Influence of obesity on the tolerance of abdominal hypertension in rats—some mechanical aspects

V.I. Turiyski1, I.V. Dimitrov2, R.G. Ardasheva1 and P.G. Vassilev3

Department of Chemistry and Biochemistry, Faculty of Pharmacy, Medical University of Plovdiv, 15A Vassil Aprilov blvd., Plovdiv 4000, Bulgaria.
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ABSTRACT
The present study investigates the relations between obesity and survival during intra-abdominal hypertension (IAH) in diet induced obesity Wistar rats. The animals from model group were fed with high-fat diet for 45 days. Intra-abdominal pressure in both groups (control and model) was elevated by manual system for air insufflations. The pressure was of value (25mmHg) corresponding to the typical values observed in abdominal compartment syndrome. Quantification of the serum levels of serum amyloid A was carried out after deflation. The results interpretation was made in correlation with clinical observations in patients with proved cardiovascular diseases caused by obesity, as well as with patients to whom surgery had caused an increased intra-abdominal pressure. Experimental observations have shown increased survival in diet induced obesity rats with IAH compared to control rats with IAH. Increased resistance to IAH is due to changes in the structure and in the mechanical characteristics of the abdominal wall, following obesity.

Key words: Abdominal hypertension, Obesity, Rat.

INTRODUCTION
The significance of obesity for the outcome of a variety of surgical interventions is a subject of many studies (Choban and Flankbaum, 1997; Drenick, 1981; Bokey et al. 1995). It has been reported that obesity is not a factor that affects the treatment efficiency during postsurgical period, although other reports do state for that (Benoist et al. 2000). Arising of IAH as either a consequence from pathological processes in the abdominal cavity or surgical interventions is a fundamental and practical problem (Deenichin, et al., 2013). The interference of functional and morphological changes accompanying obesity (Ferrannini, 1995) including diet-induced changes (Sood et al. 2014) with abdominal hypertension builds up a complex clinical picture. Because of the critical characteristics of the abdominal compartment syndrome in patients having different etiology of IAH, there is insufficient number of reports making attempts to define the relationship between obesity, IAH and therapeutic intervention outcome.

We used a model of animal obesity, mainly because some of the parameters of IAH, set out in this experiment, can be neither combined nor realized in the clinical practice. This would help many fundamental biophysical and pathophysiological cases to be solved.
Artificially induced IAH was performed in following steps:
1) The animals were anaesthetized by xylazine 2%-10mg/kg +ketamine (Calipsol) 5%-100mg/kg, injected intraperitoneally.
2) The animals were fixed on electrical thermophore maintaining the temperature constant (+37°C) during the experiment.
3) Modified percutaneous fixing of venflon was performed in order to induce pneumoperitoneum (Rezende-Neto et. al., 2003).
4) Intra-abdominal pressure of animals was elevated by manual insufflation and performed at two stages: coupling of a high-pressure system with the venflon and gradually (for 10 minutes) increase the intra-abdominal pressure up to 25mmHg. The process was controlled by shpygmo-manometer.
5) The increased intra-abdominal pressure had been maintained for time period between 30 (thirty) and 180 (one hundred and eighty) minutes.

Quantification of the serum levels of serum amyloid A (SAA): After lightly decompression, 1.5 to 2 ml peripheral blood was collected. It was centrifuged at 3 500 rpm for 5 minutes and the serum was collected. The levels of SAA in blood serum were quantified by ELISA method using commercially available kits from MyBioSource (Rat Serum amyloid A (SAA) ELISA kit – MyBioSource Inc., San Diego, CA, USA). The processes was maintained in accordance with the manufacturer’s recommendations. The quantitative analyze was performed by an ELISA microplate reader (HumanReader). All samples were measured in duplicates. Serum SAA concentration is presented as ng/ml. The results obtained are presented as median and 95% CI. Differences with p<0.05 were considered as statistically significant.

RESULTS AND DISCUSSION
The experimental data were grouped using the criterion “survival in condition of IAH of 25 mm/Hg”. Quantification of the results was done by comparing percentage ratios representing the survival as a function of IAH duration. Each ratio connects the duration of the artificially induced IAH and respective number of animals from the given group survived the condition. The comparisons were made at different stages of the syndrome defined as short-term, intermediate and long-term. In order to optimize the accuracy of some extrapolations and conclusions this differentiation was considered with established relations with the life duration in rats and humans (Andreollo et al., 2012; Sengupta, 2011).

General time distribution of survival in groups: Figure 1 illustrates the distribution of the experimental animals according to the criterion “survival”, under condition of artificially induced IAH (25 mmHg). The passed IAH durations were plotted on the abscissa in discrete intervals: an interval up to 30 minutes was assumed as short-term, intervals up to 1 hour and between 1 and 3 hours were assumed as intermediate, and over 3 hours - as long-term. The groups formed using this criterion were labeled with a letter from a to g.

As a time period that defines survival, we accepted to be 30 minutes after IAH was increased up to 25 mmHg. It was the shortest period of time under which we had observed (Deenichin et al., 2010) indications about physiological changes, caused by the syndrome. By analogy, the 3 hours time limit was appropriate to define “long-term” IAH, and it can be extrapolated to an average period of 3.75 days in humans, defined in accordance with international classifications (Sengupta, 2011).

![Figure 1: Distribution of rats from control and model groups in terms of survival under a condition of intraabdominal hypertension; In percents: a=37.5, b=10, c=0, d=10.5, e=12.5, f=21.6, g=50, h=57.9. The total number of animals for each group (control and model) separately corresponds to 100%](image-url)
Relations established:

1a. Absolute survival was reported to 57.7% of the experimental and to 50% of the control rats (comparing the indicators h and g) - report for the number of the animals, remained completely vital after 3 hours with induced IAH.

1b. Fast lethality was observed in 37.5% of the control and 10% of the model rats (comparing the indicators a and b). This quantity showed in which of the experimental groups the lethality during the first phase of the IAH prevailed.

1c. Survival at intermediate and long-term IAH: it is 90% in the model group (d+f+h) and 62.5% in the control group (c+e+g).

Changes in the serum levels of SAA were measured, as an additional marker that shows a probable presence of pathophysiological changes (inflammation) (Xing et al., 1999).

The concentrations of SAA detected in blood serum of the control animals were elevated. In the subgroup A (n=10) of the control group it was 7.21 ng/ml (95% CI 6.36-8.78), and in the subgroup B (n=7) it was 8.32 ng/ml (95% CI 6.21-9.48). In the obese animals with induced IAH (n=18) the serum SAA level was 7 ng/ml (95% CI 6.07-9). There is not statistically significant difference neither between the three groups (p=0.665), nor between the experimental group compared with the control groups (with both, A and B subgroups). The p-value is: p=0.807 for the comparison of the control with the lean IAH-induced animals, p=0.565 for the control compared with the IAH-induced obese animals, and p=0.369 for both of the experimental groups - lean and obese animals with induced IAH.

Both, obesity and the critical elevation of intrabdominal pressure have a great impact on the physiological functions (Woods et al., 2003). Applying DIO on laboratory rats allows the investigation of a wide variety of pathological changes and the structures and systems that they affect (Boustany et al., 2004). It is reported, by Xing et al., (2011) that DIO causes changes in the mechanical characteristics of the abdominal wall muscles. Due to the changed collagen structure, the muscle tonus and the elasticity of the abdominal wall are both decreased in obese rats (Xing et al., 2011). The mentioned above might reflect on the abdominal wall compliance and might be one of the passive factors that lead to the development of abdominal hypertension.

To this effect, increasing of the compliance would be favorable for decreased rate of further intra-abdominal pressure elevation and all of the ischemia effects that follow it. The changed abdominal wall elasticity in rats with DIO (Fig. 2) under conditions of same values of the Young’s modulus would provoke increasing of the compliance in obese, compared with control animals.

It was important to note that in our experiment the values of the IAH are significantly lower, and below the values, defined by Xing et al. (2011) as critical (Table 1).

![Figure 2: Comparison between tensibility of abdominal wall of control and model rats (with DIO) (modified from Xing L. et al, (12))](image)

<table>
<thead>
<tr>
<th>group</th>
<th>Mechanical tension, range(N/mm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>controls</td>
<td>Literature data *</td>
</tr>
<tr>
<td>0.45±1.2</td>
<td>0.03±0.004</td>
</tr>
<tr>
<td>DIO-rats</td>
<td>0.25±0.7</td>
</tr>
</tbody>
</table>

The above mentioned changes in the mechanical characteristics of the abdominal wall muscles fit well with our experiment results, because decreased escalation of IAH, due to increased compliance was expected to be accompanied with delayed activation of the ischemic processes. Therefore, a risk of development of negative changes was reduced (it is illustrated by the very high percentage in group g, Fig. 1). The later ws consequence of retained splanchnic perfusion pressure in safety limits (Cheatham et al., 2000).

However, the presence of “silent IAH” (Chalkias et al., 2012), would shift down the threshold between normal IAP and IAH (Deenchin, et al., 2013). The rank correlation coefficient: increased IAP/BMI (body mass index), calculated for obese individuals (Schachtrupp et al., 2006), has an average value of 0.76. Experiments have reported (Schein et al., 1995) that the abdominal wall compliance decreased in presence of basal IAH. That would respond to a decreased tolerance to hypertension, and changed stress-relaxation time. Our experiment established such tendency only for the initial stage of induced IAH (1 of 4 groups) – relatively increased lethality of the rats with DIO during the first 30 minutes.

Arterial hypertension, established in rats with DIO, has a significant role in the development of hypoxia and inflammation (Boustany et al., 2004). There were evidences that serum levels of the proinflammatory SAA were moderately increased in DIO rats (Uhlar and Whitehead, 2012), would shift down the threshold between normal IAP and IAH (Deenchin, et al., 2013). The rank correlation coefficient: increased IAP/BMI (body mass index), calculated for obese individuals (Schachtrupp et al., 2006), has an average value of 0.76. Experiments have reported (Schein et al., 1995) that the abdominal wall compliance decreased in presence of basal IAH. That would respond to a decreased tolerance to hypertension, and changed stress-relaxation time. Our experiment established such tendency only for the initial stage of induced IAH (1 of 4 groups) – relatively increased lethality of the rats with DIO during the first 30 minutes.

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REFERENCES


CONCLUSION

On the basis of various findings on the subject applied to our results, we could make the following conclusion: Increased survival is established for DIO rats with artificially induced IAH. There is a reason to believe, that the increased resistance to IAH is due to changes in the structure and in the mechanical characteristics of the abdominal wall, following obesity.

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