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Concentric Myocardial Remodeling in Patients with Chronic Kidney Disease

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Abstract **The aim** of the research was to study the mechanisms of early remodeling of the myocardium in different stages of chronic kidney disease. **Background.** An increase of the Left ventricular mass and a change in its geometric model increase the risk of cardiovascular diseases and worsen the prognosis of patients with chronic kidney disease. Concentric myocardial remodeling (C-remodeling) was established by echocardiography in the presence of normal left ventricular myocardium and an increase in the relative thickness of the left ventricle walls. **Material and methods.** The study included 106 patients (50 men and 56 women) observed at the Republican Specialized Scientific and Practical Medical Center for Nephrology and Kidney Transplantation at the age of 44.9±13.6 years with normal left ventricular mass, without verified or possible coronary artery disease, hemodynamically significant valvular disorders and heart failure II-IV FC (by NYHA). Predialysis stage of chronic kidney disease occurred in 74 (69.8%), dialysis - in 32 (30.2%) patients. The duration of dialysis was 18.5 (3.0; 41.3) months. **Results.** Concentric myocardial remodeling represents the initial stage of developing of the left ventricle hypertrophy. This conclusion is confirmed by a significant increase in Left ventricular mass index during Concentric myocardial remodeling. As the results of our studies have shown, risk factors for Concentric myocardial remodeling in patients with chronic kidney disease are age, duration of previous hypertension, higher values of clinical blood pressure, which is consistent with previous findings about a similar relationship in patients with essential hypertension. **Conclusion.** Leading risk factors for Concentric myocardial remodeling in patients with chronic kidney disease include age, female gender, duration of previous hypertension, systolic blood pressure, diastolic blood pressure and hemoglobin levels, and more severe renal impairment. An additional risk factor for Concentric myocardial remodeling in hemodialysis patients is its volume overload.

Keywords Chronic kidney disease, Cardiovascular diseases, Myocardial remodeling

1. Introduction

Cardiovascular disorders (CVD), according to the world's leading dialysis centers, are the leading cause of morbidity and mortality in patients with chronic kidney disease (CKD) [1-4]. Mortality among dialysis patients from CVD is 40-60% of all deaths, which is 20-30 times higher than mortality in the general population. It was found that the predictor of a high risk of CVD and an unfavorable prognosis is an increase in the Left ventricular mass (LVM), regardless of arterial hypertension (AH) and coronary heart disease [5-6,1,7-9]. Modern studies have demonstrated that not only an increase of LVM, but also a change in the geometric LV model of the heart, which is identified as preclinical cardiovascular pathology (especially in asymptomatic patients), has a significant prognostic value at CKD [10-13]. It was found that the risk of developing cardiovascular complications is highest at concentric hypertrophy (CVD develops 4 times more often than at unchanged LV geometry), less with eccentric hypertrophy and concentric remodeling of the myocardium. The issue of risk factors and mechanisms of early changes in LV geometry in CKD remains unclear [5-6,11].

The aim of the research was to study the mechanisms of early remodeling of the myocardium in different stages of chronic kidney disease.

2. Material and Methods

The study included 106 patients (50 men and 56 women) observed at the Republican Specialized Scientific and Practical Medical Center for Nephrology and Kidney Transplantation at the age of 44.9±13.6 years with normal left ventricular mass, without verified or possible coronary artery disease, hemodynamically significant valvular disorders and heart failure II-IV FC (by NYHA). Predialysis stage of chronic kidney disease occurred in 74 (69.8%), dialysis - in 32 (30.2%) patients. The duration of dialysis was 18.5 (3.0; 41.3) months. The causes of CKD were:

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chronic glomerulonephritis (n=52), pyelonephritis (n=15), polycystic kidney disease (n=12), obstructive nephropathy (n=9), hypertensive nephroangiosclerosis (n=7), tubulointerstitial nephritis (n=3), other nephropathies (n=5). The diagnosis was not clear in 3 patients, due to the detection of the disease in the CKD stage. All patients were performed a standard clinical, laboratory and instrumental examination for patients with CKD. Predialysis CKD was classified according to creatinine clearance (Ccr) by the Cockcroft-Gault calculation method: Ccr (male)= (140-age) x weight (kg)/ Cr (mmol/l) x 0,81; Ccr (female)= Ccr (male) x 0.85. Clinical and laboratory parameters were taken into account as average monthly. The dry weight of dialysis patients was defined as the lowest post-dialysis weight without symptoms of hypovolemia in two months prior to the study and was used as the basis for establishing interdialysis weight. Blood pressure (BP) was measured with a mercury sphygmomanometer using the Riva-Rocci-Korotkov auscultatory method. The cuff was applied to the contralateral arm without an arteriovenous fistula or shunt in hemodialysis patients. BP was established as the mean of two measurements observed in two dialysis sessions, one pre-dialysis and one post-dialysis BP and presented as pre-dialysis and post-dialysis BP. Arterial hypertension was diagnosed at systolic BP (SBP) ≥140 mm Hg. and/or diastolic BP (DBP) ≥90 mmHg. Echocardiographic investigation was carried out on the Aloca SSD-2000 ultrasound system (Japan) in accordance with the recommendations of the American Echocardiographic Society. All hemodialysis patients were examined the day after routine dialysis in the middle of the week. Measurements of the LV end diastolic (EDD) and end systolic dimensions (ESD), LV posterior myocardial wall thickness (PMWT) and Interventricular septal thickness (IVST) were performed in the M-mode from the parasternal access. The relative wall thickness (RWT) of the LV was calculated using the following formula: RWT= IVST + PMWT / EDD. LV volume parameters were calculated by the L.Teichgolz method. The following indicators were also calculated: stroke volume (SV, ml), stroke index (SI, ml), ejection fraction (EF,%). The value of the total peripheral resistance (TPR) was calculated by the formula: TPR =80*BPav/MV, dyn * sek * cm^{-5}, where BPav – average BP, which was calculated as BPav = DBP+SBP-DBP/3, mmHg. LV myocardial mass was calculated by the R.B.Devereux formula [4]: LVM=0.8 * 1.04{(IVST + PMWT +EDD) 3 – (EDD) 3 } + 0.6 g. LV mass (LVMI) and the LV volume indices (LVVI) were defined as the ratio of LVM and LVV to body surface area (BSA). To calculate the BSA, the formula was used: BSA (m^2) = (0,0001) * (71.84) * (wt 0,425) * (ht 0,725), where wt - weight (kg), ht - height (cm). LV hypertrophy (LVH) is stated in absolute values LVMI ≥134 g/m^2 in males and ≥110 g/m^2 in females [3]. LV geometry was characterized based on LVMI and Relative Wall Thickness (RWT). It was considered normal if LVMI was not increased and RWT was less than 0.45. Concentric myocardial remodeling was diagnosed in cases when at unchanged LVMI, the RWT increased to 0.45 or more. Standard methods of descriptive statistics were used to analyze and evaluate the data obtained: calculation of means and their standard deviations (M±SD) for a normal distribution, median and interquartile range for a non-normal distribution. The Kolmogorov-Smirnov criterion was used to test the hypothesis of the normality of the distribution. The Kruskal-Wallis criteria and the Mann-Whitney U-test were used to analyze the differences in quantitative characteristics. The significance of quantitative differences was determined using Student's t-test for independent samples. Differences were considered significant at $p<0.05$. The SPSS 8.0 statistical software package from SPSS Inc (USA) was used for data processing.

3. Results

According to the selection of patients with unchanged LVMI, two groups of patients were distinguished based on RWT: group I consisted of 59 (55.7%) patients with normal geometry of the left ventricle, group II - 47 (44.3%) patients with myocardial C-remodeling.

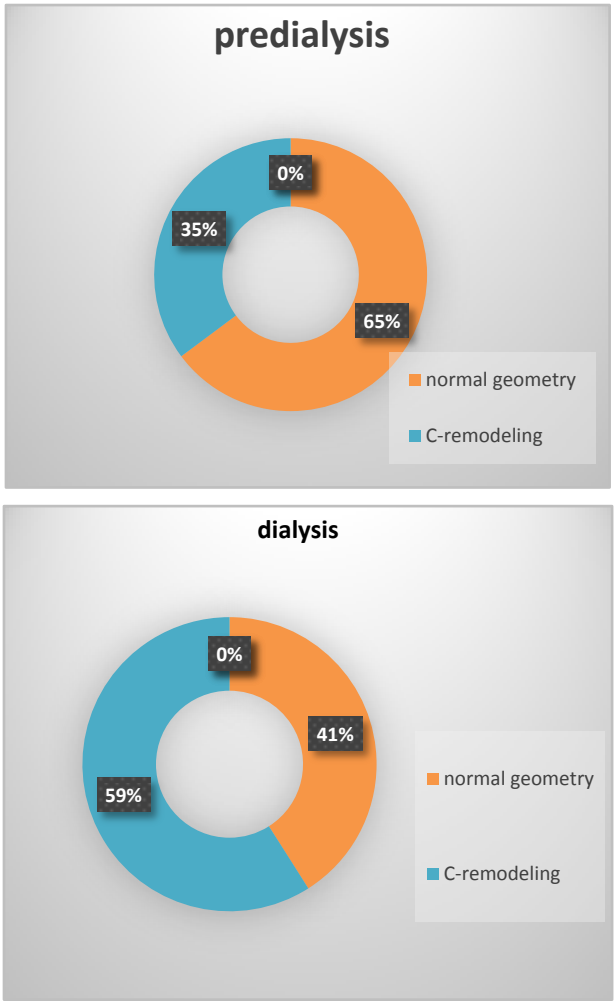

Figure 1. The frequency of myocardial C-remodeling at different stages of CKD

When analyzing the relationship between the frequency of C-remodeling and the stage of CKD, it turned out that normal LV geometry occurred in 48 (64.8%) cases of pre-dialysis and only in 13 (41%) cases of dialysis CKD ($p<0.05$). At the same time, the frequency of myocardial C-remodeling was 26 (35.2%) cases in the predialysis and 19 (59%) cases in the dialysis stages of CKD ($p<0.001$) (Figure 1).

Comparative characteristics of echocardiographic parameters in patients with normal LV geometry and C-remodeling are presented in Table 1.

Table 1. Echocardiographic parameters of patients with CKD with unchanged the left ventricle geometry and concentric myocardial remodeling

Index	Chronic kidney disease			p
	Group without LVH	Normal geometry	C-remodeling	
LVMM, g	170.2±42.9	162.3±43.2	175.1±35.8	0.01
LVMI, g/m^2	101.9±17.7	90±20,75	103,5±15,7	0.01
RWT	0.51±0.13	0.38±0.03	0.58±0.1	0.001
IVST, mm	10.8±1.8	9.3±0.5	12.3±1.3	0.001
PMWT, mm	10.2±1.6	8.6±0.6	10.3±1,4	0.001
ESD, mm	29.9±4.4	27.65±3.65	31.75±4.3	0.01
EDD, mm	46.2±6.2	42.3±3.9	51.75±4.4	0.01
ESV, ml	36.8±11.3	30.7±7.95	44.5±10.4	0.001
EDV, ml	109.4±34.5	92.7±31.3	130.2±26.6	0.003
LVVI ml/m^2	58.9±22.9	43.3±11.4	81±15.35	0.001
SV, ml	74±28.4	63.8±30.4	85.9±21.3	0.045
HI l/min/m^2	3.192±0.8	2.75±0.7	3.502±0.8	0.01
EF, %	63.8±8.95	62.7±10.6	65.4±6.1	0.43
RWT, dyn* sec* 8 cm^{-5}	1.530±6.1	1.81±6.2	1.35±420	0.01

As shown in the table, with C-remodeling, the indicators of ESD ($p<0,01$) and EDD ($p<0,01$), ESV ($p<0,001$) and EDV ($p<0,003$), SV ($p<0,045$), HI ($p<0,01$) were higher, and TPR lower ($p<0,01$), compared with the normal geometry of the left ventricle, while in patients with normal LV geometry and C-remodeling, EF did not differ. In contrary, PMWT ($p<0,001$) and IVST ($p<0,001$), RWT ($p<0,001$), LVM ($p<0,01$) and LVMI ($p<0,01$) were significantly higher at myocardial C-remodeling compared with echocardiographic parameters in patients with a normal geometric LV model [7-8,10].

Comparative characteristics of patients with normal left ventricular geometry and C-remodeling of the myocardium, presented in Table 2, did not reveal significant differences in sex, weight, height, body mass index (BMI).

At the same time, it turned out that patients with C-remodeling of the myocardium were older ($p<0.005$), had lower hemoglobin levels ($p<0.05$) and serum creatinine content ($p<0.05$) was higher. Patients with dialysis CKD with myocardial C-remodeling showed a greater interdialysis weight gain (2.33±0.78 and 1.33±1.3 kg; $p<0.05$) compared with the group of patients with unchanged left ventricular geometry. Thus, it was found that in patients with CKD and normal LV mass, the geometric model of LV was changed with a high frequency and myocardial C-remodeling was developed [4,5,14]. In the predialysis stage of CKD, the frequency of C-remodeling corresponds to the prevalence of C-remodeling of the myocardium in patients with essential hypertension. However, in patients with dialysis CKD, C-remodeling of the myocardium is much more common than in essential arterial hypertension [9,14-15].

Table 2. Clinical characteristics and laboratory parameters of patients with normal geometry of the left ventricle and concentric myocardial remodeling

Index	Chronic kidney disease			p
	Group without LVH	Normal geometry	C-remodeling	
Age, years	44.9±13.9	36±9	50.6±14.2	0.005
Sex, % male	54	52	57	-
Weight, cm	169±8	168±9	169±8	-
Body mass, kg	72.6±12	71.2±13	73.4±11	-
BMI, kg/m^2	25.3+5.1	24±4.6	26.3±5.4	0.31
Cr, µmol/l	931,1±268,4	642,5±208,6	988,1±374,7	0.05
Dialysis duration, months	18.5 (2.0; 41.3)	19.0 (2.5; 33)	18.0 (1.0;44.0)	0.86
Interdialysis weight gain, kg	1.86±1.15	1.33±1.3	2.33±0.78	0.05
Hemoglobin, g/l	97.7±22.8	96.9±21.3	88.2±24.4	0.05

Thus, according to various clinical studies, its prevalence in hypertensive patients ranged from 13 to 19% when C-remodeling was established based on the determination of RWT by the thickness of the posterior LV wall. However, its frequency increased to 39% when PMWT and IVS were included in the determination criteria. It should also be emphasized that in the above works, LVMI <125 g/m^2 for both sexes were taken as normal values of myocardial mass, and therefore women with LV hypertrophy, whose LVMI was in the range from 110 to 125 g/m^2, could be assigned to the group with C-remodeling of the myocardium. KC-remodeling of the myocardium represents the initial stage of LVH development. This conclusion is confirmed by a significant increase in LVMI during myocardial C-remodeling. As the results of our studies have shown, the risk factors for myocardial C-remodeling in patients with CKD are age, duration of previous hypertension, higher values of clinical BP, which is consistent with the previously obtained conclusions about a similar relationship in patients with essential hypertension.

We established a relationship between the absence of nocturnal BP reduction (nondipper) and myocardial C-remodeling in women with CKD, but not in men. A higher relative risk of myocardial C-remodeling was found in women with essential hypertension. However, in patients with essential hypertension, the risk factor for myocardial

C-remodeling was an increase in total peripheral vascular resistance.

According to the results of our study, in patients with CKD, on the contrary, risk factors for myocardial C-remodeling should be considered a large volume overload of the myocardium due to anemia, which was reflected in an increase in cardiac output and a decrease in peripheral vascular resistance. In prospective Canadian research that included 430 patients in its study, it was found that a decrease in hemoglobin by an average of 1 g / dl was accompanied by an increase in the risk of developing LV dilatation by 49% in groups of patients comparable in age, blood pressure, serum albumin and the presence of sugar diabetes. According to P. Parfrey et al., AH is a predictor of both concentric hypertrophy and LV dilatation. Histological examination reveals hypertrophy and dystrophy of myocytes, focal necrosis, a picture of diffuse interstitial fibrosis, fibroblast proliferation with an increase in collagen content in the intercellular space [6]. The causes of fibrosis are manifold and include aging, ischemia, exposure to a number of hormones such as catecholamines, angiotensinogen II and aldesterone.

The possible involvement of toxic factors in the occurrence of myocardial C-remodeling may be indicated by an increase in its frequency after a decrease in kidney function [3,15-16]. In addition, an independent cause of myocardial C-remodeling development in dialysis patients may be insufficient correction of fluid volume, which is confirmed by greater interdialysis weight gain in this group of patients.

4. Conclusions

In patients with CKD, C-remodeling of the myocardium is widespread. The frequency of myocardial C-remodeling increases as renal function decreases.

C-remodeling of the myocardium represents the initial stage of the development of left ventricular myocardial hypertrophy. In turn, high systolic AH increases LV afterload, and a decrease in diastolic AH leads to a decrease in coronary perfusion, contributing to myocardial ischemia.

Our studies have shown that, in patients with CKD grade 3-4, there is an association between systolic and diastolic arterial hypertension and left ventricular hypertrophy.

A highly significant correlation was found between mean arterial pressure and left ventricular myocardial mass index, which did not depend on age and creatinine clearance.

AH is the main trigger in the occurrence of left ventricular hypertrophy only at the initial stage of CKD [10]. CKD progression, the value of AH as the main risk factor for left ventricular hypertrophy decreases and the main role passes to other risk factors, as evidenced by the lack of relationship between the left ventricular myocardial mass index and AH in the predialysis period.

There is often no nocturnal decrease of AH in patients with uremia, which correlates with an increase of left ventricular myocardial mass [14]. At the same time, according to other authors, the correlation between the value of diastolic pressure and the mass index of the left ventricular myocardium [8,17], the thickness of the interventricular septum is weak.

The leading risk factors for myocardial C-remodeling in patients with CKD include age, female gender, duration of previous hypertension, SBP, DBP and hemoglobin levels in the blood, more severe renal dysfunction. An additional risk factor for myocardial C-remodeling in hemodialysis patients is its volume overload.

Adequate blood pressure control, timely correction of anemia at the predialysis stage of chronic renal failure will slow down the process of myocardial remodeling, the development of left ventricular hypertrophy and improve the prognosis of patients with CKD.

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The article is published for the first time and is part of a scientific work.

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