LEFT VENTRICULAR MYOCARDIAL REMODELING IN PATIENTS WITH END-STAGE CHRONIC RENAL DISEASE CORRECTED BY PROGRAM HEMODIALYSIS

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The aim of the investigation was to assess structural and functional changes in the left ventricular (LV) myocardium in patients with end-stage chronic kidney disease (ECKD) receiving regular program hemodialysis (PHD) treatment depending on concomitant pathology.

Materials and Methods. We examined 88 patients with PHD ECKD and 15 patients before starting dialysis by 2-dimensional echocardiography with pulse-wave Doppler.

Results. PHD patients with ECKD were characterized by typical concentric remodeling and hypertrophy of LV (61.7%), normal LV geometry (33.3%), LV hypertrophy decrease after 30–36 months of PHD, the presence of pulmonary hypertension (50.7%) with LV systolic function maintained (ejection fraction 64±1.4%) and no increase of LV cavity. The slight growth of LV cavity was observed in a few cases (2.5% — eccentric remodeling, and 2.5% — eccentric hypertrophy).

Conclusion. Revealing LV cavity enlargement in patients with ECKD requires more precise definition of cardiological ailment diagnosis and administration of the appropriate therapy.

Key words: end-stage chronic kidney disease; chronic kidney disease; program hemodialysis; left ventricular myocardial remodeling.

The survival and quality of life of the patients with the end-stage chronic kidney disease (ECKD) receiving replacement therapy by program hemodialysis (PHD) depend on many factors, among which cardiovascular complications occupy the primary place [1]. According to the data of various investigators, cardiovascular ailments amount to 30–52% of causes of the total lethality of patients with ECKD [2–4].

A high risk of cardiovascular complications in patients on PHD is connected with the process of remodeling of the heart myocardium, accompanied by the impairment of its function [5–6]. Arterial hypertension (AH) [6, 7], volume overload, anemia, neurohumoral effects are factors responsible for the development of remodeling and hypertrophy of the left ventricle (LV) in patients with ECKD [8–13].

Information on the effect of the duration of PHD on the degree of LV hypertrophy intensity is contradictory. Some authors state that its occurrence and intensity increase with the duration of treatment [5, 7]. Long-term PHD is not considered by others to change the extent of LV hypertrophy essentially [10], which is linked to a good correction of AP [14]. The most common variant of LV hypertrophy in patients with ECKD is concentric hypertrophy [5], eccentric LV hypertrophy occurs 2.5–3 times rarer [14–16].

Data on the rate of systolic disorders of the LV function in dialysis patients also varies widely. Some researchers do not consider systolic dysfunction to be characteristic of the patients on dialysis [6, 10, 17], others find its signs in 36–62% of uremic sufferers [5, 17]. Such divergence may depend on the tested cohort, in which patients with a marked cardiac insufficiency and heavy cardiovascular diseases might initially be present — in larger or smaller

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quantities in different authors. Besides, in a number of studies incorrect, from the modern point of view, methods of measurements (M-mode of electrocardiogram may give the oversized dimensions of LV, especially that of the end-diastolic, and interventricular septum thickness) and calculations (Teichholz, Devereux) were used. Therefore, investigations of the processes of LV myocardium remodeling in patients with ECKD remain urgent.

The aim of the investigation was to assess structural and functional changes in the left ventricular myocardium in patients with end-stage chronic kidney disease receiving regular program hemodialysis treatment.

Materials and Methods. We examined 88 patients with ECKD having received PHD treatment for 2–126 months by the time of investigation. Group 1 included 42 patients with chronic glomerulonephritis (CGN) at the age from 22 to 72, males — 23, females — 19, with disease duration from 2 to 45 years, duration of ECKD — from 1 to 18 years, and duration of PHD therapy — from 2 to 126 months. Group 2 comprised 10 patients with diabetes mellitus (DM) (7 people with diabetes mellitus type 1, 3 people with diabetes mellitus type 2), of them there were 4 males and 6 females at the age of 28–65 years, with DM duration from 2 to 25 years, ECKD duration from 1 to 11 years, PHD therapy duration — from 2 to 48 months. Group 3 was composed of 36 patients with other causes of ECKD: chronic pyelonephritis — 11 individuals, polycystic renal disease — 15, other congenital abnormalities and hypertension — 10 people; of them there were 16 males, 20 females from 25 to 72 years of age, with the main disease duration from 6 to 47 years, ECKD duration from 2 to 10 years, PHD therapy duration from 2 to 60 months. A control group consisted of 15 patients with ECKD before starting dialysis.

The study complies with the Declaration of Helsinki (the Declaration was passed in Helsinki, Finland, June, 1964, and revised in October, 2000, Edinburg, Scotland) and was performed following approval by the Ethic Committee of Nizhny Novgorod State Medical Academy. Written informed consent was obtained from every patient.

Such clinical data as presence and degree of AH, associated clinical conditions (ischemic heart disease — IHD, anemia) were assessed. AH duration varied from 1 to 34 years. The AH degree in the period prior the dialysis was evaluated according to the available medical records. I degree AH was found in 32 patients (39.0%) (AP<140/90–100 without treatment or undergoing monotherapy), II degree AH — in 18 (22.2%) (AP — 140/100–169/109 without treatment or receiving one-, two-component therapy), and III degree — in 17 (21.0%) (AP — 170/110 or more without hypertensive therapy or 140–159/90–100 with continued intake of 3–4 antihypertensive drugs). All patients underwent the following procedures: measurements of office AP according to Korotkov method, taking standard ECG, daily monitoring of ECG and AP.

Hemoglobin and biochemical blood indexes were determined using standard methods, intact parathyroid hormone — by immunoradiometric assay. Mean values of these parameters during a month prior examination were used.

Echocardiographic (echoCG) examination was conducted using the Aloka SSD 3500 apparatus (Japan) according to the standard method in the B- and PW-modes of scanning with 2.5–3.0 MHz ultrasound signal. The following parameters were assessed: end-diastolic index (EDI) — end-diastolic lateral size of the LV cavity, measured on the level of the mitral valve chordae, indexed by body surface area; end-systolic and end-diastolic LV volumes according to Simpson (ESV and EDV, respectively); stroke volume (SV) as a difference between EDV and ESV; ejection fraction (SV/EDV in %). LV myocardium weight was calculated by the formula "area–length" indexed by body surface area (LVMWI), then eccentricity index (T_{IVS}+T_{LVPW}/EDS, where IVS — interventricular septum, LVPW — LV posterior wall, EDS — end-diastolic size), and sphericity index (EDS/L, where L — LV length in the period of diastole) were determined. Percent of inferior vena cave collapse was counted. Using Doppler cardiography in the PW-mode, a mean pressure in the pulmonary artery was calculated: *lgP*=2.87*PAAT*/*PAET*–2.4, where *PAAT* and *PAET* is time of flow acceleration and ejection in the pulmonary artery in case of tricuspid insufficiency absence, or by the percent of inferior vena cave collapse and regurgitation velocity on the tricuspid valve — in case of tricuspid failure. LV diastolic function was studied in the pulsed Doppler mode: the correlation of A and E peaks of transmitral blood flow, the time of deceleration of the early diastolic LV relaxation were estimated. All indices were compared with the baseline values according to the literature data [18, 19]. During echoCG-examination valve pathology and post-infarction changes were assessed, resulting in exclusion from data calculations 4 patients of group 1 — 2 with post-infarction aneurism and 2 with valve regurgitation of more than I degree, and 3 patients from group 3 — 2 with post-infarction aneurism and 1 with valve regurgitation. Valve regurgitation in two cases was caused by a marked fibrosis of the mitral and aortic valves, in one case it was connected with II degree anemia and subvalve dysfunction, in three cases it was combined with post-infarction aneurism.

Results and Discussion. The groups of patients were comparable in gender, age, duration of ECKD, chronic kidney disease (CKD), except for the group with DM, whose average age and other time indices were insignificantly less than in other groups (Table 1).

Mean values of the lateral LV size were within the baseline values in all tested groups, speaking of the absence of cavity dilatation in the majority of patients (Table 2).

Table 1

Clinical characteristics of patients

Characteristics	Group 1 — CGN	Group 2 — DM	Group 3 — other diseases	Control group
A number of patients in the groups (n=103)	42	10	36	15
Of them:				
males (n=51)	23	4	16	8
females (n=52)	19	6	20	7
Age, years	45.1±6.7	39.9±4.4	54.1±2.8	56.1±3.2
Disease duration, years:				
CKD	15.4±2.0	19.4±3.1	16.0±2.4	11.8±3.5
ECKD	7.8±0.9	4.2±1.1	6.1±0.8	3.2±0.8
Duration of PHD, months	39.0±4.9	18.8±4.8	27.3±3.2	—
Post-infarction aneurism	2	—	1	—
Valve regurgitation, II–III degree	3	—	2	—
Angina pectoris	8	2	8	—
I degree anemia	11	2	10	—
II degree anemia	3	2	2	—

Table 2

Morphological indices of echoCG in patients with end-stage chronic kidney disease

Indices, baseline values	Group 1 — CGN (n=38)	Group 2 — DM (n=10)	Group 3 — other diseases (n=33)	Control group (n=15)	p
EDI mm/m^2 (N=23–29 mm/m^2)	25.4±0.5	25.0±0.6	26.8±0.5	24.4±0.6	p_{1-3}=0.051 p_{2-3}=0.01 p_{3-c}=0.003
Eccentricity index (N<0.45 relative units)	0.51±0.02	0.55±0.02	0.49±0.02	0.58±0.02	p_{1-c}=0.002 p_{2-3}=0.05 p_{3-c}=0.005
Sphericity index (N=0.55–0.65 relative units)	0.50±0.01	0.48±0.02	0.54±0.01	0.50±0.01	p_{1-3}=0.005 p_{2-3}=0.011 p_{3-c}=0.01
LVMWI, g/m^2 (N<117 g/m^2)	116.0±5.9	121.0±6.3	112.4±5.4	143.8±7.8	p_{1-c}=0.01 p_{2-c}=0.03 p_{3-c}=0.005

At the same time, there were differences in the mean value of EDI: among individuals, receiving PHD, it was the least in the group with DM (statistically significant differences with group 3). It agrees with the data on diabetic cardiomyopathy — "a small rigid heart". But the least index of EDI was in the control group (statistically significant differences with group 3). Beyond the baseline were the mean values of sphericity (SI) and eccentricity (EI) indices in all patient groups. Mean values of EI were increased, indicating to the concentric type of remodeling or LV hypertrophy. The highest value was revealed in the control group, differences being statistically significant with all examined groups. Mean values of SI were decreased in all groups of patients, showing the predominant change of LV form in the direction of cavity elongation. Differences among the groups were statistically insignificant. The main index of LV hypertrophy — LVMWI — was the highest in the control group, differences were statistically significant with all examined groups. In patients of group 1 and 3 the mean value of LVMWI approximated the upper border of the norm, whereas in the group with DM slightly exceeded it, considerable variability of individual indices was observed.

In the majority of patients in all groups normal lateral size of LV cavity was determined (Table 3). In 21% of patients in group 1 and in 6% of patients in group 3 it was reduced, being characteristic of concentric hypertrophy and concentric remodeling. In 3 patients of group 1 and 4 patients of group 3 EDI was slightly increased by 10% relative to the upper border of the baseline value, 4 of them had heavy anemia, 2 — angina pectoris fuctional class III, 1 — myocarditis in the history.

The predominant type of LV hypertrophy was a concentric one in all groups of patients (LVMWI — over 117 g/m^2 at EI$\geqslant$0.45). Normocentric hypertrophy type was

found in 7% of cases in group 1 and 3% of cases in group 3 (increase in LVMWI at EI<0.45 and normal EDI). Eccentric LV hypertrophy was revealed only in 5% of patients in group 1 (increase of LVMWI, EI<0.45, EDI>29 mm/m^2). Asymmetric hypertrophy of LV was not determined at all.

Among the types of LV myocardium remodeling concentric type also prevailed: increase of EI at normal values of LVMWI. And only in patients of group 3 eccentric remodeling was revealed: increase of EDI and reduction of EI (<0.30). Eccentric type of hypertrophy and remodeling were indicative of disadaptive stage of the pathologic processes in myocardium [20].

SI in the majority of patients (74% — in group 1, 100% — in group 2, 67% — in group 3) spoke of elongation of the cavity form, which corresponded to the adequate myocardial reaction to the load in the form of AH. Spherisation of the LV form was found only in 2 patients of group 3, showing that the processes of remodeling were disadaptive [21].

Analyzing the relation of LV hypertrophy (LVMWI) to the degree of AH (Table 4), it was established that the mean values of LVMWI at all grades of AH in each group increased with the growth of AH, but differences were not always significant due to an essential spread of individual values. It may be explained by a complex genesis of LV hypertrophy and participation in it other factors in addition to AH.

Functional indices of LV (Table 5) in all groups of patients were within the norm and did not have group differences. Of all functional indices only mean pressure in the pulmonary artery exceeded normal values. The mean group value was the highest in the predialysis group, and the least — in the group of patients with DM.

Table 3

Prevalence of morphological changes of the left ventricle in patients with end-stage chronic kidney disease, %

Indices	Group 1 — CGN (n=38)	Group 2 — DM (n=10)	Group 3 — other diseases (n=33)
EDI:			
normal	71	100	82
decreased	21	—	6
increased	8	—	12
LV hypertrophy:			
concentric	26	50	80
normocentric	7	—	3
eccentric	5	—	—
Concentric remodeling	47	50	26
Eccentric remodeling	—	—	6
Change of the LV cavity form:			
normal	26	—	27
elongation	74	100	67
spherisation	—	—	6

Table 4

Relation of left ventricle hypertrophy (MWI, g/m^2) to the degree of arterial hypertension

Groups	AH 0	AH I	AH II	AH III	p
Group 1 — CGN	n=5 80.1±4.3	n=20 97.2±4.3	n=7 116.1±13.2	n=6 162.7±13.2	p_{0-I}<0.024 p_{II-III}<0.015
Group 2 — DM	—	n=1 82	n=4 111.0±8.2	n=5 133.8±8.3	—
Group 3 — other diseases	n=9 86.6±7.6	n=11 96.5±6.9	n=7 120.5±7.0	n=5 148.7±11.4	p_{I-II}<0.015
Control	—	—	—	n=15 143.8±7.8	—

Table 5

Functional indices of echoCG in patients with end-stage of chronic kidney disease (p>0.05)

Indices, baseline values	Group 1 — CGN (n=38)	Group 2 — DM (n=10)	Group 3 — other diseases (n=33)	Control group (n=15)
Ejection fraction (N=51–70%)	63.5±2.0	64.6±2.2	62.8±1.4	60.4±1.2
Stroke volume index, ml/m^2 (N=35–50 ml/m^2)	39.0±1.7	35.0±1.7	39.0±1.4	36.2±1.3
Cardiac index, L/m^2 (N=2.6–3.2 L/m^2)	2.78±0.13	2.90±0.22	2.76±0.11	2.80±0.18
Mean pressure in the pulmonary artery, mm Hg (N=15–19 mm Hg)	22.9±2.5	17.2±3.2	24.4±2.9	29.0±5.5

All differences between the groups were not statistically significant; considerable spread of individual values was observed.

Correlation of pulmonary hypertension with the presence of fuctional class II–II exertional angina was also analyzed. It was found, that the mean pressure in the pulmonary artery in patients with angina syndrome (35.47±2.35 mm Hg, n=18) significantly ($p<0.001$) exceeded that of the patients without angina (21.66±1.46 mm Hg; n=63). It indicated to the role of the joined IHD in the genesis of pulmonary hypertension. However, the median of the mean pressure was beyond the normal values. It is likely to be connected with hypervolemia, changes of the pulmonary circulation vessels, broncho-pulmonary pathology, left ventricle insufficiency of nonischemic origin [17]. To separate the influence of these factors is rather problematic.

Diastolic disorders were revealed in 93.8% of patients, including: diastolic dysfunction type I — in 50.6%, pseudonormal type — in 33.3%, type II (restrictive type) — in 9.9% of patients, being the evidence of relaxation disturbance, increase of myocardium rigidity in the majority of patients with ECKD.

Correlation between indices of remodeling (LVMWI, EI, SI) and age of the patients, CKD duration, dialysis age, AH, anemia degree and creatinine level was studied among other investigation tasks. A weak significant positive correlation ($r=0.28$; $p<0.02$) was established between the form of LV cavity (SI) and age, which reflected the transition from elongated cavity form to normal, and in some patients to spherisation of LV cavity. It may be explained by the increase of sclerotic processes over age, but the relation with the duration of CKD, ECKD or PHD was not established. Significant positive correlation was revealed between the presence of exertion angina and SI ($r=0.25$; $p<0.05$), and with the value of the mean pressure in the pulmonary artery ($r=0.28$; $p<0.02$), showing the tendency to LV spherisation and pressure elevation in the pulmonary artery in patients with ECKD and joined IHD. When patients with IHD were excluded from the calculations, significant correlation between SI and age was not found, suggesting that correlation of SI with age in the total mass of patients was caused mainly by the addition of IHD.

A weak significant correlation ($r=-0.27$; $p<0.02$) was found to be between SI and ejection fraction, which reflects reduction of contractile function during the transition from the elongated cavity form to the normal one and the tendency to spherisation of LV. Insufficiently close correlation between EI and LVMWI ($r=0.46$; $p<0.001$) spoke of the variety of LV hypertrophy types — concentric, normocentric, eccentric. Significant positive correlation between EI and ejection fraction ($r=0.33$; $p<0.005$) showed the dependence of myocardium contractile function on the relative LV wall thickness, which was quite natural for the adequate reaction of myocardium to the load (AH).

A significant positive correlation of LV hypertrophy (LVMWI) with age ($r=0.23$; $p<0.05$), degree of AH before dialysis according to the history data ($r=0.36$; $p<0.001$) was estimated; significant correlation between LVMWI and AP at the time of investigation was not determined.

Dialysis duration and LV hypertrophy relations were identified: LVMWI in patients, receiving PHD less than 30 months (116.87±5.55 g/m^2, n=45), was statistically significantly greater ($p<0.05$) than in patients being on it over 30 months (99.44±4.81 g/m^2, n=36). The data obtained testified to the decrease of LV hypertrophy 2.5–3 years after the beginning of PHD, which may be connected with the adequate AH control.

Significant negative correlation ($r=-0.25$; $p<0.05$) between the level of hemoglobin and cardiac index (cardiac output per minute indexed by body surface area) was determined, that corresponded to the hyperkinetic type of blood circulation, characteristic for anemia. Insignificant negative correlation of the hemoglobin level and EDI ($r=-0.14$), EI ($r=-0.11$), SI ($r=-0.11$), LVMWI ($r=-0.15$), stroke index ($r=-0.11$) may speak of the role of anemia in the genesis of LV hypertrophy, cavity spherisation, and reduction of systolic function.

Conclusion. For patients with end-stage chronic kidney disease on the program hemodialysis concentric remodeling of the left ventricle myocardium (33.3%), concentric hypertrophy of the left ventricle (28.4%) and its decrease 30–36 months after program hemodialysis, presence of pulmonary hypertension (50.7%), diastolic dysfunction (93.8%) with maintaining LV systolic function and absence of LV cavity enlargement are typical.

LV hypertrophy develops long before the beginning of dialysis therapy (its highest value in the predialysis group of patients, positive correlation with age, and the level of AP prior dialysis confirm this statement). Estimated negative correlation between LVMWI and dialysis duration speak of the reduction of LV hypertrophy owing to the adequate AP control, decrease of blood circulation volume, and hemodynamic overload.

At the same time, remodeling of myocardium and LV hypertrophy in ECKD have complex genesis: according to the data of this investigation anemia and joined IHD together with arterial hypertension play a role in LV remodeling.

A slight enlargement of LV cavity and its spherisation were observed in single cases in patients with accompanied pathology — in case of IHD and severe anemia. Though these conditions are pathogenetically connected with ECKD, the disease itself does not lead to LV cavity dilatation. Consequently, revealing LV cavity enlargement in patients with ECKD requires more precise definition of cardiological ailment diagnosis and administration of the appropriate therapy.

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