Ventilation–perfusion distributions and gas exchange during carbon dioxide-pneumoperitoneum in a porcine model

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Key points
- Pneumoperitoneum (PP) with carbon dioxide used for laparoscopic surgery results in conflicting ventilation effects.
- In a pig model, PP improved V/Q match with better oxygenation and gas exchange.
- This may be due to increased PaCO2 causing enhanced hypoxic pulmonary vasoconstriction.

Background. Carbon dioxide (CO2)-pneumoperitoneum (PP) of 12 mm Hg increases arterial oxygenation, but it also promotes collapse of dependent lung regions. This seeming paradox prompted the present animal study on the effects of PP on ventilation–perfusion distribution (V/Q) and gas exchange.

Methods. Fourteen anaesthetized pigs were studied. In seven pigs, single photon emission computed tomography (SPECT) was used for spatial analysis of ventilation and perfusion distributions, and in another seven pigs, multiple inert gas elimination technique (MIGET) was used for detailed analysis of V/Q matching. SPECT/MIGET and central haemodynamics and pulmonary gas exchange were recorded during anaesthesia before and 60 min after induction of PP.

Results. SPECT during PP showed no or only poorly ventilated regions in the dependent lung compared with the ventilation distribution during anaesthesia before PP. PP was accompanied by redistribution of blood flow away from the non- or poorly ventilated regions. V/Q analysis by MIGET showed decreased shunt from 9 (SD 2) to 7 (2)% after induction of PP (P<0.05). No regions of low V/Q were seen either before or during PP. Almost no regions of high V/Q developed during PP (1% of total ventilation). PaO2 increased from 33 (1.2) to 35.7 (3.2) kPa (P<0.01) and arterial to end-tidal PCO2 gradient (PACO2a) increased from 0.3 (0.1) to 0.6 (0.2) kPa (P<0.05).

Conclusions. Perfusion was redistributed away from dorsal, collapsed lung regions when PP was established. This resulted in a better V/Q match. A possible mechanism is enhanced hypoxic pulmonary vasoconstriction.

Keywords: blood flow; gas exchange; laparoscopy; lung; measurement techniques; model; pig; respiratory; surgery

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During general anaesthesia and mechanical ventilation, lungs are compressed by a cranial shift of the diaphragm, promoting atelectasis formation.1 Intra-abdominal insufflation of carbon dioxide (CO2) for laparoscopic surgery (pneumoperitoneum, PP) causes further shift of the diaphragm and increased lung collapse, decreased respiratory compliance, and increased airways pressure, as shown in clinical and experimental studies.2–5 In addition, CO2 is absorbed across the peritoneal epithelium. This is a likely cause of the recurrent findings of acidemia, hypercapnoea, and cardiovascular instability during PP.6–7 CO2 may also strengthen hypoxic pulmonary vasoconstriction (HPV), either by causing hypercapnoea or acidosis, or both.6,8

Perfusion of non-ventilated alveoli causes shunt and impaired oxygenation of blood.9–10 CO2 elimination may also be impaired.11–12 Despite the increase in atelectasis by PP, shunt need not increase and arterial oxygenation need not decrease,13 although a decrease in PaO2 has also been reported.9,10 This seeming paradox of more atelectasis and less shunt has not yet been explained.

The present animal experiment was initiated to study the effects of PP on ventilation–perfusion distribution and gas exchange by isotope technique (single photon emission computed tomography, SPECT) and multiple inert gas elimination technique (MIGET).

Methods
After approval by the local animal ethics committee, 14 2-month-old piglets [mean body weight 30 (2) kg] of the Hampshire, Yorkshire, and Swedish country breeds from a local breeder were studied.
Anaesthesia and mechanical ventilation

All pigs were anaesthetized by an i.m. injection of xylazine (2.2 mg kg\(^{-1}\); Rompun\textsuperscript{®}; Bayer, Leverkusen, Germany), tiletamine/zolazepam (6 mg kg\(^{-1}\); Zoletil\textsuperscript{®}; Virbac, Carros, France), and atropine (0.04 mg kg\(^{-1}\); NM Pharma, Stockholm, Sweden). The pigs’ lungs were mechanically ventilated after intubation with an ID 7.0 mm cuffed tracheal tube (Mallinkrodt, Athlone, Ireland). Anaesthesia was maintained by continuous infusion of fentanyl (5 μg kg\(^{-1}\) h\(^{-1}\); Leptanal\textsuperscript{®}; Janssen-Cilag AB, Sweden), ketamine (25 mg kg\(^{-1}\) h\(^{-1}\); Ketaminol vet\textsuperscript{®}; Intervet, Boxmeer, The Netherlands), and propofol (3 mg kg\(^{-1}\) h\(^{-1}\); Diprivan\textsuperscript{®}; Astra, Södertälje, Sweden). Pancuronium was given as infusion for muscle relaxation (V\(_{\text{aw}}\) 6 kPa). Tidal volume (\(V_t\)), airway pressures (\(P_{\text{aw}}\)), and flow were continuously recorded. Static compliance (\(C_s\)) of the total respiratory system was calculated as 

\[
C_s = V_t / (P_{\text{aw plateau}} - P_{\text{aw end expiration}})
\]

where \(P_{\text{aw plateau}}\) and \(P_{\text{aw end expiration}}\) are airway pressures measured after end-inspiratory and end-expiratory halts of 3 s.

Monitoring

For pressure measurements and arterial blood sampling, an 18 G catheter was inserted in the left carotid artery. A thermistor-tipped Swan–Ganz catheter (CritiCath\textsuperscript{TM} SP5107H-14 TD; Becton Dickenson, Franklin Lakes, NJ, USA) and another 18 G catheter were introduced into the left external jugular vein. 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 the mid-thoracic level at end-expiration. End-expiratory carbon dioxide tension (\(P_{\text{Eco2}}\)) was measured by capnography implemented in the ventilator (Servo i). Arterial and mixed venous blood samples were analysed with ABL 300 blood gas analyzer and OSM 3 oximeter (Radiometer, Copenhagen, Denmark). \(P_{\text{aco2}}\) was calculated. Cardiac output (Qt) was measured by thermodilution with 10 ml of saline boluses injected into the right atrium. The first measurement was ignored, and the cardiac output was derived from the mean of the three consecutive measurements. The injections were evenly distributed over the respiratory cycle.

SPECT technique

SPECT was used to analyse the spatial ventilation and perfusion distributions during anaesthesia and PP. Ventilation distribution was assessed by inhalation of krypton (\(^{81}\text{Kr}\)) in that plane.

MIGET technique

Determination of the \(V_{a}/Q\) distribution was undertaken with the MIGET.\textsuperscript{16} 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 analysed together with an expired gas sample by gas chromatography (Model 5890, Series II; Hewlett-Packard, Waltham, MA, USA). 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), and also separation of regions of high $V_a/Q$ ratios ($10<V_a/Q<100$) from dead space ($V_d$) ($V_d/Q>100$). The mean $V_a/Q$ of the ventilation and perfusion distributions ($V_{mean}, Q_{mean}$) was calculated. Moreover, the standard deviation of the logarithmic distribution of perfusion (LogSDQ) and ventilation (LogSDV) was calculated as measures of the dispersion (mismatch) of blood flow and ventilation. Finally, the $P_{aO_2}$ that can be predicted from the $V_a/Q$ distributions was compared with measured $P_{aO_2}$ (by blood gas analysis).

**Study protocol**

In both groups (MIGET and SPECT; n=14), pigs were ventilated with a $V_t$ of 10 ml kg$^{-1}$, PEEP 5 cm H$_2$O, and $F_{I_2}O$ 0.5. On the basis of previous results from our laboratory, $F_{I_2}O$ was increased to 1.0 for 30 min in order to induce atelectasis in the range of 3–5%. $F_{I_2}O$ was then decreased to 0.5 before creation of PP.

PP was created by insufflation of CO$_2$ into the abdominal cavity via a VERRES needle with a common CO$_2$ insufflator (7060-Insufflator Pelvi Pneu Semm Systems; Wisap, Munich, Germany) until the abdominal pressure ($P_{abdom}$) reached 12 mm Hg. Mechanical ventilation was maintained with the same respirator settings (unaltered ventilation) as before induction of PP. SPECT and MIGET could not be done in the same respirator settings (unaltered ventilation) as before creation of PP.

At the end of the experiment, pigs were killed by an overdose of potassium chloride. The investigations were performed in the experimental laboratories of the Department of Clinical Physiology, and in the Department of Nuclear Medicine at the University Hospital in Uppsala.

**Statistics**

Statistical analysis was performed with the Prism 4 software package (GraphPad Software Inc, San Diego, CA, USA) on a Macintosh computer. Power calculations using a two-sided design at a significance level of 5% ($a=0.05$) and a probability of 80% ($\beta=0.20$) to detect a difference of at least 35% in the development of atelectasis (and subsequent change in ventilation) revealed that a minimum of seven pigs were needed in each group.

Data were tested for normal distribution with the Shapiro–Wilks W-test. Normally distributed data are presented as mean and standard deviation (cardiopulmonary, ventilation, and gas exchange variables) and were analysed by repeated-measures one-way analysis of variance (ANOVA) with the post hoc Bonferroni correction. Non-normally distributed data were analysed by Friedman’s ANOVA and Tukey’s HSD. MIGET data were tested with an unpaired t-test. Differences were considered statistically significant if $P<0.05$.

**Results**

**Respiration and haemodynamics**

Respiratory and haemodynamics data were similar in the MIGET and SPECT groups, and data have therefore been pooled in Table 1. $P_{aO_2}$, $P_{aCO_2}$, $P_{aCO_2}$, and $P_{aCO_2}$ increased during PP, and pH decreased. Peak airway pressure and airway plateau pressure almost doubled, and respiratory compliance decreased to less than half the value before PP.

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

**Ventilation and perfusion distributions (SPECT group)**

The distributions of ventilation and blood flow in the caudal–cranial direction during anaesthesia before and during PP are shown in Figure 1 and in the dorsal–ventral direction in Figure 2. 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 PP, a shift of ventilation and blood flow along the x-axis away from the transversal 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 (Figs 1 and 2). 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 PP.

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 (Fig. 2). This indicates that near the diaphragm, there is reduced ventilation but persistence of blood flow. With PP, 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 analysing 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 PP as did \( C \) [C before PP: caudal–cranial: 4 (2), dorsal–ventral: 19 (3); C during PP: caudal–cranial: 5 (2), dorsal–ventral: 15 (3), \( P < 0.05 \)]. Moreover, a simplified estimation of the \( V/Q \) 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 PP [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 PP. These findings describe a better match of ventilation and blood flow during PP.
Ventilation–perfusion matching (MIGET group)

The $V_a/Q$ distributions are shown in Figure 3 and Table 2. The distributions had a remaining sum of squares of 1.24 (0.56), which indicates high methodological accuracy. Shunt decreased after creation of PP. No low $V_a/Q$ was seen either before or during PP. A small amount of high $V_a/Q$ appeared during PP, whereas $V_D$ was unaltered. $V_{\text{mean}}$ and $Q_{\text{mean}}$ expressed as $V_a/Q$ ratio came closer to each other during PP ($P<0.05$; Table 2). This suggests an improved match of ventilation and perfusion. LogSDQ and logSDV were not significantly altered by PP (Table 2). The difference in $P_{\text{aCO}_2}$ 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 $P_{\text{aCO}_2}$ of around 35 kPa, which is a further support of good methodological accuracy.

Discussion

The main findings of the present study are that pulmonary blood flow shifts away from the dorsal to ventral regions to a higher extent than ventilation during PP. Ventilation is most likely shifted away because of atelectasis formation, as shown previously both in clinical and experimental studies. Thus, atelectasis was about 4% during anaesthesia in our porcine model and increased to 10% during PP. These redistributions result in improved oxygenation and gas exchange during PP.

It is well known that humans develop atelectasis in dependent lung regions after induction of anaesthesia. In supine subjects, PP to an abdominal pressure of 12 mm Hg caused a cranial shift of the diaphragm of 1–3 cm, decreased lung volumes and increased airway pressures, and increased the formation of atelectasis but did not, in most studies, increase the shunt. In the present study, pulmonary shunt decreased during PP and areas with low $V_a/Q$ were not seen. This is in line with previous results using MIGET in humans. Also, haemodynamic responses to PP are similar to studies gathered in the European Association for Endoscopic Surgery guidelines. The dead space measured by the multiple inert gas technique showed normal values for pigs throughout the investigation. It was not altered by the insufflation of CO$_2$, again in keeping with previous findings in humans. Acidosis and hypercarbia were seen in similar previous studies. Such changes may affect HPV and enhance redistribution of blood flow. Use of another gas for creation of PP, or abdominal lift, caused no changes in acid–base balance and oxygenation.

What is new in the present study is the demonstration of a shift of blood flow away from dorsal, dependent regions during PP, a redistribution that was larger than the decrease in ventilation that was reasonably caused by the lung collapse. A possible explanation may thus be more efficient HPV.

| Table 2 Ventilation–perfusion matching (MIGET group; $n=7$). Baseline, 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 ($0.1 < V_a/Q < 1$); high $V_a/Q$, high ventilation to perfusion ratio ($1 < V_a/Q < 10$); 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; $V_{\text{mean}}$, mean of ventilation distribution; $Q_{\text{mean}}$, mean of blood flow distribution; ($V–Q$)$_{\text{mean}}$, difference between $V_{\text{mean}}$ and $Q_{\text{mean}}$. Data given as mean (sd). $P$-value ($P<0.05$) is calculated as unpaired t-test of PP in comparison with baseline. |
|--------------------------|--------------------------|
|                         | Baseline | PP 60 min |
| Shunt (% QT)            | 9.0 (2.0) | 7.0 (2.0)* |
| Low $V_a/Q$ (% QT)      | 0            | 0            |
| 0.1 <$V_a/Q$ < 1 (% QT) | 53 (6)     | 55 (3)      |
| 1 <$V_a/Q$ < 10 (% QT)  | 38 (6)     | 37 (4)      |
| Dead space (% VE)       | 38 (2)     | 39 (3)      |
| Log SDV                 | 0.86 (0.03) | 0.83 (0.03) |
| Log SDQ                 | 0.84 (0.02) | 0.80 (0.03) |
| $V_{\text{mean}}$       | 1.89 (0.37) | 1.58 (0.41) |
| $Q_{\text{mean}}$       | 0.87 (0.16) | 0.99 (0.2)  |
| ($V–Q$)$_{\text{mean}}$ | 1.03 (0.45) | 0.58 (0.24)* |
However, the opposite, an increase in $P_{aCO_2}$ (Table 1), was seen and $V_D$ was not altered, as mentioned above (Table 2). $P_{aCO_2}$ on the other hand, increased (Table 1) and this may be caused, after ruling out an increase in $V_D$, by an increase in shunt. The shunt enables mixed venous blood to pass through non-ventilated lung tissue and increase $P_{aCO_2}$. An increase in $P_{aCO_2}$ has even been nicknamed ‘shunt-dead space’, although it need not reflect a real $V_D$.20

The increase in $P_{aE_CO_2}$ has been shown to be a good predictor of the increase in atelectasis during PP (assuming constant dead space),3 whereas $P_{aCO_2}$ and shunt do not guide in estimating atelectasis.2 10 Furthermore, the absorption of $CO_2$ during PP, which should increase both $P_{aCO_2}$ and $P_{aE_CO_2}$ at constant ventilation, showed no effect on $P_{aCO_2}$, as judged from the maintained $P_{aE_CO_2}$ with increasing $CO_2$ levels in blood and expired air in a previous study from our group.3 Thus, the increased $P_{aE_CO_2}$ may reasonably be explained by enhanced atelectasis formation.

PP 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 PP, besides reduced shunt and $P_{aCO_2}$, comes from the more closely located $V_{mean}$ and $Q_{mean}$ on the $V/Q$ axis, both with SPECT and MIGET data.

Anaesthetic drugs may modulate the HPV. Ketamine, as used in our study, may act as a bronchodilator,24 but no effect on HPV has been reported. It should also be mentioned that total i.v. anaesthesia with ketamine is common in respiratory studies.25 26 HPV can be blunted by vagal stimulation,27 but atropine, as used in our study, should protect against this effect.28

Limitations of the study include that HPV is well developed in pigs29 30 that may have enhanced the redistribution of perfusion. Still, findings in this study on pulmonary vascular pressures, shunt, and gas exchange are comparable with findings in humans.2 13 31 Another limitation of the study is that the MIGET 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 longer than MIGET) of the measurements were different.

In conclusion, we have shown an improved gas exchange and oxygenation, caused by redistribution of blood flow away from collapsed lung tissue during PP. A likely, but not yet proven, explanation for enhanced HPV, possibly mediated via increased $P_{aCO_2}$. This may be of clinical interest when giving patients anaesthesia for laparoscopic surgery.

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Conflict of interest

None declared.

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