV compared to both CV+ZEEP  
PaO2/FIO2: higher during ventilation with PEEP (1) + (2) |
| **CV+PEEP** | Vr: 10 mL/kg  
PEEP: 0 cmH2O n=14 |  |
| **CV+ZEEP** | Vr: 10 mL/kg  
PEEP: 0 cmH2O n=15 |  |

<table>
<thead>
<tr>
<th>Zupancich et al. 2005</th>
<th>Prospective, single-centre, randomized controlled trial</th>
<th>Adult patients undergoing elective on-pump coronary artery bypass grafting surgery n=40</th>
</tr>
</thead>
</table>
| **PV** | Vr: 8 mL/kg  
PEEP: 10 cmH2O n=20 | Inflammatory mediators in plasma and BAL: IL-6, IL-8, lower during PV in both.  
PaCO2: higher during PV |
| **CV** | Vr: 10-12 mL/kg  
PEEP: 2-3 cmH2O n=20 |  |

<table>
<thead>
<tr>
<th>Reis Miranda et al. 2005</th>
<th>Prospective, single-centre, randomized controlled trial</th>
<th>Adult patients undergoing elective on-pump coronary artery bypass grafting or valve surgery n=62</th>
</tr>
</thead>
</table>
| **Late open lung** | Vr: 4-6 mL/kg  
PEEP: 10 cmH2O starting at postop ICU arrival n=18 | Inflammatory mediators in plasma: IL-8 decreased after CPB in both open lung groups; IL-10 decreased faster after CPB in early open lung group |
| **Early open lung** | Vr: 4-6 mL/kg  
PEEP: 10 cmH2O starting after intubation n=22 |  |
| **V** | Vr: 6-8 mL/kg  
PEEP: 5 cmH2O n=22 | Evidence of perioperative myocardial infarction (ck-MB and ECG): no differences between groups |
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Patients</th>
<th>Ventilation</th>
<th>Inflammatory mediators</th>
<th>PaO2/FIO2</th>
<th>PaCO2</th>
<th>Notes</th>
</tr>
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<tbody>
<tr>
<td>Wrigge et al. 2004</td>
<td>Prospective, single-centre, randomized controlled trial</td>
<td>Adult patients undergoing major abdominal surgery n=30</td>
<td>PV: Vt: 6 mL/kg PEEP: 10 cmH2O Paw Limit 35 cmH2O n=15</td>
<td>Inflammatory mediators in plasma: no differences between groups for TNFα, IL-1, IL-6, IL-8, IL-10, IL-12</td>
<td>PaO2/FIO2: no differences between groups</td>
<td>PaCO2: higher during PV</td>
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<tr>
<td>Wolthuis et al. 2008</td>
<td>Prospective, single-centre, randomized controlled trial</td>
<td>Adult patients undergoing a surgical procedure in general anesthesia ≥5h n=46</td>
<td>PV: Vt: 6 mL/kg PEEP: 10 cmH2O n=24</td>
<td>Inflammatory mediators in plasma and BAL: lower myeloperoxidase and nucleosome level in BAL during PV</td>
<td>PaCO2: higher during PV PPCs: no differences between groups</td>
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<tr>
<td>Weingarten et al. 2010</td>
<td>Prospective, single-centre, randomized controlled trial</td>
<td>Adult patients aged &gt;65y undergoing major open abdominal surgery under general anesthesia n=40</td>
<td>PV: Vt: 6 mL/kg PEEP: 12 cmH2O RM with stepwise PEEP increase until 15 cmH2O n=20</td>
<td>Inflammatory mediators in plasma: no differences between groups</td>
<td>PaO2/FIO2 + PaCO2: higher during PV Compliance higher and resistance lower during PV</td>
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<tr>
<td>Memtsoudis et al. 2012</td>
<td>Prospective, single-centre, randomized controlled trial</td>
<td>Adult patients undergoing elective lumbar decompression and fusion in prone position under general anesthesia n=26</td>
<td>PV: Vt: 6 mL/kg PEEP: 8 cmH2O n=13</td>
<td>Inflammatory mediators in plasma: no differences between groups</td>
<td>PaCO2: higher during PV</td>
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</tbody>
</table>

BAL, bronchoalveolar lavage; CK-MB, muscle-brain type creatine kinase; CPB, cardiopulmonary bypass; CV, conventional ventilation; ECG, electrocardiogram; EVLWI, extravascular lung water index; FIO2, inspired fraction of oxygen; ICAM, intercellular adhesion molecule; ICU, intensive care unit; IL, interleukin; Paw, airway pressure; Ppeak, peak pressure; Pplat, plateau pressure; PaCO2, partial pressure of arterial carbon dioxide; PaO2, partial pressure of arterial oxygen; PaO2/FIO2, ratio of partial pressure of arterial oxygen to inspired fraction of oxygen; PEEP, positive end-expiratory pressure; PMN, polymorphonuclear leukocyte; PPCs, postoperative pulmonary complications; PV, protective ventilation; OLV, one-lung ventilation; Paw, airway resistance; RM, recruitment manoeuvre; sICAM, soluble intercellular adhesion molecule; TNFα, tumour necrosis factor alpha; TLV, two-lung ventilation; Vt, tidal volume; ZEEP, zero end-expiratory pressure
Recent evidence for intraoperative protective ventilation

Randomized controlled trials using non-clinical primary outcomes
The literature search identified eleven RCTs that compared a protective ventilation strategy with a non-protective ventilation strategy during general anesthesia for surgery with regard to non-clinical primary outcome in patients undergoing thoracic surgery, \textsuperscript{78,82,83,103,104} cardiac surgery, \textsuperscript{93,105,106} abdominal surgery, \textsuperscript{78,98,107} or spinal surgery, \textsuperscript{108} as depicted in table 3. In eight RCTs the protective ventilation strategy consisted of both lower tidal volumes and higher levels of PEEP; \textsuperscript{78,83,98,103,105-108} in two RCTs, it consisted of either lower tidal volume, \textsuperscript{82} a higher level of PEEP. \textsuperscript{93} In one RCT, lung recruitment manoeuvres were used during the protective ventilation strategy. \textsuperscript{104}

The effects on inflammatory responses are slightly contradictory. While four RCTs showed no difference in local levels of inflammatory mediators between patients on protective and those on non-protective ventilation, \textsuperscript{78,98,105,108} six RCTs showed that protective strategies were associated with lower levels of inflammatory mediators. \textsuperscript{82,83,93,103,106,107}

Randomized controlled trials using clinical primary outcomes
In total, 8 RCTs were identified that compared a protective ventilation strategy with a non-protective ventilation strategy during surgery with regard to a clinical primary outcome in patients planned for abdominal surgery, \textsuperscript{86,109-111} thoracic surgery, \textsuperscript{85,112} cardiac surgery, \textsuperscript{113} or spinal surgery, \textsuperscript{114} as shown in table 4. In four RCTs the protective strategy consisted of both lower tidal volumes and higher levels of PEEP, \textsuperscript{110-112,114} in the four remaining RCTs it consisted of either lower tidal volumes, \textsuperscript{85,109,113} or higher levels of PEEP. \textsuperscript{86}

Four trials reported on PPCs in the first postoperative days, including bronchitis, hypoxemia, and atelectasis, \textsuperscript{114} pneumonia, need for invasive or non-invasive ventilation for acute respiratory failure, \textsuperscript{110} a modified “Clinical Pulmonary Infection Score” and chest x-ray abnormalities, \textsuperscript{111} and hypoxemia, bronchospasm, suspected pulmonary infection, pulmonary infiltrate, aspiration pneumonitis, development of ARDS, atelectasis, pleural effusion, pulmonary oedema, and pneumothorax. \textsuperscript{86}

In a Chinese single-centre RCT, \textsuperscript{114} investigators compared protective ventilation (tidal volume 6 mL/kg and 10 cmH\textsubscript{2}O PEEP) versus non-protective (tidal volume 10 to 12 mL/kg and 0 cmH\textsubscript{2}O PEEP) in 60 elderly American Society of Anesthesiologists class II and III patients scheduled for spinal surgery. Patients receiving protective ventilation had less PPCs.

In a French multi-centre trial (Intraoperative PROtective VEntilation, IMPROVE), \textsuperscript{110} protective ventilation (tidal volume 6 to 8 mL/kg and PEEP 6 to 8 cmH\textsubscript{2}O) was compared with non-protective ventilation (tidal volume 10 to 12 mL/kg and 0 cmH\textsubscript{2}O PEEP) in 400 non-obese patients at intermediate to high risk of pulmonary complications after planned major abdominal surgery. The primary outcome (postoperative pulmonary and extra-pulmonary complications) occurred less often in patients receiving ‘protective’ ventilation. Such complications have been ascribed to the release of inflammatory mediators by the lungs into the systemic circulation, affecting the lungs, \textsuperscript{115} as well as peripheral organs. \textsuperscript{50} These patients also had a shorter length of hospital stay, but mortality was unaffected.
<table>
<thead>
<tr>
<th>Reference/Year published</th>
<th>Study design</th>
<th>Patient population/Number</th>
<th>Intervention</th>
<th>Control group</th>
<th>Clinical primary outcomes</th>
<th>Secondary outcomes</th>
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<tr>
<td><strong>Thoracic surgery</strong></td>
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<tr>
<td>Maslow et al. 2013</td>
<td>Prospective, single-centre, randomized controlled trial</td>
<td>Adult patients undergoing elective pulmonary resection n=34</td>
<td>PV Vt: 5 mL/kg, TLV and OLV PEEP: 5 cmH₂O, TLV and OLV n=17</td>
<td>CV Vt: 10 mL/kg, TLV and OLV ZEEP, TLV and OLV n=17</td>
<td>Rate of atelectasis: lower with CV; length of hospital stay: no differences between groups</td>
<td>PaCO₂ abd dead space: higher during PV C₉₀: higher during CV</td>
</tr>
<tr>
<td>Shen et al. 2013</td>
<td>Prospective, single-centre, randomized controlled trial</td>
<td>Adult patients undergoing thoracoscopic esophagectomy n=101</td>
<td>PV Vt: 8 mL/kg, TLV VT: 5 mL/kg OLV PEEP: 5 cmH₂O, TLV and OLV n=53</td>
<td>CV Vt: 8 mL/kg, TLV VT: 8 mL/kg OLV ZEEP, TLV and OLV n=48</td>
<td>PPCs: lower rate with PV Mortality: no difference between groups</td>
<td>PaO₂/FIO₂ and PaCO₂: higher during PV Inflammatory mediators in BAL: lower IL-1β, IL-6 and IL-8</td>
</tr>
<tr>
<td><strong>Cardiac surgery</strong></td>
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<tr>
<td>Sundar et al. 2011</td>
<td>Prospective, single-centre, randomized controlled trial</td>
<td>Adult patients undergoing elective cardiac surgery n=149</td>
<td>PV Vt: 6 mL/kg PEEP/FIO₂: according to ARDS Network table n=75</td>
<td>CV Vt: 10 mL/kg PEEP/FIO₂: according to ARDS Network table n=74</td>
<td>Rate of reintubation: lower with PV Number of patients requiring ventilation 6h postoperatively: lower with PV</td>
<td>Gas exchange: no difference between groups</td>
</tr>
<tr>
<td><strong>Abdominal surgery</strong></td>
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<tr>
<td>Treschan et al. 2012</td>
<td>Prospective, single-centre, randomized controlled trial</td>
<td>Adult patients undergoing elective upper abdominal surgery ≥3 h under combined general and epidural anesthesia n=101</td>
<td>PV Vt: 6 mL/kg PEEP: 5 cmH₂O n=50</td>
<td>CV Vt: 12 mL/kg PEEP: 5 cmH₂O n=51</td>
<td>Rate of atelectasis: lower with CV</td>
<td>PaO₂/FIO₂: higher during CV C₉₀ and R₉₀: higher during CV PaO₂ at postoperative day 5: higher with CV</td>
</tr>
</tbody>
</table>
**Review intraoperative protective ventilation**

**Chapter 3**

**Futier et al. 2013**

Prospective, randomized controlled multi-centre study

- **Adults patients at intermediate to high risk of pulmonary complications undergoing major abdominal surgery**  
  n=400

- **PV**  
  T: 6-8 mL/kg  
  PEEP: 6-8 cmH2O  
  ZEEP
  n=200

- **CV**  
  T: 10-12 mL/kg  
  ZEEP
  n=200

- **Composite primary outcome of major pulmonary or extrapulmonary complications: lower with PV**

- **Reduced rate of atelectasis, pneumonia, need for ventilation within 7 days and sepsis with PV.**

- **Reduced length of hospital stay with PV**

**Severgnini et al. 2013**

Prospective, single-centre, randomized controlled trial

- **Adult patients undergoing elective open abdominal surgery ≥2 h**  
  n=56 (1 excluded)

- **PV**  
  T: 7 mL/kg  
  PEEP: 10 cmH2O  
  ZEEP
  n=28

- **CV**  
  T: 9 mL/kg  
  ZEEP
  n=27

- **Pulmonary function tests: improved with PV**

- **PaO2 at postoperative days 1, 3, 5: higher with PV**

- **Rate of chest x-ray abnormalities: lower with PV**

- **Length of hospital stay: no difference between groups**

**PROVE Network Investigators 2014**

Prospective, international, multicenter, randomized controlled trial

- **Adults patients at intermediate to high risk of pulmonary complications undergoing major abdominal surgery**  
  n=900

- **PV**  
  T: 8 mL/kg  
  PEEP: 12 cmH2O  
  RM with stepwise increase of VT after induction and before extubation
  n=445

- **CV**  
  T: 8 mL/kg  
  PEEP: 0-2 cmH2O  
  ZEEP
  n=449

- **Rate of PPCs: no difference between groups**

- **Rate of intraoperative hypotension and amount of vasoactive drugs given: higher during PV**

- **Rate of desaturation: lower during PV**

- **Mortality and length of hospital stay: no difference between groups**

**Spinal surgery**

**Ge et al. 2013**

Prospective, single-centre, randomized controlled trial

- **Adult patients undergoing spine fusion**  
  n=60

- **PV**  
  T: 6 mL/kg  
  PEEP: 10 cmH2O  
  RM every 15 min
  n=30

- **CV**  
  T: 10-12 mL/kg  
  ZEEP
  n=30

- **Rate of PPCs, lower with PV**  
  **PaO2/FIO2, higher during PV**

ARDS, acute respiratory distress syndrome; BAL, bronchoalveolar lavage; CV, conventional ventilation; FIO2, inspired fraction of oxygen; ICU, intensive care unit; IL, interleukin; PaCO2, partial pressure of arterial carbon dioxide; PaO2, partial pressure of arterial oxygen; PaO2/FIO2, ratio of partial pressure of arterial oxygen to inspired fraction of oxygen; PEEP, positive end-expiratory pressure; PPCs, postoperative pulmonary complications; PV, protective ventilation; OLV, one-lung ventilation; Raw, airway resistance; RM, recruitment manoeuvre; TLV, two-lung ventilation; VT, tidal volume; ZEEP, zero end-expiratory pressure.
Figure 5. Odds ratios for postoperative pulmonary complications of “protective” versus “non-protective” ventilation in trials
An Italian single-centre trial investigated the effectiveness of protective ventilation (tidal volume 7 mL/kg and 10 cmH₂O PEEP with recruitment manoeuvres) versus non-protective ventilation (tidal volume 9 mL/kg and zero end-expiratory pressure) in 56 patients scheduled for open abdominal surgery lasting more than 2 hours. The modified “Clinical Pulmonary Infection Score” was lower in patients receiving protective ventilation. These patients also had fewer chest x-ray abnormalities and higher arterial oxygenation compared to patients receiving non-protective ventilation.

Finally, in an international multicenter trial conducted in Europe and the Americas (PROtective Ventilation using High versus Low PEEP, PROVHILO), the PROtective VEntilation (PROVE) Network-investigators compared PEEP of 12 cmH₂O combined with recruitment manoeuvres versus PEEP of 2 cmH₂O without recruitment manoeuvres in 900 non-obese patients at high risk for postoperative pulmonary complications planned for open abdominal surgery under ventilation at tidal volumes of 8 mL/kg. The incidence of PPCs was not different between patients receiving protective ventilation and patients receiving non-protective ventilation.

Challenges of studies using bundles
As shown in preceding subsections “Randomized controlled trials using non-clinical primary outcomes” and “Randomized controlled trials using clinical primary outcomes”, most RCTs addressing intraoperative mechanical ventilation compared bundles of interventions consisting of tidal volumes and levels of PEEP, usually accompanied by a lung recruitment maneuver. Notably, recruitment manoeuvres differed between the trials. In the Italian single-centre RCT, investigators used incremental titration of tidal volumes until a plateau pressure of 30 cmH₂O, directly after induction of anesthesia, after any disconnection from the ventilator and immediately before extubation, similar as in PROVHILO. In IMPROVE, recruitment was performed with a continuous positive airway pressure of 30 cmH₂O for 30 seconds every 30 minutes, also known as sustained inflation, after tracheal intubation. Finally, in the Chinese single-centre RCT, the recruitment manoeuvres followed a similar approach, but to plateau pressures of up to 35 cmH₂O, and they were performed every 15 minutes. It is difficult, if not impossible to conclude from these trials what caused the benefit: tidal volume reduction or increase of PEEP, or both, and to determine the role of recruitment manoeuvres. Moreover, to what extent the recruitment manoeuvre has succeeded in reopening lung has not been analysed in the different studies.

The results of the PROVHILO trial, however, suggest that low tidal volumes rather than PEEP combined with lung recruitment manoeuvres are responsible for lung protection in the intraoperative period. This interpretation is also supported by an analysis of different studies on the odds ratios of lower tidal volumes, higher levels of PEEP, as well as their combination regarding the development of PPCs (figure 5).

Certainly, these conclusions are only valid for the studied population, that is, non-obese patients at risk of PPCs undergoing elective abdominal surgery. Other patient populations could still benefit from higher levels of PEEP and recruitment manoeuvres.

Challenges of composite outcome measures
Composite outcome measures offer the benefit of an increased event rate, which is helpful
to ensure adequate statistical power of a trial. It is reasonable to combine related outcomes that represent different aspects of a single underlying pathophysiological process, like PPCs for VILI. There are, though, two major limitations regarding the use of composite outcomes. First, the component variables can differ importantly in terms of severity and frequency. Second, differences in the frequency of component variables in a composite outcome may be masked.

**Drawbacks of protective ventilation**

The term "protective" in the context of mechanical ventilation implies a decrease in the major components of VILI, namely atelectrauma, volutrauma and biotrauma. However, a strategy that is protective to lungs may also cause harm to other organ systems. The potential for harm caused by protective ventilation was reported in PROVHILO, in which patients receiving higher PEEP and lung recruitment manoeuvres developed intraoperative hypotension more frequently and needed more vasoactive drugs. These findings are at least in part in line with the finding that protective ventilation was associated with a higher incidence of intraoperative hypotension in the French trial.
Standard of care versus unusual settings: Were the control groups of recent trials representative of clinical practice?

In RCTs addressing intraoperative protective mechanical ventilation, the strategy used to treat control groups can play an important role when drawing conclusions for daily practice of general anesthesia. Metaanalyses suggest that lower tidal volumes are protective not only during long-term ventilation in critically ill patients, but also short-term ventilation during general anesthesia for surgery. Accordingly, anaesthesiologists have been using tidal volumes of approximately 8 to 9 mL/kg on average, and seldom higher than 10 mL/kg, as also illustrated in figure 6A. In contrast to this practice, the tidal volumes used in the control groups of recent RCTs were as high as 9 to 12 mL/kg, except to PROVHILO (figure 6B), which used a tidal volume of 7 mL/kg both in the intervention and in the control group. Similarly, levels of PEEP in the control arms of three out of four recent RCTs on protective mechanical ventilation were much lower than the standard of care at the moment the respective studies were designed (figure 6C and 6D). Taken together, these facts suggest that, among the most important recent RCTs on intraoperative protective mechanical ventilation, only the PROVHILO trial used a control group that reproduced the standard of anesthesia care at the time it was conducted. Accordingly, the PROVHILO trial addressed a major question regarding mechanical ventilation during anesthesia, namely whether the combination of high PEEP with recruitment manoeuvres confers protection against PPCs. In this study, high PEEP was not individualized, but based on previous findings from computed tomography and physiological studies.

Intraoperative mechanical ventilation according to the utmost recent evidence

A number of reviews and commentaries have suggested that intraoperative mechanical ventilation for surgery should consist of low tidal volumes (6 to 8 mL/kg), moderate levels of PEEP (6 to 8 cmH₂O), and periodic lung recruitment manoeuvres (e.g. every 30 min). However, previous reviews and recommendations have been based on bundles, which do not permit to infer on the contribution of individual measures. Furthermore, the results of the largest RCT in this field (PROVHILO) could not be taken into account. Also, a recommendation regarding the use of positive pressure ventilation during induction and emergence of anesthesia, as proposed recently, is not supported by outcome data. Currently, the only recommendations that can be given for clinical practice are summarized in figure 7. In non-obese patients without ARDS undergoing open abdominal surgery, mechanical ventilation should be performed with low tidal volumes (approximately 6 to 8 mL/kg) combined with low PEEP (≤ 2 cmH₂O), since higher PEEP combined with recruitment manoeuvres does not confer further protection against PPCs and can deteriorate the hemodynamics. If hypoxemia develops and provided that other causes have been excluded (e.g. hypotension, hypoventilation, pulmonary embolism etc.), the FiO₂ should be increased first, followed by increase of PEEP, and recruitment manoeuvres based on stepwise increase of tidal volume during regular mechanical ventilation, according to the rescue algorithm described in the PROVHILO trial, provided no contra-indication is present. In patients with ARDS undergoing open abdominal surgery, intraoperative mechanical ventilation should be guided by the ARDS network protocol, whereby higher PEEP values may be useful in more
Future perspectives

Despite the increasing number of highly qualitative RCTs on intraoperative mechanical ventilation, a number of issues remain unaddressed. While metaanalyses strongly suggest that low tidal volumes during intraoperative mechanical ventilation protect against postoperative pulmonary events, no single RCT has been able to prove this claim. Since metaanalyses in this field frequently include studies that tested intervention bundles, for example low tidal volume and high PEEP with recruitment manoeuvres versus high tidal volumes without PEEP, the estimation of the effects of single measures, for example low tidal volume or PEEP, is prone to criticism. Therefore, RCTs are most relevant for clinical practice if they test single interventions, and if control groups reproduce current standards. Whereas direct testing of the hypothesis that intraoperative low tidal volumes protect against PPCs is still lacking, ethical issues preclude such a trial.

Figure 7. Proposed settings of protective mechanical ventilation in non-obese patients during open abdominal surgery according to the concept of intraoperative permissive atelectasis

Settings of volume-controlled mechanical ventilation in non-obese patients during open abdominal surgery

<table>
<thead>
<tr>
<th>Non-injured lungs (no ARDS)</th>
<th>Injured lungs (ARDS)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial settings</strong></td>
<td><strong>Initial settings</strong></td>
</tr>
<tr>
<td>$V_t = 6 \text{ - } 8 \text{ mL/kg PBW}$</td>
<td>$V_t = 6 \text{ mL/kg PBW}$</td>
</tr>
<tr>
<td>PEEP $\leq 2 \text{ cmH}_2\text{O}$</td>
<td>FIO$_2$/low PEEP table$^{122}$ to $</td>
</tr>
<tr>
<td>FIO$_2$ $\geq 0.4$ to SpO$_2$ $\geq 92%$</td>
<td>PaO$_2$ $= 55 \text{ - } 80 \text{ mmHg}$ or $</td>
</tr>
<tr>
<td>RR to $P_{ET}CO_2$ $35 \text{ - } 45 \text{ mmHg}$</td>
<td>SpO$_2$ $= 88 \text{ - } 95%$</td>
</tr>
<tr>
<td>No recruitment maneuvers</td>
<td>RR $\leq 35$ to pH$_a = 7.30 \text{ - } 7.45$</td>
</tr>
</tbody>
</table>

**Further settings**

| If SpO$_2 < 92\%$ set FIO$_2$/PEEP: $| 
| 0.5/2; 0.6/2; 0.6/3; 0.6/4; 0.6/5; $| 
| 0.7/5; 0.8/5; 0.8/6$ (as sequence) | Reduce $V_t$ up to $4 \text{ mL/kg PBW}$ to Pplat $\leq 30 \text{ cmH}_2\text{O}$ |
| consider single recruitment maneuver with stepwise $V_t$ increase$^8$ if SpO$_2 < 92\%$ | High PEEP table$^{125}$ in severe ARDS |
| consider maximal recruitment maneuver$^{125}$ if PaO$_2 < 55 \text{ mmHg}$ | $|$
Despite convincing evidence that PEEP and recruitment manoeuvres do not confer further protection, and may even impair hemodynamics during a ventilatory strategy based on low tidal volumes in open abdominal surgery, we do not know whether patients with obesity or undergoing one lung anesthesia procedures may benefit from those interventions. Also, we cannot rule out the possibility that an individual PEEP titration targeted on lung function could yield different results. Furthermore, it remains unclear how postoperative atelectasis, the most frequent of the different PPCs, influences the development of pulmonary infections, severe respiratory failure and affects other relevant outcome measures, including hospital length of stay and mortality. In addition, further studies should shed light on the potential contributions of ventilatory strategies during induction and emergence of anesthesia, as well as in the postoperative period (e.g. non-invasive ventilation). Accordingly, the potential of perioperative non-ventilatory measures (e.g. muscle paralysis, use of short-acting neuromuscular blocking agents as well as monitoring and reversal of muscle paralysis, early mobilization, and respiratory therapy etc.) for reducing PPCs should be investigated. Such studies are necessary to support future guidelines on the practice of perioperative mechanical ventilation and adjunctive measures in a broad spectrum of patients as well as surgical interventions, both open and laparoscopic.

Conclusions

The potential of intraoperative lung protective mechanical ventilation to reduce the incidence of PPCs is well established. RCTs have suggested that low tidal volumes, high PEEP and recruitment manoeuvres may be protective intraoperatively, but the precise role of each single intervention has been less clearly defined. A metaanalysis taking the utmost recent clinical data shows that the use of low tidal volumes, rather than PEEP, recruitment manoeuvres, or a combination of these two, is the most important determinant of protection in intraoperative mechanical ventilation. In non-obese patients without ARDS undergoing open abdominal surgery, mechanical ventilation should be performed with low tidal volumes (approximately 6 to 8 mL/kg) combined with low PEEP, since the use of higher PEEP combined with recruitment manoeuvres does not confer further protection against PPCs and can deteriorate the hemodynamics. If hypoxemia develops, and provided that other causes have been excluded, for example, hypotension, hypoventilation, pulmonary embolism etc., the FiO₂ should be increased first, followed by increase of PEEP, and recruitment manoeuvres based on stepwise increase of tidal volume during regular mechanical ventilation. Further studies are warranted to guide intraoperative mechanical ventilation in a broader spectrum of patients and surgical interventions.
Figure Legends

Figure 1. Alterations of the extracellular matrix in lungs during mechanical ventilation and fluid administration. CS-PG, condroitin sulphate proteoglycans; HS-PG, heparan sulphate proteoglycans; ICs, inflammatory cells; IMs, inflammatory mediators; MMPs, metalloproteases; MV, mechanical ventilation; Pi, interstitial pressure; SB, spontaneous breathing; W/D, wet/dry ratio.

Figure 2. Magnetic resonance imaging (MRI) scans of lungs of three patients before and on the first day after open abdominal surgery. Images were obtained throughout spontaneous breathing and represent an average of total lung volume (TLV) during the breath cycles. Panel A – minor atelectasis; Panel B – major atelectasis; Panel C – pleural effusion. Segmentation of lungs, atelectasis (red lines) and pleura effusion (blue lines) in MRI scans was performed manually. Values were calculated for whole lungs. Note that the amounts of atelectasis and pleura effusion, two common postoperative pulmonary complications are relatively low after surgery. L, left side of chest; MRI, magnetic resonance imaging; PreOP, preoperative; PostOP, postoperative; R, right side of chest; TLV, total lung volume.

Figure 3. Effects of high and low tidal volumes (VT) at end-inspiration and end-expiration with low and high PEEP during general anesthesia. Atelectatic lung regions (red), overinflated lung regions (blue), normally aerated lung regions (white). During ventilation with low tidal volume and low PEEP, higher amounts of atelectasis are present at end-expiration and end-inspiration with minimal areas of overinflation; During ventilation with high tidal volume and low PEEP, less atelectasis is present at end-expiration and end inspiration, with increased areas of overinflation at end-inspiration. Furthermore, a higher amount of tissue collapsing and de-collapsing during breathing is present. During ventilation with low tidal volume and higher PEEP, less atelectasis is present. However, higher overinflation occurs at end-inspiration and end-expiration, with minimal collapse and reopening during breathing cycling. PEEP, positive end-expiratory pressure; VT, tidal volume.

Figure 4. Illustrative fluctuation of airway pressure during three types of lung recruitment manoeuvres for intraoperative mechanical ventilation (red lines); Panel A, “Bag squeezing” using the airway pressure-limiting valve of the anesthesia machine. The airway pressure is difficult to control, possibly resulting in overpressure, with the risk of barotrauma, or values lower than the closing pressure of small airways when controlled mechanical ventilation is resumed, with consequent lung derecruitment; Panel B, “Stepwise increase of tidal volume” during volume-controlled ventilation. PEEP is set at 12 cmH2O, the respiratory frequency at 6 to 8 breaths/min, and tidal volume increased from 8 mL/kg in steps of 4 mL/kg until the target opening pressure (e.g. 30-40 cmH2O) is achieved. After three to five breaths at that pressure, the PEEP is kept at 12 cmH2O, tidal volume reduced to 6 to 8 mL/kg, and the respiratory frequency adjusted to normocapnia; Panel C, Stepwise increase of PEEP at a constant driving pressure of 15 to 20 cmH2O in pressure-controlled ventilation. The PEEP is increased in steps of 5 cmH2O (30 to 60 s per step) up to 20 cmH2O. After three to five breaths at a PEEP level that allows achieving the target inspiratory pressure, PEEP and tidal volume are adjusted to the respective desired levels. PEEP, positive end-expiratory pressure.
Figure 5. Odds ratios for postoperative pulmonary complications of “protective” versus “non-protective” ventilation in trials comparing different tidal volumes,85,109,113 different tidal volumes and positive end-expiratory pressure (PEEP),110,112,114 and different levels of PEEP.86

Figure 6. Settings of VT (Panel A) and PEEP (Panel B) according to observational studies of mechanical ventilation in the operation room (in Canada,128 France,129 and the USA3,75,130); settings of VT (Panel C) and PEEP (Panel D) in “non–protective” ventilation (red) and “protective” ventilation (blue) groups in four recent randomized controlled trials (Severgnini et al.,111 IMPROVE,110 Ge et al.,114 and PROVHILO86). PBW, predicted body weight; PEEP, positive end-expiratory pressure; VT, tidal volume.

Figure 7. Proposed settings of protective mechanical ventilation in non-obese patients during open abdominal surgery according to the concept of intraoperative permissive atelectasis. ARDS, acute respiratory distress syndrome; FIO2, inspiratory oxygen fraction of oxygen; PBW, predicted body weight; PEEP, positive end-expiratory pressure; Pplat, inspiratory airway plateau pressure; SpO2, peripheral oxygen saturation; RR, respiratory rate; VT, tidal volume.
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Review intraoperative protective ventilation

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