Original Article

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Intra-Abdominal Metabolism and Blood Flow During Abdominal Hypertension – A Porcine Pilot Study Under Intravenous Anaesthesia

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Abstract

Objective: To study the splanchnic metabolism and intestinal circulation in a porcine model with increased abdominal pressure.

Methods: In an experimental porcine study, performed under intravenous anaesthesia, five animals were subjected to gradually increasing intra-abdominal pressure (15 mmHg, 25 mmHg, and 35 mmHg) with pneumoperitoneum. Microdialysis and laser Doppler were the main outcome methods for monitoring the metabolic and circulatory changes.

Results: During stable anaesthesia and gradually increasing intra-abdominal pressure obtained by CO2-pneumoperitoneum, blood flow (microcirculation) was deprived and moderate signs of impaired splanchnic metabolism were recorded.

Conclusions: The model appears usable for studies of splanchnic metabolic consequences of intra-abdominal hypertension.

Key words: *Intra-abdominal hypertension, microdialysis, laser-doppler flowmetry, lactates, pyruvates, glycerol*

Introduction

Intra-abdominal hypertension (IAH) and abdominal compartment syndrome (ACS) postoperatively and in other intensive-care situations are important causes of morbidity and mortality [1–5]. The absolute number of deaths due to ACS is unknown, but it has been shown that after endovascular aortic aneurysm surgery, approximately 12% of the patients were diagnosed with ACS [5]. Although ACS is a long-known clinical problem, only recently has the pathophysiology gained interest [1–4, 6, 7]. Definitions and clinical guidelines on diagnosis and therapy of ACS were published by WSACS (World Society of the Abdominal Compartment Syndrome) [7, 8].

Intestinal ischemia initiates an inflammatory cascade, which untreated will cause increased abdominal pressure, disseminated intravascular coagulation and multiple organ failure. In the ischemic gut, permeability and oxygen extraction are increased as well as, e.g., lactate and cytokines.

IL (interleukin)-1 and TNF (tumor necrosis factor)-α are released [9, 10]. To avoid multiple organ failure, shock and mortality, early diagnosis of ACS is essential. Currently, measurement of abdominal pressure and early detection of organ failure are the only diagnostic tools provided for the clinician [8].

Microdialysis is an established invasive method to measure the local metabolic changes in the extracellular space in various tissues [11]. An increased intraperitoneal lactate/pyruvate ratio was recorded in animals subjected to gut ischemia induced by arterial cross-clamping [12]. In addition, it has been shown that intraperitoneal microdialysis enables close monitoring of postoperative metabolic changes [13]. In an experimental hypotensive shock model, microdialysis was used to reflect local tissue perfusion deficits [14].

Laser Doppler is since long an established technique to measure local microcirculation in various tissues [15–18], and has been used to estimate gut microcirculation in research models [19], as well as at elevated intra-abdominal pressure [20].

To our knowledge, no previous data exists on metabolic changes during increased intra-abdominal pressure measured by microdialysis intraperitoneally. We hypothesized that intra-abdominal hypertension causes reduced blood flow and changes in glycerol, glucose, pyruvate, and lactate concentrations measured by microdialysis intraperitoneally and intramurally in small intestines and rectum. We also investigated whether these potential changes depended on the degree of intra-abdominal hypertension. Since our facility for animal experimental surgery only allows for intravenous anesthesia, we also determined whether stable anesthesia could be established for 4–5 hours.

Materials and Methods

Animal ethics

After approval by the Animal Ethics Committee, five crossbred pigs of Swedish country breed (Hampshire and Yorkshire) of both sexes with a body weight of 30.2 (27.5–33.0) kg (mean and range) were included in this pilot study. The animals had free access to food and water prior to experimentation.

The study was conducted in accordance with the "European Convention for Protection of Vertebrate Animals used for Experimental and other Scientific Purposes" and good practice in laboratory animal science [21].

Anesthesia

Before the animals were transported to the operation facilities, sedation was managed by azaperon (0.17 mg kg-1 i.m., Stresnil®, Janssen-Cilag, Wien). Two intravenous cannulae (Venflon Pro, Becton Dickinson, Infusion Therapy, Helsingborg, Sweden) were inserted in ear veins. General anesthesia was induced by Zoletil® Forte (i.e., tiletamine, 5 mg kg-1 i.v. and zolazepam, 5 mg kg-1 i.v., Virbac, Carros, France) and azaperon (4 mg kg-1 i.v.). Atropine (1.5 mg i.v., Mylan, Stockholm, Sweden) was given to avoid excessive salivation. The animals were placed in a supine position, and oral intubation was done. Throughout the experiments the anesthesia was maintained by a continuous intravenous infusion of propofol (8 mg kg-1 h-1, Diprivan®, AstraZeneca, Södertalje, Sweden) and by intravenous bolus injections of pethidin (1 mg kg-1 h-1, Meda, Solna, Sweden). Muscle relaxants were not used to enable assessment of the depth of anesthesia. A crystalloid solution, Ringer-Acetat (Fresenius Kabi, Uppsala, Sweden) 3 ml kg-1 h-1 and a crystalloid solution with 2.5% glucose (Fresenius Kabi, Uppsala, Sweden) 1.5 ml kg-1 h-1 were infused throughout the experiment using an automatic infusion device (Alaris GP, Cardinal Health Care, Rolle, Switzerland). The animals were ventilated and volume-controlled by a Monnal D. ventilator (Láir Liquide DMM, le Plessis Robinson, France). The inspiratory oxygen concentration was 21%. The respiratory rate was set to 15 min-1. A rectal temperature of 35.5°C to 37°C was maintained by the application of a thermal mattress (Warm Touch WT 5800, Mallinckrodt Medical, Hazelwood, Missouri, USA). Repeated pain provocations were done during the experiment to examine the depth of anesthesia. If signs of withdrawal movements after pain provocation were noted, boluses of propofol and pethidine were given as needed. At the end of the experiment, the anesthetized animals were killed with a bolus dose of propofol (200 mg i.v.) and

fast i.v. injection of potassium chloride (40 mmol). Asystolia was confirmed by ECG.

Surgical preparation

A 10cm midline laparotomy was performed, and a urinary catheter was inserted in the bladder through a small incision to measure urinary output and urinary bladder pressure. A microdialysis catheter (CMA 62, CMA Microdialysis, Stockholm, Sweden) was then inserted intramurally in the wall of the small intestine, in the mid-jejunal area. Another microdialysis catheter (CMA 62) was placed free-floating in the abdomen, and a third catheter (CMA 62) was inserted in the rectal wall via the anus. A short incision, more than 30 cm from the microdialysis catheter, was performed in another intestinal loop, and a laser Doppler probe (PM15, Perimed, Stockholm, Sweden) was placed about 10 cm from the incision intraluminally, facing the mucosa. Two laparoscopic trocars were inserted into the abdomen for carbon dioxide insufflation and to control the position of the microdialysis catheters. The catheters and the probe were all introduced into the abdomen percutaneously, and with a midline two-layer suture, an airtight abdominal wall was obtained. The carotid artery was dissected, and a polyethylene arterial cannula (Becton Dickinson Critical Care, Singapore) was inserted and used for systemic arterial blood pressures and heart rate recordings by a pressure transducer connected to an anesthesia monitor (Datex-Ohmeda AS/3, GE Healthcare Technologies, Waukesha, USA) and arterial blood sampling. ECG (lead II) and pulsoximetry were also recorded by the anesthesia monitor.

Experimental protocol

After the surgery the animals were allowed an intervention-free period of one hour to achieve stable baseline values. Thereafter, carbon dioxide was insufflated to elevate the intra-abdominal pressure stepwise to 15 mmHg, 25 mmHg and 35 mmHg using an automatically controlled insufflator (Electronik-pneu; Storz, Tuttlingen, Germany). Each pressure level was maintained for one hour. At the baseline and at the end of each hour, elevated pressure, systemic arterial blood pressure, heart rate, saturation, blood gases, body temperature, laser Doppler flux, urinary output, and intravesical pressure were measured and microdialysis samples were collected.

Intestinal mucosal blood flow

Intestinal mucosal blood flow was estimated by laser Doppler, utilizing a probe PM15 (0.25-mm fiber separation, 780-nm wavelength) (Perimed, Järfälla, Sweden) and a laser Doppler device (780-nm wavelength, 15-kHz bandwidth, 0.2-s time constant) (Periflux System 5001, Perimed, Järfälla, Sweden). Calibration of the laser Doppler system was performed according to the manufacturer's instructions. Details of laser Doppler flowmetry have been presented elsewhere [15–17, 22]. The signal expressed (flux) represents the registered number of red blood cells moving in the measured volume multiplied by the mean velocity of these cells. Since flux is an arbitrary unit, changes relative to the baseline are presented.

Microdialysis

We have previously described intraperitoneal microdialysis using an intra-abdominal free-floating catheter [23]. In brief, a 0.9-mm-thin, double-lumen concentric plastic catheter with a 30-mm semi-permeable tubular membrane in the end (cut off at 20.000 Dalton) is perfused with a physiologic solution (perfusion fluid T1, CMA Microdialysis AB, Sweden) by a CMA 106 microdialysis pump (CMA Microdialysis AB). The perfusion solution flows through the outer lumen of the catheter, via the membrane and back in the inner lumen. Over the membrane, equilibrium with the molecules in abdominal fluid or gut tissue is achieved. Finally, the solution is collected in microvials and analyzed for metabolites (glucose, pyruvate, lactate, and glycerol) in a CMA 600 microdialysis analyzer (CMA Microdialysis AB). In these experiments, analysis was performed within 24 hours. Details concerning the microdialysis method have been described elsewhere [11].

Intra-vesical pressure measurement

The intra-vesical pressure was measured by a Foley Manometer (Holtech Medical, Charlottenlund, Denmark). A 50ml container fitted with a bio-filter for venting was inserted between the Foley catheter and the drainage bag. The container was filled with urine during drainage; when the container was elevated, the 50ml urine flowed back into the animal's bladder, and IAP was read from the position of the meniscus in the transparent manometer tube between the container and the Foley catheter [24].

Arterial blood analyses

Arterial blood, collected via the carotid artery cannula, was analyzed for oxygen and carbon dioxide tension, pH, base excess, bicarbonate, arterial oxygen saturation, electrolytes, lactate, and glucose. All arterial analyses were made by an I-STAT analyzer (Abbott Point of Care, Abbott Park, USA) by using the CG4+ and CG8+ cartridges.

Statistics

In this pilot study including five subjects, data was not used for comparative analyses; only descriptive statistics are presented (median and range).

Results

Hemodynamics, body temperature and urinary output

All animals were stable from an anesthesiological point of view, without considerable blood pressure fluctuation or evident variation of anesthesia depth throughout the experiments. Systolic and diastolic arterial blood pressures and heart rate increased as the intra-abdominal pressure was elevated (Table 1). Body temperature was stable during the experiments (Table 1). Urinary output increased at the first two intra-abdominal pressure levels (15 and 25 mmHg), followed by a decrease at the intra-abdominal pressure of 35 mmHg (Table 1).

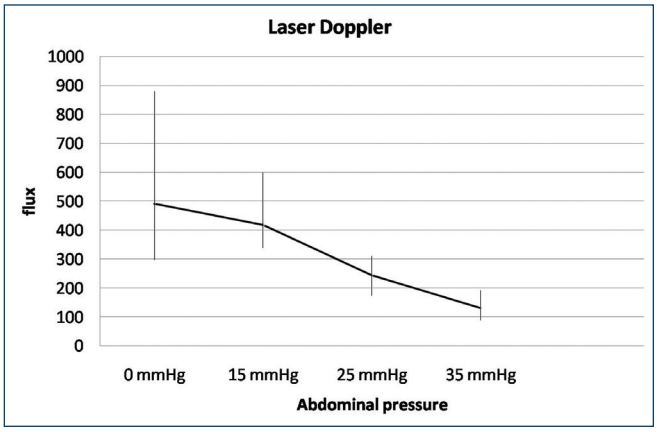

Figure 1. Blood flow in the small intestine. [Anesthetized pigs (n=5). Blood flow in the small intestine measured with laser Doppler at increasing abdominal pressures. Data is presented as median and range].

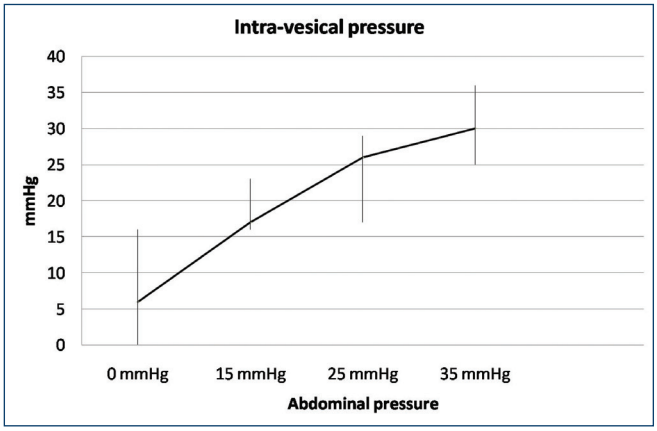

Figure 2. Intra-vesical pressure.[Anesthetized pigs (n=5). Intra-vesical pressure measured at different intra-abdominal insufflation pressures (median and range)].

Table 1. Findings of hemodynamics, urinary output, blood metabolites, and gases during baseline measurements and with elevated abdominal pressure.

		Intra-abdominal pressure		
	Baseline	**15 mmHg**	**25 mmHg**	**35 mmHg**
Systolic blood pressure (mmHg)	104 (88–109)	104 (87–123)	108 (94–114)	114 (89–130)
Diastolic blood pressure (mmHg)	47 (33–69)	63 (47–82)	71 (48–84)	70 (56–93)
Heart rate (beats min^{-1})	110 (70–158)	133 (110–145)	142 (81–200)	138 (109–172)
Body temperature (°C)	36 (35–37.3)	36.5 (35–37.5)	36 (35–37.7)	35.8 (35–37.7)
Urinary output (ml kg^{-1} h^{-1})	0.8 (0.5–1.7)	1.7 (1.2–1.8)	1.8 (0.8–1.8)	0.9 (0.2–1.3)
B-Lactate (mM)	6.5 (0.7–6.7)	5.3 (4.3–6.0)	3.1 (0.8–5.4)	3.7 (1.3–5.4)
B-Glucose (mM)	7.4 (6.4–7.9)	7.4 (6.3–10.5)	7.8 (6.9–10.0)	9 (6.8–16.2)
Hematocrite (%)	24 (19–29)	26 (21–31)	23 (21–32)	28 (22–32)
pH	7.64 (7.42–7.72)	7.50 (7.40–7.56)	7.49 (7.37–7.59)	7.41 (7.25–7.43)
PO2 (kPa)	13.6 (8.7–16.1)	9.7 (7.4–14.7)	10 (8.5–15.2)	9.9 (6.4–11.5)
PCO2 (kPa)	3.1 (2.4–5.6)	4.0 (3.4–6.0)	4.5 (3.6–7.0)	4.1 (4.4–8.9)
Base excess (mM)	4 (1–8)	1 (0–2)	2 (-2–6)	-2 (-10–4)
HCO_3 (mM)	24.9 (22.8–27.6)	23.3 (22.6–27.6)	25.6 (22.3–30.5)	25.7 (21.8–29.1)

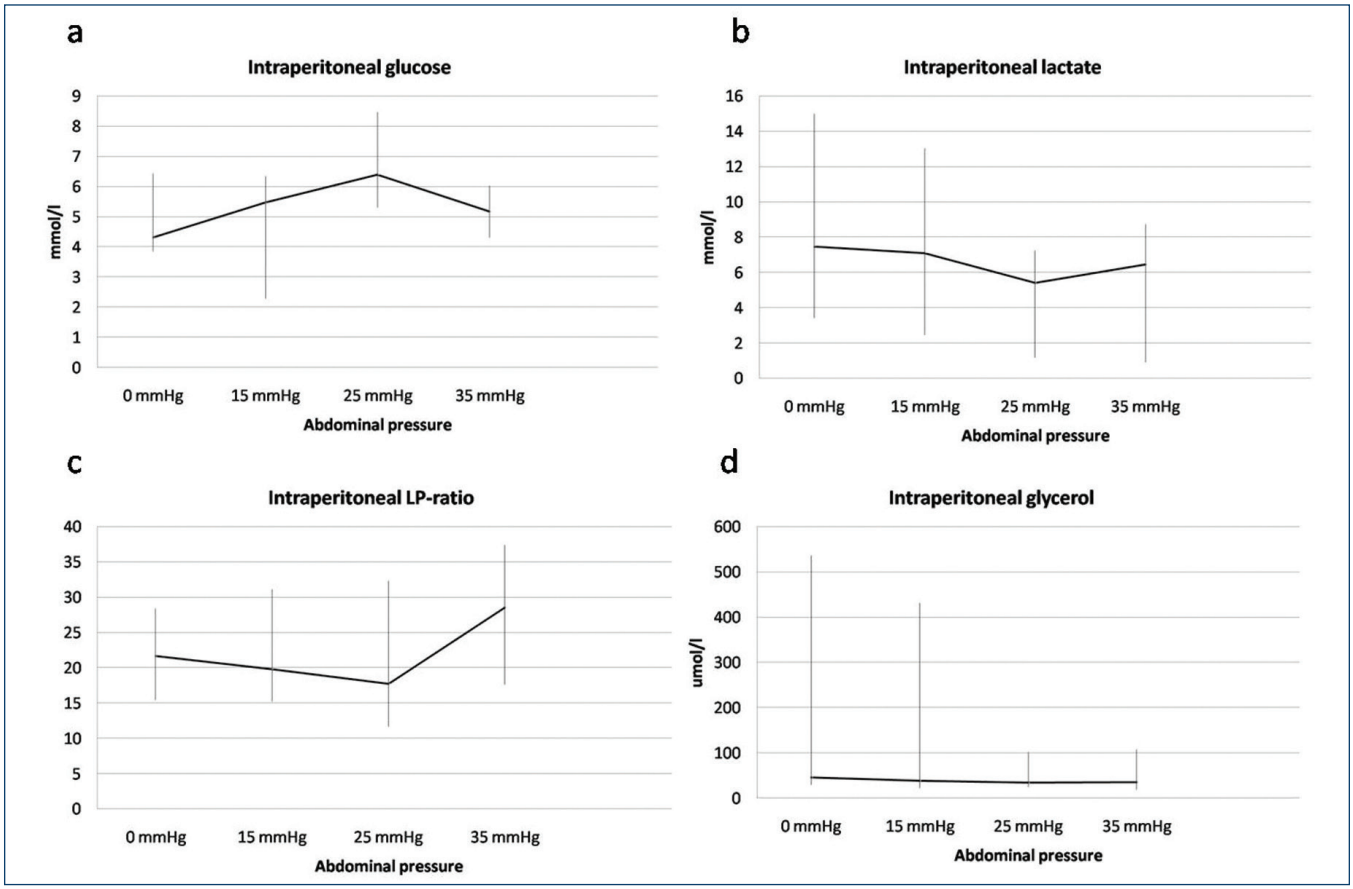

Figure 3. Microdialysis results intraperitoneally.

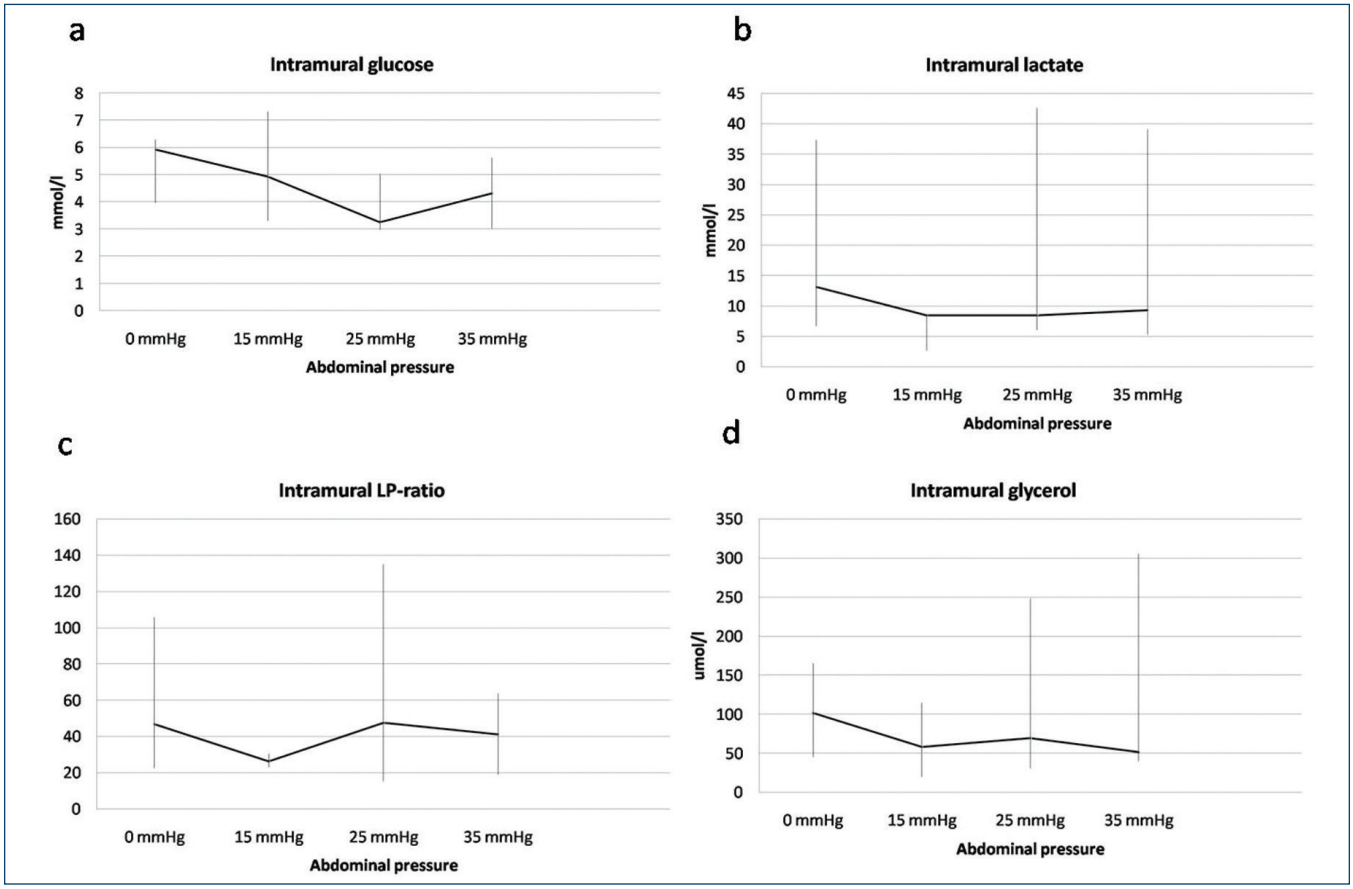

Figure 4. Microdialysis results intramurally.[Anesthetized pigs (n=5). Microdialysis results of metabolites measured intramurally. (a) Levels of glucose; (b) Levels of lactate; (c) Lactate-pyruvate ratio; (d) Levels of glycerol]

Arterial blood analyses

Arterial pO2 showed a decrease as the IAP was increased to 15 mmHg and was thereafter stable at the following IAP levels. Saturation was stable throughout the experimental period (data not shown). Arterial pH decreased by 0.24 units as the intra-abdominal pressure was elevated to 35 mmHg (Table 1). In parallel, arterial base excess decreased by 6 mM, and pCO2 increased by 1.0 kPa (Table 1). Blood lactate decreased considerably as IAP was elevated, blood glucose increased by 1.6 mM, and hematocrite increased slightly throughout the experimental period (Table 1). Electrolytes did not change over time (data not shown).

Intestinal mucosal blood flow

Perfusion arbitrary units (flux) at the baseline were 490 (300–880), with this level being set to 100%. At IAP of 15 mmHg, intestinal mucosal blood flow decreased by 5%, and was further reduced by 48% and 70% at IAP of 25 mmHg and 35 mmHg respectively (Fig. 1).

Intra-vesical pressure

As the intra-abdominal pressure was increased by carbon dioxide insufflation, the intra-vesical pressure also increased (Fig. 2). There was a close correlation between the abdominal insufflation pressure measured by the mechanical insufflator and the intra-vesical pressure.

Microdialysis

Intraperitoneal measurements

The intraperitoneal glucose concentration increased from 4.3 mM at baseline to 6.4 mM at 25mmHg whereas this increase was not continued at 35mmHg (Fig 3a). The lactate concentration displayed a wide range and was not changed dramatically during the experiment (Fig 3b). The lactate-pyruvate ratio was stable at IAP of 15 and 25mmHg and increased to 28 at 35mmHg (Fig 3c). The glycerol level was in median 46 μM at baseline and showed a wide range without marked change with elevated IAP (Fig 3d).

Small bowel intramural measurements

The intramural glucose concentration decreased in median by 30% with elevated IAP although the range was wide (Fig 4a). The median lactate concentration was stable throughout the experiments but values displayed a wide range (Fig. 4b). The lactate-pyruvate ratio was initially high at 47 in median at baseline, was half

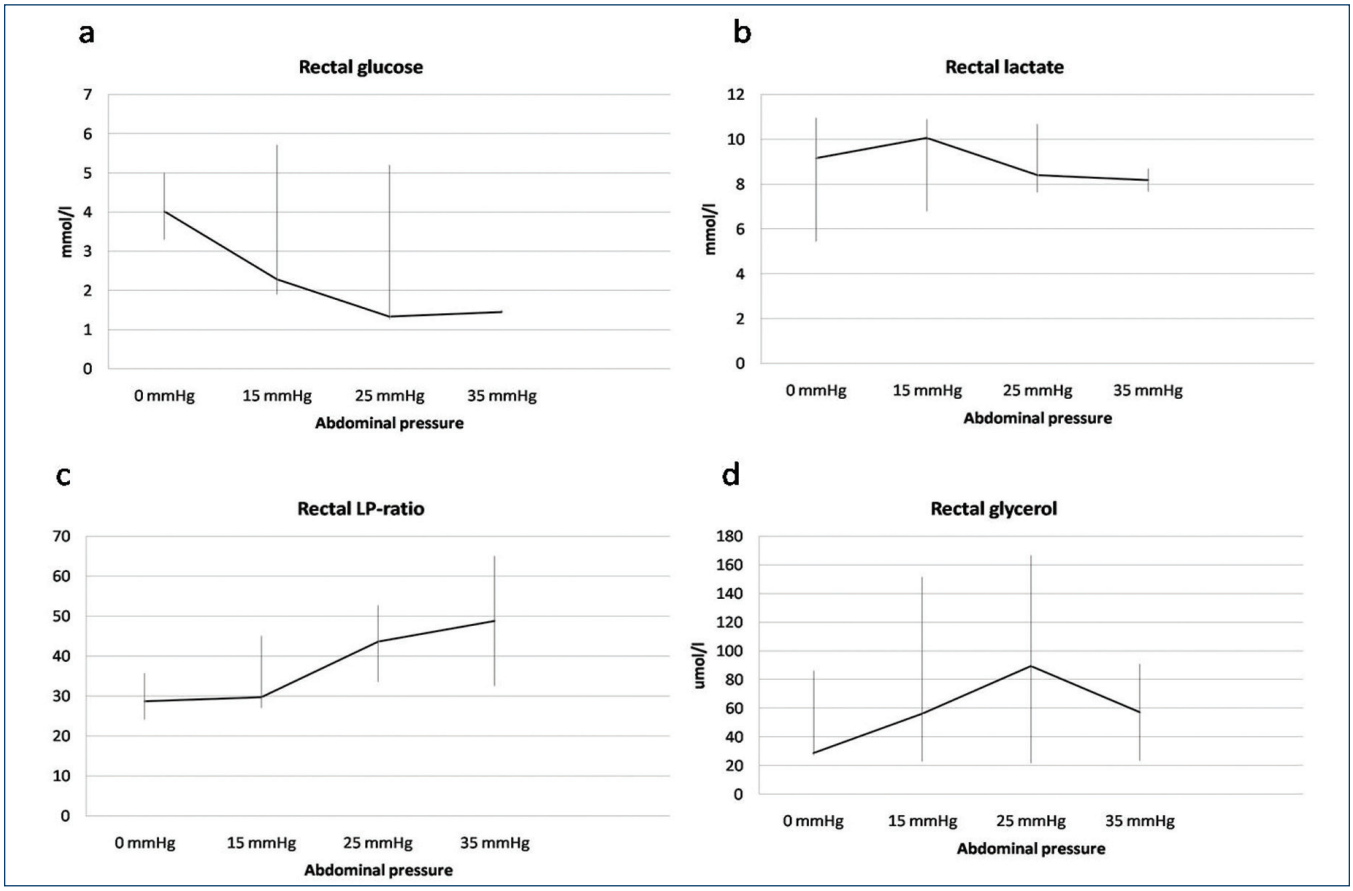

Figure 5. Microdialysis results rectally.[Anesthetized pigs (n=5). Microdialysis results of metabolites measured rectally. (a) Levels of glucose; (b) Levels of lactate; (c) Lactate-pyruvate ratio; (d) Levels of glycerol]

after one hour and increased again with elevated IAP to 41 at 35 mmHg (Fig 4c) while glycerol decreased by 50% from in median 100 mM at baseline to 50 mM at 35mmHg with a wide range of values (Fig 4d).

Rectal measurements

At the rectal site, glucose levels decreased in median as IAP was elevated (Fig 5a). Lactate concentration did not change with elevated IAP (Fig 5b). The lactate/pyruvate ratio increased from 28 at baseline to in median 48 as IAP was increased to 35 mmHg (Fig 5c). Rectal glycerol levels increased at the third hour three times comparing with baseline values and a decrease from 88 mM to 57 mM was seen as IAP increased to 35 mmHg. Rectal glycerol displayed however a wide range during the experiment (Fig 5d).

Discussion

Previously, IAH and ACS have been studied in animal models by using carbon dioxide pneumoperitoneum [25–30]. It was shown that increased intra-abdominal pressure causes effects on the visceral organs comparable to IAH and ASC in the clinical situation. Recently, it was also shown that carbon dioxide pneumoperitoneum-induced IAH impaired the microcirculation within the splanchnic area, decreased cardiac output, and negatively influenced the pulmonary function [20]. In the present study, heart rate and blood pressure increased in relation to the increased abdominal pressure, which are findings documented in pneumoperitoneum [31]. Intra-abdominal pressure measured by the gas insufflator correlated well to the pressure obtained by the catheter in the urinary bladder.

Importantly, all animals survived and were stable in hemodynamics and respiration during the entire experiments. We found it easy to maintain anesthetic depth, and evident blood pressure variations due to the anesthesia did not occur. Animals were kept stable in temperature by using warming blankets and warm i.v. fluids, and became only slightly hypothermic. Thus, we believe that a propofol-maintained anesthesia is possible and convenient for these kinds of experiments.

An increased arterial pCO2 is a well-known finding during pneumoperitoneum and is caused by carbon dioxide absorption from the peritoneal cavity. As the ventilation was not adjusted during the experiments, arterial pH decreased due to CO2 dissociation.

The decrease in base excess could be explained by systemic acidosis. The hypercapnea is not likely to have influenced any of the investigated metabolic parameters measured by microdialysis [32]. The slight increase of the hematocrite during the latter part of the experiment may have been caused by dehydration, indicating that fluid administration during these kinds of experiments should be larger than 4.5 ml kg-1 h-1.

The intestinal mucosal blood flow and perfusion were increasingly compromised following higher abdominal pressures. Although only the data at the end of each elevated intra-abdominal pressure is shown, the impaired perfusion was noted promptly after pressure elevation in all animals. Intra-abdominal pressure of 15 mmHg had only discrete effects on intestinal blood flow, whereas IAP of 25 and 35 mmHg markedly impaired the blood flow, which is consistent with a previous report [20].

The major metabolic findings were an increased lactate-pyruvate ratio at the highest IAP (35 mmHg) and decreasing glucose levels with elevated IAP at all locations. The intramural and rectal lactate-pyruvate ratio started at a level which is commonly recognised as the upper normal level [13]. The rather similar metabolic pattern that was recorded at the end of the experiments, at all locations as an effect of pneumoperitoneum, indicates ischemia as the pathophysiological cause [23]. Glycerol and lactate showed a marked increase with elevated IAP at the rectal location, whereas only slight differences were seen at the other locations. In parallel to the metabolic changes, the mucosal blood flow was reduced; measured by laser Doppler and by laparoscopy, we also observed that the intestines exhibited a light blue tinge, suggesting impaired blood flow. In the present study, we did not perform histological examinations of the visceral organs, but it has been shown that increased IAP causes histological changes in the intestines similar to ischemia [33]. From the present data, it may be suggested that the rectum exhibits the greatest sensitivity to ischemia since the metabolic changes were most evident at that location.

The microdialysis technique utilizes thin catheters and requires delicate maneuvers. Due to abdominal wall distension, the microdialysis catheter occasionally

moved into the gas-filled abdominal cavity, which was corrected by laparoscopy without causing decompression. The rectal catheter broke in two animals due to technical problems during application. On both occasions the fragile membrane was damaged and no measurements from the rectum could be obtained from these individuals. We also observed discontinuation of the laser Doppler measurements on a few occasions when the probe was dislocated, which was corrected without opening the abdomen. As the abdominal pressure increased, gas leakage occurred on a few occasions, especially at the highest pressure. The leakage led to loss of pressure during a short period, but could at all times be corrected with additional sutures in the abdominal wall.

In a recent study in humans by our group, it was demonstrated that intraperitoneal glycerol decreased, while the lactate-pyruvate ratio increased after major abdominal surgery with complications [34]. In the present study, we did not observe this change of glycerol. It cannot be excluded that the limited number of observations in this experimental study may be part of the explanation, but it is more likely that the metabolic consequences differ after acute trauma to the abdomen, with an increase in glycerol, whereas a protracted postoperative course leads to an inflammatory response and decreasing levels of glycerol.

The microdialysis values in various locations at the baseline differed, which may be interpreted as regional metabolic differences. Therefore, the trend in each location is more interesting than the absolute values. As shown in our previous human studies, this is a common finding when measuring metabolic alterations in different tissues [23].

It is known that trauma causes a rapid increase in insulin resistance and increased serum levels of glucose [35, 36]. In the present study, slightly increased blood glucose levels were recorded at the highest IAP level (35 mmHg). Whether this is due to insulin resistance or the glucose infusion (37.5 mg kg-1 h-1), or a combination of those, was not investigated. It has been shown that cell-near glucose levels decrease after surgical stress and that there is a difference between serum levels and intraperitoneal levels of glucose [37]. A similar decrease was found in the present study at all microdialysis locations.

This methodological pilot study has shown that microdialysis is useful to determine metabolic consequences caused by increased intra-abdominal pressure in the splanchnic area, most likely caused by ischemia as blood flow was correspondingly reduced. We also conclude that the metabolic deterioration is dependent on the degree of intra-abdominal hypertension. Furthermore, stable anesthesia could be established for 4–5 hours by the use of intravenous drugs. In future extended studies, with controls, we will investigate the metabolic consequences of a high intra-abdominal pressure maintained for longer periods.

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Conflicts of interest: The authors have not disclosed any potential conflicts of interest.

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