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Biochemical Changes in Experimental Rat Model of Abdominal Compartment Syndrome

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Background: Increased intra-abdominal pressure (IAP) causes tissue ischemia, subsequent hypoxia, and impairment of normal tissue metabolism. Elevation of IAP above 20 mmHg leads to progression of abdominal compartment syndrome (ACS) that is associated with organ dysfunction or failure not previously manifested.

Aim: To evaluate the effects of different grades and time of exposure to IAP on biochemical parameters and oxidative stress in organs affected by ischemia using previously developed rat model.

Results: Three experimental groups exposed to different IAP and time frames were tested for liver, kidney, and pancreas injury by measuring the activities of tissue specific enzymes in blood serum. Elevated activities of aspartate aminotransferase, pancreatic amylase, lipase, and higher concentrations of D-lactate, urea, and creatinine were found in some of the experimental groups compared to a control group of animals not subjected to increased IAP. Increased levels of biomarkers of oxidative stress as well as decrease in concentration of the major cellular antioxidant glutathione indicated the presence of oxidative injury as a result of elevated IAP.

Conclusions: The developed rat model is appropriate to study the mechanism and manifestation of tissue injury during different grades of elevated IAP but also to test approaches aimed to attenuate the detrimental effects of ACS. This study also underlines the necessity of using not a single but a set of biochemical parameters in order to assess the severity of tissue injury during elevated IAP and progression to ACS.

BACKGROUND

Elevated intra-abdominal pressure (IAP) has been described in a wide variety of clinical conditions: trauma, sepsis, abdominal surgery, acute pancreatitis, ileus, etc., and has gained considerable interest during the last decades.¹ IAP has also been observed during laparoscopic interventions that are widely used nowadays in the diagnosis and treatments of many diseases.² Increase in IAP $\geq$ 20 mmHg leads to progression of abdominal compartment syndrome (ACS) that is associated with organ dysfunction or failure not manifested before the elevation of IAP.³

Rise in IAP affects dynamic pulmonary compliance, reduces hepatosplanchnic flow and impairs liver function, decreases renal blood flow and urine output progressing from oliguria to anuria; causes compression of the inferior vena cava, and decreases cardiac output.⁴⁻⁷ Reduced blood flow to

intra-abdominal organs and restriction of the feeding blood supply decrease tissue oxygenation causing a shortage of oxygen and glucose needed for cellular metabolism.⁸ In addition, bacterial translocation has been demonstrated in rat models.⁹ These studies have identified physiologic derangements that occur with the increase in IAP, which may play a role in the development of sepsis and systemic inflammatory response syndrome in patients with ACS.

The other mechanism for tissue and organ injury during elevated IAP is the excess of reactive oxygen species generated via multiple mitochondrial and non-mitochondrial pathways. Numerous studies have shown that even moderate increase in IAP for a short period of time could result in a pro-oxidant – antioxidant imbalance, a condition generally referred to as oxidative stress.¹⁰

The effects of elevated IAP are not limited to

abdominal but also affect other body compartments, e.g. intra-thoracic, and intracranial.¹¹ The correlation between severity of IAP increase, duration of exposure, and predisposition and extent of organs damage in other compartments is not well understood.

Elucidation of the changes in organ function under elevated IAP and its progression to ACS is important for critical care management. In a previous study we reported development of a rat animal model as a necessary step from recognition to prevention of ACS.¹² In the present study we aimed to evaluate the effects of different grades and time of exposure to IAP on biochemical parameters and oxidative stress in organs affected by ischemia.

MATERIALS AND METHODS

ANIMALS

One hundred and forty Wistar rats weighting between 250 and 280 g were used in the experiments. They were housed in standard laboratory conditions: room temperature, free access to food and water, and a 12-hour light/dark cycle. Prior to the experiments, the rats were deprived of food for 12 h. The experimental protocol was approved by the Ethical Committee of the National Agency of Food Safety № 20/30.06.2011, and all the experiments were conducted in accordance with Directive 86/609/EEC.

Anesthesia was induced with intraperitoneal injection of 2% xylazine (10 mg/kg) and 5% ketamine (100 mg/kg). Rats were placed on a heating table that maintained their body temperature at 37°C during the experiments. Pneumoperitoneum was established by slow insufflation of air (room temperature) using disposable venous needle connected to a manual pump. The IAP was monitored by a sphygmomanometer and controlled constant (± 2 mmHg) during the experiments. Body temperature, depth of anesthesia, and breathing were monitored as well.

The animals were randomly allocated into 4 groups. Group A consisted of 88 animals that were kept under anesthesia without an increase in IAP; groups B, C, and D were subjected to different IAP and various time of exposure (25 mmHg/60 min, 30 mmHg/45 min, 30 mmHg/60 min, respectively). All studied parameters of animals in group A did not show any significant differences compared to untreated rats (passive group of 10 animals) and therefore, group A was further referred to as control group.

After gradual decompression for 10-15 min,

blood was collected from the portal vein. Euthanasia of the animals was carried out under anesthesia through cervical dislocation and organ specimens were harvested for *ex vivo* analyses.

SERUM

Serum values of biochemical parameters were analyzed using commercial kits provided by Analyticon Biotechnologies AG (Lichtenfels, Germany) and the assays were carried out according to the manufacturer's recommendations. The analyses included enzyme activities of aspartate aminotransferase (AsAT), pancreatic amylase, lipase, and the levels of urea and creatinine. D-lactate colorimetric assay was performed using a kit purchased from Sigma-Aldrich. Absorbance readings were recorded on Ultrospec 3300 pro spectrophotometer (Amersham Biosciences, UK).

TISSUE HOMOGENATES

Biomarkers of oxidative stress were assayed in rat brain, ileum, and gastric smooth muscle. After extensive perfusion with phosphate buffered saline, the dissected tissues were homogenized for 2 min in ice bath with 100 mM sodium phosphate buffer pH 7.4 that contained 150 mM NaCl and 1 mM EDTA. Typically, a 10% w/v homogenate was prepared. The supernatant obtained after centrifugation at 9000 g and 4°C for 5 min was used for analyses.

MARKERS OF OXIDATIVE STRESS

To evaluate the severity of oxidative stress as a result of ischemic conditions in different tissues, three biomarkers were assayed – the levels of thiobarbituric acid reactive substances (TBARS), reduced glutathione (GSH), and protein carbonyl content. The results were normalized to mg tissue protein.

Tissue level of TBARS as a biomarker of lipid peroxidation was quantified as recommended by Animal Models of Diabetic Complications Consortium (<http://www.diacomp.org/shared/protocols.aspx>). GSH assay was a modification of the method first described by Anderson.¹³ Protein carbonyls were quantified according to the method proposed by Reznick et al.¹⁴ Protein concentration was measured by Bradford's method using bovine serum albumin as a calibrator.¹⁵

STATISTICAL METHODS

The experimental data obtained were processed by Statistica 12.5 software (StatSoft, Dell). The results are presented as mean $\pm$ SEM, and Student criteria of significance $P < 0.05$ was applied in comparisons.

RESULTS

BIOCHEMICAL MARKERS OF TISSUE INJURY

Analysis of serum AsAT as an indicator of hepatocellular injury revealed that the enzyme activity showed a tendency to increase in group B (25 mm/60 min, $p=0.07$) and group C (30 mm/45 min; $p=0.1$) but was significantly higher in group D (**Table 1**). Serum urea and pancreatic lipase showed significant increase after 60 min exposure to both, 25 and 30 mmHg. Furthermore, serum creatinine was elevated in all experimental groups compared to the control group. Activity of pancreatic amylase in serum was elevated only in the group exposed to 30 mmHg for 60 min.

Serum D-lactate levels were increased in the group B exposed to IAP 25 mmHg/60 min; the mean level was 0.81 mM (min 0.50, max 1.05, $n=10$), while the abdominal normotonic group displayed mean concentration 0.25 mM (min 0.21, max, 0.30, $n=10$).

OXIDATIVE INJURY AT DIFFERENT

GSH levels dramatically decreased in stomach tissues obtained from all experimental groups with IAP (**Fig. 1**). The mean value of the control group A ($n=8$) was 829.6 ± 142.2 mol/mg but it declined to 99.1 ± 23.6 mol/mg in group D ($n=7$, $p < 0.0005$). No statistically significant differences were found for ileum tissues; GSH levels varied from 807.9 ± 115.2 mol/mg for the control group A ($n=11$) to 745.3 ± 185.2 , 527.9 ± 104.7 , and 523.9 ± 123.4 mol/mg for groups B ($n=9$), C ($n=4$), and D ($n=5$), respectively. Group D was the only one with GSH concentrations in brain specimens that differed significantly ($p=0.0001$, $n=7$) compared to those of the control group A ($n=9$) – 274 ± 127 and 1046.2 ± 181.6 mol/mg, respectively.

Typically, the concentrations of malondialdehyde and similar products of lipid peroxidation are assayed by measuring their colored adducts with thiobarbituric acid and expressed as TBARS. The mean TBARS values of all experimental groups ex-

Table 1. Serum biochemical parameters of different experimental groups with elevated intra-abdominal pressure. Asterisks show values that differ significantly from those of the control group A. The corresponding p -values and the animals' number n are indicated for each group

Biochemical parameter	Control group (A)	25 mm Hg/60 min (group B)	30 mm Hg/45 min (group C)	30 mm Hg/60 min (group D)
AsAT (U/L)	49.81 ± 17.08 ($n=17$)	65.23 ± 10.6 ($n=5$)	68.85 ± 32.04 ($n=4$)	$125.82 \pm 15.62^{****}$ ($n=6$)
Urea (mmol/L)	7.96 ± 1.89 ($n=19$)	$10.27 \pm 2.27^*$ ($n=6$)	9.44 ± 1.76 ($n=4$)	$10.03 \pm 1.86^{**}$ ($n=10$)
Creatinine (umol/L)	57.94 ± 15.48 ($n=20$)	$99.97 \pm 34.98^{***}$ ($n=7$)	$85.04 \pm 18.74^{***}$ ($n=4$)	$83.1 \pm 27.36^{****}$ ($n=9$)
Lipase (U/L)	26.33 ± 7.69 ($n=17$)	$38.24 \pm 20.11^*$ ($n=7$)	28.85 ± 14.41 ($n=4$)	$43.59 \pm 29.8^*$ ($n=9$)
Amylase (U/L)	834.67 ± 196.00 ($n=20$)	958.51 ± 182.00 ($n=8$)	1028.34 ± 287.22 ($n=5$)	$1293.97 \pm 504.02^{***}$ ($n=10$)

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.005$; **** $p < 0.0005$

posed to IAP did not differ among the brain tissues (**Fig. 2**). However, there was a tendency ($p=0.09$) of higher TBARS concentrations in ileum samples obtained from group D (10.6 ± 2.4 nmol/mg, $n=11$) compared to the control group A (4.8 ± 1.7 nmol/mg, $n=9$). Stomach tissues obtained from the experimental group exposed to 30 mmHg for 60 min contained higher levels of TBARS (12.0 ± 6.1 nmol/mg; $p < 0.05$, $n=4$) compared to the levels found for control animals (3.7 ± 1.4 , $n=8$).

Protein carbonyl content had similar values in stomach and brain tissues obtained from all the experimental groups (**Fig. 3**). Only in ileum this marker of protein oxidative damage was significantly elevated ($p < 0.0005$) reaching values as high as 5.5 ± 1.4 nmol/mg protein for group D ($n=9$), which is nearly doubled carbonyl levels of the control group A (2.8 ± 1.3 nmol/mg; $n=24$).

Figure 1. Concentration of reduced glutathione (umol/mg tissue) in stomach, ileum and brain tissues. Group A is the control group; group B – 25 mmHg/60 min; group C – 30 mmHg/45 min; group D – 30 mmHg/60 min. Asterisks indicate values that differ significantly compared to those measured for the control group ($p < 0.05$).

Figure 2. Concentration (nmol/mg tissue) of thiobarbituric acid reactive substances (TRARS) in stomach, ileum and brain tissues. Group A is the control group; group B – 25 mmHg/60 min; group C – 30 mmHg/45 min; group D – 30 mmHg/60 min. Asterisk indicates value that is significantly different to that found for the control group ($p < 0.05$).

Figure 3. Protein carbonyl content (nmol/mg tissue protein) in stomach, ileum and brain tissues. Group A is the control group; group B – 25 mmHg/60 min; group C – 30 mmHg/45 min; group D – 30 mmHg/60 min. Asterisks indicate levels that differ significantly compared to those found for the control group ($p < 0.05$).

DISCUSSION

Abdominal compartment syndrome is defined as a sustained IAP greater than 20 mmHg with new organ dysfunction or failure. Increase in pressure of the abdominal compartment above the pressure of capillaries perfusing the adjoining organs is the event leading to tissue ischemia and subsequent hypoxia. As a result, the normal metabolism of abdominal organs is impaired.

The liver and the kidneys are the organs most

frequently affected by increased IAP in experimental and clinical studies. While the liver injury evaluated by increase in AsAT activity was evident only in group D, the effect of the IAP on renal function appears undoubted since urea and creatinine were increased significantly in almost all experimental groups subjected to IAP. Similar are the observations of Avraamidou et al., who reported increased urea and creatine serum levels in porcine model of IAP (30 mmHg maintained for 3 h).¹⁶ Pancreatic amylase was not as sensitive as lipase and amylase activity was significantly higher only in the group D exposed to 30 mmHg for 60 min.

Interestingly, the values for some biochemical parameters (urea, lipase) found for group C (30 mmHg/45 min) did not differ from those of the control group. This might be an indication that the time of exposure to IAP is more critical for tissue injury than the pressure grade and warrants further studies.

Another biomarker for tissue injury is serum D-lactate concentration, a product of intestinal metabolism. During intestinal ischemia, D-lactate is transferred to the portal circulation because of increased intestinal mucosal and capillary permeability and for this reason it is considered as a valid biomarker of intestinal ischemia induced by abdominal compartment syndrome.¹⁷ In our study even the group subjected to a mild intervention (25 mmHg for 60 min) demonstrated significantly higher ($p < 0.005$) concentrations of D-lactate compared to the control group suggesting the presence of intes-

tinal injury as a result of elevated IAP.

The evidences already available in the literature indicate that oxidative stress-mediated effects are likely to constitute important primary and secondary mechanisms contributing to the development and evolution of ACS and reactive oxygen species are important mediators of tissue injury.¹⁸ Ischemia leads to activation of some cellular pro-oxidant enzymes (e.g. xanthine oxidase and NADH-dependent oxidase)^{19,20} and the release of superoxide radical and hydrogen peroxide that are products of the reactions catalyzed by these enzymes, could deplete the major intracellular antioxidants. At the same time, a tendency of decline in activity of the major antioxidant enzymes (glutathione peroxidase, catalase, superoxide dismutase) was found in an animal model even at 12-20 mmHg.¹⁸ In this study three biomarkers of oxidative stress: GSH, TBARS and protein carbonyl content were quantified and their levels indicated the presence of oxidative injury, albeit the severity varied in different tissue and experimental groups.

GSH is a cysteine-containing tripeptide that maintains the integrity of all cellular components; decreased levels of glutathione predispose cells to serious oxidative damage. Stomach was the most vulnerable in respect to loss of GSH, but the ileum and brain GSH levels were less affected by increased IAP. In the distant brain oxidative injury was registered only in group D.

In our model of acute IAP TBARS concentrations were statistically meaningfully higher only in stomach tissues obtained from experimental group D. They reached nanomolar values per milligram tissue protein and were similar to those reported by Eleftheriadis et al. in gut and liver of rats exposed to 15 mmHg for 30 min.²¹ In contrast, Gong et al. have measured micromolar concentrations in rat ileum after 4 h of intra abdominal hypertension at 20 mmHg and 4 h of reperfusion period.²²

Attack on proteins by free radicals leads to modifications in protein structure seen as an increase in protein carbonyl content. Protein oxidation was evident only in ileum tissues from all the experimental groups. In brain, protein oxidation among the groups did not change significantly and had levels typical for young animals¹⁴ in contrast to findings reported by Karabekir et al. who measured significantly higher protein carbonyls in brains obtained from rats exposed to 30 mmHg for 60 min.²³ Both biochemical and oxidative markers of damage varied among the tissue suggesting that different organs

are predisposed to specific injuries resulting from elevated IAP and its progress to ACS.

CONCLUSION

The developed rat model is appropriate to study the mechanism and manifestation of tissue injury during different grades of elevated IAP but also to test approaches aimed to attenuate the detrimental effects of ACS. This study also underlines the necessity of using not a single but a set of biochemical parameters in order to assess the severity of tissue injury during elevated IAP and progression to ACS.

ABBREVIATIONS USED IN THIS ARTICLE

ACS: abdominal compartment syndrome

AsAT: aspartate aminotransferase

GSH: glutathione

IAP: intra abdominal pressure

TBARS: thiobarbituric acid reactive substances

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Биохимические изменения при экспериментальной модели абдоминального компартмент-синдрома крысы

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Введение: Интраабдоминальная гипертензия (ИГ) вызывает тканевую ишемию с последующей гипоксией и нарушение нормального тканевого обмена. Повышение ИГ свыше 20 mmHg приводит к развитию абдоминального компартмент-синдрома (АКС), который связан с органной дисфункцией или недостаточностью, не проявлявшихся до этого.

Цель: Оценить эффекты различных степеней и времени воздействия ИГ на биохимические параметры и на оксидативный стресс органов, затронутых ишемией на основе разработанной модели крысы.

Результаты: Три экспериментальные группы, подвергнутые воздействию ИГ различных степеней и временных параметров были исследованы на предмет поражения печени, почек и поджелудочной железы измерением активности тканевых специфических энзимов в сыворотке крови. Повышенная активность аспаратаминотрансферазы, панкреатической амилазы, липазы и повышенные концентрации D-лактата, мочевины и креатинина были установлены в некоторых экспериментальных группах по сравнению с контрольной группой животных, которые не были подвергнуты воздействию ИГ. Повышенные уровни биомаркеров оксидативного стресса, как и понижение концентрации основного клеточного антиоксиданта глутатиона являются индикатором наличия оксидативных повреждений вследствие ИГ.

Выводы: Разработанная модель крысы является подходящей для исследования механизмов и проявления повреждения тканей во время воздействия ИГ различных степеней, как и для исследования подхода, направленного на ослабление вредного воздействия АКС. Данное исследование также подтверждает необходимость в применении не одного, а целого набора биохимических параметров для оценки степени тканевого повреждения во время ИГ и развития АКС.