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Open lung concept in high risk anaesthesia

Optimizing mechanical ventilation in morbidly obese patients and during one lung ventilation with capnothorax

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Abstract

Reinius, H. 2016. Open lung concept in high risk anaesthesia. Optimizing mechanical ventilation in morbidly obese patients and during one lung ventilation with capnothorax. *Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine* 1169. 77 pp. Uppsala: Acta Universitatis Upsaliensis. ISBN 978-91-554-9440-7.

Formation of atelectasis, defined as reversible collapse of aerated lung, often occurs after induction of anaesthesia with mechanical ventilation. As a consequence, there is a risk for hypoxemia, altered hemodynamics and impaired respiratory system mechanics. In certain situations, the risk for atelectasis formation is increased and its consequences may also be more difficult to manage. Anesthesia for bariatric surgery in morbidly obese patients and surgery requiring one-lung ventilation (OLV) with capnothorax are examples of such situations.

In Paper I (30 patients with BMI > 40 kg/m^2 scheduled for bariatric surgery) a recruitment maneuver followed by positive end-expiratory pressure (PEEP) reduced the amount of atelectasis and improved oxygenation for a prolonged period of time. PEEP or a recruitment maneuver alone did not reduce the amount of atelectasis.

In paper II we investigated whether it is possible to predict respiratory function impairment in morbidly obese patients without pulmonary disease from a preoperative lung function test. Patients with mild signs of airway obstruction (reduced end-expiratory flow) in the preoperative spirometry developed less atelectasis during anaesthesia.

In paper III we developed an experimental model of sequential OLV with capnothorax using electrical impedance tomography (EIT) that in real-time detected lung separation and dynamic changes in pulmonary ventilation and perfusion distributions. OLV to the left side caused a decrease in cardiac output, arterial oxygenation and mixed venous saturation.

In paper IV we used our model of OLV with capnothorax and applied a CO_2-insufflation pressure of 16 cm H_2O. We demonstrated that a PEEP level of 12-16 cm H_2O is needed for optimal oxygenation and lowest possible driving pressure without compromising hemodynamic variables. Thus, the optimal PEEP was closely related to the level of the capnothorax insufflation pressure. With insufficient PEEP, ventilation/perfusion mismatch in the ventilated lung and redistribution of blood flow to the non-ventilated lung occurred.

Keywords: Anaesthesia, mechanical ventilation, atelectasis, morbidly obese, one-lung ventilation, PEEP, recruitment maneuver, spirometry, EIT

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Till mina nära och kära

List of Papers

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

I Reinius, H., Jonsson, L., Gustafsson, S., Sundbom, M., Duvernoy, O., Pelosi, P., Hedenstierna, G., Fredén, F. (2009) Prevention of atelectasis in morbidly obese patients during general anaesthesia and paralysis: a computerized tomography study. *Anesthesiology,* 111:979-87.

II Reinius, H., Hedenström, H., Larsson, A., Ericsson, N., Hedenstierna, G., Fredén, F. Preoperative lung function tests as a predictor for atelectasis in morbidly obese patients during anaesthesia. *In manuscript*.

III Reinius, H., Batista Borges, J., Fredén, F., Jideus, L., Hedenstierna, G., Amato, M., Larsson, A., Lennmyr, F. (2015) Real-time ventilation and perfusion distributions by electrical impedance tomography during one-lung ventilation with capnothorax. *Acta Anaesthesiologica Scandinavica,* 59:354-368

IV Reinius, H., Batista Borges, J., Engström, J., Ahlgren, O., Larsson, A., Lennmyr, F., Fredén, F. Optimal PEEP during one lung ventilation with capnothorax. An experimental study. *In manuscript.*

Contents

Abbreviations

ABG	arterial blood gases
BMI	body mass index
BP	blood pressure
COPD	chronic obstructive pulmonary disease
CT	computerized tomography
CO	cardiac output
CO_2	carbon dioxide
CPAP	continuous positive airway pressure
CVP	central venous pressure
Delta P	driving pressure
DLCO	diffusing capacity for carbon monoxide
DLT	double lumen tube
EELV	end-expiratory lung volume
EIT	electrical impedance tomography
$EtCO_2$	end-tidal carbon dioxide
ERV	expiratory reserve volume
FEF	forced expiratory flow
F_IO_2	fraction of inspired oxygen
FEV_1	forced expiratory volume during the first second
FVC	forced vital capacity
HU	Hounsfield unit
IAP	intra-abdominal pressure
IC	inspiratory capacity
ICU	intensive care unite
I:E ratio	inspiratory to expiratory time ratio
MEF	maximal expiratory flow
MIF	maximal inspiratory flow
NIRS	near infrared light spectroscopy
FRC	functional residual capacity
OLV	one-lung ventilation
$PaCO_2$	partial pressure of carbon dioxide in arterial blood
PaO_2	partial pressure of oxygen in arterial blood
PEEP	positive end-expiratory pressure
P/f ratio	PaO_2/F_IO_2 ratio
PRVC	pressure regulated volume controlled ventilation
RM	recruitment maneuver

RV	residual volume
RR	respiratory rate
SD	standard deviation
TOI	tissue oxygenation index
TLC	total lung capacity
TLV	two-lung ventilation
VC	vital capacity
V_T	tidal volume
$ScvO_2$	central venous oxygen saturation
SpO_2	peripheral oxygen saturation
SvO_2	mixed venous oxygen saturation
Yrs	years
ZEEP	zero end-expiratory pressure

Introduction

Providing adequate ventilation to the patient is one of the corner stones of general anaesthesia. During mechanical ventilation oxygenation of the blood is reduced in most patients.[1–3] This reduction is to a large extent caused by formation of atelectasis.[4] The concept of atelectasis was first introduced by Benidixen et al in 1964.[3] Hedenstierna et al.[4] in 1985 confirmed that pulmonary densities are caused by a reduction of FRC and resorption of gas from poorly or non-ventilated regions. These densities occur in computerized tomography (CT) images in the dorsal, dependent regions of the lungs after induction of anaesthesia with the patient in the supine position. It has been demonstrated that atelectasis are present in 90% of anaesthetized patients within five minutes after induction.[4,5] This leads to impaired oxygenation, decreased lung compliance and reduced end-expiratory lung volume during anaesthesia. These atelectasis may also ensue into the postoperative period[6] and may cause postoperative hypoxemia and also pneumonia.[7–9]

In young, healthy patients undergoing minor surgery, pulmonary function is rarely a problem; patients are mostly easy to oxygenate during anaesthesia and postoperative atelectasis are rapidly eliminated as the patients are mobilized.[6] In more susceptible patients, in major thoracoabdominal surgery and during mechanical ventilation in high risk situations[10] atelectasis may pose a bigger problem if not handled correctly, with an increased risk of ventilator induced lung injury.[11]

Formation of atelectasis

Atelectasis formation occurs mainly from three mechanisms. 1) Compression atelectasis that occurs when pleural pressure from surrounding tissue compresses lung tissue thereby causing lung collapse. This is commonly seen in otherwise healthy obese patients during anaesthesia and during traumatic and surgically induced tension pneumothorax. 2) Gas absorption atelectasis that develops when F_IO_2 is increased and the inert nitrogen is decreased leading to lower alveolar gas tension making the alveoli more prone to collapse.[12] Gas absorption also occurs without increased F_IO_2 when airways are closed while blood flow to the region is intact, leading to lower gas tension in the alveoli.[13] 3) Surfactant depletion, leading to increased surface

tension of the alveoli and a higher tendency for alveolar collapse. This can be seen for example when ventilating a lung with cyclic opening of collapsed lung tissue (tidal recruitment).

The impairment in gas exchange in atelectasis is due to shunting of the blood in the dependent dorsal areas of the lung where most of the atelectasis are seen. Areas with reduced ventilation/perfusion ratio may also contribute to impaired gas exchange.

Open lung concept

According to a recent study by Amato et al.[14], any maneuver that leads to lower ventilatory driving pressures reduces mortality in ARDS patients. Whether this translates to less ventilator-induced lung injury in anaesthetised obese patients or during one-lung ventilation is currently unknown. However, increasing evidence suggests that ventilation with high tidal volumes and increased airway pressures is harmful to the lungs, not only in ARDS,[15] but also in mechanically ventilated ICU patients without lung injury[11] and during anaesthesia for major surgery.[11,16]

Special situations

In many patients, the risk of pulmonary complications, per- and postoperatively, is increased. Both type of surgery and coexisting morbidity increase the risk for pulmonary complications. For example, prolonged abdominal surgery and thoracic surgery are associated with a higher incidence of postoperative pulmonary morbidity.[10,17,18] Obese patients are especially prone to develop atelectasis[6] while other patients, like patients with heart disease, COPD, and tobacco smokers are predisposed to complications such as pneumonia and respiratory failure.[9,10]

Sometimes the surgical procedure in itself can cause ventilatory problems. An example of this is thoracoscopic surgery for atrial fibrillation where ventilation of one lung at a time is necessary to optimize the conditions for surgery. To further facilitate surgery by increasing exposure, the pleural cavity on the non-ventilated side is filled with carbon dioxide to a pressure of 12-14 mm Hg (equivalent to 16 to 19 cm H_2O), *capnothorax.* This combination of increased thoracic pressure and sequential non-ventilation of the lungs induce atelectasis and pose a major anaesthetic challenge in upholding adequate pulmonary gas exchange and hemodynamic stability during surgery.

Focus of this thesis

- The effect of recruitment maneuvers and PEEP in anaesthetized obese patients, measured with computerized tomography (CT).

- The possibility to predict amount of atelectasis in anaesthetized obese patients (BMI > 40 kg/m^2) with preoperative spirometry.

- Creating an experimental model of one-lung ventilation with capnothorax to perform, measure and analyze different interventions on cardiopulmonary physiology with special regard on safe and effective treatment of atelectasis.

- Using this animal model of one-lung ventilation with capnothorax to determine an optimal PEEP-level for oxygenation and ventilation without compromising hemodynamics.

Obesity

The prevalence of obesity continues to rise, both in the United States[19] and globally.[20,21] It has recently been reported that gastric bypass surgery is effective not only for weight reduction but also reduces both morbidity and mortality due to obesity.[22–24] Thus it seems likely that there will be more obese patients undergoing surgery in the future. In morbidly obese subjects compared to normal weight subjects, general anaesthesia and paralysis lead to more atelectasis, severe alterations in respiratory mechanics, and an increased risk of hypoxemia. The amount of atelectasis formation has been shown to correlate with body weight.[25] In addition, atelectasis is sustained into the postoperative period to a higher extent in morbidly obese patients. Previously, Eichenberger *et al*[6] have demonstrated that 8% of the total lung area in obese patients were atelectatic 1 h after extubation and that the atelectasis remained 24 h later. Postoperative pneumonia and respiratory failure after bariatric surgery are not very frequent, but still account for approximately one fifth of the postoperative morbidity and are associated with significantly increased 30-day mortality.[26]

Predicting atelectasis in obese patients

Detection and treatment of atelectasis and impaired gas exchange is of vital importance for the anaesthetist, especially in the obese patient where an increased amount of atelectasis may cause both peroperative and postoperative complications. The amount of atelectasis and impairment in oxygenation after induction of anaesthesia and paralysis in obese patients is highly varia-

ble,[5,27] thus there is a need for effective ways to predict and treat atelectasis and impaired oxygenation both during invasive mechanical ventilation and after extubation.

Pulmonary function in obese patients scheduled for bariatric surgery has been evaluated with spirometry, diffusing capacity and arterial blood gas analysis. The value of these tests in predicting postoperative pulmonary complications has been questioned except in selected patients.[28–30] Patients with severe obesity and patients with obstructive pulmonary disease have been suggested to benefit from more extensive pulmonary function testing.[31,32] However, to our knowledge no studies to date have addressed the issue of whether a preoperative evaluation can predict the risk of perioperative atelectasis and hypoxemia.

Prevention and treatment of atelectasis

Different strategies to improve respiratory function in anaesthetized obese patients have been investigated. Application of a positive pressure during preoxygenation decreases the formation of atelectasis.[33,34] Preoxygenation with a F_IO_2 of 0.8 and less also decreased the amount of atelectasis compared to when 100% inspired oxygen was used in normal weight subjects.[35] However, a reduction of F_IO_2 during preoxygenation reduces the time to desaturation, thereby increasing the risk for hypoxemic events in obese patients where time to desaturation is already decreased due to reduced FRC.

Increases in tidal volume or respiratory rate however during mechanical ventilation, do not improve oxygenation.[36,37] Recruitment maneuvers have been suggested to further improve oxygenation before application of PEEP in obese patients.

In normal weight patients, a recruitment maneuver with an inspiratory pressure of 40 cm H_2O for 10 seconds efficiently reduces atelectasis, improves oxygenation and also improves respiratory mechanics.[38] After a successful recruitment maneuver, atelectasis reappears very slowly if 40% O_2 is used.[39] However, with 100% O_2, it is necessary to apply PEEP to prevent atelectasis from rapidly recurring.[40] Beach chair position has also been shown to effectively improve respiratory mechanics and oxygenation in obese patients during anaesthesia, especially in combination with PEEP.[41] In postoperative mechanically ventilated obese patients (mean body mass index 51), a PEEP of 10 cm H_2O improved PaO_2, respiratory compliance and end-expiratory lung volume (EELV) after abdominal surgery.[42] This was in contrast to patients of normal weight where PEEP had no beneficial effects. The effect of PEEP and recruitment maneuvers has not been evaluated with computerized tomography (CT) in morbidly obese patients. Neither have the independent effects of recruitment maneuvers and PEEP been investigated within this group of patients.

Capnothorax

In order to provide safe measures to prevent and treat formation of atelectasis during one-lung ventilation (OLV) with capnothorax there is a need to outline the physiology of the anaesthetic situation during thoracoscopic surgery. Not least is this important with respect to high-risk patients, since these patients presently may be disqualified for surgery because of anaesthetic risk associated with marked cardiopulmonary dysfunction or morbid obesity. In order to characterize the physiology in detailed fashion that the clinical situation does not permit we set up a porcine model.

Physiology during capnothorax

The physiology during OLV with capnothorax is largely unclear since previous knowledge of OLV may not be entirely applicable.[43] Management of ventilation and hemodynamics during thoracoscopic surgery with OLV can be challenging.[44–47] This is especially true when surgical exposure is enhanced by intra-pleural CO_2 insufflation, capnothorax,[48–52] creating a condition similar to tension pneumothorax.

The procedure includes the use of the supine position, the sequential closure of the lungs and carries the risk of prolonged hemodynamic impairment and CO_2-accumulation.

The sequential bilateral OLV and insufflation of CO_2 means that both lungs will suffer almost complete atelectasis. During the second closure, the previously atelectatic lung has to provide the entire gas exchange. This may lead to an increased mechanical stress to the lung and potentially impaired gas exchange.[53] For instance, to avoid excessive hypercapnia and respiratory acidosis, ventilation beyond conventional lung protective protocols may be required. Also, in the lateral decubitus position, the perfusion during OLV tends to match the ventilation of the dependent lung.[54] However, in the supine position, the diversion of blood-flow from the non-ventilated lung may be less effective. Hypoxic pulmonary vasoconstriction will still be activated but without the added effect of gravitation.[54]

Although improved hemodynamics have been reported after moderate hypercapnia,[49] the appropriate extent of “permissive hypercapnia” in this setting is unknown.

Optimal PEEP during one-lung ventilation with capnothorax

OLV has been demonstrated to cause injury to the ventilated lung.[11,55,56] During OLV, low tidal volumes of 5 ml/kg and a PEEP of 5 cm H_2O compared with conventional ventilation with 9 ml/kg and ZEEP, caused less systemic inflammation, improved lung-function and facilitated earlier extubation[55] but can also result in lower oxygenation.[57]

Postoperative pulmonary complications are common after OLV with sequential capnothorax.[56] This underlines the rationale to use protective ventilation also during surgery, and provides an incentive to proactively optimize the peroperative situation in order to decrease the risk of postoperative pulmonary complications. Since sequential one-lung ventilation is common there is an increased risk for ventilator induced lung injury (VILI) in both lungs. Thus, respiratory and hemodynamic perturbations such as hypoxemia, carbon dioxide retention and hypotension are common during this procedure.[58–60] Optimization of the anaesthesia technique including perioperative cardiopulmonary management is likely to mitigate these perturbations. Key factors that need to be monitored and optimized during the perioperative period include complete lung separation, gas exchange and hemodynamic responses.

Alveolar recruitment improves ventilation in terms of pulmonary gas exchange in patients undergoing OLV both with and without capnothorax.[61,62] Clinically, a PEEP level of 5-10 cm H_2O is often recommended in order not to compromise venous return and circulation.[61,63] It is reasonable to assume that a PEEP level below the capnothorax pressure will have no negative effect on the hemodynamics per se. However, if PEEP is lower than the intrapleural pressure (CO_2-insufflated pressure) the ventilated lung is probably prone to collapse during expiration.

Thus, we hypothesized that a PEEP-level set at the same pressure as the CO_2 insufflation would keep the ventilated lung open allowing adequate oxygenation and gas exchange while not compromising the hemodynamics further. To that end, we designed a porcine experiment with decremental PEEP after an alveolar recruitment maneuver during OLV with capnothorax.

Aims

Paper I

The aim was to determine whether a recruitment maneuver followed by PEEP would be the most efficient way to improve respiratory function by reducing atelectasis in morbidly obese patients during general anaesthesia and paralysis in the supine position

Paper II

The aim was to investigate whether the results of a preoperative lung function test can predict the degree of alteration in lung mechanics, gas exchange and atelectasis formation after induction of anaesthesia in morbidly obese patients.

Paper III

The aim was to investigate the fundamentals of the OLV/capnothorax physiology with special regard to formation and treatment of atelectasis. To that end, we developed a porcine model to mimic the clinical setting during OLV with capnothorax. We characterized the effects on systemic perfusion and used electronic impedance tomography (EIT) for characterization of ventilation and pulmonary perfusion.

Paper IV

The aim was to identify optimal PEEP during OLV with capnothorax with a pleural insufflation pressure of 16 cm H_2O. Evaluation included electric impedance tomography (EIT), computerized tomography and lung volume measurements.

Materials

Paper I & II

Thirty patients with American Society of Anesthesiologists physical status classification system grade II or III, with a body mass index greater than 40 kg/m^2, aged 25 to 54 yrs., and scheduled for elective gastric bypass surgery en-Roux were enrolled in this prospective, single-blind randomized study. The local ethics committee at Uppsala University, Uppsala, Sweden, approved the study. Informed consent was obtained from all patients.

Exclusion criteria were: 1) age below 18 yrs., 2) pregnancy, 3) cardiac disease (history of ischemic heart disease and New York Heart Association [NYHA] class III or IV), 4) obstructive pulmonary disease, defined as forced expiratory volume below 70% of expected value.

Paper III & IV

Five piglets in paper III and eight piglets in paper IV (weighing 25 to 30 kg) of the Hampshire, Yorkshire, and Swedish country breeds obtained from a local breeder were used in the studies. The animals fasted overnight with free access to water. All piglets underwent the same study algorithm (anaesthesia, preparation, measurements and blood samples). The studies were conducted as prospective animal experiments and the Animal Ethics Committee at Uppsala University, Sweden approved the study protocols. The National Institute of Health guidelines for animal research were followed.

Methods

Paper I

Anaesthesia management

All patients received premedication with 1g of acetaminophen and 15 mg of midazolam orally 30 to 60 min before induction of anaesthesia.

Before induction of anaesthesia, preoxygenation was given during 5 min by using 100% O_2 and a tight seal mask. General anaesthesia was induced with intravenous propofol, fentanyl and rocuronium, followed by oral intubation. For maintenance, a continuous infusion of propofol and additional doses of fentanyl were given to obtain a clinically adequate depth of anaesthesia. After induction, all patients were mechanically ventilated with volume-cycled ventilation. Inspired oxygen fraction was 0.5, and ZEEP was applied. Tidal volumes were set at 10 ml/kg predicted body weight with an initial respiratory frequency of 12 breaths/min. Respiratory rate was adjusted to maintain $EtCO_2$ at 34 to 41 mm Hg, whereas tidal volumes were not changed. Inspiratory/expiratory ratio was 1:2, and the plateau pressure percentage was 28.5% of the inspiratory time.

Interventions

The patients were randomized into one of three interventions:
1) PEEP: PEEP of 10 cm H_2O; 2) RM + ZEEP: recruitment maneuver followed by ZEEP; 3) RM + PEEP: Recruitment maneuver followed by PEEP of 10 cm H_2O.

The recruitment maneuver was performed in the following way: ventilator mode was switched to pressure control, inspiratory pressure was increased to 55 cm H_2O, and an inspiratory hold was kept for 10 s. In case of a drop in systolic blood pressure by more than 20%, the recruitment maneuver would have been disrupted. In the recruitment maneuver followed by PEEP group, PEEP was applied immediately after the recruitment maneuver. Measurements were obtained: 1) before anaesthesia induction, 2) 5 min after induction and tracheal intubation, and 3) 5 min, 4) 20 min, and 5) 40 min after intervention (no CT). We aimed to do all the CT investigations at end-expiration in awake patients by asking them to exhale normally and hold their

breath until the CT was completed, and in the anaesthetized subjects by making an end-expiratory hold on the ventilator (fig. 1).

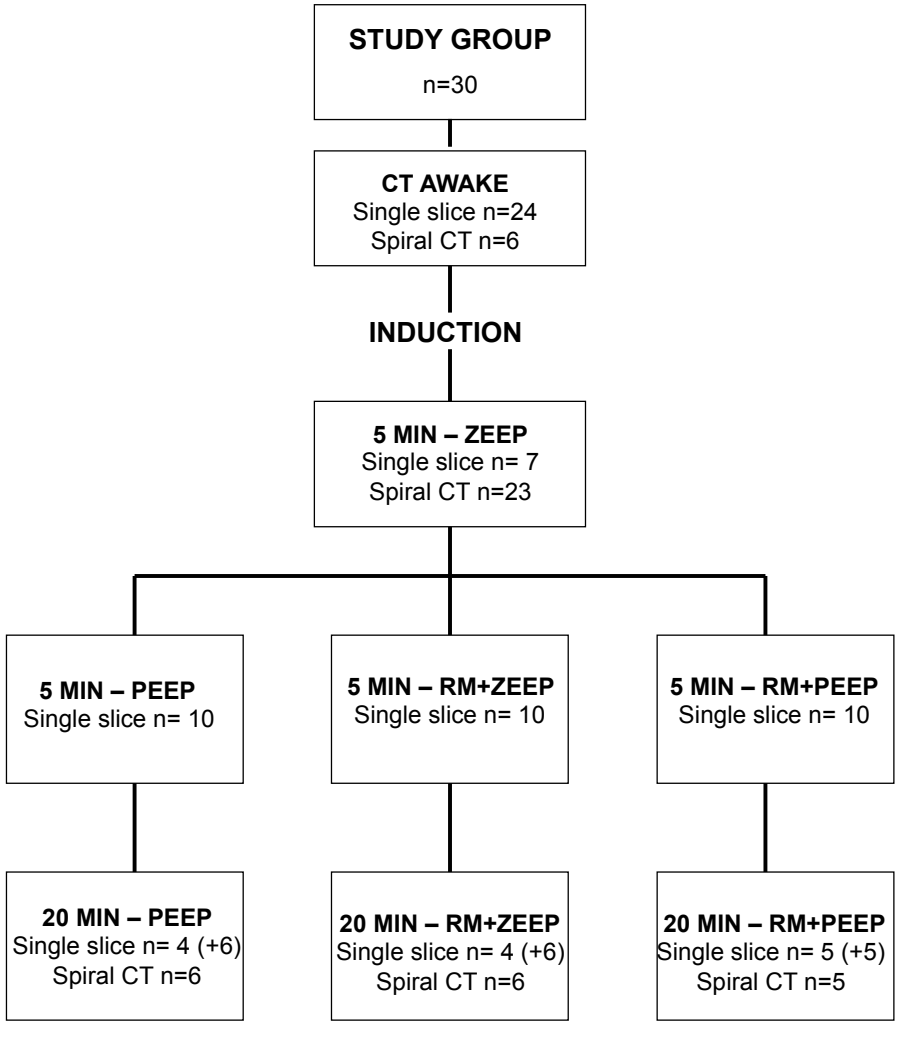


Figure 1. Computerized tomography (CT) protocol. Spiral CT was performed at two occasions in 23 of 30 patients. Spiral CT was done before and after induction of anaesthesia in 6 patients and before and 20 min after intervention in 17 patients. There were 6 patients in the PEEP and RM + ZEEP groups and 5 patients in the RM + PEEP group. Single slices were done separately and also retrieved from the spiral CT scans, so that single slices 1 cm above the diaphragm could be analyzed in all 30 patients at all four time points. CT = computerized tomography, PEEP = positive end-expiratory pressure, RM = recruitment maneuver, ZEEP = zero end-expiratory pressure.

Analysis of Spiral CT

The fractional volumes of overaerated, normally aerated, poorly aerated, and nonaerated lung tissues were calculated, with the lungs divided into three segments: base, middle, and apex. Each segment contained 8 ± 2 consecutive slices at 9-mm slice thickness. The CT images were analyzed by using the custom-made software package MALUNA (Mannheim lung analysis tool) (Maluna 2.02 Mannheim, Germany) based on the graphical programming Language G (LabView®-5.1, ImaqVision®-5.0, National Instruments, Austin, TX).

Analysis of Single-slice CT

Within the region of interest for atelectasis, the nonaerated lung tissue (-100 to +100 HU) was calculated and divided by the area of the region of interest containing the whole lungs.

Paper II

Protocol

Spirometry was performed 2 to 10 days preoperatively and included vital capacity (VC), forced vital capacity (FVC), forced expiratory volume during the first second (FEV_1) and flow-volume curves with maximal expiratory flow (MEF), maximal inspiratory flow (MIF) and expiratory flows (FEF_{25}, FEF_{50} and FEF_{75}, where 25%, 50% and 75% of the FVC have been expired, respectively). FEV_1/VC% was calculated as highest FEV_1 in percent of the highest of VC or FVC. Spirometry and diffusing capacity for carbon monoxide (DLCO) including DLCO corrected for alveolar volume (DLCO/VA) was performed using a Masterlab Trans Spirometer (Erich Jaeger AG, Würzburg, Germany). Lung volumes including total lung capacity (TLC), functional residual capacity (FRC), residual volume (RV), inspiratory capacity (IC) and expiratory reserve volume (ERV) were obtained with Masterlab Body Plethysmograph (Erich Jaeger AG, Würzburg, Germany). FRC and RV were then calculated in percent of TLC.

At each assessment, spirometry was performed at least three times to be able to meet the criteria of the American Thoracic Society/European Respiratory Society[64] and the best measurement was used for statistical analysis. Measurements were performed in the sitting position and recorded at body temperature and ambient pressure. Reference values were taken from the European Respiratory Society.[65]

An obstructive syndrome was defined as FEV_1/FVC ratio less than 70% and a restrictive syndrome as TLC less than 70% of predicted value. Also

note the change of definition of obstructive syndrome since the publication of paper I.

Measurements (see Paper I) were obtained: 1) before anaesthesia induction, 2) five min after induction and endotracheal intubation.

Anaesthetic management and computerized tomography was performed according to description in paper I.

Paper III

Anaesthetic management

The pigs were premedicated by an intramuscular injection of tiletamine and atropine. After increased depth of anaesthesia with bolus doses of propofol and fentanyl, the pigs were orally intubated. Anaesthesia was maintained by continuous infusions of propofol, fentanyl and pancuronium. An infusion of Ringers solution, 10 ml/kg/h, was administered during the first two hours of the protocol. The infusion rate was then lowered to 5ml/kg/h for the rest of the experiment. All piglets received fluid boluses of 5 ml/kg/h followed by iv. bolus doses of 0.1 mg phenylephrine if signs of hemodynamic instability occurred.

Airway & Ventilation

During baseline settings and the two-lung ventilation (TLV) periods, the animals were mechanically ventilated with pressure regulated volume controlled ventilation. Inspired oxygen fraction was 0.5, PEEP was 5 cm H_2O, tidal volume 10 ml/kg with an I:E ratio of 1:2 using a Servo *i* ventilator (Maquet, Solna, Sweden).

Respiratory rate (RR) was adjusted to keep an arterial $PaCO_2$ of 35 to 45 mm Hg throughout the protocol. If reaching maximum respiratory rate (35/min) with risk of dynamic hyperinflation, V_T was kept constant and increased $PaCO_2$ was accepted.

A median tracheotomy was performed, and the orotracheal tube was replaced by a size 35 right-sided, double-lumen tube (Mallinckrodt), positioned with the tip in the left main bronchus under fiber-bronchoscopic control.

During capnothorax the contralateral lung was ventilated with V_T set to 7 ml/kg, PEEP 5 cm H_2O, I:E ratio 1:2 and RR 12 to 35 breaths/minute with pressure regulated volume controlled ventilation.

During the protocol lung recruitment maneuvers (RM) were performed in the following way; ventilator mode was switched to pressure control, I:E ratio was changed to 1:1, respiratory rate was decreased to 8 breaths per minute and inspiratory pressure level was increased to achieve a peak pres-

sure of 40 cm H_2O with a PEEP of 15 cm H_2O. These settings were kept for two minutes.

Monitoring & Measurements

Electrical impedance tomography

EIT is a non-invasive monitoring tool that allows real-time imaging of ventilation and perfusion. EIT data were acquired using the ENLIGHT platform for impedance tomography.[66–69] The prototype is capable of producing 50 cross-sectional, real-time images of the lungs per second with thirty-two electrodes equidistantly placed around the circumference of the thorax just below the level of the axilla.

EIT gives two kind of functional images: 1) *Ventilation-maps*, where relative impedance changes reliably track local changes in the content of air within the lung, pixel by pixel.[70,71]

2) *Perfusion-maps* obtained by injecting a bolus of 5 ml of a hypertonic solution (NaCl 20%) into a central venous catheter during an expiratory breath hold for 20 seconds. The resulting regional time-impedance curves are then analyzed to quantitatively assess regional perfusion.[71–73]

Circulation and oxygenation

A flow-directed pulmonary artery catheter and a single lumen central venous catheter were inserted into the right external jugular vein. After reaching wedge position the balloon was deflated and the catheter was used for cardiac output measurements, pulmonary artery pressures and mixed venous blood gases.

A triple lumen fiber optic catheter for continuous venous saturation measuring and rapid injection of NaCl contrast boluses was placed in the left external jugular vein. An arterial catheter for continuous arterial pressure measurements and arterial blood sampling was inserted into the left femoral artery.

For measurement of cerebral Tissue Oxygenation Index (TOI), Near Infrared Light Spectroscopy (NIRS) probes were placed over the parietal skull and shielded from ambient light. A suprapubic urinary catheter was placed for monitoring of urine output and intra-abdominal pressure. Peripheral oxygen saturation (SpO_2) and electro-cardiographic monitoring was initiated (fig. 2).

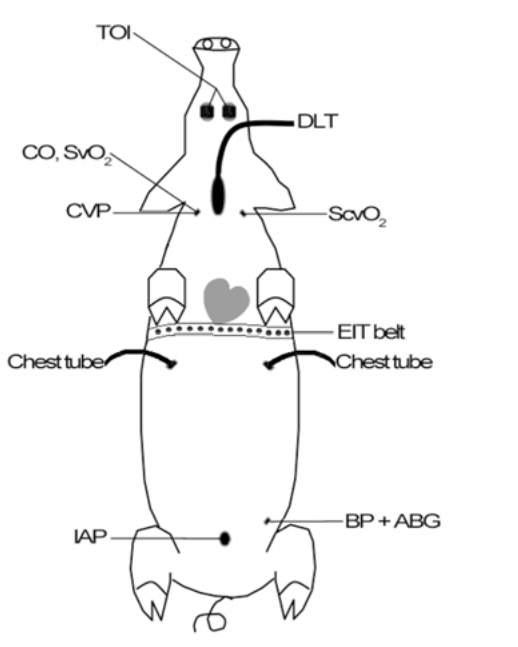


Figure 2. Set-up of experiment

Schematic illustration of the pigs after preparation.

The double lumen tube was placed under direct vision through a fiber-optic bronchoscope and tightly sutured to a tracheal ring. The chest tubes positions were verified with a chest x-ray.

ABG = arterial blood gases; BP = blood pressure; CO = cardiac output; CVP = central venous pressure; DLT = double lumen tube; EIT = electrical impedance tomography; IAP = intra-abdominal pressure; $S_{CV}O_2$ = central venous oxygen saturation; S_VO_2 = mixed venous oxygen saturation; TOI = tissue oxygenation index.

Protocol

After initial preparation and a 30 min stabilization period, an intra-pleural chest-tube was inserted into the right pleural space. This was done after clamping of the tracheal lumen side of double-lumen tube. The positions of the double-lumen tube and the chest tube as well as lung collapse were radiographically verified.

Right-sided capnothorax was then established with a CO_2-insufflator connected to a Verres-needle inserted through an airtight membrane into the chest-tube. Automatically adjusted insufflation pressure was set to 14 mm Hg. Dynamic visualization of capnothorax was followed with EIT.

During OLV with capnothorax recruitment maneuvers to the ventilated lung were performed at 20 and 40 minutes. After the RM, ventilator settings were changed to previous settings except for PEEP: 5 cm H_2O at OLV 20

min and 10 cm H_2O at OLV 40 min. Following the RM at 40 min pleural CO_2 exsufflation and suctioning in the chest-tube with 15 cm H_2O were performed.

To mimic conditions during the surgical procedure, TLV was reestablished and a RM was performed using the same settings as above. Lung expansion was verified radiographically and with EIT. TLV with baseline ventilator settings was maintained for 30 min.

This was followed by 40 min of left-sided capnothorax with right-sided OLV, performed and monitored as on the left side. After the second capnothorax period, TLV was again established and performed as the first TLV period and maintained for 30 min (fig. 3).

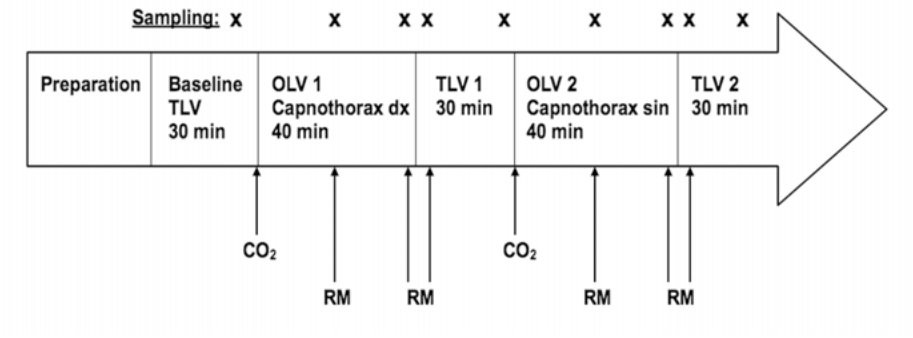


Figure 3. Workflow and data collection points (x).

Hemodynamics, ventilation, and gas exchange data were assessed in the supine position and EIT measurement was performed at each time point for data collection.

The data collection made after each intervention affecting ventilation or changes in ventilatory settings.

CO_2 = carbon dioxide; EIT = electrical impedance tomography; Dx = dexter; OLV = one-lung ventilation; RM = recruitment maneuver; sin = sinister; TLV = two-lung ventilation.

Paper IV

Anaesthetic management was conducted in the same way as in Paper III.

Airway and ventilation

Five to 10 min after premedication and immediately after deepening of anaesthesia, the trachea was intubated with an ID 7.0 mm cuffed endotracheal tube (Mallinckrodt, Athlone, Ireland). During the whole protocol, the animals were mechanically ventilated with pressure regulated volume controlled ventilation (PRVC) (Servo *i*, Maquet, Solna, Sweden) and the inspired oxygen of fraction (F_IO_2) was 1.0. During preparation with TLV, positive end-expiratory pressure (PEEP) was 5 cm H_2O, tidal volume (V_T) 10 ml/kg and I:E ratio was 1:2. A median tracheotomy was performed, and the orotracheal tube was replaced by a size 35 right-sided, double-lumen tube (Mallinckrodt), positioned with the tip in the left main bronchus under fiber-bronchoscopy control (EF-B 14L, Xion medical, Berlin, Germany). Respiratory rate (RR) was set to 20 breaths per minute and an increased $PaCO_2$ was accepted. Gas flow and airway pressures were measured at the proximal end of the endotracheal tube (CO2SMO Veterinary CO2 Monitor and Pulse Oximeter, Respironics, Pittsburgh, PA, USA). For oxygen saturation, end-tidal CO_2 and hemodynamic measurements, a standard monitor was used (SC 9000 XL, Siemens, Erlangen, Germany). End-expiratory lung volume (EELV) was measured with a washout technique using sulfurhexafluoride (SF_6).

Left-sided capnothorax was established with a CO_2-insufflator (7060-Insufflator, Pelvi-Pneu, Semm Systems, Wisap, Munich, Germany) connected to a Verres needle inserted through an airtight membrane into the chest tube. Automatically adjusted insufflation pressure was set to 16 cm H_2O.

Monitoring and measurements

Electrical impedance tomography data were acquired and analyzed as in paper III.

Computerized tomography

CT scans were acquired using a Somatom definition CT scanner (Siemens Healthcare GmbH, Erlangen, Germany). CT scans were made in three pigs at every PEEP level from 20 cm H_2O to ZEEP at end-expiratory hold. The transversal CT cut had a slice thickness of 8 mm and the exposure was done with 120kV, 210 mA and collimation of 0.6 mm.

Analysis of Computerized tomography

Using the Osiris medical imaging®-software (version 4.19, University Hospital of Geneva, www.expasy.ch/UIN), two 8 mm transverse slices separated by three 8 mm slices, i.e., 24 mm, corresponding to the EIT-belt, were analyzed for each step in the PEEP titration. These slices were chosen to minimize artefacts from the belt while as accurately as possible represent the same lung conditions as those measured with EIT. The ventilated lung was manually outlined keeping a 5 mm margin to the chest wall, the heart, mediastinal structures, major vessels and bronchi, the diaphragm, the capnothorax or partial volume-effects, but including any atelectasis. The software then registered the attenuation for each voxel in the chosen area grouping voxels less than 1 Hounsfield unit (HU) apart. In a second step the Luva©-software (version 1.0, 2005, Nico Heller) was used. Implementing commonly used arbitrary limits in HU, the software calculates the total amount of non-aerated (+100 to -100 HU), poorly aerated (-101 to -500 HU), normally aerated (-501 to -900 HU), and hyper inflated (-901 to -1000 HU) lung volume.

Circulation and oxygenation

Circulation and oxygenation was monitored as in paper III except for cerebral tissue oxygenation index that was not measured.

Protocol

Time points for data sampling are presented in figure 4. After initial preparation and a 30-min stabilization period, an intra-pleural chest tube was inserted into the left pleural space. This was done after clamping of the bronchial lumen side of the double-lumen tube. The positions of the double-lumen tube and the chest tube as well as lung collapse were radiographically verified with a Mobile C-arm x-ray device (OEC 7700, GE Healthcare, Salt Lake City, UT, USA). Real-time monitoring and visualization of capnothorax was enabled by EIT. After establishing capnothorax the contralateral lung was ventilated with V_T of 6 ml/kg, PEEP 5 cm H_2O, I:E ratio 1:2 and RR 20/min.

After 20 minutes of OLV with capnothorax and before the decremental PEEP trial, a lung recruitment maneuver (RM) of the ventilated lung was performed. The RM was performed as follows: ventilator mode was switched to pressure control; I:E ratio was changed to 1:1; respiratory rate was decreased to eight breaths per minute and inspiratory pressure level was increased to achieve a peak pressure of 40 cm H_2O with a PEEP of 20 cm H_2O. These settings were kept for 2 min. After the RM, ventilator settings were changed to previous settings except for PEEP that was set to 20 cm H_2O.

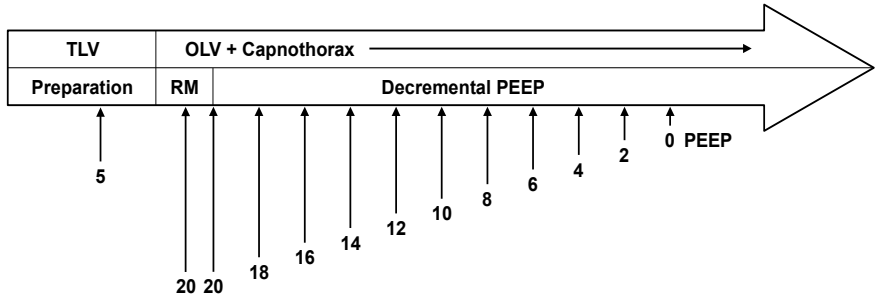


Figure 4. Timeline. Data collection was made after each intervention affecting ventilation or changes in ventilatory settings. The following cardiovascular and respiratory variables were recorded at baseline, at capnothorax 15 min and at every decremental PEEP level of 2 cm H_2O until ZEEP (indicated by arrows): Heart rate, mean arterial pressure, mean pulmonary artery pressure, central venous pressure, pulmonary artery occlusion pressure, EIT ventilation distribution, arterial and mixed venous blood gases. Cardiac output- and EIT perfusion distribution-measurements were recorded at baseline TLV, baseline OLV 15 minutes and at PEEP 20, 16, 12, 8, 4 and 0 cm H_2O.

EIT = electrical impedance tomography; OLV = one-lung ventilation; PEEP = positive end-expiratory pressure; RM = recruitment maneuver; TLV = two-lung ventilation; ZEEP = zero end-expiratory pressure.

Statistical analysis

In all studies data are expressed as means and standard deviation unless stated otherwise. In all calculations a p value less than 0.05 was considered significant.

Paper I

We assumed a difference of 50% in atelectatic area in a single CT slice between measurements of the different ventilator strategies. A sample size of 30 subjects (10 for each group) was estimated if the atelectatic area was 5% in the recruitment maneuver + PEEP group compared to 10% in the other groups with a SD of 2%. Comparisons between patient demographics were done by using analysis of variance (ANOVA) and Fisher exact test. Analysis of variance was also used to compare the levels of the outcome variables before intervention between the treatment groups. The analyses were done separately to evaluate the effect of induction of anaesthesia and the effect of different interventions. For each outcome, the following analyses were performed. A mixed-model was set up as a two-way repeated measures design by using unstructured covariance structure. This model only includes time as a factor. If the effect of time was significant and the data included more than two measures over time, pairwise comparisons between time points were done comparing least squared means estimated by the mixed-model. The same one-way design was used to evaluate the effect of induction of anaesthesia. Histograms of the residuals were examined visually to assess the fit of the above models. To obtain normality, the outcome values of atelectasis and EELV were log transformed.

Paper II

A paired t-test was used when comparing measurements over time and estimates were reported with a 95% confidence interval (CI). Data pertinent for prediction of lung function after anaesthesia were analyzed using univariate and multiple linear regression models. For each outcome variables with $p < 0.05$ in the univariate regression model were entered into a multiple regression model unless highly correlated. Correlations were calculated using

Spearman's rank correlation and a high correlation was regarded as $r > 0.8$. The R^2 value from the regression analyses was used to quantify predictive performance. SAS v9.4 and R v3.2 (R Foundation for Statistical computing, Vienna, Austria) was used for the analyses.

Paper III

In this summary of the thesis only descriptive statistics are presented due to the small number of animals. In the published paper the Shapiro–Wilk test was used to test data for normality. One-way repeated measures analysis of variance (ANOVA) and two-way repeated measures ANOVA were applied, depending on the presence of one or two within-subjects' factors, respectively. The Bonferroni adjustment for multiple tests was applied for post hoc comparisons. The statistical analyses were conducted by SPSS (version 20.0.0).

Paper IV

The Shapiro–Wilk test was used to test data for normality. Mixed-effects linear models were used to investigate if overall differences between time points were present. The mixed-effects models were set up using a repeated measures design assuming a compound structure covariance matrix with time of measurement entered as a factor variable. If the time component was significant, pair-wise comparisons between time points were made using LS-MEANS to pinpoint where significant differences were present. SAS v9.4 was used for the mixed-model analyses.

Results

Paper I

Thirty patients (23 women and 7 men) were included in the study (table 1). Another two patients were excluded from the study because of forced expiratory volume percentage less than 80% of expected.

Table 1. *Patient demographics of study population by study group in paper I, n = 30*.

Demographic	PEEP (n =10)	RM + ZEEP (n =10)	RM + PEEP (n = 10)	p value
Age (yr)	40 ± 10	37 ± 10	35 ± 8	ns
Men/Women (n°)	0/10	4/6	3/7	ns
Weight (kg)	120 ± 14	130 ± 13	126 ± 9	ns
Height (m)	1.64 ± 0.06	1.69 ± 0.08	1.69 ± 0.07	ns
BMI (kg/m^2)	44 ± 3	45 ± 4	45 ± 5	ns
Smoking history (n°)	6	5	4	ns

Data are presented as mean ± SD. BMI = body mass index; ns = non significant; PEEP = positive end-expiratory pressure; RM = recruitment maneuver; ZEEP = zero end-expiratory pressure.

Oxygenation

A recruitment maneuver followed by PEEP caused an increase in the PaO_2/F_IO_2 ratio ($p < 0.0001$) at 5 min, and this increase was sustained at 20 and 40 min after the recruitment maneuver ($p < 0.0001$). In contrast, PEEP alone or a recruitment maneuver followed by zero end-expiratory pressure did not cause any significant change in the PaO_2/F_IO_2 ratio at any time point. There was no significant difference in oxygenation among the three groups before intervention. Compared to awake, the PaO_2/F_IO_2 ratio was reduced by approximately 40% after induction of anaesthesia and paralysis ($p < 0.0001$) (fig. 5).

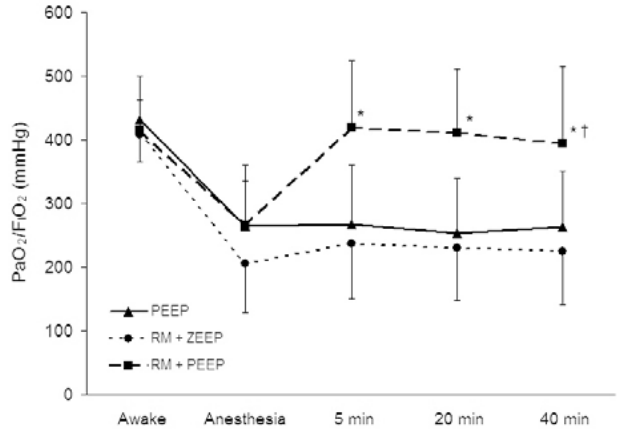


Figure 5. PaO_2/F_IO_2 in the three groups studied. Induction of anaesthesia caused a reduction of PaO_2/F_IO_2. In the RM + PEEP group, oxygenation returned to the same level as before induction of anaesthesia. In the groups with RM + ZEEP (n = 10) or PEEP (n = 10), there was no significant effect on oxygenation. * $p < 0.05$ versus anaesthesia; † $p < 0.05$ versus PEEP and RM + ZEEP. PEEP = positive end-expiratory pressure; RM = recruitment maneuver; ZEEP = zero end-expiratory pressure.

Hemodynamics

During the study, the mean arterial pressure was between 60 and 95 mm Hg, and heart rate was between 60 and 110 beats/min. There were no significant differences in hemodynamics among the groups.

Respiratory Compliance

After induction of anaesthesia, there was no significant difference in compliance among the groups. A recruitment maneuver followed by PEEP caused an increase in compliance ($p < 0.0001$). This effect was seen already at 5 min ($p < 0.0001$) and was less but still significant at 40 min ($p < 0.0001$). PEEP alone caused an increase in compliance ($p < 0.0001$). There was a small decrease in compliance in the recruitment maneuver followed by ZEEP group ($p = 0.0014$).

Spiral CT

Induction of anaesthesia and paralysis was accompanied by approximately 50% reduction of EELV. Twenty minutes after intervention, the EELV increased 32% in the PEEP group and 64% in the recruitment maneuver followed by PEEP group.

No changes in EELV were observed after a recruitment maneuver followed by ZEEP.

The atelectatic volume was 1 ± 0.5% before induction of anaesthesia and paralysis (six patients). At 5 min after induction, the mean atelectatic volume in all 23 patients who were studied with spiral CT was 11 ± 6%, with no significant difference among the groups. The increase in atelectasis after induction of anaesthesia and paralysis was most pronounced in the basal region (the part of the lung in the pleural sinuses), where it increased from 6 ± 4% to 29 ± 15% ($p < 0.0001$) (note, however, the small fraction of lung visualized in the basal CT slices), but was also present in the apical ($p = 0.0001$) and middle regions ($p < 0.0001$). Normally aerated lung-fraction decreased, but poorly aerated and overaerated fractional volumes did not change. Overaeration was always less than 1%. A recruitment maneuver followed by PEEP increased the fractional amount of normally aerated tissue, decreased the amount of poorly aerated tissue mainly at the apex and middle lung regions, and caused a major reduction of nonaerated tissue. A recruitment maneuver followed by ZEEP did not substantially affect the fractional amount of normally aerated, poorly aerated, or nonaerated tissue. In the group with PEEP without a preceding recruitment maneuver, there was an increase in normally aerated volume ($p = 0.0004$) and a reduction of poorly aerated volume ($p = 0.0014$), whereas atelectasis remained unchanged.

Single-slice CT

Single-slice CT was made in all 30 patients at the four different time points of measurement. Single-slice CT correlates with the upper part of the middle region in the spiral CT. Results from single-slice CT were comparable to spiral CT with minimal atelectasis (0.4 ± 0.7%) in awake patients and formation of atelectasis after induction of anaesthesia and paralysis (7 ± 5%). In figure 6, a representative CT scan done while awake, after induction of anaesthesia and paralysis, and 5 and 20 min after the three different interventions (PEEP, recruitment maneuver followed by PEEP, or recruitment maneuver followed by ZEEP) is shown.

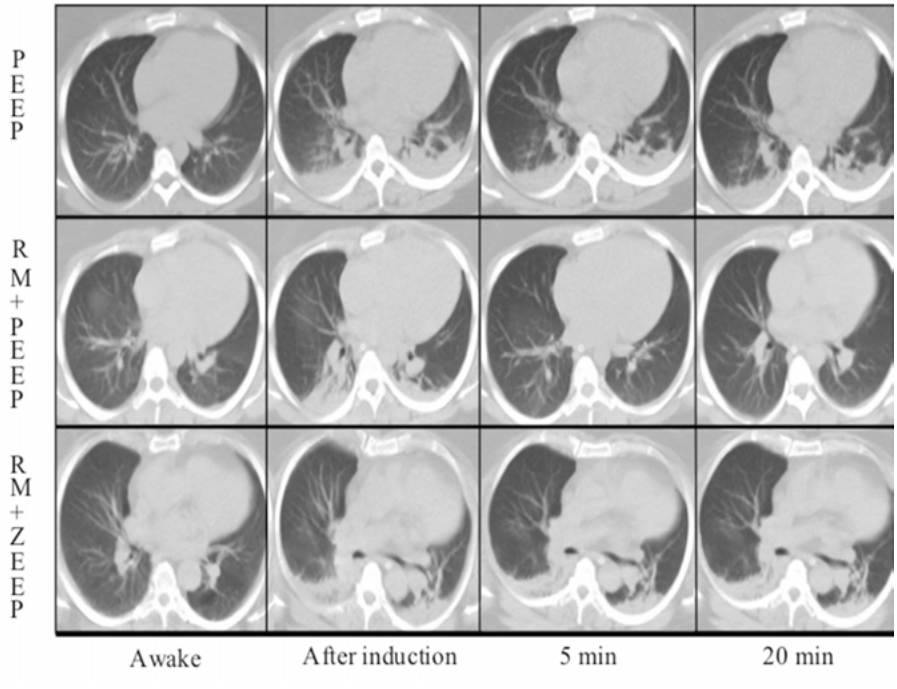


Figure 6. Representative computerized tomography (CT). A CT scan 1 cm above the diaphragm in the three different groups at all four time points. Note the sustained effect of RM + PEEP and the transient effect of RM + ZEEP. PEEP = positive end-expiratory pressure; RM = recruitment maneuver; ZEEP = zero end-expiratory pressure.

Paper II

General findings

Thirty patients (23 women and 7 men) with BMI > 40 kg/m^2 (mean 45 ± 4 kg/m^2) were included in the study. Two patients were excluded because they met the exclusion criterion of FEV_1/VC% of less than 70%.

TLC and FRC were within normal range and the ratio between them, FRC/TLC%, was also normal.

Conventional variables from forced expiratory and inspiratory vital capacities (VC, FVC, FEV_1, FIV_1) were all within normal limits, as was the transfer factor (or diffusion capacity) (DLCO). However, despite exclusion of patients with reduced FEV_1/FVC (the two mentioned above), forced expiratory flow was decreased during the latter part of expiration (FEF_{75}) but with FEF_{25} and FEF_{50} within normal range, findings suggestive of small airway obstruction. Patient characteristics and results of the lung function tests are presented in table 2.

Table 2. *Patient characteristics and results of lung function tests.*

Study population		**Lung function tests, % predicted**		**Lung function tests, % predicted**	
Age (yr.)	38 ± 9	TLC	104.7 ± 11.4	FIV_1	106.6 ±15
Men/Women (n°)	7/23	FRC	81.3 ± 13.5	FIV_1/VC	93.6 ± 4.8
Weight (kg)	124 ± 13	FRC/TLC	77.8 ± 10.5	FEF_{25}	98.2 ± 17.8
Height (m)	1.67 ± 0.07	VC	105.4 ± 12.6	FEF_{50}	83.2 ± 17.7
BMI (kg/m^2)	45 ± 4	FEV_1	102.2 ± 13.4	FEF_{75}	62.0 ± 18.4
Smoking history (n°)	20/30	FEV_1/VC	95.8 ± 4.7	DLCO	87.8 ± 23.8
Cigarette pack years	17.3 ± 9.7	MVV	92.2 ± 17.9	DLCO/VA	83.4 ± 18.3

Data are presented as mean ± SD. BMI = body mass index; FEV_1 = forced expiratory volume in 1 second; FIV_1 = forced inspiratory volume in one second; FEF = forced expiratory fraction; FRC = functional residual capacity; DLCO = diffusion capacity of the lung for carbon monoxide; DLCO/VA = diffusion capacity of the lung for carbon monoxide/alveolar volume; MVV = mandatory minute ventilation; TLC = total lung capacity; VC- vital capacity; Yr = years.

CT

Induction of anaesthesia and paralysis was accompanied by approximately 50% reduction of EELV (~ FRC) as measured in the 6 patients in whom a spiral CT was done (fig 1). Supine EELV after induction of anaesthesia was considerably smaller (697 ± 157 ml with a decrease of 690 ± 461 ml, CI 206 -1174 ml) than FRC awake (1387 ± 582 ml) (p = 0.01) (fig. 7).

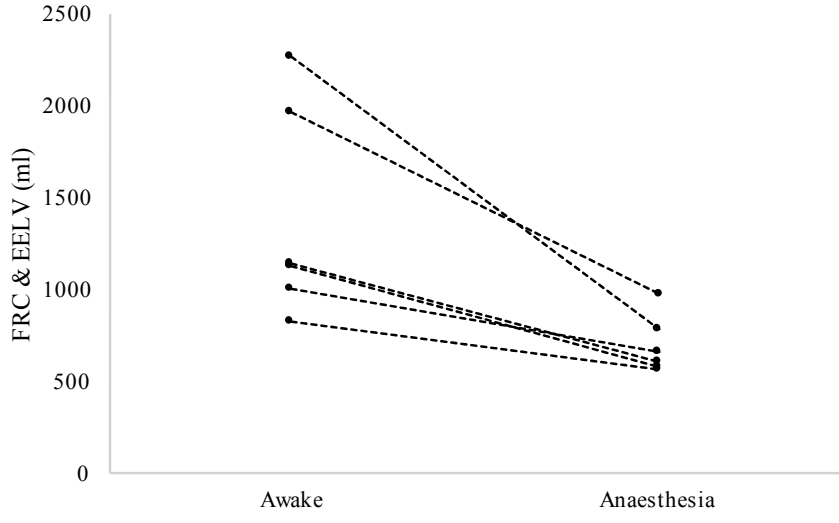


Figure 7. End-expiratory lung volume (EELV (~ FRC)) after premedication before anaesthesia (supine) and after induction of anaesthesia with muscle paralysis with ventilation without any end-expiratory airway pressure. EELV = end-expiratory lung volume; FRC = function residual capacity.

CT lung aeration

Amount of atelectasis in single slice CT (n =29) increased (with 7 ± 5%, CI 4 to 9%) from 0.4 ± 0.7% while awake in the supine position to 7 ± 5% after induction of anaesthesia ($p < 0.0001$).

In spiral CT (n = 6) the amount of atelectasis increased (with 14 ± 6%, CI 8 to 20%%) from 1 ± 0.5% to 15 ± 6% ($p = 0.002$). Poorly aerated lung tissue increased (with 14 ± 6%, CI 8 to 20%) from 28 ±12% to 42 ± 10 after induction of anaesthesia ($p = 0.002$). Normally aerated lung tissue decreased (with 29 ± 8%, CI 20 to 38%) from 71 ± 11% at awake to 42 ± 11% after induction of anaesthesia ($p = 0.0004$).

Lung function awake vs atelectasis and lung function during anaesthesia

Table 3. *Univariate regression analysis table.*

	Atelectasis			Compliance			Δ Oxygenation (PaO_2/F_iO_2)			EELV Anaesthesia		
Variable	**Beta**	**(CI)**	**p**	**Beta**	**(CI)**	**p**	**Beta**	**(CI)**	**p**	**Beta**	**(CI)**	**p**
Age	-0.001	[-0.003, 0.001]	0.407	-0.061	[-0.369, 0.247]	0.701	-0.055	[-0.491, 0.380]	0.806	**11.16**	**[2.645, 19.68]**	**0.018***
BMI	-0.001	[-0.008, 0.006]	0.711	-0.729	[-1.703, 0.245]	0.156	0.168	[-1.184, 1.520]	0.81	-12.77	[-42.20, 16.67]	0.41
Gender (Male vs Female)	-0.037	[-0.084, 0.011]	0.141	**7.903**	**[2.681, 13.125]**	**0.007***	4.783	[-4.271, 13.837]	0.31	9.687	[-180.9, 200.3]	0.922
Height	**-0.003**	**[-0.006, -0.001]**	**0.021***	**0.569**	**[0.292, 0.847]**	**<.0001***	0.059	[-0.483, 0.602]	0.832	9.537	[-1.242, 20.32]	0.098
Weight	**-0.002**	**[-0.003, -0.000]**	**0.034***	0.186	[-0.004, 0.376]	0.067	0.061	[-0.250, 0.372]	0.704	3.104	[-3.798, 10.01]	0.39
Smoking (Yes/no)	-0.021	[-0.063, 0.022]	0.351	-0.457	[-6.321, 5.407]	0.88	-2.399	[-10.661, 5.863]	0.574	14.55	[-176.0, 205.1]	0.88
Cigarette pack years	-0.001	[-0.004, 0.001]	0.386	-0.007	[-0.328, 0.313]	0.964	0.143	[-0.293, 0.579]	0.529	**14.70**	**[4.388, 25.02]**	**0.015***
VC % predicted	0.001	[-0.001, 0.002]	0.416	0.104	[-0.118, 0.325]	0.368	**0.312**	**[0.019, 0.604]**	**0.047***	3.336	[-3.385, 10.06]	0.34
FEV_1 predicted	0.001	[0.000, 0.003]	0.192	0.117	[-0.098, 0.332]	0.298	**0.345**	**[0.075, 0.616]**	**0.019***	1.578	[-5.203, 8.360]	0.65
FEF_{75} predicted	**0.001**	**[0.000, 0.002]**	**0.036***	0.045	[-0.105, 0.194]	0.564	0.165	[-0.046, 0.376]	0.136	-4.560	[-9.237, 0.117]	0.07

Univariate regression analysis of selected baseline characteristics and results of lung function tests and outcome after induction of anaesthesia. Beta signifies regression coefficient from patient characteristics and preoperative lung function testing. P-values of less than 0.05 are highlighted in bold numbers. BMI = body mass index; (CI) = 95% confidence interval; EELV = end-expiratory lung volume; FEF = forced expiratory flow; FEV_1 = forced expiratory volume during first second of expiration; Δ = difference in oxygenation between spontaneous breathing while awake and after induction of anaesthesia and muscle paralysis. * = $p < 0.05$.

Table 4. *Spearman correlations between predictor variables.*

	Age (yr)	BMI (kg/m^2)	Height (m)	Weight (kg)	Smoking (yes/no)	Cigarette pack years	VC % predicted	FEV_1 % predicted	FEF_{75} predicted	DLCO/VA % predicted
Age (yr)										
BMI (kg/m^2)	0.11									
Height (m)	0.03	-0.05								
Weight (kg)	0.25	0.55**	0.74***							
Smoking (yes/no)	-0.12	0	-0.17	-0.18						
Cigarette pack years	0.63**	-0.02	0.09	0.16	x					
VC % predicted	0.08	-0.06	-0.31	-0.21	0.14	0.17				
FEV_1 % predicted	-0.01	-0.1	-0.27	-0.22	0.05	0.15	0.91***			
FEF_{75} predicted	-0.35	-0.06	-0.22	-0.25	-0.32	-0.4	0.40*	0.55**		
DLCO/VA % predicted	0.25	-0.04	0.75***	0.60***	-0.55**	0.04	-0.51**	-0.50**	-0.11	
Gender (male/female)	-0.02	-0.14	0.67***	0.50**	-0.11	-0.23	-0.25	-0.22	-0.03	0.54**

BMI = body mass index; FEF = forced expiratory flow; FEV_1 = forced expiratory volume during first second of expiration; DLCO/VA= diffusion of the lung for carbon monoxide corrected for alveolar volume; Yr = years. * = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$.

Multiple regression analysis

Multiple regression results are presented in table 5. Two models were tested for atelectasis. Model 1 includes height, weight and FEF_{75}% predicted whereas model 2 only includes FEF_{75}% predicted. In model 1 none of the predictor variables are significant, for height and weight this could be caused by the high correlation between them (r = 0.74, table 3). Note however that although FEF_{75}% predicted is not significant in model 1, the beta estimate for FEF_{75}% predicted is the same in model 2. In both models atelectasis increases with increased $FEF_{75\%}$ predicted. Although the predictor variables are not significant in model 1, the drop in R^2 is large from 0.270 in model 1 to 0.153 in model 2.

Two models were also tested for the analyses of Semi-static lung compliance. Model 1 included gender and height whereas model 2 only included height. In model 1 the estimate for gender was not significant and lower than in the univariate analyses (beta from 7.9 to 2.3), the significant univariate effect of gender was partly due to the correlation with height. In both models Semi-static lung compliance is increased with height (cm). When removing gender in model 2 the R^2 value decreases slightly from 0.416 to 0.403.

Due to the high correlation between predictor variables significant in the univariate analyses for oxygenation, the model included only FEV_1. The fall in oxygenation increased with FEV_1.

EELV increased with age (years) (table 5).

Table 5. *Regression analysis of prediction of preoperative lung function on atelectasis, respiratory compliance, oxygenation and EELV.*

Outcome	Variable	Beta CI	P-value	Model R^2
Atelectasis (model 1)	Intercept	0.421 [-0.115, 0.957]	0.118	**0.27**
	Height (m)	-0.002 [-0.006, 0.002]	0.317	
	Weight (kg)	0.000 [-0.003, 0.002]	0.702	
	FEF_{75} predicted	0.001 [0.000, 0.002]	0.116	
Atelectasis (model 2)	Intercept	-0.001 [-0.068, 0.067]	0.988	**0.15**
	FEF_{75} predicted	0.001 [0.000, 0.002]	0.036	
Compliance (model 1)	Intercept	-46.12 [-113.213, 20.979]	0.1685	**0.42**
	Gender	2.349 [-4.583, 9.281]	0.490	
	Height (m)	0.474 [0.067, 0.882]	0.024	
Compliance (model 2)	Intercept	-61.41 [-110.409, -12.416]	0.016	**0.40**
	Height (m)	0.569 [0.278, 0.861]	0.0005	
Delta PaO_2/FIO_2	Intercept	-13.19 [-42.241, 15.871]	0.360	**0.19**
	FEV_1 % predicted	0.345 [0.062, 0.629]	0.019	
EELV	Intercept	362.84 [7.475, 718.208]	0.046	**0.25**
	Age (yr)	11.165 [2.097, 20.232]	0.018	

R^2 signifies how much of the difference in a variable from awake to anaesthetized that can be explained one or a combination of variables in the preoperative lung function test or baseline characteristics. As an example, to estimate a predicted value of EELV use the formula predicted = intercept + variable level * variable beta that is for age = 50 the predicted value for EELV would be 362.841 + 50*11.165 = 921.091. CI = 95% confidence interval; EELV = end-expiratory lung volume; FEF = forced expiratory flow; FEV_1 = forced expiratory volume during first second of expiration; Yr = years.

Paper III

Four piglets survived the entire experiment, and one suffered fatal hemodynamic collapse at the end of the first OLV period. In four cases, there was a complete separation between right and left lung during OLV, and in one case the separation was partial. Gas exchange data are presented in figure 8.

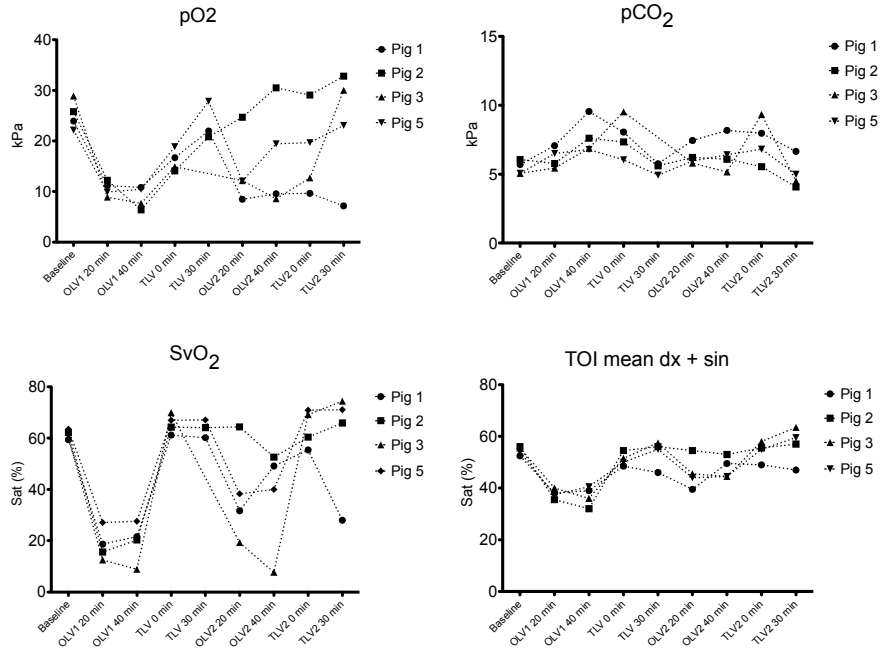


Figure 8. Gas exchange. Gas exchange measurements are presented. Samples were drawn from an arterial line (PaO_2, $PaCO_2$), a pulmonary artery catheter (SvO_2) or collected from NIRS (TOI) (mean value of readings from electrodes placed over the right and left parietal lobe of the brain). Each line represents one animal.

PaO_2 = partial pressure of oxygen in arterial blood; $PaCO_2$ = partial pressure of carbon dioxide in arterial blood; SvO_2 = mixed venous oxygen saturation; TOI = tissue oxygenation index

Hemodynamics

During right-sided capnothorax, SvO_2 as well as the NIRS tissue oxygenation index (TOI) decreased, SvO_2: 61 ± 2% to 18 ± 6% TOI dx: 55 ± 2% to 39 ± 6% and TOI sin: 54 ± 5% to 36 ± 4%. There was also an increase in central venous pressure and a decrease in mean arterial pressure and cardiac output. During the left-sided capnothorax the hemodynamic impairment was less than during the right side (fig. 9).

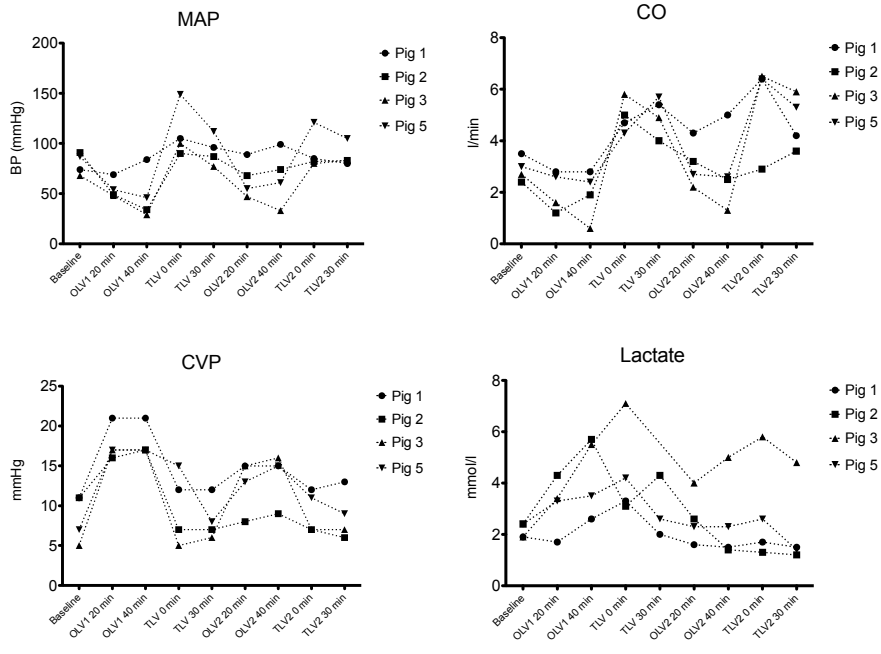
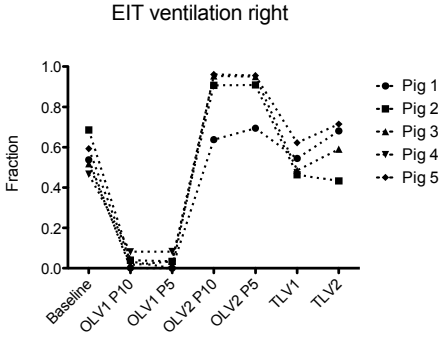


Figure 9. Hemodynamics. Hemodynamic measurements are presented. CO was measured with thermo-dilution, and lactate was measured in arterial blood drawn from the left femoral artery. Each line represents one animal.

CVP = central venous pressure; CO = cardiac output; MAP = mean arterial pressure; OLV = one-lung ventilation; TLV = two-lung ventilation.

Regional pulmonary ventilation by EIT

At baseline, the ventilation was slightly unequal between the two lungs (56 ± 8% vs. 44 ± 8%; right vs. left, respectively), and between the upper and lower regions (54 ± 6% vs. 46 ± 6%, respectively). During the first period of OLV/capnothorax, no or very minor ventilation on the right side could be seen (3 ± 3% vs. 97 ± 3%, right vs. left, respectively). During the first TLV period, ventilation was completely restored. The collapse of the left side during the second OLV/capnothorax was almost complete in three (94 ± 4% vs. 6 ± 4%, right vs. left, respectively) and partial in one (67% vs. 33%, right vs. left, respectively) of the four remaining animals (fig. 10). Representative EIT images are shown in figure 11.


EIT ventilation right
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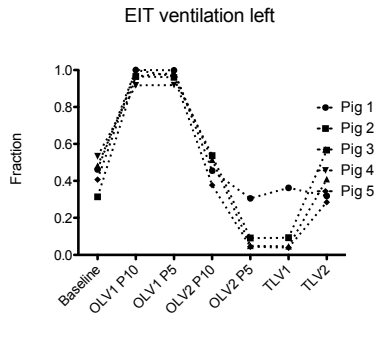
EIT ventilation left
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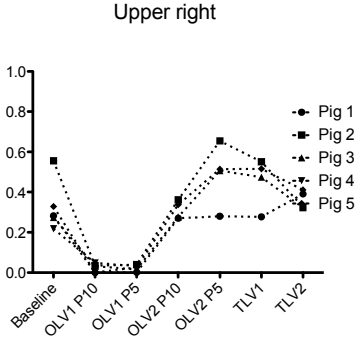
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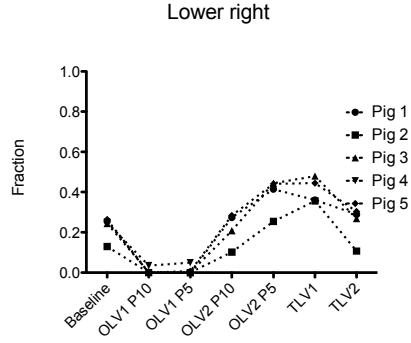
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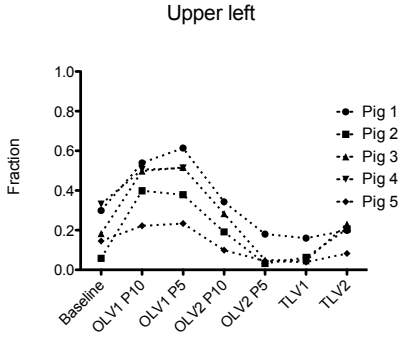
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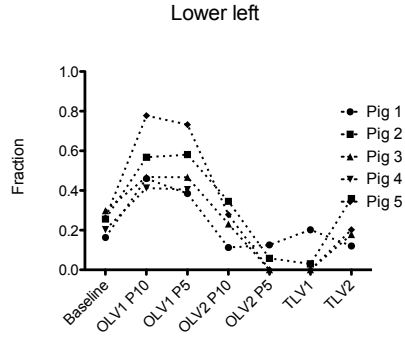
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Pig 1
Pig 2
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Pig 4
Pig 5

Figure 10. Regional pulmonary ventilation distribution by electrical impedance tomography. Regional pulmonary ventilation distributions by EIT from the following steps are presented: baseline, OLV with capnothorax on the right side at PEEP levels of 5 and 10 cm H_2O (OLV 1 20 min, 40 min), two-lung ventilation (TLV 1 30 min), OLV with left capnothorax at the same PEEP levels (OLV 2 20 min, 40 min) and final bilateral ventilation (TLV 2 30 min). Each line represents one animal. The y axes depict the regional pulmonary ventilation distributed in two kinds of regions-of-interest (ROI): right and left lungs and four quadrants. It is shown in the proportion (fraction) of the total pulmonary ventilation for each ROI in each step.

EIT = electrical impedance tomography; OLV = one-lung ventilation; PEEP = positive end-expiratory pressure; TLV = two-lung ventilation.

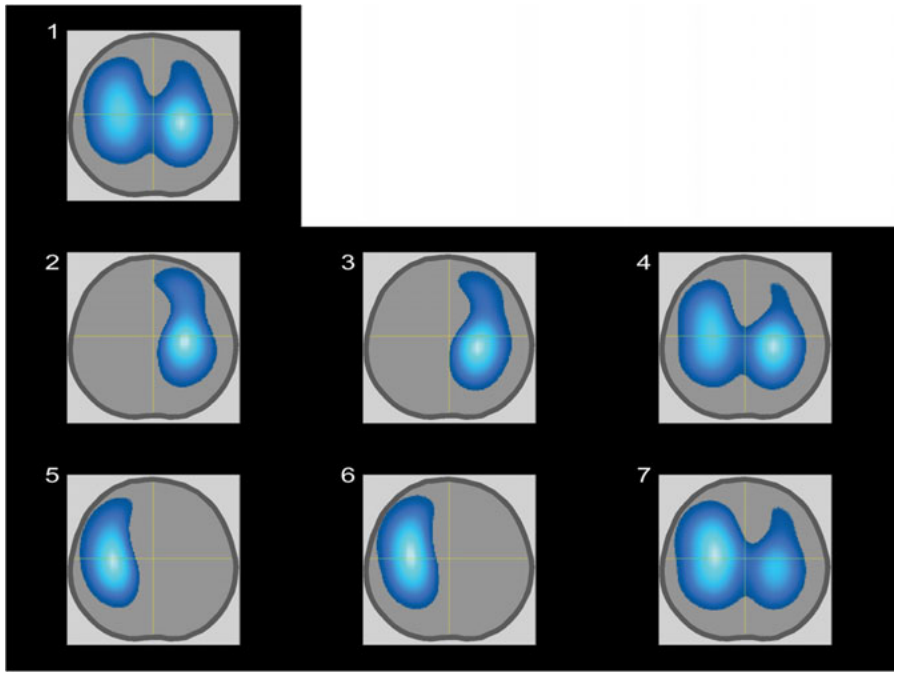
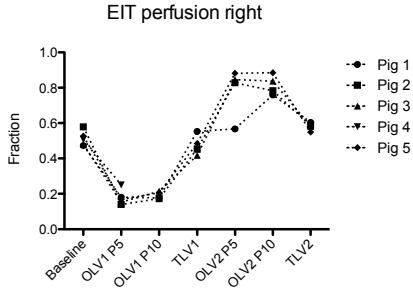


Figure 11. Representative images of regional pulmonary ventilation distribution by electrical impedance tomography. 1. At baseline with bilateral ventilation. 2. OLV 1, left-sided one-lung ventilation with right-sided capnothorax, PEEP 5 cm H_2O. 3. OLV 1, left-sided one-lung ventilation with right-sided capnothorax, PEEP 10 cm H_2O. 4. Two-lung ventilation after the first capnothorax period. 5. OLV 2, right-sided one-lung ventilation with left-sided capnothorax, PEEP 5 cm H_2O. 6. OLV 2, right-sided one-lung ventilation with left-sided capnothorax, PEEP 10 cm H_2O. 7. Two-lung ventilation after the second capnothorax period.

EIT = electrical impedance tomography; OLV = one-lung ventilation; PEEP = positive end-expiratory pressure.

Regional pulmonary perfusion by EIT

Perfusion maps were pixel-wise calculated based on the impedance changes in response to hyper-tonic saline injection as described. At baseline, the perfusion distribution was equal between the right and left lung (51 ± 4% vs. 49 ± 4%, respectively). During the first OLV/capnothorax, perfusion decreased in the non-ventilated and increased in the ventilated lung (18 ± 2% vs. 82 ± 2%, right vs. left) (fig. 12). TLV restored the perfusion. During the second OLV/capnothorax period, a similar distribution of perfusion was seen in the animals with successful separation (84 ± 4% vs. 16 ± 4%, right vs. left). Representative EIT images are shown in figure 13. The case with incomplete collapse of the left side showed a perfusion of 43%, which decreased to 24% across the second OLV/capnothorax.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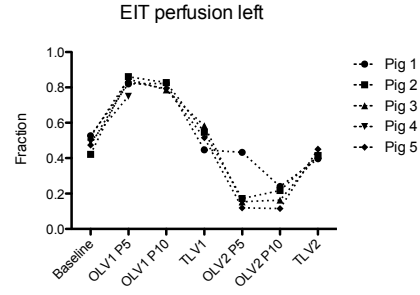
EIT perfusion left
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TLV2
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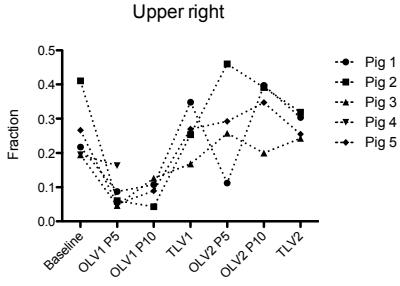
Pig 5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TLV2
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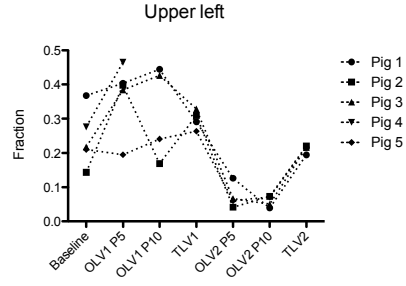
Pig 4
Pig 5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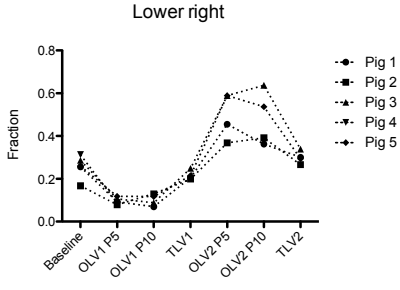
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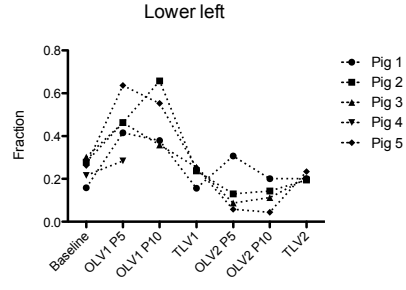
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Pig 5

Figure 12. Regional pulmonary blood flow distribution by electrical impedance tomography. Regional pulmonary blood flow distributions by EIT from the following steps are presented: baseline, OLV with capnothorax on the right side at PEEP levels of 5 and 10 cm H_2O (OLV 1 20 min, 40 min), two-lung ventilation (TLV 1 30 min), OLV with left capnothorax at the same PEEP levels (OLV 2 20 min, 40 min), and final bilateral ventilation (TLV 2 30 min). Each line represents one animal. The y axes depict the regional pulmonary blood flow distributed in two kinds of regions-of-interest (ROI): right and left lungs, and four quadrants. It is shown the in proportion (fraction) of the total pulmonary blood flow for each ROI in each step.

EIT = electrical impedance tomography; OLV = one-lung ventilation; PEEP = positive end-expiratory pressure.

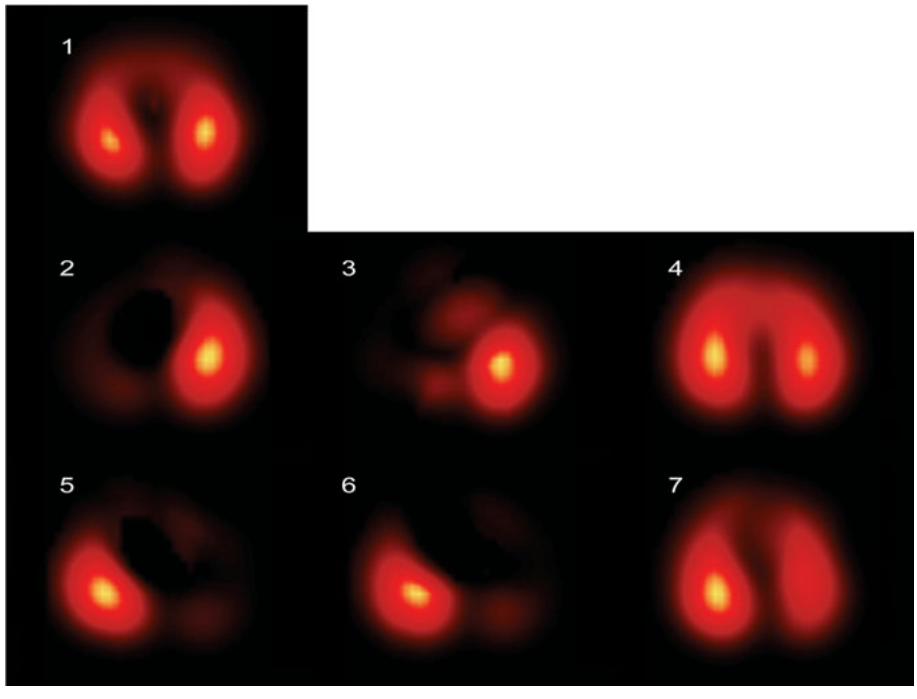

Figure 13. Representative images of regional blood flow distribution by electrical impedance tomography. (1) At baseline with bilateral ventilation; (2) OLV 1, left-sided one-lung ventilation with right-sided capnothorax, PEEP 5 cm H_2O; (3) OLV 1, left-sided one-lung ventilation with right-sided capnothorax, PEEP 10 cm H2O; (4) Two-lung ventilation after the first capnothorax period; (5) OLV 2, right-sided one-lung ventilation with left-sided capnothorax, PEEP 5 cm H_2O; (6) OLV 2, right-sided one-lung ventilation with left-sided capnothorax, PEEP 10 cm H_2O; (7) Two-lung ventilation after the second capnothorax period.

OLV = one-lung ventilation; PEEP = positive end-expiratory pressure.

Paper IV

Complete airway separation was established in all pigs and there was no unexpected mortality.

There was a loss of capnothorax pressure in one pig, at PEEP 4 cm H_2O, resulting in decreased atelectasis in the ventilated lung and an increase in cardiac output, mean arterial pressure and mixed-venous oxygen saturation, data from that pig were excluded from analysis from the moment of loss of capnothorax pressure.

Hemodynamics

Cardiac output, CVP and lactate were stable with no significant change during the decremental PEEP trial (p = 0.12 p = 0.94 and p = 0.11, respectively). Mean arterial pressure increased from 72 ± 15 mm Hg with a peak at 14 cm H_2O PEEP of 83 ± 9 and then declined to 63 ± 15 mm Hg at ZEEP (p = 0.005). Hemodynamic, gas exchange and ventilatory variables are presented in table 6.

Table 6. *Hemodynamics, gas exchange and ventilation*.

PEEP (cm H_2O)	Baseline[1]		Baseline[2]		20		18		16		14		12		10		8		6		4		2		0		Sig.
MAP	82	[14]	82	[11]	72	[15]	70	[18]	81	[7]	83	[9]	81	[12]	76	[11]	77	[7]	74	[12]	65	[14]	68	[21]	63	[15]	p = 0.005
SvO_2	73	[8]	44	[9]	46	[14]	54	[17]	54	[7]	60	[9]	61	[13]	52	[9]	54	[6]	43	[9]	37	[17]	33	[15]	28	[16]	p = <.0001
HR	108	[26]	126	[36]	144	[41]	146	[43]	139	[47]	140	[47]	140	[45]	152	[39]	154	[40]	164	[40]	167	[39]	171	[35]	174	[26]	p = 0.037
CO	3.3	[0.8]	2.5	[0.8]	2.8	[0.7]			3	[0.4]			3.1	[0.6]			2.6	[0.4]			2.7	[0.5]			3.4	[0.9]	p = 0.12
CVP	8	[1]	17	[1]	18	[1]	17	[3]	17	[3]	17	[2]	17	[2]	17	[0.8]	17	[1]	17	[1]	17	[2.9]	17	[3]	17	[2]	p = 0.94
Lactate	1.3	[0.3]	1.1	[0.3]	1.6	[0.5]	1.3	[0.4]	1.5	[0.6]	1.4	[0.5]	1.3	[0.4]	1.4	[0.4]	1.4	[0.3]	1.4	[0.5]	1.7	[0.4]	2.3	[1.3]	2.4	[1.6]	p = 0.11
EIT[3]					74.1	[16.9]	72.1	[13.6]	70.1	[18,7]	73.0	[14.0]	70.6	[13.2]	69.9	[11.6]	68.5	[11.9]	67.0	[13.7]	65.0	[19.5]	59.7	[18.8]	60.6	[17.0]	p = 0.003
EIT[4]					88.7	[3.2]			89.2	[2.6]			89.1	[3.1]			87.6	[3.0]			84.8	[3.4]			84.5	[5.8]	p = 0.02
ΔP	21	[4]	25	[4]	22	[5]	21	[5]	20	[5]	20	[6]	21	[7]	22	[7]	24	[7]	28	[7]	32	[7]	35	[7]	38	[6]	p = <.0001
EELV	551	[82]	185	[38]	642	[90]	598	[89]	513	[76]	466	[77]	393	[63]	337	[69]	280	[74]	225	[65]	185	[82]	160	[81]	149	[101]	p = <.0001
pH	7.45	[0.03]	7.25	[0.05]	7.21	[0.06]	7.20	[0.07]	7.21	[0.05]	7.18	[0.06]	7.19	[0.06]	7.18	[0.06]	7.17	[0.07]	7.14	[0.07]	7.12	[0.07]	7.08	[0.07]	7.04	[0.09]	p = 0.0002
PaO_2	63	[9]	29	[22]	34	[12]	46	[12]	45	[12]	48	[12]	49	[14]	46	[13]	42	[16]	26	[14]	24	[15]	12	[5]	11	[5]	p = <.0001
$PaCO_2$	5.7	[0.4]	9.0	[0.9]	9.5	[1.3]	9.4	[1.4]	9.4	[1.0]	9.8	[0.9]	9.8	[1.2]	10.5	[2.3]	10.4	[2.3]	10.7	[1.7]	11.3	[2.2]	12.2	[2.2]	12.5	[1.7]	p = <.0001

Measurements of hemodynamics, gas exchange and ventilation variables from baseline with two-lung ventilation to ZEEP during the decremental PEEP trial. [1] Baseline 15 minutes; [2] Baseline capnothorax; [3] EIT ventilation dorsal (%); [4] EIT perfusion right lung (%). CVP = central venous pressure; CO = cardiac output; ΔP = driving pressure; EELV = end-expiratory lung volume; EIT = electrical impedance tomography; HR = heart rate; MAP = mean arterial pressure; $PaCO_2$ = partial pressure of carbon dioxide in arterial blood; PaO_2 = partial pressure of oxygen in arterial blood; PEEP = positive end-expiratory pressure; ZEEP = zero end-expiratory pressure. Standard deviation is presented within brackets.

Ventilation and gas exchange

The PaO_2 increased from 34 ± 12 kPa to a maximum of 48 ± 14 kPa when the PEEP was stepwise decreased from 20 cm H_2O to 12 cm H_2O ($p = 0.005$). With further down titration of the PEEP there was a substantial decrease in PaO_2 to 11 ± 5 kPa at ZEEP ($p < 0.0001$).

Likewise, SvO_2 increased from 46 ±14% at PEEP 20 cm H_2O to the highest observed SvO_2 (61 ± 16%) at PEEP 12 cm H_2O ($p = 0.01$), followed by a decrease to 28 ± 16% at ZEEP ($p < 0.001$).

The pattern of $PaCO_2$ differed from that of the oxygenation since there was no observed peak during the decrement of PEEP. Instead, $PaCO_2$ increased from 5.7 ± 0.4 kPa to 9.0 ± 0.9 kPa ($p < 0.0001$) as OLV and capnothorax was initiated. $PaCO_2$ increased continuously during the decremental PEEP trial from 9.8 ± 1.2 kPa at PEEP 12 cm H_2O to reach 12.5 ± 1.7 kPa ($p < 0.0001$) at ZEEP. Similarly, the pH gradually decreased from 7.45 ± 0.03 at baseline to 7.21 ± 0.06 ($p = 0.004$) at the start of the PEEP trial. The pH then decreased from 7.21 ± 0.06 at PEEP 16 cm H_2O to 7.04 ± 0.09 at ZEEP ($p = 0.0002$).

The driving pressure (plateau pressure – PEEP) was stable from 22.1 ± 4.6 cm H_2O at PEEP 20 cm H_2O to 19.6 ± 5.8 cm H_2O at PEEP 14 cm H_2O ($p = 0.056$). Reduction of PEEP below 12 cm H_2O increased driving pressure, reaching 38.3 ± 6.1 cm H_2O at ZEEP ($p < 0.001$) (fig. 14).

EELV decreased linearly from 642 ± 90 ml at PEEP 20 cm H_2O to 149 ± 101 ml at ZEEP ($p < 0.001$)

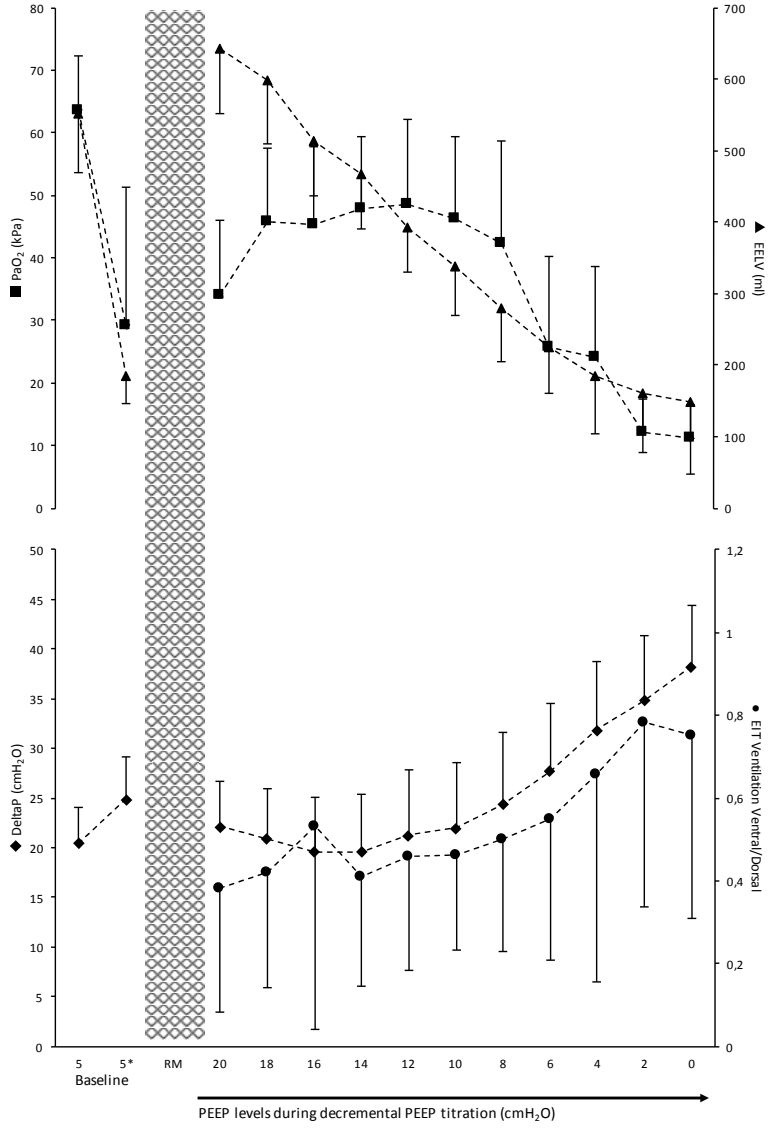

Figure 14. Merged graph showing PaO_2, delta P, EELV and ventilation distribution ratio from EIT maps between ventral and dorsal parts of the ventilated lung during the decremental PEEP trial (EIT ventilation). Delta P = driving pressure; EELV = end-expiratory lung volume; EIT = electrical impedance tomography; PaO_2 = partial pressure of oxygen in arterial blood; PEEP = positive end-expiratory pressure.

Regional pulmonary ventilation by EIT

EIT ventilation maps were derived from impedance data from each PEEP-titration step of 2 cm H_2O and confirmed complete airway separation in all animals. ROIs dividing the lungs into ventral and dorsal parts were analyzed. Ventilation is presented as ventral/dorsal ratio of ventilation in the right lung (fig. 14).

The distribution of ventilation within the ventilated right lung shifted across the experiment. Most of the ventilation was in the dorsal part of the right lung, with the highest proportion of ventilation to this region at PEEP 14 cm H_2O, followed by a gradual shift to more ventral parts at lower PEEP levels ($p = 0.002$).

Regional pulmonary perfusion by EIT

EIT perfusion maps were derived from impedance data acquired at PEEP-titration steps of 4 cm H_2O, starting at PEEP 20 cm H_2O. As with the ventilation, ROIs dividing the lungs into ventral and dorsal parts were used for analysis.

At the higher PEEP levels there was no significant change in perfusion distribution between the right and left lung when lowering PEEP ($p = 0.82$). Conversely, at lower levels between 12 cm H_2O and ZEEP, perfusion to the ventilated lung decreased from 89 ± 3% to 84 ± 1% of the total blood flow ($p = 0.02$).

Similarly, a non-significant tendency of a shift of perfusion distribution within the ventilated lung to the ventral region from 18.2 ± 6.8% to 21.5 ± 7.6% was observed during the decrease of PEEP from 12 cm H_2O to ZEEP ($p = 0.16$) (fig. 15).

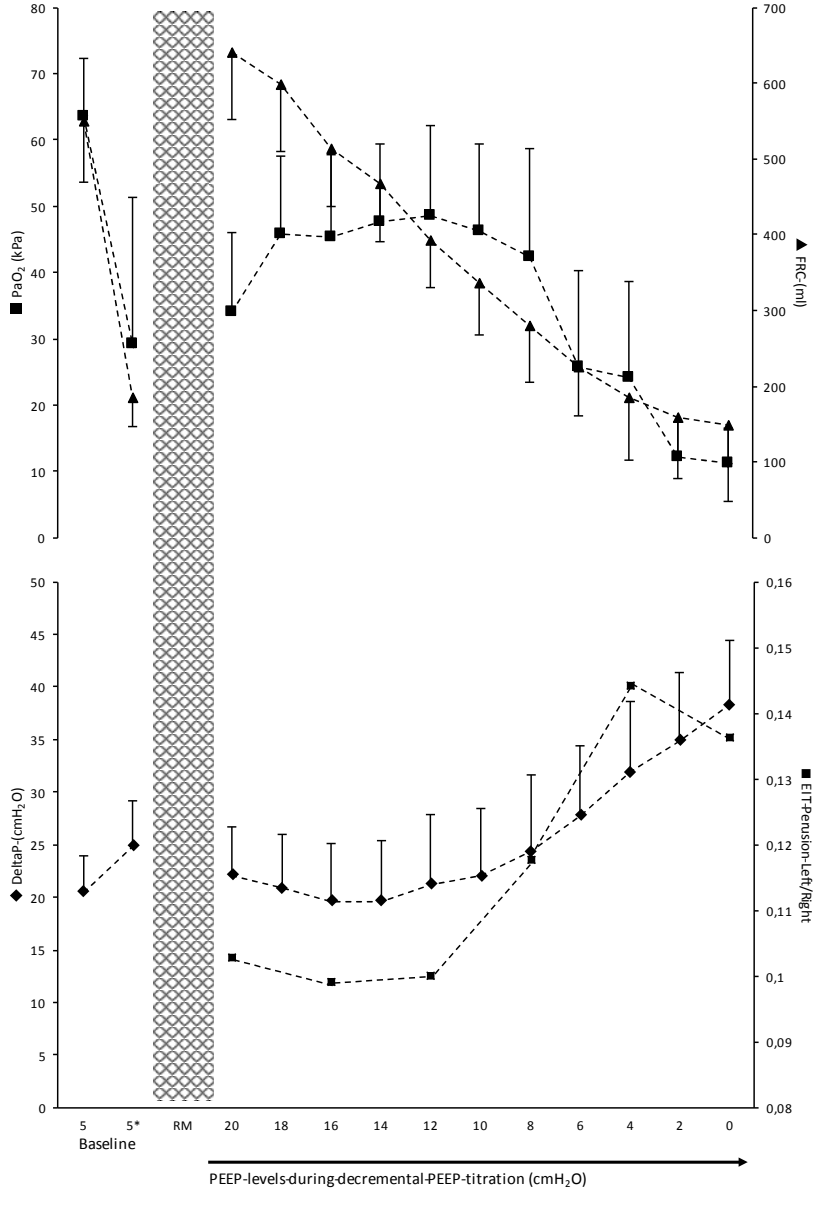

Figure 15. Merged graph showing PaO_2, driving pressure, EELV and perfusion distribution ratio from EIT maps between the left and right lung during the decremental PEEP trial. Delta P = driving pressure; EELV = end-expiratory lung volume; EIT = electrical impedance tomography; PaO_2 = partial pressure of oxygen in arterial blood; PEEP = positive end-expiratory pressure.

Computerized tomography

In addition to the EIT-measurements, computerized tomography was made in a subset of the animals (n=3). In two of the cases atelectasis started to develop at the PEEP level of 14 cm H_2O and in one pig atelectasis appeared at PEEP 10 cm H_2O (fig. 16). The loss of capnothorax insufflation pressure at PEEP 4 cm H_2O in pig number seven was clearly depicted with an almost non-detectable amount of atelectasis at PEEP 2 cm H_2O (fig. 18).

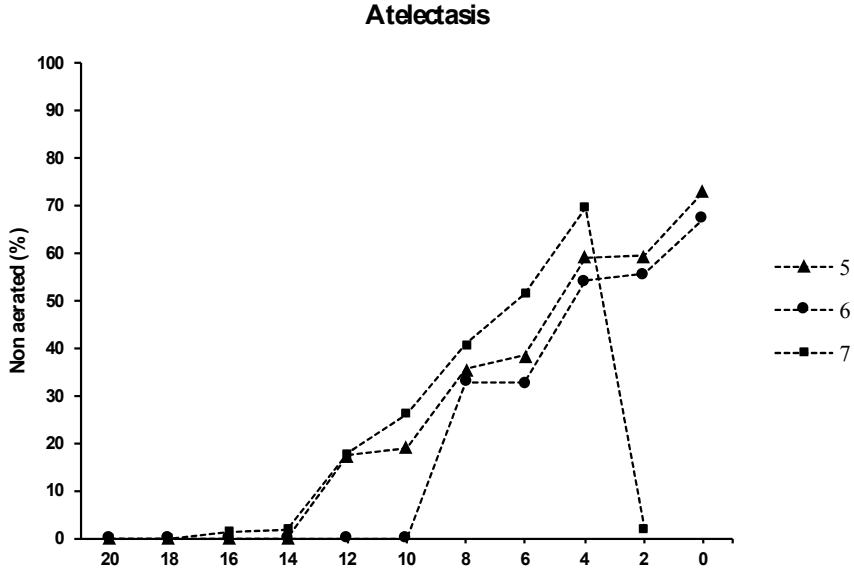

Figure 16. Amount of atelectasis in the ventilated right lung during the decremental PEEP trial calculated from CT images. Data from two 8 mm transverse thoracic computed tomography (CT) slices separated by three 8 mm slices i.e. 24 mm, corresponding to the EIT-belt, where chosen for analysis at each step in the PEEP titration (see text). Data are presented as amount of atelectasis in% of lung tissue mass during the decremental PEEP trial in the three pigs where CT was made. Increase in atelectasis started at PEEP 14 cm H_2O in two pigs and at PEEP 10 cm H_2O in one pig. CT = computerized tomography; PEEP = positive end-expiratory pressure.

Representative CT images are presented in figure 17. Note the dramatic decrease in atelectasis in pig 7 at PEEP 2 cm H_2O due to accidental loss of capnothorax pressure after measurements at PEEP 4 cm H_2O (fig. 18).

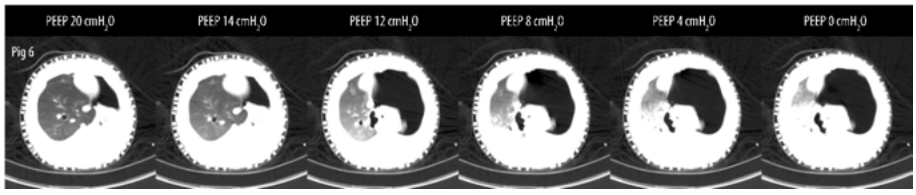

Figure 17. Representative CT images of the lungs during the decremental PEEP trial with images from PEEP 20 cm H_2O to the left to ZEEP at the right side of the figure. Aerated lung tissue decreased and atelectasis increased when the PEEP was lowered below 10 cm H_2O. Note the leftward mediastinal shift at PEEP levels of 20 and 14 cm H_2O making the surgical space smaller. CT = computerized tomography; PEEP = positive end-expiratory pressure; ZEEP = zero end-expiratory pressure.

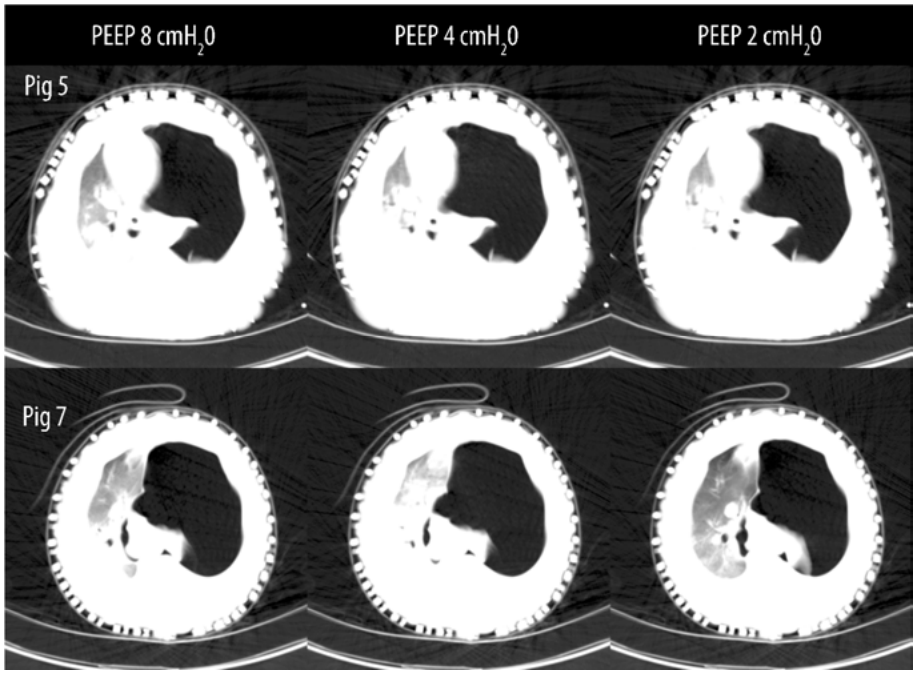

Figure 18. CT images representing the accidental loss of the capnothorax pressure in one animal at PEEP 4 cm H_2O. Note the dramatic increase in aerated lung tissue and abolished atelectasis in pig 7 at PEEP 2 cm H_2O. PEEP = positive end-expiratory pressure.

Discussion

Atelectasis and poorly aerated lung tissue contributes to hypoxemia and higher insufflation pressures during mechanical ventilation if appropriate measures are not taken. Recent studies suggest that even shorter periods of ventilation with large tidal volumes, high insufflation pressures and tidal recruitment may cause damage to the lungs.[74–76] These injurious effects are due to over distension and opening, closing and reopening of parts of the lung during the respiratory cycle.

Patient factors and type of surgery both affect the risk for development of atelectasis. Morbid obesity and thoracoscopic surgery with one-lung ventilation (OLV) are examples of such risk factors.

Large amounts of research have been published since the start of this project. The studies in this thesis are mere grains of sand in the combined knowledge in the field of mechanical ventilation. A lot of research in both the anaesthesia setting and during critical care still remains to be done before optimal care can be provided during conventional mechanical ventilation. Evidence suggests that protective ventilation with low tidal volumes during major surgery decreases the risk for postoperative pulmonary complications.[11,16] We also know how to manage mechanical ventilation to keep the lungs open during anaesthesia in most cases. However, it is still unknown whether an open lung approach with individualized PEEP and minimized driving pressures during anaesthesia in patients without lung injury translate to less VILI and postoperative lung complications. Physiologic reasoning points in the direction of benefit of recruitment maneuvers and higher PEEP.[77] However, a recently published study[78] failed to demonstrate a reduction of postoperative pulmonary complications with this approach. Since there are risks involved with both recruitment maneuvers[79,80] and higher levels of PEEP,[78] prudent clinicians will think twice before performing recruitment maneuvers with high insufflation pressures and setting “optimal” PEEP before outcome evidence exists that support these measures. This reasoning is sound and in line with the ethic of “primum non nocere” - not doing harm. As long as a correct risk/benefit analysis based on scientific evidence is not in clear favor of the open lung concept in specific situations, many patients will suffer from the consequences of atelectasis both during anaesthesia and into the postoperative period.

Prevention and treatment of atelectasis in morbidly obese

In paper I, spiral CT was done in a majority of the patients, which made it possible to calculate EELV at different time points. In addition, the fractional volumes of overaerated, normally aerated, poorly aerated, and nonaerated lung tissue have been calculated, with the lungs divided in three different regions from base to apex. All CT investigations were done at end-expiration; therefore, the results were optimized for comparison between awake and anaesthetized patients.

Anaesthesia and paralysis decreased the fractional amount of normally aerated tissue from 71% to 50% and increased the fractional amount of poorly aerated tissue from 28% to 39% and nonaerated tissue from 1% to 11%. This is in line with previous results in which obese patients were investigated with single-slice CT before and after induction of anaesthesia and paralysis, reporting 10% atelectasis.[33] In contrast, previous studies in normal weight subjects have reported approximately 3% atelectasis when performing spiral CT during anaesthesia and ZEEP.[81]

The recruitment maneuver of 55 cm H_2O for 10 seconds reduced atelectasis, as seen in the group with recruitment maneuver followed by PEEP. In most patients, this pressure was sufficient to abolish atelectasis; in some cases, however, there were still some atelectasis remaining. We also observed a marked increase in EELV, a reduction in poorly aerated tissue associated with an increase in normally aerated tissue, improved respiratory compliance and oxygenation. Our results are in agreement with previous studies in which application of PEEP preceded by a recruitment maneuver was more effective than PEEP alone.[82,83] Concerning the insufflation pressures during the recruitment maneuvers and the PEEP-levels used in the study, it is likely that, for a comparable airway pressure, the transpulmonary pressure, which is the real alveolar distending pressure, is lower in the anaesthetized morbidly obese than in normal weight subjects. This is caused by increased chest wall elastance[42,84] and higher intraabdominal pressure as illustrated by a return of EELV to almost preanaesthesia values in obese patients when the abdominal wall was opened.[85] Thus, we estimated that a pressure of 55 cm H_2O for 10 s during the recruitment maneuver would optimize the beneficial effect of the recruitment maneuver while minimizing possible negative effects, in terms of barotrauma and hemodynamic compromise.

The recruitment maneuver used only had a mild, short-lasting effect on blood pressure, despite the high pressures used.

PEEP alone increased the normally aerated lung fraction. This was combined with a reduction of poorly aerated lung tissue while atelectasis remained unchanged. The increase in normally aerated lung tissue was not

accompanied by an increase in PaO_2. This might be explained by a redistribution of blood to nonventilated regions or by a decrease in cardiac output.[37]

When a recruitment maneuver was applied without PEEP, the effect was short lasting. Twenty minutes after the recruitment maneuver, no beneficial effects remained. This observation suggests that the application of PEEP in morbidly obese patients is needed to keep the lung open and improve respiratory function after an effective recruitment maneuver.

Predicting atelectasis in morbidly obese patients

Following induction of anaesthesia and paralysis, atelectasis developed in the dependent lung regions, and there was a marked fall in the PaO_2/F_IO_2 ratio. This atelectasis can to some extent be predicted from preoperative spirometry despite that the presently studied patients had no obvious clinical signs of or conventional spirometric criteria suggestive of obstructive lung disease. However, patients with reduced end-expiratory flow (FEF_{75}), suggestive of mild peripheral airway obstruction, developed less atelectasis after induction of anaesthesia but FEF_{75} did not predict the fall in oxygenation. This may appear as an unexpected finding but will be discussed in the following paragraphs.

BMI ranged from 40 to 52 kg/m^2 and most spirometric lung volumes were within normal limits which is in agreement with previous findings.[31,86]

Before induction of anaesthesia and paralysis and after premedication with paracetamol and midazolam, an average EELV (~FRC) of approximately 1400 ml was measured with spiral CT with the patient in supine position. EELV then decreased to 700 ml after induction of anaesthesia, confirming previous EELV measurements in morbidly obese patients obtained by helium dilution technique during anaesthesia and paralysis in the absence of PEEP.[42,84,85] Although these patients while awake in supine position had a low FRC, gas-exchange variables were within normal range. This is in fair agreement with previous reports of morbidly obese patients.[85,87,88]

A higher FEV_1 predicted more impairment of oxygenation after induction of anaesthesia. This is in agreement with findings from previous studies.[89] However, FEV_1 did not predict an increase in atelectasis. This may be explained by our finding that more than 10% of the lung tissue turned from normally to poorly aerated after induction of anaesthesia, causing an increase in venous admixture. A low end-expiratory flow predicted 15% of the formation of atelectasis. When combined weight and height, FEF_{75} predicted 27% of atelectasis formation after induction of anaesthesia. However, in the present study this did not translate into better oxygenation. This may also be explained by the amount of lung tissue that turned from normally to poorly aerated after induction of anaesthesia, most likely causing ventilation/perfusion mismatch with impairment of oxygenation.

The reduced FEF_{75} suggests mild peripheral airway obstruction that, when awake and in the upright position, did not cause any substantial air trapping. However, when anaesthesia with muscle paralysis was induced and mechanical ventilation without PEEP was started, air trapping may have occurred. The trapped gas behind closed airways will then eventually be absorbed, causing alveolar collapse. However, how fast collapse occurs depends on the amount of trapped nitrogen. The nitrogen acts as a scaffold and prevents atelectasis formation. The nitrogen concentration will in turn depend on how well it has been washed out during pre-oxygenation and any continuing ventilation with pure oxygen. Indeed, incomplete filling of the alveoli with oxygen, as e.g. by too short or inefficient pre-oxygenation, will leave some nitrogen in the alveoli and protect from early atelectasis formation. After some time that may be half an hour or more in anaesthetized lung-healthy, normal-weight subjects, collapse will occur because of slow diffusion of nitrogen away from the alveoli.[13] Peripheral airway obstruction with increased likelihood for airway closure and gas trapping should enhance the protective effect of nitrogen against atelectasis. This seems to be further illustrated by the finding that EELV after induction of anaesthesia increased with age, suggesting more closure of small airways. For EELV cigarette pack years was significant in the univariate analyses, however, it was only analyzed in the subset of smokers. When analyzing cigarette pack years with the addition of entering non smokers the result was non significant ($p = 0.068$). This uncertainty on the influence of perioperative lung function is also of debate regarding postoperative pulmonary complications.[10]

Physiology during OLV with capnothorax

The management of patients during OLV with capnothorax is a challenge both during surgery and postoperatively.

In this new model, OLV with capnothorax caused circulatory impairment with marked changes in multiple parameters during capnothorax on the right side, significant recovery upon TLV and a milder impairment during closure of the left side.

After careful studies and measurements of the tracheal anatomy of the pig, we used a right-sided double-lumen tube that was inserted into the left main bronchus. This selected DLT has an oblique bronchial cuff that effectively sealed the left main bronchus without obliterating the right. By enlarging the tracheal opening of the DLT proximally without damaging the cuff, ventilation of the right tracheal lobe could be achieved. The risk for inadequate placement is substantial, and in some cases it may be technically impossible to ventilate all lobes due to anatomical variations. The present findings show that incomplete airway separation will risk distorting the experi-

ment substantially, and therefore EIT or equivalent methods are warranted to ensure adequate experimental conditions.

Similar to in patients, total airway separation in piglets cannot always be easily obtained. In contrast to humans, pigs have multiple lobes, of which one originates from the right side of the trachea. In the present series, the EIT was able to confirm appropriate lateralization of the ventilation in the majority of the cases, and importantly, the pig with incomplete airway separation was convincingly detected.

Although a previous study described the use of OLV with capnothorax in piglets,[111] they did not track in real time the frequent and dynamic changes in the lung structure and function with a functional imaging method as the EIT. EIT enables real-time monitoring, with a temporal resolution that allows not only measurement of the ventilation, but also faster physiological phenomena, such as the pulsatility of the lung during the cardiac cycle.[90,91] We recently presented a modified version of the EIT-based method to estimate regional lung perfusion based on the first-pass kinetics of a bolus of hypertonic contrast.[66] The novel indicator dilution method outperformed lung pulsatility as a surrogate for regional lung perfusion and we therefore used this technique in this study.

The hemodynamic effects of capnothorax may comprise two opposing mechanisms – increased cardiac output as an effect by hypercapnia[92,93] and hemodynamic impairment by intra-thoracic tension. Despite using respiratory rate to the upper limit until reaching minimal expiratory time without obvious risk for dynamic hyperinflation with air trapping, $PaCO_2$-levels and acidosis were rising during the capnothorax periods. We found a predominantly hemodynamic impairment, with marked changes during the initial, right-sided capnothorax despite resuscitation with intravenous fluids and vasoactive drugs. The recovery upon TLV was also convincing, with numerical values exceeding the baseline recordings. The recovery might have been enhanced by the presence of vasopressors, adequate preload and possibly a superimposed endogenous stress response.

The hemodynamic effects during the second, left-sided capnothorax were less pronounced. Previous studies suggest that left-sided capnothorax induces less hemodynamic impairment than right-sided capnothorax.[94] The left side has been previously observed less susceptible to such hemodynamic impairment, possibly because there are less of pressure-sensitive central veins on the left side.

The lateralized perfusion seen at the end of the last TLV may be due to incomplete recruitment of collapsed tissue, which would be compatible with the simultaneous decrease in ventilation. It has been previously demonstrated that OLV may cause diffuse alveolar damage and hyper perfusion of the ventilated lung.[53] During OLV with capnothorax both lungs have been "the ventilated lung" which is specific for this kind of surgery. In the present study hyper perfusion of the right lung was seen after a period of OLV to the

left lung followed by a period of TLV and a second period of OLV with ventilation of the right lung. This hyper perfusion may be a sign of increased inflammation in the right lung or remaining HPV in the left lung, perhaps caused by atelectasis in the left lung despite the recruitment maneuver made.

While changes in PEEP levels may compromise the hemodynamics in susceptible individuals, no apparent differences in hemodynamic parameters were seen between the common clinical levels of 5 and 10 cm H_2O in the present material.

Optimal PEEP during OLV with capnothorax

Paper IV addressed multiple aspects of optimizing PEEP in the management of OLV with capnothorax using a pleural CO_2 insufflation pressure of 16 cm H_2O. Interestingly, a PEEP range between 12 to 16 cm H_2O was not only optimal for the ventilatory parameters but also the hemodynamics were satisfactory without apparent need to be counterbalanced despite a relatively high CO_2 insufflation pressure.

At low PEEP dorsal atelectasis developed in the ventilated lung shifting the ventilation distribution from dorsal to more ventral parts. Moreover, when decreasing PEEP from 12 cm H_2O, blood flow to the non-ventilated lung increased, which likely explains further impairment of the gas exchange.

Ventilation

A useful definition of optimal PEEP may be the lowest PEEP level that maintains a maximum dynamic compliance and thereby low driving pressures.[95,96]

The lowest driving pressures for tidal ventilation were seen at PEEP 14 cm H_2O. This was probably due to over-distension in non-dependent parts of the lung at higher PEEP levels and reoccurring atelectasis when PEEP was further reduced. At a slightly lower PEEP, 12 cm H_2O, the best oxygenation was recorded.

The end-expiratory lung volume (EELV) was highest at the start of the decremental PEEP-trial at PEEP 20 cm H_2O and exhibited an almost linear decrease down to ZEEP. However, EELV just indicates the volume of the lung, not whether the lung is hyper-inflated or normal-inflated. The decrease in EELV may in part be explained by decreased aeration of the ventilated lung during lowering of the PEEP. Mediastinal shift with expansion of the non-ventilated CO_2-inflated part of the thoracic cavity into the side of the ventilated when the PEEP is lowered to below the CO_2 insufflation pressure may also explain the reduction of the EELV during the down titration of the PEEP. The mediastinal shift may also explain why measured EELV was

higher during OLV after a recruitment maneuver followed by a PEEP of 20 cm H_2O than during TLV with a PEEP of 5 cm H_2O, with the ventilated, overinflated lung expanding and causing mediastinal shift towards the non-ventilated side.

At PEEP 16 cm H_2O most of the ventilation was located in the dorsal parts of the lung. With further lowering of PEEP there was a shift of ventilation to more ventral parts of the ventilated lung. The mechanism for this was formation of atelectasis in the dorsal parts of the lung as was found in the CT scans. Since pigs have a strong HPV that counteracts shunting, the effect of atelectasis on oxygenation is less pronounced in pigs than what would be expected in the clinical situation.[97] Thus, the decrease in oxygenation in humans may begin at even higher PEEP-levels and be more pronounced than we observed in this study.

Unexpectedly, during the down-adjustment of the PEEP there was an increase in blood-flow to the non-ventilated lung detected in the EIT-lung perfusion maps. However, it is well known that the pulmonary vascular resistance is at its minimum when the lung is open, but not overinflated. Thus, when the ventilated lung started to collapse when the PEEP was reduced below 12 cm H_2O, the vascular resistance increased in this lung causing the blood flow to be redistributed to the non-ventilated lung.

An additional explanation for the increase of blood flow to the non-ventilated lung may be local vasodilation due to a locally higher partial pressure of CO_2 in the non-ventilated lung due to the uptake of insufflated CO_2 from the capnothorax.[98,99] However, conflicting results exist on the role of hypercapnic acidosis on pulmonary vascular tone, where both increase and a decrease in HPV have been demonstrated.[100–103] The increase in blood-flow to the non-ventilated lung during ventilation with PEEP-levels below 14 cm H_2O may also be explained by an external compression of the ventilated lung caused by the mediastinal shift towards the ventilated lung.

Arterial CO_2-levels increased significantly at lower PEEP-levels despite unchanged settings of respiratory rate and tidal volumes. This may be a time-dependent effect of capnothorax as lower PEEP-levels were reached but may also reflect an inefficient gas exchange. One mechanism for this may be increased shunting of blood through the non-ventilated lung at lower PEEP-levels.

It has been previously stated that there is a risk for shunting to the non-ventilated lung when applying PEEP to the ventilated lung during one-lung ventilation.[104] However, more recent studies support the use of PEEP in patients with relatively healthy lungs, improving both oxygenation and respiratory mechanics.[59,61,105] Also, the high pleural pressure during capnothorax probably contributes to diversion of blood flow to the ventilated lung.

As a comparison a PEEP level of 10 cm H_2O was considered optimal during OLV without capnothorax when a recruitment maneuver was followed by a decremental PEEP trial.[106] However, this study was performed in the

lateral position with ventilation to the dependent lung. It can be assumed that optimal PEEP would be lower but ventilation/perfusion mismatch higher if the supine position had been used. The need for a relatively high PEEP in the present study is most likely explained by the high intra-thoracic pressure due to the capnothorax with an increased atelectasis formation, mediastinal shift and decreased venous return.

CT images of the lungs were obtained from three pigs. Visual analysis of these images suggests a mediastinal shift from the right to the left (non-ventilated to ventilated) side when PEEP is lowered beneath the capnothorax-pressure of 16 cm H_2O. With further decrease of PEEP an increase in atelectasis was observed. Shift of the mediastinum towards the ventilated lung combined with the increase of atelectasis may explain the rapid increase in driving pressure needed to uphold tidal volumes. At higher PEEP levels there may be less space for surgical instruments and impaired visualization of the surgical field due to mediastinal shift towards the non-ventilated side. The assessment of surgical exposure at different pressures is however beyond the scope of the present study but can be subject to further studies.

Interestingly, atelectatic lung tissue was rapidly expanded in one animal when capnothorax pressure was lost, suggesting that capnothorax has an obvious impact on optimal PEEP level of the ventilated lung. When capnothorax pressure was suddenly lost there may have been an inadvertent recruitment maneuver due to the PRVC ventilator mode, which will continue to deliver high insufflation pressures for a few breaths until the sudden increase in compliance has been fully compensated.[107]

Hemodynamics

OLV with capnothorax will reduce venous return and thus compromise circulation.[58] However, our data suggest that there is no conflict between optimization of ventilation and hemodynamics. The overall hemodynamic situation was optimal between PEEP 12 to 16 cm H_2O. Mean arterial pressure was kept within acceptable limits and was highest between a PEEP of 12 and 16 cm H_2O. No difference in cardiac output was detected during the course of the decremental PEEP trial. Heart rate increased during the down adjustment of PEEP with a marked increase when PEEP was lowered beneath 12 cm H_2O. Mixed venous saturation levels increased from PEEP 20 to PEEP 12 cm H_2O but then decreased dramatically from PEEP 12 cm H_2O to ZEEP, which is consistent with the drop in arterial oxygen saturation caused by the increase in atelectasis and a rightward shift in the hemoglobin dissociation due to hypercapnic acidosis. Pulmonary artery pressure increased during down adjustment of PEEP indicating stronger HPV and hypercapnic acidosis.[101]

Conclusions

1. In morbidly obese patients, a recruitment maneuver followed by PEEP was sufficient to reduce the amount of atelectasis and improve oxygenation for a prolonged period of time. PEEP or a recruitment maneuver alone was not effective to reach a sustained improvement of respiratory function.

2. In morbidly obese patients without pulmonary disease, preoperative lung function tests with mild signs of airway obstruction (reduced end-expiratory flow) could predict reduced formation of atelectasis during anaesthesia.

3. In our experimental model of sequential OLV with capnothorax, EIT in real-time detected lung separation and dynamic changes in pulmonary ventilation and perfusion distributions. OLV to the left side caused a decrease in cardiac output, arterial oxygenation and mixed venous saturation.

4. In OLV with capnothorax using an insufflation pressure of 16 cm H_2O it could be demonstrated that a PEEP level of 12-16 cm H_2O is needed for optimal oxygenation and lowest possible driving pressure without compromising hemodynamic variables. Thus, optimal PEEP was closely related to the level of the capnothorax insufflation pressure. With insufficient PEEP, ventilation/perfusion mismatch in the ventilated lung and redistribution of blood flow to the non-ventilated lung occurred.

Limitations

Paper I & II

1) the number of patients included in the studies are limited and the results should be interpreted with this in mind. However, the sample size was enough to detect the large differences that occurred in the respiratory and morphological variables, 2) we used fixed levels of inspiratory pressures for recruitment maneuver and PEEP, 3) we used fixed tidal volumes of 10 ml/kg predicted body weight, and therefore different effects of higher or lower tidal volumes can not be excluded, 4) We studied our patient in the supine position. Beach chair position have been shown to effectively improve respiratory mechanics and oxygenation in obese patients during anaesthesia, especially in combination with PEEP,[41] 5) we used conventional volume controlled ventilation, recent studies have shown promising results with improved gas-exchange and respiratory mechanics while using biologically variable ventilation,[108] 6) It is possible that the level of PEEP used in the current study was not enough to maximize the beneficial effects on respiratory function. It has to be kept in mind that abdominal pressure will have influence on optimal PEEP, thus optimal PEEP may be higher during laparoscopic surgery with CO_2 insufflation in the abdomen and conversely lower after opening of the abdominal wall. However, a PEEP of 10 cm H_2O was sufficient to maintain a substantial improvement in respiratory function prior to surgery.
7) The majority of the patients included in the study were female, the most common population of patients undergoing bariatric surgery,[109] 8) we did not evaluate hemodynamics in detail in these patients undergoing conventional bariatric surgery, 9) we minimized the number of computerized tomography scans for each patient as requested by the ethical committee at Uppsala University, Sweden, and in line with good clinical and research practice,[110] 10) The patients studied had mostly normal lung function according to standardized interpretation of lung function tests and did not suffer from any subjective clinical lung function impairment. Thus, we studied differences within a relatively small span of lung function making the results from statistical analysis more uncertain.

Paper III

A limitation of the study design is that all experiments followed the same right-to-left sequence. Thus, carry-on effects such as fluid optimization may confound the observations, a bias possible to reduce by randomization of the sides' sequence. Also the lateralized perfusion seen at the end of the last TLV may be due to incomplete recruitment of collapsed tissue, which is compatible with the simultaneous decrease in ventilation.

Paper IV

An experimental study in animals has inherent differences from the clinical situation. Specifically, pigs have a stronger HPV than humans.[97] Therefore, hypoxemia in this setting would probably be more pronounced in humans. Also, the hypercapnic acidosis may have influenced parameters such as pulmonary vascular and global vascular tone, heart frequency, cardiac output and peripheral oxygen delivery. Giving priority to maintaining stabile airway pressures, we did not alter tidal volumes or respiratory rate. In clinical practice, these parameters would probably have been adjusted as well, which adds a degree of uncertainty to the interpretation of the physiology in a corresponding clinical situation. Another aspect is the laterality, since only the left side was subjected to capnothorax and part of the clinical complexity can be attributed the use of bilateral sequential OLV. Especially the hemodynamic respects are important to consider when translating findings from left to right capnothorax, since we and others have found more pronounced hemodynamic impairment during right-sided capnothorax.[43,112] When changing sides of OLV with capnothorax during anaesthesia for bilateral surgery, the ventilated side during the second OLV have already been subjected to lung collapse and may need different PEEP-levels to optimize physiology and maintain a protective ventilation strategy.[53] Finally, only one set of decremental PEEP was carried out using a fixed capnothorax insufflation pressure of 16 cm H_2O. Thus, it is not possible to conclude what is the "optimal" PEEP level when using other CO_2- insufflation pressures.

Future perspectives

A recruitment maneuver followed by PEEP effectively reduce atelectasis in morbidly obese patients after induction of anaesthesia. Since also preoxygenation with NIV/CPAP reduces atelectasis formation it seems possible to deliver anaesthesia to this group of patients with minimal atelectasis and less risk for hypoxemia and impaired respiratory system mechanics. It has also been shown that protective ventilation with low tidal volumes decreases the risk for postoperative pulmonary complications.[11] However, several important questions remain unanswered, for example: 1) Is it possible to extubate and manage this perioperative situation in a manner that keeps atelectasis from forming after extubation? 2) Does an open lung approach with individualized PEEP and minimized driving pressures translate to less VILI and postoperative lung complications?

Recently published studies[78,113,114] addressing these issues have some limitations why future studies may be of interest.

We found a mediastinal shift into the side of the non-ventilated lung at higher PEEP levels during OLV with capnothorax. This may imply a risk for inadequate surgical exposure when applying PEEP after a recruitment maneuver of the ventilated lung. Since optimization of the surgical field is the main purpose of OLV with capnothorax, optimal levels of PEEP for ventilation may actually be unacceptable for surgery or even making surgery impossible. If these findings are reproducible, it would be of interest to find the PEEP level correlating to the capnothorax pressure where this risk may occur.

The physiological changes following hypercapnic acidosis in the setting of OLV with capnothorax is unknown. It would therefore be of interest to study the effects of hypercapnic acidosis on hypoxic pulmonary vasoconstriction, gas exchange and hemodynamics in this setting.

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