

Original Article

Effects of intra-abdominal pressure on adrenal gland function and morphology in rats

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Abstract: Intra-abdominal hypertension and abdominal compartment syndrome (IAH/ACS) are life-threatening conditions and caused by several clinical status. Although there is insufficient data regarding its effects on adrenal glands. This study aimed to identify whether elevated intra-abdominal pressure (IAP) caused any alteration on the morphology and function of adrenal glands in a rat model. Twenty four Sprague-Dawley male rats were included in the study. Animals were allocated into 4 groups. IAP was elevated to 15 mmHg for one hour and four hours in group 2 and 4. Group 1 and 3 were sham groups. Blood samples were taken for the assessment of plasma adrenaline, noradrenaline, and corticosterone levels and adrenalectomies were performed to evaluate apoptosis. Blood adrenaline, noradrenaline and corticosterone levels were significantly higher in the study groups compared with the sham groups. However, there were no significant changes in apoptotic index scores in the study groups as compared to sham groups. These results support that increased IAH leads to discharge of catecholamine and corticosterone from the adrenal glands. Failure to demonstrate similar changes in apoptotic index score may be concluded as apoptosis is not a leading pathway for impairment of adrenal glands during IAH period.

Keywords: Intra-abdominal pressure, intra-abdominal hypertension, adrenal gland, apoptosis, experimental study

Introduction

Our knowledge about intra-abdominal hypertension and abdominal compartment syndrome (IAH/ACS) has progressed rapidly during the last decade and consensus about definitions and management well being established [1]. Intra-abdominal hypertension (IAH) has been shown to adversely affect various organs including cardiac, pulmonary, renal, and gastrointestinal systems. A provoking event, such as sepsis, acute pancreatitis, burns or hemorrhagic shock, leads to a capillary leak syndrome which results in the extravasations of fluid into the interstitial space and massive bowel wall edema [2-5]. This edema increases the Intra-abdominal pressure (IAP) which subsequently leads to multiorgan dysfunction. IAH has also been shown to induce disturbances at the cellular levels mainly because of neutrophil priming.

The pathophysiologic effects of IAH on various organs and systems have been extensively

studied in both animals and humans [5-8]. However, the effect of IAH on the adrenal glands has not been investigated.

Apoptosis is a well known complex process which is activated for clearing dysfunctional or aged cells in physiologic states as well as sepsis or ischemic reperfusion injury in pathologic conditions. We hypothesized that apoptosis could be detected as one of alterations on the morphology of adrenal glands during IAH.

This study aimed to identify whether IAH caused any alteration on the morphology and function of adrenal glands in a rat model.

Materials and methods

Animals

Adult male Sprague-Dawley rats, weighing 350 ± 50 g were used in the study. They were housed individually in the wire cages under standard laboratory conditions. The rats were offered

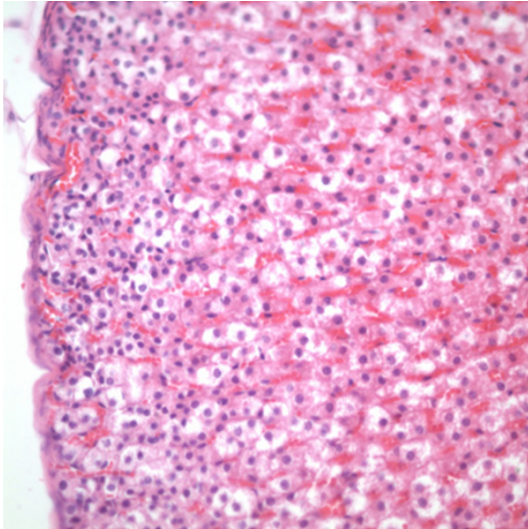


Figure 1. A crosssection of adrenal gland with hematoxylin eosin staining of one of IAH 1 h group rats (HE x 200).

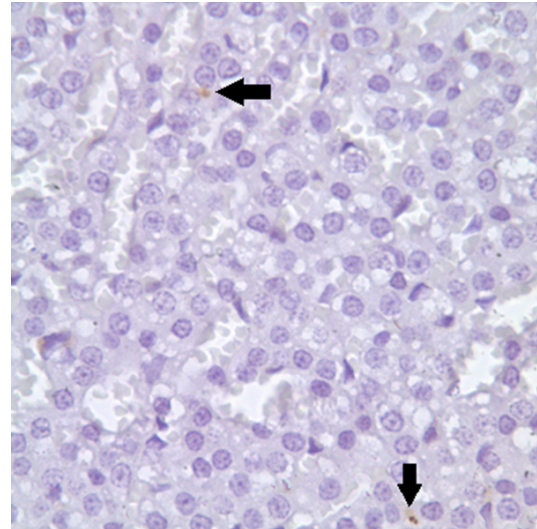


Figure 2. A crosssection of adrenal gland with in situ hybridization staining of one of IAH 1 h group rats. Apoptotic cells are shown with arrows (IHS x 400 apoptotic index score is 3).

food and water ad libitum. No enteral or parenteral antibiotics were administered at any time. All procedures were performed by the same researcher between 08:00 a.m. and 01:00 p.m. to minimize diurnal variation.

Ethical approval

Studies were conducted in accordance with the national guidelines for the use and care of laboratory animals and all procedures were approved by the Hacettepe Institutional Animal Care and Use Committee with by the ethical committee of the Faculty of Medicine of Hacettepe University.

Study groups and experimental protocol

The rats were randomly assigned to four groups (6 animals in each group). Rats in the experimental groups underwent IAH either for 1 hour (IAH 1 h) or for 4 hours (IAH 4 h). Two sets of control rats were anesthetized for either 1 hour or 4 hours (Control 1 h and Control 4 h respectively).

Anesthesia was given intramuscularly using ketamine hydrochloride (Ketalar®; Pfizer, Istanbul, Turkey) (80 mg/kg). After induction of anesthesia rats were placed on a warm pad and a pulse oxymeter (Nellcor OxiMax™, Nellcor, USA) was attached to the lower right extremity to assess peripheral oxygenization. A 20-gauge intravenous cannula (B-CAT2, Bicakcilar, Ank-

ara, Turkey) was inserted into the lower left abdominal quadrant and connected to a 60 ml syringe filled with room air. Simultaneously, the IAP was monitored through a second 20-gauge needle in the right lower abdominal quadrant. In the experimental groups the abdomen was insufflated with room air until an intraperitoneal pressure of 15 mmHg was reached. Intra-abdominal hypertension was maintained at this level throughout the experiment.

The oxygen saturations (SpO₂), heart rates, and IAPs of the animals were monitored (Dash 3000, General Electric Healthcare, USA) continuously throughout the study. At least 30 minutes were allowed for stabilization after instrumentation. Thereafter, baseline readings of oxygen saturations and heart rates were recorded for each animal.

At the end of the experiments, the values of oxygen saturations and heart rates of each animal were recorded again. Later on, blood samples were obtained and adrenal glands removed. The animals were then euthanized by exsanguinations through intracardiac puncture.

Biochemical analysis

Plasma adrenaline and noradrenaline levels were determined by the high pressure liquid chromatography method (Chromsystems Instruments & Chemicals GmbH, Munich, Germany).

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Table 1. Early (baseline) and final heart rate readings of the animals in the groups

Control 1 h			IAH 1 h			Control 4 h			IAH 4 h		
Baseline	Final	Δ	Baseline	Final	Δ	Baseline	Final	Δ	Baseline	Final	Δ
272	204	-68	300	250	-50	300	230	-70	250	137	-113
262	269	7	269	201	-68	252	221	-31	300	272	-28
273	244	-29	260	147	-113	253	208	-45	295	283	-12
286	240	-46	285	242	-43	298	287	-11	300	88	-212
290	237	-53	272	230	-42	261	267	6	300	65	-235
282	300	18	237	180	-57	286	201	-85	300	260	-40
Mean ± SD											
277 ± 10	249 ± 32	-28 ± 34	270 ± 21	208 ± 39	-62 ± 26	275 ± 22	235 ± 34	-39 ± 34	290 ± 20	184 ± 98	-106 ± 97

Δ: the difference between the baseline and final values. $P = 0.0997$ for control groups vs. IAH groups.

Table 2. Early (baseline) and final oxygen saturation readings of the animals in the groups

Control 1 h			IAH 1 h			Control 4 h			IAH 4 h		
Baseline	Final	Δ	Baseline	Final	Δ	Baseline	Final	Δ	Baseline	Final	Δ
86	83	-3	80	50	-30	94	89	-5	91	85	-6
92	91	-1	94	94	0	80	91	11	90	86	-4
89	86	-3	87	76	-11	85	88	3	94	88	-6
89	85	-4	80	84	4	93	86	-7	95	86	-9
86	93	7	79	82	3	91	89	-2	90	50	-40
93	94	1	90	92	2	88	94	6	91	94	3
Mean ± SD											
89 ± 2.9	88 ± 4.5	-0.5 ± 4.0	85 ± 6.0	79 ± 15	-4 ± 13	88 ± 5	89 ± 2	1 ± 6.8	91 ± 2	81 ± 15	-10 ± 14

$P = 0.045$ (control groups vs IAH groups). Δ: the difference between the baseline and final values. $P = 0.045$ for control groups vs IAH groups.

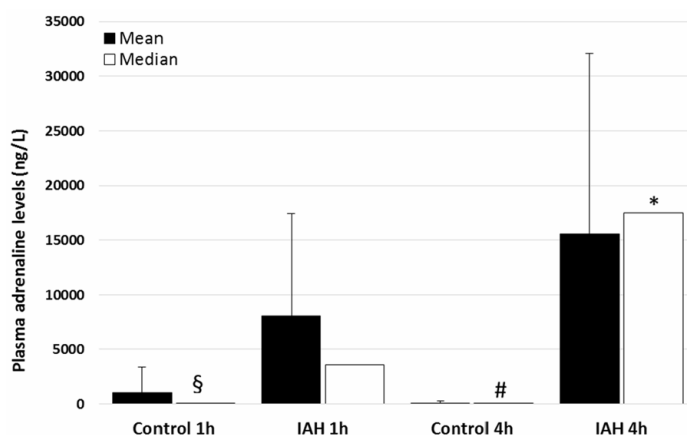


Figure 3. Effects of IAH for 1 hour and IAH for 4 hours on plasma adrenaline levels. § $P = 0.026$ for Control 1 h vs IAH 1 h, # $P = 0.017$ for Control 4 h vs IAH 4 h, * $P = 0.006$ for IAH 1 h vs IAH 4 h.

Plasma corticosterone levels were measured by the radioimmunoassay method (IMMULITE 2000 Immunoassay System, Siemens AG, Munich, Germany).

Histopathologic evaluation

Adrenal glands were promptly fixed in 10% phosphate-buffered formalin and embedded in

paraffin. From the paraffin-embedded tissue blocks, 2.5-μm sections were cut and stained with hematoxylin and eosin (H&E) for light microscopic analysis (**Figure 1**).

Apoptosis was evaluated immunohistochemically using ApopTag® Plus Peroxidase in Situ Apoptosis Detection Kit (Chemicon International, Billerica, MA, USA) as described in the manufacturer's protocol. The staining results were assessed semiquantitatively according to the extent (percentage of positive cells) (graded on a scale of 1-5; 1 = positive cells less than 10%; 2 = positive cells between 10% and 24%; 3 = positive cells between 25% and 49%; 4 = positive cells between 50% and 74%; 5 = positive cells between 75% and 100%) and intensity of staining (graded on a scale of 1-3, 1 = no staining; 2 = mild to moderate staining; 3 = strong staining). The apoptotic index score was then calculated by multiplying the staining extent score by the staining intensity score (**Figure 2**). The periadrenal tissue and adrenal paranchyma were assessed separately. Adrenal gland samples

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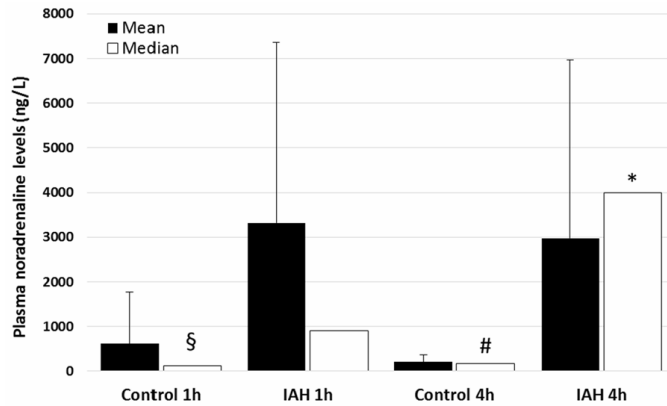


Figure 4. Effects of IAH for 1 hour and IAH for 4 hours on plasma noradrenaline levels. § $P = 0.026$ for Control 1 h vs IAH 1 h, # $P = 0.017$ for Control 4 h vs IAH 4 h, * $P = 0.006$ for IAH 1 h vs IAH 4 h.

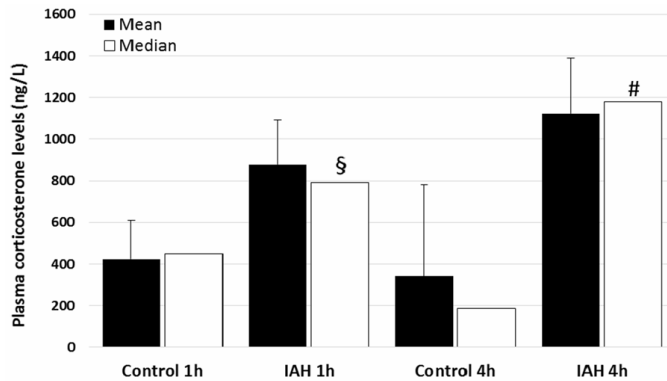


Figure 5. Effects of IAH for 1 hour and IAH for 4 hours on plasma corticosterone levels. § $P = 0.002$ for Control 1 h vs IAH 1 h, # $P = 0.015$ for Control 4 h vs IAH 4 h.

were examined by two pathologists blinded for the identities of the specimens.

Statistical analysis

All data were analyzed using the Statistical Package for the Social Sciences (SPSS) software, version 17.0 (SPSS Inc., Chicago, IL, USA). If not otherwise indicated all values were expressed as mean \pm SD. The Kruskal-Wallis variance analysis was used to determine whether there was any difference between the groups. When the P value from the variance analysis was statistically significant, the Mann-Whitney U multiple comparison test was employed to figure out which group differed from the others. All results were accepted as statistically significant when $P < 0.05$.

In each group, values of the baseline and final readings of oxygen saturations as well as those

values for heart rates were pooled (i.e. mean value for the baseline and the final readings were calculated for each group) for inter-group comparison of cardiorespiratory changes using the Wilcoxon rank test.

Results

Heart rates and peripheral oxygen saturations

Increasing IAP decreased the peripheral oxygen saturations ($P = 0.045$) (Table 1). We did not observe significant changes in the heart rates after application of IAP ($P = 0.0997$) (Table 2).

Plasma adrenaline levels

Application of IAP increased the adrenaline levels. Plasma adrenaline levels were found to be significantly higher in the IAH groups compared with the control groups ($P < 0.001$). Both 1 hour and 4 hours application of IAP increased the plasma adrenaline levels significantly ($P = 0.026$ for group Control 1 h vs. group IAH 1 h, $P = 0.017$ for group Control 4 h vs. group IAH 4 h). Moreover, plasma adrenaline levels in group IAH 4 h (mean: 15586 ± 16520 ng/L, median: 17500 ng/L) were significantly higher than those of group IAH 1 h (mean: 8074.6 ± 9318 ng/L, median: 3590 ng/L) ($P = 0.006$). There was no significant difference in plasma adrenaline levels between group Control 1 h (mean: 1025.8 ± 2371 ng/L, median: 51.4 ng/L) and group Control 4 h (mean: 98.3 ± 176 ng/L, median: 32.1 ng/L) ($P > 0.05$) (Figure 3).

Plasma noradrenaline levels

We found that the IAH resulted in an increase in plasma noradrenaline levels. Plasma noradrenaline levels were significantly higher in the IAH groups compared with the control groups ($p = 0.009$). Both 1 hour and 4 hours application of IAP increased the plasma noradrenaline levels significantly ($P = 0.026$ for group Control 1 h vs. group IAH 1 h, $P = 0.017$ for group Control 4 h vs. group IAH 4 h). Plasma noradrenaline levels in group IAH 4 h (mean: 2974 ± 3995 ng/L, median: 1680 ng/L) were significantly higher than those of group IAH 1 h (mean: $3319.6 \pm$

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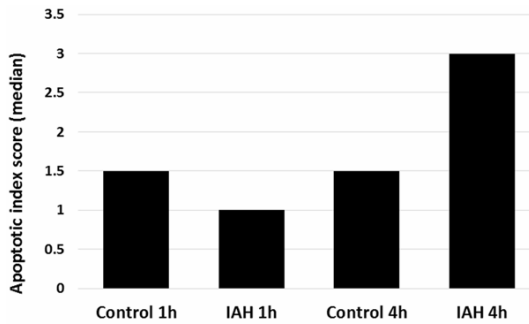


Figure 6. Cell apoptosis in adrenal parenchymal tissue. Values are medians of six animals in each group.

4042.6 ng/L, median: 897 ng/L) ($P = 0.006$). We did not find any difference in plasma noradrenaline levels between group Control 1 h (mean: 611.1 ± 1166.8 ng/L, median: 117.1 ng/L) and group Control 4 h (mean: 206.9 ± 151.8 ng/L, median: 167.5 ng/L) ($P > 0.05$) (Figure 4).

Plasma corticosterone levels

Plasma corticosterone levels were higher in the IAH groups compared with their respective control groups ($P = 0.002$ for the group IAH 1 h vs. group control 1 h, $P = 0.015$ for group IAH 4 h vs. group control 4 h). Corticosterone levels did not differ between the IAH 1 h group (mean: 877 ± 215.6 ng/ml, median: 790 ng/ml) and the IAH 4 h group (mean: 1123.3 ± 265.7 ng/ml, median: 1230 ng/ml). Similarly, there was no significant difference in plasma corticosterone levels between group Control 1 h (mean: 422.6 ± 188.6 ng/ml, median: 450 ng/ml) and group Control 4 h (mean: 341.5 ± 438.1 ng/ml, median: 185 ng/ml) ($P > 0.05$) (Figure 5).

Apoptosis

Apoptotic index scores of adrenal parenchyma tissue were not significantly different in any of the groups ($P = 0.48$) (Figure 6). However, the degree of cell apoptosis in peripheral adrenal tissue was found to be significantly higher in the four-hour groups compared with the one-hour groups ($P < 0.002$) (Figure 7).

Discussion

In the present study, we investigated the effects of IAH on the function and morphology of adrenal glands. The main finding in the study was

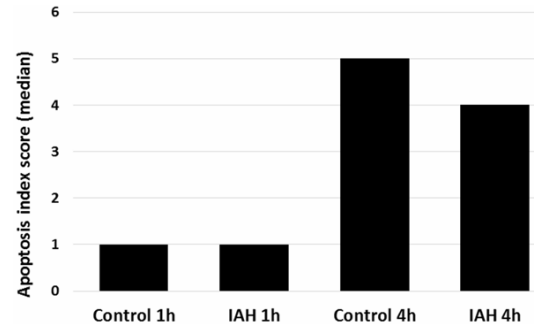


Figure 7. Cell apoptosis in peripheral adrenal tissue. Values are medians of six animals in each group ($P < 0.002$ for four-hour groups vs one-hour groups).

that IAH per se led to an increase in plasma concentrations of catecholamines and corticosterone.

IAH and ACS are life-threatening conditions with a high mortality and morbidity rate and caused by several clinical conditions, such as trauma, intra-abdominal infection, and intestinal obstruction [5, 9-13]. The affinity for and awareness of IAH and ACS is rising due to developments in intensive care, improvements in health technology, and accumulation of scientific knowledge. However, there is inadequate knowledge about IAH and ACS and their effects on the endocrine system, especially the adrenal gland, and studies on this topic are limited. The effects of IAH on the adrenal glands were first presented by Caldwell et al. in 1986. In their study, the IAP of dogs was increased via experiments, and perfusion of the organs was assessed by scintigraphy with no detectable changes in adrenal gland perfusion [14].

Sare et al. assessed tyrosine hydroxylase activity at the adrenal medulla and hypothalamus of rats whose IAP was increased to 15 mmHg by carbon dioxide [15]. Tyrosine hydroxylase is a pacing enzyme occurring with the synthesis of catecholamines and tyrosine. It is found in the brain, heart, chromaffin cells, and sympathetic ganglions. The synthesis of catecholamines has a negative effect on tyrosine hydroxylase. That study detected an increase in tyrosine hydroxylase activity in the hypothalamus and a decrease in the adrenal medulla. These findings were interpreted as a result of hypoperfusion of the adrenal gland or the negative effects of the catecholamines, but the results contrasted with Caldwell et al. [14].

In this study, we have demonstrated increased catecholamine and corticosterone levels in moderate IAP, which supports the findings of previous studies [15-19]. However, histopathologic changes, at least in apoptosis, could not be detected at 15 mmHg pressure. Also, the apoptotic index scores of peripheral tissues increased, for example in vascular and connective tissues, but this is irrelevant since the protocol is also related to the duration of the experiment ($P < 0.001$). Adrenal gland histology is protected with normal architecture, and physiologic responses continue, even with the moderate pressure of 15 mmHg. However, Schachtrupp et al. observed that an IAP of 15 mmHg lasting for 24 hours in a porcine model was found to result in a low-grade, morphologic impairment of the lungs, liver, kidneys, and bowel [6]. IAP was increased at varying levels (6 to 30 mmHg) at durations ranging from 30 minutes to 24 hours, and the organ failure gestation period changed in different models with time periods ranging between 15 minutes to 18 hours [6, 7, 15, 17-26]. Unlike with the liver, kidneys, and intestine, to evaluate histopathologic changes of the adrenal gland, the IAP must be raised to a level of more than 15 mmHg [8, 18, 21, 22].

We have used 15 mmHg pressure value in this study. It is the simulation of our clinical practice. We created an IAH model but not an ACS model. For this reason our findings may be a clue for routine laparoscopic surgery but not for patients under the risk of ACS in ICU. Our results must be interpreted from the point of view of temporarily increased IAP conditions such as routinely performed laparoscopic surgery.

We used room air for elevating the IAP in this model while other research models involving IAH and ACS used solids [25], fluids [17, 26] and various gases [15, 19, 22, 27]. Mikami et al. compared air room, nitric oxide, and carbon dioxide when elevating the IAP to 10 mmHg and 20 mmHg in pigs to investigate the rising catecholamine levels. They detected an increase in these levels in the IAP of the 20 mmHg group, but no relationship between gas type and catecholamine levels was found [19]. On the other hand, another clinical trial presented insufflations with carbon dioxide which caused elevated plasma catecholamine levels [16]. The eventual conclusion was that air room insufflations

are suitable for researching the effects of endocrine in IAH and ACS experimental models.

This study presented an experimental model regarding the effects of IAH on adrenal function on adult male rats. Sex hormones combined with stress hormones are synthesized in similar pathways, for example corticosterone is synthesized from progesterone in female rats [28]. Therefore, using adult male rats is appropriate for showing the effects of IAH on endocrine function as an experimental model.

Applied anesthetic agents should not produce elevated plasma catecholamine levels. We used ketamine HCl for anesthesia. Wang et al. [29] reported that phenobarbital decreases plasma levels of stress hormones, and Hirota et al. [30] reported that barbiturates decrease plasma catecholamine levels via the inhibition of voltage-sensitive Ca^{+2} channel blockage in rats. Another experimental study with rats from the same authors compared barbiturates, ketamine, and propofol as anesthetic agents, and it was shown that ketamine was the only agent which did not change plasma catecholamine levels [31]. As a result, ketamine is the favored anesthetic agent in studies similar to ours.

The effects of increased IAP first appear in the cardiovascular and respiratory systems [32-34]. There has been no significant change in pulse in recent findings, and p values near a significant level ($P = 0.0997$) may be due to the limited sample size.

No consensus exists regarding the standard model to be used for experimentation involving IAH and ACS. Schachtrupp et al. evaluated 27 defined experimental models and remarked that rat models were the most logical choice for biochemical and histologic assessment for explaining the local hemodynamic effects of IAH and ACS [35]. Furthermore, they defined the best model as being "pathological" due to hemodynamic failure via intestinal edema.

Lack of experimental protocols with longer planned hours and higher pressure levels, sample size smallness, besides that could not represent precisely as a pathological model are weakness for this study.

In a conclusion our study with an IAP of 15 mmHg lasting for either one or four hours in rat models, the IAP was found to lead to a decrease

in oxygen saturation and an elevation of plasma catecholamine and corticosterone levels, but no change occurred in the adrenal gland morphology. This rat model is basic and acceptable for evaluating the effects of IAH on the adrenal gland. It remains unclear whether histologic adrenal gland impairment is due to increased IAP. Consequently, new experimental models with prolonged and higher IAP and well-designed, randomized, clinical trials for explaining the effects of IAH and ACS on the endocrine system and adrenal gland are still needed.

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