Abdominal Hypertension and Decompression: The Effect on Peritoneal Metabolism in an Experimental Porcine Study

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WHAT THIS PAPER ADDS
This experimental study explores the changes in abdominal metabolites during intra-abdominal hypertension with organ dysfunction, with focus on decompression with subsequent reperfusion. Using microdialysis early reactions in metabolite concentrations are observed, potentially useful as markers for effective abdominal compartment syndrome treatment.

Objective: The aim of this study was to investigate the abdominal metabolic response and circulatory changes after decompression of intra-abdominal hypertension in a porcine model.

Methods: This was an experimental study with controls. Three-month-old domestic pigs of both sexes were anesthetized and ventilated. Nine animals had a pneumoperitoneum-induced IAH of 30 mmHg for 6 hours. Twelve animals had the same IAH for 4 hours followed by decompression, and were monitored for another 2 hours. Hemodynamics, including laser Doppler-measured mucosal blood flow, urine output, and arterial blood samples were analyzed every hour along with glucose, glycerol, lactate and pyruvate concentrations, and lactate–pyruvate (l/p) ratio, measured by microdialysis.

Results: Laser Doppler-measured mucosal blood flow and urine output decreased with the induction of IAH and showed a statistically significant resolution after decompression. Both groups developed distinct metabolic changes intraperitoneally on induction of IAH, including an increased l/p ratio, as signs of organ hypoperfusion. In the decompression group the intraperitoneal l/p ratio normalized during the second decompression hour, indicating partially restored perfusion.

Conclusion: Decompression after 4 hours of IAH results in an improved intestinal blood flow and a normalized intraperitoneal l/p ratio.

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Article history: Received 4 September 2013, Accepted 11 January 2014, Available online 14 February 2014
Keywords: Glycerol, Intra-abdominal hypertension, Lactate, Laser Doppler flowmetry, Microdialysis, Pyruvate

INTRODUCTION
Abdominal compartment syndrome (ACS) after open repair of ruptured aortic aneurysm was described by Fietsam et al. in 1989;1 over the last 15 years the role of increased abdominal pressure as a cause of postoperative complications and organ failure has become evident. ACS is now defined as sustained abdominal pressure >20 mmHg associated with new organ dysfunction or failure, while the term intra-abdominal hypertension (IAH) should be used when organ dysfunction has not occurred.2

In a recent review, Carr has pointed out that the risk of ACS can be predicted with known risk factors, and the condition prevented.3 Early intervention is crucial and with limited abdominal hypertension medical therapy or minimally invasive treatment may be sufficient;4,5 in established ACS, laparotomy to reduce the high pressure and further organ-preserving measures seem to be the only effective and life-saving treatment. However, it should be noted that recurrent ACS may occur after decompressive laparotomy.6

Early diagnosis of increased intra-abdominal pressure (IAP) with organ failure is thus central, requiring pressure measurement, most commonly via the urinary bladder.7 The abdominal perfusion pressure (APP) is defined as the mean arterial pressure (MAP) reduced by IAP. As the majority of diagnostic tools for ACS only indirectly reflect organ dysfunction, the decision to perform a laparotomy in a critically ill patient is sometimes delicate.

In a clinical study utilizing microdialysis, we have demonstrated that intra-abdominal metabolic derangement, measured by microdialysis, occurs in patients developing IAH after repair of ruptured abdominal aortic aneurysm (rAAA).8 Continuous monitoring may not only show deranged metabolism in IAH or ACS, but possibly also restoration of aerobic metabolism after treatment.
The aim of this study was to explore whether decompression of IAH reverses the metabolic derangement as evaluated by intra-abdominal microdialysis.

**MATERIALS AND METHODS**

**Animals**

This study was approved by the regional animal ethics committee and carried out 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. Twenty-one crossbred pigs of both sexes (Swedish country breed, Hampshire and Yorkshire, mean weight 31 kg, range 26–35 kg) were used in the study. The animals had free access to food and water until the start of the experiment.

**Anesthesia, ventilation, and fluid treatment**

The anesthesia protocol has been published previously. In brief, the animals were sedated at the farm at the start of the day of the experiment. Intravenous (IV) general anesthesia was induced and maintained with propofol (8 mg/kg/h IV, Diprivan; AstraZeneca, Södertälje, Sweden), and the animals were intubated. To prevent hypercapnea due to CO₂ absorption from the abdomen, the animals were slightly hyperventilated. Anesthetic depth was controlled throughout the day by pain provocations. Ringer-Acetat (3 mL/kg/h; Fresenius Kabi, Uppsala, Sweden) and a 2.5% glucose solution (1.5 mL/kg/h; Fresenius Kabi) were used to maintain fluid balance. The animals were maintained at a stable body temperature (data not shown). At the end of the experiments, the animals were euthanized by an IV bolus injection of propofol (200 mg) and pethidin (1 mg/kg), and a rapid IV injection of potassium chloride (40 mmol). Asystole was confirmed with electrocardiography (ECG). Throughout the experiments the animals were well anesthetized and without signs of pain.

**Surgical preparation and instrumentation**

The surgical preparation and instrumentation has been described previously. In brief, a midline laparotomy was performed together with insertion of a catheter into the carotid artery (Becton Dickinson Critical Care, Singapore) for recording arterial blood pressure and heart rate, and for arterial blood sampling. Microdialysis catheters (CMA 62; CMA Microdialysis, Stockholm, Sweden) were inserted free-floating intraperitoneally, in the jejunal wall, and in the rectal wall via the anus. A urinary catheter for measurement of urinary output and bladder pressure was inserted. A laser Doppler probe (PM15; Perimed, Järfalla, Sweden) was inserted free-floating in the abdomen, if required. Laparoscopic trocars were used to insufflate gas and to correct the position of the probes and catheters in the abdomen if required. ECG recording and pulse oximetry were performed (Datex-Ohmeda AS/3; GE Healthcare Technologies, Waukesha, WI, USA).

**Experimental protocol and measurements**

After preparation, an intervention-free hour followed to obtain baseline data. Two experimental groups were created. Nine animals were planned to be in each group, but owing to catheter failure at jejunal and rectal levels in the decompression group three extra animals were added. Both groups had a CO₂-pneumoperitoneum of 30 mmHg induced. The IAH group had the pressure maintained for 6 hours, while the decompression group (IAH-D) was decompressed after 4 hours and then followed for an additional 2 hours. Baseline data and data at the end of each of the 6 hours were recorded, including systemic arterial blood pressure, heart rate, body temperature, IAP, laser Doppler flux, and urine output. Arterial blood samples and microdialysis samples were also obtained at the same timings.

**Microdialysis**

The microdialysis technique has been described previously. In brief, the concentration of different tissue metabolites is measured by this technique. The catheters can be placed in tissues or be free-floating in the body cavities. A physiologic solution (Perfusion fluid T1; CMA, Järfalla, Sweden) perfuses slowly (0.3 μL/minute) through a double-lumen catheter with a semi-permeable dialysis membrane (cut-off: 20,000 Dalton) at the tip, and equilibration over the membrane takes place. The microdialysate is collected in microvials and analyzed by photometry. In this study, concentrations of glucose, glycerol, lactate, and pyruvate were measured in a CMA 600 microdialysis analyser (CMA 600; CMA Microdialysis AB, Järfalla, Sweden).

**Intestinal mucosal blood flow**

Mucosal blood flow was measured by a laser Doppler probe (PM15; Perimed, Järfalla, Sweden) sending a laser beam of 780-nm wavelength. By the Doppler signal, an estimation of red blood cell flow in the jejunal mucosa was obtained as “flux”. Changes relative to baseline are presented.

**Statistics**

All data are presented with the mean and 95% confidence interval (CI). A linear mixed model for repeated measurements was used for statistical analysis. Group, time, and interaction were treated as independent variables using an autoregressive correlation structure. Ninety-five percent CI was calculated for every hour, but statistical analysis was only performed at baseline, 4 hours, and 6 hours. Logistic transformation of laser Doppler flux, lactate, lactate–pyruvate (l/p) ratio, and glycerol was performed owing to a known skewed distribution; results are presented as geometric means with asymmetric CIs. A p-value of ≤.05 was considered statistically significant. SPSS version 17 (SPSS, Chicago, IL, USA) was used for statistical calculations.
RESULTS

Abdominal pressure and hemodynamics

Abdominal CO₂ insufflation increased IAP to the required level of approximately 30 mmHg in all animals. The pressure was normalized after desufflation in the IAH-D group, while it remained stable in the IAH group throughout the experimental period. MAP increased (p < .001) at 4 hours in both groups compared with baseline and was significantly decreased on decompression (p = .05). On decompression, APP increased in the IAH-D group (p = .007). Heart rate increased significantly or near significantly in the IAH (p = .001) and IAH-D (p = .051) groups at induction of IAH compared with baseline, and decreased on decompression (p = .001) (Table 1).

Intestinal blood flow

Intestinal blood flow (IBF) measured as laser Doppler flux was determined to be 100% at baseline. At 4 hours of IAH, the flux had decreased in all animals compared with baseline (p = .001). Decompression increased IBF in the IAH-D group in a within-group analysis (p = .009) (Table 1).

Arterial blood analyses

Arterial oxygen partial pressure (PO₂) did not differ between the groups and was stable throughout the course of the experiment. Arterial CO₂ partial pressure (PCO₂) increased during IAH compared with baseline, and the IAH-D group showed a decrease after decompression (p = .047). Arterial pH decreased during IAH compared with baseline and normalized after decompression (p < .001). The hematocrit increased during IAH compared with baseline, but did not change significantly after decompression. Serum levels of glucose and lactate were unchanged over the course of the experiment, although an increase in serum lactate was seen in the IAH-D group as IAH was induced. This increase leveled-off during the first 4 hours (Table 2).

Abdominal metabolite concentrations

The intraperitoneal, intramural, and rectal glucose concentrations at 4 and 6 hours displayed some variation, but did not decrease during IAH and did not change on decompression (Fig. 1). The intraperitoneal glycerol concentrations increased (p = .001) during IAH compared with baseline. The glycerol concentration did not change significantly at any site after decompression (Fig. 2). The intraperitoneal and jejunal lactate concentrations did not increase during IAH, while the corresponding rectal level increased compared with baseline (p = .001). Decompression did not

\begin{table}
\centering
\begin{tabular}{l|c|c|c|c|c|c|c}
\hline
\textbf{Group} & \textbf{Baseline} & \textbf{1 h} & \textbf{2 h} & \textbf{3 h} & \textbf{4 h} & \textbf{5 h} & \textbf{6 h} \\
\hline
\textbf{Heart rate (beats/min)} & & & & & & & \\
\hline
\textbf{MAP (mmHg)} & & & & & & & \\
IAH-D & 69 (62–81) & 76 (65–90) & 82 (75–96) & 88 (80–100) & 93 (85–109) & 98 (86–111) & 98 (86–111) \\
\hline
\textbf{IAP (mmHg)} & & & & & & & \\
\hline
\textbf{APP (mmHg)} & & & & & & & \\
\hline
\textbf{IBF (% of baseline)} & & & & & & & \\
IAH & 100  & 82 (46–120) & 56 (27–100) & 33 (15–53) & 15 (6–23) & 3 (1–15) & 3 (1–15) \\
IAH-D & 100  & 38 (23–60) & 28 (15–49) & 14 (8–22) & 7 (4–14) & 4 (2–8) & 4 (2–8) \\
\hline
\textbf{Urine output (ml/h)} & & & & & & & \\
IAH-D & 57 (36–90) & 16 (10–26) & 9 (6–14) & 6 (3–10) & 3 (1–6) & 3 (1–6) & 3 (1–6) \\
\hline
\end{tabular}
\caption{Hemodynamics, intra-abdominal pressure (IAP), blood flow, and diuresis in the intra-abdominal hypertension (IAH) group and IAH and decompression (IAH-D) groups.}
\end{table}

Note: Data are expressed as means and 95% confidence intervals. MAP = mean arterial blood pressure; APP = abdominal perfusion pressure calculated as MAP minus IAP; IBF = intestinal blood flow measured by laser Doppler. 

**Table 1.** Hemodynamics, intra-abdominal pressure (IAP), blood flow, and diuresis in the intra-abdominal hypertension (IAH) group and IAH and decompression (IAH-D) group.

- **Significant difference between groups at the actual time point.**
- **Statistically significant difference between hours 4 and 6 within groups.**
- **Significant difference between groups after decompression.**

References:


change the lactate level at any site (Fig. 3). The rectal, but not the intraperitoneal or jejunal, pyruvate concentration increased during IAH compared with baseline \( (p = .019) \). At 4 hours pyruvate was different between groups intraperitoneally. The intraperitoneal pyruvate concentration, however, increased at decompression in a within-group analysis \( (p = .012) \) (Fig. 4). The intraperitoneal \( l/p \) ratio was increased at 4 hours compared with baseline \( (p = .001) \) and was lowered after decomposition \( (p = .004) \). Rectal and jejunal \( l/p \) ratios were unaffected (Fig. 5).

**DISCUSSION**

In this study the main findings were a reduced IBF and reduced urine production, as well as increased MAP when the animals were exposed to IAH. These results are in line with previously published findings. \(^5\) Decompression after 4 hours gave rise to a decrease of the MAP, while the APP, IBF and urinary output increased. The main metabolic consequences of IAH were a significant increase of the \( l/p \) ratio and the glycerol concentration intraperitoneally. After decompression, the intraperitoneal \( l/p \) ratio decreased significantly, while glycerol only showed a trend towards reduction. Comparable data are sparse. Meier et al. \(^15\) and Benninger et al. \(^16\) showed in experimental studies that metabolic changes occurred in the rectus muscle and abdominal organs when IAH was induced for 3 and 6 hours, respectively. Decompression did not resolve the metabolic derangement completely within 2 hours in those studies. \(^15\) Some clinical data can be extrapolated from our prospective study on 16 patients after endovascular repair of ruptured aortic aneurysm. \(^13\) Of six patients who developed increased abdominal pressure with new organ failure requiring decompression and monitored by intraperitoneal microdialysis, four had still usable microdialysis catheters after decompression, and their \( l/p \) ratio tended to decrease as they improved clinically (unpublished data).

Recent advances in the management of ACS include the searching for and validation of alternative treatments to the gold standard, laparotomy. The World Society of the Abdominal Compartment Syndrome Updated Guidelines 2013 recommend conservative treatments (grade 1C and 2C evidence). \(^17\) Sedation and muscle relaxation of a patient with elevated abdominal pressure in an intensive care environment, together with induced defecation, adjusted fluid balance, and minimally invasive evacuation of fluid or blood in the abdomen is demonstrated to be a possible treatment for ACS. \(^5\) These advances, together with better awareness of ACS, may reduce the mortality rate after ACS. \(^19\) To enable a better evaluation of metabolic consequences and risk of organ failure, more sophisticated diagnostic options are required. In clinical practice, one has to rely on an indirectly determined abdominal pressure and assessment of mainly renal function. Specifically, in regard to the serious complication of colonic ischemia, intra- or extraluminal colonic pH measurement (tonometry) after open surgery for rAAA has been shown to be useful. \(^20\) \(^21\)
Figure 1. Abdominal glucose concentrations. Data are expressed as means with 95% confidence intervals.

Figure 2. Abdominal glycerol concentrations. Data are expressed as means with 95% confidence intervals. Note. # Significant difference between groups at the actual time point. * Statistically significant difference between baseline and hour 4 or between hours 4 and 6 within groups. ¤ Significant difference between time points, irrespective of group.
Although the experimental setting with previously healthy animals without underlying trauma, fluid resuscitation, recent major surgery, and so on, when developing IAH, does not fully reflect the clinical situation, it is important to note that normalization of the abdominal pressure in this study was able to restore organ function, reflected metabolically as a decreased l/p ratio.

Determination of cell-near intraperitoneal metabolism by microdialysis offers an opportunity to detect changes preceding organ failure in the splanchnic area. Peritoneal access for catheter insertion is usually easy and minimally invasive. Our results also point to a more reliable measurement with a free-floating catheter in the peritoneal cavity compared with intestinal wall measurements. The rectal measurements are partly comparable to the intraperitoneal ones, but without statistically significant changes after decompression. It may be that the rectal catheters are inserted with some variation as full control over the placement is not achieved. This, together with potential tissue hematoma, might be the reason why the intraperitoneal catheter better displays changes in abdominal metabolism. Solligård et al.²² have, however, shown that free luminal catheter microdialysis in the rectum is feasible and clinically applicable.

Although only the intraperitoneal l/p ratio changed significantly after decompression, glycerol levels showed a trend in the same direction. These findings, combined with the fact that glucose levels did not decrease, do not point towards complete ischemia as the main reason for organ failure. Decreasing pyruvate during IAH and increasing pyruvate after decompression are the main reasons behind the changed I/p ratio in this study and an earlier clinical study;⁸ the lactate change is less pronounced. Therefore, the change in I/p ratio is not interpreted as being connected with the change in serum lactate in the IAH-D group. Of the metabolites measured here, the I/p ratio is well known to be the most sensitive marker of metabolic changes. Therefore, it is in line with earlier research in that significant change was only seen in I/p ratio during the short post-decompression period. A certain degree of hypoxia combined with an inflammatory response seems to be a reasonable explanation for the findings during IAH. At decompression we have recorded metabolic improvement, which speaks against any reperfusion damage, most likely due to limited ischemia during IAH.

If the early resolution of the intraperitoneal I/p ratio after decompression, shown in this study, is verified in further experimental and clinical studies, the use of microdialysis might add to clinical decision-making. Today, the diagnosis of ACS can often be troublesome. Considering the very challenging task of evaluating organ function during recurrer ACS and when urinary output is impaired owing to, for example, hypotension, the need for direct markers of organ function is obvious.
Figure 4. Abdominal pyruvate concentrations. Data are expressed as means with 95% confidence intervals. Note. # Significant difference between groups at the actual time point. * Statistically significant difference between baseline and hour 4 or between hours 4 and 6 within groups. ¤ Significant difference between time points, irrespective of group.

Figure 5. Abdominal lactate—pyruvate ratios. Data are expressed as means with 95% confidence intervals. Note. # Significant difference between groups at the actual time point. * Statistically significant difference between baseline and hour 4 or between hours 4 and 6 within groups. ¤ Significant difference between time points, irrespective of group.
In this study a few animals in the IAH group had higher MAP during the experiment. The reason for the initial difference in IBF between the groups is unclear, but perhaps caused by differences in MAP between the groups. As this difference was reduced at 4 hours it is not thought that there were any metabolic consequences of interest for this study.

As in earlier studies, serum lactate was noted to increase (only significant in one group) as IAH was induced and to decrease during the IAH period. Several studies have described increased serum lactate in ACS patients, but there is also evidence that serum lactate has limitations when predicting organ dysfunction in IAH.

LIMITATIONS

The use of CO₂ pneumoperitoneum in experiments of this kind may be a confounder, as the acid–base balance may be affected. However, most experimental studies use this method and data may therefore be comparable. Differences in acid–base balance at baseline were noted. This gave rise to a limited, but significant, pH difference. This inequality leveled-off during the first 4 hours. Catheter failures were recorded in the jejunal and rectal locations, causing some data loss. We focused on early findings during the first 2 hours following decompression. With longer follow-up more extensive metabolic changes might have been recorded at the rectal level as the change in pyruvate and l/p ratio was relatively similar intraperitoneally and rectally. However, our experience is that the data loss increases after 6 hours. In this study, bolus doses of fluid to compensate for the circulatory effects of IAH and decompression were not included, which probably had an impact on the circulatory findings in the IAH-D group during the last 2 hours. In future studies, a model with pathophysiological alterations causing IAH (i.e., ischemia, hemorrhage), and compensatory fluid treatment, as in the clinical setting, would be important improvements.

CONCLUSIONS

Determination of intra-abdominal metabolism by microdialysis, using a free-floating intraperitoneal catheter, showed restoration of the l/p ratio after decompression of IAH, and a corresponding increase of the splanchnic blood flow. Further studies are required for better understanding and evaluation of, to what extent the method is useful in the clinical setting.

ACKNOWLEDGMENTS

We thank Mr. Anders Magnuson, BSc, our institute’s statistician for excellent statistical tutoring. Mrs. Nina Adolfsson-Karlsson, RN, and Mrs. Monica Clomén, RN, Örebro University Hospital, Örebro, Sweden, for very good laboratory assistance.

CONFLICT OF INTEREST

None.

FUNDING

The study was financially supported by the Medical Research Council in Örebro, Sweden, and Nyckelfonden, Örebro, Sweden.

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muscle in a porcine model of critical intra-abdominal hyper-


