ECHOCARDIOGRAPHIC CHARACTERISTICS OF MYOCARDIAL STATUS IN PATIENTS WITH DIFFERENT STAGES OF CHRONIC KIDNEY DISEASE AND ITS DYNAMICS IN DIALYSIS PATIENT UNDER SPIRONOLACTONE THERAPY

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Abstract

Background: The study aimed to evaluate myocardial status in patients with chronic kidney disease stages III–V and assess the effect of spironolactone in dialysis patients.

Materials and Methods: A total of 46 patients with chronic kidney disease stages III–IV and 83 with stage V on maintenance hemodialysis were examined. Thirty-eight hemodialysis patients received spironolactone 25 mg/day for 6 months. Echocardiography was used to assess left ventricular dimensions, myocardial mass and relative wall thickness. Left ventricular hypertrophy was defined as left ventricular mass index ⩾125 g/m² in men and ⩾110 g/m² in women; relative wall thickness ⩾0.45 was considered increased.

Results: In spironolactone-treated patients (Group 1), left atrial diameter decreased from 4.58 ± 0.11 cm to 4.40 ± 0.11 cm; end-diastolic diameter from 4.15 ± 0.13 cm to 3.94 ± 0.17 cm; posterior wall thickness from 1.29 ± 0.03 cm to 1.23 ± 0.04 cm; Left ventricular myocardial mass from 238.46 ± 19.11 g to 206.18 ± 21.45 g; and Left ventricular mass index from 132.2 ± 10.81 g/m² to 113.32 ± 11.75 g/m². In untreated patients (Group 2), parameters showed minimal change: left atrial diameter 4.03 ± 0.11 cm to 3.90 ± 0.09 cm; Left ventricular myocardial mass 293.39 ± 17.13 g to 291.52 ± 15.43 g; Left ventricular mass index 173.57 ± 10.47 g/m² to 176.94 ± 10.06 g/m².

Conclusion: In anuric hemodialysis patients, spironolactone 25 mg/day significantly reduced left ventricular posterior wall thickness, myocardial mass and volume, and left atrial size, indicating a cardioprotective effect.

Introduction

Cardiovascular complications in patients with chronic kidney disease (CKD) are highly prevalent and significantly impact prognosis. Patients with end-stage renal disease (ESRD) face an exceptionally high annual mortality risk, exceeding 20% in the United States and other developed countries.[1]. Nearly half of all deaths are attributed to cardiovascular events, a rate up to 10 times higher than in the general population with normal kidney function, with this risk increasing significantly in dialysis patients.[2-5] Of particular concern is the fact that in the cohort of young patients (25–35 years), mortality from cardiovascular complications is several hundred times higher compared to those in the older age group (70 years and above).[6].

The influence of traditional risk factors does not fully explain the high prevalence of cardiovascular

complications at various stages of CKD, particularly in its terminal stage. It is evident that non-traditional risk factors also play a significant role. For instance, there is no consensus regarding the status of the hemostatic system in CKD, generalized endothelial dysfunction, or mineralocorticoid receptor activation. Aldosterone hyperproduction is thought to play a critical role in the development of endothelial dysfunction and cardiovascular remodeling in CKD, especially in dialysis patients.[7,8]

Despite the very high risk of cardiac events, current treatment options remain insufficiently effective in improving outcomes for patients with CKD.[8-12]

It is important to note that the elevated risk of cardiovascular complications emerges early in kidney function decline, with the highest mortality risk observed among younger patients. This heightened risk results from the complex interplay of hemodynamic, metabolic, and endocrine disturbances accompanying renal dysfunction, all of which affect the myocardium and blood vessels.[7] Among the main factors contributing to kidney and cardiovascular system damage in CKD patients are angiotensin II and aldosterone. Previously, angiotensin II was considered the primary mediator in these processes, but this perspective has changed. Today, aldosterone is recognized as an independent mediator of cardiovascular complications, with evidence showing that aldosterone induces cellular fibrosis, hypertrophy of vascular smooth muscle cells, and cardiomyocyte apoptosis.[8,10,13]

Left ventricular hypertrophy (LVH) is now regarded as the primary structural cardiac alteration in CKD. Initially, LVH was thought to be compensatory, acting as a myocardial adaptation mechanism to increased pre- and afterload. However, data from the Framingham Heart Study, which demonstrated a significant increase in the risk of acute myocardial infarction, sudden cardiac death, and other cardiovascular complications in patients with LVH, refuted this notion.[14] Further research revealed that structural and functional changes in the myocardium in arterial hypertension (AH) are not always accompanied by an increase in myocardial mass. As a result, the term "remodeling" has been adopted to encompass both hypertrophy and dilation of the left ventricle, leading to changes in geometry and sphericity. The Framingham study results indicate that LVH is a stronger predictor of adverse outcomes than other known risk factors. Additionally, it has been shown that in women, LVH is a more significant risk factor than in men for increased cardiovascular mortality.[14] Other studies have found that the risk of serious cardiovascular events increases in parallel with left ventricular mass, even at levels below commonly used thresholds.[9]

The aim of our study was to assess the condition of the myocardium in patients with CKD stages III–V and the impact of spironolactone therapy on this condition.

Material and methods

This observational study included 129 patients with chronic kidney disease (CKD): 46 patients with CKD stages III–IV and 83 patients with stage V CKD undergoing maintenance hemodialysis (HD). Among the HD patients, 38 received spironolactone therapy at a dose of 25 mg/day for 6 months. The study was conducted at the Research Institute of Nephrology, Pavlov First Saint Petersburg State Medical University, Saint Petersburg, Russian Federation.

Inclusion criteria were age ⩾18 years, confirmed diagnosis of CKD stage III–V (according to KDIGO guidelines), and informed consent for participation. Exclusion criteria included unstable cardiovascular conditions, active infection or malignancy, and use of other mineralocorticoid receptor antagonists within the last 3 months.

All patients underwent transthoracic echocardiography (EchoCG) to assess left ventricular (LV) parameters. The following measurements were evaluated: LV internal dimensions, LV myocardial mass (LVMM) calculated using the American Society of Echocardiography (ASE) formula, and relative wall thickness (RWT). LVMM was indexed to body surface area (LVMI). LV hypertrophy and remodeling were defined as follows: LVMI ⩾125 g/m² for men and ⩾110 g/m² for women; increased RWT was defined as ⩾0.45. Patterns of LV geometry

were classified as normal geometry, concentric hypertrophy, eccentric hypertrophy, or concentric remodeling, in accordance with current guidelines.

Ethical approval: The study protocol was approved by the institutional ethics committee, and all patients provided written informed consent, Protocol No. 12/08 dated March 14, 2014.

Statistical analysis was performed using Statistica v6.0 (*StatSoft Inc., Tulsa, OK, USA*). Continuous variables were expressed as mean ± standard deviation (SD). Intergroup differences were assessed using Student's t-test. A p-value <0.05 was considered statistically significant.

Results

Echocardiographic parameters in patients with different stages of chronic kidney disease (CKD) are presented in Table 1.

Table 1. Echocardiographic parameters in patients with CKD (mean ± standard error)

Parameters	CKD stages		p-value
	III-IV (n=46)	V (n=83)	
LA, cm	4.61±0.09	4.32±0.08	0.0001*
LVEDD, cm	4.97±0.98	4.56±0.1	0.0002*
PWTLV, cm	1.31±0.42	1.24±0.02	0.131
IVST, cm	1.43±0.55	1.25±0.02	0.003*
LVMM	347.89±21.12	262.47±13.06	0.0001*
LVMI, g/m²	179.35±10.2	166.2±15.2	0.0001*
RWT	0.56±0.02	0.56±0.01	1.0
p < 0.05 - statistical significance of differences			

As shown in Table 1, the thickness of the LV walls—as well as the left ventricular myocardial mass (LVMM) and left ventricular mass index (LVMI)—in both patient groups significantly exceeded the normal reference values. When comparing patients with CKD stages III–IV and those with stage V CKD, all parameters, except for posterior wall thickness (PWTLV), left atrial dimension (LA), and relative wall thickness (RWT), differed significantly between the groups.

Assessment of the type of left ventricular hypertrophy (LVH) revealed that the majority of patients (95.5%) exhibited abnormal LV geometry, while only 4.5% had normal ventricular sphericity. Concentric hypertrophy was the most prevalent pattern, identified in 50.6% of patients, followed by concentric remodeling (29.2%) and eccentric hypertrophy (15.7%).

Subsequently, patients with stage V CKD were randomized into two groups based on spironolactone use. The first group included patients who received spironolactone, and the second group consisted of those who did not. Echocardiographic dynamics were tracked in 21 patients in group 1 and in 23 patients in group 2. The corresponding data are presented in Table 2.

Table 2. Dynamics of Echocardiographic Parameters in Patients with Stage V CKD Receiving Spironolactone (mean ± standard error)

Parameters	CKD stages				P value	
	V - with Spironolactone, (n = 21)		V - no Spironolactone (n = 23)			
	baseline	after 6 months	baseline	after 6 months	baseline	after 6 months
LA, cm	4.58 ± 0.11	4.4 ± 0.11	4.03 ± 0.11	3.9 ± 0.09	0.0001*	0.0001*
LVEDD, cm	4.15 ± 0.13	3.94 ± 0.17	4.99 ± 0.13	5.01 ± 0.1	0.0001*	0.0001*
PWTLV, cm	1.29 ± 0.03	1.23 ± 0.04	1.19 ± 0.03	1.21 ± 0.03	0.0001*	0.066

IVST, cm	1.26 ± 0.03	1.23 ± 0.04	1.24 ± 0.03	1.23 ± 0.04	0.033	1.0
LVMM	238.46 ± 19.11	206.18 ± 21.45	293.39 ± 17.13	291.51 ± 15.43	0.0001*	0.0001*
LVMI, g/m²	132.2 ±1 0.81	113.32 ± 11.75	173.57 ± 10.47	176.94 ± 10.06	0.0001*	0.0001*
RWT	0.62 ± 0.02	0.65 ±0.03	0.49 ± 0.02	0.48 ± 0.01	0.0001*	0.0001*
*p < 0.05 - statistical significance of differences						

As shown in Table 2, patients receiving spironolactone exhibited a statistically significant reduction in left atrial dimension (LA), left ventricular end-diastolic diameter (LVEDD), posterior wall thickness of the left ventricle (PWTLV), left ventricular myocardial mass (LVMM), and left ventricular mass index (LVMI).

Analysis of diastolic function revealed that 33 patients with CKD stages III–IV and 39 patients with CKD stage V had type I diastolic dysfunction, while 1 patient in each group had type II dysfunction. After spironolactone therapy, 14 hemodialysis patients who previously had type I diastolic dysfunction showed normalization of diastolic function.

Discussion

The results of our study indicate that patients with CKD, both those in predialysis stages and those receiving hemodialysis (HD), show significantly enlarged left ventricular (LV) dimensions compared to normal values. Left ventricular hypertrophy (LVH) and myocardial remodeling in patients with impaired kidney function have multifactorial origins. Four groups of factors contributing to structural and functional myocardial remodeling in chronic kidney disease (CKD) have been identified. The first group includes factors that increase preload and afterload on the myocardium, such as hypertension, hypervolemia, anemia, and arteriovenous fistula blood shunting.[4,5,10] The second group consists of causes that decrease myocardial oxygen supply, including atherosclerosis, coronary artery calcification, dyslipoproteinemia, and uremic pericarditis. The third group includes factors that have an inotropic effect on myocardial contractility in the presence of electrolyte disturbances, such as hyperkalemia, hypermagnesemia, and metabolic acidosis.[4,5] The fourth group comprises factors that inhibit myocardial metabolism, such as uremic toxins (urea, creatinine, purines, oxalates, guanidines, middle molecules like parathyroid hormone, ß2-microglobulin), low-molecular-weight substances (homocysteine, hippuric acid, etc.), and catecholamines.[4,5] In addition to the above-mentioned factors, the development of LVH is influenced by disturbances in neurohormonal systems, particularly the activation of the renin-angiotensin-aldosterone system and secondary hyperparathyroidism due to calcium-phosphate metabolism disturbances.[8,11]

The geometric model of LVH is determined by the combined impact of hemodynamic and neurohormonal factors. There is no consensus in the literature regarding the prevalence of different types of geometry. Some authors suggest that the distribution of remodeling variants depends on the severity of the disease, with concentric remodeling and concentric LVH being more common in severe stages.[12] Moreover, because concentric remodeling and LVH are associated with significant diastolic dysfunction, increased myocardial meridional stress, and changes in the left atrium and right ventricle, they are considered the most prognostically unfavorable.

Concentric LVH develops as a result of pressure overload (increased preload on the myocardium), leading to increased cardiomyocyte thickness and a reduction in LV volume. In the case of pressure overload, such as in hypertension, this type of remodeling ensures high LV pressure needed to overcome increased blood flow resistance. This leads to an increase in the number of parallel

myofibrils, and the sum of the individual myofibril tensions results in increased pressure within the LV cavity.

Volume overload (fluid retention, sodium retention, anemia, and blood shunting through the AV fistula) leads to eccentric hypertrophy (increased afterload on the myocardium), resulting in elongation of myocytes and increased LV volume. In pressure overload, remodeling aims to create a larger stroke volume. Due to physiological limitations that prevent sarcomeres from significantly reducing their length, the increase in stroke volume is achieved by adding sarcomeres in series, leading to LV cavity enlargement. The increased wall stress of the LV is required to maintain the same pressure within the LV cavity, thus necessitating wall thickening, which leads to cavity dilation and eccentric hypertrophy.[10]

The significance of determining LV geometry lies in the fact that the structure of myocardial damage significantly influences prognosis. The Framingham study analyzed the prognosis of patients with various LV geometry types and found that concentric hypertrophy had a worse prognosis compared to eccentric hypertrophy. Concentric remodeling also showed a higher rate of complications compared to normal geometry. Thus, assessing the relative wall thickness (RWT) and LV mass index (LVMI) is important for prognosis evaluation.[14]

Geometry abnormalities lead to diastolic dysfunction and, eventually, systolic dysfunction of the LV. While it is thought that systolic and diastolic dysfunction are part of the same process,[10] patients with renal failure most commonly exhibit type I (pseudonormal) diastolic dysfunction, which is characterized by impaired LV relaxation. This results in significant residual blood in the left atrium after early diastole (E wave peak), so the main volume of blood enters the left ventricle during active atrial systole (A wave peak). LV relaxation impairment is most often caused by hypertension and LVH, where the hypertrophied myocardium loses its ability to relax as quickly as normal tissue. However, in dialysis patients, diastolic dysfunction is often observed without accompanying LVH, which is due to hyperhydration. In addition, factors such as age and dialysis quality also affect diastolic function. Type II diastolic dysfunction (restrictive) indicates a more severe LV dysfunction and is associated with a significant reduction in myocardial contractility.[10]

In our study, type I diastolic dysfunction was diagnosed in 71.7% of patients with CKD stages III-IV and in 47% of patients with CKD stage V. In the group of patients with CKD stage V who did not receive spironolactone, type I diastolic dysfunction progressed to type II in 1 patient after 6 months. Conversely, in the group of patients receiving spironolactone, 1 patient showed improvement from type II to type I.

For reducing and preventing cardiovascular complications in chronic heart failure (CHF), various groups of antihypertensive drugs are used (angiotensin receptor antagonists, ACE inhibitors, diuretics, beta-blockers). The discovery of the pathogenic role of aldosterone in the development of fibrosis in the heart and vessels has led to the investigation of aldosterone receptor antagonists in the management of heart failure and the prevention of cardiovascular complications. A significant study in this field is the randomized, placebo-controlled RALES Mortality Trial, which assessed the impact of low-dose spironolactone on mortality in patients with CHF (NYHA class III-IV) and an LV ejection fraction of less than 35%, who were also receiving standard therapy, including ACE inhibitors, loop diuretics, and cardiac glycosides. The trial was terminated early after it was found that the mortality in the spironolactone group was significantly lower compared to the control group. Mortality from all causes in the spironolactone group was 27% lower than in the placebo group ($p = 0.0001$). Mortality from cardiac causes decreased by 31%, total hospitalizations decreased by approximately 17%, and hospitalizations due to CHF decompensation decreased by approximately 36%. The overall number of deaths and hospitalizations was reduced by approximately 22% with the addition of spironolactone ($p < 0.0002$).

According to our study, after 6 months of spironolactone therapy, there was a statistically significant reduction in the posterior wall thickness, myocardial mass and volume, and left atrial size. The thickness of the interventricular septum (IVS) did not change significantly, likely due to the relatively short observation period.

The efficacy assessment was based primarily on echocardiography; the study did not include cardiac MRI or remodeling biomarkers (e.g., NT-proBNP).

Limitations. This study has several limitations. First, the sample size was small and conducted at a single center, which limits the generalizability of the findings. Second, the follow-up period was relatively short, making it difficult to assess long-term cardiac remodeling or clinical outcomes. Third, concomitant cardiovascular medications and differences in volume status among hemodialysis patients may have acted as confounding factors, influencing the degree of left ventricular improvement observed with spironolactone.

What's known? Left ventricular hypertrophy and remodeling are common in chronic kidney disease (CKD); aldosterone antagonists may reduce myocardial remodeling in certain patient groups.

What's new? For the first time in a clinical study, a significant reduction in left ventricular hypertrophy and left atrial size was demonstrated in anuric hemodialysis patients receiving a low dose of spironolactone without marked hyperkalemia.

Conclusion

The prevalence of left ventricular hypertrophy (LVH) and myocardial and vascular remodeling patterns in chronic kidney disease (CKD) is multifactorial. Despite numerous experimental and clinical studies, information about myocardial remodeling and left ventricular (LV) geometry types in patients with combined cardiorenal pathology is still limited, with very little data available from the Russian population. The discovery of the pathogenetic role of aldosterone in the development of fibrosis in the heart and vessels has led to the study of the impact of aldosterone receptor antagonists on heart failure manifestations and the prevention of cardiovascular complications. However, it is important to note that there is still no full clarity regarding the mechanisms of these complications, and they remain a subject of research to this day. Furthermore, the study of the mechanisms behind myocardial hypertrophy development and progression in CKD remains an ongoing challenge in modern nephrology.

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