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Early Diagnosis of Renal Dysfunction in Patients with Chronic Heart Failure who have had and have not had Covid-19

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Abstract This article discusses early diagnosis of renal dysfunction in patients with chronic heart failure who have had and have not had Covid-19.

Keywords Diagnosis, Renal dysfunction, Patients with chronic heart failure, Covid-19

1. Introduction

As it is known, chronic heart failure (CHF) is one of the vulnerable problems of modern cardiology. The prevalence of CHF according to population studies in countries around the world varies from 0.3% to 5.3%. According to the Framingham Heart Study, the lifetime risk of heart failure in men is 21% and 20% in women [5]. In the United States alone, the proportion of deaths due to chronic heart failure has increased from 5.8% to 9.9% over 20 years [8].

The work of the heart and blood circulation in the body is controlled by vascular tone and blood volume, the balance of which is provided by the kidneys. The kidneys, in turn, being an organ involved in important metabolic, humoral processes, are subject to acute and chronic effects in various cardiovascular diseases (CVD), including CHF, and affect their formation and progression. Renal dysfunction is associated with a higher recurrence rate of myocardial ischemia, myocardial infarction, serious hemorrhagic complications, acute heart failure, atrial and ventricular fibrillation. Even a slight decrease in kidney function leads to a deterioration in the course of the main cardiological pathology, the occurrence of complications of which - a decrease in the contractile function of the myocardium, in turn, affects the work of the kidneys in the most negative way.

Traditionally, kidney dysfunction is usually determined by such indicators as blood creatinine, micro and macroalbuminuria, cystatin, glomerular filtration rate (GFR). Recently, scientists have begun to study the functional and anatomical structure of the renal nephron in more depth, in order to identify even earlier markers of renal dysfunction. In this connection, our study was aimed at identifying renal dysfunction in its early stages, before microalbuminuria starts.

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Purpose: to identify markers of early kidney damage - renal dysfunction in CHF patients with systolic dysfunction.

2. Materials and Methods

The study included 225 patients with chronic heart failure II-III FC according to the classification of the New York Heart Association (NYHA). Group I consist of 165 patients, which are patients with CHF who have had Covid-19, and group II - 60 patients with CHF who have not had Covid-19. The average age of patients in group I was 64.03±0.8, and in group II - 64.5±3.4 years. In the first group of patients with CHF, men were 98 (59.4%), and women 67 (40.6%), in the second group, there were 37 (61.7%) men, 23 (38.3%) women. The average duration of the disease from the anamnesis was 5.3±0.5 years in the first group, 4.2±0.3 years in the second.

According to the functional class, CHF patients were divided into 2 groups. In the first group - with II FC - 35 (21.2%), with III FC - 130 (78.8%) patients, in the second group - with II FC - 18 (30%), with III FC - 42 (70%) patients. From the anamnesis, the duration of the disease was 5.3+0.5 years in group I, and 4.2 years in group II. With CHF II FC in group I there were 35 (21.2%), in group II - 18 (30%) patients, with CHF III FC in group I there were 130 (78.8%), and in group II 42 (70%) of patients.

According to the structure of comorbidity, the following changes were noted. Anemia was detected in group I in 109 (66%) cases and in group II in 35 (58%) patients, respectively. In group I - 105 (63.6%) patients had a history of myocardial infarction, and in group II - in 36 (60%). Coronary artery bypass grafting and stenting were performed

in 45 (27.3%) patients of group I, and in 19 (31.6%) patients from group II. Various types of arrhythmias were detected in 51 (30.9%) patients of group I, and in 11 (18.3%) patients of group II. In 59 (37.75%) patients of group I, obesity was detected, in group II - in 15 (25%), in both groups, 8% of patients were diagnosed with COPD.

All patients underwent echocardiographic examination using the SONOSCAPE S20 (China) equipment. Patients with systolic dysfunction were selected, i.e. ejection fraction less than 50% according to Simpson.

Immunoenzymatic assay of Cystatin C, TNF-α, were carried out on a Rayto analyzer using Vector Best (Russia), Collagen Type IV α1 from Elabscience (America). A biochemical blood test was carried out using a Midray BA-88A biochemical analyzer. Blood creatinine was checked using the reagent of the German company "Human" (Germany) according to the Jaffe method.

Daily microalbuminuria was determined using the benzethonium chloride reagent by the colorimetric method on a photometer with an optical density of 430 nm.

Nephrine was determined in the morning portion of urine using an enzyme immunoassay kit (ELISA Kit) manufactured by CUSABIO (China) with the calculation of the concentration per unit of urine creatinine in the test sample.

Cystatin C in blood serum was determined using a DiaSys Diagnostic Systems kit (Germany).

3. Results

The filtration function of the kidneys, as noted above, was traditionally assessed by the level of endogenous creatinine. In the study of a biochemical blood test, the creatinine level in the examined patients was 114.3±3.3 µmol/l ($p<0.001$) in the first group, and in the group of patients who did not have Covid-19, it was 94.7±3.2 µmol / l. As many parameters are known to affect the level of creatinine, it was therefore assumed that cystatin-C is a more reliable indicator of renal dysfunction, the content of which, unlike creatinine, is not affected by gender, age, body weight and muscle mass, and nutritional characteristics.

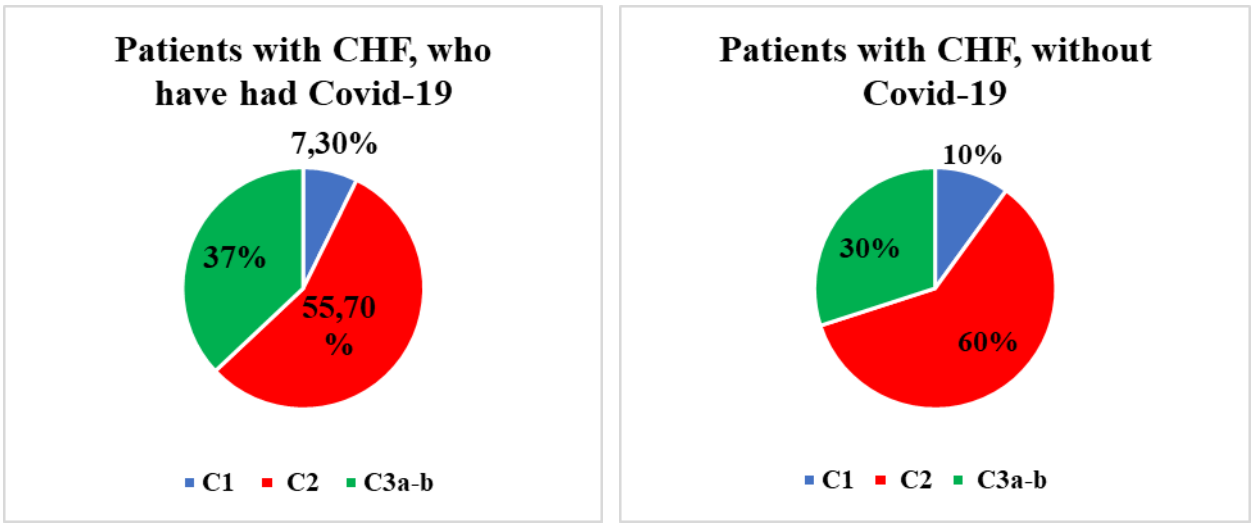
Table 1. Indicators of biochemical analysis of blood in patients with chronic heart failure and systolic dysfunction

№	Indicators	I group, n=165	II group, n=60
1	Hemoglobin, g/l	111,34±1,1	110.7±1,3
2	Creatinine, µmol / l	114,3±3,3***	94,7±3,2
3	Potassium, µmol / l	4,4±0,08	4,48±0,07
4	Cystatin C, ng/ml	1,36±0,04**	1,2±0,03
5	GFR by cystatin-C	54,7±1,9*	62,3±2,7
Notes: reliability indicators before and after treatment *-$p<0.05$; **-$p<0.01$; ***-$p<0.001$			

As can be seen from Table 1, the level of blood cystatin C in the first group of patients was 1.36±0.04 ng/ml ($p<0.01$), in group II it was 19-1.2±0.03. GFR was calculated for cystatin-C, using the CKD-EPI formula, 2012. In group I patients, GFR was 54.7±1.9 ($p<0.05$), in group II - 62.3±2.7. Thus, the results revealed a violation of glomerular filtration, there was a decrease in GFR in both groups, a slight increase in the content of cystatin-C in group I, and in the same group a significant decrease in GFR, which may be due to the direct effect of the virus on podocytes, which further worsened glomerular filtration.

According to the level of GFR, patients were distributed at the stage of chronic kidney disease. Fig. 1.

Thus, in-group I, 22 (13.3%) patients had CKD stage C1, 92 (55.7%) patients had C2, and 51 (31%) - C3 a-b stages. In the II group of patients, 9 (15%) patients had CKD C1, 36 (60%) - C2, and 15 (25%) C3a and b stages. The figure shows that in the first group, the percentage of patients with CKD stages 3a and 6 is higher, which is undoubtedly associated with the complications that occurred during the glomerular virus infection.



Note: C1-GFR is normal (≥90ml/min/1.73m^2); C2-GFR 60-89 ml/min/1.73m^2; C3a: 45-59 ml/min/1.73m^2; C3b: 30-44 ml/min/1.73m^2

Figure 1. Distribution of patients by stages based on the level of glomerular filtration rate

Next, we found out an even earlier possible kidney injury. As it is known, the vascular glomerulus of the kidney has about 50 capillary loops, the wall of which is a glomerular filter. It has been established that the glomerular filter consists of three elements: the epithelium of the glomerulus, the endothelium of its capillaries, and the basement membrane located between them. The epithelium of the glomerulus, a podocyte, consists of a large cell body with a nucleus, mitochondria, the Golgi apparatus, and other inclusions [1].

With any damage to the kidneys, increased excretion of nephrin into the urine observed, thus forming podocytopathy. Nephrin is a transmembrane protein of podocytes with m.m. 160 kDA, a product of the NPHS1 gene, is the main structural protein of the slit filtration diaphragm and belongs to the adhesive proteins of the immunoglobulin superfamily involved in the formation of the renal filter [2,7].

The earliest sign of podocyte damage, determined only by electron microscopy, is the flattening of the pedicles of the podocyte. This process is carried out due to the restructuring of the actin cytoskeleton, the redistribution of actin microfilaments, due to which the processes of podocytes lose their shape. As a result of the spreading of the processes of podocytes, the slit diaphragm is stretched, the interpodocyte space increases, and only then does proteinuria occur. That is, before proteinuria, albuminuria, podocytes are first affected, and we can identify and prove even earlier damage to the glomerular basement membrane and glomerular function by detecting nephrin in the urine of patients [3,4].

Thus, to detect an earlier organic lesion of the renal filter in CHF patients with systolic dysfunction, the levels of cystatin and nephrin in the urine were determined.

Table 2. Biochemical indicators of renal dysfunction in patients with chronic heart failure in the urine

№	Indicators	I group, n=165	II group, n=60
1.	**Cystatin C, ng/ml, >0.1**	0.37 ±0.02*	0.2 ±0.015
2.	**Nephrin, pg/ml**	98,7±3,67**	68.9±3.0
3.	**Microalbuminuria, mg/day**	264±23,67*	204±16,2
Notes: reliability indicators before and after treatment *-p<0.05; **-p<0.01; ***-p<0.001			

The table shows that the level of cystatin-C in the urine in patients of group I was 0.37±0.02 (p<0.05), in group II 0.2+0.015 (p<0.01). Therefore, we have noted an increase in the excretion of cystatin in the urine, which will naturally reduce GFR.

As can be seen from Table 2, in group I, the level of nephrin in the urine was 98.7±3.67 ng/ml (p<0.001), in group II - 68.9±3.0 ng/ml, which is significantly higher than the reference values. Almost all patients were found to have nephrinuria, which indicates structural damage to podocytes. In group I patients, microalbuminuria was detected, which amounted to 264±23.67 p<0.01, in group II - 204±16.2.

When studying the correlation, a strong positive relationship between nephrinuria and urinary cystatin was revealed, which amounted to 0.583, p<0.01, as well as a strong positive relationship with blood cystatin, amounting to 0.508, p<0.01. fig. 2.

Thus, we can conclude that even before the appearance of proteinuria, there is a violation of the structure of the nephrin itself, as well as the protein complex associated with it, which leads to a violation of the architectonics of podocytes, smoothing of the processes of their legs, and as a result of which clinically significant albuminuria occurs.

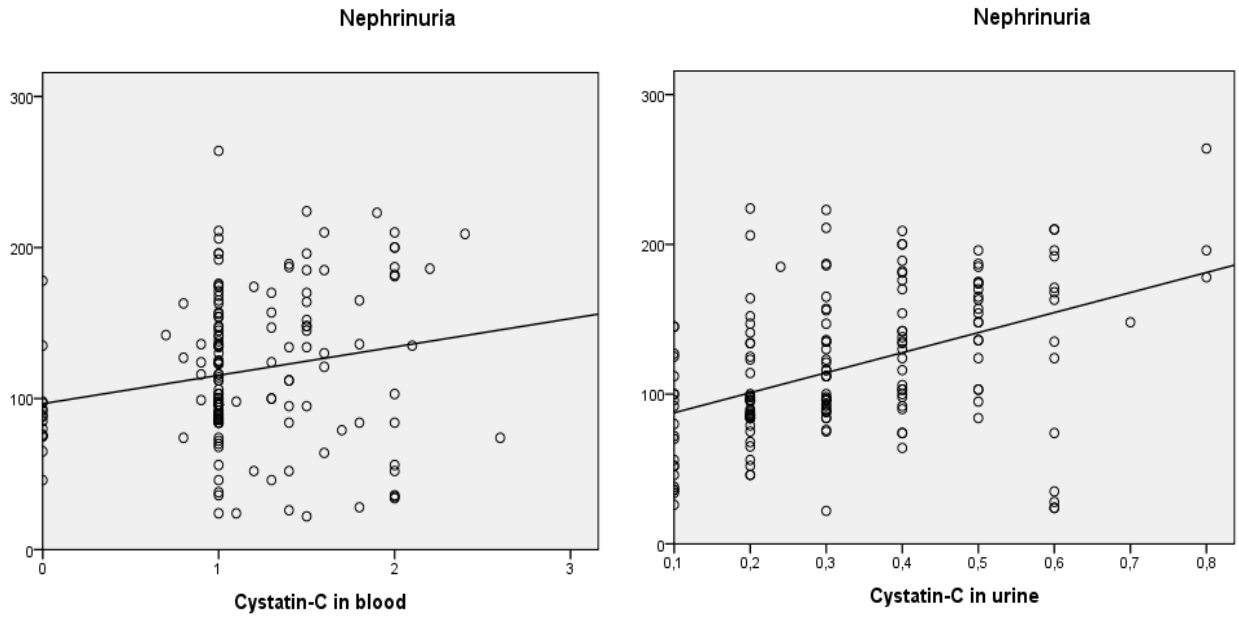


Figure 2. Correlation graph of cystatin C in blood and urine with nephrinuria

4. Conclusions

Based on the study, a violation of glomerular filtration was revealed, an increase in blood creatinine was detected, a decrease in GFR was noted in both groups, a greater increase in the content of cystatin-C in group I than in group II, and in the same group a significant decrease in GFR, which is due, possibly, to the direct effect of the virus on podocytes, which further worsened glomerular filtration.

In groups I and II of patients, the level of nephrin in the urine was 98.7±3.67 ng/ml ($p<0.001$), in group II - 68.9±3.0 ng/ml, which is significantly higher than the reference values, and this proves damage to the podocyte structure.

When studying the correlation, a strong positive relationship of nephrinuria with urine cystatin, as well as with blood cystatin, was revealed, which once again confirms the primary damage to the podocytic link of the renal glomerulus.

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