

ADAPTATION DISORDERS CAUSED BY NEPHRECTOMY

© I.S. Shormanov¹, M.S. Los², M.V. Kosenko¹

¹ Yaroslavl State Medical University of the Ministry of Healthcare of the Russian Federation, Yaroslavl, Russia;

² Regional Clinical Hospital, Yaroslavl, Russia

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Currently, nephrectomy is performed for various diseases, and the number of this type of surgery does not have a clear tendency to decrease. Operational stress is accompanied by a triggering mechanism for a wide range of disorders, among which psycho-emotional and vegetative (vascular) reactions are important clinical markers. The study of the systemic adaptive reactivity of the body after nephrectomy will provide an integrated approach to the study of the problem of the postoperative period and the rehabilitation of the patient in clinical practice. **Objective:** to identify the effect of nephrectomy on the overall adaptive response of animals when white rats are exposed to damaging physical loads (acute hyperthermia) and chemical (acute alcohol poisoning, nephrotoxic agents) of nature, normobaric hypoxia, limiting muscular loads and immobilization stress. **The results** of the experiment showed that laboratory animals with a single kidney become more sensitive (1.5 times) to nephrotoxic agents. Analysis of the effect of nephrectomy on the overall adaptive response of animals under the influence of various damaging factors to reduce the body's resistance to hypoxia by 20% ($p > 0.05$); to limit muscular loads – by 25% ($p > 0.05$); hyperthermia – by 25% ($p < 0.05$); chemical agents – by one third ($p < 0.05$); to immobilization stress – by 28% ($p < 0.05$). **Conclusion.** The study demonstrated a significant negative impact of nephrectomy on the overall adaptive capacity of the body and allowed to clarify the functional characteristics of the general adaptation disorders in connection with this operation.

Keywords: nephrectomy; postoperative stress; adaptation.

РАССТРОЙСТВА АДАПТАЦИИ, ВЫЗВАННЫЕ НЕФРЭКТОМИЕЙ

© И.С. Шорманов¹, М.С. Лось², М.В. Косенко¹

¹ ФГБОУ ВО «Ярославский государственный медицинский университет» Минздрава России, Ярославль;

² ГБУЗ Ярославской области «Областная клиническая больница», Ярославль

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В настоящее время нефрэктомию выполняют по поводу различных заболеваний, а количество данного вида операций не имеет четкой тенденции к уменьшению. Операционный стресс запускает большой спектр нарушений, среди которых важными клиническими маркерами являются психоэмоциональные и вегетативные (сосудистые) реакции. Изучение системной адаптационной реактивности организма после нефрэктомии позволяет обеспечить комплексный подход к изучению проблемы послеоперационного периода и реабилитации пациента. **Цель исследования** — выявить влияние нефрэктомии на общую адаптивную реакцию животных при воздействии повреждающих нагрузок физической (острая гипертермия) и химической (острое алкогольное отравление, нефротоксические агенты) природы, нормобарической гипоксии, предельных мышечных нагрузок и иммобилизационного стресса. **Результаты.** Эксперименты показали, что белые крысы с единственной почкой в 1,5 раза более чувствительны к нефротоксическим агентам. В результате анализа влияния нефрэктомии на общую адаптивную реакцию животных было установлено, что под воздействием различных повреждающих факторов сопротивляемость организма к гипоксии снижается на 20 % ($p > 0,05$); к предельным мышечным нагрузкам — на 25 % ($p > 0,05$); к гипертермии — на 25 % ($p < 0,05$); к химическим агентам — на треть ($p < 0,05$); к иммобилизационному стрессу — на 28 % ($p < 0,05$). **Вывод.** Исследование продемонстрировало достоверное негативное влияние нефрэктомии на общую адаптационную способность организма и позволило уточнить функциональные характеристики общих адаптационных нарушений в связи с этой операцией.

Ключевые слова: нефрэктомия; послеоперационный стресс; адаптация.

INTRODUCTION

Currently, nephrectomy is performed for the treatment of various diseases. There is no clear tendency of decrease in the number of this surgery. Total kidney removal is more common in patients with severe co-morbidities; however, this procedure increased the risk of perioperative complications that compromise the quality of life [1, 2]. Recent studies have focused on surgical stress as a factor that triggers a cascade of cellular-molecular adaptation mechanisms that affect the long-term surgical treatment in these patients [3, 4]. A significant hormonal-mediator imbalance is proved to develop both in the systemic circulation and in the remaining kidney during the first week following nephrectomy. Vasoconstrictive reactions increase, adversely affects the blood flow volume in a single kidney and also worsens its microcirculation along with kidney's trophic and reparative capabilities as well as the ability of postoperative repair of the heart and central nervous system [5]. With oxidative stress and an imbalance of biogenic amines, severe autonomic reactions develop immediately after nephrectomy, leading to vascular dystonia, cardiovascular system dysfunction, and hemodynamic instability that should be considered stress-induced disorders of the adaptive response [6, 7]. Acute surgical stress causes significant restructuring of pituitary gland function that is manifested as a disturbance in the synthesis and secretion of adrenocorticotropin, insulin, prolactin, gonadotropins, and sex steroid hormones. These mechanisms can underlie the activation of the renin-angiotensin system in the ischemic kidney and trigger the pathological mechanisms of arterial hypertension and circulatory vascular disorders in the kidney [8–10]. After nephrectomy, the level of urea, total cholesterol, and triglycerides in the blood rises sharply on postoperative day one, resulting in the development of atherosclerotic changes in the aortic arch and the descending aorta. A histological examination of the aorta after nephrectomy revealed an increase in the expression of the nitrotyrosine and collagen gene with no change in the degree of macrophage infiltration, resulting in worsening of the clinical course of vascular diseases in laboratory models of atherosclerosis [11].

According to clinical studies, on the fifth day after open nephrectomy, the level of α 1-anti-trypsin (an oxidative stress marker) significantly increases in the blood, and up to postoperative day 8, a compromised immune status is observed [12]. In addition, during the first 48 h after nephrectomy, a pronounced cascade

release of interleukins (IL-6 and IL-10) is maintained; their blood levels correlate significantly with the severity of surgical stress and can be considered as a biochemical marker. Do to the presence of such cytokine aggression, aseptic inflammation associated with the activation of cyclooxygenase 2 rapidly develops in the kidney tissue [13]. At the same time, urinary excretion of lysosomal enzymes (lysosomal exoglycosidase and its isoform, α -fucosidase, β -galactosidase, α -mannosidase, and β -glucuronidase) increases and is considered as a marker of tubular dysfunction of a remaining kidney [14, 15]. Concurrently, the activity of superoxide dismutase and catalase is significantly reduced in the remaining kidney, and the activity of glutathione peroxidase is increased, indicating abnormal functioning of the antioxidant organ adaptation system [16].

Experimental data indicate that stress-induced disorders associated with nephrectomy can subsequently negatively affect both the psychoemotional and cognitive functions of the patients [17, 18]. S. Degaspari et al. (2015) revealed an increased expression level of the regulatory nuclear protein NF- κ B, a high level of tumor necrosis factor α , and a low level of the expression of the KLOTHO "youth gene" in the hippocampus and frontal cortex with increased secretion of glucocorticoids by the adrenal glands after the removal of 5/6th of the kidney. The authors interpreted these findings as signs of neuroinflammation with insufficient renal function that can lead to cognitive impairments [17].

Thus, surgical stress is accompanied by a spectrum of homeostasis disorders, among which, psychoemotional and autonomic (vascular) reactions are important clinical markers of its severity. A study of the systemic adaptive response of the body after a nephrectomy will provide an integrated approach to the study of the challenges arising during the postoperative period and patient rehabilitation in clinical practice.

We aimed to investigate the effect of nephrectomy on the general adaptive response to damaging stress induced by physical (acute hyperthermia) and chemical (acute alcohol poisoning, nephrotoxic agents) factors, normobaric hypoxia, maximum tolerable muscle loads, and immobilization stress.

MATERIAL AND METHODS

Outbred male white rats weighing 160–180 g were used. The weight of the animals in one group varied within \pm 5–10 g. The study was in compliance with The International Guiding Principles for Biomedical Research Involving Animals.

All the animals were divided into 2 groups. Group 1 underwent no surgical manipulations. Group 2 underwent left-sided nephrectomy. The operation was performed under general anesthesia using intraperitoneal administration of a Diprivan solution at a dose calculated using the weight of the animal. In order to analyze the effect of nephrectomy on the general adaptive response of animals to damaging stress induced by physical (acute hyperthermia) and chemical (acute alcohol poisoning, nephrotoxic agents) factors, normobaric hypoxia, maximum tolerable muscle loads, and immobilization stress.

In the first stage of the study, for mercury dichloride (HgCl_2) administered intragastrically in 30 healthy white rats, we determined the minimum toxic dose (MTD) at which no animal died; doses at which death of 16%, 50%, 84%, and 100% of the animals was observed were labeled LD_{16} , LD_{50} , LD_{84} , and LD_{100} , respectively. The toxicity effect of HgCl_2 as an agent of acute renal failure in animals after nephrectomy was determined using the Miller and Tainter method. The chemical factor exposure on the animal was performed via intragastric administration of 40% ethanol. The LD_{50} of ethanol was also calculated using the Miller and Tainter method. A normobaric normocapnic hypoxic hypoxia model was created by placing rats in a 3-L pressure chamber. Carbon dioxide was removed with soda lime. An indicator of the resistance to the effects of hypoxia was the duration of the animals' life. The body resistance to the action of maximum tolerable muscle loads was studied on a model of forced swimming with a load equal to 8% of the body weight until exhaustion in water at a temperature of 30 °C to 32 °C. Stress syndrome was simulated by immobilizing the rats on the back for 24 h. We studied the following indicators: weights of the adrenal gland and thymus; ulceration of the mucous

membrane (rate of animals with ulcers); degree of ulceration (number of ulcers in one rat); Paul's index, calculated using the following formula: ulceration degree x rate of rats with ulcers (%) / 100. Muscular loads under hypoxia were modeled by free swimming of the rats in a 3-L pressure chamber. An indicator of animal resistance was the duration of swimming in minutes. Exposure to physical factors was modeled using acute hypo- and hyperthermia. Acute hypothermia was simulated by free swimming of rats in water at a temperature of 10 °C. An indicator of animal resistance was the time of active swimming in minutes. Acute hyperthermia was simulated by placing the animals in a thermal chamber at a temperature of 60 °C. The indicators of the body's resistance were the time of onset of seizures and life duration in minutes. In order to objectify the research results, we calculated the coefficient of the adaptogenic effect (CAE) that reflects the ability of drugs to increase the body's resistance to certain influences as per the following formula: 100% protective effect - (100% - % of effect in the experiment) / 100% protective effect. Statistical data were analyzed using the application statistics software package Statistica 10.0.

RESULTS

The parameters of acute toxicity using HgCl_2 in healthy rats were as follows: MTD - 20 mg/kg, LD_{16} - 38 mg/kg, LD_{50} - 64 ± 7 mg/kg, LD_{84} - 85 mg/kg, and LD_{100} - 100 mg/kg ($p < 0.05$). After the nephrectomy, toxicity with HgCl_2 was determined on the 30th day after surgery. In this group, the LD_{50} of HgCl_2 decreased significantly by 1.5 times to 42 ± 6 mg/kg ($p < 0.05$).

The effect of nephrectomy on the general adaptive response of animals under the influence of acute alcohol poisoning, normobaric hypoxia, and maximal tolerable muscle loads is presented in Table 1.

Table 1

The effect of nephrectomy on the overall adaptive response of white rats

Таблица 1

Влияние нефрэктомии на общую адаптивную реакцию белых крыс

Damaging factor	Healthy animals, $n = 10$	Day 30 after nephrectomy, $n = 10$	
	Life duration, min ($M \pm m$)	Life duration, min ($M \pm m$)	CAE
LD50 of 40% ethanol	25.1 ± 2.8	$17.5 \pm 1.9^*$	-0.30
Normobaric hypoxia	59.4 ± 5.1	47.8 ± 3.7	-0.20
Maximal tolerable muscle loads	19.2 ± 3.7	14.5 ± 1.3	-0.25

Note. *significant changes compared to the control group for $p < 0.05$; CAE - coefficient of adaptogenic effect.

Table 2

Tolerability of 24 h immobilization stress by white rats

Таблица 2

Переносимость белыми крысами 24-часового иммобилизационного стресса

Group, <i>n</i> = 10	Thymus		Adrenal gland		Gaster		
	WC	CAE	WC	CAE	UD (<i>M</i> ± <i>m</i>)	%	PI
Intact	0.92 ± 0.04	0	0.075 ± 0.005	0	0	0	0
Stress	0.55 ± 0.06*	-0.40	0.112 ± 0.013*	0.49	6.2 ± 1.1*	100	6.2
Day 30 after N/e	0.80 ± 0.05	-0.13	0.090 ± 0.005*	0.20	1.1 ± 0.6**	20	0.22
N/e + stress	0.65 ± 0.04*	-0.29	0.138 ± 0.012*.#	0.84	4.5 ± 0.8*.#	100	4.5

Note. N/e – nephrectomy; WC – weight coefficient; UD – degree of gastric mucosa ulceration (number of ulcers in a one rat); % – rate of rats with ulcer; PI – Paul's index. * – significant changes compared to the intact group for $p < 0.05$; ** – significant changes comparing with the control group for $p < 0.05$; # – significant changes compared to the nephrectomy group for $p < 0.05$.

Table 3

Effect of nephrectomy on the tolerability of acute hyperthermia in white rats

Таблица 3

Влияние нефрэктомии на переносимость белыми крысами острой гипертермии

Animal group, <i>n</i> = 10	Time of seizures onset, min (<i>M</i> ± <i>m</i>)	Life duration, min (<i>M</i> ± <i>m</i>)	CAE
Healthy animals	10.5 ± 0.5	15.0 ± 0.2	0
Day 30 after nephrectomy	8.1 ± 0.6*	11.4 ± 0.8*	-0.24

Note. *significant changes compared to the control group for $p < 0.05$; CAE – coefficient of adaptogenic effect.

The LD₅₀ of ethanol in healthy rats was 25.1 ± 3.2 mL/kg. Nephrectomy significantly reduced the tolerance to ethanol in white rats by almost 1/3rd ($p < 0.05$). The decrease in body resistance to hypoxia after nephrectomy was 20% ($p > 0.05$), to maximal tolerable muscle loads 25% ($p > 0.05$).

Resistance of animals to immobilization stress (stress syndrome) was determined by studying the dynamics of the following Selye triad indicators: the state of the thymus, adrenal glands, and gastric mucosa. In rats under stress vs. intact animals, thymic hypotrophy (organ weight significantly decreased by 41%), adrenal hypertrophy (their weight coefficient increased 1.5 times), and 100% damage to the gastric mucosa (average number of ulcers in one rat was 6.2 ± 1.1, the Paul's index was 6.2) were registered (Table 2).

On the 30th day after the nephrectomy, a tendency toward thymus hypotrophy was observed in the rats, and the adrenal gland weight coefficient and the degree of ulceration of the gastric mucosa were significantly increased ($p < 0.05$). In sum, there was poorer tolerance to emotional pain due to experimental nephrectomy in animals.

Acute hyperthermia was simulated by placing animals in a thermal chamber at a temperature of 60 °C. The indicators of body resistance were the time of seizures onset and life duration in minutes (Table 3). According to the obtained data, nephrectomy significantly reduced the tolerance to hyperthermia (CAE decreased by almost a quarter [-0.24, $p < 0.05$]) and hypothermia (CAE decreased by almost a quarter [-0.24]).

The analysis of the influence of the damaging external factors on the general adaptive ability of the organ-

ism in animals with one kidney showed its significant decrease. The total CAE was -0.21 ± 0.03 ($p < 0.05$)

CONCLUSION

This study demonstrated a significant negative effect of nephrectomy on the general adaptive ability of animals and allowed to clarify the functional characteristics of general adaptive disorders associated with nephrectomy.

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Information about the authors:

Igor S. Shormanov — Doctor of Medical Sciences, Professor, Head, Department of Urology with Nephrology. Yaroslavl State Medical University of the Ministry of Healthcare of the Russian Federation, Yaroslavl, Russia. E-mail: i-s-shormanov@yandex.ru.

Marina S. Los — Candidate of Medical Sciences, Urologist, Regional Clinical Hospital, Yaroslavl, Russia. E-mail: 922099@mail.ru.

Maxim V. Kosenko — Senior Lecturer, Department of Physical Culture and Sports. Yaroslavl State Medical University of the Ministry of Healthcare of the Russian Federation, Yaroslavl, Russia. E-mail: Maxim.kosenko76@yandex.ru.

Сведения об авторах:

Игорь Сергеевич Шорманов — д-р мед. наук, профессор, заведующий кафедрой урологии с нефрологией. ФГБОУ ВО «Ярославский государственный медицинский университет» Минздрава России, Ярославль. E-mail: i-s-shormanov@yandex.ru.

Марина Сергеевна Лось — канд. мед. наук, врач-уролог. ГБУЗ Ярославской области «Областная клиническая больница», Ярославль. E-mail: 922099@mail.ru.

Максим Вадимович Косенко — старший преподаватель кафедры физической культуры и спорта. ФГБОУ ВО «Ярославский государственный медицинский университет» Минздрава России, Ярославль. E-mail: Maxim.kosenko76@yandex.ru.