CARDIOPROTECTIVE AND NEPHROPROTECTIVE EFFECTS OF PHARMACOLOGICAL ALDOSTERONE RECEPTOR BLOCKADE IN SUBTOTALLY NEPHRECTOMIZED WISTAR RATS

Karabaeva A.Zh.[1], Zaynalov A.K.[2], Tazhdinov D.B.[3], Kaniyev S.A.[4], Mausymbayeva I.R.[3], Medetbayeva A.M.[2], Abduzhalilov I.A.[1]

1 - Non-profit unitary organization Kazakhstan-Russian Medical University, Almaty, Kazakhstan
2 - "Private Clinic Almaty", Almaty, Kazakhstan
3 - Modern Medicine Center "Mediterra", Almaty, Kazakhstan
4 - Syzganov National Scientific Center of Surgery, Almaty, Kazakhstan.

DOI: 10.35805/BSK2025IV004
Karabaeva A.Z.,
https://orcid.org/0009-0006-0035-3115
Tazhdinov D.B.,
https://orcid.org/0009-0004-7261-3663
Kaniyev S.A.,
https://orcid.org/0000-0002-1288-0987
Maussymbayeva I.R.,
https://orcid.org/0009-0005-3675-3308
Medetbayeva A.M.,
https://orcid.org/0009-0004-4338-3731
Abduzhalilov I.A.,
https://orcid.org/ID0009-0009-3667-6217

recieved: 31.10.2025
accepted: 12.11.2025

Author for correspondence:
Karabaeva A Z.
Doctor of Medical Sciences, Associate Professor, Non-profit unitary organization Kazakhstan-Russian Medical University, aigul_karl@mail.ru, +77012228761, ORCID ID 0009-0006-0035-3115

Conflict of interest:
The authors declare that the reare no conflicts of interest.

Keywords:
aldosterone, spironolactone, left ventricular hypertrophy, chronic kidney insufficiency

Abstract

Background: This study evaluated the cardioprotective effect of spironolactone in Wistar rats subjected to 5/6 nephrectomy.

Materials and Methods: Chronic kidney insufficiency was induced in Wistar rats via 5/6 nephrectomy. Animals were assigned to three groups: Group 1 — Chronic kidney insufficiency rats treated with spironolactone (0.2 mg/day), Group 2 — Chronic kidney insufficiency rats without treatment, and Group 3 — sham-operated controls. Before euthanasia, mean arterial pressure, heart rate, and 24-hour urine output were recorded. Plasma was analyzed for aldosterone, urea, creatinine, electrolytes, and total protein. The myocardial hypertrophy index was used to assess cardiac changes.

Results: Heart rate did not differ significantly among groups. Mean arterial pressure was significantly higher in both Chronic kidney insufficiency groups than in controls (151.3 ± 2.7 mmHg in Group 1, 151.4 ± 2.3 mmHg in Group 2, vs. 121.15 ± 1.8 mmHg in controls, $p<0.05$). In Group 1, the myocardial hypertrophy index was similar to controls (2.52 ± 0.06 vs. 2.35 ± 0.09, $p>0.05$), whereas in Group 2 it was significantly greater (2.8 ± 0.11, $p<0.05$). Histological analysis revealed no arteriole wall thickening or connective tissue increase in Groups 1 and 3, while Group 2 showed pronounced arteriole wall thickening.

Conclusion: Spironolactone-mediated aldosterone receptor blockade exerts a cardioprotective effect in Wistar rats with Chronic kidney insufficiency induced by 5/6 nephrectomy, independent of systemic Mean systemic arterial pressure changes.

Introduction

It is known that, cardiovascular pathology currently holds a leading position among the causes of mortality in patients with renal dysfunction of varying degrees.[1,2,3] Chronic kidney disease (CKD) is a progressive condition associated with a high risk of cardiovascular complications. The mechanisms underlying CKD involve activation of the renin-angiotensin-aldosterone system (RAAS), leading to inflammation, fibrosis, and structural changes in both the kidneys and the heart. Myocardial structural alterations are characterized by the development of interstitial fibrosis and changes in the arterioles and capillary bed, driven by the effects of aldosterone and factors specific to uremia, such as hyperhydration, electrolyte imbalances, parathyroid hormone, uremic toxins, middle molecules, and others.

These factors contribute to decreased myocardial perfusion, altered

cardiomyocyte metabolism (including intracellular calcium redistribution, impaired adrenergic responses, oxidative stress, and energy deficits),[4] ultimately resulting in left ventricular (LV) hypertrophy, as well as systolic and diastolic dysfunction. Among the various causes of LV geometric changes, aldosterone is now recognized as a key factor. Its effects are mediated through the binding of non-epithelial mineralocorticoid receptors (MR) in the myocardium.[5]

To correct cardiovascular system disorders mediated by aldosterone, aldosterone receptor blockers are prescribed for patients with heart failure. Similar studies have been conducted in patients with anuria on chronic hemodialysis. These studies have shown that low doses of aldosterone receptor blockers, without significantly affecting potassium levels, can mitigate the adverse effects of aldosterone in non-epithelial tissues.[6] However, these studies are limited in number and involve small patient cohorts.

Subtotal nephrectomy in *Wistar rats* is a widely used model of experimental CKD, enabling researchers to study pathogenesis and evaluate pharmacotherapy efficacy. In this context, our study aimed to investigate the effects of the aldosterone receptor blocker spironolactone on the course of uremia and the cardiovascular system in rats with experimental CKD.

Material and methods

The study was conducted on 47 adult male Wistar rats (weighing 180–200 g) from the Rappolovo breeding center. Chronic kidney disease (CKD) was induced through a two-stage surgical procedure involving the resection of 5/6 of renal tissue.It was conducted in the vivarium of the I.P. Pavlov Institute of Physiology, Russian Academy of Sciences, St. Petersburg.

1. First Stage: Two-thirds of the left kidney mass was resected according to the Harris C. method.[7]
2. Second Stage: One week later, the right kidney was completely removed.

Following the second stage, the rats were assigned to experimental groups based on the study objectives:

- Group 1 (Experimental): Rats received the aldosterone receptor blocker spironolactone (*Gedeon Richter, Hungary*) in a dose of 0.2 mg/day via drinking water. To prevent hyperkalemia, they were also administered furosemide (*Aventis Pharma Ltd, India*) at a dose of 0.25 mg/day.
- Group 2 (CKD Control): Rats with CKD that did not receive spironolactone.
- Group 3 (Sham-Control): Sham-operated rats served as controls.

The animals were observed for 10 weeks following the second stage of nephrectomy, corresponding to approximately seven human years (as the average lifespan of a rat is 2.5–3 years). Before slaughter, the following measurements and analyses were performed:

- Mean systemic arterial pressure (MAP): Assessed using a cuff method.
- Heart rate (HR): Recorded for all animals.
- Plasma Aldosterone Concentration (PAC): Measured using an enzyme-linked immunosorbent assay (ELISA).
- Biochemical Markers: Blood and urine samples were analyzed for urea, creatinine, potassium, sodium, and total protein concentrations, normalized to blood volume and individual diuresis.

Left Ventricular Hypertrophy Assessment: The degree of left ventricular (LV) hypertrophy was quantified using the myocardial hypertrophy index, calculated as the ratio of LV mass to body weight.[7]

Histological Analysis: Paraffin-embedded hearttissue samples from the left and right ventricles were stained with hematoxylin-eosin for histological examination.

Ethical approval: The experiment was approved by the Ethics Committee of the Institute of Physiology and the Institute of Nephrology of the Russian Academy of Sciences. Протокол № 10/09 от 25.02.2014 г

Statistical Analysis: Statistical analyses and morphometric were performed using *Statistica 6.0* and *VideoTest 5.2 software*. Differences were considered significant at $p < 0.05$. The Student's *t*-test was used to evaluate the significance of differences between groups.

Results

Biochemical parameters of blood plasma and PAC levels in the experimental animals are presented in Table 1.

Table 1. Plasma Aldosterone Concentration and Biochemical Indicators of Blood Plasma in Rats (M±m)

Indicator	Group 1, n=15	Group 2, n=15	Group 3, n=17	P value		
PAC, pg/mL	281.67 ± 39.02$^{\alpha\beta}$	207.55 ± 32.86$^{\alpha\gamma}$	145.42 ± 17.41$^{\beta\gamma}$	0.0001$^{\alpha}$*	0.0001$^{\beta}$*	0.0001$^{\gamma}$*
Potassium, mmol/L	7.92 ± 0.26$^{\alpha\beta}$	7.74 ± 0.24$^{\alpha\gamma}$	4.34 ± 0.1$^{\beta\gamma}$	0.059$^{\alpha}$	0.0001$^{\beta}$*	0.0001$^{\gamma}$*
Sodium, mmol/L	149.53 ± 1.49$^{\alpha\beta}$	152.32 ± 1.47$^{\alpha\gamma}$	149.01 ± 1.61$^{\beta\gamma}$	0.0001$^{\alpha}$*	0.353$^{\beta}$	0.0001$^{\gamma}$*
Urea, mmol/L	18.6 ± 0.47$^{\alpha\beta}$	18.7 ± 0.91$^{\alpha\gamma}$	6.08 ± 0.19$^{\beta\gamma}$	0.708$^{\alpha}$	0.0001$^{\beta}$*	0.0001$^{\gamma}$*
Creatinine, mmol/L	0.07 ± 0.001$^{\alpha\beta}$	0.07 ± 0.002$^{\alpha\gamma}$	0.04 ± 0.002$^{\beta\gamma}$	1.0$^{\alpha}$	0.0001$^{\beta}$*	0.0001$^{\gamma}$*
Total Protein, g/L	62.92 ± 1.22$^{\alpha\beta}$	62.82 ± 1.79$^{\alpha\gamma}$	63.62 ± 1.86$^{\beta\gamma}$	0.859$^{\alpha}$	0.225$^{\beta}$	0.226$^{\gamma}$
* p < 0.05 - statistical significance of differences						

From the results in Table 1, it is evident that PAC levels in the experimental groups exceeded those in the control group. However, the difference was statistically significant only in the group of CKD animals receiving spironolactone. Since spironolactone competes with aldosterone for binding to mineralocorticoid receptors (MR), its exogenous administration leads to receptor occupancy. This suppresses the feedback mechanism, resulting in elevated PAC levels.

Regarding biochemical indicators, it was observed that potassium, urea, and creatinine levels in Groups 1 and 2 were significantly higher compared to the control group.

During the experiment, daily excretion of electrolytes, nitrogen metabolites, and protein was also measured. The corresponding data are presented in Table 2.

Table 2. Daily Excretion Values in Rats from Experimental Groups (M±m)

Indicator	Group 1, n=15	Group 2, n=15	Group 3, n=17	P value		
Potassium, mmol/24 h	2.02 ± 0.15$^{\alpha\beta}$	2.01 ± 0.21$^{\alpha\gamma}$	0.92 ± 0.08$^{\beta\gamma}$	0.881$^{\alpha}$	0.0001$^{\beta}$*	0.0001$^{\gamma}$*
Sodium, mmol/24 h	0.18 ± 0.03$^{\alpha\beta}$	0.24 ± 0.07$^{\alpha\gamma}$	0.26 ± 0.07$^{\beta\gamma}$	0.005$^{\alpha}$*	0.0003$^{\beta}$*	0.426$^{\gamma}$
Urea, mmol/24 h	5.66 ± 0.9$^{\alpha\beta}$	5.54 ± 0.45$^{\alpha\gamma}$	4.41 ± 0.63$^{\beta\gamma}$	0.648$^{\alpha}$	0.0001$^{\beta}$*	0.0001$^{\gamma}$*
Creatinine, mmol/24 h	0.08 ± 0.01$^{\alpha\beta}$	0.08 ± 0.01$^{\alpha\gamma}$	0.08 ± 0.01$^{\beta\gamma}$	1.0$^{\alpha}$	1.0$^{\beta}$	1.0$^{\gamma}$
Proteinuria, mmol/24 h	0.04 ± 0.01$^{\alpha\beta}$	0.07 ± 0.02$^{\alpha\gamma}$	0.01 ± 0.001$^{\beta\gamma}$	0.0001$^{\alpha}$	0.0001$^{\beta}$*	0.0001$^{\gamma}$*
Dailyurine-output, ml	13.56 ± 1.78$^{\alpha\beta}$	12.16 ± 1.26$^{\alpha\gamma}$	3.79 ± 0.3^{6}$^{\beta}\gamma$	0.019$^{\alpha}$*	0.0001$^{\beta}$*	0.0001$^{\gamma}$*
* p < 0.05 - statistical significance of differences						

From the data presented in Table 2, it is evident that the experimental groups showed significantly higher daily excretion of potassium and protein in the urine compared to the control group. This is likely attributed to a reduction in the mass of functioning nephrons and the development of renal insufficiency following subtotal nephrectomy. Although no statistically significant differences were found in the daily protein excretion and urine output between the group receiving spironolactone and the group with CKD, a clear trend toward reduced proteinuria was observed in animals undergoing spironolactone therapy. These findings highlight the nephroprotective effects of aldosterone receptor blockers.

Our results align with experimental studies conducted by other researchers.

Another study demonstrated a significant reduction in proteinuria in SHR-SP rats treated with spironolactone. [8]

Further, we evaluated the effects of spironolactone therapy on myocardial fibrosis. This assessment was conducted by calculating the left ventricular (LV) myocardial hypertrophy index, defined as the ratio of myocardial mass to body weight,[6] and through morphological examination of myocardial tissue.

The experiment revealed that myocardial hypertrophy developed in both experimental groups. However, in the group treated with spironolactone, the myocardial hypertrophy index was comparable to that of the control group (2.52 ± 0.06 in the spironolactone group versus 2.35±0.09 in the control group, $p > 0.05$). In contrast, the group with CKD that did not receive the aldosterone receptor blocker exhibited a significant increase in myocardial mass 10 weeks after nephrectomy (2.88 ± 0.11, $p < 0.05$). This indicates the cardioprotective properties of spironolactone (Figure 1).

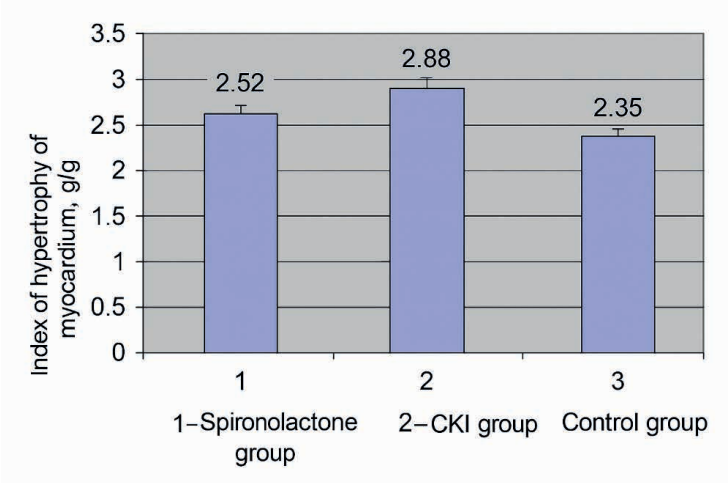

Figure 1.
Myocardial Hypertrophy Index in Rats. Index of hypertrophy of the myocardium: 1 –group of spironolactone; 2 - group of CKI; 3 – the control group

Morphometric analysis of the myocardium revealed that in the control group, the cardiomyocytes are nearly rectangular in shape and are arranged parallel to one another. Typical anastomoses were observed between the contractile fibers, formed by the branching of cardiomyocyte processes from one fiber to another, and areas where cardiomyocytes from adjacent fibers of the same direction fused. The average thickness of the cardiomyocytes was 13.6 μm, and the trьansverse striation was preserved. The cytoplasm was clear, with no signs of clouding or homogenization. The cardiomyocytes contained 1-2 nuclei, with the nuclei being predominantly oval in shape, and the longitudinal axis of the nuclei was aligned along the longitudinal axis of the cardiomyocytes. The average nuclear length was 10.04 μm, and the thickness was 2.09 μm. In the vascular-stromal component, the walls of the arterioles were not thickened, and no significant increase in connective tissue components was detected (Figure 2).

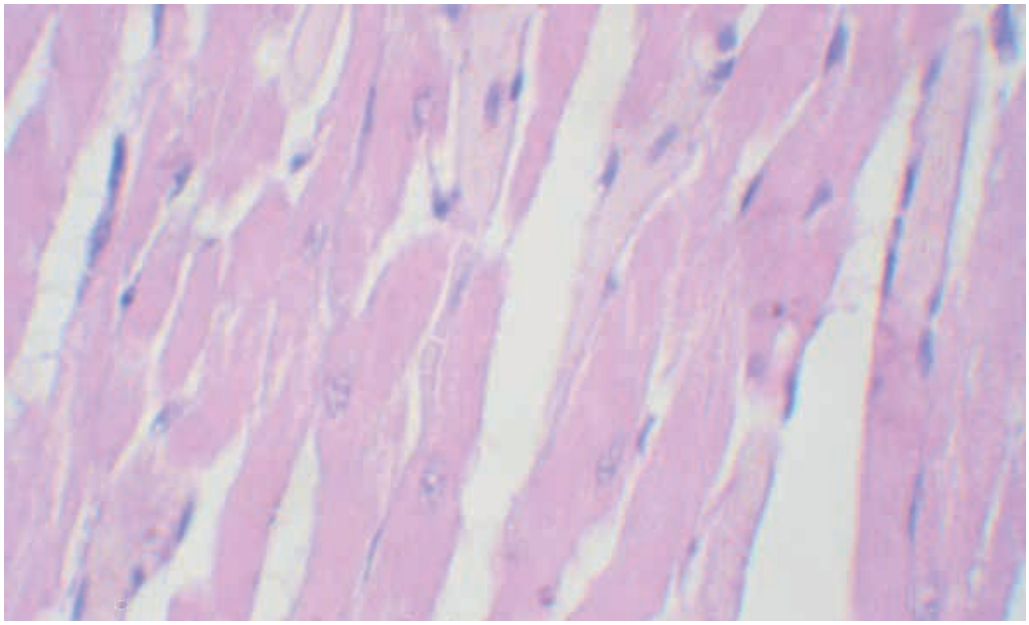

Figure 2. Morphology of Cardiomyocytes in the Control Group (Sham-operated). Hematoxylin & eosin staining, ×400

In the 5/6 nephrectomy group, the cardiomyocytes are elongated, and the transverse striation is preserved. Myocytes with contractile-lytic changes appear in the muscle fibers; intercalated discs are expanded and loosened. These changes are focal in nature.

The cardiomyocytes contain 1-2 nuclei, with the nuclei being predominantly oval in shape. The average size of the nuclei is 9.8 μm, with an average nuclear length of 6.73 μm and thickness of 2.05 μm.

Vascular-stromal component: the walls of the arterioles are thickened, but the lumen of the vessels is not narrowed. No significant increase in connective tissue components is detected (Figure 3).

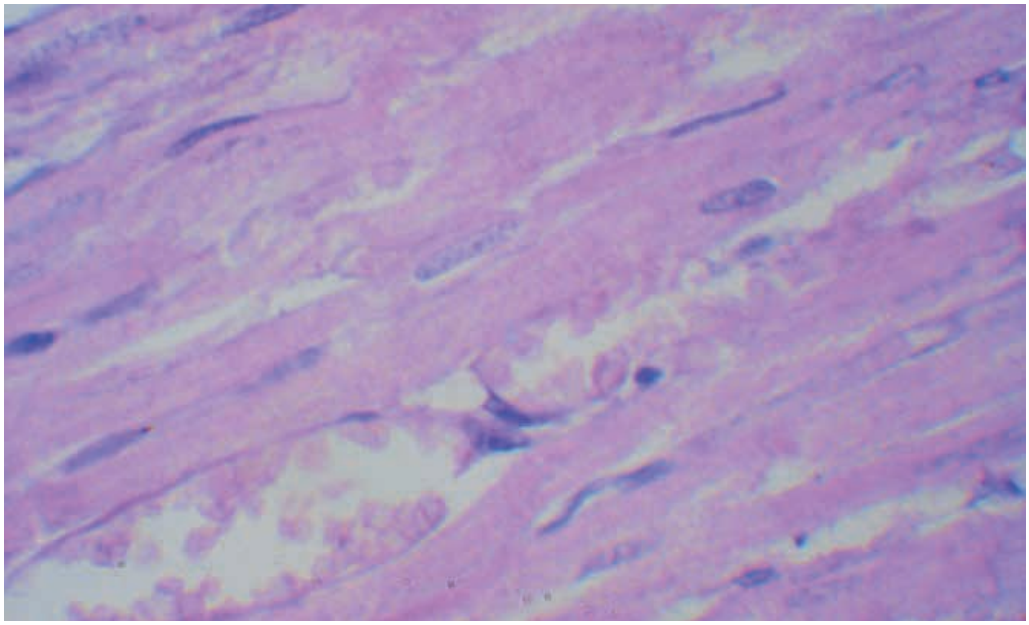

Figure 3. Morphology of Cardiomyocytes in Group 1 (5/6 Nephrectomy). Hematoxylin & eosin staining, ×400

In the 5/6 nephrectomy + spironolactone group, the cardiomyocytes have an elongated rectangular shape, and the transverse striation is preserved.

The cardiomyocytes contain 1-2 nuclei, predominantly oval in shape. Their average thickness is 15.22 μm.The average nuclear length is 10.08 μm, and the thickness is 2.75 μm.

Vascular-stromal component: the walls of the arterioles are not thickened. No significant increase in the connective tissue component is detected (Figure 4).

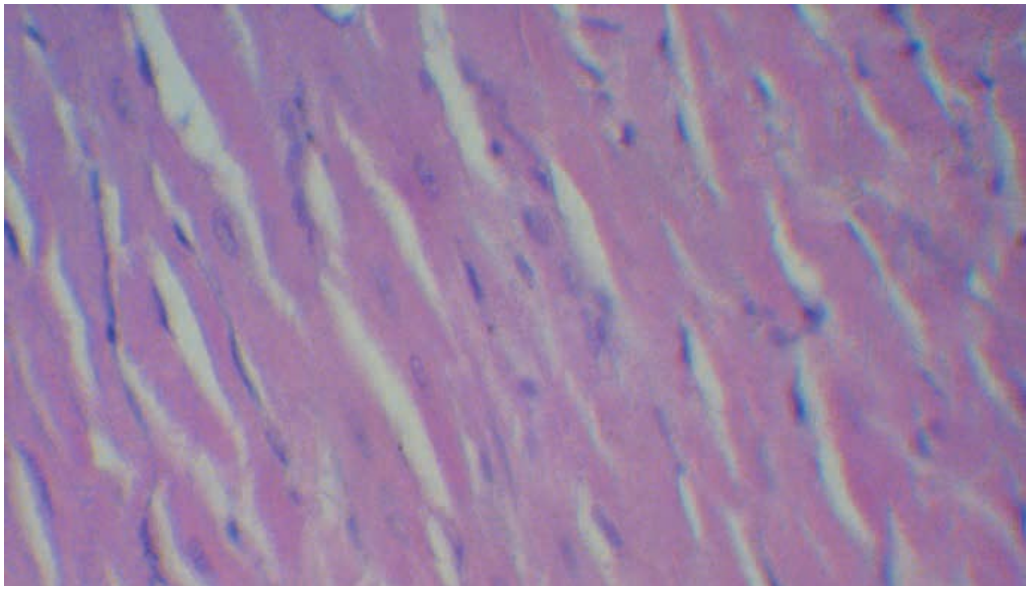

Figure 4.
Morphology of cardiomyocytes in Group 2 (5/6 nephrectomy + spironolactone). Hematoxylin & eosinstaining, ×400

Thus, in the group of animals with renal insufficiency that received spironolactone, compared to similar animals that did not receive the drug, a clear cardioprotective effect of pharmacological blockade of aldosterone receptors was observed.

This study also evaluated the effect of spironolactone on the mean arterial pressure and heart rate. The data are presented in Table 3.

Groups	Mean BP, mmHg	HR, beats/min	P value
Group 1 (Spironolactone)	151.3±2.7	393.8±17.6	0.0001 *
Group 2 (Without Spironolactone)	151.4±2.3	369±14.1	0.0001 *
Group 3 (Control)	121.15±1.8	347.8±10.3	0.0001 *
* p < 0.05 - statistical significance of differences			

Table 3.
Indicators of Blood Pressure and Heart Rate in Experimental Animals, M±m

Discussion

The conducted study showed that in experimental animals there was an increase in the levels of urea and creatinine in the blood serum, daily excretion of potassium and protein in urine, and blood pressure, which are all associated with a reduction in the number of functional nephrons and the development of renal insufficiency following nephrectomy. Our results are consistent with findings from other experimental studies.[9]. Moreover, animals in group 2 showed a significantly higher aldosterone concentration PAC, which can be attributed to the administration of spironolactone. Since spironolactone competes with aldosterone for binding to mineralocorticoid receptors, exogenous administration of spironolactone blocks these receptors, leading to suppression of the feedback mechanism and consequently an increase in PAC.[10]

In our study, all animals with experimental chronic kidney disease developed myocardial hypertrophy. It should be emphasized that the pathogenesis of myocardial hypertrophy in uremia remains insufficiently clear. At the early stage of renal insufficiency, it may be considered as a compensatory reaction to the increased preload on the heart due to developing arterial hypertension. However, as CKD progresses, adaptive mechanisms give way to maladaptive ones and hypertrophy becomes one of the main causes of left ventricle dysfunction.[10] Over the past decade, the pathophysiological aspects of cardiovascular complications in kidney diseases have been reassessed. Experimental studies have shown that aldosterone is one of the main factors in the hyper-

trophy and fibrosis of the myocardium, blood vessels, and kidneys in the context of renal failure.[11] It exerts its harmful effects through the classic mineralocorticoid mechanism. It is also possible that aldosterone participates in fibrogenesis through direct effects on the corresponding receptors localized in the cytosol of vascular fibroblasts.

The results of our study show that in the group of animals treated with the mineralocorticoid receptor blocker spironolactone, the myocardial hypertrophy index did not differ significantly from that of the control group, which is consistent with the findings of other authors and confirms that mineralocorticoid receptor blockade reduces left ventricular hypertrophy and, consequently, lowers the risk of developing cardiovascular complications.[12] Organ- and angioprotective clinical effects from the use of RAAS blockers in patients at high cardiovascular risk lead to global epidemiological effects, such as reduced morbidity and mortality rates in the population.[6]

Additionally, our results indicated that in the group of animals with renal insufficiency treated with spironolactone, there was no thickening of the arteriolar walls, unlike in animals that did not receive spironolactone.

Our work also demonstrated that the cardioprotective effect of spironolactone occurs independently of its influence on systemic blood pressure. This evidence suggests that spironolactone exerts its cardioprotective effect directly through its action on non-epithelial mineralocorticoid receptors in the myocardium, rather than through hemodynamic factors.

Limitations. In the present experiment, the effect of a mineralocorticoid receptor antagonist—spironolactone—was evaluated on morphological and hemodynamic parameters in a model of experimental arterial hypertension induced by 5/6 nephrectomy in *Wistar rats*. When interpreting the obtained data, it should be noted that the scope of interventions was limited to the use of a single drug at a fixed dose, without comparison to other pharmacological agents that may influence myocardial remodeling processes. Furthermore, although morphometric and hemodynamic parameters were assessed in the study, echocardiographic evaluation of structural and functional myocardial changes was not performed, which could have provided additional insight into the nature and extent of remodeling.

What's known? Prior to the present study, it had been established that mineralocorticoid receptor antagonists are capable of reducing myocardial remodeling in arterial hypertension. However, data on the effects of spironolactone under conditions of chronic kidney disease induced by partial nephrectomy were limited and fragmented.

What's new? For the first time, in a model combining 5/6 nephrectomy-induced arterial hypertension in *Wistar rats* and comparative analysis with spironolactone, it was demonstrated that its administration reduces the myocardial hypertrophy index, highlighting the potential of mineralocorticoid receptor blockade in correcting cardiac alterations associated with chronic kidney disease.

Conclusion

Thus, the analysis of our results leads us to conclude that aldosterone is a significant factor in the development and progression of myocardial and vascular remodeling in chronic kidney disease, and the blockade of aldosterone receptors by spironolactone in *Wistar rats* with 5/6 nephrectomy provides a cardioprotective effect regardless of blood pressure levels.

Acknowledgments. The authors express their sincere gratitude to the staff of the Research Institute of Nephrology and the Research Institute of Physiology (St. Petersburg) for their invaluable assistance in conducting the experiment. Special thanks are extended to Professor Esayan Ashot Movsesovich, Head of the Department of Nephrology and Dialysis of the Postgraduate Education Faculty at the Research Institute of Nephrology, and to Professor Kayukov Ivan Glebovich of the same department, for their valuable advice and continuous support throughout all stages of the study.

Authors' Contributions: K.A., Z.A., T.D.: Concept and design of the study, control of the research, approval of the final version of the article; K.Sh, M.I., M.A.: Collection and preparation of data, primary processing of the material and their verification Performance of the statistical analysis; K.A., M.A., A.I.: Writing the text

of the article (introduction, discussion, conclusion). K.A., T.D., M.I, K.Sh.: Writing the text of the article (methods, results). All authors reviewed, edited, and approved the final version of the manuscript

Funding: None

References

1. Savarese G, Lindberg F, Filippatos G, Butler J, Anker SD. Mineralocorticoid receptor overactivation: targeting systemic impact with non-steroidal mineralocorticoid receptor antagonists. *Diabetologia*. Feb 2024;67(2):246-262. doi:10.1007/s00125-023-06031-1

2. Gregg LP, Hedayati SS. Management of Traditional Cardiovascular Risk Factors in CKD: What Are the Data? *Am J Kidney Dis*. Nov 2018;72(5):728-744. doi:10.1053/j.ajkd.2017.12.007

3. Amornritvanich P, Anothaisintawee T, Attia J, McKay GJ, Thakkinstian A. Efficacy of Mineralocorticoid Receptor Antagonists on Kidney and Cardiovascular Outcomes in Patients With Chronic Kidney Disease: An Umbrella Review. *Kidney Med*. Feb 2025;7(2):100943. doi:10.1016/j.xkme.2024.100943

4. Moss ME, Jaffe IZ. Mineralocorticoid Receptors in the Pathophysiology of Vascular Inflammation and Atherosclerosis. *Front Endocrinol (Lausanne)*. 2015;6:153. doi:10.3389/fendo.2015.00153

5. Hasegawa T, Nishiwaki H, Ota E, Levack WM, Noma H. Aldosterone antagonists for people with chronic kidney disease requiring dialysis. *Cochrane Database Syst Rev*. Feb 15 2021;2(2):CD013109. doi:10.1002/14651858.CD013109.pub2

6. Minakuchi H, Wakino S, Urai H, et al. The effect of aldosterone and aldosterone blockade on the progression of chronic kidney disease: a randomized placebo-controlled clinical trial. *Sci Rep*. Oct 6 2020;10(1):16626. doi:10.1038/s41598-020-73638-4

7. O'Sullivan J, Finnie SL, Teenan O, et al. Refining the Mouse Subtotal Nephrectomy in Male 129S2/SV Mice for Consistent Modeling of Progressive Kidney Disease With Renal Inflammation and Cardiac Dysfunction. *Front Physiol*. 2019;10:1365. doi:10.3389/fphys.2019.01365

8. Barrera-Chimal J, Jaisser F, Anders HJ. The mineralocorticoid receptor in chronic kidney disease. *Br J Pharmacol*. Jul 2022;179(13):3152-3164. doi:10.1111/bph.15734

9. Kolkhof P, Joseph A, Kintscher U. Nonsteroidal mineralocorticoid receptor antagonism for cardiovascular and renal disorders - New perspectives for combination therapy. *Pharmacol Res*. Oct 2021;172:105859. doi:10.1016/j.phrs.2021.105859

10. Fujii W, Shibata S. Mineralocorticoid Receptor Antagonists for Preventing Chronic Kidney Disease Progression: Current Evidence and Future Challenges. *Int J Mol Sci*. Apr 23 2023;24(9)doi:10.3390/ijms24097719

11. Osman W, Al Dohani H, Al Hinai AS, Hannawi S, FA MS, Al Salmi I. Aldosterone renin ratio and chronic kidney disease. *Saudi J Kidney Dis Transpl*. Jan-Feb 2020;31(1):70-78. doi:10.4103/1319-2442.279963

12. Wang M, Han X, Yu T, et al. OTUD1 promotes pathological cardiac remodeling and heart failure by targeting STAT3 in cardiomyocytes. *Theranostics*. 2023;13(7):2263-2280. doi:10.7150/thno.83340