The Effect of CO₂-Pneumoperitoneum on Ventilation Perfusion Distribution of the Lung

CHRISTOF STRANG
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Abstract

Laparoscopic operations are a common and popular way for abdominal procedures. They are usually performed by insufflation of carbon dioxide (CO2) into the abdominal cavity. However, insufflation of CO2 may interfere with cardiac and circulatory as well as respiratory functions. The CO2-pneumoperitoneum (PP) may cause hypercarbia and acidosis. The direct effects of CO2 and acidosis lead to decreased cardiac contractility, sensitization of the myocardium to arrhythmogenic effects of catecholamines and systemic vasodilatation. There may even be long-lasting post-operative effects on breathing control.

The pneumoperitoneum may also cause several respiratory changes, e.g. decreased functional residual capacity (FRC) and vital capacity (VC), formation of atelectasis, reduced respiratory compliance and increased airway pressure. Still, arterial oxygenation is mostly maintained or even improved during PP.

In view of the apparently contradictory results in respiratory mechanics and gas exchange, the present studies were performed to evaluate respiratory changes on gas exchange and ventilation-perfusion distributions during PP in a porcine model. It was demonstrated that atelectasis during anaesthesia and PP may be estimated by an increased arterial to endtidal PCO2-gradient (study I). Perfusion was redistributed away from dorsal, collapsed lung regions when PP was established. This resulted in a better ventilation-perfusion match (study II). Increasing abdominal pressure shifted blood flow more and more away from collapsed lung tissue, decreased pulmonary shunt and improved oxygenation from 8 to 16 mmHg PP, despite an increase of atelectasis formation (study III). CO2-PP enhanced the shift of blood flow towards better ventilated parts of the lung compared to Air-PP. Moreover, sodium natriumprussiwide worsened the ventilation-perfusion match even more and blunted the effects previously seen with carbon dioxide. CO2 should therefore be the mediator of enhancing HPV during PP.

In conclusion, pneumoperitoneum with CO2 causes atelectasis with elimination of ventilation in the dependent lung regions. However, an efficient shift of blood flow away from collapsed, non-ventilated regions results in a better ventilation-perfusion matching and better oxygenation of blood than without PP. A prerequisite for the beneficial effect is the use of carbon dioxide for the abdominal inflation, since it enhances HPV.

Keywords: lung, atelectasis; computed tomography; multiple inert gas elimination technique; model, pig; Pa–ECO2 ratio; surgery, laparoscopy; lung, blood flow; single photon emission computed tomography; ventilation/perfusion distribution; gas exchange; hypoxic pulmonary vasoconstriction

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urn:nbn:se:uu:diva-149746 (http://urn.kb.se/resolve?urn=nbn:se:uu:diva-149746)
To my parents and my wife
List of Publications

The thesis is based on the following publications, which are referred to in the text using the Roman numerals I-IV.


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Abbreviations

ASA American Society of Anesthesiologists
Crs Static Compliance
CO₂ Carbon Dioxide
CO Cardiac Output
CT Computed Tomography
CVP Central Venous Pressure
EELV End-Expiratory Lung Volume
FiO₂ Fraction of Inspired Oxygen
FRC Functional Residual Capacity
H₀ Null Hypothesis
HPV Hypoxic Pulmonary Vasoconstriction
HR Heart Rate
HU Hounsfield Unit
IAP Intra Abdominal Pressure
ID Inner Diameter
IPPV Intermittent Positive Pressure Ventilation
logSDQ Standard Deviation of Logarithmic Distribution of Perfusion
logSDV Standard Deviation of Logarithmic Distribution of Ventilation
MALUNA Mannheim Analysis Tool
MAP Mean Arterial Pressure
MIGET Multiple Inert Gas Elimination Technique
MPAP Mean Pulmonary Arterial Pressure
MV Minute Ventilation
PAC Pulmonary Artery Catheter
PaO₂ Partial Pressure of Oxygen in arterial Blood
PaO₂/FiO₂ Ratio of Inspiratory Fraction of Oxygen and arterial Oxygen Tension
PaCO₂ Partial Pressure of Carbon Dioxide in arterial Blood
Pa-ECO₂ Arterial to End-tidal Carbon Dioxide Difference
PECO₂ End-tidal Carbon Dioxide
PAOP Pulmonary Artery Occlusion Pressure
Pₐₕ Airway Pressure
Pabd Abdominal pressure
PEEP Positive End-Expiratory Pressure
PVR Pulmonary Vascular Resistance
RAAS Renin-Aldosterone-Angiotensine System
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<tr>
<td>ROI</td>
<td>Region of Interest</td>
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<tr>
<td>RR</td>
<td>Respiratory Rate</td>
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<td>RSS</td>
<td>Remaining Sum of Squares</td>
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<td>SaO₂</td>
<td>Arterial Oxygen Saturation</td>
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<td>SNP</td>
<td>Sodium Natriumprusside</td>
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<td>SPECT</td>
<td>Single Photon Emission Computed Tomography</td>
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<tr>
<td>SpO₂</td>
<td>Peripheral arterial Oxygen Saturation</td>
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<td>SvO₂</td>
<td>Mixed venous Oxygen Saturation</td>
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<td>SVR</td>
<td>Systemic Vascular Resistance</td>
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<tr>
<td>VC</td>
<td>Vital Capacity</td>
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INTRODUCTION

Clinical background

After the introduction of laparoscopic procedures, laparoscopic techniques (used either as a diagnostic tool or as therapeutic access method) are the most common procedures in surgery worldwide [1]. In addition, the indication for laparoscopic procedures increased heavily in the last years. Laparoscopic procedures are associated with lower mortality, less pain, faster recovery and shorter hospital stay than open procedures [2, 3]. Furthermore patients with a high American Society of Anesthesiology (ASA) classification profit even more from a laparoscopic approach than from an open approach [4].

Pathophysiological basis of CO₂-Pneumoperitoneum

The pneumoperitoneum is a crucial element in laparoscopic surgery. It is usually performed by insufflation of carbon dioxide (CO₂) into the abdominal cavity. However, insufflation of CO₂ may interfere with cardiac and circulatory as well as respiratory functions. Pneumoperitoneum decreases venous return, preload, and cardiac output (CO) and increases heart rate (HR), mean arterial pressure (MAP), as well as systemic (SVR) and pulmonary vascular resistance (PVR) [5]. These haemodynamic and cardiovascular changes mostly occur because of increased abdominal pressure (IAP) [6, 7] and stimulated neurohumoral vasoactive systems (vasopressin and renin-aldosterone-angiotensine system (RAAS)) [8], but are independent of what gas is used for insufflation [9]. However, in otherwise healthy patients these changes are not dangerous when IAP does not exceed 16mmHg [10]. Increased IAP, between 12 and 16 mmHg, decreases venous return, which results in reduced preload and CO, without adequate intravascular volume loading [11]. Additionally, changes in body position, especially head-up tilt position, intensify these negative effects of a pneumoperitoneum [12], whereas head-down or Trendelenburg position has a positive effect on venous return [13]. Pneumoperitoneum increases sympathetic cardiac activity [14] and induces a haemodynamic stress response by activation of the neurohumoral vasoactive system (i.e.,
vasopressin and RAAS) resulting in increased HR, increased SVR and PVR, and increased arterial blood pressure [15]. This stress response leads to an increase in oxygen consumption, which might be deleterious for patients with compromised cardiac function [1]. In clinical studies on ASA III and IV patients distinct intraoperative haemodynamic changes during pneumoperitoneum were described, but cardiovascular stability was unaffected if appropriate invasive monitoring and pharmacologic interventions were used [4, 16, 17]. In the majority of patients (ASA I and II), the haemodynamic effects of a pneumoperitoneum are without consequences and vanish after desufflation. Since the effects of increased IAP on haemodynamics are volume dependent, adequate preoperative intravascular loading is essential, especially in patients with cardiac diseases, to prevent cardiovascular side effects of a pneumoperitoneum [7]. To minimize the effects of haemodynamic stress response on myocardial oxygen consumption, esmolol (β-blocker) or clonidine (α-blocker) can safely be used to block receptors if volume depletion is not present [18]. Haemodynamic and circulatory changes are independent from the used gas (CO₂ or helium) [9], but the effects on haemodynamics were smaller during gasless laparoscopy [19]. Therefore, gasless laparoscopy might be an alternative for patients with limited cardiac function [1].

The CO₂-pneumoperitoneum (PP) may cause hypercarbia and acidosis [1]. The direct effects of carbon dioxide and acidosis lead to decreased cardiac contractility, sensitization of the myocardium to arrhythmogenic effects of catecholamines and systemic vasodilatation [20]. The pneumoperitoneum may also cause several respiratory changes, e.g. decreased functional residual capacity (FRC) and vital capacity (VC) [21], formation of atelectasis [22], reduced respiratory compliance [23] and increased airway pressure to provide a given tidal volume [5]. Still, arterial oxygenation is mostly maintained or even improved during PP [24]. During general anaesthesia and mechanical ventilation, lungs are compressed by a cranial shift of the diaphragm, promoting atelectasis formation [25]. Intraabdominal insufflation of CO₂ for laparoscopic surgery (pneumoperitoneum; PP) causes further shift of the diaphragm [26-28], and increased lung collapse, decreased respiratory compliance and increased airways pressure, as shown in clinical and experimental studies [21, 24, 29]. In addition CO₂ is absorbed across the peritoneal epithelium, and even more so in patients with morbid obesity [21, 30]. Perfusion of non-ventilated alveoli strongly affects oxygenation of blood [31] and CO₂-elimination may also be impaired. In anaesthetized patients pneumoperitoneum causes an increase in atelectasis but need not increase shunt or lower arterial oxygenation [16, 24]. This seeming paradox has not yet been explained. Another consequence of the absence of a correlation between atelectasis and oxygenation is that measurement of PaO₂ or calculation of shunt can not be used to assess the
amount of collapsed lung. Laparoscopic surgical procedures are performed at varying abdominal pressures [32]. More extensive laparoscopic surgery increases the need of prolonged insufflation time and increased abdominal pressure. It is not clear, whether laparoscopic procedures reduce the risk for clinically important pulmonary complications [33]. These factors make it imperative that the physiologic changes that occur during laparoscopy must be understood and monitored carefully [5, 34].
AIMS OF THE STUDIES

The objective of the studies, which this thesis comprises, was to investigate the effect of CO₂-Pneumoperitoneum on respiratory mechanics and gas exchange in an experimental porcine model.

A particular focus is on the seeming paradox of increased atelectasis but maintained or improved oxygenation.

The knowledge obtained by these studies could facilitate the implementation of a lung protective ventilation approach in laparoscopic surgery and may contribute to improved patient care and better outcome.

The specific objectives, studied in porcine experiments were:

1. To examine the effects of CO₂-Pneumoperitoneum on atelectasis formation and the possibility to monitor atelectasis formation by recording PO₂ and PCO₂. The null hypothesis (H₀) was tested that there was no correlation between regional lung collapse and CO₂-elimination in a porcine model of pneumoperitoneum.

2. To evaluate the effects of CO₂-pneumoperitoneum on ventilation-perfusion distribution and gas exchange by isotope technique (single photon emission computed tomography) and multiple inert gas elimination technique.

3. To investigate whether increasing abdominal CO₂-pressure from 8 to 16 mmHg affects pulmonary gas exchange, and whether it does so to increasing extent.

4. To compare the effects of inflating the abdomen (pneumoperitoneum) with either carbon dioxide or air on the distribution of ventilation and perfusion their matching (VA/Q) and their correlation to oxygenation.
METHODS

Study protocols

Study I

The study evaluated whether ventilation with different FiO$_2$ and pulmonary suctioning before pneumoperitoneum modifies the amount of pulmonary atelectasis, haemodynamic variables and gas exchange in patients during CO$_2$-pneumoperitoneum.

In Group 1 (n=5) pigs were ventilated with a $V_T$ of 10 ml·kg$^{-1}$, FiO$_2$ of 0.5 and PEEP of 5 cmH$_2$O. Based on data from the literature and results from our laboratory minor development of atelectasis was expected. In Group 2 (n=5) FiO$_2$ was increased to 1.0 for 30 minutes and in group 3 (n=5) a negative pressure of $-15$ cm H$_2$O was applied to the tracheal tube for 20 seconds in order to produce a large range of atelectasis similar to findings in anaesthetized normal-weight as well as morbidly obese patients. After these procedures groups 2 and 3 were given the same ventilation as Group 1.

Pneumoperitoneum was created by insufflation of CO$_2$ into the abdominal cavity via VERRES needle with a common CO$_2$ insufflator (7060-Insufflator Pelvi Pneu Semm Systems; Wisap, Munich, Germany) until the abdominal pressure ($P_{ab}$) reached 12mmHg. Mechanical ventilation was maintained in the same mode and pattern as before induction of pneumoperitoneum. Measurements of gas exchange and haemodynamics and recordings with CT were made during anaesthesia after the period of FiO$_2$ 1.0 in Group 2 and negative pressure in Group 3, before and after 10 and 90 minutes of CO$_2$-pneumoperitoneum.

Study II

The study investigated the effect of CO$_2$-pneumoperitoneum on ventilation-perfusion distribution with Single Photon Emission Computed Tomography (SPECT) and Multiple Inert Gas Elimination Technique (MIGET).

In both groups (MIGET and SPECT; n = 14) pigs were ventilated with a $V_T$ of 10 ml kg$^{-1}$, PEEP 5 cmH$_2$O and FiO$_2$ 0.5. Based on previous results from our laboratory FiO$_2$ was increased to 1.0 for 30 minutes in order to
induce atelectasis in the range of 3 to 5% [29]. FiO₂ was then decreased to 0.5 before creation of CO₂-pneumoperitoneum.

Pneumoperitoneum was created by insufflation of CO₂ into the abdominal cavity via a VERRES needle with a common CO₂ insufflator (7060-Insufflator Pelvi Pneu Semm Systems; Wisap, Munich, Germany) until the abdominal pressure (Pₐbd) reached 12mmHg. Mechanical ventilation was maintained with the same respirator settings (unaltered ventilation) as before induction of pneumoperitoneum. SPECT and MIGET could not be done in the same pig because of technical and logistic reasons. Therefore in 7 pigs, the distributions of ventilation and perfusion were studied by SPECT and in the other 7 pigs the Vₐ/Q relationship was studied by MIGET. Measurements of gas exchange, haemodynamics and SPECT/MIGET were made during anaesthesia and 60 min after induction of pneumoperitoneum.

Study III

The study established whether increasing abdominal pressure from 8 to 16 mmHg affects pulmonary gas exchange, and whether it does so to increasing extent.

In all groups (MIGET, SPECT and CT; n=6 in each group) pigs were ventilated with a Vₜ of 10 ml kg⁻¹, PEEP 5 cmH₂O and FiO₂ 0.5. Based on previous results from our laboratory FiO₂ was increased to 1.0 for 30 minutes in order to induce atelectasis in the range of 3 to 5% [29]. FiO₂ was then decreased to 0.5 before creation of CO₂-pneumoperitoneum.

Pneumoperitoneum was created by insufflation of CO₂ into the abdominal cavity via a VERESS needle with a common CO₂ insufflator (7060-Insufflator Pelvi Pneu Semm Systems; Wisap, Munich, Germany) until the abdominal pressure (Pₐbd) reached 8, 12 or 16 mmHg. All variations of abdominal pressure sequence were possible, i.e. 12-8-16 mmHg, 16-8-12 mmHg, 8-12-16 mmHg and 16-12-8 mmHg. Mechanical ventilation was maintained with the same respirator settings (unaltered ventilation) as before induction of pneumoperitoneum. SPECT, MIGET and CT could not be done in the same pig because of technical and logistic reasons. Therefore in 6 pigs, the Vₐ/Q relationship was studied by MIGET and in another 6 pigs the distributions of ventilation and perfusion were studied by SPECT. Further 6 pigs were transferred to the radiology department and spiral CT scans of the chest were obtained. Measurements of gas exchange, haemodynamics and MIGET were made during anaesthesia and 60 min after induction of pneumoperitoneum at every pressure level. SPECT was only made during pneumoperitoneum, because of technical reasons (Figure 1).
Study IV

The experiment investigated the influence of CO\textsubscript{2} during pneumoperitoneum on hypoxic pulmonary vasoconstriction (HPV) in laparoscopic surgery. All pigs were ventilated with a V\textsubscript{T} of 10 ml kg\textsuperscript{-1}, PEEP 5 cmH\textsubscript{2}O and FiO\textsubscript{2} 0.5. Based on previous results from our laboratory, FiO\textsubscript{2} was increased to 1.0 for 30 minutes in order to induce atelectasis in the range of 3 to 5% [29]. FiO\textsubscript{2} was then decreased to 0.5 before creation of pneumoperitoneum. 27 pigs were divided in three groups. In the first group (n=9) pneumoperitoneum was created by insufflation of CO\textsubscript{2} into the abdominal cavity via a VERESS needle with a common CO\textsubscript{2} insufflator (7060-Insufflator Pelvi Pneu Semm Systems; Wisap, Munich, Germany) until the abdominal pressure (P\textsubscript{abd}) reached 12 mmHg. In the second group pneumoperitoneum was inflated with Air till 12 mmHg abdominal pressure (n=9). In the third group (n=9) abdominal pressure of 12 mmHg was maintained by CO\textsubscript{2}, additionally intravenous 0.5 mg\textsuperscript{-1}kg\textsuperscript{-1}min sodium natriumprusside (SNP) was infused to reduce HPV. Mechanical ventilation was maintained with the same respirator settings (unaltered ventilation) as before induction of pneumoperitoneum. SPECT and MIGET could not be done in the same pig because of technical and logistic reasons. Therefore in
6 pigs, the $V_{A}/Q$ relationship was studied by MIGET and in another 3 pigs
the distributions of ventilation and perfusion was studied by SPECT in each
group. Measurements of gas exchange, haemodynamics and MIGET were
made during anaesthesia and 60 min after induction of pneumoperitoneum.

Animal Experiments

Subjects

The studies were conducted as prospective, randomised, controlled animal
experiments. The Animal Ethics Committee of Uppsala University (Sweden)
approved the study protocols and the use of animals.

A total of seventy-four male and female, 2-3-month-old
Yorkshire/Swedish country piglets, weight 27-30kg, obtained from a local
breeder, were used. The animals fasted overnight and had free access to
water. All pigs underwent the same study protocol (anaesthesia,
instrumentation, measurement algorithms). The animals were randomly
assigned to experimental groups by pulling a sealed envelope.

Anaesthesia

A similar anaesthesia protocol was used in all animals in line with the
laboratory standard. Anaesthesia was induced by an $i.m.$ injection of
xylazine (2.2mg·kg$^{-1}$, Bayer, Germany), tiletamine/zolazepam (6mg·kg$^{-1}$,
Virbac, France) and atropine (0.04mg·kg$^{-1}$, NM Pharma, Sweden) in all pigs.

Anaesthesia was maintained by continuous administration of fentanyl (5
µg·kg$^{-1}·h^{-1}$, Leptanal®, Janssen-Cilag AB, Sweden), pancuronium
(0.3mg·kg$^{-1}·h^{-1}$, Pavulon®; Organon, Oss, Netherlands), ketamine (25mg·kg$^{-1}·h^{-1}$,
Ketaminol vet.; Intervet, Boxmeer, Netherlands) and propofol
(3mg·kg$^{-1}·h^{-1}$, Diprivan®, Astra, Södertälje, Sweden). Prior to manipulation,
the adequate depth of surgical anaesthesia was confirmed by absence of both
the hind limb flexion reflex and corneal reflex responses according to the
laboratory standard of the Animal Ethics Committee of Uppsala University.

The animals received 12±2ml·kg$^{-1}·h^{-1}$ of isotonic saline during the study.
All pigs were killed through an intravenous bolus injection of potassium
chloride (150meq) at the end of the study.
Instrumentation

The pigs were instrumented with a left carotid arterial catheter (20G; Becton-Dickinson Critical Care Systems, Singapore), a flow-directed Swan-Ganz thermodilution pulmonary artery catheter (PAC, 7.0French, Baxter, USA), a central venous catheter (4.0French, Becton-Dickinson) and a suprapubic urinary catheter (Sympakath®, Ruesch AG, Switzerland).

Body temperature was monitored and kept constant by thermoconvection. Pigs were allowed to stabilise for 30min after instrumentation.

Ventilation and haemodynamic measurements

Ventilation and haemodynamic variables [cardiac output, heart rate (HR), mean arterial pressure (MAP), mean pulmonary artery pressure (MPAP), central venous pressure (CVP), pulmonary artery occlusion pressure (PAOP), arterial and mixed venous blood gases] were recorded during anaesthesia baseline and 60 minutes during pneumoperitoneum. Systemic, pulmonary arterial and central venous pressures were displayed on a monitor (SC 9000 XL; Maquet Critical Care AB, Solna, Sweden) and were recorded with reference to atmospheric pressure at the midthoracic level at end-expiration. End-expiratory carbon dioxide tension (PE\textsubscript{CO}_2) was measured by capnography implemented in the ventilator (Servo i; Maquet Critical Care AB, Solna, Sweden). Arterial and mixed venous blood samples were analyzed with ABL 300 blood gas analyzer and OSM 3 oximeter (Radiometer, Copenhagen, Denmark). Cardiac output (CO) was determined by thermodilution. The thermal indicator was 10 ml of saline 8-10°C and was injected into the right atrium. The first measurement was ignored and the cardiac output was derived from the mean of three consecutive measurements. The injections were evenly distributed over the respiratory cycle.

Venous admixture (“shunt”) was calculated according to the standard shunt equation. Based on the measurements of oxygen content in arterial, mixed venous and pulmonary end-capillary blood.

Ventilation management

After endotracheal intubation (ID 7.0mm; Mallinckrodt, Ireland), the pigs were mechanically ventilated (intermittent positive pressure ventilation, IPPV) with a FiO\textsubscript{2}=0.50 and PEEP=5cmH\textsubscript{2}O provided by a ventilator (Servo i; Maquet Critical Care AB, Solna, Sweden). Respiratory rate was adjusted to achieve normocapnia (PaCO\textsubscript{2} = 4.7 to 6 kPa). Tidal volume (V\textsubscript{t}), airway pressures (P\textsubscript{aw}) and flow were continuously recorded. Static compliance (C\textsubscript{rs})
of the total respiratory system was calculated as $C_{rs} = V_t \left[ P_{aw \text{ plateau}} - P_{aw \text{ end expiration}} \right]$, where airway pressures were measured after end-inspiratory and end-expiratory halts of 3 seconds. After 30 minutes of stabilisation ventilation management followed the study protocols.

**Computed Tomography**

**Study I and Study III:** A frontal tomogram of the chest was obtained during ventilation to determine the borders of the lung. An end-expiratory transversal spiral computed tomography (CT) (140 kV, 111 mA) covering the whole lung, with 1mm slice thickness was acquired with a Somatom Plus 4 CT scanner (Siemens, Erlangen, Germany). The scanning time for the transverse images was ≈ 3 seconds. The CT scanning was analyzed by using the custom-made software package MALUNA (Mannheim Lung Analysis Tool). The total lung volume was calculated by creating a region of interest (ROI) around each lung scan excluding the mediastinum and the big vessels. Each voxel of the CT scan is characterized by a CT number, which is related to the tissue density and numerically expressed in Hounsfield units (HU). The scale ranges from +1000 HU (bone) to 0 HU (water) and -1000 HU (air). For example, a voxel with -200 HU consists 20% gas and 80% tissue, and a voxel with -700 HU consists 70% gas and 30% tissue. For further analysis the lung was divided into four categories: areas with densities ranging from -1000 to -900 Hounsfield units were classified as over aerated, from -900 to -500 HU as normally aerated, from -500 to -100 HU as poorly aerated and from -100 to +100 HU as nonaerated (atelectasis).

**Ventilation-Perfusion Techniques**

**Multiple Inert Gas Elimination Technique**

**Study II - IV:** Determination of the $V_A/Q$ distribution was done with the Multiple Inert Gas Elimination Technique (MIGET) [35]. Six inert gases of different solubilities in blood were dissolved in isotonic saline and infused into a peripheral vein. Arterial and mixed venous blood samples were tonometered with gas and analyzed together with an expired gas sample by gas chromatography (Model 5890, Series II; Hewlett-Packard, Waltheim, MA). These data enable the construction of a virtually continuous distribution of $V_A/Q$ ratios against blood flow or ventilation, with separation of shunt ($V_A/Q < 0,005$) from regions of low $V_A/Q$ ratios (0,005 $< V_A/Q < 0,1$; poorly ventilated lung units in relation to their perfusion), as well as
separation of regions of high $V_A/Q$ ratios ($10 < V_A/Q < 100$) from dead space ($V_D$) ($V_A/Q > 100$). The mean $V_A/Q$ of the ventilation and perfusion distributions ($V_{mean}, Q_{mean}$) were calculated. Moreover, the standard deviation of the logarithmic distribution of perfusion ($LogSDQ$) and ventilation ($LogSDV$) were calculated as measures of the dispersion (mismatch) of blood flow and ventilation. Finally, the $PaO_2$ that can be predicted from the $V_A/Q$ distributions was compared with measured $PaO_2$ (by blood gas analysis).

Single Photon Elimination Computed Tomography

**Study II - IV:** Single Photon Emission Computed Tomography (SPECT) was used to analyze the spatial ventilation and perfusion distributions during anaesthesia and pneumoperitoneum [36]. Ventilation distribution was assessed by inhalation of Krypton ($^{81m}$Kr; $t_{1/2}$: 12 sec), being produced by a rubidium generator on site (Mallinkrodt; Netherlands) [37]. Lung blood flow was assessed by intravenous injection of $^{99m}$Tc-labeled macroaggregated albumin ($^{99m}$Tc-MAA) (Pulmocis; CISbiointernational, Gif sur Yvette, France). The animals were put in the supine position with their front legs stretched cranially. Since pneumoperitoneum caused a cranial shift of the diaphragm a new SPECT was done directly after the insufflation of the abdominal cavity, measuring the radioactivity from the first isotope injection. This enabled a background subtraction of the radioactivity when the second injection was done during pneumoperitoneum. In order to obtain high pulmonary emission activity in relation to the contribution of activity from preceding measurements, the injected activity was increased from 50 MBq $^{99m}$Tc-MAA for the first SPECT scan to 100 MBq $^{99m}$Tc-MAA for the next SPECT.

Images were acquired on a dual-head gamma camera (Millenium; General Electric Systems, Milwaukee, WI) equipped with all-purpose, medium-energy collimators. SPECT acquisition was made in 60 projections (30 per head) and stored in a 128 by 128 matrix, resulting in a pixel size of 4.42 mm$^2$. A low-resolution CT scan (covering the same volume as the SPECT) was performed immediately after each SPECT to evaluate lung borders and to enable attenuation correction. The overall scan time for SPECT and CT was approximately 40 min.

Data were reconstructed first on an eNTEGRA workstation and later on a Xeleris workstation (General Electric Systems). The reconstruction was performed with an iterative model (OSEM, four iterations and eight subsets) and a Hann filter (cut-off 0.85) for the post-reconstruction filtering on both workstations. The reconstructed volumes were then corrected for radiation spillover using a HERMES workstation (Hermes Medical Solution, Stockholm, Sweden). For each reconstructed slice the contents were
analyzed by commercial (HERMES) and custom made software. After evaluation of the lung borders with the CT, the left and the right lungs were chosen as the ROI by drawing the external boundaries of the lung along the inside of the ribs and the internal boundaries along the mediastinal organs. The lungs were divided into 35 equally thick portions in the dorsal to ventral direction, for assessment of the vertical ventilation-perfusion distribution. Similarly, the lungs were divided into 48 equally thick slices from caudal to cranial lung regions for analysis of ventilation-perfusion distribution in that plane.

**Study III**: Changing abdominal pressure during pneumoperitoneum enabled a background subtraction of the radioactivity. In order to obtain high pulmonary emission activity in relation to the contribution of activity from preceding measurements, the injected dose was increased from 50 MBq $^{99m}$Tc-MAA for the first SPECT, to 100 MBq $^{99m}$Tc-MAA for the second SPECT and to 150 MBq $^{99m}$Tc-MAA for the third SPECT, respectively.

**Statistical analysis**

Statistical analysis was performed using the Prism 4 software package (GraphPad Software Inc., San Diego, CA, USA) and the JNP IN 5.1 software package (SAS Institute Inc., Cary, NC, USA). A $p$ value of less than 0.05 was considered significant for all statistical procedures.

**Study I**: Power calculations using a two-sided design at a significance level of 5% ($a=0.05$) and a probability of 80% ($b=0.20$) to detect a difference of at least 35% in the development of atelectasis revealed that a minimum of 5 pigs was needed in each group.

Data were tested for normal distribution with the Shapiro-Wilks W test. Normally distributed data are presented as mean±standard deviation (cardiopulmonary, ventilation and gas exchange variables). These data were analysed by a repeated measures one-way analysis of variance with post-hoc Bonferroni correction. Non-normally distributed data were analysed by Friedman’s analysis of variance (ANOVA) and Tukey’s HSD. Comparison between two variables was tested by linear regression analysis. CT data were slice-wise analysed by two-sample t-tests and repeated measures ANOVA.

**Study II**: Power calculations using a two-sided design at a significance level of 5% ($a=0.05$) and a probability of 80% ($b=0.20$) to detect a difference of at least 35% in the development of atelectasis (and subsequent change in ventilation) revealed that a minimum of 7 pigs was needed in each Group.

Data were tested for normal distribution with the Shapiro-Wilks W test. Normally distributed data are presented as mean±standard deviation (cardiopulmonary, ventilation and gas exchange variables) and were analysed by repeated measures one-way analysis of variance with post-hoc
Bonferroni correction. Non-normally distributed data were analysed by Friedman’s analysis of variance (ANOVA) and Tukey’s HSD. MIGET data was tested with a unpaired t-Test.

**Study III:** Power calculations using a two-sided design with a significance level of 5% (a=0.05) and a probability of 80% (b=0.20) showed that a minimum of 6 pigs was needed in each group to detect a difference of at least 35% between baseline and different abdominal pressure levels.

Data were tested (and approved) for normal distribution with the Shapiro-Wilks W test. Data are presented as median with s and were analysed by repeated measures one-way analysis of variance with post-hoc Bonferroni correction. Correlations were analyzed by a regression analysis.

**Study IV:** Power calculations using a two-sided design at a significance level of 5% (a=0.05) and a probability of 80% (b=0.20) to detect a difference of at least 35% in the change of pulmonary gas exchange (oxygenation and ventilation-perfusion matching) by MIGET revealed that a minimum of 6 pigs and spatial ventilation-perfusion distribution by SPECT revealed that a minimum of 3 was needed in each group.

The data were tested for normal distribution with the Shapiro-Wilks W test. The data are presented as mean±standard deviation in the case of normal distribution (cardiopulmonary, gas exchange and ventilation variables) and were analyzed by repeated measures one-way analysis of variance with post-hoc Bonferroni correction.
RESULTS

The effects of pneumoperitoneum on respiration and haemodynamics

**Study I:** In group 1 oxygenation was normal (PaO₂/FiO₂ = 62±3.7 kPa) and Pa-E’CO₂ was low (0.04±0.05 kPa). In group 2 oxygenation was slightly impaired (PaO₂/FiO₂ = 50±8 kPa) and Pa-E’CO₂ had increased to 0.3±0.07 kPa. In group 3 PaO₂/FiO₂ (34±8.4 kPa, p<0.05) and Pa-E’CO₂ (0.6±0.2 kPa, p<0.05) were significantly different as compared to group 1 and 2.

Peak airway pressure and airway plateau pressure almost doubled and respiratory compliance decreased to less than half the value before pneumoperitoneum in all 3 groups.

**Study II:** PaO₂, PA-aO₂, PaCO₂ and Pa-ECO₂ increased during CO₂-pneumoperitoneum, and pH decreased. Peak airway pressure and airway plateau pressure almost doubled and respiratory compliance decreased to less than half the value before pneumoperitoneum.

Central venous, mean pulmonary arterial and pulmonary capillary wedge pressures increased during CO₂-pneumoperitoneum. No changes in cardiac output were seen.

**Study III:** PaO₂ did not change from anaesthesia baseline when 8 and 12 mmHg CO₂-pneumoperitoneum was applied but increased when abdominal pressure was increased to 16 mmHg. PaCO₂ and Pa-ECO₂ increased during CO₂-pneumoperitoneum, with the highest values at the highest abdominal pressure (16 mmHg). Peak airway pressure and airway plateau pressure almost doubled and respiratory compliance decreased to less than half with the highest level of CO₂-pneumoperitoneum (16 mmHg).

Central venous, mean pulmonary arterial and pulmonary capillary wedge pressures increased and the calculated pulmonary vascular resistance (PVR) remained unaltered during CO₂-pneumoperitoneum. No changes in cardiac output, stroke volume or heart rate were seen, not even at the highest abdominal pressure.

**Study IV:** PaO₂ did not change from anaesthesia baseline when Air-pneumoperitoneum was applied but increased during CO₂-
pneumoperitoneum and decreased during CO₂-pneumoperitoneum with intravenous SNP. PaO₂ increased during CO₂-pneumoperitoneum, decreased during SNP-pneumoperitoneum and was unaffected during Air-pneumoperitoneum. Pa-ECO₂ increased during pneumoperitoneum, with no differences between the groups. Peak airway pressure and airway plateau pressure almost doubled and respiratory compliance decreased to less than half with pneumoperitoneum in all three groups.

Central venous and pulmonary capillary wedge pressures increased during pneumoperitoneum. No changes in cardiac output were seen in the CO₂-pneumoperitoneum and Air-pneumoperitoneum groups, but a slight decrease was noted in the SNP group.

The effects of pneumoperitoneum on atelectasis formation

**Study I:** In group 1 little atelectasis was detected by CT. In group 2 atelectasis had increased to 3±2% (p<0.05, compared to group 1). In group 3 atelectasis had increased to 7±3% (p<0.05, compared to group 1 and 2).

Induction of CO₂-pneumoperitoneum increased atelectasis in all groups (although not significantly for atelectasis in group 1).

*Figure 2:* Examples of CT scans during anaesthesia and during CO₂-pneumoperitoneum in all groups.

![Anaesthesia PP Group 1 Group 2 Group 3](image)

**Study III:** The end-expiratory lung volume (EELV) decreased after induction of pneumoperitoneum with a modest further decrease when abdominal pressure was increased. Atelectasis corresponding to 4±1% of
total lung volume was seen under anaesthesia (“baseline”) (Table 1). During CO₂-pneumoperitoneum the amount of atelectasis increased and normally aerated lung tissue decreased in proportion to the abdominal pressure. Poorly and over aerated lung tissue did not change after induction of CO₂-pneumoperitoneum (Table 1).

Table 1: Anaesthesia = Ventilation with 50% O₂; Pneumoperitoneum: 3 different abdominal pressures by CO₂-insufflation; Atelectasis = -100 to 100 Hounsfield units (HU); Poor Aeration = -500 to -100 HU; Normal Aeration = -850 to -500 HU; Over Aeration = -850 to -1000 HU; EELV: end-expiratory lung volume. Data given as mean ± standard deviation (n=6) * = P-value (p<0.05) is calculated as ANOVA test in comparison to anaesthesia. ** = P-value (p<0.05) is calculated as ANOVA test in comparison to 8 mmHg PP

<table>
<thead>
<tr>
<th>Variable</th>
<th>Anaesthesia</th>
<th>CO₂-Pneumoperitoneum</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
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</tr>
<tr>
<td>Atelectasis, %</td>
<td>4±1</td>
<td>9±2*</td>
</tr>
<tr>
<td>Poor aeration, %</td>
<td>42±3</td>
<td>44±3</td>
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<tr>
<td>Normal aeration, %</td>
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<td>41±6</td>
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<td>Over aeration, %</td>
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<td>0.39±0.08</td>
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<td>EELV, ml</td>
<td>772±32</td>
<td>668±31*</td>
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</table>

The correlation between atelectasis formation and arterial to end-tidal carbon dioxide difference and atelectasis formation and oxygenation during pneumoperitoneum

Study I: Induction of CO₂-pneumoperitoneum increased atelectasis and Pa-E’CO₂ in all groups (although not significantly for atelectasis in group 1). There was a significant correlation between the amount of atelectasis and Pa-E’CO₂ in each group before and during CO₂-pneumoperitoneum and when all data were pooled (r² = 0.92) (Figure 3).

There was good correlation between oxygenation and the amount of atelectasis before (r²=0.91), but not after induction of CO₂-pneumoperitoneum (r²=0.36) (Figure4).
Figure 3: Plot of Pa-E’CO₂ vs atelectasis in all groups. The linear regression analysis resulted in the equation Y = 0.06x+0.66, r² = 0.92. A good correlation was seen when all data were pooled. Separate regression equations for data obtained during anaesthesia before and during CO₂-pneumoperitoneum, respectively, did not differ from the overall regression and are not shown.

Figure 4: Plot of PaO₂/FiO₂ vs atelectasis in all groups. The linear regression analysis resulted in the equation Y = 55.6-1.47, r² = 0.40. No significant correlation was seen during CO₂-pneumoperitoneum when all data were pooled. Separate regression analysis of PaO₂/FiO₂ vs atelectasis during CO₂-pneumoperitoneum showed even poorer correlation (r²=0.36).
The effects of pneumoperitoneum on ventilation perfusion distribution (Multiple Inert Gas Elimination Technique)

**Study II:** The $V_A/Q$ distributions are shown in Figure 5 and Table 2. The distributions had a remaining sum of squares (RSS) of 1.24±0.56, which indicates high methodological accuracy. Shunt decreased after creation of pneumoperitoneum. No low $V_A/Q$ was seen either before or during pneumoperitoneum. A small amount of high $V_A/Q$ appeared during pneumoperitoneum whereas $V_D$ was unaltered. $V_{mean}$ and $Q_{mean}$ expressed as $V_A/Q$ ratio came closer to each other during pneumoperitoneum (p<0.05; see Table 2). This suggests an improved match of ventilation and perfusion. LogSDQ and LogSDV were not significantly altered by pneumoperitoneum (Table 2). The difference in PaO$_2$ that can be predicted from the $V_A/Q$ distribution and measured from blood gas analysis was small (1.6±0.8 kPa) for the measured PaO$_2$ of around 35 kPa, which is further support of good methodological accuracy.

Table 2: Anaesthesia = Ventilation with 50% O$_2$; PP = pneumoperitoneum with abdominal pressure of 12 mm Hg by CO$_2$ insufflation; Shunt = perfusion of non-ventilated areas ($V_A/Q<0.005$); low $V_A/Q$ = low ventilation to perfusion ratio (0.005< $V_A/Q$ <0.1); regions of normal ventilation to perfusion ratios (0.1< $V_A/Q$ <1 and 1<$V_A/Q$<10); high $V_A/Q$ = high ventilation to perfusion ratio (10<$V_A/Q$<10); Dead Space = ventilated but non-perfused areas (10< $V_A/Q$ <100); Log SDV = log standard deviation of ventilation distribution; log SDQ = log standard deviation of perfusion distribution; $V_{mean}$ = mean of ventilation distribution; $Q_{mean}$ = mean of bloodflow distribution; (V-Q)$_{mean}$ = difference between $V_{mean}$ and $Q_{mean}$. Data given as mean ± SD (n=7). * = P-value (p<0.05) is calculated as unpaired t-test of PP in comparison to baseline.

<table>
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<th>Anaesthesia</th>
<th>CO$_2$-pneumoperitoneum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shunt, % QT</td>
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<td>7.0 ± 2.0*</td>
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<td>53 ± 6</td>
<td>55 ± 3</td>
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<tr>
<td>1&lt;$V_A/Q$&lt;10, % QT</td>
<td>38 ± 6</td>
<td>37 ± 4</td>
</tr>
<tr>
<td>High $V_A/Q$, % VE</td>
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<tr>
<td>Dead Space, % VE</td>
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<tr>
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<tr>
<td>Log SDQ</td>
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<tr>
<td>$Q_{mean}$</td>
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<tr>
<td>(V-Q)$_{mean}$</td>
<td>1.03 ± 0.45</td>
<td>0.58 ± 0.24*</td>
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Study III: The $V_{A}/Q$ distributions are shown in Table 3. Shunt was unaltered after creation of CO$_2$-pneumoperitoneum with abdominal pressure of 8 mmHg but decreased with CO$_2$-pneumoperitoneum of 12 and 16 mmHg. No low $V_{A}/Q$ was seen either before or during CO$_2$-pneumoperitoneum. A small amount of high $V_{A}/Q$ appeared during CO$_2$-pneumoperitoneum whereas $V_{D}$ was unaltered. $V_{\text{mean}}$ and $Q_{\text{mean}}$ expressed as $V_{A}/Q$ ratio came closer to each other during CO$_2$-pneumoperitoneum with
12 and 16 mmHg abdominal pressure (p<0.05; see Table 3). This suggests an improved match of ventilation and perfusion. LogSDQ and LogSDV, on the other hand, were not altered by CO2-pneumoperitoneum (Table 3).

Table 3: Anaesthesia = Ventilation with 50% O2; Pneumoperitoneum: 3 different abdominal pressures by CO2-insufflation; Shunt = perfusion of non-ventilated areas (VA/Q<0.005); low VA/Q = low ventilation to perfusion ratio (0.005< VA/Q <0.1); regions of normal ventilation to perfusion ratios (0.1< VA/Q <1 and 1<VA/Q<10); high VA/Q = high ventilation to perfusion ratio (10 < VA/Q < 100); Dead Space = ventilated but non-perfused areas (VA/Q > 100); Log SDV = log standard deviation of ventilation distribution; Log SDQ = log standard deviation of perfusion distribution; Vmean = mean of ventilation distribution; Qmean = mean of bloodflow distribution; (V-Q)mean = difference between Vmean and Qmean. Data given as mean ± standard deviation (n=6). * = P-value (p<0.05) is calculated as ANOVA in comparison to anaesthesia. ** = P-value (p<0.05) is calculated as ANOVA in comparison to 8 mmHg PP

<table>
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<th>Variable</th>
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<th>CO2-Pneumoperitoneum</th>
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<td>Baseline</td>
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<tr>
<td>Shunt, % QT</td>
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<td>1&lt;VA/Q&lt;10, % QT</td>
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<td>(V-Q)mean</td>
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Study IV: The VA/Q distributions are shown in Table 4. Shunt was decreased during CO2-pneumoperitoneum, unaltered after creation of Air-pneumoperitoneum and increased when intravenous SNP was added during CO2-pneumoperitoneum. No low VA/Q was seen either before or during pneumoperitoneum. A small amount of high VA/Q appeared during pneumoperitoneum whereas VD was unaltered. Vmean and Qmean expressed as VA/Q ratio came closer to each other during CO2-pneumoperitoneum and further increased with SNP-pneumoperitoneum (p<0.05; see Table 4). This
suggests an improved match of ventilation and perfusion in the CO₂ group. LogSDQ and LogSDV, on the other hand, were not significantly altered by pneumoperitoneum (Table 4).

Table 4: Anaesthesia = Ventilation with 50% O₂; Pneumoperitoneum: CO₂: 12mmHg carbon dioxide-pneumoperitoneum, AIR: 12 mmHg Air-pneumoperitoneum; SNP: 12mmHg CO₂-pneumoperitoneum plus intravenous SNP; Shunt = perfusion of non-ventilated areas (VA/Q<0.005); low VA/Q = low ventilation to perfusion ratio (0.005<VA/Q<0.1); regions of normal ventilation to perfusion ratios (0.1<VA/Q<1 and 1<VA/Q<10); high VA/Q = high ventilation to perfusion ratio (10<VA/Q<100); Dead Space = ventilated but non-perfused areas (VA/Q > 100); Log SDV = log standard deviation of ventilation distribution; log SDQ = log standard deviation of perfusion distribution; Vmean = mean of ventilation distribution; Qmean = mean of bloodflow distribution; (V-Q)mean = difference between Vmean and Qmean. Data given as mean with SD. * = p-value (p<0.05) is calculated as ANOVA in comparison to anesthesia; ** p-value (p<0.05) is calculated as ANOVA in comparison to CO₂-PP; *** p-value (p<0.05) is calculated as ANOVA in comparison to Air-PP.

<table>
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<td>Vmean</td>
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<td>Qmean</td>
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<td>(V-Q)mean</td>
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<td>1±0.16**</td>
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The effects of pneumoperitoneum on ventilation perfusion distribution (Single Photon Emission Computed Tomography)

**Study 2:** The distributions of ventilation and blood flow in caudal-cranial direction during anaesthesia before and during CO\textsubscript{2}-pneumoperitoneum are shown in Figure 6 and in the dorsal-ventral direction in Figure 7. The ventilation and perfusion distributions along the caudal-cranial axis were similar to each other, indicating a rather good match of ventilation and perfusion. During CO\textsubscript{2}-pneumoperitoneum a shift of ventilation and blood flow along the x-axis away from caudal towards cranial regions was seen. The starting point on the x-axis was kept constant relative to the spine. The shift of ventilation and perfusion can therefore be explained both by a cranial displacement of the diaphragm and by increase of atelectasis in juxtadiaphragmatic regions. The displacement along the caudal-cranial axis was similar for ventilation and blood flow. Thus, no worsening of the matching of ventilation and blood flow along the horizontal (caudal-cranial) axis occurred with CO\textsubscript{2}-pneumoperitoneum.

The distributions of ventilation and blood flow along the vertical (dorsal-ventral) axis showed a larger difference between them than along the caudal-cranial axis. Thus, ventilation was distributed to ventral regions to a much larger extent than perfusion. This indicates that near the diaphragm there is reduced ventilation but persistence of blood flow. With CO\textsubscript{2}-pneumoperitoneum there were further shifts of ventilation and blood flow towards ventral regions with more marked redistribution of perfusion than of ventilation.

The matching of the ventilation and blood flow can also be roughly estimated by analyzing the area inscribed by the ventilation and perfusion curves. We used the following mathematical calculation: the area inscribed by the ventilation and perfusion curves for the part where perfusion is larger than ventilation, \( A = \sum (Q - V) \) (also shown in Fig 2), and the area inscribed by the perfusion curve, \( B = \sum Q \), and calculated the percentage of perfusion going to less ventilated than perfused regions as \( C = A/B \times 100 \). The Area A decreased in the dorsal to ventral direction during pneumoperitoneum as did C (C before CO\textsubscript{2}-pneumoperitoneum: caudal-cranial: 4±2, dorsal-ventral: 19±3; C during CO\textsubscript{2}-pneumoperitoneum: caudal-cranial: 5±2, dorsal-ventral: 15±3*, p<0.05). Moreover, a simplified estimation of the \( V_A/Q \) matching was made by calculating the mean of ventilation and perfusion distributions (\( V_{\text{mean}}, Q_{\text{mean}} \)) and the scatter around the mean (similar to logSDV and logSDQ by MIGET). \( V_{\text{mean}} \) was unaltered by CO\textsubscript{2}-pneumoperitoneum (1.36±0.13 and 1.40±0.09) and \( Q_{\text{mean}} \) increased from 0.81±0.11 to 0.96±0.15 (p<0.05). Furthermore LogSDV decreased (0.52±0.04 to 0.47±0.03; p<0.05) as did LogSDQ (0.45±0.07 to 0.34±0.04; p<0.05) during
CO$_2$-pneumoperitoneum. These findings describe a better match of ventilation and blood flow during CO$_2$-pneumoperitoneum.

Figure 6: Ventilation and blood flow distributions in caudal-to-cranial direction (horizontal axis) during anaesthesia before (upper panel) and during CO$_2$-pneumoperitoneum (lower panel). Ventilation (V) and blood flow (Q) are shown in percent of their peak values.

Note the shift of ventilation and perfusion away from the caudal region after induction of CO$_2$-pneumoperitoneum and the balanced $V_A/Q$ distribution.
Figure 7: Ventilation and blood flow distributions from dorsal to ventral (vertical axis) during anaesthesia before (upper panel) and during CO$_2$-pneumoperitoneum (lower panel). Ventilation (V) and blood flow (Q) are shown in percent of their peak values. “Area A”, as described in results, is shown in both panels. Note the larger difference in ventilation and perfusion distributions than in the caudal-to-cranial direction shown in Fig 5. Note also the smaller area “A” during CO$_2$-pneumoperitoneum, indicating less of “over-perfused” areas relative to their ventilation. This should improve oxygenation as compared to the recording during baseline before CO$_2$-pneumoperitoneum.
Study III: The ventilation and perfusion distributions along the caudal-cranial axis were similar to each other, indicating a rather good match of ventilation and perfusion (Figure 8). With increasing abdominal pressure during CO₂-pneumoperitoneum minor shift of ventilation and blood flow along the x-axis away from caudal towards cranial regions was seen. The starting point on the x-axis was kept constant relative to the spine so that any shift of ventilation and perfusion would be visible, whether caused by cranial displacement of the diaphragm or by increase of atelectasis in juxtadiaphragmatic regions (Figure 9 and 10). Thus, no worsening of the matching of ventilation and blood flow along the horizontal (caudal-cranial) axis occurred with CO₂-pneumoperitoneum.

The distributions of ventilation along the vertical (dorsal-ventral) axis were essentially unaffected by CO₂-pneumoperitoneum although a small shift away from dorsal to ventral regions was seen with the highest abdominal pressure. The distribution of perfusion showed a clear shift of blood flow away from dorsal towards ventral regions, and more so with increasing abdominal pressure (Figure 9). This shift in blood flow correlated with the increase in arterial carbon dioxide tension as shown in Figure 10 where present data (CO₂-pneumoperitoneum 8, 12 and 16 mmHg) are shown together with baseline data in a previous study[38].
Figure 8: Ventilation (V) and blood flow (Q) distributions in caudal-to-cranial direction (horizontal axis) (upper panel and lower panels, respectively). V and Q are shown in percent of their peak values. No changes occurred in blood flow and ventilation away from the caudal region after induction of CO₂-pneumoperitoneum.
Figure 9: Ventilation (V) and blood flow (Q) distributions in dorsal-to-ventral direction (horizontal axis) (upper and lower panels, respectively). V and Q are shown in percent of their peak values. Note the shift in perfusion away from dorsal, dependent regions with increasing abdominal pressure. Note also the much smaller shift of ventilation. These findings might be explained by shift of ventilation in proportion to the cranial displacement of the diaphragm and additional shift of blood flow that must be explained by additional mechanisms, presumably hypoxic pulmonary vasoconstriction that becomes stronger with increasing abdominal pressure (and PaCO2). * = P-value (p<0.05) is calculated as ANOVA-Test comparing 16 mmHg PP to 8 mmHg PP. ** = P-value (p<0.05) is calculated as ANOVA-Test in comparing 12 mmHg pneumoperitoneum to 8 mmHg pneumoperitoneum.
Figure 10: Shift of blood flow away from dependent towards non-dependent lung regions (y axis) with increasing PaCO₂ when data from baseline (taken from [38]) and the three CO₂-pneumoperitoneum levels have been pooled. The insert shows how the blood flow shift was calculated (Q50: the location of the 50% of maximum flow point on the dorsal-ventral axis in percent of the normalized distance from the dorsal aspect of the lung).

Data are shown as mean±SD. The correlation is $r^2 = 0.80$ (p<0.0001). Note that at baseline (leftmost data point) Q50 was at 13% of the lung distance from the dorsal border with a corresponding PaCO₂ of 5 mmHg and at the highest CO₂-pneumoperitoneum (16 mmHg)(rightmost data point) Q50 was at 22% of lung distance. CO₂-pneumoperitoneum at 8 and 12 mmHg were accompanied by Q50 and PaCO₂ in between baseline and CO₂-pneumoperitoneum 16 mmHg data.
Study IV: The ventilation and perfusion distributions along the caudal-cranial axis were similar to each other during anaesthesia baseline, indicating a rather good match of ventilation and perfusion (Figure 11). During 12mmHg pneumoperitoneum in all groups a minor shift of ventilation and blood flow along the x-axis away from caudal towards cranial regions was seen. The starting point on the x-axis was kept constant relative to the spine so that any shift of ventilation and perfusion would be visible, whether caused by cranial displacement of the diaphragm or by increase of atelectasis in juxtadiaphragmatic regions (Figure 11). Thus, no worsening of the matching of ventilation and blood flow along the horizontal (caudal-cranial) axis occurred with pneumoperitoneum.

The distribution of ventilation along the vertical (dorsal-ventral) axis was shifted away from the dependent region in all three groups when the abdominal pressure was increased (pneumoperitoneum), reasonably explained by formation or increase of atelectasis. The distribution of perfusion showed a clear shift of blood flow away from dorsal towards ventral regions during CO2-pneumoperitoneum (Figure 12). The shift was much smaller during Air-PP and even less during intravenous SNP administration during CO2-pneumoperitoneum (Figure 12).
Figure 11: SPECT: Ventilation (V) and Blood flow (Q) distributions in caudal-to-cranial direction (horizontal axis) (upper panel and lower panels, respectively). Ventilation and blood flow are shown in percent of their peak values.

Note the shift in blood flow and ventilation away from the caudal region after induction of pneumoperitoneum. Note the rather slight increase in Q in the dependent parts of the lung in the SNP group during pneumoperitoneum. (Mean±SD of all 9 pigs studied during anaesthesia (baseline) and Mean±SD of 3 pigs during CO₂, air and SNP-pneumoperitoneum.) * = P-value (p<0.05) is calculated as ANOVA-Test comparing anaesthesia baseline to air-, SNP- and CO₂-pneumoperitoneum.
Figure 12: SPECT: Ventilation (V) and Blood flow (Q) distributions in dorsal to ventral direction (vertical axis) (upper and lower panels, respectively). V and Q are shown in percent of their peak values. Note the shift in blood flow and ventilation away from the caudal region after induction of pneumoperitoneum. Note the shift in perfusion away from dorsal, dependent regions with CO₂-pneumoperitoneum. Note also the increase in perfusion in the dependent lung regions during air-pneumoperitoneum and furthermore during SNP-peritoneum. There was no shift of ventilation during the three different pneumoperitoneum situations. These findings might be explained by shift of ventilation in proportion to the cranial displacement of the diaphragm and additional shift of blood flow that must be explained by additional mechanisms, supposedly hypoxic pulmonary vasoconstriction that becomes stronger with increasing PaCO₂. (Mean±SD of all 9 pigs studied during anesthesia (baseline) and Mean±SD of 3 pigs during CO₂, Air and SNP-pneumoperitoneum.) Upper panel: * = P-value (p<0.05) is calculated as ANOVA-Test comparing anaesthesia baseline to air-, SNP- and CO₂-pneumoperitoneum. Lower panel: * = P-value (p<0.05) is calculated as ANOVA-Test comparing CO₂- to SNP-pneumoperitoneum. ** = P-value (p<0.05) is calculated as ANOVA-Test in comparing CO₂- to Air-pneumoperitoneum.
DISCUSSION

Summary of main results

**Study I:** The data indicates that the atelectasis that developed during anaesthesia in a porcine model increased further during CO₂-pneumoperitoneum with no worsening of PaO₂/FiO₂ but with an increase in Pa-E’CO₂. Thus, PaO₂/FiO₂ did not correlate to atelectasis during CO₂-pneumoperitoneum, precluding arterial oxygenation as a predictor of the amount of collapsed lung. On the other hand, the strong correlation between Pa-E’CO₂ and the amount of atelectasis makes Pa-E’CO₂ of potential value in predicting atelectasis during anaesthesia and CO₂-pneumoperitoneum.

**Study II:** The main findings are that pulmonary blood flow shifts away from dorsal to ventral regions to a higher extent than ventilation during CO₂-pneumoperitoneum. Ventilation is most likely shifted away because of atelectasis formation, as shown previously both in clinical and experimental studies [24, 29]. Thus atelectasis was about 4% during anaesthesia in our porcine model and increased to 10% during CO₂-pneumoperitoneum [29]. These redistributions result in improved oxygenation and gas exchange during CO₂-pneumoperitoneum.

**Study III:** The experimental data confirm that 1/ atelectasis increased during CO₂-pneumoperitoneum in proportion to the increase in abdominal pressure and 2/ pulmonary blood flow shifted away from dorsal to ventral regions to a higher extent than ventilation during increasing abdominal CO₂ pressure during pneumoperitoneum. These redistributions were accompanied by reduced shunt and improved oxygenation and the improvement was larger the more the abdominal CO₂ pressure was increased.

**Study IV:** The data demonstrate that 1/ CO₂-pneumoperitoneum enhanced the shift of blood flow towards better ventilated parts of the lung compared to Air-pneumoperitoneum and 2/ SNP worsened the ventilation-perfusion match even more and blunted the effects previously seen with CO₂-pneumoperitoneum. CO₂ should therefore be the mediator of enhanced HPV during CO₂-pneumoperitoneum.
Atelectasis formation during anaesthesia and pneumoperitoneum

Atelectasis can be described as the reversible loss of aerated lung. Atelectasis occurs in the dependent parts of lungs of 90% of patients who are anaesthetised. Atelectasis may be the result of one or more of the following mechanisms: inhibition of surfactant, gas resorption or compression of regional lung. It is well known that humans develop atelectasis in dependent lung regions after induction of anaesthesia [31, 39]. Compression atelectasis occurs during anaesthesia as a result of a number of factors including chest geometry, overall cephalad diaphragm displacement, shift of thoracic central vascular blood into the abdomen and altered diaphragmatic dynamics. All three mechanisms may contribute to atelectasis during general anaesthesia [40]. Absorption and compression are considered to be the two mechanisms most implicated in perioperative atelectasis formation [41]. Development of atelectasis is associated with the development of several pathophysiologic effects, including decreased compliance, impairment of oxygenation. A major consequence of atelectasis is impaired lung mechanics. The decreased compliance is conventionally considered to be due to a reduction in lung volume, such that inspiratory – expiratory cycles commencing from a lower FRC are completed on a less-efficient section of the motional pressure–volume curve [42]. Impairment of gas exchange, often the most obvious effect of atelectasis, in the absence of supplemental oxygen will lead to worsened arterial oxygenation. The basis for impaired gas exchange in atelectasis is the absence of ventilation in the collapsed or filled alveoli, while there is still perfusion of such non-ventilated lung units [39].

Intraperitoneal insufflation of CO₂ has different effects on the respiratory system. In supine human subjects CO₂-pneumoperitoneum at an abdominal pressure of 12 mmHg caused a cranial shift of the diaphragm of 1 to 3cm [28], decreased lung volumes and increased airway pressures [21, 22], which leads to more atelectasis formation. Alveolar recruitment maneuvers and positive end-expiratory pressure is effective, but may be short lived and associated with more frequent use of vasopressors [43, 44]. Positive end-expiratory pressure alone showed no beneficial effect [45]. Therefore Talab et al. suggested to conduct an intraoperative alveolar recruitment with a vital capacity maneuver followed by positive end-expiratory pressure 10 cmH₂O to prevent lung atelectasis [46].

In our studies as well as in clinical studies the aggravation of atelectasis caused by induction of CO₂-pneumoperitoneum was not paralleled by increased shunt or impaired arterial oxygenation. Thus, an increased atelectasis but a decreased intrapulmonary shunt and increased PaO₂ were demonstrated in supine patients 45 minutes after intraperitoneal CO₂-
insufflation [22, 24, 47]. Consequently, oxygenation indices may not adequately reflect the magnitude of lung collapse during pneumoperitoneum.

Our studies showed that assessment of arterial to end-tidal PCO₂-difference may help to quantify the amount of atelectasis in patients undergoing laparoscopic surgery. Pa-E´CO₂ can be increased either by an increase in PaCO₂ or a decrease in PE´CO₂. The former occurs during alveolar hypoventilation or when mixed venous blood passes through the lung through shunt vessels without delivering CO₂ to alveolar air, as in atelectatic tissue. The latter occurs when there is a parallel dead space, as ventilation of non- or poorly perfused alveoli, i.e. Vزاد [48-50].

When shunt is small the effects on Pa-E´CO₂ are negligible, but large shunts can increase Pa-E´CO₂ [50]. This phenomenon has been nick-named “shunt dead space” although it has basically nothing to do with dead space [51]. The magnitude of shunt was moderate in our studies but enough to cause a modest increase in Pa-E´CO₂, as deducted from mathematical modelling [52]. Moreover, when ventilated lung is reduced by the cranial displacement of the diaphragm during CO₂-pneumoperitoneum (with subsequent increase in atelectasis formation) a shift of ventilation can be anticipated so that previously normally ventilated regions become over-ventilated in relation to their perfusion. If an alveolar dead space is calculated by standard formula on CO₂ elimination [(PaCO₂-PE´CO₂)/PaCO₂], then a linear correlation between atelectasis and Vزاد was found (r² = 0.68) in study I with an, on average, 12% increase during CO₂-pneumoperitoneum. This fits with a redistribution of ventilation with excessive ventilation of previously more normally ventilated regions, keeping in mind the limited ability by the CO₂ technique to discriminate between “true” Vزاد and high ventilation in relation to perfusion. We have refrained from making this an original observation in the Results section of study I because of the similarity between the equation for Vزاد and the expression Pa-E´CO₂. Moreover, the correlation is less good for Vزاد than for Pa-E´CO₂ (r² = 0.92), suggesting that Vزاد and shunt act in common to produce the elevated Pa-E´CO₂.

**Gas Exchange during pneumoperitoneum**

Development of atelectasis leads to impairment of pulmonary gas exchange. In our studies, pulmonary shunt decreased and oxygenation was improved or maintained during CO₂-pneumoperitoneum. Furthermore areas of low Vₐ/Q were not seen. Andersson et al. demonstrated in humans with multiple inert gas elimination technique that oxygenation increased and pulmonary shunt decreased during CO₂-pneumoperitoneum [24]. The dead space measured by MIGET showed normal values for pigs throughout the investigations. It was
not altered by the insufflation of carbon dioxide, again in keeping with previous findings in humans [24].

CO₂-pneumoperitoneum leads to acidosis in arterial and venous blood, because of resorption of CO₂ through the abdominal cavity [53], which is in line with findings in multiple studies [54-58]. Use of another gas for creation of pneumoperitoneum, or abdominal lift, caused no changes in acid-base balance and oxygenation [8, 9, 19].

New in our studies is the demonstration of a shift of blood flow away from dorsal, dependent regions during CO₂-pneumoperitoneum, a redistribution that was larger than the decrease in ventilation that was reasonably caused by the lung collapse. Also CO₂-pneumoperitoneum shifted ventilation and perfusion away from caudal regions along the horizontal axis but to a similar extent so that a fairly good matching of ventilation and blood flow was maintained. Further support of a better matching during CO₂-pneumoperitoneum, besides reduced shunt, comes from the more closely located Vmean and Qmean on the V/Q axis, both with SPECT and MIGET data.

In study IV we changed CO₂ for air and found no beneficial effect on distribution of blood flow and oxygenation of blood. Moreover, SNP shifted blood flow to dependent lung regions and worsened the Vₐ/Q matching and oxygenation. This was likely by blunting the HPV. The shift in blood flow distribution, assessed by SPECT, was paralleled by a change in the Vₐ/Q distribution, as assessed by MIGET. Thus, a decrease of pulmonary shunt was seen during CO₂-pneumoperitoneum, no change was seen during Air-pneumoperitoneum and an increase was seen during administration of SNP. No lung regions with low Vₐ/Q were seen, either before or during pneumoperitoneum, and no change in V₃/D/V₅. This is in line with previous findings in humans [24]. This has made us consider the increase in PaCO₂ and not the abdominal pressure per se to be the cause of the lung blood flow redistribution.

Effects of carbon dioxide on hypoxic pulmonary vasoconstriction during pneumoperitoneum

HPV is unique to the pulmonary circulation, as other circulations (coronary, cerebral, and systemic) dilate in response to hypoxia [59]. Pulmonary vessels constrict in response to alveolar hypoxia, resulting in an increase in pulmonary arterial pressure and diversion of blood flow away from the hypoxic area [60]. Hypoxic pulmonary vasoconstriction is to be a primary adaptive mechanism of the pulmonary circulation necessary to preserve arterial blood oxygenation in the face of regional lung disease. It works by increasing pulmonary vascular resistance to hypoxic alveoli, thereby
diverting pulmonary blood flow away from these regions. The reduction in blood flow from poorly ventilated (hypoxic) alveoli to better ventilated alveoli preserves the matching of alveolar ventilation ($V_A$)-perfusion ($V_A/Q$) and arterial oxygenation [61].

CO$_2$-pneumoperitoneum leads to an increase of PaCO$_2$ with a subsequent decrease of arterial pH. The resorption of carbon dioxide leads to a greater H$^+$ concentration by its spontaneous and carbonic anhydrase-catalysed combinations with water to form carbonic acid. The protons thus generated are free to react (or be buffered) with titratable groups in certain amino acids resulting in secondary and tertiary structural changes of many proteins and enzymes in cell membranes and cellular aqueous environments. In addition to its direct acidifying properties, carbon dioxide can react with some free amine groups in proteins to form carbamate residues [62-65].

There are a number of physiological effects, due to alterations in pH and the CO$_2$ tension in arterial blood (PaCO$_2$), that need to be considered [66-68]. These effects of hypercapnic acidosis are vagally mediated large airway constriction, direct small airway dilatation, increased parenchymal compliance, enhanced HPV and improved $V_A/Q$ matching [65]. The vascular, airway, and compliance effects of CO$_2$ are best considered as mechanisms that serve $V_A/Q$ matching. They may either alter regional ventilation to keep pace with a primary change in perfusion, or alter regional perfusion to match a primary change in ventilation [69]. The strength of hypercapnic vasoconstriction is generally weaker than that of HPV and a more important effect may be by augmenting HPV [65]. The route by which CO$_2$ was added to the lungs (inhaled versus intravenous infusion) resulted in comparable effects [69, 70]. Anaesthetic drugs may modulate the HPV. Ketamine, as used in our study, may act as a bronchodilatator [71] but no effect on HPV has been reported. It should also be mentioned that total intravenous anaesthesia with ketamine is common in respiratory studies [72, 73]. HPV can be blunted by vagal stimulation [74], but atropine, as used in our study, should protect against this effect [75].

**Effects of increasing pressure on CO$_2$-pneumoperitoneum**

Atelectasis formation increased during CO$_2$-pneumoperitoneum in proportion to the increase in abdominal pressure. This is in line with data in humans [76]. Pulmonary blood flow shifted away from dorsal to ventral regions to a higher extent than ventilation during increasing abdominal CO$_2$ pressure during pneumoperitoneum. These redistributions were accompanied by reduced shunt and improved oxygenation and the improvement was larger the more the abdominal CO$_2$ pressure was increased. With rising
abdominal pressure in CO\textsubscript{2}-pneumoperitoneum, diffusion and absorption of CO\textsubscript{2} increases into the systemic vascular bed [77] with subsequent effect on the acid-base balance of the blood [57]. Hypercarbia was seen in similar previous studies [54]. This has made us consider the increase in PaCO\textsubscript{2} and not the abdominal pressure per se to be the cause of the lung blood flow redistribution. Support for this comes also from the correlation we found between shift of blood flow and increase in PaCO\textsubscript{2} when anaesthesia data (without CO\textsubscript{2}-pneumoperitoneum) from study II [38] and data of the three abdominal pressure levels were pooled (Figure 9).

Since HPV is augmented by the increase in PaCO\textsubscript{2} [65, 78] HPV may have acted more efficiently with redistribution of blood flow away from non-ventilated areas with increasing abdominal pressure. Thus, the increased PCO\textsubscript{2} may explain the reduced shunt despite more atelectasis formation with increasing abdominal pressure [79].

MIGET data showed a decreasing Vmean with increasing abdominal CO\textsubscript{2} pressure. The lowering of Vmean at an abdominal pressure of 16 mmHg was similar in magnitude to the increase in an estimated alveolar (or shunt) dead space (Pa-ECO\textsubscript{2}/ PaCO\textsubscript{2}), i.e. by approximately 14% compared to baseline before pneumoperitoneum. The narrowing of the gap between Vmean and Qmean (Table 3) suggests improved V\textsubscript{A}/Q matching. This should have been accompanied by a decreased logSDQ that we did not see, presumably due to methodological limitations. The bottom line is still that increased abdominal CO\textsubscript{2} pressure seemed to improve matching of ventilation and lung blood flow. Further analysis of MIGET data demonstrated a decrease of pulmonary shunt on increasing abdominal pressure and no lung regions with low V\textsubscript{A}/Q were seen, either before or during pneumoperitoneum at any of the three pressure levels. This is in line with previous findings in humans [24]. Minimal amount of high V\textsubscript{A}/Q was seen with CO\textsubscript{2}-pneumoperitoneum and V\textsubscript{D}/V\textsubscript{T} was not altered by the insufflation of CO\textsubscript{2}, the latter being similar with previous findings in humans [24].

Limitations of the experimental studies

The major limitation of the animal experiments include that HPV is well developed in pigs [60, 80] that may have enhanced the redistribution of blood flow. Still, findings in the studies on pulmonary vascular pressures, shunt and gas exchange are comparable with findings in humans [16, 24]. HPV will decrease blood flow to non-ventilated lung regions and consequently Pa-E\textsuperscript{‘}CO\textsubscript{2}. Ventilation pattern was not changed during the study, which induced mild hypercarbia during CO\textsubscript{2}-pneumoperitoneum in all animals. However the effect of hypercarbia was essential for the results of all studies. In a clinical setting minute ventilation might be increased during
intraperitoneal CO₂-insufflation in order to maintain normocarbia, which may affect Pa-E’CO₂. However, the magnitude of PaCO₂ should have no effect on the Pa-E’CO₂ [49].

Another limitation of the studies are that the MIGET, CT and SPECT studies could not be done in the same animals, because of technical and logistic reasons. Study protocols were comparable, only time schedules (SPECT required 40 min longer data collection than MIGET) of the measurements were different.

Hyperoxia per se may increase the speed of atelectasis formation but once established it remains fairly constant. In study I we showed that hyperoxia over 30 minutes in the anaesthetised pig created atelectasis in the same amount as seen in anaesthetised humans [29].

A respiratory hold is a necessity when making a spiral CT scan unless one accepts breathing during the exposure. A breath hold is also the standard procedure by most research groups. It might be claimed that an inspiratory breath hold may allow recruitment and an expiratory hold collapse of lung. We used as short holds as possible, 3 seconds which were also the same as used for the measurement of respiratory compliance (disregarding a pause for the mechanics measurement may invalidate the analysis of compliance and resistance). The animals had rather high PaO₂, however similar to our previous studies and corresponding to results in studies from other groups. High oxygen concentrations may have promoted atelectasis formation, although we have not seen any increase over time. It might be added that multiple inert gas elimination technique data may be affected by gas trapping in a gas pocket as e.g. abdominal gas. This will result in a longer equilibration time before a steady state has been reached and not until then can blood and expired gas samples be taken. We have tested this in pre-tests and found that the infusion times we have used are sufficient. Our quality tests by calculating remaining sum of squares (RSS) for the six gases to fit a regression line show very low RSS, indeed a mean of 1.6 is far better than the RSS of 6 that shall, as a rule of thumb, be found in 50% of the rounds.

In study II and IV pulmonary atelectasis was not directly measured by computed tomography, but by the Pa-ECO₂ gradient. Recently, we demonstrated in study I that the Pa-ECO₂ gradient is a good marker to estimate pulmonary atelectasis during CO₂-pneumoperitoneum [29].

A further limitation in study IV is that intravenous SNP may cause a decrease of cardiac output [81] with potential effects on blood flow distribution, however, we did not see any significant change in the study. We considered inhaling a vasodilatator to avoid general haemodynamic effects, but we might then not reach the vascular bed exerting HPV.
CONCLUSIONS

(1) Atelectasis that developed during anaesthesia in a porcine model increased further during CO₂-pneumoperitoneum with no worsening of PaO₂/FiO₂ but with an increase in Pa-E’CO₂. The magnitude of atelectasis correlates with an increase of arterial to end-tidal carbon dioxide difference in a porcine model of pneumoperitoneum. Thus, assessment of arterial to end-tidal carbon dioxide difference may help to quantify the amount of atelectasis in patients undergoing laparoscopic surgery. However, this has to be validated under clinical conditions.

(2) Pneumoperitoneum with carbon dioxide causes atelectasis with elimination of ventilation in the dependent lung regions. However, an efficient shift of blood flow away from collapsed, non-ventilated regions results in a better ventilation-perfusion matching and better oxygenation of blood than without pneumoperitoneum. A prerequisite for the beneficial effect is the use of carbon dioxide for the abdominal inflation, since it enhances HPV.

(3) Increasing carbon dioxide pressure induced an increasing shift of blood flow away from collapsed lung tissue, a decrease of pulmonary shunt and an increased oxygenation during 12 and 16 mmHg CO₂-pneumoperitoneum, despite an increase of atelectasis formation.

(4) Air-pneumoperitoneum did not cause a similar shift of blood flow away from collapsed lung as did CO₂-pneumoperitoneum at comparable abdominal pressure. Moreover, attenuation of pulmonary vasoconstrictor response prevented redistribution of lung blood flow away from collapsed lung regions. These findings suggest an enhancement of hypoxic pulmonary vasoconstriction mediated by elevated PaCO₂.

The overall conclusion will thus be that the porcine model of pneumoperitoneum, developed here, allows investigations of pathophysiological effects of abdominal insufflation with different gases and
that the use of CO$_2$ instead of air promotes a shift of blood flow away from the atelectasis that is inevitably caused by the rise in abdominal pressure and cranial shift of the diaphragm. These observations may be of clinical interest when giving patients anaesthesia for laparoscopic surgery.
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