Towards safer liver resections

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Chapter

Effects of prolonged pneumoperitoneum on hepatic perfusion during laparoscopy

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Abstract

**Objective:** To assess the influence of prolonged pneumoperitoneum (PP) on liver function and perfusion in a clinically relevant porcine model of laparoscopic abdominal insufflation.

**Background:** PP during laparoscopic surgery produces increased intra-abdominal pressure (IAP) which potentially influences hepatic function, and microcirculatory perfusion.

**Methods:** Six pigs (49.6±5.8kg) underwent laparoscopic intra-abdominal insufflation with 14 mmHg CO₂ gas for 6 hours followed by a recovery period of 6 hours. Two animals were subjected to 25 mmHg CO₂ gas. Hemodynamic parameters were monitored and damage parameters in the blood were measured to assess liver injury. Liver total blood flow and function were determined by the indocyanine green (ICG) clearance test. Intraoperative hepatic hemodynamics were measured by simultaneous reflectance spectrophotometry (venous oxygen saturation StO₂, and relative tissue haemoglobin concentration rHb) and laser Doppler flowmetry (blood flow and flow velocity). Post-mortem liver samples were collected for histological evaluation.

**Results:** A decrease in microvascular perfusion was detected during PP. Following six hours of PP, ICG clearance increased (p<0.001) indicating a compensatory improvement of overall liver blood flow resulting in concomitantly improved microcirculatory perfusion (p=0.024). Minimal parenchymal damage (AST) of the liver was seen after 6 hours of PP (p=0.006), which seemed related to PP pressure. Minor histological damage was observed.

**Conclusions:** The liver sustains no additional damage due to prolonged PP during laparoscopic surgery. Our findings suggest that prolonged PP does not hamper liver function or cause liver damage after extended laparoscopic procedures.
**Introduction**

Advantages of laparoscopic surgery are well recognized and include reduced postoperative pain, shorter length of hospital stay, and superior cosmetic results.\(^1\,^2\) Within the field of liver surgery, the use of laparoscopy has increased substantially in recent years.\(^3\) Disadvantages associated with laparoscopic surgery include prolonged operation times and elevations in intra-abdominal pressure (IAP). Laparoscopic operations require insufflation of the abdominal cavity (pneumoperitoneum, PP) with carbon dioxide (CO\(_2\)) gas to achieve adequate surgical exposure for instrumentation and surgical manoeuvres. However, pneumoperitoneum obviously produces elevated IAP with continuous compression of intra-abdominal organs which potentially influences hepatic microcirculatory perfusion. Intra-peritoneal pressures during PP are higher (14 mmHg) than the normal pressure in the hepatic portal system (7-10 mmHg), and may therefore cause changes in liver portal blood flow and consequently, hepatic function. Indeed, elevations in aspartate aminotransferases (AST) and alanine aminotransferases (ALT) levels have been reported after laparoscopic operations; however, these elevations were transient and returned to normal within the first three postoperative days.\(^4\,^5\)

Several studies described the effects of PP on intra-abdominal blood flow and reported diminished blood flow in the portal vein and hepatic artery.\(^1\,^7\,^10\) Since these studies focused on the effects of blood flow after one hour of PP, two interesting questions emerged: firstly, to which extent does diminished blood flow influence liver function and secondly, what are the consequences after prolonged PP? The indocyanine green (ICG) clearance test is the most frequently used test for determining liver total blood flow and function\(^11\,^12\), and has previously been shown to be significantly reduced after one hour of PP, suggesting a decrease of liver function.\(^9\) However, it has been shown that this short-lived decline in liver function is associated with only a transient elevation of liver enzymes (AST and ALT). With laparoscopic liver resection however, the duration of PP increases with longer periods of surgery. In addition to its effects on blood flow and liver function, the impact of continuous insufflation on hepatic microcirculation, as the principal site of metabolic exchange between the blood and tissue parenchymal cells, is also essential for assessing the influence of prolonged PP. These issues become more relevant with laparoscopic liver resection in which the liver may be subjected to additional injury when applying vascular inflow occlusion (Pringle’s manoeuvre).

The Oxygen to See (O2C) is an instrument designed to perform simultaneous laser Doppler flowmetry and tissue spectrophotometry using a single compact probe to detect microperfusion parameters.\(^13\) This device is capable of intraoperatively providing the characteristics of hepatic microcirculation.\(^14\,^15\) The O2C system has been extensively used for determinations of microcirculatory parameters in a wide range of surgical procedures in maxillofacial\(^16\), cardiothoracic\(^17\,^18\), plastic\(^19\,^20\), and neurosurgical\(^21\,^22\) specialties.
This study was undertaken to investigate the influence of prolonged PP on liver function and hepatic microcirculatory parameters in a clinically relevant, porcine model of extended abdominal insufflation.

Methods

The study protocol was approved by the institutional Animal Experimentation Committee of the Academic Medical Center of the University of Amsterdam. Care and handling of the animals were in accordance with the European guidelines for Institutional and Animal Care and Use Committees.

Animals

Twelve female Landrace pigs (van Beek, The Netherlands) with a mean body weight of 47.0±1.7 kg were used in this study. All animals were allowed to feed and drink ad libitum and remained quarantined one week prior to the start of the investigation to permit adaptation to environmental conditions. All experiments were initiated in the morning following an over-night fast. An intramuscular (IM) injection of premedication consisting of ketamine (Nimatek, Eurovet, Bladel, The Netherlands; 15 mg/kg body weight), midazolam (Dormicum®, Actavis, Hafnarfjordur, Iceland; 1.5 mg/kg body weight), and atropinesulphate (Pharmachemie, Haarlem, The Netherlands; 0.01 mg/kg body weight) was administered prior to induction of anaesthesia. The pigs were resting in a dorsally recumbent position on the operating table, and core body temperature was maintained at 37 ºC for the duration of the experimental procedures. All animals were orotracheally intubated. Prior to surgery, the animals received bolus doses of ketamine, midazolam, sufentanil (Hameln pharmaceuticals, Hameln, Germany) and pancuronium bromide (Pavulon, Organon, Oss, The Netherlands). Anaesthesia was continued with sufentanil (5-8 μg/kg/hr body weight), ketamine (10-14 mg/kg/hr body weight), midazolam (1-1.5 mg/kg/hr body weight) and pancuronium bromide (0.10-0.15 mg/kg/hr body weight) intravenously. Anaesthesia was maintained with oxygen/air FiO₂ 45% O₂ (1.5;3 L/min). All animals received NaCl 0.9% (Baxter, Utrecht, The Netherlands; 8-10 mL/kg/hr), and eloheas 6% (Tetraspan®; Braun, Melsungen, Germany; 2-3 mL/kg/hr) for electrolyte and metabolic homeostasis. Glucose 20% (Baxter Benelux, Brussel, Belgium) was given intravenously to maintain glucose-levels between 5 and 10 mmol/L. Catheters were placed in the brachial artery, popliteal artery, and jugular vein respectively to continuously monitor heart rate (HR), mean arterial blood pressure (MAP), central venous pressure (CVP), and for collection of blood samples. Open introduction was performed for bladder catheterization and placement of a 10 mm trocar in the abdomen for laparoscopy followed by closure of the abdominal wall.
Experimental design

Six animals underwent laparoscopic intra-abdominal insufflation for 6 hours via a 10 mm trocar (Olympus, The Netherlands) with CO₂ gas (14 mmHg) followed by a recovery period of 6 hours. Two animals were subjected to 25 mmHg intra-abdominal insufflation during 6 hours, and were observed in a simulated recovery phase of two hours. Four pigs served as controls and did not undergo intra-abdominal insufflation. Hemodynamic parameters, such as arterial oxygen saturation (SpO₂), HR, MAP, CVP, rectal temperature, and respiratory minute volume were continuously recorded. Arterial blood gas samples derived from the brachial artery were collected every hour and were analyzed using an automated analyzer (Blood gas, Oximeter, and Electrolyte Systems, ABL, Radiometer Medical, Copenhagen, Denmark); measurements were obtained for pH, oxygen saturation, carbon dioxide, sodium, potassium, and haemoglobin. Glucose levels were also determined every hour.

The experiments started after a stabilization period of 60 minutes (0 mmHg) in which baseline values were recorded. After 6 hours of insufflation (14 or 25 mmHg) blood samples were collected for determination of liver injury parameters, and measurements of liver function using the indocyanine green (ICG) clearance test. Post-PP recovery measurements were performed at 2 and 6 hours. AST, ALT, alkaline phosphatase (AP), gamma-glutamyltranspeptidase (γGT), bilirubin, lactate, and lactate dehydrogenase (LDH) were evaluated by routine clinical chemistry for assessment of liver function. The left peripheral ear vein was cannulated for administration of ICG solution for assessment of liver function. Hepatic hemodynamics were examined continuously for the entire duration of the protocol by simultaneous reflectance spectrophotometry (StO₂, and rHb) and laser Doppler flowmetry (blood flow and flow velocity) using Oxygen to See (O₂C, LEA Medizintechnik GmbH, Giessen, Germany). At the end of each experiment all animals were sacrificed by infusion of KCl (60-90 mmol) under general anaesthesia. For histological examination, post-mortem biopsies of both the left and right liver lobes were obtained. An overview of the experimental design and measurement time-points is presented in Figure 1.

Assessment of hepatic function and perfusion

Hepatic function

Hepatic function was determined using laboratory measurements, and the ICG clearance test. AST, ALT, AP, and γGT were determined as liver damage parameters. ICG clearance was determined by the LiMON® method. 0.5 mg/kg of ICG solution (ICG-PULSION®, Medical Systems AG, Munich, Germany) dissolved in 5 mL of sterile distilled water was injected in the left peripheral ear vein in all animals, and for all measurements of liver perfusion. The LiMON® device (LiMON; Pulsion Medical Systems AG, Munich, Germany) measures ICG elimination by pulse spectrophotometry. Details of this technique have been described elsewhere. Briefly, accurate and continuous recording of ICG blood levels was
possible using a dichromatic densitometer, placed on the tail of the pig. Liver blood flow and function were determined by calculating the ICG clearance from the ICG retention rate 15 min after administration (R15). As ICG-clearance depends on liver perfusion, it also is a parameter of total liver blood flow.

Hepatic microperfusion assessments

Hepatic microperfusion parameters were assessed using O2C. The O2C device (Type LW 1/1/1, LEA Medizintechnik GmbH, Giessen, Germany) combines laser Doppler flowmetry and tissue spectrophotometry in one flat probe (LF1.027, LEA Medizintechnik GmbH, Giessen, Germany) and detects a wide range of microperfusion parameters. The optical methods for measuring these parameters have been previously described in detail.13,15,24-28 The O2C probe was inserted in a sterile bag (Ultracover®, Microtek Medical B.V., Zuthpen, The Netherlands) that exactly matched the probe dimensions and was subsequently fixed to the left lateral liver lobe with Histoacryl® (Aesculap, Tuttlingen, Germany) after a small midline laparotomy. Once the O2C probe was positioned and fixed, the abdominal wall was closed using Vicryl Plus sutures (2-0 FS-1, and CTX 1, Johnson&Johnson, St-Stevens-Woluwe, Belgium) in two layers to prevent leakage of CO2 gas. Hepatic microperfusion parameters were measured continuously for the entire duration of the experimental procedure.

Histology

In all animals post-mortem biopsies were obtained from the middle of the right and left lobes of the liver. The hematoxylin and eosin (H&E) sections were blindly evaluated by a liver pathologist experienced in liver disease. Steatosis was estimated as the percentage of involved hepatocytes: grade 0 (absent; <5%), grade I (mild; 5-33%), grade II (moderate; 33-66%), or grade III (severe; >66%).29 Portal inflammation was arbitrarily graded as follows: 0 (absent), 1 (mild), 2 (moderate), or 3 (severe). Sinusoidal dilation (with and without congestion) as: 0 (absent), 1 (mild; involving ≤ one-third of the (centro-) lobular area), 2 (moderate; involvement ≤ 2/3 of the parenchyma), or 3 (severe; involving ≥ 2/3 of the liver parenchyma).30 Intralobular inflammation and lytic necrosis were graded as: 0 (not present), 1 (<2 foci per x10 objective), 2 (2-4 foci per x10 objective), 3 (5-10 foci

![Figure 1. Time line of experimental design (in 14 mmHg pneumoperitoneum [PP] group). All animals were subjected to the same procedures: Continuous assessments: hemodynamics Every hour: blood gas analysis, glucose levels Baseline measurements: continuous O2C, after 1 hour blood samples (liver function), and ICG-clearance Repeated measurements after 6, 8, and 12 hours: Continuous O2C Blood samples for liver function ICG clearance 12 hours: liver biopsy for histological examination](image-url)
per x10 objective), and 4 (> 10 foci per x10 objective). Portal edema was scored as the percentage of the portal tracts involved: 0 (not present), 1 (<25%), 2 (25-50%), 3 (50-75%), and 4 (>75%). The presence of areas with confluent necrosis of the parenchyma was scored as: 0 (absent), 1 (affecting <25%), 2 (affecting 25-50%), 3 (affecting 50-75%), and 4 (affecting >75%). Centrolobular ischemic changes were evaluated separately as: 0 (not present), 1 (mild; <50% of central veins affected), or 2 (moderate; >50% of central veins affected).

Statistical analysis
The differences between the groups were compared using the two-tailed unpaired Student’s t-test for parametric data. The Mann-Whitney U test was used for non-parametric data. Analysis of variance (ANOVA) by using a linear mixed model for repeated measurements was performed for the comparison of several time points within groups. The relationship between the presence of PP and hemodynamic parameters was studied by chi²-test. Results of histology were determined by the chi²-test, and Fisher’s Exact test, where appropriate. Correlation between variables was tested using the Pearson’s r correlation coefficient. The results were considered to be of statistical significance when p<0.05. All data analysis was performed using PASW Statistics version 18.0 for Windows (SPSS Inc., Chicago, Illinois, USA). Values are expressed as means ± SD.

Results
Hemodynamic parameters
There were no significant differences in MAP between all groups during insufflation or in the recovery period (results not shown). CVP increased significantly during insufflation (baseline 6.0±0.4 mmHg versus 11.0±0.5 mmHg after 6 hours of PP; p<0.01) and returned to baseline after desufflation in the 14 mmHg group (figure 2). The same trend was seen in the 25 mmHg PP group with a baseline value of 7.5±0.7 mmHg increasing to 14.8±3.1 mmHg after 6 hours of PP, and returning to 8.5±1.2 after 2 hours of recovery (p<0.001 between 6 hours of PP and 2 hours of recovery). After 6 hours of PP, the CVP was significantly higher in the 25 mmHg group, as compared to the 14 mmHg group (p<0.001).

Blood gas analysis
The levels of pCO₂ increased significantly during PP (baseline 36.7±0.7 mmHg vs 46.1±1.1 mmHg after 6h of PP; p=0.019) which is related to the CO₂-gas used for PP. This resulted in respiratory acidosis and consequently, a decrease in pH- and pO₂ values. pH decreased significantly from 7.49±0.01 at baseline to 7.41±0.01 after 6 hours of PP (p<0.05). Baseline mean pO₂ was 247.5±5.9 mmHg and after 6 hours of PP, decreased to 202.7±4.9 mmHg (p<0.05). Similar findings were observed for PP at 25 mmHg, but with greater differences. A pCO₂ baseline value of 48.4±22.1 mmHg was observed which
increased to 66.1±35.6 mmHg after 6 hours of PP (NS); pH at baseline was 7.47±0.08 and decreased to 7.35±0.12 after 6 hours of PP (NS), while pO2 decreased from baseline 192.8±27.1 mmHg to 180.9±34.5 mmHg after PP (NS). After desufflation, a significant decrease of pCO2 was observed in the 14 mmHg PP group at 0h, 2h, and 6h of recovery (Rec), as compared to 6h of PP (p<0.01) (B) As a consequence, pO2 decreased significantly during insufflation (*p<0.05 for 3h, and 6h PP vs BSL) in the 14 mmHg PP group, after which an increase was observed after desufflation (*p<0.05 for 2h, and 6h Rec vs 6h of PP), as well as for pH (C, *p<0.05 for 3h, and 6h PP vs BSL; and 0h, and 2h Rec vs 6h PP).

Figure 3. (A) The levels of pCO2 increased significantly during 6 hours of PP (*p<0.05 for 3h and 6h PP vs BSL) in the 14 mmHg PP group. After desufflation, a significant decrease of pCO2 was observed at 0h, 2h, and 6h of recovery (Rec), as compared to 6h of PP (p<0.01) (B) As a consequence, pO2 decreased significantly during insufflation (*p<0.05 for 3h, and 6h PP vs BSL) in the 14 mmHg PP group, after which an increase was observed after desufflation (*p<0.05 for 2h, and 6h Rec vs 6h of PP), as well as for pH (C, *p<0.05 for 3h, and 6h PP vs BSL; and 0h, and 2h Rec vs 6h PP).

Biochemical parameters
Mean baseline AST was 36.5±3.8 U/L in the 14 mmHg PP group (figure 4). A marginal, but statistically significant increase in AST was found after 6 hours of PP (57.0±16.6 U/L; p=0.006). The elevated AST values persisted during the recovery period, while ALT levels did not show any statistically significant differences (results not shown). In the 25 mmHg
PP group the liver damage parameter AST also increased (baseline: 38.8±11.7 U/L, and 6 hours PP: 69.0±46.7; p=0.001). AST levels were significantly higher in the 25 mmHg PP group after six hours of PP, as compared to the 14 mmHg PP group (p=0.001).

Liver perfusion and microcirculation

ICG clearance increased significantly after six hours of PP and continued to be increased during desufflation (*p<0.001 for 6h PP, and 2h of recovery vs baseline; figure 5), suggesting an improved total liver blood flow over time. The profile of ICG clearance in the 25 mmHg group was comparable with ICG clearance at 14 mmHg (5.4±0.4% baseline; 7.1±1.2% after 6 hours of PP; and 8.8±0.07% after 2 hours of recovery; p=0.006 for 2h Rec vs baseline). No significant differences in ICG clearance were observed between the 14 mmHg and 25mmHg PP groups.

During PP, the measurements of hepatic microcirculation showed a decreased intrahepatic flow in both groups, with a more prominent decrease observed in the pigs undergoing 25 mmHg PP. An almost immediate restoration (p=0.024) in hepatic microcirculatory blood flow was found after desufflation in the pigs undergoing 14 mmHg PP (figure 6.A.), with a similar profile in the pigs that underwent 25 mmHg PP. After 2
hours and 6 hours recovery, hepatic microcirculatory blood flow was not significantly changed.

Blood flow velocity also slightly decreased during 6 hours of PP (NS, figure 6.B). Oxygen saturation was elevated after an insufflation period of 6 hours which subsequently normalized in the recovery period (14 mmHg PP group). There were no significant differences between the 14 mmHg and 25 mmHg PP groups.

Histology
No significant differences were seen for any of the histological parameters evaluated between the right and left liver lobes of the same pig, or between the 14 mmHg and 25 mmHg PP groups at all time-points. No steatosis or centrolobular ischemic changes were found in any animal; portal and lobular inflammation was mild in all pigs. Sinusoidal dilatation in both groups ranged from 0-2 (median grade 2), focal lytic necrosis from 0-1 (median 0), portal oedema from 1-3 (median 1), and confluent necrosis from 0-1 (median 0) (NS, within or between groups).

Discussion
We determined the effect of prolonged PP on liver function and perfusion in a porcine model of laparoscopic abdominal insufflation. The results of our study show a decrease in microvascular perfusion during PP which was restored after desufflation. A concomitant increase of the ICG-clearance rate was observed after PP which remained, on average, increased during desufflation, indicating a compensatory improvement of overall liver blood flow. Increased total liver blood flow of the liver, hence contributed to the restoration of microcirculatory perfusion. Our results demonstrate that under these circumstances, the liver sustains limited parenchymal damage as concluded from marginally elevated AST levels in the blood, and the absence of major histological injury after prolonged PP (14 mmHg).
We used the O2C probe to assess hepatic microcirculatory blood flow after prolonged pneumoperitoneum. To our knowledge, no studies have correlated the effects of PP on hepatic function as measured by ICG clearance, as well as on liver microcirculation. A significant negative correlation was seen for ICG clearance and microvascular blood flow after 6 hours of PP ($r=-0.813$, $p=0.049$) in the 14 mmHg PP group, with a similar profile in the 25 mmHg PP group after 6 hours of PP ($r=-1.000$, $p<0.01$). A negative correlation was also observed between ICG clearance and blood flow velocity after 6 hours of PP ($r=-1.000$, $p<0.01$). No other significant differences were found.

It is important to consider that clearance of ICG from the blood depends on total blood flow of the liver. Therefore, the ICG clearance rate also reflects total liver circulatory dynamics.$^{31,32}$ Several authors report a decrease in liver blood flow as IAP increased in pigs with different cut-off values for IAP.$^{9,33}$ This finding is in line with the results of the present study in which microvascular perfusion decreased during 6 hours of PP as the IAP increased, with a concomitant increase in microcirculatory parameters after desufflation, and increased ICG-clearance.

Some recent experimental studies have demonstrated an impairment of liver function after pneumoperitoneum. Hepatic injury was shown after 60-90 minutes of PP in rat models.$^{34,35}$ Also, liver regeneration rate was impaired, and oxidative stress and hepatocellular damage were increased in rats undergoing PP before heptectomy.$^{36}$ These findings are not in accordance with our study. However, these differences may be explained by the choice of animal model, of which the porcine model obviously is more compatible with the clinical situation. Using a swine model too, Nsadi et al$^{37}$ reported no hepatocellular injury or microcirculatory changes in pigs undergoing PP, which is in line with our results. Yet, with the application of portal triad clamping, the authors found increased hepatocellular damage parameters and an increased necrotic index. These results suggest caution when combining PP with portal triad clamping.

In literature, only one clinical study demonstrated the feasibility of O2C for intraoperative evaluation of hepatic microcirculation.$^{14}$ Studies focusing on hepatic perfusion during prolonged PP and its effect on liver function, are lacking. With this in mind, it is important to consider some weaknesses of the O2C device. Firstly, disturbances through motion can falsify values for relative microcirculatory blood flow and velocity. This problem can be resolved by immobilizing the O2C probe on the liver surface, as was taken care of in our study. Secondly, there are no absolute values for single parameters and therefore, the measured values can not be interpreted without baseline values.$^{14}$ In all animals of the present study, baseline measurements were obtained in order to assess changes in hepatic microcirculation while each animal served as its own control. Thirdly, if the probe is not properly affixed, stray light can influence oxygen saturation and haemoglobin concentration values. In the present study, the probe was isolated from any external light sources since the abdomen was closed after the placement of the trocar for laparoscopy. Several other methods for evaluation of liver perfusion have been used, such as a transonic hepatic blood flow measurement, intravital fluorescence microscopy, or
transesophageal Doppler ultrasonography. However, since most of these techniques are invasive, they are less useful for evaluating liver perfusion in a (pre)clinical setting.

Not only the level of IAP during laparoscopic surgery is responsible for changes in liver function and perfusion, but also the duration of pneumoperitoneum influences (micro)circulatory hemodynamics. Hypoxia due to elevated levels of carbon dioxide potentially triggers vasoregulatory mechanisms, and alters blood pressure and thus, deprives the liver of the much needed oxygen to support the rich metabolism of the liver. One study evaluated the effects of 15 mmHg IAP over a period of 24 hours and reported a reduction in function and morphological changes in the liver, lungs, kidneys, and bowel. Serum ALT and AP were significantly elevated and low-grade liver necrosis was observed. No literature currently exists establishing the effects of prolonged PP on hepatic perfusion and liver damage. In this study we chose a clinically relevant pneumoperitoneum time of 6 hours representing the duration of several complex abdominal laparoscopic procedures used today, such as major liver resections of three Couinaud segments or more.

In conclusion, a decrease in liver microvascular perfusion was detected during six hours of PP. After desufflation, hepatic microcirculatory blood flow was restored with a concomitant increase of ICG-clearance indicating a compensatory improvement of overall liver blood flow. The liver thereby sustained limited parenchymal damage during PP which was related to PP pressure. Our findings suggest that prolonged PP does not hamper liver function after extended laparoscopic procedures.

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References


