ОРИГИНАЛЬНАЯ СТАТЬЯ

INFORMATIVITY OF RADIONUCLIDE RENAL SCINTIGRAPHY AND BIOCHEMICAL MARKERS IN DETECTION OF RENAL DYSFUNCTION IN PATIENTS UNDERGOING MYOCARDIAL REVASCULARIZATION

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Acute renal injury (AKI) is a common complication of cardiac surgery. Diagnostic criteria of acute renal dysfunction based on serum creatinine concentrations do are not suitable for early detection of AKI.

Purpose. To evaluate the diagnostic significance of radionuclide scintigraphy and biochemical markers in the detection of renal dysfunction in patients with coronary artery disease (CAD) in the early postoperative period after coronary artery bypass grafting (CABG).

Material and methods. A randomized controlled trial comprised a total of 108 CAD patients (all men aged 54.94 ± 0.72 years) who underwent direct myocardial revascularization by CABG. All patients received dynamic renal scintigraphy with 99mTc-DTPA and blood tests measuring serum concentrations of creatinine, lipocalin (NGAL), and Cystatin C before and after CABG.

Results. After CABG, the mean values of total glomerular filtration rate (GFR) and GFR for each kidney significantly decreased whereas the serum concentrations of neutrophil gelatinase-associated lipocalin (NGAL) and Cystatin C in blood serum significantly increased.

In the postoperative period, the creatinine clearance also significantly decreased. Statistical analysis revealed direct correlations of cardiopulmonary bypass duration with the changes in GFR ($R = 0.42$; $P = 0.017$) and s-NGAL ($R = 0.39$, $P = 0.02$) in cardiac surgery patients.

Conclusion. Radionuclide method is not inferior to testing biochemical markers in the evaluation of early postoperative renal dysfunction in regard to diagnostic value and informativeness.

Keywords: dynamic renal scintigraphy, NGAL, Cystatin C, renal dysfunction, coronary artery bypass grafting.

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ИНФОРМАТИВНОСТЬ РАДИОНУКЛИДНОЙ СЦИНТИГРАФИИ ПОЧЕК И БИОХИМИЧЕСКИХ МАРКЕРОВ ПРИ ВЫЯВЛЕНИИ ПОЧЕЧНОЙ НЕДОСТАТОЧНОСТИ У ПАЦИЕНТОВ С РЕВАСКУЛЯРИЗАЦИЕЙ МИОКАРДА

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Острое повреждение почек (ОПН) – частое осложнение кардиохирургических вмешательств. Диагностические критерии острой почечной дисфункции, основанные на концентрации креатинина в сыворотке, не подходят для раннего выявления ОПН.

Цель. Оценить диагностическую значимость радионуклидной сцинтиграфии и биохимических маркеров в выявлении нарушений функции почек у пациентов с ишемической болезнью сердца (ИБС) в раннем послеоперационном периоде после аортокоронарного шунтирования (АКШ).

Материал и методы. В рандомизированном контролируемом исследовании приняли участие 108 пациентов с ИБС (все мужчины в возрасте 54,94 ± 0,72 года), которым была выполнена прямая реваскуляризация миокарда методом АКШ. Всем пациентам была проведена динамическая сцинтиграфия почек с 99mTc-DTPA и анализы крови с измерением сывороточных концентраций креатинина, липокалина (NGAL) и цистатина С до и после АКШ.

Результаты. После АКШ средние значения общей скорости клубочковой фильтрации (СКФ) и СКФ для каждой почки значительно снизились, тогда как сывороточные концентрации липокалина, связанного с желатиназой нейтрофилов (NGAL) и цистатина С в сыворотке крови, значительно увеличились. В послеоперационном периоде также значительно снизился клиренс креатинина. Статистический анализ выявил прямую корреляцию продолжительности искусственного кровообращения с изменениями СКФ (R = 0,42; P = 0,017) и s-NGAL (R = 0,39, P = 0,02) у кардиохирургических пациентов.

Заключение. Радионуклидный метод по диагностической значимости и информативности не уступает биохимическим маркерам в оценке раннего послеоперационного нарушения функции почек.

Ключевые слова: динамическая сцинтиграфия почек, NGAL, цистатин С, почечная дисфункция, аортокоронарное шунтирование.

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Introduction.

Coronary artery bypass grafting surgery (CABG) is among the most effective methods of treatment for coronary heart disease. At the same time, acute changes in renal function after CABG represent a challenging clinical problem [1-3]. Transient renal dysfunction and/or acute kidney injury (AKI) may be observed after open heart surgery with cardiopulmonary bypass in 5-28% of patients (according to other data – in up to 40% of patients), regardless of age and the condition of the cardiovascular system [4, 5]. In this case, the development of renal dysfunction even if transient can seriously impact the duration of hospital treatment and prognosis of underlying disease [3, 6].

Currently, in cardiac surgery practice, AKI diagnosis is based on the assessments of urinary output, serum creatinine (SCr), and/or SCr clearance [1, 3, 7]. This classification has proven to be valuable in evaluating the risk of short- and long-term complications in patients with ischemic renal damage. Creatinine clearance can be calculated based on SCr values, which, according to many researchers, reflect GFR [3, 8]. In turn, GFR reduction is one of the main manifestations of renal dysfunction. Two methods of calculation are primarily used: Cockcroft–Gault formula and MDRD formula (The Modification of Diet in Renal Disease Study) [9, 10].

However, traditional markers such as creatinine and urea concentrations are sensitive not enough for early AKI diagnosis, since the changes in SCr do not reflect the corresponding GFR decrease in some cases [7, 11]. The kidneys have a significant functional reserve, so the creatinine concentration does not change until the renal parenchyma loses about 60% [11, 12]. In addition, SCr can vary over a wide range, depending on many extrarenal factors [12]. Therefore, creatinine is not an ideal marker for measuring GFR.

Cystatin C, a cationic low-molecular-weight cysteine protease, produced by all nucleated cells with a constant rate and not metabolized in serum, has been proposed as a glomerular test agent (GFR surrogate). The production of Cystatin

C, unlike creatinine, is considered to be low-dependent on various factors: age, sex, muscle mass, and hydrovolemia [13]. It is generally accepted that over 99% cystatin C elimination is due to glomerular filtration [13, 14]. Thus, the assessment of this marker allows to detect AKI development earlier and with greater specificity than serum creatinine measurements [15].

Neutrophil gelatinase-associated lipocalin (NGAL) may be even earlier predictor of AKI. NGAL expression is increased in the cells of tubular epithelium multifold in the presence of ischemic and toxic kidney injury. Blood plasma NGAL concentrations (s-NGAL) and NGAL excretion with urine (u-NGAL) increase 24-48 hours before the rise in creatinine level and 10 hours before the increase in serum Cystatin C concentration [15, 16]. Therefore, there is a reason to consider NGAL an early sensitive non-invasive AKI marker [17]. Moreover, the levels of s-NGAL and u-NGAL have similar diagnostic and prognostic significances [18].

However, the assessment of cystatin C and lipocalin levels has not been widely implemented in everyday clinical practice.

The function of urinary system can be studied using radionuclide research methods enabling to assess glomerular filtration, tubular secretion, urodynamics, the state of parenchyma and blood supply to the kidneys, topography of the entire organ, and its individual parts [17]. In particular, radionuclide renal scintigraphy enables to detect abnormalities in the renal function at early stages of disease and to diagnose the severity and the level of damage, when clinical and/or biochemical manifestations are yet absent [17].

The purpose of this investigation was to evaluate the diagnostic significance of radionuclide renal scintigraphy and biochemical markers in the detection of renal dysfunction in patients with coronary artery disease in the early postoperative period after CABG.

Material and methods

Table №1. Clinical and intraoperative data of patients enrolled in the study.

Variables	n = 108	%
Age*, years	55.0 (49; 59)	
NYHA class, n (%)		
I	4	3.7
II	65	60.2
III	39	36.1
LVEF*, %	52.0 (41; 62)	
AMI in anamnesis, n (%)	93	86
LV aneurysm, n (%)	31	28,7
Coronary arteries with stenosis >50%		
1	13	12
2	32	29.6
3	63	58.4
Grafts per patient		
1	13	12
2	36	33.3
3	41	38
4-5	18	16.7
Kidney diseases in anamnesis, n (%)	18	16.7

* Data are presented as median (interquartile range); *NYHA*: New York Heart Association, *AMI*: acute myocardial infarction; *LVEF*: left ventricular ejection fraction

Patient selection.

A total of 108 patients (all men aged 54.94 ± 7.25 years) who underwent first-time CABG were enrolled in the study. All patients had the following primary diagnosis: CAD with angina pectoris functional class 2 to 4, complicated by CHF NYHA I-III. Ninety-three (86%) patients suffered one or more acute myocardial infarctions with the formation of postinfarction cardiosclerosis. The clinical profiles of the matched patients are described in Table 1.

All consecutive patients were examined after informed consent was obtained. All patients underwent dynamic renal scintigraphy with 99mTc-diethylenetriaminepentaacetic acid (99mTc-DTPA) before and 6-7 days after CABG and were subjected to measuring the concentration of SCr in the time period not exceeding 48 hours from the day of renal scintigraphy. The following parameters were calculated in the course of the study: total glomerular filtration rate (GFR, mL/min) and GFRs for each kidney; blood clearance (min) as half-time of radiopharmaceutical excretion from blood; creatinine clearance in blood serum prior to CABG and 5 hours after the beginning of the operation.

Forty patients were subjected to measuring the blood serum amounts of lipocalin-2 prior to CABG and 5 hours after the beginning of surgery and Cystatin C before and 24 hours after surgery.

Renal Function Evaluation.

Dynamic renal scintigraphy with 99mTc-DTPA was performed in a sitting position of a patient whose back faced a detector of the gamma-camera so that the heart and the kidneys were within the field of view. The radiopharmaceutical was introduced intravenously at a dose of 30–40 mBq (0.8–1.0 mCi) and a volume of 1.0 to 1.5 mL. To calculate GFR, syringe activity was recorded before and after the infusion of radiopharmaceutical to a patient.

All the scintigraphic studies were performed with gamma camera Philips Forte (Philips Medical Systems, Netherlands). Processing of the acquired scintigrams was performed using JetStream® Workspace Release 3.0 software package (Philips Medical Systems, Netherlands).

Laboratory Methods.

Serum NGAL was tested by Human Lipocalin-2/NGAL ELISA kit; serum Cystatin C was assessed by Human Cystatin C ELISA (ELISA, BioVendor Laboratory Medicine, Inc.). The principle of the technique was based on quantitative solid phase immunoenzyme sandwich analysis. The Cockcroft–Gault equation was used to calculate creatinine clearance [9].

Statistical analysis.

Statistical analysis was performed with STATISTICA software. To evaluate significance of differences between dependent samples, nonparametric Wilcoxon rank-sum test and Sign-test were used. To detect the presence of correlation relationships between data, Spearman rank correlation coefficient was used. For all statistical evaluations, differences in data with p-values of less than 0.05 were considered statistically significant.

Results.

Before surgery, initial reduction of varying degree in GFR in one or two kidneys was found in 80 (74.1%) patients. The mean GFR values were 107.72 ± 9.75 mL/min (total GFR): 49.96 ± 7.37 mL/min for the left kidney and 57.72 ± 6.01

Table №2. Comparative results of the DVH analysis for two cases – the planned dose distribution (plan) and the total delivered dose distribution for 6 fractions (sum).

Variables	Before CABG	After CABG	P-level
Creatinine, mM/L	89.0 (81; 97)	92.0 (82.2; 102)	0.236
Creatinine clearance, mL/min	97.8 (78.3; 122.8)	75.5 (52.9; 99.1)	< 0.05
Total GFR, mL/min	109.95 (104.25; 113.75)	99.45 (92.65; 107.55)	< 0.01
Blood clearance, min	17.5 (16.2; 20.1)	22.4 (20.6; 24.4)	< 0.01
GFR left, mL/min	50.3 (45.9; 56.3)	44.55 (39.25; 52,90)	< 0.01
GFR right, mL/min	59.1 (55.3; 62.15)	52.85 (48.4; 57.25)	< 0.01
Lipocalin, ng/mL	53.07 (41.46; 82.64)	143.75 (131.27; 214.71)	< 0.01
Cystatin C, ng/mL	721.0 (613.4; 794.95)	954.35 (697.25; 1068.00)	< 0.05

Data are presented as median (interquartile range); *CABG*: coronary artery bypass grafting, *GFR*: glomerular filtration rate.

mL/min for the right kidney (Table 2).

We found pronounced renal dysfunction (the GFR decline in one or both kidneys by more than 30% of normal values) in 12 (11.1%) patients; 48 (44.4%) patients had moderate disturbance of the filtration function. It should be noted, that only 18 (16.7%) individuals had chronic kidney disease in the past medical history. Statistical analysis allowed to detect the presence of correlation relationship between GFR determined by the radionuclide method and SCr clearance ($R = 0.30$, $p = 0.005$).

In our study, the mean value of lipocalin-2 in all patients before surgical treatment was 67.02 ± 41.99 ng/mL which exceeded the corresponding mean value in individuals without cardiovascular diseases (Table 2) [19]. We discovered the inverse relationship between s-NGAL levels and ejection fraction of LV (LVEF) in study patents ($R = -0.37$, $p = 0.02$). Statistical analysis also allowed to detect the presence of the inverse relationship between GFR and lipocalin level in study patents before revascularization ($R = -0.33$, $p = 0.03$).

Table 2 shows the statistically significant changes in the values of renal functional activity after CABG with cardiopulmonary bypass. Indeed, there were significant reduction in the mean values of total GFR and GFR for each kidney as well as statistically significant increase in the blood clearance. Pronounced renal dysfunction (a decrease in total GFR by 15% and more compared with the initial level) due to nonpulsatile blood flow occurred in 35% of patients; insignificant decrease in the filtration activity was found in 18 patients (16.7%).

Significant increase in the concentration of s-NGAL occurred 5 hours after surgery relative to the preoperative value (from 67.02 ± 41.99 to 171.65 ± 89.91 ng/mL, $p < 0.001$). Statistical analysis revealed the significant correlations between the duration of cardiopulmonary bypass and the changes in GFR ($R = 0.42$; $p = 0.017$), as well as between the duration of cardiopulmonary bypass and the changes in s-NGAL levels in cardiac surgery patients ($R = 0.39$, $p = 0.02$). The clearance of creatinine also significantly decreased in the postoperative period.

Table 2 shows a significant increase in blood serum concentration of Cystatin C, which occurred 24 hours after surgery, relative to preoperative value (from 722.05 ± 188.31 to 916.66 ± 283.92 ng/mL, $p < 0.05$). However, in comparison with lipocalin, the severity of postoperative increase in cystatin C was less pronounced. Besides, we could not detect the presence of direct correlation of the cystatin C levels with cardiopulmonary bypass duration ($R = 0.01$, $p = 0.95$) and the cross-clamp time ($R = 0.08$, $p = 0.73$).

Discussion.

Abnormal glomerular filtration and the increased lipocalin-2 level in preoperative period indicate the development of cardiorenal syndrome caused by chronic heart failure as result of reducing renal perfusion and increasing renal vascular resistance [20, 21].

The study showed that the s-NGAL and Cystatin C levels were associated with cardiovascular diseases including chronic heart failure [19, 22]. Choi K. M. with coworkers demonstrated that mean s-NGAL levels were 82.6 ± 38.7 ng/mL in patients with angiographically confirmed coronary artery stenosis versus 43.8 ± 27.8 ng/mL in control group [19]. Authors believe that changes in s-NGAL level can be useful for evaluation of CAD risk because they are independently associated not only with coronary atherosclerosis, but also with insulin resistance and systolic blood pressure [19]. Ix J.H. with coworkers compared the levels of creatinine and cystatin C as predictors of an unfavourable prognosis during the Heart and Soul Study [22]. The study showed that the highest quintile of cystatin C (≥ 1.3 mg/L) was associated with a significant increase in the risk of all-cause mortality, cardiovascular events, and incident heart failure. However, according to our data, the mean level of cystatin C in the examined patients was 722.05 ± 188.31 ng/mL (Table 2), which corresponds to the level of this marker in practically healthy individuals (for men is 0.74 ± 0.10 mg/L (740 ± 100 ng/mL)) [23]. Moreover, our study demonstrated that there was no correlation between the levels of cystatin C with LVEF ($p = 0.80$), as well as with GFR calculated using radionuclide method ($p = 0.21$).

Several works demonstrated that lipocalin levels significantly correlate with serum creatinine, creatinine clearance, and GFR calculated using MDRD formulas [24-26]. However, in our study, we did not find such a relationship. It may be due to the fact that the plasma NGAL levels are associated not only with the morphologic and functional states of renal tubules, but also with other functions of this protein. In particular, NGAL is involved in recovery of damaged epithelium as a protein of acute phase of inflammation as well as in remodeling of atherosclerotic plagues and myocytes in the presence of myocardial damage [27].

In the context of cardiopulmonary bypass, nonpulsatile blood flow triggers cascade of proinflammatory reactions increasing the levels of circulating catecholamines and mediators of inflammation and acute-phase response including lipocalin [27, 28]. There is evidence that the early rise in the level of NGAL in blood plasma 2 to 6 h after cardiac surgery is caused by the lipocalin release into the circulation due to the inflammatory neutrophil activation triggered by surgery [29]. The other adverse side effect of extracorporeal circulation consists in the renal macro- and microemboli leading to renal vasoconstriction and ischemic injury of renal parenchyma which, in turn, leads to functional disorders of the renal parenchyma (reduction in GFR) and expression of lipocalin as a marker of AKI [17, 28, 30].

The observed increase in the s-NGAL level in cardiac patients during the first hours after surgery agrees with data of other researchers. Mishra J. with coworkers observed an elevation of the lipocalin level in blood plasma 2 h after the beginning of surgery with cardiopulmonary bypass in children [29]. Authors also found correlation between duration of surgery and changes in the NGAL level [29].

It was proved that a significant increase in the level of Cystatin C can be informative already in the early stages of renal function impair [31]. Cystatin C concentration in blood increases 1-2 days before the rise in the level of creatinine and is regarded as a sign of stage I-II AKI in patients in the postoperative period [32]. Despite this, there are the number of questions regarding possible use of cystatin C as an indicator of AKI. The concentration of cystatin C in the serum can vary much more than that of SCr [33]. The factors affecting its concentration include age, sex, height, weight, smoking, serum level of C-reactive protein, steroid therapy, and the presence of rheumatoid arthritis [34, 35]. Svensson A.S. and coworkers demonstrated that processes not related to renal function, in particular, acute inflammation, have a significant effect on postoperative changes in the level of Cystatin C, and this can be mistakenly interpreted as the development of AKI [36]. Therefore, at present, the benefits of determining Cystatin C for the diagnosis of renal dysfunction cannot be considered proven.

In summary: the radionuclide method is not inferior to biochemical markers in assessing early postoperative renal dysfunction in regard to its diagnostic significance and informativeness.

Statement of Ethics.

The study protocol complied with the Declaration of Helsinki and was approved by the Ethics and Research Committee of Cardiology Research Institute, Tomsk National Research Medical Centre. All patients gave their written informed consent.

The authors declare no conflicts of interest.

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