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Assessment of Kidney Dysfunction in Patients with Chronic Heart Failure

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Abstract

BACKGROUND: Heart failure and kidney disease share common pathophysiological pathways which can lead to mutual dysfunction, known as cardiorenal syndrome. The formation of cardiorenal syndrome in patients with chronic heart failure (CHF) is a natural manifestation of a functionally interconnected process at the organ level. Renal dysfunction is a common and independent factor in the progression of the disease, a high incidence of cardiovascular events, and death in the population.

AIM: The aim of the study of the relationship between kidney dysfunction and the clinical course of the disease, quality of life, and indicators of the left ventricular systolic function in patients with CHF.

MATERIALS AND METHODS: The study involved 150 patients with CHF I–III functional class according to the New York Heart Association. Exercise tolerance (6 min walk test) was assessed, the clinical condition was assessed using the clinical assessment scale, and the quality of life of patients with CHF (QoL) was assessed according to the Minnesota QOL questionnaire. An assessment of the functional state of the kidneys was carried out: The level of serum creatinine was determined; glomerular filtration rate (GFR) was calculated using the calculation formulas CKD-EPI. The assessment of renal blood flow was carried out using the ultrasound apparatus "SONOACEX6" (Korea). The structural and functional state of the myocardium and the process of left ventricle (LV) remodeling were assessed using the "MEDISON ACCUVIX V20" echocardiograph (Korea), using a 3.25 MHz transducer in standard echocardiographic positions, by the transthoracic method in accordance with the recommendations of the American Association of Echocardiography.

RESULTS: The results of the study of physical performance according to 6 min walk test in patients of Group I with CHF GFR >60 ml/min/1.73 m^2 were 363.59 ± 7.6 m, respectively. The decrease in the distance traveled according to the 6 min walk test data in Group II of patients with eGFR ≤60 ml/min/1.73 m^2, exercise tolerance was more pronounced than in patients of Group I and this figure was 248.7 ± 11.0 m, which was 46.2% lower than the results of Group I of the study ($p < 0.001$). Analysis of the parameters of clinical manifestations according to the data of the clinical assessment scale showed that in patients of Group I, the total score was 5.5 ± 0.13 points. In CHF patients with renal dysfunction, changes were also noted at the level of the lobar and segmental renal arteries, characterized by a significant increase in pulsatility index and resistance index, there was a decrease in speed indicators during diastole, systole, and the average blood flow velocity. Further analysis of the parameters of LV systolic function ejection fraction (EF), as well as fractional shortening of the LV in systole (Fs%), showed that in Group II, these indicators had significant differences with Group I. There was a significant difference in EF by 10.5% and 25.4% and Fs% by 11.2% ($p < 0.001$).

CONCLUSION: In CHF patients with impaired renal function, changes in renal blood flow were characterized by a significant increase in pulsatile and resistive indices, a decrease in the rate of renal blood flow at the level of the lobar and segmental renal arteries.

Introduction

Despite the achievements of modern cardiology, chronic heart failure (CHF) still remains a prognostically unfavorable condition. Mortality among patients with CHF is 4–8 times higher than in the general population, half of all patients die within 5 years after diagnosis. In patients with IV functional class (FC) CHF, mortality within 6 months reaches 44% [1].

Heart failure and kidney disease share common pathophysiological pathways which can lead to mutual dysfunction, known as cardiorenal syndrome.

It has been established that in patients with CHF, the presence of renal dysfunction is a predictor of an unfavorable clinical outcome. The prevalence of impaired renal function in CHF, according to various studies, ranges from 25% to 60%. One of the early markers of renal dysfunction is the glomerular filtration rate (GFR) [2].

The formation of cardiorenal syndrome in patients with CHF is a natural manifestation of a functionally interconnected process at the organ level. Renal dysfunction is a common and independent factor in the progression of the disease, a high incidence of cardiovascular events, and death in the population of

patients with asymptomatic and/or clinically manifested CHF, which is due to the pathogenetic features of the formation of CRS in patients with CHF of ischemic origin [3].

The persistence of subclinical renal dysfunction during treatment, even when RF control is achieved and organ damage regresses, may adversely affect the patient's prognosis. Assessment of the functional state of the kidneys is important for the choice of preventive and therapeutic measures [4].

In heart failure patients, renal impairment is related to hemodynamic and non-hemodynamic factors. Both decreased renal blood flow and renal venous congestion due to heart failure could lead to impaired renal function. Kidney disease and worsening renal function are independently associated with poor prognosis in heart failure patients, both in acute and chronic clinical settings [5].

The leading role in its formation is played by systemic oxidative stress, an increase in the content of circulating pro-inflammatory cytokines, which cause the loss of negative charges of the glomerular capillary endothelium and an increase in the permeability of the glomerular filter. Another cause of RD is glomerular hypertension, which is detected already at an early stage of HF progression and is associated with impaired renal hemodynamics [6].

Consequently, an accurate evaluation of renal function plays a key role in the management of HF patients. Serum creatinine (Cr) levels and GFR estimates are the corner stones of renal function evaluation in clinical practice. However, to overcome their limits, several emerging glomerular and tubular biomarkers have been proposed over the last years. Alongside the renal biomarkers, imaging techniques could complement the laboratory data exploring different pathophysiological pathways. In particular, Doppler evaluation of renal circulation is a highly feasible technique that can effectively identify HF patients prone to develop renal dysfunction and with a worse outcome [7].

Materials and Methods

The study involved 150 patients with CHF I–III FC according to the New York Heart Association (NYHA). According to the results of the study, out of 150 patients, 70 (53.3%) were women and 80 (61.7%) were men. The average age of the patients was 60.9 ± 0.4 years (Table 1).

Table 1: Clinical characteristics of patients

Total CHF patients	150 (100%)
Men	80 (61.7%)
Women	70 (53.3%)
CHF I FC	38 (25.3%)
CHF II FC	62 (41.4%)
CHF III FC	50 (33.3%)
LV EF<40%	13 (8.7%)
LV EF = 40–49%	31 (20.7)
LV EF>50%	106 (70.8%)
GFR>60 ml/min/1.73 m^2	81 (54%)
GFR≤60 ml/min/1.73 m^2	69 (46%)

CHF: Chronic heart failure, FC: Functional class, LV EF: Left ventricle ejection fraction, GFR: Glomerular filtration rate.

Exercise tolerance (6 min walk test) was assessed, the clinical condition was assessed using the clinical assessment scale, and the quality of life of patients with CHF (QoL) was assessed according to the Minnesota QoL questionnaire. The functional state of the kidneys was assessed: The level of Cr was determined; GFR was calculated using the calculation formulas CKD-EPI. Renal blood flow was assessed using the SONOACEX6 ultrasound (Korea) by color Doppler mapping, as well as pulsed wave Doppler and energy mapping with a 3.5 MHz sector sensor at a scanning angle of not more than 60°. The following indicators were used: The systolic velocity (Vs), the diastolic velocity (Vd), mean blood velocity (Vmean), resistive index (RI), pulsatility index (PI) determined at the level of the right and left renal arteries, as well as intraorganic (segmental and lobar) arteries.

The structural and functional state of the myocardium and the process of left ventricle (LV) remodeling were assessed using the "MEDISON ACCUVIX V20" echocardiograph (Korea), using a 3.25 MHz transducer in standard echocardiographic positions, by the transthoracic method in accordance with the recommendations of the American Association of Echocardiography.

The LV systolic function was assessed by determining the LV end-systolic volume (LV ESV), end-diastolic volume (LV EDV), and ejection fraction (LV EF) which were calculated based on the obtained data using the Simpson formula.

Patients with acute decompensated heart failure (AD HF), acute worsening of kidney function, or severe renal failure (GFR <15 ml/min) were excluded from the study. The study was approved by the local ethics committee, and all patients provided written informed consent. Patients showing a Doppler pattern, suggesting that renal artery stenosis were excluded.

Statistical processing

The data obtained during the study were subjected to statistical processing on a Pentium-IV personal computer using the Microsoft Office Excel-2020 software package, including the use of built-in statistical processing functions. The methods of variational parametric and non-parametric statistics were used with the calculation of the arithmetic mean of the studied indicator (M), standard deviation (SD), standard error of the mean (m), and relative values (frequency, %), the statistical significance of the measurements obtained when comparing the average values was determined

by the criterion Student's (t) with the calculation of the probability of error (p) when checking the normality of the distribution (according to the kurtosis criterion) and the equality of general variances (F – Fisher's criterion). The data in dynamics were analyzed by the corresponding paired criteria. When the number of observation groups was more than 2, the differences between the mean values were assessed using one-way ANOVA analysis of variance. Significant level $p < 0.05$ was taken as statistically significant changes. Statistical significance for qualitative variables was calculated using the Chi-squared test and the z-test. To analyze the dependencies of features, Pearson's correlation coefficient (r) was calculated.

Results

To assess the clinical and functional parameters in patients with CHF FC I–III, depending on the severity of renal dysfunction, all examined patients were divided into two study groups: Group I consisted of 81 patients with CHF FC I–III with GFR >60 ml/min/1.73 m^2 and Group II consisted of 69 patients with CHF FC I–III with eGFR ≤60ml/min/1.73 m^2.

The results of the study of physical performance (PP) according to 6 min walk test in patients of Group I with CHF GFR >60 ml/min/1.73 m^2 were 363.59 ± 7.6 m, respectively. The decrease in the distance traveled according to the 6 min walk test data in Group II of patients with eGFR ≤60 ml/min/1.73 m^2, exercise tolerance was more pronounced than in patients of Group I and this figure was 248.7 ± 11.0 m, which was 46.2% lower than the results of Group I of the study ($p < 0.001$).

Analysis of the parameters of clinical manifestations according to the data of the clinical assessment scale showed that in patients of Group I, the total score was 5.5 ± 0.13 points. In patients of Group II with eGFR ≤60 ml/min/1.73 m^2, there was a deterioration in the clinical condition, characterized by an increase in the clinical assessment scale by 19.9% compared with the clinical assessment scale in patients of Group I ($p < 0.001$) amounting to 6.86 ± 0.14 points, respectively (Table 2).

Table 2: Indicators of exercise tolerance and quality of life parameters in patients with CHF I–III FC, depending on the severity of RD (M ± SD)

Indicator	GFR >60 ml/min/1.73 m^2 (n = 81)	GFR ≤60 ml/min/1.73 m^2 (n = 69)
6 min walk test, m	363.59 ± 41.3	248.7 ± 23.2***
SI QoL, points	34.1 ± 2.4	41.06 ± 3.1***
The clinical assessment scale, points	5.5 ± 0.39	6.86 ± 0.44***

***p < 0.001 in relation to CHF with GFR >60 ml/min/1.73 M^2. GFR: Glomerular filtration rate, M: Mean, SD: Standard deviation.

Analysis of the indicators of the Minnesota questionnaire showed that the quality of life of patients with CHF also depends on the severity of renal dysfunction, so with the progression of the severity of RD, the total index of quality of life of patients increased. In particular, the baseline indicators of patients' QoL according to the Minnesota questionnaire showed that the total index in Group I patients with CHF eGFR >60 ml/min/1.73 m^2 was 34.1 ± 0.6 points. As RD progressed, the total QoL scores increased by 17.04% compared with the data of Group I, amounting to 41.06 ± 0.6 ($p < 0.001$) points in Group II patients with eGFR ≤60 ml/min/1.73 m^2.

The study of renal blood flow in CHF patients with eGFR >60 ml/min/1.73 m^2 at the level of the right and left renal arteries showed an increase in PI by 19.3% ($p < 0.05$) and 20.5% ($p < 0.05$), RI – by 5.4% ($p < 0.001$) and 3.4% ($p > 0.05$), decrease in speed indicators: Speed Vmean – by 22.4% ($p < 0.001$) and 25.5% ($p < 0.01$), decrease in Vd – by 14.1% ($p > 0.05$) and 8.9% ($p > 0.05$) cm/s, and Vs – by 8.6% ($p > 0.05$) and 9.1% ($p > 0.05$), respectively, compared with the control group. At the same time, in CHF patients with eGFR ≤60 ml/min/1.73 m^2 at the level of the right and left renal arteries, a highly significant increase in PI was noted – by 24.9% ($p < 0.001$) and 22.5% ($p < 0.001$), a decrease Vmean – by 38.3% ($p < 0.001$) and 34.8% ($p < 0.001$), Vd – by 31.9% ($p < 0.001$) and 28.5% ($p < 0.001$), and Vs – by 21.8% ($p < 0.01$) and 20.3% ($p < 0.01$), respectively, compared with the control group (Table 3).

Similar changes were observed at the level of the right and left segmental renal arteries in CHF patients with eGFR ≤60 ml/min/1.73 m^2 with an increase in RI by 15.9% ($p < 0.05$) and 14.6% ($p < 0, 01$) and PI – by 31.1% ($p < 0.001$) and 32.8% ($p < 0.001$), decrease in Vmean speed by 24.1% ($p < 0.01$) and 22.5% ($p < 0.001$) 0.01), and Vd – by 16.7% ($p < 0.05$) and 15.3% ($p < 0.05$) cm/s, respectively, compared with the indicators of CHF patients with eGFR >60 ml/min/1.73 m^2.

In CHF patients with renal dysfunction, changes were also noted at the level of the lobar and segmental renal arteries, characterized by a significant increase in PI and RI indices, there was a decrease in speed indicators during diastole, systole, and the average blood flow velocity.

Analysis of LV systolic function depending on the presence of kidney dysfunction showed that in Group II with GFR ≤60 ml/min/1.73 m^2, there was an increase in LV EDV by 10.1% ($p < 0.001$) and LV ESV by 20.7% ($p < 0.001$) in relation to the data of Group I with GFR >60 ml/min/1.73 m^2. Further analysis of the parameters of LV systolic function EF, as well as fractional shortening of the LV in systole (Fs%), showed that in Group II, these indicators had significant differences with Group I. There was a significant difference in EF by 10.5% and 25.4% and Fs% by 11.2% ($p < 0.001$) (Table 4). There was an average positive correlation between GFR and LV EF ($r = 0.51$, $r = 0.40$; $p < 0.05$) in groups of patients with eGFR ≤60 ml/min/1.73 m^2 and GFR ≥60 ml/min/1.73 m^2. Analysis also showed the

Table 3: Characteristics of renal hemodynamic parameters (renal and segmental arteries) in patients with CHF depending on renal dysfunction (M ± SD)

Indicator	Right renal artery		Left renal artery		Right segmental artery		Left segmental artery	
	GFR >60 ml/min (81)	GFR <60 ml/min (69)	GFR >60 ml/min (81)	GFR <60 ml/min (69)	GFR >60 ml/min (81)	GFR <60 ml/min (69)	GFR >60 ml/min (81)	GFR <60 ml/min (69)
Vs cm/s	57.85 ± 5.5	53.76 ± 6.2*	56.81 ± 7.2	52.37 ± 7.5*	45.27 ± 5.9	41.72 ± 0.3**	45.50 ± 0.32	42.86 ± 0.34*
RI	0.701 ± 0.053	0.721 ± 0.0035*	0.717 ± 0.0052	0.723 ± 0.042*	0.63 ± 0.004	0.66 ± 0.004*	0.625 ± 0.003	0.66 ± 0.003*
Vd cm/s	16.34 ± 3.3	13.75 ± 2.1	16.61 ± 3.3	14.14 ± 2.8*	16.29 ± 0.24	14.78 ± 0.25*	15.06 ± 0.15	12.98 ± 0.19*
Vmean cm/s	28.29 ± 3.4	19.34 ± 4.3**	27.93 ± 4.2	20.11 ± 4.4**	23.97 ± 0.17	21.10 ± 0.27	23.20 ± 0.24	21.40 ± 0.26
PI	1.24 ± 0.31	1.47 ± 0.31*	1.27 ± 0.21	1.49 ± 0.22*	1.21 ± 0.16	1.24 ± 0.15*	1.22 ± 0.017	1.26 ± 0.19*

Where *Significance p <0.05, **significance p <0.01 between groups. GFR: Glomerular filtration rate, M: Mean, SD: Standard deviation.

dependence of renal blood flow velocity and RI on the LV EF (HR: 2.36; 95% CI: 1.34–4.5; p = 0.028).

Table 4: Indicators of LV systolic function in patients with CHF depending on GFR (M ± SD)

Indicator	GFR >60ml/min/1.73 m^2 (n = 81)	GFR ≤60ml/min/1.73 m^2 (n = 69)
LV EF, %	52.7 ± 8.31	47.64 ± 4.36***
LV EDV, ml	131.22 ± 18.47	145.9 ± 19.61***
LV ESV, ml	61.4 ± 7.18	77.43 ± 6.47***
Heart rate	73.84 ± 4.39	75.81 ± 5.26
FS%	28.23 ± 2.19	25.4 ± 1.74***

***p <0.001 – significance between indicators in patients with GFR ≤60 and GFR >60 ml/min/1.73 m^2.
GFR: Glomerular filtration rate, M: Mean, SD: Standard deviation, LV EF: Left ventricle ejection fraction, LV EDV: Left ventricle end-diastolic volume, LV ESV: Left ventricle end-systolic volume.

Discussion

Impaired kidney function is the most important predictor of poor prognosis in patients with CHF, even more significant than the severity of CHF and LV EF. With GFR <60 ml/min/1.73 m^2, the risk of mortality increases by 2.1 times, with reduced LV systolic function, the risk of death in patients with HF increases by 3.8 times, with unchanged systolic function – by 2.9 times. The main indicator of LV dysfunction that determines the prognosis of CHF is LV EF, so the level of creatinine is also an independent predictor of poor prognosis of RD [8].

RD in patients with CHF is an important factor that worsens the clinical manifestations of the disease, reduces the PP and quality of life of patients. This is based on the deterioration of the cardiovascular system, as well as a decrease in kidney function with a deterioration in the cardiorenal relationship. These negative processes develop against the background of complex disorders of autonomic and neurohumoral regulation [9].

More pronounced structural changes in the heart in patients with CHF, and their further progression, are associated with the activation of the neurohumoral system, which contribute to the activation of several pathogenetic mechanisms – activation of the sympathetic-adrenal and renin-angiotensin-aldosterone systems, which are involved both in the processes of heart remodeling and in the progression of cardiorenal relationships [10].

In patients with CHF, neurohormonal mechanisms are activated to restore tissue perfusion, and excessive activity of the sympathetic nervous system due to impaired baroreceptor reflexes leads to increased release of renin from the juxtamedullary cells of the kidneys. An increase in the level of renin leads to an increase in the production of angiotensin II (Ang II), which has a multiple maladaptive systemic effect on the heart, blood vessels, and kidneys. In the kidneys, Ang II causes vasoconstriction of the renal efferent arterioles and an increase in the proportion of renal plasma filtered through the glomeruli [11].

Inadequate renal blood flow or perfusion pressure causes renin release by the juxtaglomerular cells of the afferent arterioles due to a low blood flow condition in the ascending loop of Henle and pressure sensitive baroreceptors. This leads to sodium retention, increased vascular congestion, and further deterioration of renal function due to constriction of the renal afferent arterioles [12].

Ciccone *et al*. confirmed quantification of arterial renal perfusion provides a new parameter that independently predicts CHF patient outcome, thus strengthening its possible role in current clinical practice to better characterize renal function and stratify patient's prognosis [13].

In studies by M. Iacoviello et al. the studied relationship between impaired renal blood flow and deterioration of kidney function in patients with CHF in univariate, as well as in direct stepwise multivariate logistic regression analysis showed that in the subgroup of patients with higher values of the resistive index, there was a progressive increase, there were observed changes in absolute creatinine (p<0.001 by ANOVA analysis) and a relative decrease in GFR-EPI (p<0.05 by ANOVA analysis), as well as an increased risk of worsening kidney function. Patients with worsening renal function when compared with those without worsening renal function showed an increased probability of admission for AD HF. Moreover, at 1 year, they showed a greater absolute reduction of LV EF and a greater occurrence of functional status worsening, defined as the increase of NYHA class. The best cutoff of arterial RI was 70, with a sensitivity of 91% and a specificity of 50% and its possible role in current clinical practice to better define the risk of cardiorenal syndrome progression is strengthened [14].

Conclusion

Thus, in patients with CHF, the assessment of renal blood flow provides information on cardiorenal

pathophysiology, reflecting the hemodynamic impact on renal function, and may contribute to the early diagnosis of renal dysfunction. In CHF patients with impaired renal function, changes in renal blood flow were characterized by a significant increase in pulsatile and resistive indices, a decrease in the rate of renal blood flow at the level of the lobar and segmental renal arteries.

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