DOI:

УДК 616.61-002.2-06:[616.12-008.331.1+616.379-008.64]

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РОЛЬ УРЕМИЧЕСКОЙ ИНТОКСИКАЦИИ В РАЗВИТИИ СЕРДЕЧНО-СОСУДИСТОГО РЕМОДЕЛИРОВАНИЯ У ПАЦИЕНТОВ С ХРОНИЧЕСКОЙ БОЛЕЗНЬЮ ПОЧЕК 3А-5Д СТАДИЙ

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The Role of Uremic Intoxication in the Development of Cardiovascular Remodeling in Patients with Chronic Kidney Disease Stages 3a-5d

Резюме

В последние десятилетия распространенность хронической болезни почек (ХБП) в популяции имеет отчетливую тенденцию к росту. Это связано, прежде всего, с увеличением частоты встречаемости главных факторов, приводящих к ее развитию: сахарного диабета и артериальной гипертензии. Прогрессирование ХБП на фоне действия обозначенных факторов приводит к неуклонной потере почками их фильтрационной способности и развитию осложнений, связанных с этим процессом. К ним относятся, прежде всего, метаболические нарушения, расстройства кислотно-основного равновесия, дизэлектролитемии, уремическая интоксикация, гипергидратация, белково-энергетическая недостаточность, саркопения. Большинство из них участвует в развитии эндотелиальной дисфункции и формировании сердечно-сосудистого ремоделирования (ССР), как ключевого компонента кардиоренального континуума. При этом наблюдается взаимное негативное влияние патологии сердечно-сосудистой системы на функцию почек и проявлений ХБП на сердечно-сосудистую гемодинамику. Этот «порочный круг» приводит к развитию терминальной почечной недостаточности и повышению сердечно-сосудистого риска и смертности от болезней системы кровообращения пациентов на поздних стадиях ХБП. В связи с чем настоящая работа посвящена изучению роли уремической интоксикации и, в частности, индоксил сульфата, в развитии ССР у пациентов с ХБП на разных стадиях болезни.

Ключевые слова: *сердечно-сосудистое ремоделирование, кардиоренальный континуум, хроническая болезнь почек, индоксил сульфат*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

Источники финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

Статья получена 26.03.2021 г.

Принята к публикации 12.08.2021 г.

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Для цитирования: Гасанов М.З., Коломыйцева М.Н., Батюшин М.М. РОЛЬ УРЕМИЧЕСКОЙ ИНТОКСИКАЦИИ В РАЗВИТИИ СЕРДЕЧНО-СОСУДИСТОГО РЕМОДЕЛИРОВАНИЯ У ПАЦИЕНТОВ С ХРОНИЧЕСКОЙ БОЛЕЗНЬЮ ПОЧЕК 3А-5Д СТАДИЙ. Архивъ внутренней медицины. 2021; 11(5): 370-379. DOI: 10.20514/2226-6704-2021-11-5-370-379

Abstract

In recent decades, the prevalence of chronic kidney disease (CKD) in the population has a clear upward trend. This is due, first of all, to an increase in the frequency of occurrence of the main factors leading to its development: diabetes mellitus and arterial hypertension. The progression of CKD against the background of the action of these factors leads to a steady loss of the kidneys of their filtration capacity and the development of complications associated with this process. These include, first of all, metabolic and acid-base disorders, electrolyte abnormalities, uremic intoxication, overhydration, protein-energy wasting, sarcopenia and others. Most of them are involved in the development of endothelial dysfunction and the formation of cardiovascular remodeling (CVR), as a key component of the cardiorenal continuum. At the same time, there is a mutual negative influence of pathology of the cardiovascular system on renal function and manifestations of CKD on cardiovascular hemodynamics. This "vicious circle" leads to the development of end-stage renal disease and an increase in cardiovascular risk and mortality from diseases of the circulatory system in patients with advanced stages of CKD. In this connection, this work is devoted to the study of the role of uremic intoxication and, in particular, indoxyl sulfate, in the development of CVR in patients with CKD at different stages of the disease.

***Key words**: cardiovascular remodeling, cardiorenal syndrome, chronic kidney disease, Indoxyl sulfate*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

The authors declare no funding for this study

Article received on 26.03.2021

Accepted for publication on 12.08.2021

For citation: Gasanov M.Z., Kolomyitseva M.N., Batyushin M.M. The Role of Uremic Intoxication in the Development of Cardiovascular Remodeling in Patients with Chronic Kidney Disease Stages 3a-5d. The Russian Archives of Internal Medicine. 2021; 11(5): 370-379. DOI: 10.20514/2226-6704-2021-11-5-370-379

CCA — common carotid artery, CI — confidence interval, CKD — chronic kidney disease, CVR — cardiovascular remodeling, DM — diabetes mellitus, ESRD — end-stage renal failure, GFR — glomerular filtration rate, HD — hemodialysis, IHD — ischemic heart disease, IS — indoxyl sulfate, LBFV — linear blood flow velocity

Introduction

Today, there is a definite trend towards an increase in the number of patients with chronic kidney disease (CKD) with a heterogeneous etiological structure. Some patients develop end-stage renal failure (ESRD) as the disease progresses [1]. On the one hand, CKD aggravates the course of arterial hypertension, coronary heart disease, cerebrovascular disease, as well as microvascular disorders in diabetes mellitus (DM). This causes hemodynamic and metabolic disorders and significantly increases the cardiovascular risk and mortality of patients from circulatory system diseases, including at the early stages of the disease [2]. According to the SPRINT study, the presence of CKD significantly increased the incidence of adverse cardiovascular events (2.84%/year versus 1.55%/year, $p < 0.001$) [3]. On the other hand, diabetes mellitus, arterial hypertension and other cardiovascular diseases accelerate renal function loss, closing the vicious circle and contributing to cardiovascular mortality [4, 5]. In this connection, CKD is not only a nephrological issue but a multidisciplinary problem. Significant efforts are required for a more detailed study of the pathogenetic mechanisms of the development of cardiorenal syndrome.

In this aspect, the progression of cardiovascular remodeling (CVR) plays a key role in the development of cardiovascular pathology in CKD [6]. CVR is associated with a wide range of metabolic and hemodynamic disorders, with uremic intoxication, electrolyte disorders, systemic inflammation, arterial hypertension, vascular calcification, hyperphosphatemia, proteinuria, and anemia contributing the most. These factors and their high prevalence in patients with CKD form the basis of the cardiorenal continuum [7, 8].

Uremic toxins that accumulate in the body during CKD exhibit biological activity and cause toxic effects. The classification of the European Working Group on Uremic Toxins EUTox (2012) identifies free water-soluble low molecular weight compounds (0.5 kDa), medium molecular weight molecules (0.5–60.0 kDa) and protein-bound compounds depending on the size and binding properties [9]. Their content in patients with CKD significantly exceeds that in the group of healthy individuals and is directly linked to uremia symptoms. Albumin-associated indoxyl sulfate (IS) is of particular interest for our study as a key marker of uremic intoxication in the discussed cohort of patients. Its concentration in blood increases in conditions of impaired

kidney filtration capacity. IS plays an important role in the progression of CVR, especially in the group of dialysis patients, since it does not completely penetrate the dialysis membrane and accumulates in the body and causes complications [10, 11]. The wide range of the biological effects of IS, such as potentiation of systemic inflammation, activation of inflammatory response and oxidative stress, vascular wall calcification, effect on adipocytes and immune cells, and stimulation proliferation of endothelial cells, can lead to endothelial dysfunction and the progression of CVR [12–15]. Also, IS can realize its profibrotic effect by influencing the differentiation of smooth muscle and epithelial cells of the proximal tubules of kidneys [16].

Despite the progress achieved in the study of the pathophysiological mechanisms of the effect of uremic toxins on CVR processes, we did not find any work on the comparative assessment of IS levels and indices of morphometry of vascular wall and blood flow velocity. However, it is of research interest. This paper intends to assess the role of uremic intoxication in CVR and the importance of IS as a promising molecular marker of this pathological process.

The purpose of this study was to investigate the role of uremic intoxication and, particularly IS, in CVR in patients with CKD at different stages of the disease.

The inclusion criteria were: CKD stages 3A-5D, use of long-term hemodialysis in patients with CKD stage 5D. The study had the following exclusion criteria: acute or exacerbation of a chronic infection requiring active treatment, alcoholism, drug addiction, as well as mental disorders, pregnancy, breastfeeding, immunosuppressive therapy currently or in the past three months, hereditary metabolic diseases and lack of consent to participate in the study.

We carried out a one-stage cross-sectional study. At the first stage, clinical and anamnestic, and anthropometric data were collected from all patients, and concomitant diseases were identified. Next, laboratory and instrumental examination was carried out: CBC (Sysmex XT 2000i analyzer, Japan), CU (Dirui H-1000 urine analyzer), blood biochemistry (ARCHITECT CI8200 analyzer, USA), as well as ultrasound (basins of brachial, carotid and renal arteries), EchoCG (on Toshiba Aplio 300 machine, Japan), test with endothelium-dependent vasodilation, determination of the concentration of indoxyl sulfate (IS) in blood serum (Luminex MAGPIX machine (USA), "Indoxyl sulfate" laboratory kit BlueGene Corp, (USA)) by ELISA (measurement range — 1–25 ng/ml, sensitivity of the method is 0.1 ng/ml).

At the second stage, a statistical analysis of the data obtained was carried out to study the role of IS in CVR. In order to determine intergroup differences, we divided all patients into two groups: Group 1 — patients with CKD 5D receiving treatment with programmed hemodialysis, group 2 — patients with CKD 3A-5.

Statistical processing of the results was carried out using Statistica 10.0 and IBM SPSS Statistics 25 software. The nature of the distribution of quantitative parameters was determined via the Kolmogorov — Smirnov test with Lilliefors correction, as well as the Shapiro — Wilk test with a sample size of less than 30, with an additional assessment of kurtosis and asymmetry. Quantitative parameters with a normal distribution of samples were represented by the mean and standard error of the mean, and with a distribution different from normal, by the median (Me) and the 25th and 75th percentiles. The reliability of differences between qualitative parameters was determined using the nonparametric criterion χ^2, between quantitative parameters in groups — using the Mann — Whitney test. The Kruskal — Wallis test was used when there were more than two groups. Correlation analysis was carried out using the Spearman test, while the strength of the connection was determined using the Chaddock scale. The critical level of statistical significance when testing null hypotheses is $p < 0.05$. In order to determine the quality of the diagnostic criteria developed by us, we used ROC analysis (Receiver Operating Characteristic curve) with the analysis of AUC (area under the curve).

Materials and Methods

We examined 70 patients with CKD stages 3A-5D. The average age of the patients was 59.3 ± 12.5; there was no significant difference between the groups (group 1 — (58.72 ± 12.50) years, group 2 — (59.91 ± 12.67) years, p_{1-2}= 0.74. The average age of the patients depending on the stage of CKD was: Stage 3A — (63.20 ± 11.78) years, Stage 3B — (59.27 ± 13.70) years, Stage 4 — (55.86 ± 13.80) years, Stage 5 — (62.5 ± 4.9) years, Stage 5D — (58.72 ± 12.50) years, p_{3A-5D} = 0.81). The sample included 30 men (42.3%) and 40 women (57.7%); there was no statistically significant difference between the groups for this parameter (p_{1-2} = 0.089, p_{3A-5D} = 0.17). The etiological structure of CKD in patients was quite diverse and was determined as follows: the most frequently diagnosed: chronic tubulointerstitial nephritis (22 patients — 31%), hypertensive nephropathy (25 patients — 35.2%), as well as diabetic nephropathy (15 patients — 21.1%) and chronic glomerulonephritis (15 patients — 21.1%). It should be noted that the overwhelming majority of patients had arterial hypertension

Table 1. Laboratory serum counts of patients of the 1st and 2nd groups

Indicator	1st group	2nd group	p
	Me[Q1;Q3]		
*Creatinine, μmol / l	810,35 [671,7;949,1]	146,0 [113,0;174,0]	<0,001
*Urea, mmol / l	20,25 [16,99;23,61]	9,9 [7,9;12,6]	<0,001
*GFR, ml / min / 1.73m^2	5,0 [4,0;5,5]	37,5[29,0;45,0]	<0,001
Uric acid, μmol / l	404,26 [363,55;441,8]	391,5 [308,0;446,0]	0,3
*Sodium, mmol / l	137,6 [135,0; 139,55]	139,45 [138,2;141,2]	0,01
*Potassium, mmol / l	5,76 [4,93;6,23]	4,64 [4,34;4,98]	<0,001
*Calcium, mmol / l	1,1 [1,08;1,23]	1,08 [1,01;1,14]	0,008
*Chloride, mmol / l	101,5 [99,0;103,0]	104,0 [102,0;105,0]	0,002

Note: * — the levels are statistically significant based on the Mann-Whitney U test

Table 2. Laboratory serum counts in patients ranked by stage of CKD

Indicator	CKD G3a	CKD G3b	CKD G4	CKD G5	CKD G5D	p
	Me[Q1;Q3]	Me[Q1;Q3]	Me[Q1;Q3]	Me[Q1;Q3]	Me[Q1;Q3]	
*Creatinine, μmol / l	107,0 [104,0;123,0]	146,0 [129,5;153,0]	177,0 [171,0;200,5]	411,0 [331,0;491,0]	810,4 [671,7;949,1]	<0,001
*Urea, mmol / l	7,6 [5,7;9,9]	9,5 [8,95;12,4]	12,4 [10,8;15,0]	16,9 [15,6;18,2]	20,25 [16,99;23,61]	<0,001
*GFR, ml / min / 1.73m^2	51,0 [47,0;55,0]	37,0 [34,0;39,5]	28,0 [25,0;28,5]	11,0 [10,0;12,0]	5,0 [4,0;5,5]	<0,001
Uric acid, μmol / l	400,5 [324,0; 443,0]	420,0 [307,0;479,5]	358,0 [319,0;392,0]	348,0 [250,0;446,0]	404,3 [363,6;441,8]	0,78
Sodium, mmol / l	139,9 [138,5;141,4]	139,4 [138,2;141,1]	139,7 [138,4;140,6]	137,3 [136,9;137,7]	137,6 [135,0;139,6]	0,51
*Potassium, mmol / l	4,6 [4,3;4,9]	4,6 [4,4;4,9]	5,0 [4,4;5,0]	4,8 [4,8;4,8]	5,8 [4,9;6,2]	0,001
*Calcium, mmol / l	1,0 [1,0;1,1]	1,1 [1,0;1,1]	1,1 [1,1;1,2]	1,1 [1,1;1,2]	1,1 [1,1;1,2]	0,02
*Chloride, mmol / l	103,5 [102,0;107,0]	104,0 [103,0;105,0]	105,0 [103,0;106,0]	102,5 [99,0; 106,0]	101,5 [99,0;103,0]	0,03

Note: * — the levels are statistically significant based on the Mann-Whitney U test

(61 patients — 85.9%), while 46.5% had stage III, 42.3% had stage II, and 1.4% of patients had stage I. Comorbidities pathogenetically associated with CKD included the following: diabetes mellitus (DM) — 19 patients — 26.8%, obesity (23 patients — 32.4%), urolithiasis (15 patients — 21.1%), ischemic heart disease (IHD) — 27 patients — 38.0%). The history of CKD averaged (9.24 ± 9.70) years [5; 37].

The number of patients with CKD on long-term HD was 36 (50.7%); 34 subjects (47.9%) were not receiving HD. The distribution of patients by CKD stages was as follows: Stage 3A — 10 patients (14.3%), 3B — 15 (21.4%), 4 — 7 (10%), 5 — 2 (2.9%), 5D — 36 (51.4%).

The group of dialysis patients was found to have a statistically significant increase in the concentration of routine markers of impaired renal filtration capacity, urea and creatinine, as well as a significant difference in the levels of potassium, calcium and chlorine (Table 1). Laboratory characteristics of patients according to CKD stages are shown in Table 2.

Results and Discussion

Analysis of the data obtained showed that the median IS concentration was 5.65 [4.33; 7.12] ng/ml, while significant differences were observed between the comparison groups — the highest concentration was found in the dialysis group compared to the pre-dialysis group: 6.17 [4.62;8.28] ng/ml and 5.3 [4.2;6.28] ng/m, respectively ($p_{1-2} = 0.009$). The level of IS also tended to increase with the progression of CKD (Kruskal — Wallis test, $p._{3A-5D} = 0.05$), respectively in stages: 3A — 4.6 [4.1;6.6] ng/ml, 3B — 5.3 [4.3;5.9] ng/ml, 4 — 5.5 [4.4;6.5] ng/ml and 5 — 6.1 [6.0;6.3] ng/ml. We discovered a moderate negative correlation between the level of GFR and IS ($r = -0.33$) (Fig. 1).

An increase in IS levels with a decrease in GFR indicates increasing uremic intoxication with CKD progression. The data obtained are confirmed by an increase in such known parameters of renal dysfunction as creatinine and urea against the background of disease progression (Tables 1, 2). It should be noted that IS is not only

presented as a byproduct but is also a key regulator of muscle tissue metabolism, endothelial function, oxidative stress, and other processes in the discussed cohort of patients, which needs further investigation.

In order to assess intracardiac hemodynamics and CVR, all patients underwent echocardiography, as well as ultrasound of renal, carotid and brachial arteries.

Due to the pronounced effect of endogenous uremia on the endocardium, we analyzed the state of heart valves: the greatest changes in the form of insufficiency were determined for mitral and tricuspid valves (Fig. 2, 3). It should be noted that tricuspid valve insufficiency was detected statistically significantly more often in the group of patients receiving HD treatment (p_{1-2} = 0.008). Based on the Kendall — Tau test, a significant difference in the frequency of this parameter was revealed depending on the CKD stage (Ƭ = 0.23, p_{3A-5D} = 0.021).

Valvular dysfunction in patients indirectly demonstrates adaptive processes occurring in the cardiovascular system of patients with CKD in response to impaired homeostasis and changes in hemodynamics that are manifested, among other things, by hyperhydration and increased pre- and afterload. Such changes are especially pronounced in patients receiving HD treatment due to the presence and functioning of vascular access and regular HD procedures.

We found a statistically significant difference in the diameter of the aorta in the area of the sinus of Valsalva between groups 1 and 2 (p_{1-2} = 0.005) (Table 3). Also, there was a tendency towards a decrease in the diameter of the aorta in the sinotubular junction for patients receiving HD compared with the pre-dialysis group (p_{1-2} = 0.038) (Table 3). However, an analysis (performed using Kruskal — Wallis test) of echocardiography in the groups of patients ranked by CKD stages showed statistically significant differences only in the aortic diameter in the area of the sinus of Valsalva (p_{3A-5D} = 0.02). In the follow-up group, myocardial hypertrophy was observed significantly more often, in particular, of the interventricular septum (p_{1-2} = 0.007), as well as the posterior wall of the left ventricle (p_{1-2} = 0.011) (Table 3). The discussed changes demonstrate cardiovascular remodeling mainly in the group of dialysis patients, probably due to the peculiarities of the redistribution of fluid in the body, as well as endothelial dysfunction.

The E/a index is a component of the comprehensive assessment of left ventricular diastolic function. It was lower than 1.0 in both groups and significantly lower in the group of patients receiving treatment with long-term HD (p_{1-2} = 0.05), which corresponded to diastolic dysfunction and indicated more pronounced disorders of intracardiac hemodynamics in group 1.

When assessing hemodynamics in the brachial artery system, a significant increase in linear blood flow velocity was found in the group of patients on long-term HD, and a moderate negative correlation (r = –0.42) of this parameter with the CKD stage was found (Table 4). The greatest differences in blood flow velocity were determined in systole (p_{1-2} = 0.008) compared with diastole (p_{1-2} = 0.011), as well as in the systolic-diastolic

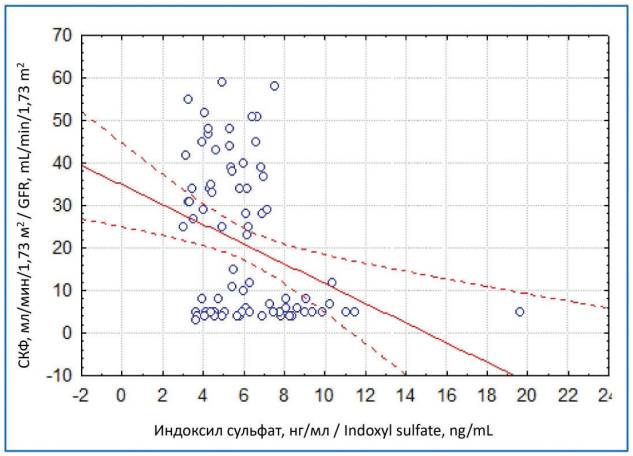

Figure 1. *Correlation between the level of IS and GFR in the general cohort of patients*

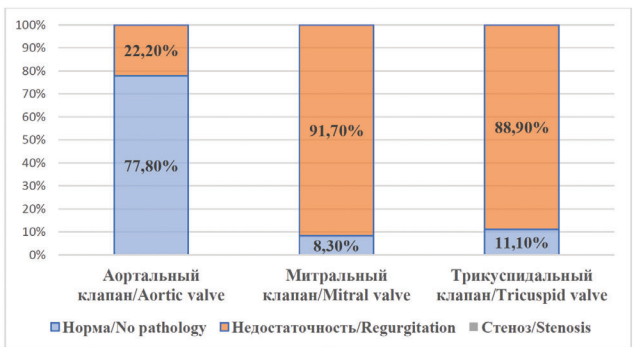

Figure 2. *Features of changes in the heart valve apparatus in patients with CKD5D*

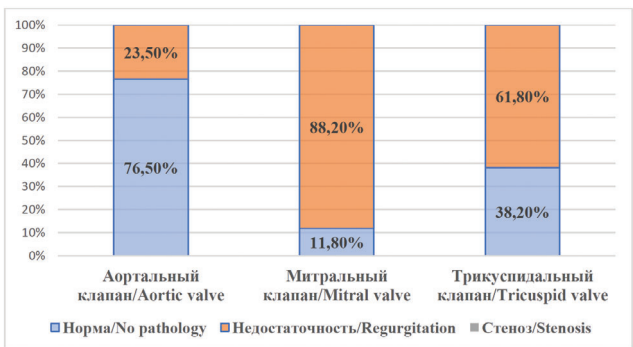

Figure 3. *Changes in the heart valve apparatus in patients with CKD stages 3A-5*

Table 3. *Echocardiography parameters in patients of the 1st and 2nd groups*

Indicator	1st group	2nd group	p
	Me[Q1;Q3])		
*Aortic diameter (Valsalva sinus), mm	31,5 [28,0;33,0]	33,0 [32,0;34,0]	0,005
*Aortic diameter (sinotubular junction), mm	32,0 [30,0;34,0]	33,0 [32,0;34,0]	0,038
EF, %	58,5 [53,5;64,0]	60,0[56,0;63,0]	0,4
CO, L/min	5,5 [4,2;6,5]	4,5 [4,1;5,3]	0,07
*IVST, mm	12,5 [12,0;13,4]	12,0 [11,2;12,3]	0,007
*LVPWT, mm	12,4 [12,0;13,5]	12,0 [11,2;12,3]	0,011
E/A ratio	0,7 [0,7;0,8]	0,8 [0,7;0,9]	0,05

Note: * — the levels are statistically significant based on the Mann-Whitney U test; EF — ejection fraction, CO — cardiac output, IVST — interventricular septum thickness, LVPWT — left ventricular posterior wall thickness, E/A ratio — the ratio of peak velocity blood flow from left ventricular relaxation in early diastole (the E wave) to peak velocity flow in late diastole caused by atrial contraction (the A wave)

Table 4. *Indicators of blood flow in the brachial artery in patients of the 1st and 2nd groups*

Indicator	1st group	2nd group	p
	Me[Q1;Q3])		
*Blood flow velocity along the brachial artery in systole, cm/s	4,6 [4,1;5,3]	4,1[3,7;4,7]	0,008
*Blood flow velocity along the brachial artery in diastole, cm/s	4,2 [3,9;4,9]	3,9[3,5;4,5]	0,011
* Difference in linear velocities of blood flow along the brachial artery in systole and diastole, cm/s	47,5[35,0;59,0]	56,0 [48,0;69,0]	0,015
*Diameter of the brachial artery in systole, mm	63,0 [47,5;77,0]	76,0 [67,0;83,0]	0,008
Diameter of the brachial artery in diastole, mm	16,5 [11,0;21,5]	18,0 [17,0;20,0]	0,057
Resistance index of the brachial artery	0,8 [0,7;0,8]	0,8 [0,7;0,8]	0,6

Note: * — the levels are statistically significant based on the Mann-Whitney U test

difference (p_{1-2} = 0.015). Also, lower values of the diameter of the brachial artery in systole were found in patients of group 1 (p_{1-2} = 0.008). Apparently, this is due to more pronounced vascular stiffness in patients receiving HD treatment with underlying hypercholesterolemia, generalized atherosclerosis and vascular calcification.

In groups 1 and 2, significant changes in renal blood flow were found as CKD progressed. A decrease in blood flow velocity was observed at all levels of the architectonics of renal arteries: in the mouth, hilum, in segmental and interlobar arteries, primarily in group 1 compared to group 2 (Table 5). Maximum changes were observed in the area of segmental and interlobar arteries, on both the right and the left, and the values of these parameters were significantly lower in dialysis patients (Table 5). The distribution of patients in the entire cohort by CKD stages showed statistically significant differences in renal blood flow parameters using the Kruskal — Wallis test: (p_{RI} = 0.24, $p_{Vmax\ mouth}$ = 0.035, $p_{Vmaxseg}$ = 0.016, $p_{Vmin\ segm}$ = 0.007, $p_{Vmin\ inter}$ = 0.02) and left ($p_{Vmax\ mouth}$ = 0.025, $p_{Vmin\ mouth}$ = 0.011, p_{Vmax} = 0.011, $p_{Vminhil}$ = 0.004, $p_{Vmaxseg}$ = 0.015, $p_{Vminseg}$ = 0.001, $p_{Vmaxinter}$ = 0.004, $p_{Vmininter}$ = 0.001).

The obtained data paint the picture of intrarenal hemodynamics in patients with CKD and the severity of renal blood flow disorders, especially in group 1. The reasons for this can be both nephrosclerosis, which develops with underlying uncontrolled hyperglycemia or high blood pressure, and other reasons, including uremic intoxication that potentiates endothelial dysfunction and subsequent vascular remodeling. These processes accelerate CKD progression and worsen the prognosis of the disease.

Blood flow in the systems of common, internal, and external carotid arteries, as well as in the brachiocephalic trunk, was investigated to assess the hemodynamics in cerebral arteries. The greatest intergroup differences were determined in terms of the linear velocity of blood flow into systole in the common carotid artery (p_{1-2} = 0.03) (Fig. 4) and external carotid artery (p_{1-2} = 0.04) (Fig. 5). There was no significant difference in linear blood flow velocity (LBFV) in the carotid system depending on the stage of CKD. There was a decrease in LBFV in the common and external carotid arteries in group 1 compared to group 2, which is probably due to the peculiarities of cardiac remodeling in the group of dialysis patients (myocardial hypertrophy, diastolic dysfunction, valvular pathology are more common), an increase in MVC, loss of kidney filtration capacity and other reasons. Apparently, this outweighs the contribution of endothelial dysfunction of the main arteries with underlying uremic intoxication to the disbalance of vascular resistance and effect on central hemodynamics. However, this issue requires further study.

Table 5. *Renal blood flow parameters in patients of the 1st and 2nd groups*

Indicator	1st group	2nd group	P
	Me[Q1;Q3]		
V_{max} in the proximal right main renal artery, cm/s	54,0[52,5;57,5]	74,5 [61,0;85,0]	0,002
V_{min} in the proximal right main renal artery, cm/s	21,0 [21,0;23,5]	24,5 [21,0;29,0]	0,4
Resistance index in the main proximal renal artery on the right	0,6 [0,6;0,6]	0,6 [0,6;0,7]	0,13
V_{max} in the distal right main renal artery, cm/s	55,0 [49,5; 57,5]	67,5 [54,0;78,0]	0,07
V_{min} in the distal right main renal artery, cm/s	22,0 [17,0;23,0]	30,0 [21,0; 32,0]	0,03
V_{max} in the right segmental arteries, cm/s	22,0 [21,0; 32,5]	50,0 [36,0;54,0]	0,001
V_{min} in the right segmental arteries, cm/s	9,0 [9,0;10,5]	19,0 [13,0;20,0]	0,001
V_{max} in the right interlobar arteries, cm/s	13,0 [13,0;17,0]	22,0 [20,0;26,0]	0,008
V_{min} in the right interlobar arteries, cm/s	6,0 [5,0;6,5]	11,0 [10,0;11,0]	<0,001
V_{max} in the proximal left main renal artery, cm/s	59,0 [50,5;59,0]	75,0 [67,0;89,0]	0,001
V_{min} in the proximal left main renal artery, cm/s	23,0 [21,5;24,0]	32,5 [23,0;33,0]	0,03
Resistance index in the main proximal renal artery on the left	0,6 [0,6;0,6]	0,7 [0,6;0,7]	0,021
V_{max} in the distal left main renal artery, cm/s	51,0[49,0;57,0]	77,0 [57,0;87,0]	0,014
V_{min} in the distal left main renal artery, cm/s	23,0[16,0;25,0]	31,0[21,0;31,0]	0,021
V_{max} in the left segmental arteries, cm/s	23,0[23,0;28,0]	53,0[40,0;53,0]	0,006
V_{min} in the left segmental arteries, cm/s	8,0[7,5;10,0]	19,0[12,0;19,0]	0,003
V_{max} in the left interlobar arteries, cm/s	14,0[14,0;18,0]	23,0[23,0;31,0]	<0,001
V_{min} in the left interlobar arteries, cm/s	5,0[4,5;5,0]	11,0[11,0;12,0]	<0,001

Note: * — the levels are statistically significant based on the Mann-Whitney U test; Vmax — maximum blood flow velocity, Vmin — minimum blood flow velocity; RI — resistance index

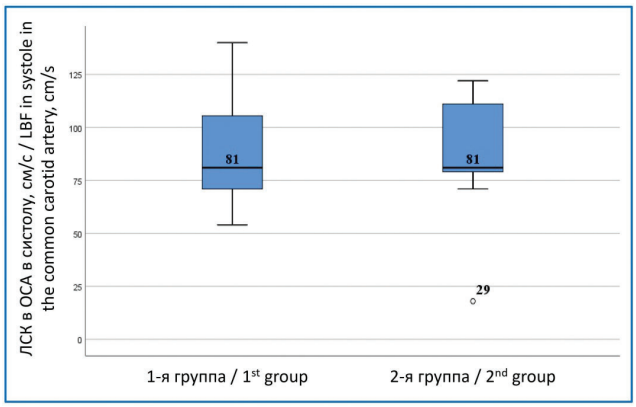

Figure 4. *Linear blood flow velocity in systole in the common carotid artery in patients of the 1st and 2nd groups (p_{1-2} = 0.03)*

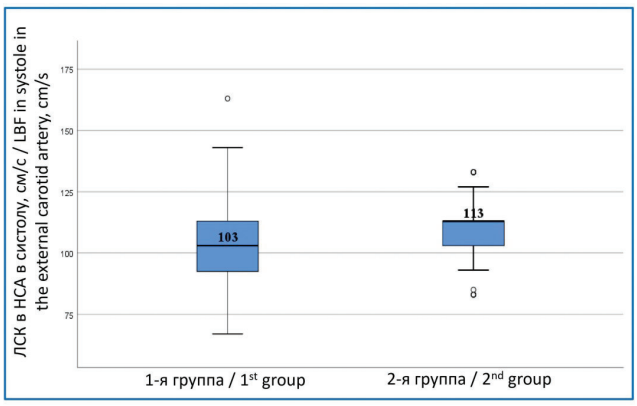

Figure 5. *Linear blood flow velocity into systole in the external carotid artery in patients of the 1st and 2nd groups (p_{1-2} = 0.04)*

When conducting a correlation analysis of factors that had significant differences between groups 1 and 2 using the Spearman test, we discovered synergistic changes in hemodynamic parameters in the vessels of brachial, carotid and renal arteries, myocardial hypertrophy, as well as levels of metabolic and electrolyte imbalance. Correlation analysis of the IS level showed the most significant relationship according to the Chaddock scale with urea (r = 0.6, p < 0.001), phosphorus (r = 0.4, p < 0.001), and the thickness of renal parenchyma (r = 0.66, p = 0.02), and a weak relationship with the diameter of the aorta in the sinotubular region (r = 0.3, p = 0.011) and linear blood flow velocity in the CCA in systole (r = 0.2, p = 0.04), which demonstrates the relationship between the value of the parameter of the indicated uremic molecular marker and the significance of the CVR processes.

We also carried out ROC analysis to get a deeper understanding of the role of IS in the development of CVD and the possibility of using it as a biological marker of the progression of this phenomenon in CKD. The area under the ROC curve, which corresponds to

the relationship between the concentration of IS and the probability of dilation of the brachial artery less than 10 % (as an indirect parameter of the presence of endothelial dysfunction in the patient) after a test with endothelium-dependent vasodilation, was 0.64 ± 0.07 (95% CI = 0.5–0.8). The resulting model was statistically significant (p = 0.04) [17].

The threshold value of the IS level at the cut-off point is 5.76 ng/ml. When equal or higher than this value, the IS level was predicted to have a high risk of CVR. The sensitivity and specificity of the method were 77.3% and 55.2%, respectively (Fig. 6).

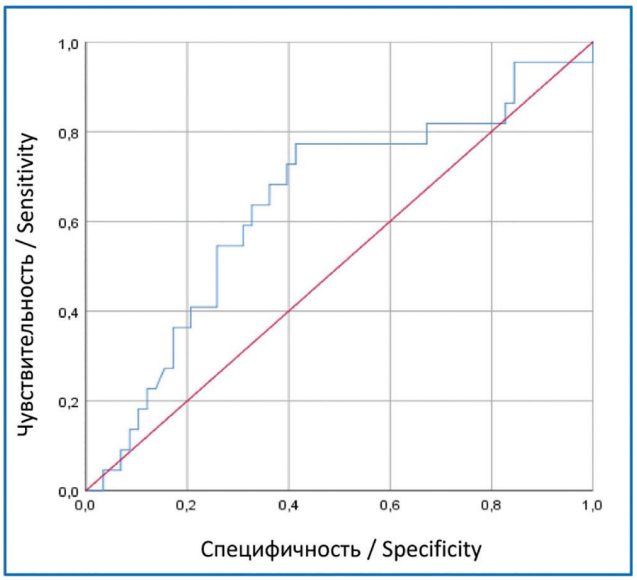

Figure 6. *ROC-curve of the dependence of the narrowing of the brachial artery on the level of Indoxyl sulfate*

Testing with endothelium-dependent vasodilation is an additional method available in practical healthcare for the indirect assessment of endothelial dysfunction in a patient. The determination of IS level and considering this parameter, together with the data obtained on changes in the diameter and LBFV of the brachial artery after the test, improves the prognostic value of this method and represents an effective model for assessing the likelihood of endothelial dysfunction in patients with CKD with underlying uremic intoxication.

The area under the ROC curve of the increasing thickness of intima-media complex (TIMC) of the common carotid artery, as one of the predictors of CVR, on the IS level was 0.680 ± 0.066 (95% CI = 0.6–0.8). The resulting model was statistically significant (p = 0.021). It should be noted that there was no significant difference in TIMC values between CKD stages (p > 0.05).

If the IS threshold point is equal to or greater than 4.8 ng/ml, a high risk of increased TIMC of the common carotid artery is predicted. The sensitivity and specificity of the method are 75.0% and 54.2%, respectively (Fig. 7). An increase in TIMC in patients with CKD with underlying uremic intoxication is a potential unfavorable predictor of not only CVD but also cardiovascular events.

The area under the ROC curve, which corresponds to the relationship between the thickness of renal parenchyma according to ultrasound and IS concentration, was 0.66 ± 0.06 (95% CI = 0.54–0.78). The resulting model was statistically significant (p = 0.03). The cutoff point of the IS level was 5.3 ng/ml with a sensitivity and specificity of 78.8% and 55.3%, respectively (Fig. 8).

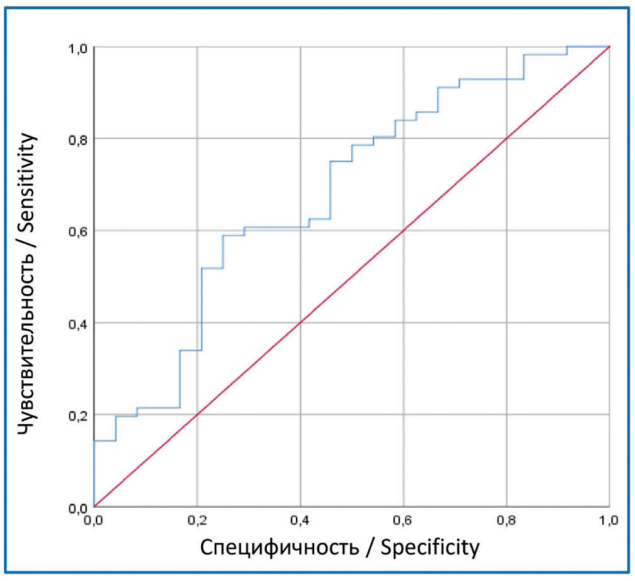

Figure 7. *ROC-curve of the dependence of the increase in ICIM in the common carotid artery on the level of Indoxyl sulfate*

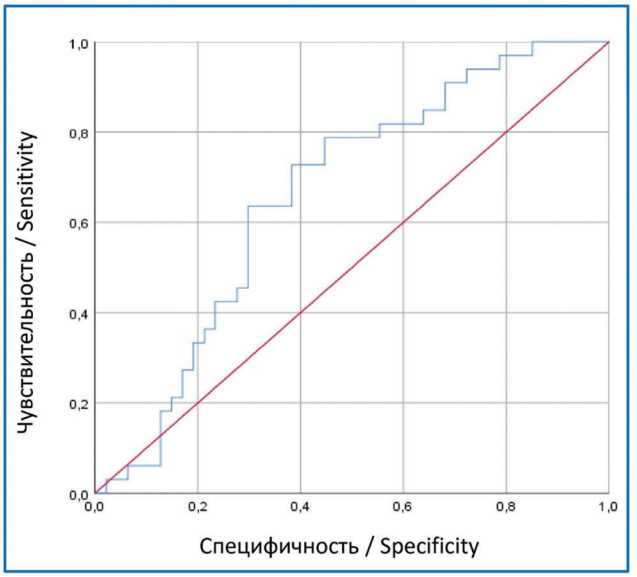

Figure 8. *ROC-curve of the dependence of the thickness of the parenchyma of the right kidney on the level of Indoxyl sulfate*

CKD progression is clearly associated with nephrosclerosis, decreased kidney size, including parenchyma, according to ultrasound data, and impaired kidney function, which is associated with uremic intoxication. The discussed diagnostic model indirectly demonstrates the ability to predict the rate of CKD progression depending on the level of IS.

Conclusion

The analysis of the results obtained made it possible to identify cardiovascular system remodeling features in patients with CKD at different stages of the disease and to assess the contribution of IS as a parameter of uremic intoxication in its development. It was found that in patients receiving treatment with long-term hemodialysis, the indicated changes were observed significantly more often and were accompanied by a high level of IS. This may not only indirectly indicate the role of the latter in this pathological process but also allows using the determination of the IS level as an additional diagnostic marker to determine the severity of the course and prognosis of CKD.

The contribution of other factors to CVR in patients with CKD requires a comprehensive assessment and further study of the pathogenetic mechanisms of their effects. Repeated determination of the IS level, as well as ultrasound examination of the cardiovascular system over time, will allow not only to make a prognostic model for assessing the likelihood of CVR and the rate of its progression in the group of patients under discussion but also to carry out timely pharmacological correction.

Вклад авторов:

Все авторы внесли существенный вклад в подготовку работы, прочли и одобрили финальную версию статьи перед публикацией

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