FUNCTIONAL STATE OF KIDNEYS IN PATIENTS WITH IHD

Abstract. The aim of the study: to study the functional state of the kidneys in patients with ischemic heart disease (IHD) in the long-term period after myocardial revascularization. Material and research methods. The study included 160 patients with ischemic heart disease (IHD), hospitalized for coronary angiography and decisions on the appropriateness and choice of revascularization technique. The study did not include patients with eGFR less than 60 ml/min. All patients were prescribed standard IHD therapy. On the second day after the endovascular procedure, coronary angiography/percutaneous coronary intervention (CAG/PCI), all patients underwent determination of the blood creatinine concentration to identify patients who developed contrast-induced nephropathy (CIN). In dynamics, three months later, at the end of the first and second years of observation after revascularization, all patients underwent determination of the functional state of the kidneys: the concentration of blood creatinine, with the calculation of GFR, the concentration of parathyroid hormone, phosphorus, uric acid in the peripheral blood. According to the results of coronary angiography, 21 patients underwent surgical revascularization (coronary artery bypass grafting CABG) within a month after CAG. Endovascular revascularization (stenting of the coronary arteries) was performed in 139 patients. CIN in the early period after endovascular intervention was observed in 37 patients. The study showed that during 2 years of follow-up after coronary revascularization, there was a progressive decrease in eGFR: by the 3rd month, eGFR decreased by -17.39 ± 1.17%, by the end of the 1st year - by -43.62 ± 1.28%, by the end of the second year of follow-up - by -46.50 ± 1.79% The decrease in eGFR was significantly more pronounced in the group of patients who had CIN in the early period after endovascular intervention (37 patients): (-39, 82 ± 2.02% by the end of the 3rd month, -54.61 ± 2.94% by the end of the 1st year and -60.10 ± 3.99% by the end of the 2nd year of follow-up versus -10, 65 ± 0.57%, -40.32 ± 1.27% and -42.41 ± 1.85% in patients with CIN, respectively, p <0.001). By the third month of follow-up, the dynamics of eGFR in the groups, depending on the revascularization method, did not differ (-16.36 ± 3.30% and -17.55 ± 1.25%, respectively). By the end of the 1st year of follow-up, in patients who underwent surgical
revascularization, the decrease in eGFR was significantly more pronounced than in patients who underwent coronary artery stenting (-51.80 ± 3.51% versus -42.39 ± 1.35%, p <0.05), and the differences increased even more during the second year of observation (-57.99 ± 4.75% versus -44.76 ± 1.89%, p <0.05). Violation of the functional state of the kidneys was manifested by an increase in the concentration of blood phosphorus, parathyroid hormone and uric acid. The concentration of these markers increased during observation in parallel with a decrease in eGFR. The concentration of these substances was higher in patients after CIN, compared with patients with an uncomplicated postprocedural period. The concentration of uric acid was initially higher in the group of patients who underwent CABG compared with patients who underwent percutaneous coronary intervention PTCI. Conclusion. In patients with IHD after revascularization, there is a significant decrease in the glomerular filtration function of the kidneys by the 3rd month after the endovascular procedure and lasts at least 2 years. The most significant decrease was observed in patients with diabetes mellitus, as well as in patients who underwent CIN in the early period after endovascular intervention. The progression of CKD continues to be accompanied by an increase in the concentration of parathyroid hormone, uric acid and blood phosphates.

Keywords: ischemic heart disease, chronic kidney disease, chronic heart failure, revascularization, contrast-induced nephropathy, glomerular filtration rate.

Actuality: Ischemic heart disease (CHD) is today one of the most common non-infectious pathologies in the world. Its prevalence reaches 6% among people over 20 years old (up to 8% among men). [11]. Ischemic heart disease in any clinical form leads to the development of ischemic cardiomyopathy, which is the structural basis of chronic heart failure (CHF) and glomerulosclerosis, the structural basis of chronic kidney disease (CKD). This web of pathophysiological mechanisms is clinically defined as type II cardiorenal syndrome. The combination of CKD and chronic heart failure (CHF) significantly worsens the prognosis and quality of life of patients [3].

Correction of the cardiorenal syndrome is based on the effect on pathogenetic mechanisms: elimination of myocardial ischemia is carried out in two directions - coronary revascularization and pharmacological drugs aimed at reducing myocardial oxygen demand. However, even after coronary revascularization, the started pathogenetic circles do not stop, and it is possible that the processes of
myocardial fibrosis themselves increase the apoptosis of cardiomyocytes and glomerulosclerosis [4,9].

**The aim of the study:** to study the functional state of the kidneys in patients with ischemic heart disease (IHD) in the long-term period after myocardial revascularization.

**Material and research methods.** The study included 160 patients with ischemic heart disease, hospitalized for coronary angiography and a decision on the feasibility and choice of revascularization technique. In 94 patients, the cause of hospitalization was exertional angina of FC III-IV, in 60 - progressive angina, 6 patients were admitted due to heart failure as a clinical form of coronary artery disease. Due to the limitations of the method and to achieve the goal of studying the pathogenetic features of type II cardiorenal syndrome, the study did not include patients with eGFR less than 60 ml/min. On average, the concentration of creatinine was 90.08 ± 1.72 µmol / L. All patients were prescribed standard CHD therapy (antiplatelet agent - aspirin or clopidogrel, and in the case of endovascular revascularization - dual antiplatelet therapy; beta-blocker, acetyl-CoA reductase inhibitor - atorvastatin).

On the second day after the endovascular procedure, coronary angiography / percutaneous coronary intervention (CAG/PCI), all patients underwent repeated determination of the blood creatinine concentration to identify patients who developed contrast-induced nephropathy (CIN). CIN was determined when creatinine concentration increased by 25% or more from the initial level. [7].

In dynamics, three months later, at the end of the first and second years of follow-up after revascularization, all patients underwent a second examination, including the determination of the functional state of the kidneys: the concentration of blood creatinine, with the calculation of GFR, the concentration of parathyroid hormone, phosphorus, uric acid in the peripheral blood.

To assess the functional state of the kidneys, the concentration of blood creatinine was determined with the calculation of eGFR (Hojs R et al. Clin Nephrol. 2008; 70 (1): 10-7). Serum parathyroid hormone concentration was determined by ELISA. The concentration of forfor and uric acid in the serum of peripheral blood was carried out with an automatic analyzer.
Research results and their discussion. According to the results of coronary angiography, 21 patients underwent surgical revascularization (CABG) within a month after CAG. Endovascular revascularization (stenting of the coronary arteries) was performed in 139 patients.

On the second day after the endovascular procedure (CAG/PCI), all patients underwent repeated determination of the blood creatinine concentration to identify patients who developed contrast-induced nephropathy (CIN). CIN in the early period after endovascular intervention was observed in 37 patients.

The study showed that during 2 years of follow-up after coronary revascularization, there was a progressive decrease in eGFR: by the 3rd month, eGFR decreased by $-17.39 \pm 1.17\%$, by the end of the 1st year - by $-43.62 \pm 1.28\%$, by the end of the second year of observation - by $-46.50 \pm 1.79\%$. These results of the study suggest that the advanced mechanism of progression of CHF and CKD, expressed in the development of myocardiosclerosis and glomerulosclerosis, is self-progressive. Along with this, it should be noted that the progression continues even after an adequately performed revascularization of the coronary bed. Perhaps in some cases, even after coronary revascularization, the started pathogenetic circles do not stop. Normally, to maintain renal oxygenation and glomerular filtration level, it is necessary to maintain an adequate difference between the arterial pressure of the bringing arteriole and the venous pressure of the outgoing arteriole. In heart failure, an increase in central venous pressure leads to a decrease in the perfusion gradient in the capillaries of the glomerulus and, accordingly, a decrease in glomerular filtration [5,8]. Violation of glomerular hemodynamics and slowing of blood flow in the glomeruli is compensated by an increase in pressure in the afferent arteriole and its dilatation, an increase in filtration pressure (due to vasoconstriction of the outflow arteriole), hypertrophy of the glomerular capillaries, hyperfiltration (leading to proliferation of the mesangium, fibrosis and sclerosis) [4].

The decrease in eGFR was significantly more pronounced in the group of patients who had CIN in the early period after endovascular intervention (37 patients): $(-39.82 \pm 2.02\%)$ by the end of the 3rd month, $-54.61 \pm 2.94\%$ by the end of the 1st year and $-60.10 \pm 3.99\%$ by the end of the 2nd year of observation.
versus -10.65 ± 0.57%, -40.32 ± 1.27% and -42.41 ± 1.85% in patients with CIN, respectively, p <0.001 for intergroup comparisons of the relative dynamics of eGFR at all three time points). According to the literature, the development of contrast-induced nephropathy further leads to the emergence and progression of renal failure, which, provided that even a short course of hemodialysis is necessary, increases the hospitalization period, as well as mortality, both during hospitalization and in the long-term period [10, 2].

In the course of the analysis, in order to level the effect of CIN on analytical results, we formulated a hypothesis that a decrease in the functional ability of the kidneys develops gradually and may be associated with an endovascular procedure or surgical revascularization. For this purpose, patients with IHD were divided into groups, depending on the method of revascularization: the CABG group (21 patients) and the PTCI group (139 patients). Initially, eGFR in the groups was comparable and amounted to 105.66 ± 3.74 ml / min and 102.71 ± 1.59 ml / min, respectively (unreliable). By the 3rd month of follow-up, the dynamics of eGFR in the groups, depending on the revascularization method, did not differ (-16.36 ± 3.30% and -17.55 ± 1.25%, respectively), as a result, by the 3rd month eGFR observation in the CABG and PTCI groups was also comparable, although it also differed in the initial data (90.14 ± 6.05 ml / min and 86.46 ± 2.37 ml / min, respectively). Later, by the end of the 1st year of follow-up, the following pattern emerged: in patients who underwent surgical revascularization, the decrease in eGFR was significantly more pronounced than in patients who underwent stenting of the coronary arteries (-51.80 ± 3.51% versus -42.39 ± 1.35%, p <0.05), and the differences increased even more during the second year of observation (-57.99 ± 4.75% versus -44.76 ± 1.89%, p <0.05 ). As a result, by the end of the second year of observation, eGFR in the CABG group was significantly lower than in the PTCI group (44.63 ± 5.37 ml / min versus 56.54 ± 2.01 ml / min, p <0.05). This pattern can be explained by the fact that in the CABG group there were more patients with diabetes - 80.95% (17 patients out of 21) compared with PTCA patients - 12.23% (17 patients out of 139, chi square = 49.83, p < 0.001). One of the manifestations of diabetic microangiopathy is nephropathy with impaired glomerular filtration.
Diabetes mellitus is considered one of the main causes of renal failure and an independent predictor of the risk of progression of CKD [1].

Violation of the functional state of the kidneys was manifested not only by a decrease in the glomerular filtration rate, but also by an increase in the concentration of blood phosphorus, parathyroid hormone and uric acid (Table 1). Comparative analysis revealed that the concentration of all the listed markers increased during the observation process in parallel with a decrease in eGFR. At the same time, the concentration of these substances was higher in patients who underwent CIN compared with patients with an uncomplicated post-procedural period. The groups identified depending on the revascularization method in terms of the concentration of phosphorus and parathyroid hormone did not differ. The concentration of uric acid was initially higher in the group of patients who underwent CABG compared with patients who underwent PTCA, probably due to the large proportion of patients with diabetes in this subgroup.

To date, tubular phosphate reabsorption has been found to decrease in proportion to the severity of CKD. At normal GFR (120 ml / min), approximately 10% of filtered phosphate is excreted, whereas at very low GFR (<20 ml / min), phosphate excretion in the nephron increases by approximately 80-90%. Epidemiological studies have shown that higher serum phosphate or FGF23 levels are predictors of more rapid decline in renal function in the CKD population. Disruption of phosphorus-calcium metabolism triggers a complex complex of pathological reactions leading to the activation of parathyroid hormone secretion with the development of a pathological response of the parathyroid glands to the concentration of calcium and phosphorus in the extracellular fluid, with a violation of the secretion and action of parathyroid hormone and the formation of secondary and tertiary hyperparathyroidism. There may be a relationship between chronic kidney disease (CKD) and asymptomatic hyperuricemia, with increasing evidence that elevated uric acid (UC) levels are the cause of kidney damage. [18, 6].

Conclusion. The present study has demonstrated that in patients with IHD after revascularization, there is a significant decrease in the glomerular filtration function of the kidneys by the third month after the endovascular procedure and lasts for at least 2
years. The most significant decrease was observed in patients with diabetes mellitus, as well as in patients who underwent CIN in the early period after endovascular intervention. CKD progression continues for at least 2 years after revascularization and is accompanied by an increase in the concentration of parathyroid hormone, uric acid, and blood phosphates, which is a reflection of the cardiorenal syndrome.

Table 1

Dynamics of indicators of the functional state of the kidneys in patients with IHD within 2 months after revascularization against the background of standard therapy

|                  | initially | 3 months | 1 year  | 2 years |
|------------------|-----------|----------|---------|---------|
| Phosphorus, pg / ml |           |          |         |         |
| CIN+             | 1,32±0,10 | 1,55±0,11** | 1,52±0,10* | 1,64±0,09*** |
| CIN-             | 1,20±0,06 | 1,22±0,04^^ | 1,20±0,04* | 1,32±0,04***^ |
| CABG             | 1,24±0,11 | 1,31±0,13 | 1,27±0,13 | 1,38±0,11* |
| PTCI             | 1,23±0,06 | 1,30±0,04 | 1,28±0,04 | 1,40±0,04* |
| Parathyroid hormone, pg / ml |           |          |         |         |
| CIN+             | 74,72±10,21 | 93,05±10,85* | 190,76±28,96*** | 193,05±28,99*** |
| CIN-             | 72,15±8,13  | 73,08±7,38  | 111,37±7,72***^ | 112,83±7,74*** |
| CABG             | 73,28±9,21  | 79,05±13,94 | 114,62±18,09*** | 116,54±18,15*** |
| PTCI             | 72,98±8,13  | 77,50±6,87  | 132,01±10,33*** | 133,62±10,35*** |
| Uric acid, μmol / L |           |          |         |         |
| CIN+             | 4,86±0,14  | 5,99±0,20*** | 7,54±0,28*** | 9,07±0,37*** |
| CIN-             | 4,97±0,09^  | 4,82±0,09^*** | 6,06±0,11****^ | 7,25±0,14****^ |
| CABG             | 4,53±0,17   | 5,37±0,26*** | 6,67±0,36*** | 7,94±0,46*** |
| PTCI             | 5,01±0,09^  | 5,05±0,09   | 6,36±0,13*** | 7,63±0,16*** |
| Creatinine, μmol / L |           |          |         |         |
| CIN+             | 91,49±2,35 | 141,27±10,42*** | 228,85±15,93*** | 310,43±25,38*** |
| CIN-             | 89,76±1,97 | 94,93±3,15****^ | 146,61±4,64****^ | 194,11±7,10****^ |
| CABG             | 87,38±3,44 | 102,76±9,74*** | 191,89±17,31*** | 275,64±30,19*** |
| PTCI             | 90,58±1,78 | 106,08±4,05*** | 161,66±6,09*** | 212,76±8,97*** |

Note: * - reliability of differences with the initial data, ^ - reliability of differences between groups at the stages of observation. One sign - p <0.05, two signs - p <0.01, three signs - p <0.001

References:
1. American Diabetes Association. Standards of medical care in diabetes – 2014 // Diabetes Care. – 2014. – V. 37. – Suppl. 1. – P. 14-80.
2. Azzalini L1, Spagnoli V1, Ly HQ2. Contrast-Induced Nephropathy: From Pathophysiology to Preventive Strategies. //Can J Cardiol. 2016 Feb;32(2):247-55.
3. Chrysohoou C, Bougatsos G, Magkas N, Skoumas J, Kapota A, Kopelias J, Bliouras N. et al. Peritoneal dialysis as a therapeutic solution in elderly patients with cardiorenal syndrome and heart failure: A case-series report. Hellenic J Cardiol. 2019
4. De Vecchis R., Baldi C. Cardiorenal syndrome type 2: from diagnosis to optimal management. Ther. Clin. Risk Manag. 2014;10:949–961.
5. Di Lullo L, Reeves PB, Bellasi A, Ronco C. Cardiorenal Syndrome in Acute Kidney Injury. Semin Nephrol. 2019;39(1):31–40.
6. Eliseev M.S. Chronic kidney disease: the role of hyperuricemia and the possibility of urate-lowering therapy. Modern Rheumatology Journal. 2018;12(1):60-65. (In Russ.)
7. Fliser D., Laville M., Covic A. et al., “A European Renal Best Practice (ERBP) position statement on the Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines on acute kidney injury: part 1: definitions, conservative management and contrast-induced nephropathy,” Nephrology Dialysis Transplantation, vol. 27, no. 12, pp. 4263–4272, 2012.
8. Hadjiphilippou S, Kon SP. Cardiorenal syndrome: review of our current understanding. J R Soc Med. 2016;109(1):12–17.
9. Iyngkaran P., Thomas M., Majoni W., Anavekar N.S., Ronco C. Comorbid Heart Failure and Renal Impairment: Epidemiology and Management. Cardiorenal Med. 2017;2:281–297.
10. Ji L, Su X, Qin W, Mi X, Liu F, Tang X, Li Z, Yang L. Novel risk score of contrast-induced nephropathy after percutaneous coronary intervention.//Nephrology (Carlton). 2015 Aug;20(8):544-51. doi: 10.1111/nep.12429.
11. Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the global burden of disease study 2010. Lancet. 2012;380:2224–60.
12. Mann D.L., Hassenfuss G. Pathophysiology of Heart Failure in part IV Heart Failure of Braunwald’s Heart Diseases. Edn Mann DL, Zipes DP, Libby P. Bonow, RO: Elsevier Saunders; 2015.