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Original Contribution

KIDNEY HAEMODYNAMICAL DISORDERS IN ABDOMINAL HYPERTENSION RATS

V. Turiyski[1], A. Tolekova[2*], R. Ardasheva[1], N. Sirakov[3], K. Velkova[3], A. Kristev[1]

[1]Department of Medical Physics and Biophysics, Faculty of Pharmacy, Medical University of Plovdiv, Bulgaria
[2]Department of Physiology, Pathophysiology and Pharmacology, Medical Faculty, Trakia University, Stara Zagora, Bulgaria
[3]Department of Diagnostic Imaging, Medical Faculty, Medical University of Plovdiv, Bulgaria.

ABSTRACT
Purpose: The aim of study is to analyze changes in renal blood circulation in abdominal hypertensive rats. **Methods**: Two groups of anesthetized male Wistar rats were examined: control group and group exposed to artificially elevated abdominal pressure. The later has been achieved by insufflations of air in abdominal cavity. X-ray angiographies of both groups were conducted after introduction of contrast medium. **Results:** The experiments have shown dramatic changes in time-related parameters of renal haemodynamics in abdominal hypertensive rats: appearance of contrast medium in kidney parenchyma before contrasting of heart and impaired synchrony in contrasting of kidneys **Conclusions**: Pneumoperitoneum upsets excretory function of kidneys, thus causing significant haemodynamical disorders. It could lead to further development of improper renal endocrinal and metabolic activity.

Key words: Abdominal hypertension, renal haemodynamics, angiography, rat

INTRODUCTION

The pressure is one of the main physical factors with key significance for the biological functions of higher organisms. Variations in pressure in various body compartments directly affect haemodynamics and, hence, the functionality of all internal organs and systems (1).

A sustained increase of the intra-abdominal pressure over 20-25 mmHg leads to the development of "Abdominal Compartment Syndrome" (ACS). Well known fact is that ACS is the main reason with organ failure development, which was not existing prior to the elevated pressure in one or more organs or systems. In this context it is appropriate to track the changes in some of increased intra-abdominal pressure (IIAP) related target tissues organs and systems at pressures which by definition cause a state of ACS. Such target structure is the renal system.

Renal ischemia promotes activation of the renin-angiotensin-aldosteron system (RAAS). If it lasts long enough, this response progresses in acute tubular necrosis and renal dysfunction. (2, 3).

An appropriate subject for direct evaluation of the changes induced by IIAP is a model, developed on rat. The use of models with experimental animals is a classical approach in attempt to solve such problems, connected with diseases' conditions. The choice of using rats in creation of a model in complex in vivo and in vitro examinations is well argued by the similarities they have with humans in various physiological and anatomical characteristics. A thorough look at the behavioral profile, the genome and other characteristic, brings us the idea of using this species and not other lab animals.

MATERIALS

Animals and anesthetic protocol

Male Wistar rats (totally 36 animals) with body weight in the range 250-320g were provided by the Animal house of Medical University Plovdiv, Bulgaria. Rats were housed in standard laboratory conditions (23-25˚C, 50-55% humidity and 12/12h light/dark cycle) and fed with standard commercial food and given water ad libitum. Two groups were

***Correspondence to:** *A. Tolekova, Department of Physiology, Pathophysiology and Pharmacology, Medical Faculty, Trakia University, Stara Zagora, Bulgaria*

formed: control group– 16 rats for angiography of abdominal and thoracic haemodynamics, model group – 20 rats for angiography of abdominal and thoracic haemodynamics during abdominal hypertension. The experiment was performed according the requirements of both the national legislation and the European Directive 2010/63/EU of 22.09.2010 on the protection of animals used for scientific purposes.

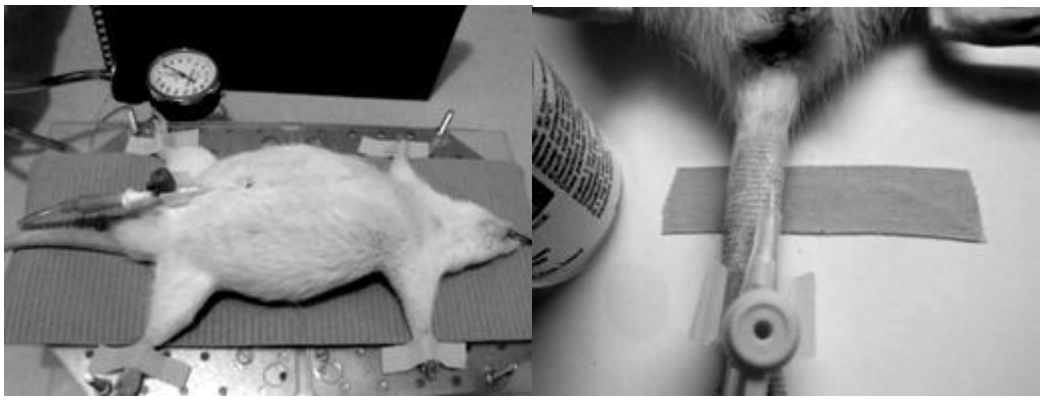
At the beginning of the experiments the animals were anaesthetized by xylazine 2% – 10mg/kg + ketamine (Calipsol) 5% – 100mg/kg, injected intraperitoneally.

METHODS

Artificially induced IAH in rats was performed in following steps:

Percutaneous fixing of venflon was done in order to induce pneumoperitoneum. Intra-abdominal pressure elevated by manual insufflation of room air included: 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 shpygmomanometer. The increased intra-abdominal pressure has been maintained stabile (± 2 mm/Hg) for the period of the experiment.

The anesthetized rats were injected with Omnipaque-iohexol (0.2ml/kg) through venflon (0.7 mm) **(Figure 1.b)** inserted into tail vein preliminarily cleaned by alcohol. Exposures were performed at any 15 seconds in face projection (rats have been fixed "on back" on plastic table **(Figure 1.a)** for period of 10 to 20 minutes. X-ray apparatus Opera T-90 was used with following parameters: 46 kV, 300 mA, 0.12 s, 320 mAS, 640 mS at focus length of 70 cm.



a) b)

Figure 1. a). Intraperitoneally insufflation of air; b). Venflon mounted in tail vein before introduction of contrast medium

In the haemodynamic parameters' analysis, the contrast density was determined quantitatively using the RadiAntDICOM software program in Hounsfield units. The data acquisition and processing for subsequent analysis was carried out with specialized software from the KORELIA family. The User-Oriented Interface (4) and the Process Recognition Module (5) facilitate data processing. KORELIA-Ident offers means for interpolation and graphical visualization of experimental data with a cubic spline (6), as well as computational procedures for evaluation and comparison of process parameters (7).

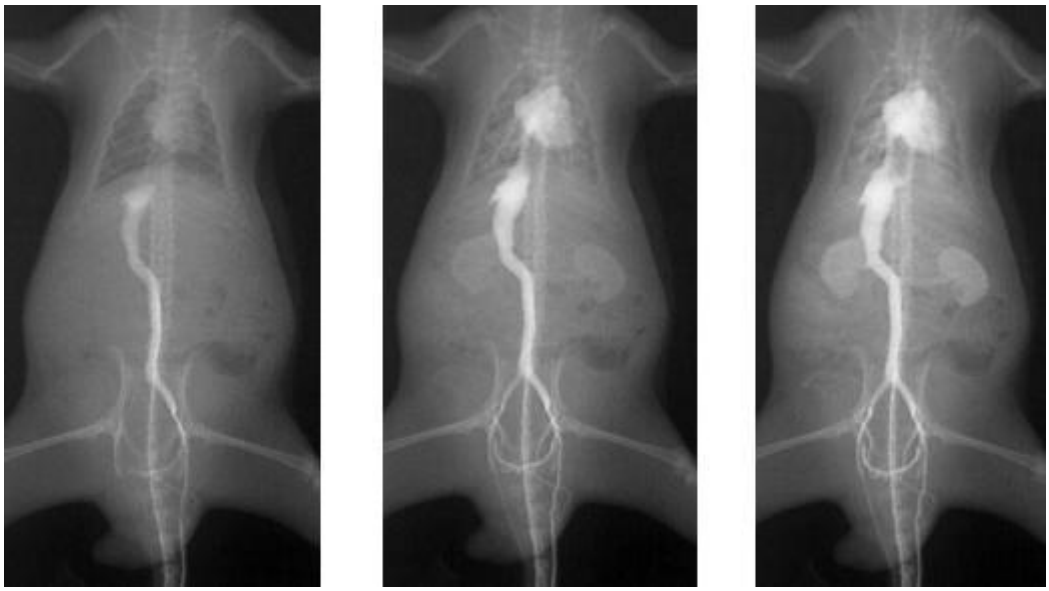
For convenience of data illustrating and comparing, the absorption indicated by the ordinate is in conditional units (RU). When performing zero contrast calculations (0 ordinate level), the radiographic density of the respective tissues was taken before the contrast agent was introduced.

RESULTS

Hemodynamic of rat's kidneys

Control animals

Immediately after contrast injection and up to 15 seconds, in most rats in the group we observed contrasted heart, brain and lung vessels. There is an early nephrographic effect as well as contrast of the parenchyma of abdominal organs. Between the 15th and the 60th second contrased renal venous vessels, renal shadows, saturation of kidney shadows and liver are observed. The first three minutes after the start of the study, intensive contrast of the venous kidney and liver vessels and contrasting of the renal calyx system were observed. Bilateral contrasting ureters and bladder are recorded between 3 and 4 minutes.

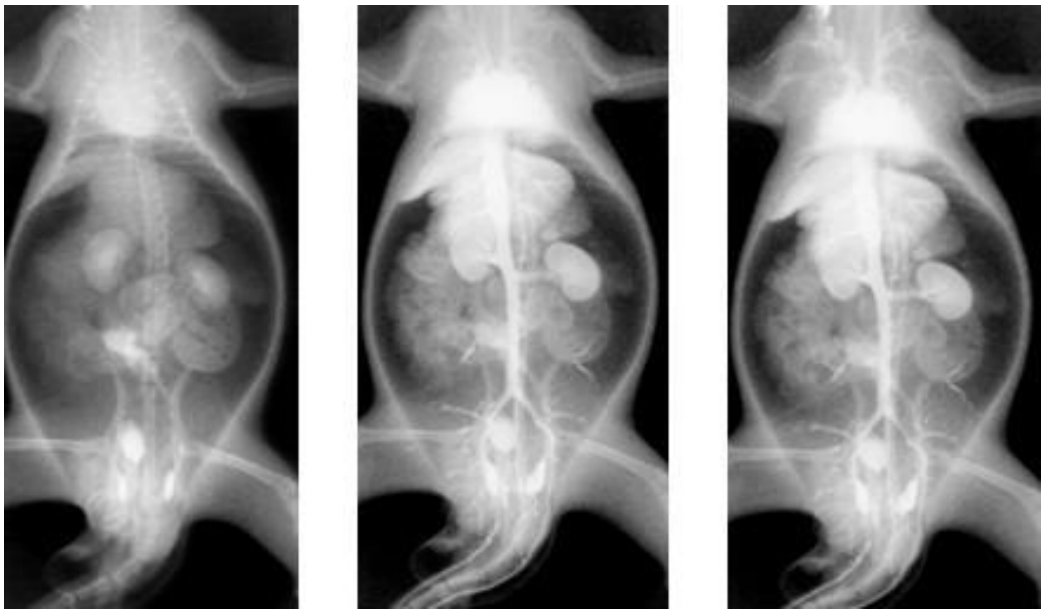


a) **b)** **c)**

Figure 2. a), b), c). Angiography of rat from control group: 5, 15, and 30 sec. after the administration of contrast medium.

Rats with IIAP

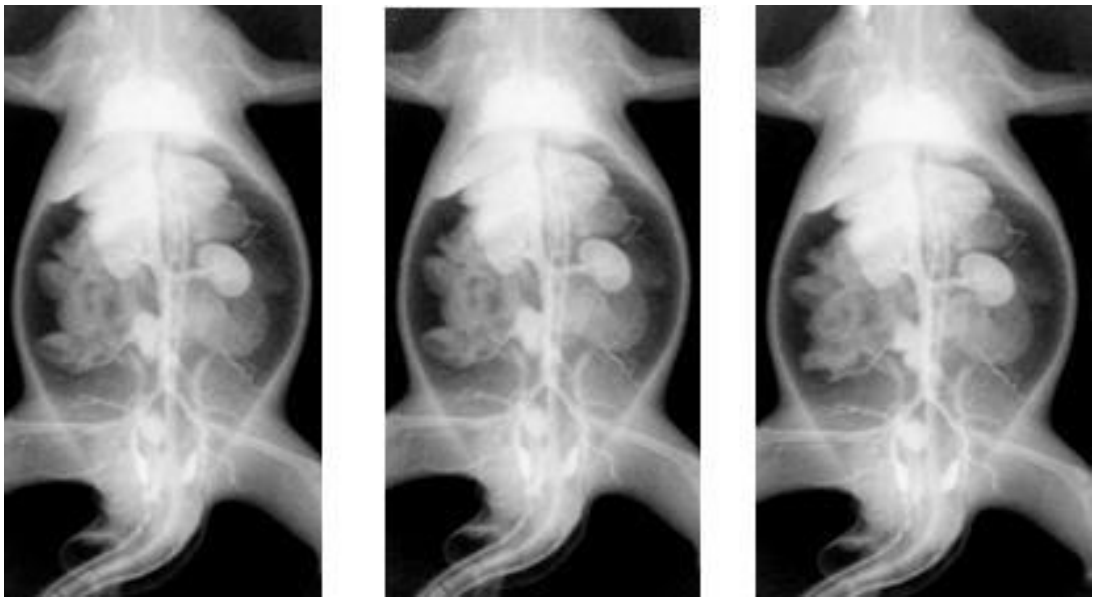
The contrasting of vessels and organs after the administration of contrast media in the tail's vein in rats with IIAC is visualized in discrete time intervals in **Figure 3 a), b) and c)**



a) **b)** **c)**

Figure 3. a),b),c). Angiography of rat with IIAC: 5, 120 and 300 sec after the administration of contrast medium.

Within the 15-th to 60-th second after the injection of the contrast media, most of the experimental animals with IIAC were observed to spread the contrast to the level of the abdominal aorta bifurcation or the heart. From 1-st to 2-nd minutes initial contrasting of heart cavities, cerebral vessels, thoracic and abdominal aorta is registered. Between 2-nd and 3-rd minutes there is a slight nephrographic effect, contrasting of lung vessels and the heart. Low contrast of the thoracic and abdominal aorta is registered. After 3 minutes, an initial nephrographic effect, poorly contrasting thoracic and abdominal aorta, and initial contrasting of the renal veins were observed.



a) b) c)

Figure 4. a), b), c). Angiography of a rat with IIAC -5,10 and 18 min after the administration of contrast media.

Five minutes after administrating the contrast media, thoracic and abdominal aorta, renal and hepatic veins are contrasted. Liver enhancement and contrasting of mesenteric veins are observed. Stomach and intestinal contrasting, as well as initial contrasting of ureters, is visualized after 5 minutes of the CM administration

Graphic images of the curves reflecting the dynamics of contrast density change in control rats are characterized by the presence of two distinct segments. The initial segment (up to 60 seconds) of both kidneys has a very low rate of change in the contrast density, so the curve travel of both kidneys is almost parallel to the x axis. The second segment is characterized by the presence of high amplitude deviations with ascending and descending arms and different maximal amplitude of left and right kidney. The maximal amplitude of left kidney was 21,593 RU at 102.72 seconds. The dynamics of change in contrast density in the right kidney is significantly more pronounced. The maximum reached 51.108 RU at 90.83 second **(Figure 5.a)**.

The contrast density dynamics and the graphical image characteristics show significant differences in the animals with increased intra-abdominal pressure compared to those in the control group. The curves are characterized by two upward arms, each of which is followed by a segment parallel to the x axis. In the left kidney, the upward arm starts at 29.96 seconds and reaches the first local extremal point of 16.615 RU at 46.99 seconds. By 59.74 second the line is almost horizontal on the x axis. Next is the second upward arm with an amplitude of 21,647 RU at 80.32 second. There are no significant differences between the amplitudes of the global extremal point of the left kidneys of control and experimental animals. Differences are observed in the periods of their occurrence. In experimental animals with increased intra-abdominal pressure, the generation of the high amplitude deviation preceded that generated in the control animals **(Figure 5.b).**

The curve dynamics in the right kidney have the same characteristics. Its beginning is at 29.96 sec. The first extremal point is generated at 46.99 sec, but the rate of change and the amplitude reached is significantly higher than that of the left kidney. The horizontal segment has the same duration and the second upward arm is generated at 59.74 second. It reaches a maximal of 39.07 RU at 79.84 second. Notable that the maximal point of experimental animals graphics is the lower than in the control animals. In addition, this curve shows that the extremal point is generated earlier than in the control animals **(Figure 5.b).**

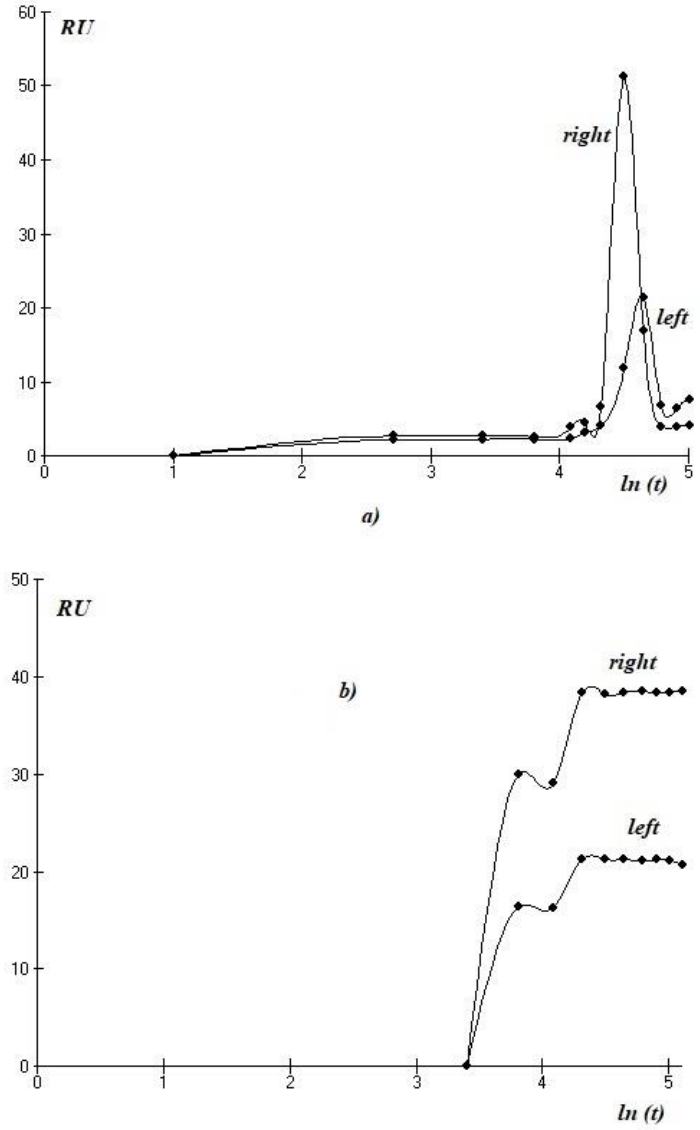


Figure 5. a). b).Dynamic of contrast density changes in kidneys (control group - a, group with experimentally induced pneumoperitoneum-b)). Values on X-axis correspond to log(time), values on Y-axis are depicted as relative units (RU).

DISCUSSION

Elevated intra-abdominal pressure is the basis for significant hemodynamic and urodynamic disturbances that cause renal insufficiency (8). Changes found during our experiment demonstrate the sequence in the occurrence of the violations. Increased intra-abdominal pressure significantly reduces transmural blood pressure in arterial and venous vessels, and delays the fill with contrast of renal parenchyma (9). The disturbance in hemodynamics of the venous circulation is leading. The morphological and functional characteristics of the venous vessels allow increased extravascular pressure (as a result of increased intra-abdominal pressure) to cause vascular collapse of the venous wall. The collapse of vena cava caudalis causes blood flow to stop in the area of pressure and lack of contrast medium in the areas of detection after the initial injection time. Venous filling of the heart is compromised. At the same time, arterial wall characteristics prevent blood flow arrest in the arterial part of the bloodstream, but reduced preload decreases the stroke volume, and pressure on the arterial wall by increased intra-abdominal pressure elevates vascular resistance and reduces renal blood flow and GFR (10). Accumulation of blood before the site of collapse increases the pressure to the degree of overcoming the obstruction and the subsequent partial recovery of the venous blood flow, which is already turbulent in nature. The presence of a high pressure gradient between pre- and post-collapse region explains the high velocity of

venous blood flow at the moment of the breakthrough. Due to the existing constriction, albeit to a lesser extent, blood accumulation occurs again in front of the contraction site and consequently a rise in pressure, which leads to a repeat increase in the velocity of venous blood flow. These changes clearly indicate the primary intravenous circulation disorders with increased intra-abdominal pressure and relative arterial stability over the study period. The filling with contrast of renal parenchyma in animals with EAP is reported to occur earlier than the contrast of the heart as well as earlier than the appearance of renal shadows in control. This clearly shows the change in venous hemodynamics of the kidneys. Blood flow after overcoming the barrier is not only at high speed but also increases locally the pressure (11), which is the cause of an early venous renal shadows. Opposite, in control animals the contrast of the kidneys is due to the normal convection of contrast with arterial blood through a renal artery. Noteworthy is also the higher contrast density, which is expressed in higher amplitude deviations of the right kidney graphs in both control and experimental animals. This could be explained with different morphometric parameters of the vascular bed and the mass of the two kidneys (12).

In conclusion, pneumoperitoneum may impair the excretory function of the kidneys, causing significant haemodynamic disturbances which will subsequently lead to endocrine and metabolic disorders.

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