

## PATHOMORPHOLOGY OF ADAPTIVE CHANGES IN THE REMAINING KIDNEY IN THE EARLY POSTOPERATIVE PERIOD AFTER NEPHRECTOMY

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🌀 **Objective.** To study the adaptive capacity of a single remaining kidney in the early postoperative period of nephrectomy in an experiment. **Materials and methods.** The experiment involved 35 laboratory white rats, which were divided into three experimental groups. Group 1 ( $n = 5$ ) intact animals, group 2 ( $n = 15$ ) animals underwent nephrectomy on the left; group 3 ( $n = 15$ ) animals underwent nephrectomy and additionally were created 90 minute hypoxic hypoxia. Histological material was collected on the 5<sup>th</sup>, 21<sup>st</sup> and 60<sup>th</sup> days after surgery. **Results.** Characteristic morphological changes in the only remaining kidney were an increase in the size of the glomeruli and a decrease in their number. Nephron fibrosis was detected, accompanied by increased production of antigens by the tubular epithelium, which is likely a response to a cascade increase in oxidative stress and increased release of cytokines that stimulate the production of intrarenal collagen. **Conclusion.** Nephrectomy and hypoxia are provocateurs for the development of systemic distress syndrome, the result of which is the formation of a “vicious pathogenetic circle”, which reduces the functionality of the renal tissue. This can be considered as one of the early preclinical mechanisms for the initiation of single kidney disease in the future.

🌀 **Keywords:** nephrectomy; single kidney; hypoxia; adaptation.

## ПАТОМОРФОЛОГИЯ АДАПТАЦИОННЫХ ИЗМЕНЕНИЙ В ОСТАВШЕЙСЯ ПОЧКЕ В РАННЕМ ПОСЛЕОПЕРАЦИОННОМ ПЕРИОДЕ ПОСЛЕ НЕФРЭКТОМИИ

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🌀 **Цель исследования.** Изучение адаптационных возможностей единственной оставшейся почки в раннем послеоперационном периоде после нефрэктомии в эксперименте. **Материалы и методы.** В эксперименте участвовало 35 лабораторных белых крыс, которые были разделены на три экспериментальные группы. Группа 1 ( $n = 5$ ) — интактные животные; группа 2 ( $n = 15$ ) — крысы, которым выполняли нефрэктомию слева; группа 3 ( $n = 15$ ) — крысы, которым выполняли нефрэктомию слева и дополнительно создавали 90-минутную гипоксическую гипоксию. Забор гистологического материала производили на 5, 21 и 60-е сутки после операции. **Результаты.** Характерными морфологическими изменениями в единственной оставшейся почке были увеличение размеров клубочков и уменьшение их количества. Выявлен фиброз нефронов, сопровождающийся повышенной выработкой антигенов эпителием канальцев, которая, вероятно, является ответом на каскадное усиление окислительного стресса и повышенное высвобождение цитокинов, стимулирующих выработку интра-ренального коллагена. **Выводы.** Нефрэктомия и гипоксия — провокаторы развития системного дистресс-синдрома, в результате которого формируется «порочный патогенетический круг», снижающий функциональные возможности почечной ткани. Это может рассматриваться как один из ранних доклинических механизмов инициации заболеваний единственной почки в будущем.

🌀 **Ключевые слова:** нефрэктомия; единственная почка; гипоксия; адаптация.

## INTRODUCTION

The first successful human nephrectomy was performed by Gustav Simon in 1869. Currently, the main indications for the kidney removal are tumors and traumatic injuries. Since the end of the nineteenth century, the restoration timing and mechanisms for a solitary kidney function after the removal of the other kidney as well as the nature of adaptation processes and the quality and longevity of the patients' lives with a solitary kidney have been well studied. According to the available data, in the first few h after nephrectomy, an intense venous congestion of the renal parenchyma occurs, which is extremely similar to acute inflammation. This event is immediately followed by leukocyte infiltration of the interstitium and vascular dilatation. After 72 h of nephrectomy, the tubular epithelium enlarges, and intense mitotic division occurs, which practically covers the tubular lumen. After 4–10 days of the surgery, the hyperemia gets resolved, but the glomeruli and tubules with the surrounding large epithelial cells remain abnormally dilated in some places. During the course of morphological studies, the dependence on the rate and degree of compensatory renal hypertrophy on the patient's age was demonstrated, as in patients aged <30 years, and a significant acceleration in renal hypertrophy was registered radiographically after 1 month of nephrectomy. In terms of the functional capabilities, a solitary kidney in a 30-year-old patient corresponds to the functioning of 2 kidneys in a person aged >60 years. The function of the tubules of a healthy solitary kidney reaches the normal level within a short period of time after nephrectomy irrespective of the degree of anatomical hypertrophy; however, its complete recovery occurs much later relative to the time required to eliminate anatomical disorders of the renal tissues. Renomegaly in patients aged >50 years is barely noticeable even after a year of nephrectomy [1–3]. The glomerular filtration function of the remaining solitary kidney also deteriorates with age. Schlichter et al. [4] indicated a proportional relationship between the functioning of the remaining kidney with age. The reserve capacity of the kidney depends on the number of hibernating nephrons. In a solitary kidney, after contralateral nephrectomy, no new glomeruli and tubules are formed, rather hypertrophy of the functioning nephrons occur. Despite this, regardless of the patient's age and the time elapsed since the sur-

gery, the functional capacity of the solitary kidney generally reduces [5, 6]. At the same time, it is the volume of the functioning parenchyma (glomeruli and tubules of the kidney) that predetermines the level of filtration in the kidneys, which is considered by several researchers as the key predictor of functional disorders in the kidney during the postoperative period irrespective of the duration of the disorder of the direct renal blood supply during surgery [7–10]. The lack of complete recovery of the filtration capacity of a solitary kidney predetermines potential high frequency (of up to 87%) of kidney diseases in the future, which develops in the presence of an annual progressive loss of glomerular filtration of approximately 2% within 1–7 years and by >5%/year after the period of  $\geq 7$  years of nephrectomy [11, 12]. A decrease in the functional capacity of the only remaining kidney is generally accompanied by a decrease in the general adaptive capacity of the person [13].

*The present study aimed to investigate the adaptive capabilities of a solitary kidney during the early postoperative period after nephrectomy.*

## MATERIALS AND METHODS

The present experiment involved 35 laboratory white rats categorized into 3 groups. Group 1 ( $n = 5$ ) included intact animals; group 2 ( $n = 15$ ) included rats that underwent left nephrectomy; and group 3 ( $n = 15$ ) included rats that underwent nephrectomy and an additional 90-min hypoxic hypoxia. The pathomorphological experimental study was performed for duration of 60 d. The sampling of histological material was performed on the day 5, 21, and 60 of the study. The structural components of the nephron along its entire length were the subject of the targeted study. The amount and average size of renal glomeruli were determined, and the integrity and structure of the glomerular basement membranes were assessed. In addition, the severity of sclerotic changes in glomeruli, the degree of renal vascular endothelial change in response to injury, proliferative activity depending on the experiment stage, the degree of damage to the epithelium of the proximal and distal tubules, the integrity of the basement membranes, and the severity of inflammatory infiltration were also assessed. The sample preparations were stained with hematoxylin and eosin, followed by that with Masson's trichrome for histochemical analysis (for the identification of

the connective tissue component and the degree of maturity of collagen fibers) and periodic acid-Schiff (PAS; for the assessment of the structure of basement membranes and vascular wall). The vascular endothelium and the epithelium of the renal tubules are primarily the most sensitive areas to the toxic effects and hypoxia. The degree of damage to the vascular wall, such as swelling, endothelial edema, and dissociation of its elements, was assessed by the level and intensity of podoplanin and the CD34 expression on the endothelium of lymphatic and blood vessels, respectively. To identify and determine the line of differentiation of the inflammatory infiltrate elements, immunohistochemical examinations with monoclonal antibodies to CD3 (T-line of differentiation) and CD20 (B-line of differentiation) were performed. The level of proliferative activity in response to the damage was assessed by reactions with Ki-67 based on the count of cells with a positive nuclear expression per 100 elements of a similar morphological series. To visualize the preservation and changeability in the epithelium of the renal tubules, a reaction with panCK (AE1/AE3) was performed.

## RESULTS AND DISCUSSION

The average size of the rat kidney in group 1 was 1.5 cm longitudinally and 1.0 cm transversely. The structure of the renal tissues was clearly traced. The glomeruli were located in the cortex. In a field of view of 1 mm<sup>2</sup> area, the number of glomeruli ranged from 8 to 13 (average: 10.6). The size of the glomeruli/100 pieces was 57.0–108.6 μ (average: 75.6 μ). The glomeruli showed the correct histological structure. PAS-positive basement membranes of the capsule were non-split and unilamellar. The capillaries (CD34<sup>+</sup>) were plentiful and formed a dense network. No signs of mesangium proliferation were noted. The epithelium of the proximal and distal tubules was unilamellar, without any signs of metabolic damage. The organization of chromatin in the nuclei and cytoplasm was homogeneous without any signs of necrobiotic changes. The basal membranes of the tubules were closed and thin throughout. Both the types of tubules were tightly adjacent to each other and the distance between them did not increase. The lumen of the tubules was empty or slit-like, with no inclusions. Both the types of tubules expressed panCK, with a more intense proximal response. No fibrosis of the nephrons was detected on staining with Masson's trichrome. Inflammatory infiltration

was not significant; 1–2 lymphocytes (CD3/CD20) were visualized in the section without epithelial tropism. The arterioles (CD34<sup>+</sup>) showed no signs of endothelial proliferation, and the wall was neither hyalinized nor sclerosed (Fig. 1).

On the day 5 after nephrectomy in group 2, the size of the kidneys was 1.6–1.7 cm longitudinally and 1.0–1.1 cm transversely. In one field of view of 1 mm<sup>2</sup> area, the number of glomeruli ranged from 7 to 12 (average: 9.2). The size of the glomeruli per 100 pieces was 50.6–128.6 μ (average: 78.8 μ). In other terms, the histological structure and the results of histochemical staining and immunohistochemical examination were found to be similar to those of the intact kidneys of the group 1 rats.

In group 3 rats, the size of the kidneys was 1.7–1.8 cm longitudinally and 1.1 cm transversely. In one field of view of 1 mm<sup>2</sup> area, the number of glomeruli ranged from 7 to 10 (average: 8.5). The size of the glomeruli per 100 pieces was 63.5–107.7 μ (average: 94.2 μ). Thus, there was a tendency toward decrease in the glomerular density and an increase in size. The decrease in the number of glomeruli can be attributed to moderate edema of the interstitium with dilated arteriolar lumen. The latter were characterized by scarcely swollen CD34-positive endothelium and insignificantly thickened walls. The glomeruli were plentiful, with no signs of the mesangium proliferation. The basement membranes both in the glomeruli and in the tubules of both the types were intact throughout. The distal tubule epithelium showed a tendency to increase the volume of the cytoplasm, and its apical vacuolization was noted. No signs of condensation in the cytoplasm and chromatin in the nuclei were noted. The lumen of the proximal tubules was dilated, and their epithelium was flattened. Some of the proximal tubules were elongated and compressed due to edema. No inclusions were visualized in the lumen of the tubules. The epithelium was panCK-positive with displacement in the intensity of the reaction toward the proximal region. No distinct inflammatory infiltration was noted. The proliferative activity was increased in the zone of collector tubule formation to approximately 15% (Fig. 2).

On the day 21 after nephrectomy in group 2 rats, the size of the kidney was 1.8 cm longitudinally and 1.3 cm transversely. In one field of view of 1 mm<sup>2</sup> area, the number of glomeruli ranged from 4 to 7 (average: 5.2). The size of the glomeruli per 100 pieces

was 54.8–119.0  $\mu$  (average: 93.9  $\mu$ ). As compared with that on day 5, significant changes were noted only in an increase in the size of glomeruli and a decrease in their numbers per section of the surface area. Damage to the epithelial cells in the tubules was marked in the distal sections in the form of vacuolization with condensation of the cytoplasm focal. These changes were supported by the decreased immunoreactivity of the epithelium to panCK in comparison to that of the epithelium of the proximal tubules, where the reaction was vivid and intense. No necrotic changes were noted. Inflammatory infiltration due to CD3<sup>+</sup> solitary lymphocytes in the interstitium showed no tendency to epithelial tropism. In addition, there were no signs of vascular endothelial proliferation (CD34). The basement membranes of both the glomeruli and the tubules were intact along the entire length and throughout the entire section area. The proliferative activity was approximately 20% in the collecting system of the kidneys (Fig. 3).

In the group 3 rats, the size of the kidneys averaged 2.1 cm longitudinally and 1.3 cm transversely. In one field of view of 1 mm<sup>2</sup> area, the number of glomeruli ranged from 5 to 8 (average: 6.5). The sizes of the glomeruli per 100 pieces were 72.5–115.1  $\mu$  (average: 93.4  $\mu$ ). No structural changes in the kidney tissues were noted in comparison to that on day 5. A plethora of interstitial capillaries without any signs of dystrophic changes in their endothelium was recorded. Focal perivascular (around the arterioles) and periglomerular fragile fibrosis, as visualized by Masson's trichrome staining, was registered in the individual fields of vision (Fig. 4).

After 60 d of nephrectomy in the group 2 rats, the longitudinal dimension of the only remaining kidney was 2.0–2.1 cm, while the transverse dimension was 1.3 cm. In one field of view of 1 mm<sup>2</sup> area, the number of glomeruli ranged from 6 to 8 (average: 6.9). The size of the glomeruli per 100 pieces was 55.13–122.7  $\mu$  (average: 86.73  $\mu$ ) (Fig. 5).

The morphological characteristics of the glomeruli remained unaltered, considering that the capillary network was abundant, without any signs of the mesangium proliferation; and the basement membranes were single-circuit. Fibrosis and sclerosis were unmarked. In the tubular system, the changes were distinct only in the epithelium of the proximal tubules, in comparison with those on day 5 and 21. The changes included dilated lumen, high epithelium, and increased cytoplasmic volume. The epi-

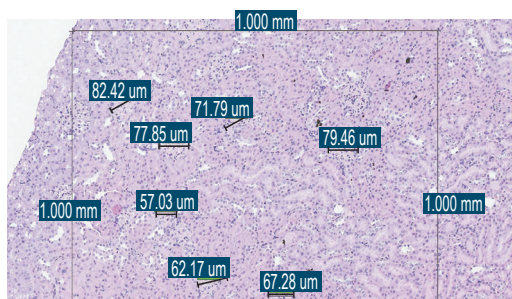
thelial cells develop a shape ranging from cubic to nail-head (that imparts the epithelium a cobblestone appearance). Sinusoids and arterioles are plethoric. The endothelium was intact. Reactivity toward panCK was reduced in both the distal and proximal tubule epithelium. In the distal tubules, the reaction was weak and focal, while, in the proximal tubules, it was diffuse in all structures, with the intensity less pronounced in comparison to that on day 21 of the experiment. The proliferative activity at this stage was noted in all single elements of the epithelium of the distal tubules. Non-specific binding was achieved on the proximal tubular epithelium.

In the group 3 rats, on day 60 after nephrectomy, the longitudinal dimension of the remaining kidney was 2.1–2.2 cm, while the transverse dimension was 1.4–1.5 cm. In one field of view of 1 mm<sup>2</sup> area, the number of glomeruli was 2–9 (average: 5.3). The sizes of the glomeruli per 100 pieces were 63.9–126.2  $\mu$  (average: 97.9  $\mu$ ). The morphological characteristics and immunophenotype were similar to those on day 21 of the experiment (Fig. 6).

Our study results revealed that the characteristic morphological changes in the only remaining kidney were an increase in the size of the kidney glomeruli and a decrease in their numbers. These changes tend to increase over a period of time after nephrectomy. In case of deficiency in the amount and quality of glomeruli, intrarenal nephron fibrosis can develop. In fact, the latter causes an impairment of the renal tissue architectonics and is often accompanied by an increase in the production of antigens by the epithelium of the tubules in response to a cascading increase in the oxidative stress and an increased release of cytokines (particularly, in the transforming fibroblast growth factor) that stimulate the production of intrarenal collagen. These changes were most pronounced in the group 3 rats, which, under the unfavorable conditions of systemic distress syndrome, were induced by nephrectomy and hypoxia. Thus, a “vicious pathogenetic circle” is developed that can be considered as one of the early preclinical mechanisms of initiation of potential diseases of the solitary kidney in the future.

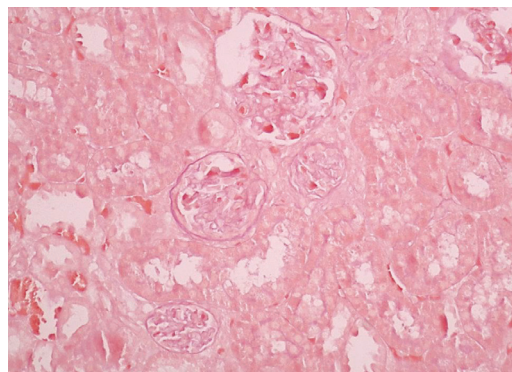
## CONCLUSIONS

Nephrectomy and hypoxia induce changes in the remaining kidney after nephrectomy, which increases the risk of a decrease in the functionality of the renal tissues that are manifested by several characteristic morphological signs. These changes can be



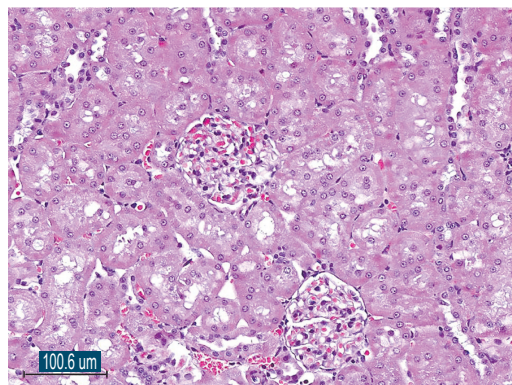
**Fig. 1.** The histological structure of the tissue of a single kidney and the size of the glomeruli of the intact rat (1<sup>st</sup> group). Hematoxylin-eosin,  $\times 200$

**Рис. 1.** Гистологическая структура ткани и размер гломерул единственной почки интактной крысы (1-я группа). Окраска гематоксилином и эозином,  $\times 200$



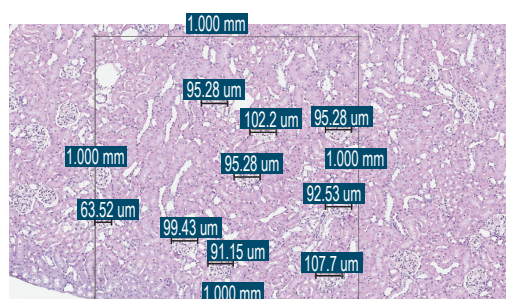
**Fig. 3.** Histochemical examination of the kidney of the rat of the 2<sup>nd</sup> group, the 21<sup>st</sup> day of the experiment. PAS reaction,  $\times 200$

**Рис. 3.** Гистохимическое исследование почки крысы 2-й группы, 21-е сутки эксперимента. PAS-реакция,  $\times 200$



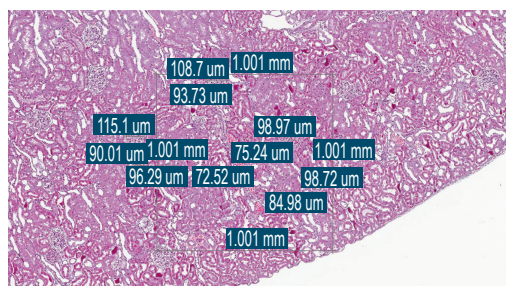
**Fig. 5.** The histological structure of the tissue of a single kidney and the size of the glomeruli of the rat of the 2<sup>nd</sup> group, on the 60<sup>th</sup> day of the experiment. Hematoxylin-eosin,  $\times 100$

**Рис. 5.** Гистологическая структура ткани и размер гломерул единственной почки крысы из 2-й группы, 60-е сутки эксперимента. Окраска гематоксилином и эозином,  $\times 100$



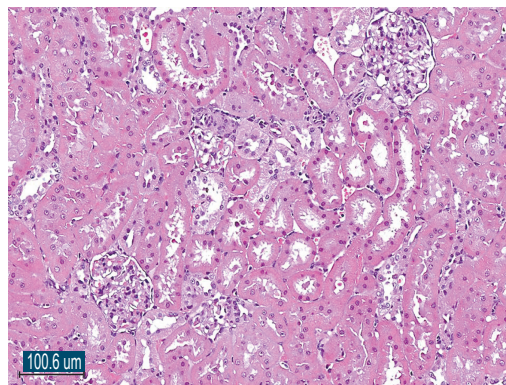
**Fig. 2.** The histological structure of the tissue of a single kidney and the size of the glomeruli of the rat of the 3<sup>rd</sup> group, on the 5<sup>th</sup> day of the experiment. Hematoxylin-eosin,  $\times 200$

**Рис. 2.** Гистологическая структура ткани и размер гломерул единственной почки крысы 3-й группы, 5-е сутки эксперимента. Окраска гематоксилином и эозином,  $\times 200$



**Fig. 4.** The histological structure of the tissue of a single kidney and the size of the glomeruli of the rat of the 3<sup>rd</sup> group, on the 21<sup>st</sup> day of the experiment. Hematoxylin-eosin,  $\times 200$

**Рис. 4.** Гистологическая структура ткани и размер гломерул единственной почки крысы 3-й группы, 21-е сутки эксперимента. Окраска гематоксилином и эозином,  $\times 200$



**Fig. 6.** The histological structure of the tissue of a single kidney and the size of the glomeruli of the rat of the 3<sup>rd</sup> group, on the 60<sup>th</sup> day of the experiment. Hematoxylin-eosin,  $\times 100$

**Рис. 6.** Гистологическая структура ткани и размер гломерул единственной почки крысы из 3-й группы, 60-е сутки эксперимента. Окраска гематоксилином и эозином,  $\times 100$

considered as one of the early preclinical mechanisms indicating initiation of potential diseases of the solitary kidney in the future.

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