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Pulmonary Atelectasis in General Anaesthesia

*Clinical Studies on the Counteracting Effects of
Positive End-Expiratory Pressure*

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Abstract

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Partial lung collapse, i.e., pulmonary atelectasis, is common during general anaesthesia. The main causal mechanism is reduced lung volume with airway closure and subsequent gas absorption from preoxygenated alveoli. Atelectasis impairs oxygenation and forms the pathophysiological basis for postoperative pulmonary complications. Positive end-expiratory pressure (PEEP) counteracts the loss in lung volume, but its role in preventing atelectasis during anaesthesia is not clear.

All studies included in this thesis were prospective randomized clinical trials. In the first study, oxygenation was used as a surrogate measure of atelectasis in obese patients undergoing laparoscopic gastric bypass. The subsequent studies used single-slice computed tomography (CT) to evaluate atelectasis in healthy patients undergoing non-abdominal surgery.

Paper I: We studied the use of continuous positive airway pressure (CPAP) and PEEP during induction of anaesthesia and a reduced inspired oxygen fraction (FiO_2) during emergence. Oxygenation was maintained in the group that received CPAP during induction, followed by a PEEP of 10 cmH_2O . Postoperative oxygenation was impaired in the group that received a high FiO_2 during emergence.

Paper II: An early oxygen washout manoeuvre to quickly restore nitrogen levels and thus stabilize the alveoli, had no effect on atelectasis at the end of surgery. Both study groups exhibited small atelectasis after being ventilated with a moderate PEEP of 6-8 cmH_2O during anaesthesia.

Paper III: The effect of PEEP versus zero PEEP on atelectasis formation and oxygenation at the end of surgery was compared. The PEEP group maintained oxygenation better and exhibited less atelectasis than the zero-PEEP group, with atelectasis involving a median 1.8% of total lung area compared with 4.6% in the zero-PEEP group ($P = 0.002$).

Paper IV: Postoperative atelectasis was compared between a group in which PEEP was maintained during emergence preoxygenation with FiO_2 1.0 and a group in which PEEP was withdrawn just before the start of emergence preoxygenation with FiO_2 1.0. The two groups had small atelectasis when fully awake at 30 min after extubation, with no statistically significant difference between them.

In conclusion, preserved end-expiratory lung volume is the key to avoiding atelectasis, in particular when an increased oxygen reserve is required during airway manipulation. PEEP is both necessary and sufficient to minimize atelectasis in healthy patients undergoing non-abdominal surgery.

Keywords: General anaesthesia, pulmonary atelectasis, positive end-expiratory pressure, oxygen, computed tomography, continuous positive airway pressure, mechanical ventilation

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*Till min mamma Kristina
och pappa Kjell*

*Do, or do not. There
is no try.*

– Master Yoda

List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

- I. Edmark L, **Östberg E**, Scheer H, Wallquist W, Hedenstierna G, Zetterström H: Preserved oxygenation in obese patients receiving protective ventilation during laparoscopic surgery: a randomized controlled study. *Acta Anaesthesiol Scand* 2016; 60:26–35
- II. **Östberg E**, Auner U, Enlund M, Zetterström H, Edmark L: Minimizing atelectasis formation during general anaesthesia – oxygen washout is a non-essential supplement to PEEP. *Ups J Med Sci* 2017; 122:92–8
- III. **Östberg E**, Thorisson A, Enlund M, Zetterström H, Hedenstierna G, Edmark L: Positive end-expiratory pressure alone minimizes atelectasis formation in nonabdominal surgery: A randomized controlled trial. *Anesthesiology* 2018; 128:1117–24
- IV. **Östberg E**, Thorisson A, Enlund M, Zetterström H, Hedenstierna G, Edmark L: Positive end-expiratory pressure and postoperative atelectasis: A randomized controlled trial. *In press, Anesthesiology* 2019

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Abbreviations

ARDS	Acute respiratory distress syndrome
ASA	American Society of Anesthesiologists physical status
BMI	Body mass index
CI	Confidence interval
CPAP	Continuous positive airway pressure
CT	Computed tomography
EELV	End-expiratory lung volume
ETCO ₂	End-tidal carbon dioxide concentration
ETO ₂	End-tidal oxygen concentration
EVA	Estimated venous admixture
FIO ₂	Inspired oxygen fraction
FRC	Functional residual capacity
HPV	Hypoxic pulmonary vasoconstriction
HU	Hounsfield units
IBW	Ideal body weight
IQR	Interquartile range
PaCO ₂	Arterial carbon dioxide partial pressure
PaO ₂	Arterial oxygen partial pressure
PaO ₂ /FIO ₂	Ratio of the arterial oxygen partial pressure to the inspired oxygen fraction
PACU	Post-anaesthesia care unit
PEEP	Positive end-expiratory pressure
PETCO ₂	End-tidal carbon dioxide pressure
PPC	Postoperative pulmonary complication
RM	Recruitment manoeuvre

SaO ₂	Arterial oxygen saturation
SD	Standard deviation
SpO ₂	Peripheral oxygen saturation
TCI	Target-controlled infusion
\dot{V}_A/\dot{Q}	Alveolar ventilation to lung perfusion ratio
VILI	Ventilator-induced lung injury
ZEEP	Zero end-expiratory pressure

Introduction

Pulmonary atelectasis

During induction of anaesthesia, patients routinely breathe 100% oxygen as a safety measure in case of unexpected airway or ventilation difficulties.¹⁻³ The supine position, together with a loss in respiratory muscle tone caused by the anaesthesia, results in a reduction in the pulmonary resting volume (end-expiratory lung volume, EELV)⁴ and closure of small airways.⁵⁻⁸ Behind these closed airways, oxygen-rich alveolar gas is continuously absorbed by the pulmonary circulation, until the alveoli collapse.^{9,10} This phenomenon is termed absorption atelectasis, and is the mechanism behind the observation that 90% of patients develop atelectasis in dependent lung regions shortly after induction of anaesthesia.^{9,11-14} Atelectasis contributes to impaired oxygenation,^{15,16} and plays an important role in the pathophysiology behind the development of other postoperative pulmonary complications (PPCs).¹⁷⁻²⁰ Such complications, including oxygenation difficulties and pneumonia, are more common than postoperative cardiac complications and are associated with a prolonged hospital stay and increased health-care costs as well as with increased morbidity and mortality.²¹⁻²⁷ Although PPCs occur most frequently in high-risk patients undergoing thoracic or major abdominal surgery, the risks cannot be ignored in the large population of healthy patients undergoing other types of surgery. In a recent large international observational study, the risk of developing a severe PPC for low-risk patients undergoing various surgical procedures was 1.6%.²⁵ With an estimated number of over 230 million surgeries being performed globally every year,²⁸ and a large proportion of these being performed on relatively healthy patients undergoing non-major surgery, even a small reduction in the overall complications for this group will involve a large number of individuals.

Protective ventilation and positive end-expiratory pressure

Alongside atelectasis, mechanical ventilation *per se* can cause injury to the lungs.²⁹ During spontaneous breathing, downward movement of the diaphragm combined with contraction of the rib muscles results in a negative

intrathoracic pressure that sucks air into the lungs. In contrast, during mechanical ventilation, gas is being forced into the lungs by a positive pressure. Although the result, i.e., air entering the lungs, might seem to be the same, from a physiological point of view these two modes of ventilation are entirely different entities.³⁰ Ever since the polio epidemic in the 1950s resulted in the dawn of widely used ventilation support, it has been known that positive pressure ventilation by any of several mechanisms can be harmful.^{31,32} Paradoxically, along with enabling essential life support, mechanical ventilation can thus induce or worsen lung injury. A modern term for this is ventilator-induced lung injury (VILI), which refers to the damage to the lungs caused by high inflation pressures (barotrauma) and over-inflation (volutrauma).^{33,34} A third mechanism, termed atelectrauma has also been identified, which is the result of the cyclic opening and closing of minor airways.^{35–38} All three mechanisms cause injury to alveolar epithelial cells and vascular endothelial cells and may induce inflammation.^{39,40}

In 1963, Bendixen et al. demonstrated improved oxygenation in anaesthetized patients after periodic hyperinflation of the lungs.⁴¹ They concluded that pulmonary atelectasis is common during anaesthesia, and that it leads to venous admixture by shunting. Their recommendation to use large tidal volumes during mechanical ventilation was adopted to prevent this. Of note, the authors also mentioned an alternative way of counteracting atelectasis by “increased resistance to expiration”, although this was only used experimentally at that time.^{42,43} The routine use of large tidal volumes was later questioned, and practice started to change after two studies showing that ventilation with lower tidal volumes and positive end-expiratory pressure (PEEP) increased survival among patients with acute respiratory distress syndrome (ARDS).^{44,45} Subsequent studies indicated that critically ill patients without ARDS also benefitted from so-called lung-protective strategies.^{46–50} The term ‘protective ventilation’ was later attached to a strategy of combining low tidal volumes, PEEP, and recruitment manoeuvres (RMs).

Following these findings in the intensive-care setting, lung-protective strategies started to influence the nature of routine mechanical ventilation during anaesthesia.^{51,52} In contrast to the lungs of patients being treated in the intensive-care unit, in the operating theatre and during general anaesthesia, it is usually healthy lungs that are being ventilated, and for a shorter period. Therefore, efforts to deliver a protective ventilation strategy might be less important. However, evidence is accumulating that these patients may also benefit from a protective approach, especially the use of low tidal volumes.^{53–58} Unfortunately, large studies on protective ventilation in this setting have produced conflicting results.^{59–62} This may in part be explained by different definitions of PPCs and differences in study populations, together with differences re-

garding levels of PEEP, tidal volumes, and timing of RMs. Another explanation may be that in studies where an intervention group receives a ventilation concept, that includes several interventions, it might be difficult to draw conclusions about which, if any, of the different interventions have an effect on the chosen outcome.^{63,64}

RMs, i.e., hyperinflation of the lungs, have been used as one component of lung-protective ventilation during anaesthesia.^{65,66} However, high peak inspiratory pressures are needed to fully expand collapsed lung tissue, also in healthy lungs.⁶⁷ Hemodynamic compromise is a common adverse effect^{68,69} and pulmonary barotrauma has been reported.⁷⁰ It is not clarified which patients that benefit from RMs, although some authors have advocated for their routine use during anaesthesia.^{71,72}

Thus, although mechanical ventilation remains a cornerstone of the anaesthetic care of most patients undergoing surgery, robust evidence-based recommendations on how to perform it are still lacking. Furthermore, the diversity among patients needing anaesthesia is a particular challenge to clinicians. It is possible to identify distinct patient groups with characteristics who might exhibit specific risks/needs; for example, obese patients undergoing laparoscopic gastric bypass and patients undergoing major open abdominal surgery.^{73,74} Another large subgroup is healthy patients undergoing low-risk surgery procedures. A protective ventilation profile with, for example, repeated RMs might be beneficial in the first two groups, but useless or even harmful in the last group.

The same uncertainty applies to the specific use of PEEP.⁷⁵⁻⁷⁷ It has been shown that PEEP can improve oxygenation⁷⁸ by counteracting airway closure and restoring or increasing EELV in anaesthetized patients.⁷⁹ A few studies have also demonstrated that PEEP might prevent atelectasis formation.^{80,81} However, although PEEP has been used for decades, it has predominantly been in the intensive-care setting during mechanical ventilation in a variety of pathological situations, most importantly ARDS.⁸² In intensive care, it is now considered an integral part of a protective ventilation strategy. Nonetheless, its precise role during anaesthesia, and more specifically its effect on atelectasis prevention in healthy patients undergoing elective surgery, remains uncertain. Thus, the recommended level of PEEP, or even whether it should be used at all during general anaesthesia, remains controversial.^{18,75,83}

This thesis has its focus on PEEP. The alveolar oxygen concentration and hence the inspired oxygen fraction (FIO₂) is invariably a crucial factor in atelectasis formation. Therefore, the overall aim was to improve knowledge

about the effects of PEEP and its interaction with FIO_2 in influencing atelectasis formation and venous admixture during general anaesthesia in adult patients.

Aims of the studies

Paper I – to study the effects of continuous positive airway pressure (CPAP) followed by PEEP during preoxygenation and induction of anaesthesia on perioperative oxygenation in obese patients undergoing laparoscopic gastric bypass. A secondary aim was to study the effects of low oxygen concentration during emergence on postoperative oxygenation in the same patient group.

Paper II – to investigate whether an immediate restoration of a low oxygen content after preoxygenation and intubation would limit atelectasis formation as analysed by computed tomography (CT) at the end of surgery.

Paper III – to test the hypothesis that PEEP as a single intervention would be sufficient to minimize atelectasis formation and thus maintain oxygenation in healthy lungs during non-abdominal surgery.

Paper IV – to study emergence from anaesthesia and test the hypothesis that withdrawing PEEP prior to emergence preoxygenation would reduce postoperative atelectasis formation.

Materials and methods

Paper I

This was a randomized controlled trial undertaken at Västerås Hospital from March 2012 until March 2014. The primary outcome measure was oxygenation calculated as the estimated venous admixture (EVA).

Study population

Forty patients scheduled for laparoscopic gastric bypass under general anaesthesia were included. Inclusion criteria were body mass index (BMI) greater than 35 kg/m², American Society of Anesthesiologists (ASA) physical status I or II, and age 24–49 years. We excluded patients with an anticipated difficult airway, smokers, and patients with BMI greater than or equal to 50 kg/m² or any history of significant ischaemic heart disease or respiratory disease (chronic obstructive pulmonary disease or non-optimally treated asthma).

Anaesthesia and monitoring

We used standard anaesthesia monitoring in addition to an indwelling arterial catheter for invasive blood pressure monitoring and arterial blood gas sampling. The Datex-Ohmeda S/5 Avance (GE Healthcare, USA) was used for ventilation together with a side-stream adapter for registration of ventilatory parameters and gas concentrations.

All patients were preoxygenated supine and in a 20 to 30-degree head-up tilt with an FIO₂ of 1.0 for 3 min. For patients in the intervention group (A), we used a CPAP of 10 cmH₂O during preoxygenation and induction. Target-controlled infusions (TCIs) of propofol and remifentanyl were used for induction of anaesthesia. Tracheal intubation was facilitated by rocuronium. Thereafter, all patients were ventilated with an FIO₂ of 0.4, a tidal volume of 7 ml/kg ideal body weight (IBW), and a PEEP of 10 cmH₂O. End-tidal carbon dioxide concentration (ETCO₂) was kept between 4.5 and 5.5 kPa by adjusting the respiratory frequency. Anaesthesia was maintained with remifentanyl (TCI) and sevoflurane. During emergence, the intervention group was divided into two groups with different FIO₂; patients in group A₁ were given an FIO₂ of 0.31

whereas patients in group A₂ were ventilated with a standard FIO₂ of 1.0, similar to the control group (C).

Arterial blood gases and estimation of venous admixture

All samples were obtained with the patients breathing air and in a 20 to 30-degree head-up tilt. The first blood sample, T₁, was drawn before induction. Samples T₂ and T₃ were taken during anaesthesia, and before and after capnoperitoneum, respectively. Sample T₄ was obtained one hour after extubation.

Since mixed venous blood was not collected, we calculated an estimated venous admixture (EVA), using the assumption that the arterio-venous oxygen content difference was 40 ml/l.

Paper II

This randomized controlled, evaluator-blinded study was undertaken between September 2014 and May 2015 at Köping Hospital. The primary outcome measure was atelectasis area at the end of surgery.

Study population

We included 24 patients scheduled for orthopaedic day surgery. The inclusion criteria were ASA physical status I and II, age 40–75 years, and BMI less than 30 kg/m². Patients with any significant respiratory or ischaemic heart disease were excluded, as were those with an anticipated difficult airway. Active smokers and ex-smokers with a history of more than six pack-years were also excluded, because a previous study indicated increased atelectasis among this group.⁸⁴

Anaesthesia and monitoring

In addition to standard anaesthesia monitoring, we measured blood pressure invasively using an arterial catheter placed in the radial artery. All patients were preoxygenated with FIO₂ 1.0 for 3 min. TCIs with propofol and remifentanyl were used to induce and maintain anaesthesia, and a single dose of rocuronium was administered during induction to facilitate tracheal intubation. The patients were ventilated using the Datex-Ohmeda S/5 Avance (GE Healthcare) with an FIO₂ of 0.30–0.35. Tidal volumes were set to 7 ml/kg IBW and PEEP to 6 cmH₂O, or 8 cmH₂O in the case of BMI greater than or equal to 25 kg/m². The respiratory rate was set to 9–11 per min to maintain an ETCO₂ of approximately 5 kPa. Mean arterial blood pressure was maintained above

60 mmHg throughout anaesthesia, using small doses of phenylephrine or ephedrine as required.

Intervention

As soon as correct positioning of the endotracheal tube was confirmed, the control group was ventilated using the settings described above. The intervention group first received an oxygen washout manoeuvre consisting of a pre-set volume-controlled ventilation. We used (1) a high fresh gas flow of 10 l/min; (2) a low oxygen content, i.e., air; (3) large tidal volumes of 15 ml/kg IBW; (4) PEEP 10 cmH₂O; and (5) a respiratory rate of 10 breaths/min. The manoeuvre was considered sufficient and complete when the end-tidal oxygen concentration (ET_{O₂}) had decreased to 25%. Thereafter, the patients in the intervention group were ventilated using the same settings as the control group.

Computed tomography

At the end of surgery, the endotracheal tube was clamped at end-expiration, and the ventilator was changed to a portable Vivo 50 (Breas Medical AB, Sweden), maintaining the same ventilator settings. A CT scan was obtained in the Radiology Department using a GE LightSpeed VCT XTe machine (GE Healthcare). With the patient in a supine position, we first obtained a frontal scout view at end-expiration. Thereafter, a single-slice transverse scan was performed, also at end-expiration (Fig. 1). A cursor was carefully positioned as basally as possible to achieve a single-slice scan approximately 5 mm above the right diaphragm dome.

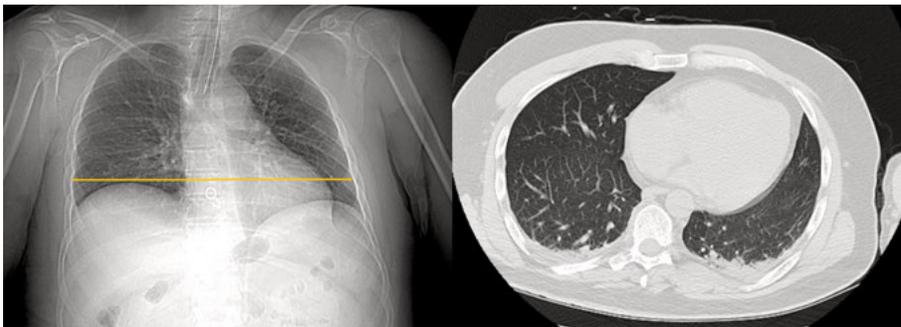


Figure 1. Computed tomography images of one of the participating patients during anaesthesia. Frontal scout view (left) with cursor positioned approximately 5 mm above the right diaphragm dome. Basal axial scan with atelectasis visible in dorsal lung regions (right), in this case corresponding to 4.1% of total lung area.

The total lung area was measured by delineating the contours of both lungs. The atelectasis area was then carefully outlined posteriorly but with some margin ventrally beyond the lung parenchyma haziness, using a separate region of interest (ROI) technique (Fig. 2).

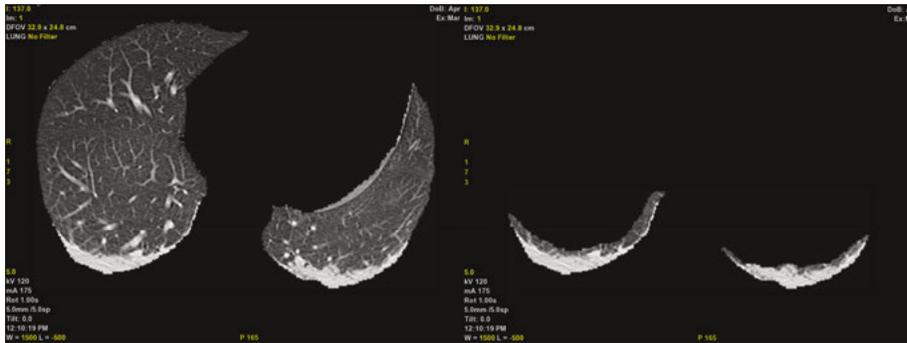


Figure 2. Computed tomography measurements performed with the AW server software, in the same patient as in Figure 1. Region of interest (ROI) outlined for total lung area (left) and separate ROI outlined for the atelectasis area with some margin (right).

Workstation software (AW Server, GE Healthcare) was used to calculate the actual area of atelectasis, which was defined as -100 to +100 Hounsfield units (HU)¹³ (Fig. 3). The assessments were all performed by the same radiologist, who was blinded to the group assignment.

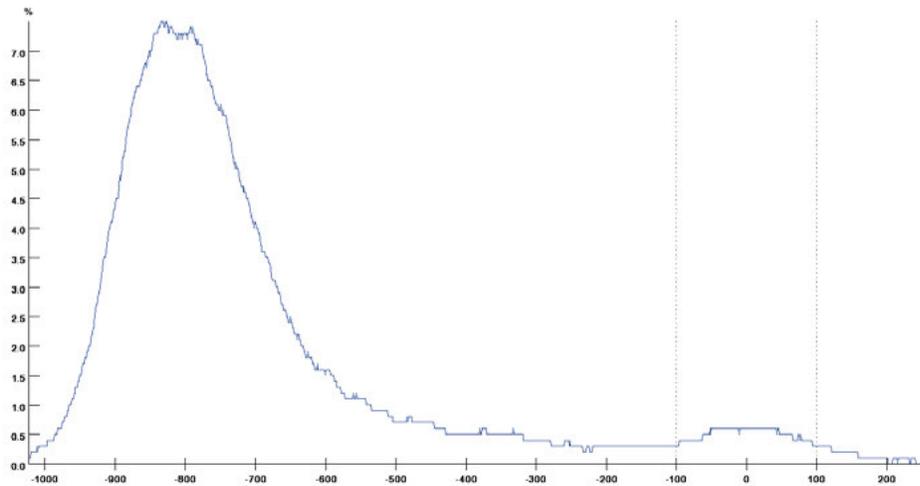


Figure 3. Histogram of the atelectasis region of interest performed using the AW server software, for the same patient as shown in Figures 1 and 2. The area of atelectasis was defined as -100 to +100 Hounsfield units (x-axis).

Arterial blood gases and estimation of venous admixture

The blood-gas samples were obtained with the patients in a 15 to 20-degree head-up tilt. The first sample was drawn when the patients were breathing room air, before anaesthesia. The second sample was drawn during anaesthesia after the completion of surgery and with the patient still being ventilated with an FIO_2 of 0.30–0.35.

We estimated oxygenation by calculating EVA, with the assumption that the arterio-venous oxygen content difference was 40 ml/l.

Paper III

This randomized controlled trial investigated the effect of continuous PEEP on atelectasis formation during anaesthesia. The study was undertaken at Köping Hospital between November 2015 and October 2016. The primary outcome measure was atelectasis area at the end of surgery.

Study population

Twenty-four patients scheduled for non-abdominal day surgery were included in the study. Inclusion criteria were ASA physical status I and II, age 40–75 years and BMI less than 30 kg/m². Patients with any significant respiratory or ischaemic heart disease were excluded, as were those with an anticipated difficult airway. Active smokers and ex-smokers with a history of more than six pack-years were also excluded.

Anaesthesia and monitoring

In addition to standard anaesthesia monitoring, we used an indwelling catheter in the radial artery to measure blood pressure. All patients received standard preoxygenation with FIO_2 1.0 for 3 min. Induction and maintenance of anaesthesia were performed with TCI of propofol and remifentanyl. A single dose of rocuronium was used to facilitate tracheal intubation. The study subjects were ventilated using the portable Vivo 50 (Breas Medical AB) in a volume-controlled mode with an FIO_2 of 0.30–0.35. Tidal volumes were set to 7 ml/kg IBW and the respiratory rate to 10 breaths/min and further adjusted to maintain ETCO_2 at approximately 5 kPa. The intervention group received PEEP 7 cmH₂O or 9 cmH₂O for patients with a BMI greater than or equal to 25 kg/m², whereas the control group received zero PEEP (ZEEP). RMs were not used in either group.

Computed tomography

After completion of surgery and while still anaesthetized, the patients were transported to the Radiology Department. This could be done without disconnecting or changing the ventilator settings, since a portable ventilator was used for mechanical ventilation during surgery. CT scanning, analysis, and calculation of atelectasis area were performed in the same way as in study II, by a radiologist who was blinded to the group assignment and patient outcome.

Arterial blood gases and oxygenation

The blood gas samples were drawn from the arterial line with the patients in a 15 to 20-degree head-up tilt. The first sample was obtained before anaesthesia when the patients were breathing room air. The second and third samples were collected midway through surgery and at the end of surgery with an FIO_2 of 0.30–0.35. Oxygenation was estimated by calculating the ratio of the arterial oxygen partial pressure to the inspired oxygen fraction ($\text{PaO}_2/\text{FIO}_2$ ratio).

Paper IV

This was a randomized controlled trial investigating the effects of PEEP versus ZEEP during awakening from anaesthesia. The study was undertaken between December 2017 and August 2018 at Köping Hospital. The primary outcome measure was the change in atelectasis from before awakening to after extubation.

Study population

In total, 30 patients undergoing elective hernia repair or orthopaedic day surgery participated. The included study subjects were 40–75 years old and were considered ASA class I or II. Exclusion criteria were BMI greater than or equal to 30 kg/m^2 , any significant respiratory or ischaemic heart disease, and patients being active smokers or ex-smokers with a history of more than six pack-years.

Anaesthesia and monitoring

Standard anaesthesia monitoring was supplemented with invasive blood pressure measurements via an arterial catheter placed in the radial artery. Routine preoxygenation with a slight head-up tilt and FIO_2 1.0 for 3 min was followed by induction of anaesthesia with TCI of propofol and remifentanyl and a single dose of rocuronium. Mechanical ventilation was performed with the portable Hamilton-T1 ventilator (Hamilton Medical, Switzerland). During surgery, the

ventilator settings were the same for both groups: FIO_2 0.35, tidal volume 7 ml/kg IBW, and PEEP 7 or 9 cmH_2O , with the higher setting in patients whose BMI was greater than or equal to 25 kg/m^2 . The respiratory frequency was set to 10 breaths/min and adjusted to maintain ETCO_2 at approximately 5 kPa. RMs were not used.

Computed tomography and emergence from anaesthesia

After completed surgery, the patients, still anaesthetized, were transported to the Radiology Department. A baseline CT scan was obtained using either the GE LightSpeed VCT XTe (GE Healthcare) or the Toshiba Aquilion PRIME (Canon Medical Systems, USA). In the control group, PEEP was maintained during emergence preoxygenation with FIO_2 1.0 and subsequent awakening. In the intervention group, PEEP was withdrawn and set to zero (ZEEP) while FIO_2 was still 0.35. The lungs were assumed to have achieved a new steady state EELV at ZEEP after 2 min,⁸⁵ and thereafter emergence preoxygenation was started with FIO_2 1.0 as for the control group. Extubation was undertaken in the post-anaesthesia care unit (PACU). Approximately 30 min after extubation, the patients were transported back to the Radiology Department for a second CT scan. This scanning was also done at end-expiration but with all study subjects fully awake and breathing room air. Calculation of atelectasis area was performed as described for studies II and III by a radiologist blinded to the study group assignment.

Arterial blood gases and oxygenation

A baseline blood gas sample was drawn from the arterial line in the awake state when the patients were still breathing room air. The second blood gas was obtained at the end of surgery during mechanical ventilation with PEEP and FIO_2 0.35. The third sample was drawn approximately 40 min after extubation, with all subjects again breathing room air. We estimated oxygenation by calculating the ratio of the arterial oxygen partial pressure to the inspired oxygen fraction ($\text{PaO}_2/\text{FIO}_2$ ratio).

Statistical analysis

All four studies were preceded by power calculations to assess the number of study subjects needed to detect a clinically significant reduction in the primary outcome measure. For study I, this meant a difference in arterial oxygen saturation (SaO₂) of 2 percentage units between groups. For the remaining studies, it implied either a reduction in atelectasis area of 50% (studies II and III) or a 50% reduction in the increase in atelectasis area (study IV) compared with the respective control group.

In general, we did not assume that the data were normally distributed. Therefore, we used the Mann-Whitney U-test for comparisons between groups. Related samples within each group were analysed with the Wilcoxon signed-rank test. For all tests, a two-sided *P* value of less than 0.05 was considered significant, unless Bonferroni corrections were made for multiple comparisons. The 95% confidence intervals for the difference in medians were calculated with the Hodges-Lehmann estimator (study I) or derived by the percentile bootstrap method (studies III–IV). A post hoc sensitivity analysis to the primary outcome analysis was performed in study IV using a linear regression model after log transformation of data, with inclusion of the baseline atelectasis area as a covariate in the model. Statistical analyses were performed with IBM SPSS Statistics versions 20, 22, and 24 (IBM Corporation, USA) and R versions 3.4.2 and 3.5.1 (www.r-project.org).

Ethics

The four studies were approved by the Regional Ethics Committee in Uppsala and pre-registered at [ClinicalTrials.gov](https://www.clinicaltrials.gov). The study protocols were also approved by the local Radiation Safety Committee before commencement.

CT scanning was included in the protocols for studies II–IV. The trade-off between possible study benefits and radiation exposure of the study participants was carefully considered for each study. Full spiral CT scans of the thorax were not performed. Instead, each CT scan was limited to an initial scout and then a basal single-slice transverse scan. The total radiation dose received by each study participant was measured to be 0.3 mSv in studies II and III, and 0.6 mSv in study IV, which included two CT scans (CTDosimetry, [Impactscan.org](https://www.impactscan.org)). A full thoracic CT scan is typically 5 mSv. For comparison, the natural background radiation in Sweden is measured to be 1.5 mSv/year. The annual average radiation dose received by the Swedish population, including medical examinations, is estimated to be 2.4 mSv/person (Swedish Radiation Safety Authority 2007). Moreover, most of the previously published studies using CT have used two or more slices, resulting in a higher radiation dose than in the studies included here.

The CT studies involved transportation of anaesthetized patients from the operating room to the Radiology Department, and after scanning was completed, to the PACU. The studies were performed at Köping Hospital, where the Radiology Department is located in the same building as the operating theatres but three floors below, with an elevator directly connecting the two units. During transportation and CT, the patients were monitored and closely supervised by two consultant anaesthetists and one certified registered nurse anaesthetist. No complications related to transportation occurred during the studies.

Participation in studies II–IV prolonged the patient's anaesthesia by approximately 15 min. This fact, together with information regarding CT scanning and transportation, was explicitly communicated to the Regional Ethics Committee and included in the written and oral information given to all participants.

Results and discussion

Paper I

All 40 included patients completed the study and all data were analysed. No complications were recorded. Baseline characteristics and physiological data were similar between groups, except for a lower median BMI and a greater proportion of men in the control group. There were no intergroup differences regarding ventilation or haemodynamic data during the anaesthesia.

At 5 min after intubation (T_2), EVA was lower in the intervention group (A) compared with the control group (C) (Table 1). The difference in medians was -5.0% (95% CI, -9.4 to -1.1%), $P = 0.048$.

At the end of surgery and before extubation (T_3), EVA was unaltered in the intervention group. Oxygenation had improved in the control group as illustrated by a lower EVA, and at this time point there was no longer any difference between the groups.

One hour after emergence and extubation (T_4), EVA had increased in the 30 patients given an FI_{O_2} of 1.0. The group given an FI_{O_2} of 0.31 during emergence (A_1) maintained their oxygenation as illustrated by an unaltered EVA compared with before emergence.

Table 1. Oxygenation data expressed as estimated venous admixture (% of cardiac output) in the study groups, paper I.

	Group A (n = 20)		Group C (n = 20)	P value
Preoperative (T₁)	8.4 (2.5–11.4)		8.2 (6.5–12.6)	0.49
Perioperative (T₂)	8.2 (5.5–11.0)		13.2 (7.3–19.5)	0.048*
Perioperative (T₃)	8.4 (5.5–10.5)		9.9 (4.4–13.4)	0.36
Postoperative (T₄)	Group A₁ (n = 10)	Group A₂ (n = 10)	Group C (n = 20)	
	8.3 (4.0–11.5)	12.6 (8.5–22.1)†	14.2 (5.4–20.0)‡	

Values are the median (interquartile range). *Mann-Whitney *U*-test comparing group C with group A. †*P* = 0.012 comparing group A₂ with the same patients at T₃, Wilcoxon signed-rank test. ‡*P* = 0.048 comparing group C with the same group at T₃, Wilcoxon signed-rank test.

The results are in accordance with previous similar studies, suggesting that the use of CPAP/PEEP during preoxygenation and induction of anaesthesia is beneficial in terms of oxygenation in obese patients.^{86,87} The fact that the control group improved its oxygenation from the time point immediately after intubation to the time point after surgery, before emergence, was somewhat surprising. This may partly be explained by an augmented hypoxic pulmonary vasoconstriction (HPV) and consequently less venous admixture from areas with alveolar collapse. An increased HPV in this setting may be mediated by an increased arterial partial pressure of carbon dioxide (PaCO₂) during capnoperitoneum.⁸⁸ However, an alternative explanation for the improved oxygenation might be that the PEEP used during surgery managed to recruit some collapsed lung units. This has previously been observed with PEEP 10 cmH₂O in non-obese patients.^{12,15} Such an effect would be more noticeable in the control group, since this group likely developed larger atelectasis in the early anaesthesia phase because of the lack of CPAP/PEEP during induction.

The postoperative impaired oxygenation in both study groups breathing 100% oxygen during emergence, as illustrated by an increase in EVA, is most likely explained by increased atelectasis. A high oxygen concentration during awakening has previously been demonstrated by Benoit et al. to be associated with increased postoperative atelectasis.⁸⁹ Using a lower FIO₂ of 0.31 during emergence seems to avoid one unwanted effect (postoperative atelectasis) but adds another, namely a decreased safety margin in case of airway problems during extubation.

Paper II

All included patients received the allocated treatment and their data were analysed. Baseline characteristics and physiological data did not differ between the groups. Two patients had minor complications. One patient in the oxygen washout group had an episode of profound hypotension after induction, and one patient in the control group experienced a bronchospasm that required suctioning of the airways. These two patients had larger atelectasis than any other study subject.

The time required to complete the oxygen washout, i.e., for ET_{O_2} to reach 25% or below, was a mean (SD) of 1.6 min (0.4 min). Peak airway pressures were below 30 cmH₂O in all patients, and no episodes of desaturation were recorded. The group receiving standard treatment (control) required a mean (SD) of 20 min (3.3 min) to reach the targeted FI_{O_2} of 0.30–0.35.

The area of atelectasis, expressed as percentage of the total lung area, was a median (IQR) 2.0 (1.5–2.7) in the oxygen washout group, and 1.8 (1.4–3.3) in the control group, $P = 0.98$.

There was no difference between the two groups for the absolute values of estimated venous admixture at the end of surgery. Comparisons within each group showed that oxygenation improved in the oxygen-washout group from the first (before anaesthesia) to the second (end of surgery) blood gas (Fig. 4). EVA decreased in this group from a mean (SD) of 7.6% (6.6%) to 3.9% (2.9%), $P = 0.019$. For the control group, there was no significant difference between EVA before anaesthesia and that at the end of surgery.

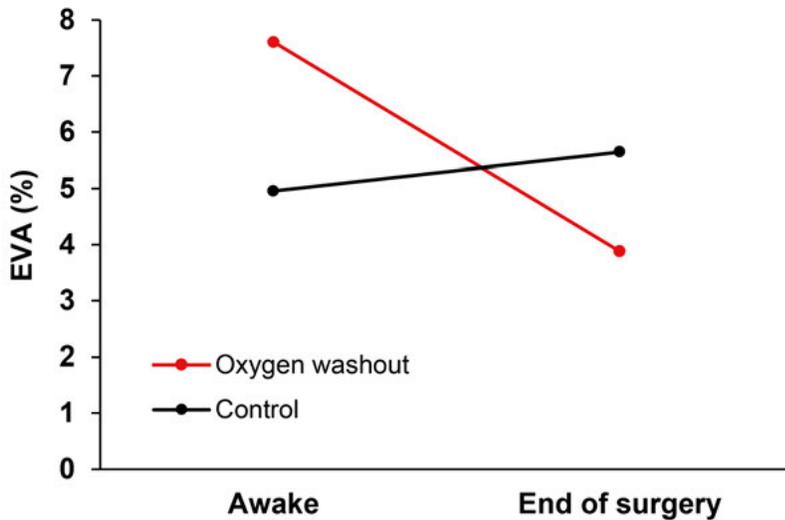


Figure 4. Changes in mean values of EVA for the two study groups in paper II, $P = 0.028$. The first blood gas was taken prior to the start of anaesthesia with all patients breathing room air. The second blood gas was taken at the end of surgery during mechanical ventilation with an FI_{O_2} of 0.30–0.35.

EVA = estimated venous admixture (% of cardiac output).

The mean baseline value of EVA was higher in the oxygen-washout group (7.6%), however this was not significantly different to that in the control group (5.0%) (Fig. 4). A comparison of the groups regarding the change in oxygenation levels between the awake state before anaesthesia and the end of surgery showed that there was a significant difference between the groups. The change in EVA in the oxygen-washout group was (mean) -3.7 percentage units and the corresponding change in the control group was (mean) +0.6 percentage units, $P = 0.028$. This post hoc analysis of the study data was performed after the manuscript was published.

This was the first study to investigate the extent of atelectasis at the end of surgery in patients being ventilated with PEEP. Both groups exhibited notably small areas of atelectasis. A possible explanation is that the beneficial and combined effect of an early applied PEEP and preserved haemodynamics during induction had been previously underestimated. Although the control group was exposed to higher oxygen concentrations over a longer time, substantial airway closure following induction of anaesthesia was possibly avoided by the application of PEEP directly after tracheal intubation. Furthermore, the improvement in oxygenation observed in the oxygen-washout group is likely explained by a gradual recruitment effect of PEEP. Any such effect might be

greater in patients already exhibiting an increased EVA in the awake state, assuming an increased airway closure.

Although not being the primary intention of the study, the results of study II indicated that a moderate PEEP alone is sufficient to minimize atelectasis formation and to maintain oxygenation. This observation generated the hypothesis that was subsequently tested in study III.

Paper III

Baseline characteristics and physiological data were similar in the two study groups. All the 24 included patients received the allocated treatment and completed the study. There was no difference between the study groups regarding the need for vasoactive drugs to maintain blood pressure during anaesthesia. No patient complications were recorded.

The atelectasis area, expressed as the percentage of total lung area, was a median (range) 1.8 (0.3–9.9) in the PEEP group and 4.6 (1.0–10.2) in the ZEEP group. The difference in medians was 2.8% (95% CI, 1.7–5.7%), $P = 0.002$.

The PEEP group maintained their oxygenation and carbon dioxide elimination, whereas the ZEEP group exhibited a decrease in $\text{PaO}_2/\text{FIO}_2$ ratio and higher carbon dioxide partial pressures (Table 2). At the end of surgery, the dynamic compliance for the PEEP group was a median (range) of 51 (29–71) ml/cmH₂O and for the ZEEP group 34 (26–50) ml/cmH₂O, $P = 0.001$.

Table 2. Oxygenation and arterial carbon dioxide levels in the two study groups, paper III.

	PEEP group (n = 12)	ZEEP group (n = 12)	P value
Pre-induction			
FiO ₂	0.21	0.21	
PaO ₂ , mmHg	91 (76–114)	94 (79–104)	
PaCO ₂ , mmHg	38 (34–43)	38 (32–44)	
PaO ₂ /FiO ₂ ratio, mmHg	432 (361–543)	446 (375–496)	
End of surgery			
FiO ₂	0.33 (0.30–0.40)	0.33 (0.30–0.49)	0.63
PaO ₂ , mmHg	160 (79–196)	118 (71–202)	0.16
PaCO ₂ , mmHg	41 (35–46)	48 (41–52)	< 0.001
PETCO ₂ , mmHg	36 (34–43)	44 (38–52)	< 0.001
PaO ₂ /FiO ₂ ratio, mmHg	500 (239–576)	355 (197–567)	0.06
Change in PaO ₂ /FiO ₂ ratio during anaesthesia, mmHg	+33 (-122 to +119)	-73 (-250 to + 60)	0.03
Respiratory frequency, breaths/min	10 (9–11)	13 (10–14)	< 0.001
Minute ventilation, l/min	4.7 (3.5–5.5)	5.8 (4.5–7.7)	0.002

Values are the median (range). The blood gas samples at pre-induction were taken with all study subjects breathing room air. The blood gas samples at end of surgery were taken during anaesthesia at the time of CT scanning. PETCO₂ is the dry value displayed by the Vivo ventilator.

FiO₂ = inspired oxygen fraction; PaO₂ = arterial oxygen partial pressure; PaCO₂ = arterial carbon dioxide partial pressure; PETCO₂ = end-tidal carbon dioxide pressure; PaO₂/FiO₂ ratio = ratio of the arterial oxygen partial pressure to the inspired oxygen fraction.

The findings of study III have important clinical implications. They clearly show that atelectasis is radiologically and functionally relevant, even in healthy patients after non-abdominal surgery and ventilation with ZEEP. Moreover, the results demonstrate that in the vast majority of patients, PEEP as a single intervention is sufficient to minimize atelectasis formation and maintain normal pulmonary gas exchange. However, even with PEEP, a few patients will develop atelectasis. Only in this latter group will RMs and other possible measures be indicated to prevent or reverse alveolar collapse.

Paper IV

Patient characteristics and ventilatory data were similar in the two study groups. The 30 included patients all received their allocated treatment and were included in the analysis. The most common type of surgery was inguinal hernia repair. No complications occurred.

Baseline atelectasis was small with no significant difference between the two groups. Atelectasis increased in both groups during awakening, but there was no statistically significant difference between groups in the change in atelectasis from before to after awakening (Table 3). For the groups combined, the awakening procedure contributed a median 39% (95% CI, 29–56%) to the total area of postoperative atelectasis.

Table 3. Atelectasis areas in the two study groups, paper IV.

	PEEP group (n = 16)	ZEEP group (n = 14)	<i>P</i> value	Groups combined (95% CI)
Atelectasis at end of surgery				
cm ²	3.7 (0.2–9.8)	2.7 (1.0–6.4)	0.12	3.3 (2.5–3.9)
% of total lung area	1.5 (0.1–4.1)	1.1 (0.4–2.9)	0.21	1.3 (1.1–1.6)
Atelectasis after awakening				
cm ²	5.2 (2.4–14.3)	4.9 (3.0–12.7)	0.85	5.2 (4.3–5.7)
% of total lung area	2.5 (1.0–7.3)	2.4 (1.3–5.3)	0.61	2.5 (2.0–3.0)
Change in atelectasis				
cm ²	1.6 (-1.1 to 12.3)	2.3 (-1.6 to 7.8)	0.40	2.1 (1.2–2.9)

Values are the median (range) or the median (95% CI). The first computed tomography (CT) scan in both groups was done at the end of surgery while patients were still under anaesthesia and mechanically ventilated with PEEP. The second scan was done after awakening, approximately 30 min after extubation. CT scans were performed at end-expiration and at 5 mm above the right diaphragm dome.

There was no difference between the groups in the change in oxygenation from before awakening to approximately 40 min after extubation. Postoperative oxygenation was maintained in both groups compared with oxygenation in the preoperative awake state.

This study confirmed the findings of studies II and III establishing that PEEP as a single intervention is sufficient to minimize atelectasis formation after non-abdominal surgery in this patient group. Furthermore, although atelectasis increased during awakening it remained small, approximately 2.5% of total lung area at 30 min after extubation, and had no effect on oxygenation. The

extent of postoperative atelectasis was the same in both groups, irrespective of whether PEEP was maintained or withdrawn during emergence preoxygenation. A reasonable interpretation of this finding is that preoxygenation with FIO_2 1.0 before emergence is well tolerated in healthy patients undergoing non-abdominal day surgery. This in turn is made possible by minimal baseline atelectasis at the end of surgery combined with limited airway closure in the early postoperative period. In other patient categories, for example high-risk patients undergoing major surgery, the roles of the awakening procedure and PEEP during emergence preoxygenation still need clarification.

Merged results from studies II–IV

The patients participating in studies II–IV were similar and they all underwent non-abdominal day surgery. Furthermore, the area of atelectasis measured by CT at the end of surgery was, or was part of, the primary outcome measure in all the studies. Some of the patient characteristics and combined data from these studies are displayed in Table 4.

Table 4. Merged data from CT studies II–IV.

	PEEP during anaesthesia (n = 66)	ZEEP during anaesthesia (n = 12)	<i>P</i> value
Male/female, n	44/22	9/3	–
Age, years	56 (50–63)	57 (50–68)	–
Weight, kg	79 (70–87)	75 (67–82)	–
BMI, kg/cm ²	25 (23–27)	24 (22–27)	–
IBW, kg	67 (60–75)	72 (61–74)	–
ASA physical status I/II	42/24	8/4	–
Type of surgery, n			
Orthopaedic, extremity	31	6	–
Inguinal hernia	31	6	–
Other non-abdominal	4	0	–
PEEP level, cmH ₂ O			
0	0	12	–
6	15	0	–
7	19	0	–
8	9	0	–
9	23	0	–
Duration of surgery, min	53 (35–64)	46 (29–55)	0.15
Time at CT, min	105 (83–122)	96 (88–104)	0.20
Atelectasis, cm ²	3.5 (2.5–5.7)	9.6 (6.8–13.3)	< 0.001
Atelectasis, % of total lung area	1.6 (1.0–2.4)	4.6 (4.1–7.1)	< 0.001
PaO ₂ /FIO ₂ ratio awake, mmHg	425 (389–460)	446 (398–471)	0.36
EVA awake, % of cardiac output	5.5 (3.2–10.2)	5.0 (1.8–7.5)	0.34
PaO ₂ /FIO ₂ ratio at CT, mmHg	504 (420–561)	355 (315–396)	0.001
EVA at CT, % of cardiac output	3.2 (1.2–6.7)	9.2 (6.9–12.2)	0.007

Values are the median (interquartile range). *t*₀ = start of preoxygenation.

Computed tomography scans were done during anaesthesia at end-expiration and at 5–10 mm above the right diaphragm dome. PaO₂/FIO₂ ratio awake and EVA awake were calculated from arterial blood gases obtained with patients breathing room air before anaesthesia induction. PaO₂/FIO₂ ratio at CT and EVA at CT were calculated from blood gases obtained during general anaesthesia and FIO₂ 0.30–0.35, at the time of CT scanning.

ASA = American Society of Anesthesiologists physical status; BMI = body mass index; CT = computed tomography; EVA = estimated venous admixture; IBW = ideal body weight; PaO₂/FIO₂ ratio = ratio of the arterial oxygen partial pressure to the inspired oxygen fraction.

General discussion

The studies included in this thesis explored factors associated with preventing or treating atelectasis formation during all three phases of anaesthesia, i.e., induction, maintenance, and awakening. The clinically most important finding is that PEEP, as a single intervention, reduces atelectasis formation to a negligible level (median 1.6% of total lung area) in healthy patients undergoing non-abdominal surgery. The results also add support to the proposal that high FIO_2 is well tolerated as long as airway closure is avoided.⁸⁰ To put the above atelectasis in perspective, the area of atelectasis that has been observed in normal-weight patients after induction of anaesthesia with zero PEEP, ranges between 4 and 7% of the total lung area in a CT slice obtained close to the diaphragm.^{13,80,81,90–94}

Study I dealt in part with induction of anaesthesia. Preoxygenation before induction remains an integral safety measure to increase oxygen storage, because difficulties with ventilation and intubation can occur unexpectedly.^{1,3} Preoxygenation efficiency has been shown to increase with the use of CPAP followed by mechanical ventilation with PEEP,^{86,95,96} or CPAP in combination with pressure-support ventilation.^{97–100} CPAP will increase EELV, and in combination with a high FIO_2 , apnoea time is prolonged and PaO_2 is better maintained. In clinical anaesthesia, the one obvious effect of CPAP during preoxygenation is that the time required to achieve an ETO_2 above 90% is shortened.^{98,99} In this context however, it is important to distinguish between efforts to improve or hasten preoxygenation and attempts to prevent atelectasis formation. Following preoxygenation with CPAP and subsequent tracheal intubation, early application of an adequate PEEP level is crucial to maintaining EELV. Otherwise, absorption atelectasis will follow, the extent of which might be more pronounced because of the newly oxygen-filled larger lung volume achieved by CPAP. Further, some as yet unpublished data from a recent study (Cajander et al., personal communication) indicate a possible increased risk of gastric insufflation when a PEEP is used before the airway is secured. This could potentially increase the risk of gastric regurgitation and aspiration. Until future studies have demonstrated its safe use, it is important to be aware of potential pitfalls using this technique and to perform a risk-benefit analysis for each patient.

However, PEEP should be applied immediately after securing the airway by endotracheal intubation. The current data suggest that this applies even when CPAP is not used during preoxygenation. For example, the small atelectasis observed in the control group in study II could be explained by the early application of PEEP and the consequent avoidance of airway closure. This would counteract the potentially negative effects of the longer period of high alveolar oxygen concentration in this group. In addition, the results obtained in study III showed that the early application of a moderate PEEP without RMs resulted in minimal atelectasis at the end of surgery. This apparent effect of PEEP alone is perhaps best explained by the combined effect of an early application of PEEP, thereby *preventing* some of the early atelectasis formation, and possibly later *treating* (by recruitment) already-formed atelectasis. Support for this suggestion can be found in a previous study that indicated that atelectasis is an evolving process from the start of induction, but is not completed at the time of intubation⁹⁴ (Fig. 5). Thus, the immediate application of PEEP may have preventive effects.

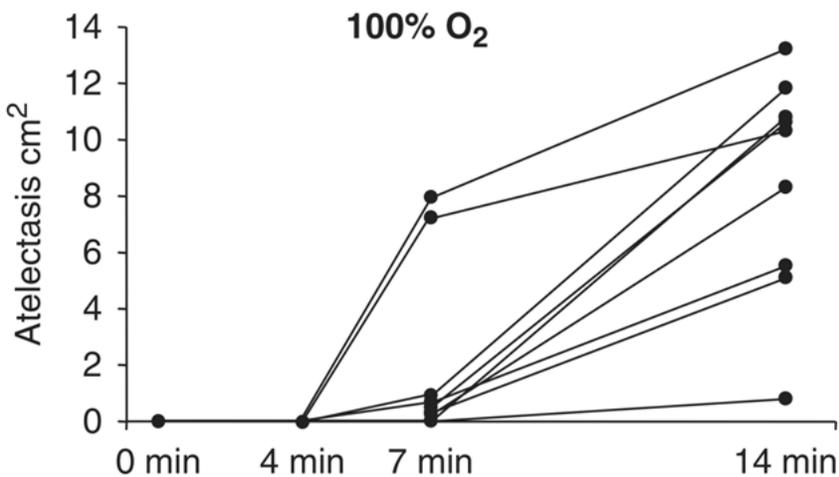


Figure 5. Increase in the amount of atelectasis after induction of anaesthesia in individual patients being preoxygenated with 100% oxygen. The time point 7 min after the start of preoxygenation corresponds to immediately after intubation.

Edmark et al., *Acta Anaesthesiol Scand* 2011; 55:75–81. By permission.

Another important factor related to the early phase of anaesthesia is the high oxygen concentration that remains in the lungs after preoxygenation. After uneventful endotracheal intubation, the oxygen reserve generated for safety purposes becomes unnecessary and potentially harmful.¹⁰¹ If no active measures are taken, it may take 20 min to lower this oxygen concentration and reach a reasonable target ETO_2 of less than 35% (study II). Some currently used anaesthesia machines are equipped with software enabling automated

end-tidal control, in which case the above will be less of a problem. Without this software, and despite the negative results of study II, it might still be recommended that the pulmonary oxygen levels be lowered as soon as possible after successful intubation. This makes sense from a physiological point of view, given our knowledge about the mechanisms behind early atelectasis formation. In addition, any positive effect of the oxygen washout in study II might have been obscured by the effects of an early application of a moderate PEEP, which may have prevented early airway closure in this study group. The need to avoid residual high oxygen concentrations is probably more urgent in a situation where airway closure is more likely to occur, such as in obese patients undergoing laparoscopic surgery.

The early phases of anaesthesia have been the predominant focus for research in this field since it became known that atelectasis formation is closely related to induction of anaesthesia.⁴¹ This remained true after CT became the established method for quantifying atelectasis.¹² Although Cai et al. used CT at the end of surgery to study the effect of different tidal volumes on atelectasis formation, their patients were ventilated with ZEEP and 100% O₂,⁹² which is not consistent with current clinical practice. Studies II–IV in this thesis are the first published studies using CT to examine atelectasis at the end of surgery after ventilating patients with PEEP. The findings of these separate studies stand alone. However, the study subjects and the type of surgery they underwent were similar in the three studies, which offers an opportunity to combine the results to provide a clearer picture of the effects of PEEP during non-abdominal surgery (Table 4). For all 66 patients who received a moderate PEEP during mechanical ventilation, the atelectasis area at the end of surgery was a median (IQR) of 1.6% (1.0–2.4%) of total lung area (95% CI, 1.3–2.0%). None of these patients received any RMs, with the possible exception of the 12 patients in study II who underwent an oxygen washout manoeuvre that included larger tidal volumes (15 ml/kg IBW) and higher PEEP (10 cmH₂O) for a mean of 1.6 min. For the 12 patients ventilated without PEEP, the area of atelectasis was a median (IQR) of 4.6% (4.1–7.1%), (95% CI, 4.1–7.1%). These combined results constitute a strong indication that healthy patients undergoing non-abdominal surgery should receive a moderate PEEP to minimize atelectasis and maintain oxygenation. Further, for this patient group, routine RMs seem unnecessary and should only be used when clearly indicated. The combined data also add support to previous findings that mechanical ventilation with minimal PEEP or ZEEP should be avoided, especially in combination with low tidal volumes.¹⁰²

The finding that PEEP is both necessary and sufficient to minimize atelectasis in most healthy patients undergoing non-abdominal surgery, also has important implications for the awakening procedure. In study IV, the postoperative atelectasis area expressed as a percentage of total lung area was 2.5% for

both groups, regardless of whether PEEP was maintained and despite using FIO_2 1.0 during emergence. This result is similar or better than those obtained in several previous studies testing the ability of CPAP, vital capacity manoeuvres, and/or lower FIO_2 during and after emergence to limit postoperative atelectasis formation.^{84,89,103} Our results indicate that minimal atelectasis at the end of surgery provides a beneficial starting-point for subsequent awakening, during which a high FIO_2 seems well tolerated, possibly partly because of limited postoperative airway closure after this type of surgery in healthy patients. Overall, an important clinical implication of the studies is that a high oxygen concentration during either early or late phases of anaesthesia is well tolerated provided that airway closure is avoided. In most healthy patients undergoing non-abdominal surgery, intra-operative airway closure can be counteracted by an early application of a moderate/adequate PEEP. Postoperative airway closure appears to be clinically insignificant in pain-free patients after minor day surgery and after receiving short-acting anaesthetics. These patients probably have no or very little interference with normal tidal breathing and/or deep breathing.

The studies presented in this thesis are small but have the strengths of investigating PEEP in healthy lungs under controlled conditions. In study II, the patients received 6 or 8 cmH_2O depending on BMI. In studies III and IV, we used 7 or 9 cmH_2O for the respective BMI categories. The slightly higher levels used in the latter two studies were in part chosen to see whether they would result in even smaller atelectasis without compromising haemodynamic stability. Although these studies were not designed to investigate outcome differences between small increments in PEEP, we did not observe any additional beneficial effect with the higher levels. Thus, based on these results, a PEEP of 6 cmH_2O is recommended for normal-weight healthy patients undergoing non-abdominal surgery. The higher level of 8 cmH_2O is recommended for overweight patients with a BMI of 25–30 kg/m^2 . Higher and perhaps individually titrated PEEP levels are recommended for obese patients with BMI greater than or equal to 30 kg/m^2 .¹⁰⁴

Other factors affecting atelectasis formation

The amount of atelectasis formed during general anaesthesia is associated with BMI,¹⁰⁵ and possibly ASA physical status and smoking.⁸⁴ There is also a possible correlation with age, but this is a more complicated association. There is an age-dependent increase in closing capacity which exceeds functional residual capacity (FRC) in older patients and results in airway closure already in the awake state before anaesthesia induction.¹⁰⁶ This may paradoxically be protective against atelectasis formation because the high oxygen concentration used during preoxygenation may not reach these already closed lung

units, and the alveoli may therefore be partially protected from collapse by their rich nitrogen content. On the other hand, chest wall compliance decreases with increasing age because of anatomical factors and ossification of rib cartilage.¹⁰⁷ If or when the lungs are affected by atelectasis, re-expansion may be more difficult in older patients.

In the three studies included in this thesis that quantified atelectasis, the participants were aged 40–75 years. Any observable negative effects related to increased closing capacity may have been blurred by the use of PEEP in most study subjects. The merged data for these studies, showed no detectable significant correlation between age and atelectasis formation. However, the studies were not designed to investigate any such correlation. With respect to BMI, the study protocols included differentiated PEEP levels to diminish BMI as a confounder. Despite this, the merged data showed a slight positive linear correlation between BMI and atelectasis ($r = 0.281$, $n = 78$, $P = 0.013$; Pearson product-moment correlation). This could indicate that the chosen PEEP levels were too low for some overweight patients.

There is no published evidence that sex is correlated with atelectasis formation. Based on our current understanding of how atelectasis forms, such an association would be surprising. In the combined data obtained for this thesis, no correlation was found between sex and atelectasis.

As stated, one of the aims of this thesis was to investigate the physiological effects of PEEP (studies II–IV). To avoid interference from factors other than general anaesthesia, a fairly homogeneous study population, i.e., healthy patients undergoing non-abdominal day surgery, was chosen. Despite this, outliers with very small or very large atelectasis were identified in all three CT studies. In some cases, the large atelectasis could probably be explained by circumstances or characteristics that were close to fulfilling the exclusion criteria, for example, borderline BMI and/or smoking or recent lower respiratory tract infection. Excessive bronchial secretions, bronchospasm, and persistent or pronounced hypotension were identified as possible explanatory factors in some cases.

Anaesthesia-related hypotension is a potential but unrecognized factor affecting atelectasis formation. Decreased cardiac output and hypotension are common during induction of anaesthesia, especially in older patients and/or patients taking antihypertensive medication.¹⁰⁸ Systemic hypotension causes a shift in pulmonary blood flow to the dorsal lung regions, and in an early study, was shown to be associated with both increased venous admixture and decreased pulmonary dynamic compliance.¹⁰⁹ These findings could in part be explained by the induction of atelectasis, which was not well known at that

time. An increased proportion of cardiac output, possibly with lower than normal oxygen content, passing through dorsal lung regions represents ideal conditions for increased gas absorption from newly preoxygenated lung units,¹¹⁰ with subsequent atelectasis formation. Notably, few previous publications about atelectasis have provided information about whether, or how, haemodynamic stability was maintained during and after induction. Invasive blood pressure monitoring was an integral part of the three CT studies presented here, and study protocols mandated that mean arterial blood pressure was maintained at or above 60 mmHg. This might partly explain why the atelectasis areas observed in the present studies were generally smaller than those reported from earlier comparable studies. Interestingly, despite administration of vasopressors, substantial hypotension was observed in a small number of patients and was associated with larger atelectasis. Further, the late deterioration in oxygenation observed in the control group in study III, possibly caused by late development of atelectasis, could also be explained by effective maintenance of blood pressure in the early phase of anaesthesia. Even if gas is trapped behind closed airways, a normal distribution of pulmonary blood flow avoids excessive gas absorption from susceptible lung units, and thus delays the collapse of alveoli. This hypothetical mechanism needs to be demonstrated, but would challenge the established concept that atelectasis always forms early after induction of anaesthesia. If the hypothesis is shown to be correct, avoiding an increased proportion of pulmonary blood flow to areas with low alveolar ventilation (\dot{V}_A) to lung perfusion (\dot{Q}) ratios (\dot{V}_A/\dot{Q}) by maintaining blood pressure will be added to PEEP as a tool to prevent or delay atelectasis formation.

A small number of patients presented with larger than expected atelectasis, without any obvious complicating or explanatory factors. Individual patient characteristics, for example variations in thoracic or pulmonary elasticity, and specific events during anaesthesia may explain why some patients are more prone to develop atelectasis. In one of our patients, it is tempting to believe that a large heart caused increased pressure on the small airways, contributing to airway closure and atelectasis (Fig. 6). Any patient identified with significant oxygenation difficulties during anaesthesia may need a ventilatory strategy comprising both RMs and individualized PEEP to minimize atelectasis formation and the risk of postoperative pulmonary complications.^{18,104,111,112}

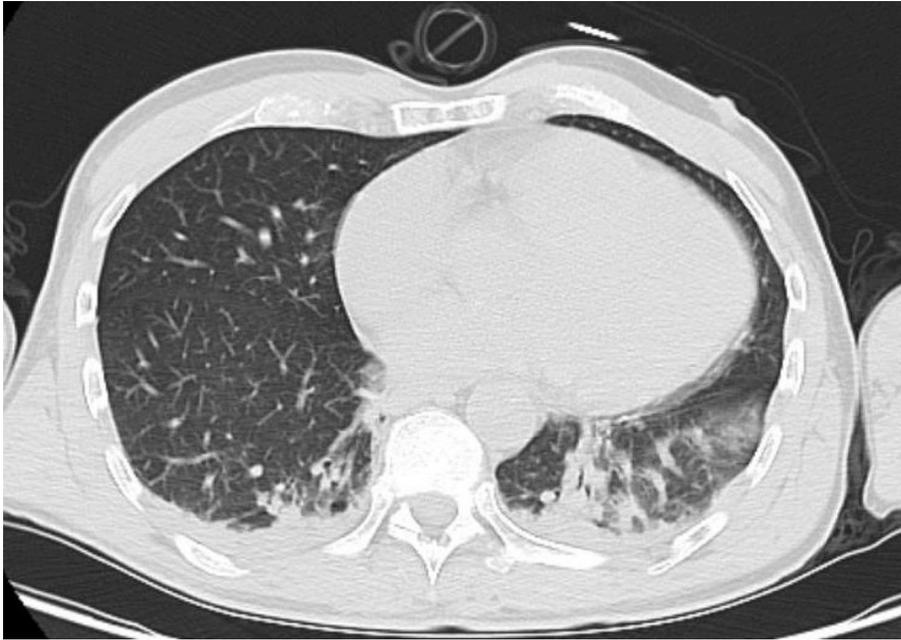


Figure 6. Computed tomography scan of one of the participants in study III. Note the large heart and the substantial area of atelectasis evident in the pulmonary tissue below. The computed tomography scan was performed during anaesthesia at end-expiration approximately 5 mm above the right diaphragm dome.

Methodological aspects and study limitations

General anaesthesia impairs oxygenation for two main reasons. First, atelectasis forms and leads to intrapulmonary shunting of venous blood.^{15,113} Second, increased perfusion to areas with already low \dot{V}_A/\dot{Q} leads to additional venous admixture of pulmonary end-capillary blood.¹¹⁴ Exact measurements of venous admixture requires sampling of mixed venous blood through a pulmonary artery catheter, but because of its invasiveness this is seldom done. Instead, the oxygenating capacity of the lungs is normally estimated, which can be done in several ways. The choice of oxygenation index is complex and remains controversial. In studies I and II, we chose to calculate and use EVA, because it has been suggested to be the best oxygenation index if mixed venous blood is not collected.¹¹⁵ Nevertheless, use of the $\text{PaO}_2/\text{FIO}_2$ ratio is more widespread, and this oxygenation index was used in studies III and IV. Impaired oxygenation is a fundamental consequence of atelectasis and may serve as a surrogate indicator of the amount of atelectasis. However, an estimated or measured impairment in oxygenation can still not differentiate between the contribution from shunt (atelectasis) and \dot{V}_A/\dot{Q} mismatch. Therefore, CT remains the gold standard for quantifying atelectasis formation, and therefore

this method was used to directly measure atelectasis area in the study subjects participating in studies II–IV.

CT provides detailed images of pulmonary tissue and has been used since the 1980s to measure atelectasis.^{12,116} The CT workstation software enables quantification of lung zones with different levels of aeration based on varying attenuation values. Atelectasis, for example, has been defined as having attenuation values of -100 to +100 HU.¹³ Although the major part of the analysis is computerized, defining the border between the pleura and the dorsal thoracic wall must be done manually. Because atelectasis normally forms dorsally, and since it exhibits attenuation values close to those of the adjacent soft tissue on the inside of the thoracic cavity, the utmost care must be taken to accurately delineate the posterior border of the atelectasis and thus avoid calculation errors (Fig. 7). This procedure becomes even more critical with smaller areas of atelectasis. To rule out any inter-observer errors, the same radiologist performed the CT scan analysis in each of studies II–IV.



Figure 7. Example of a computed tomography scan of one of the participating patients in study II. Note that the exact posterior border of the atelectasis area is difficult to visualize. The computed tomography scan was done during anaesthesia at end-expiration and at 5–10 mm above the right diaphragm dome.

Instead of examining the entire thoracic cavity, most CT studies have used limited measurements to minimize radiation exposure to the study participants. The basal lung regions are generally most affected by atelectasis;⁹¹ therefore, a basal CT slice just above the diaphragm has been considered representative to illustrate the extent of atelectasis formation. However, it is important to acknowledge that this will underestimate the total amount of collapsed lung for two reasons. First, atelectasis distributed along the dorsal lung regions towards the apex is not included in the scan.¹¹⁷ Second, atelectasis comprises compressed lung tissue that has a higher tissue density than aerated lung tissue. Therefore, the actual area of collapsed lung is larger, and has been estimated to be four times greater than that estimated from the CT image.¹³

To conclude, the care of patients undergoing surgery is complex and must be versatile. This thesis focuses on a narrow aspect of respiratory care of patients during anaesthesia. After surgery and emergence from anaesthesia, continuous and professional postoperative care may be equally important to minimize the risk of PPCs, especially in high-risk patients. Several large trials of physiotherapy show promising results in preventing PPCs, especially after major surgery.^{118,119} This highlights the importance of taking a holistic approach to the perioperative care of patients undergoing anaesthesia and surgery. The work presented here highlights the crucial role of PEEP in counteracting airway closure and atelectasis during anaesthesia and mechanical ventilation.

Conclusions

- In obese patients undergoing general anaesthesia for laparoscopic surgery, oxygenation can be preserved by using a CPAP of 10 cmH₂O during preoxygenation and induction, followed by a PEEP of 10 cmH₂O. Postoperative oxygenation might be impaired if a high FIO₂ is used during emergence.
- An early oxygen washout after preoxygenation and intubation quickly restores nitrogen levels in the alveoli. In healthy patients undergoing non-abdominal surgery and being ventilated with a moderate PEEP, this manoeuvre has no further effect on the size of atelectasis at the end of surgery.
- For healthy patients undergoing non-abdominal surgery, a moderate PEEP is both necessary and sufficient to minimize atelectasis formation and maintain oxygenation. In this group of patients, RMs should only be utilized when clearly indicated. Mechanical ventilation with ZEEP is associated with several unfavourable physiological consequences and should be avoided.
- In most healthy day-surgery patients, postoperative atelectasis formation is limited without affecting oxygenation. Withdrawing PEEP before emergence preoxygenation does not reduce atelectasis formation after non-abdominal surgery. Conditional on a baseline open lung achieved by intraoperative PEEP, emergence preoxygenation with 100% oxygen is well tolerated and thus recommended for maximum safety margins.

Strategy for minimizing atelectasis formation in perioperative care

This recommendation applies to healthy normal-weight patients undergoing non-abdominal surgery. In accordance with established guidelines,¹ it encompasses a maximum oxygen reserve during both induction and emergence.

1. Preoxygenate for 3 min with 100% O₂ with the patient in a slight head-up tilt position.
2. Use PEEP immediately when commencing mechanical ventilation after endotracheal intubation or insertion of a laryngeal mask airway.
3. Use PEEP 6 cmH₂O if BMI < 25 kg/m² and PEEP 8 cmH₂O if BMI ≥ 25 kg/m².
4. Set FIO₂ to 0.35. Possibly use a higher fresh gas flow initially to achieve a more rapid reduction in ETO₂.
5. Use RMs followed by individualized PEEP only if indicated by signs of atelectasis, i.e., decreased oxygenation with no other explanation. A suggested cut-off for when to consider an RM is SpO₂ < 94% if ventilating with FIO₂ 0.35. Individual patient risks as well as type and duration of surgery must be considered.
6. Use 100% O₂ during emergence preoxygenation and maintain PEEP.
7. In general, after total intravenous anaesthesia, supplementary oxygen en route to PACU is not necessary if spontaneous breathing is adequate as indicated by SpO₂ ≥ 94%, and transport time is less than 5 min.
8. Give supplementary oxygen in PACU only when SpO₂ < 94%.¹²⁰

Future perspectives

Recent large international multicentre trials have reported conflicting results regarding protective ventilation during anaesthesia.^{59,60,62} Protective strategies comprising several components have been tested against “standard practice”, making it difficult to draw conclusions about which of the interventions was beneficial. At present, there seems to be a reasonable consensus that low tidal volumes should be routine, not only in critical care but also during mechanical ventilation in the operating theatre.¹¹² On the other hand, the use of PEEP, or the level of PEEP, and the use of RMs is still a matter of debate, especially during major surgery. To make a significant contribution to the current knowledge, any new large trial should ideally be refined in terms of intervention, its study population, and its outcome measures. Moreover, if PPCs are chosen as an outcome measure, any intraoperative interventions regarding ventilation strategy should be accompanied by a detailed study plan and description of the awakening procedure. This is because a chosen FIO_2 and/or PEEP level during emergence preoxygenation and awakening may well have an impact on postoperative atelectasis formation and hence the incidence of PPCs, especially after major surgery or in high-risk patients.

Meanwhile, further explanatory studies are needed to clarify some of the obscure pathophysiological mechanisms involved in atelectasis formation. A worthwhile objective would be to explore the possible role of intraoperative hypotension as a contributor to atelectasis. Furthermore, a follow-up trial to our study IV could perhaps determine whether withdrawing or maintaining PEEP matters during emergence preoxygenation and awakening in patients undergoing major abdominal surgery. Such patients would probably exhibit more airway closure during the early postoperative phase, and therefore be more susceptible to high oxygen concentrations and more prone to develop postoperative atelectasis, compared with the patients investigated in study IV.

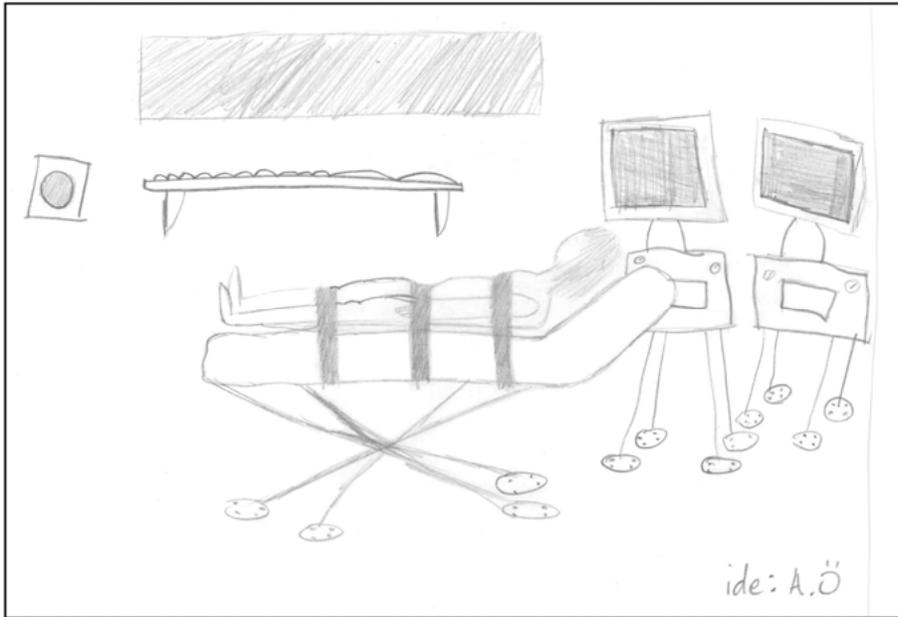


Figure 8. A possible future solution for prevention of airway closure and hence atelectasis formation – general anaesthesia in zero gravity.

Idea and illustration by Anni Östberg, 2015.

Sammanfattning på svenska (Summary in Swedish)

Varje år genomförs i världen över 230 miljoner större operationer, de flesta i generell anestesi, d.v.s. patienterna sövs.²⁸ Hos nästan alla vuxna patienter som sövs utvecklas atelektaser vilket innebär att delar av lungan faller samman. Det sker framför allt i lungavsnitt nära ryggen och diafragma (mellangärdet). Atelektaser leder till försämrad syresättning under operationen och ökar risken för postoperativa lungkomplikationer t.ex. lunginflammation.¹⁷⁻¹⁹ Dessa komplikationer är vanligare än hjärtkomplikationer och orsakar både förlängd vårdtid och ökade sjukvårdskostnader, liksom ökad dödlighet.²¹⁻²⁷ Risken är störst hos äldre, överviktiga och multisjuka som genomgår stora operationer. Hos friska, normalviktiga personer som genomgår sövning och kirurgi återfår troligen lungan sin ursprungliga volym ganska snart efter väckningen, och för dem är riskerna små. Men eftersom ett så stort antal människor sövs och opereras årligen så har även små minskningar av risken stor betydelse.

Bildandet av atelektaser förklaras dels av den höga syrgashalt som rutinmässigt och av säkerhetsskäl används vid nedsövningen, dels av en sänkt vilolungvolym när andningsmuskulaturen slappnar av när kroppen sövs.¹²¹ Den minskade vilolungvolymen orsakar avstängda partier i lungorna där alveolerna (lungblåsorna) nyligen fyllts med inandad ren syrgas. Atelektaser uppstår när den passerande lungcirkulationen suger åt sig syrgasen, varpå de avstängda lungblåsorna faller samman. Det är möjligt att blåsa upp de sammanfallna lungdelarna med hjälp av höga luftvägstryck, en så kallad rekryteringsmanöver, men det är oklart vilka patienter som skulle gynnas av detta. Det finns också potentiella biverkningar med lungrekrytering, till exempel minskar det venösa återflödet till hjärtat vilket påverkar blodcirkulationen negativt. Forskningen kring atelektaser har huvudsakligen inriktat sig på att hitta sätt att förhindra att de uppstår, genom t.ex. minskad initial syrgashalt, men detta leder samtidigt till minskad säkerhetsmarginal i händelse av svårigheter att ventilera patienten. Ett annat sätt är att motverka minskningen av vilolungvolymen. Inom intensivvården har man länge använt sig av ett utandningsmotstånd (PEEP) i samband med respiratorvård. PEEP har till viss del använts även vid mekanisk ventilation av sövda patienter som opereras, men tydliga riktlinjer

saknas då forskningen inte kunnat visa hur stort utandningsmotståndet bör vara, eller vilka patienter som har behov av det.

Detta avhandlingsarbete har fokuserat dels på betydelsen av syrgashalten under olika delar av anestesi, dels syftat till ökad kunskap kring effekterna av PEEP, både under anestesi och inför väckningen. Ett övergripande mål har varit att komma närmare ett optimalt sätt att ventilerat sövda patienter, så att lungan hålls öppen och fri från atelektaser både under operationen och efter väckningen.

De arbeten som ingår i avhandlingen var samtliga kliniska och prospektiva randomiserade studier. I det första arbetet användes syresättning som ett surrogatmått för atelektaser hos överviktiga patienter som genomgick laparoskopisk överviktskirurgi. I de följande studierna användes datortomografi (CT) för kvantifiering av atelektasyta hos friska patienter som genomgick dagkirurgisk icke bukkirurgi.

Studie I: Två former av utandningsmotstånd, CPAP och PEEP, studerades under nedsövningen, liksom minskad syrgashalt vid väckningen. Gruppen med CPAP/PEEP under och efter nedsövningen hade bibehållen syresättning, till skillnad från jämförelsegruppen. Den grupp som fick en hög syrgashalt vid väckningen hade försämrad syresättning en timme postoperativt.

Studie II: En tidig syrgasutvädring i syfte att återställa en hög kvävgashalt i lungan och därmed stabilisera alveolerna visade sig inte ha effekt på mängden atelektaser i slutet av operationen. Både grupperna uppvisade endast små mängder atelektaser efter att ha ventilerats med ett måttligt PEEP, 6–8 cmH₂O, under anestesi.

Studie III: Här jämfördes atelektasutveckling och syresättning i slutet av anestesi hos två grupper som ventilerades antingen med eller utan ett måttligt PEEP. Gruppen med PEEP uppvisade statistiskt signifikant mindre atelektaser och bättre syresättning än gruppen utan PEEP.

Studie IV: I detta arbete undersöktes mängden atelektaser med CT före och efter väckning. Jämförelse gjordes mellan en grupp med bibehållet PEEP under rutinemässig väckning med 100% syrgas, och en grupp där PEEP avlägsnades precis innan syrgasen höjdes till 100% inför väckningen. Vid en tidpunkt ungefär 30 min efter väckning hade grupperna likartad mängd små atelektaser samt bibehållen syresättning jämfört med innan sövning.

Avhandlingen visar att bibehållen vilolungvolym utgör nyckeln till undvikande av atelektasutveckling under anestesi, särskilt vid användande av de höga syrgashalter som generellt rekommenderas i samband med nedsövning

och väckning. Att lungan är öppen och fri från atelektaser när väckningen påbörjas verkar vara fördelaktigt. Det viktigaste fyndet av klinisk relevans är att ett måttligt PEEP som enda intervention resulterar i minimala mängder atelektaser hos friska patienter som genomgår icke bukkirurgi. Ett måttligt PEEP kan därför rekommenderas till alla friska vuxna som genomgår anestesi.

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