ORIGINAL ARTICLE

CONTENTS

Structural characteristics of the kidney in conditions of experimental hypothermia

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ABSTRACT

Aim: To investigate histological, ultrastructural, and morphometric changes in the wall of arterial vessels, glomerular and peritubular capillaries, and convoluted tubules of the kidney under the influence of a cold factor in an experiment.

Materials and Methods: The experiment was conducted on 80 mature white Wistar male rats, 10 of which served as controls. Animals were divided into 7 groups of 10 animals each according to experimental time points: at the peak of cooling and at 1, 3, 7, 14, 21, and 30 days of the recovery period. All procedures with animals were performed according to bioethical standards. Experimental-morphological analysis was conducted using histological, electron microscopic, and morphometric research methods.

Results: It was established that hypothermia causes vasoconstriction of the kidney's arterial vessels. From day 1 of the post-hypothermic period, edematous changes develop, which increase maximally by day 3 and persist through day 7 of the experiment. Starting from day 14, edematous changes decrease and structural organization of kidney parenchyma is restored. Reparative processes are completed by day 30.

Conclusion: Profound renal hypothermia causes a complex process: early vascular spasm leading to ischemia, subsequent inflammatory enhancement of damage with maximum effect at days 3-7, followed predominantly by reversible recovery with isolated foci of irreversible remodeling.

KEYWORDS: kidney parenchyma, nephron, intrarenal arteries, podocytes, endotheliocytes.

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INTRODUCTION

The effect of extreme temperatures on the human body is an important problem in modern medicine, with special attention deserved to the effects of low temperatures [1,2]. In a World Health Organization report, it was noted that under conditions of war in Ukraine, destruction of infrastructure, population displacement, and limited access to heating significantly increase the risk of low temperature exposure affecting the health of the population: extreme cold in such conditions can lead to increased morbidity [3]. Furthermore, military personnel during combat operations remain in low-temperature conditions for extended periods, which increases the risk of frostbite and cold injuries, especially during prolonged outdoor exposure.

Special attention should be given to the effects of low temperatures on organs of the urinary system, particularly the kidneys, which play a key role in maintaining homeostasis. The vascular network and kidney parenchyma are highly sensitive to changes in temperature regime, as even brief cold exposure can cause disruption of microcirculation, vascular spasm, ischemic changes, and development of dystrophic and inflammatory processes in nephrons.

AIM

To investigate histological, ultrastructural, and morphometric changes in the wall of arterial vessels, glomerular and peritubular capillaries, and convoluted tubules of the kidney under the influence of a cold factor in an experiment.

MATERIALS AND METHODS

The experiment was conducted on 80 sexually mature white Wistar male rats weighing 170-190 g, 10 of which served as controls. Animals were divided into 7 groups

Table 1. Lumen of arterial vessels at various levels following cold factor exposure (μm)

Day	Interlobar arteries	Arcuate arteries	Interlobular arteries	Afferent arterioles
Control	116.26 ± 14.39	32.91 ± 0.56	11.66 ± 1.21	6.95 ± 0.24
Cold	69.32 ± 7.91*	23.01 ± 0.95*	7.22 ± 0.71*	4.25 ± 0.56*
1	75.88 ± 8.71*	24.54 ± 0.81*	7.23 ± 0.52*	4.85 ± 0.84*
3	79.14 ± 7.31*	26.55 ± 1.31*	7.44 ± 0.44*	4.83 ± 0.55*
7	95.52 ± 10.05	27.96 ± 1.35*	7.54 ± 0.51*	4.76 ± 0.67*
14	98.37 ± 16.81	28.41 ± 1.87*	7.89 ± 0.61*	5.66 ± 0.75*
21	133.96 ± 11.73	32.43 ± 1.27	10.43 ± 1.31	5.66 ± 0.75
30	125.26 ± 10.43	32.49 ± 1.32	11.36 ± 0.75	6.23 ± 0.95

*Note: * indicates statistically significant difference from control animals; for each experimental time point n = 10; data presented as Mean ± SD.*

Table 2. Area of the middle coat of arterial vessels at various levels following cold factor exposure (μm^2)

Day	Interlobar arteries	Arcuate arteries	Interlobular arteries	Afferent arterioles
Control	10432.9 ± 2122.7	2194.8 ± 459.9	625.6 ± 16.5	144.3 ± 16.5
Cold	15955.3 ± 1234.2*	4365.6 ± 341.3*	930.6 ± 17.1*	146.6 ± 22.4*
1	20544.6 ± 2123.4*	8990.1 ± 650.6*	890.3 ± 12.3*	216.9 ± 12.3*
3	20822.6 ± 2115.6*	8069.4 ± 812.5*	805.5 ± 15.1*	340.3 ± 19.1*
7	14966.3 ± 1928.1	6120.9 ± 840.9*	791.9 ± 13.2*	346.5 ± 19.1*
14	14985.8 ± 2671.4	3965.7 ± 251.7*	725.3 ± 19.9*	256.2 ± 14.3*
21	10740.1 ± 1280.1	2450.7 ± 370.8	635.6 ± 25.6	185.2 ± 19.6
30	10856.3 ± 1130.7	2196.3 ± 265.5	603.1 ± 25.3	115.2 ± 12.3

*Note: * indicates statistically significant difference from control animals; for each experimental time point n = 10; data presented as Mean ± SD.*

of 10 animals each according to experimental time points: at the peak of cooling and at 1, 3, 7, 14, 21, and 30 days of the recovery period.

Modeling of deep hypothermia in animals with achievement of rectal body temperature of +12°C was performed as follows. Animals were placed in a cold chamber that did not restrict their movement or breathing. The temperature in the chamber was gradually lowered to -30°C to -33°C. Continuous observation of animal behavior was maintained. Initially, the behavior was calm; after a short time, excitement appeared followed by increased defecation and urination. Subsequently, inhibitory processes began, which ended with a sharp decrease in motor activity. At this time, rectal body temperature was measured in the animals, and upon reaching +12°C, the experiment was concluded. Animal care, all procedures with them, and euthanasia were performed in accordance with general bioethical requirements and rules for animal experimentation.

Material sampling for light optical and electron microscopic examination, block preparation, section fabrication, and their staining were conducted using generally accepted methods [4]. To objectively characterize the damaging effects on components of the glomerular filter and tubular reabsorption, histometry of their constituents was performed [5] with modification [6].

RESULTS

REMODELING OF ARTERIAL VESSELS OF THE KIDNEY AT VARIOUS LEVELS UNDER THE INFLUENCE OF THE COLD FACTOR AND AT VARIOUS TIMES OF THE POST-HYPOTHERMIC PERIOD

Morphometric data indicating the state of vasoconstriction or vasodilation of arterial vessels are presented in Table 1, and edematous changes are presented in Table 2.

At the peak of hypothermia, vasoconstriction of arterial vessels of various caliber occurs (Table 1). The internal elastic membrane becomes unevenly undulating; sometimes its folds deeply penetrate the muscular layer. In the lumen of individual arcuate arteries, exfoliated endotheliocytes are observed. The most pronounced morphological changes in the structural components of arterial vessel walls occur on day 3 of the post-hypothermic period. The vessel lumen somewhat increases and becomes filled with formed blood elements. Edematous changes increase significantly, resulting in an increased area of the muscular coat (Table 2). In arcuate arteries, the internal elastic membrane is locally destroyed and sometimes significantly penetrates the muscular coat, whose area also increases. In the lumen of interlobular

arteries, significant accumulation of erythrocyte masses is observed. Myocytes have vacuolated sarcoplasm and deformed nuclei. The lumen of afferent arterioles has an irregular oval shape and is also filled with erythrocytes. In the perivascular space, numerous formed blood elements are observed.

Morphometric parameters on day 7 of the post-hypothermic period differ little from those of previous time points. Edematous-dystrophic changes in arterial vessels were still present to a significant degree. Starting from day 14 after cold exposure, reparative processes increase at more rapid rates. Numerical values on day 21 of the post-hypothermic period occupy an intermediate position between days 14 and 30. Reparative processes are largely completed by day 30 of the experiment.

Changes in kidney parenchyma following cold factor exposure and at various times of the recovery period. It was established that immediately after cold factor exposure, kidney corpuscles (glomeruli) have normal shape, increase slightly in size, and loops of glomerular capillaries are somewhat constricted. Edematous-dystrophic changes develop in the kidney parenchyma, and the glomerular capsule dilates. Accumulation of formed blood elements is noted. In convoluted tubules, granular dystrophy is observed.

On day 3 of the post-hypothermic period, there is significant deepening of the above-described phenomena. The volume of kidney corpuscles increases. Concurrently, reduced kidney corpuscles are also observed. In the cortical substance, massive accumulation of formed blood elements sometimes occurs, indicating hemorrhage into the kidney parenchyma. Convoluted tubules of nephrons are locally dilated. In nephrocytes of convoluted tubules, there is pronounced cloudy swelling. In the medullary substance, dilated venous vessels are present, which are significantly engorged with blood.

By day 7 of the post-hypothermic period, the above-described changes persist at the same level. Significant granular dystrophy of nephrocytes in convoluted tubules is preserved; in certain locations they are dilated. In the medullary substance, dilated portions of nephron loops and collecting ducts are revealed.

From day 14 onward, significant reduction of edematous processes is observed. In some cases, adhesive processes between the layers of the glomerular capsule occur, with necrotic processes in kidney corpuscles accompanied by significant deformation of the vascular glomerulus. The lumen of convoluted tubules of nephrons is dilated with layers of exfoliated epithelium. In the medullary substance, dilated portions of nephron loops are filled with exfoliated epithelium.

By day 21 of the study, the processes become even more pronounced. Kidney corpuscles decrease in size. In the lumen of convoluted tubules of nephrons, exfoliated cells are encountered. In the cytoplasm of nephrocytes, granular and vacuolar dystrophy are observed.

On day 30 of the experiment, reparative processes in the kidneys are largely completed. The volume of kidney corpuscles returns almost to normal. Convoluted tubules of nephrons locally have dilated lumens. In certain areas, connective tissue proliferation is found at the site of damaged kidney parenchyma, and vascular glomerulus wrinkling is observed.

ULTRASTRUCTURE OF THE FILTRATION BARRIER, GLOMERULAR CAPILLARIES, AND KIDNEY PARENCHYMA UNDER COLD FACTOR EXPOSURE

At the peak of hypothermia, the nuclei of endotheliocytes acquire an oval shape, often with invaginations. The cytoplasm contains a small number of oval mitochondria with occasional disrupted cristae and a cleared matrix. In the cytoplasm, large quantities of free ribosomes and polysomes are frequently encountered. The lumen of glomerular capillaries is narrowed due to endotheliocyte edema and filled with erythrocytes. The basal membrane maintains its trilaminar structure. In podocytes, nuclei are rounded or oval with clear outlines; chromatin is distributed in clumps. The cytoplasm contains a large quantity of cisternae and vacuoles. The podocyte processes (foot processes) are dilated and deformed (Fig 1A). In nephrocytes of proximal convoluted tubules, the microvilli of the brush border lose their basal-apical orientation and orderliness. The quantity of lysosomes and vacuoles increases. Mitochondria are elongated and swollen, with damaged cristae in certain areas (Fig 1B, 1C).

By day 1, edematous-dystrophic changes increase and reach their maximum on day 3 of the study (Fig 1D). The cytoplasm of endotheliocytes of glomerular capillaries becomes edematous, significantly narrowing their lumen. The nuclei of cells are also edematous, with irregular outlines; nucleoplasm has a granular cleared matrix. Mitochondria in endotheliocytes are predominantly rounded in shape, with relatively clear outlines and occasional preserved cristae. Individual glomerular capillaries are densely packed with erythrocytes. Their basal membrane at bending sites is significantly thickened; its trilaminar nature is poorly expressed. In podocytes, nuclei are enlarged with invaginations of the karyolemma. Mitochondria have unclear outlines and occasional cristae. The Golgi complex is dilated. The cytoplasm is light with a large quantity of ribosomes, polysomes, vesicles, and vacuoles (Fig 2A). The most

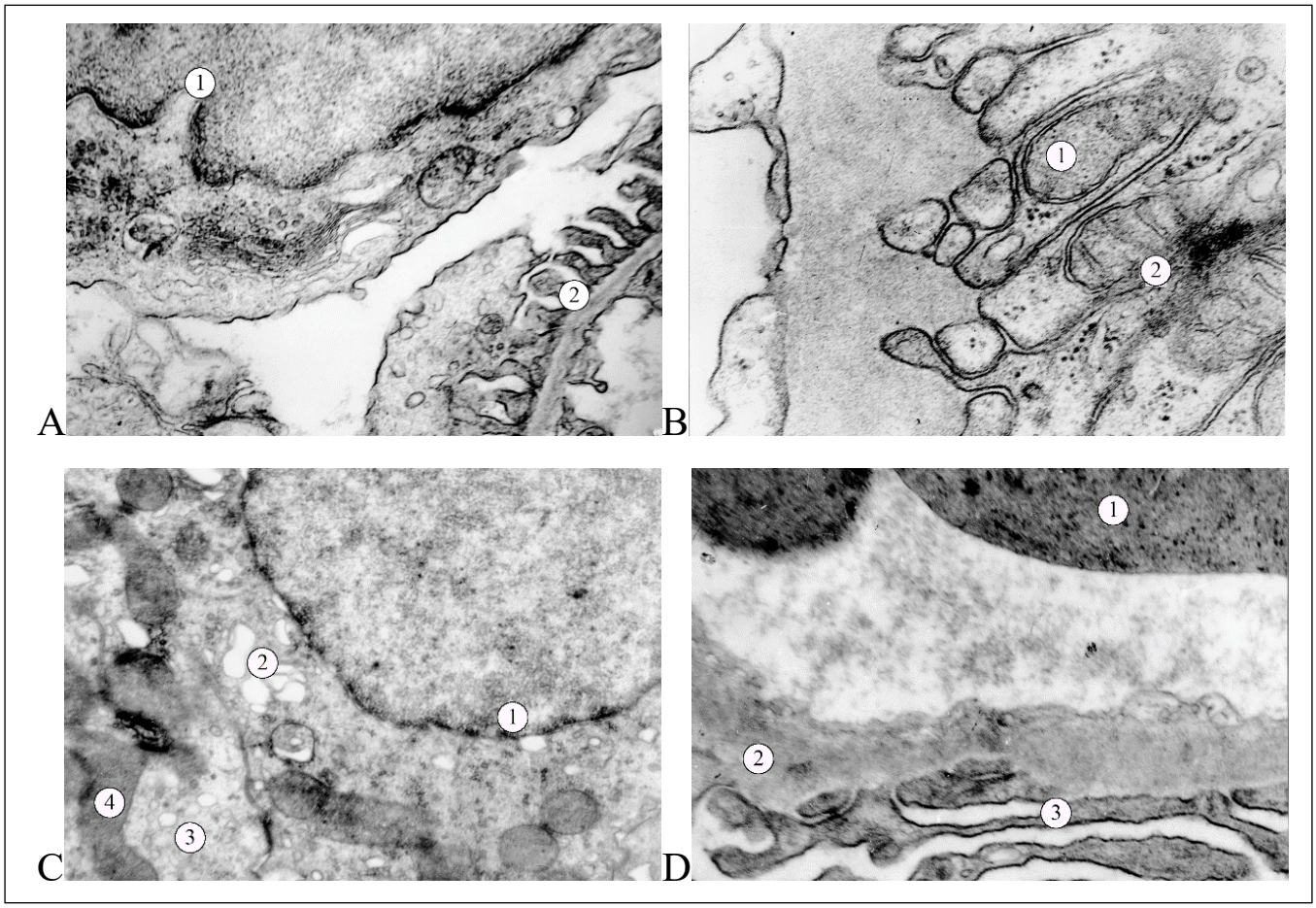

Figure 1. Submicroscopic changes in renal structures at the peak of hypothermia and on day 1 of the post-hypothermic period. A. Podocyte ultrastructure at the peak of hypothermia: (1) nuclear envelope invaginations; (2) podocyte foot process effacement. B. Basal domain of a proximal renal tubular epithelial cell at the peak of hypothermia (1) mitochondria; (2) plasma membrane folds. C. A distal renal tubular epithelial cell at the peak of hypothermia: (1) nucleus; (2) Golgi apparatus; (3) electron-lucent cytoplasm; (4) mitochondrion. D. Glomerular filtration barrier on day 1 of the post-hypothermic period: (1) erythrocyte sludging; (2) basement membrane; (3) podocyte foot processes. Electron micrographs. Magnification: A ×6,000, B ×32,000, C ×24,000, D ×8,000.

pronounced ultrastructural changes are present in nephrocytes of proximal and distal convoluted tubules (Fig 2B, 2C). Dilation and desquamation of microvilli of the brush border is observed. Frequently, there is destruction of the cell membrane with extrusion of organelles into the tubule lumen. The nucleus is swollen with deep invaginations of the karyolemma. The Golgi complex is represented by dilated cisternae. The endoplasmic reticulum appears as dilated, interconnected microtubules. The cytoplasm of nephrocytes is light, with a large quantity of free ribosomes and large round lysosomes. The basal portion of nephrocytes contains swollen, dilated mitochondria. Peritubular capillaries are engorged with formed blood elements. Endothelial cells have swollen nuclei. The cytoplasm is light with the presence of free ribosomes and vacuolization.

On day 7 of the post-hypothermic period, damage to the filtration barrier and nephrocytes of proximal and distal convoluted tubules decreases (Fig 2D). Starting from day 14 of the experiment, reparative processes intensify, and by day 30 of the recovery period, they are largely completed. However, in some cases at the site of damaged podocytes, myelin-like formations are found, which significantly deform the capsular space.

DISCUSSION

The data obtained in this work show that deep hypothermia causes changes not in isolated structures, but in a complex of vascular, glomerular, and tubulointerstitial damage. These results correspond to current understanding of cold-induced kidney injury, which is associated simultaneously with vasoconstriction, hypoxia, mitochondrial dysfunction, inflammatory reaction, and the peculiarities of subsequent organ rewarming [7-9].

Worth noting is the established fact that narrowing of the lumen of arterial vessels at all levels, deepening of the folds of the internal elastic membrane, and increase in the area of the middle coat of arterial walls indicate dominance of a vasoconstrictor response in the early

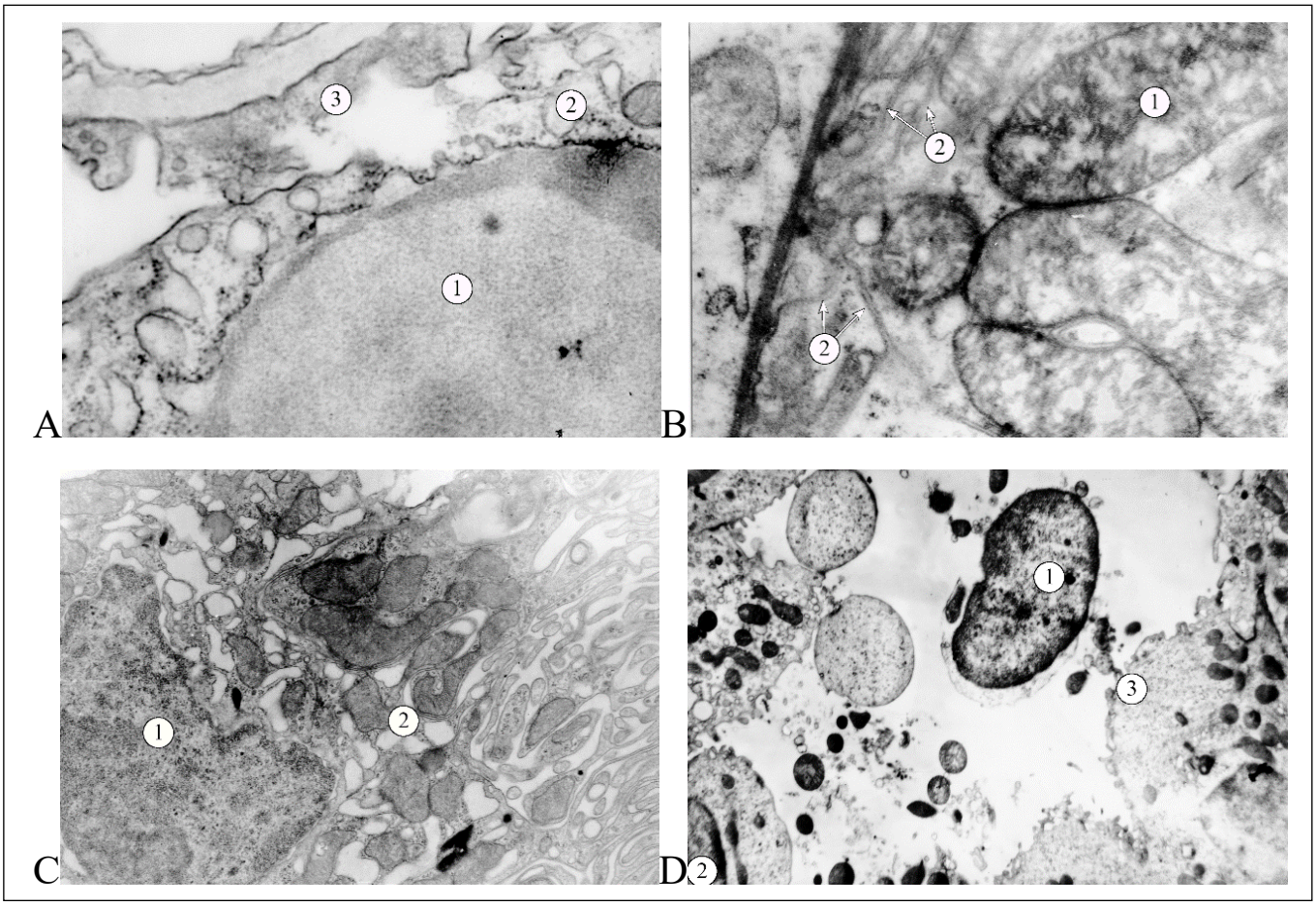

Figure 2. Kidney ultrastructure on days 3 and 7 of the post-hypothermic period. A. A podocyte on day 3 of the post-hypothermic period: (1) nucleus; (2) cytoplasmic vacuoles; (3) blurred plasma membrane boundaries. B. Basal domain of a proximal renal tubular epithelial cell on day 3 of the post-hypothermic period: (1) mitochondria; (2) plasma membrane folds. C. A distal renal tubular epithelial cell on day 3 of the post-hypothermic period: (1) nucleus; (2) cytoplasmic vacuoles; (3) mitochondrion. D. A distal tubule on day 7 of the post-hypothermic period: (1) nucleus of a desquamated epithelial cell in the lumen; (2) distal renal tubular epithelial cell; (3) apical domain of the epithelial cell lining. Electron micrographs. Magnification: A, B ×16,000; C ×5,000; D ×4,000.

phase of cold exposure, which is consistent with current data showing that cold and warm ischemia are among the key factors in subsequent injury to transplanted or ischemized kidney[7,8]. This is explained by the fact that even a cooled kidney requires energy support, particularly in the cortico-medullary zone and in areas with high ATP requirements [8,9].

Importantly, the maximum severity of injury in our study was observed not at the peak of cooling, but predominantly at days 3-7 of the post-hypothermic period, indicating that cold is only an initiating factor, while damaging factors include excessive production of reactive oxygen species, accumulation of succinate, disruption of oxidative phosphorylation, and activation of pro-inflammatory pathways[10-13], which develop after restoration of blood flow and temperature. Therefore, the increase in volume of kidney corpuscles, swelling of vessel walls, desquamation of endothelium, venous congestion, and perivascular hemorrhages in later time periods should be interpreted as manifestations of the reperfusion component of injury [10-12, 14-15].

Particularly revealing are the ultrastructural changes we identified: endotheliocyte edema, capillary lumen narrowing, disruption of the clarity of the trilaminar structure of the basal membrane, and deformation and approximation of podocyte foot processes. These demonstrate that cold factor disrupts not only hemodynamics but also the very architecture of the filtration barrier itself.

Our findings on endothelial desquamation, capillary overfilling with erythrocytes, and perivascular hemorrhages can be considered morphological confirmation of the leading role of endothelial dysfunction in the genesis of cold-induced kidney injury, as indicated by other authors [7,14,16].

The deformation of foot processes and narrowing or dilation of the capsular space we identified indicate that hypothermia can significantly alter the barrier properties of the visceral layer of the capsule. Podo-

cytes are cells with high structural specialization that are extremely sensitive to oxidative stress [11,12,17].

In our study, nephrocytes of the proximal and distal convoluted tubules proved to be the most sensitive to cold exposure. Granular dystrophy, vacuolization, destruction of the brush border, swelling and destruction of mitochondria, and desquamation of cells into the tubule lumen were observed, which fully corresponds to current understanding that tubular epithelium is the primary target of ischemia-reperfusion injury of the kidney [7,10-12,18].

Mitochondria play an important role in cold and ischemic kidney injury. Mitochondrial dysfunction initiates ROS-dependent damage to proteins, lipids, and DNA, activates apoptosis, necrosis, ferroptosis, and pathological or insufficient mitophagy [11-13,19]. Therefore, the swelling and destruction of mitochondria we identified in nephrocytes should be viewed not simply as an associated sign, but as a central link in pathogenesis.

In our work on days 3 and 7, leukocyte infiltrates, perivascular accumulation of blood cells, venous congestion, hemorrhages, and progressive dystrophic changes in parenchyma were observed. Current experimental data show that following cold storage and reperfusion, pro-inflammatory signaling axes are activated in the kidney, which maintain injury even after elimination of the primary ischemic factor [14]. Hypothermic machine perfusion, conversely, can reduce inflammation [20]. This indicates that in our experiment, late morphological changes were due to secondary inflammatory reaction.

At the same time, the results of our work do not contradict the concept of potentially protective role of controlled hypothermia. Current clinical and experimental studies show that properly dosed cooling or hypothermic perfusion can improve early graft function and limit metabolic requirements of the organ [21-24]. Thus, clinical studies confirm the advantages of continuous hypothermic machine perfusion compared to static cold storage [21,22], while optimization of oxygenation and controlled rewarming further reduce the consequences of reperfusion stress [23,24].

It is notable that by day 30, there was almost complete restoration of the structure of kidney corpuscles, vessels, and convoluted tubules. This indicates the significant reparative potential of the kidney following a single hypothermic episode and explains why a significant portion of acute tubular kidney injury following ischemia is reversible [7,11,17,18]. However, the presence in some animals of shrunken glomeruli, adhesions between capsular layers, and connective tissue proliferation indicates incomplete recovery of tubular epithelium. This, combined with persistent mitochondrial dysfunction, inflammation, and activation of pro-fibrotic systems, forms the transition from acute injury to chronic kidney disease [7,12,13,17].

In the clinic, hypothermia is neither harmful nor beneficial; its effect is determined by the balance between metabolic reduction and the risk of vascular-reperfusion injury [9, 21-27]. This is precisely why the structural changes we describe have not only experimental-morphological but also practical significance. They clarify that the most vulnerable links are the arterial wall, vascular endothelium, podocytes, and epithelium of convoluted tubules. Accordingly, promising directions for correction may include agents that affect microcirculation, mitochondrial metabolism, oxidative stress, and inflammatory processes [11-13, 28-29].

Deep hypothermia of the kidney causes a complex process: early vascular spasm and ischemia, subsequent inflammatory enhancement of injury with maximum effect at days 3-7, followed predominantly by reversible recovery with isolated foci of irreversible remodeling. The epithelium of convoluted tubules and components of the glomerular filtration barrier show the greatest vulnerability, which is explained by their high energy dependence and sensitivity to endothelial-mitochondrial dysfunction. From a practical standpoint, this determines the advisability of using controlled hypothermia as an anti-ischemic agent, but only with optimization of cooling duration, adequate oxygenation, protection of microcirculation, and controlled rewarming of the organ [12-13, 20-26, 28-29].

CONCLUSIONS

1. Morphometrically, it was established that deep hypothermia causes vasoconstriction of arterial vessels at all levels, which weakens after one day. The lumen of interlobular arteries is restored by day 7 following cold exposure, but vasoconstriction of arcuate and interlobular arteries and afferent arterioles persists through day 21 of the study.
2. The most pronounced edematous changes are determined from days 3 to 7 of the recovery period, as evidenced by an increase in both the area of the middle coat of arterial vessels and the volume of kidney corpuscles. During this period, focal desquamation of endothelial cells of the intima of arterial vessels, microthromboses, significant dilation of venous vessels, and perivascular leukocyte infiltrates are observed.
3. Reparative processes begin to intensify significantly from day 14 and are completed by day 30 of the recovery period, as indicated by normalization of the lumen of arterial vessels, decrease in the area of

their middle coat and volume of kidney corpuscles, absence of vacuolization of smooth muscle tissue of the vascular wall, and restoration of normal structure of kidney corpuscles.

4. Among the components of the nephron, the most sensitive to the effects of deep hypothermia are epitheliocytes of proximal and distal convoluted tubules, with the most sensitive sites for cold exposure being the microvilli of the brush border, expressed in loss of their proper orientation and orderliness in the basal-apical direction, desquamation of microvilli, and mitochondrial disorganization.
5. By the end of the experiment, kidney corpuscles with signs of persistent damage are frequently encountered, manifested as collapsed glomerular capillaries, dilation of the glomerular capsular space, adhesions between the parietal and visceral layers of the capsule, and connective tissue proliferation at sites of leukocyte infiltrates, indicating the beginning of sclerotic processes. At the same time, enlargement of cell nuclei, invagination of the nuclear envelope, dilation of endoplasmic reticulum microtubules and Golgi cisternae, and thickening of mitochondrial cristae are observed, indicating compensatory hypertrophy.

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CONFLICT OF INTEREST

The Author declare no conflict of interest

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