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LEFT VENTRICULAR HYPERTROPHY – RISK FACTOR FOR POOR OUTCOME IN HAEMODIALYSIS PATIENTS

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REMODELOVANJE LEVE KOMORE – FAKTOR RIZIKA ZA NEPOVOLJAN ISHOD BOLESNIKA KOJI SE LEČE REDOVNIM HEMODIJALIZAMA

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ABSTRACT

Background. Cardiovascular diseases are the leading cause of death in haemodialysis (HD) patients. Left ventricular hypertrophy (LVH) is a powerful predictor of cardiovascular morbidity and mortality in these patients. **Aim.** The aim of this study was to determine the prevalence of LVH, all cause and cardiovascular mortality, and to assess the predictive value of LVH for the outcome of HD patients during a two-year follow-up. **Methods.** The study included 115 patients (71 males and 44 females, average age 53.30 ± 12.17 years) on regular HD for the last 4.51 ± 4.01 years (average Kt/Vsp 1.17 ± 0.23). Patients were distributed in four groups according to LV morphology. **Results.** LVH was present in 82 (71.31%) patients. Patients with concentric LVH had significantly higher serum homocysteine then patients with normal LV morphology. Risk factors contributing to the development of LVH were anaemia, systolic hypertension, hyperhomocysteinaemia and low HDL-cholesterol. Anaemia is an independent risk factor for LVH in HD patients. The average two-year all-cause mortality rate in the examined patients was 13.74%. The mean two-year cardiovascular mortality rate was 8.51%. During a two-year follow-up period patients with an LV mass index (LVMi) >120g/m2 and end-diastolic volume index (iEDV) >90 mL/m2 had a significantly lower overall survival rate, while patients with LVMi >120g/m2 and iEDV ≤90mL/m2 had a significantly lower cardiovascular survival rate than patients with LVMi≤120g/m2 and iEDV≤90mL/m2. **Conclusion.** Left ventricle remodelling is a significant risk factor for poor outcome in patients on regular haemodialysis.

Key words: left ventricular hypertrophy, haemodialysis, mortality

SAŽETAK

Uvod. Kardiovaskularne bolesti su najčešći uzrok smrti bolesnika na hemodijalizi. Hipertrofija leve komore je snažan prediktor kardiovaskularnog morbiditeta i mortaliteta kod ovih bolesnika. **Cilj.** Cilj rada je bio da utvrdi prevalenciju hipertrofije leve komore, da utvrdi stopu opšteg i kardiovaskularnog mortaliteta, kao i da ispita prediktivnu vrednost hipertrofije leve komore za ishod bolesnika koji se leče hemodijalizom, u toku dvogodišnjeg praćenja. **Metod.** U radu je ispitano 115 bolesnika (71 muškarac i 44 žene) prosečne starosti 53,30 ± 12,17 godina, koji se leče redovnim hemodijalizama 4,51 ± 4,01 godina, prosečnog Kt/Vsp indeksa 1,17 ± 0,23. U zavisnosti od morfologije leve komore bolesnici su podeljeni u četiri grupe. **Rezultati.** Hipertrofiju leve komore ima 82 (71,31%) bolesnika koji se leče redovnim hemodijalizama. Bolesnici sa koncentričnom hipertrofijom imaju statistički značajno veću koncentraciju homocisteina u serumu u odnosu na bolesnike sa normalnom morfologijom leve komore. U faktore rizika koji doprinose razvoju hipertrofije leve komore spadaju anemija, povećan sistolni arterijski krvni pritisak, hiperhomocisteinemija i niska koncentracija HDL holesterola. Anemija je nezavisan faktor rizika za razvoj hipertrofije leve komore kod bolesnika koji se leče redovnim hemodijalizama. Prosečna dvogodišnja stopa opšteg mortaliteta ispitivanih bolesnika iznosi 13,74%, a prosečna dvogodišnja stopa kardiovaskularnog mortaliteta 8,51%. U toku dvogodišnjeg praćenja ispitivanih bolesnika, bolesnici sa LVMi>120 g/m2 i iEDV>90 ml/m2 imaju statistički značajno manju stopu preživljavanja od svih uzroka smrti, a bolesnici sa LVMi > 120 g/m2 i iEDV ≤ 90 ml/m2 imaju statistički značajno manju stopu preživljavanja od kardiovaskularnih uzroka smrti, u odnosu na bolesnike sa LVMi ≤ 120 g/m2 i iEDV ≤ 90 ml/m2. **Zaključak.** Remodelovanje leve komore je značajan faktor rizika za razvoj nepovoljnog ishoda bolesnika koji se leče redovnim hemodijalizama.

Ključne reči: hipertrofija leve komore, hemodijaliza, mortalitet

INTRODUCTION

Cardiovascular diseases are the leading cause of morbidity and mortality in patients treated with chronic haemodialysis (1-4). The annual cardiovascular mortality rate among these patients is 9%. The most frequent cardiovascular complications include left ventricular hypertrophy (LVH), ischaemic heart disease and congestive heart failure (1-4). Several risk factors, such as hypertension, anaemia, arteriovenous fistula, volume overload, oxidative stress, microinflammation, hyperhomocysteinaemia and disturbed calcium and phosphorus

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metabolism have been identified as stimulating LVH in the HD population (5).

Hypertension and atherosclerosis cause LV pressure overload which initiates remodelling: parallel addition of new sarcomeres and increased wall thickness at normal chamber radius (wall thickness/ventricle diameter ratio >0.45 - concentric LVH) (4-6).

Left ventricular volume overload caused by high water and salt intake, anaemia and increased arteriovenous fistula blood flow (Q_{AV}≥1000 mL/min) results primarily in the addition of new sarcomeres in series, and, secondarily, in the addition of sarcomeres in parallel. This results in increased LV wall thickness and LV diameter (h/r <0.45) - eccentric left ventricular hypertrophy (4-6).

Left ventricular hypertrophy evolves through two phases. The first is beneficial, adaptive hypertrophy as a response to the increased tensile stress of the LV wall. However, sustained volume and pressure overload lead progressively to a maladaptive hypertrophic response. This phase is characterized by the loss of myocardial cells, deterioration of systolic function and development of heart failure, eventually with lethal outcome (4-6).

The prevalence of LVH in patients on regular HD is 75%, making it an important predictor of cardiovascular morbidity and mortality in these patients (4, 5). The clinical strategy for decreasing all causes and cardiovascular mortality in HD patients includes early identification of high-risk patients, individual adaptation of the dialysis regime and maintaining a better haemodynamic and electrolyte balance (7-9). The strategy for identifying high-risk patients should include determining serum cardiac troponins (troponin I - cTnI and troponin T - cTnT), electrocardiographic parameters (QTc interval length and dispersion) and echocardiographic indices (LV mass index - LVMi and end-diastolic LV volume index - iEDV) (7-9).

Early detection of high-risk patients enables timely implementation of an adequate therapeutic approach. The primary therapeutic strategy for lowering the cardiovascular mortality rate in HD patients should include antiaggregation therapy, statins and beta-blockers, while the secondary strategy encompasses coronary revascularization and percutaneous implantation of a cardioverter defibrillator (PCD) (7-9).

The aims of this study were to determine the prevalence of risk factors for the development of LVH, to determine the independent risk factors for the development of LVH, to determine all cause and cardiovascular mortality, and to assess the influence of LV remodelling on outcome in HD patients.

PATIENTS AND METHODS

We studied 115 patients on chronic standard bicarbonate HD in the Haemodialysis Ward, Clinic for Urology and Nephrology, Clinical Center "Kragujevac" in Kragujevac. All patients were haemodynamically stable, virtually anuric (residual diuresis <200 mL/24h) and had been undergoing HD for at least 6 months. The follow-up period was two years. Patients presented neither clinical nor echocardiographic signs of acute coronary syndrome or congestive heart failure up to three months prior to the commencement of the study. All patients gave informed consent for participation in the study, according to the Declaration of Helsinki.

The following variables were analysed: haemoglobin, shunt blood flow (QAV), mean arterial blood pressure (MAP), serum albumin, homocysteine, C-reactive protein, total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides and lipoprotein (a), calcium, phosphate, intact parathyroid hormone (iPTH), cTnI and cTnt, and calcium-phosphorus product (Ca x PO4).

Laboratory studies

Blood sampling was performed after 12-hours of overnight fasting, before the HD session and heparin administration. Samples for the measurement of serum cTn were taken after 20 to 30 minutes of quiet resting in a semirecumbent position.

Haemoglobin concentration was determined by the colourimetric method (reference range 110-180 g/L). Haematocrit was determined automatically on a COULTER® A^C machine, based on the equation: Hct(%)= (RBCxMCV)/10 (reference range 0.35-0.60).

Serum albumin levels were measured by photometric colour test with bromcresol green. The normal range was 38 46 g/L and a concentration <36 g/L suggested malnutrition.

Serum calcium was determined with a photometric colour test (reference range 2.20-2.65 mmol/L) and serum phosphate with a photometric UV test (reference range 0.80-1.45 mmol/L). Serum iPTH was measured by radioimmunoassay (IRMA). The reference range for healthy persons is 11.8 - 64.5 pg/mL, while values between 200-300 pg/mL are considered appropriate for HD patients.

CRP serum concentration was determined using the immunochemical nephelometric method. It was calculated as the mean value from two measurements taken in three months. The normal concentration was ≤5 mg/L. Microinflammation was suggested when CRP was over 5 mg/L.

Total homocysteine serum concentration was measured by Fluorescence Polarisation Immunoassay (normal value ≤15 μmol/L).

Measurement of serum cTnT was performed based on electrochemiluminescence immunoassay technology (ECLIA method – ElektroChemiLumineszenz ImmunoAssay), using the Roche Diagnostics troponin T kit. The recommended diagnostic threshold for cardiac ischaemia is 0.1 ng/mL. Serum TnI was determined with ADV AxSYM cTnI immunoassay technology (Abbott laborato-

ries). A level of >0.15 ng/mL was considered positive for myocardial necrosis.

Echocardiographic study

All patients underwent echocardiographic examination on a SHIMADZU-2200 machine with a 2.5 MHz transducer probe. Examinations were performed 15 to 20 hours after the dialysis session by a single experienced cardiologist without previous knowledge of the subjects' clinical characteristics, in order to avoid end-diastolic LV diameter alterations induced by the interdialytic volume gain and subjectivity.

Left ventricular mass index, which is normally ≤131 g/m2 in men and ≤100 g/m2 in women, was used as an indicator of LVH. LVMi was calculated as follows:

$$\text{LVMi} = \frac{0.00083 x \left[(LVEDD + IVSd + LVPWd)^3 - (LVEDD)^3\right]}{BSA} + 0.6 \text{ g/m2.}$$

The left ventricular end-diastolic volume index was quantified as follows:

$$\text{iEDV} = \frac{(LVEDD)^3 x 0.001047}{BSA} \text{ mL/m2.}$$

Normally, iEDV is ≤90 mL/m2.

Left ventricle fractional shortening (LVFS), representing a measure of systolic function, is normally 42 ± 8%. It was calculated as follows:

$$\text{LVFS} = \frac{(LVEDD - LVESD)}{LVEDD} x100 \text{ \%.}$$

The left ventricular ejection fraction (LVEF) was calculated as an indicator of systolic function, based on the following equation:

$$\text{LVEF} = \frac{(LVEDV - LVESV)}{LVEDV} x100\% \text{ .}$$

The normal range is 67 ± 9%.

Abbreviations in the formulas stand for: IVSd - interventricular septal wall thickness in diastole (mm), LPWd - LV posterior wall thickness in diastole (mm), LVEDD - LV end-diastolic diameter (mm), LVESV - LV end-systolic volume (mL), LVEDV - LV end-diastolic volume (mL), BSA - body surface area (m2).

Left ventricular hypertrophy was defined as IVSd >11 mm, LVPWd >11 mm and LVMi >131 g/m2 for men and >100 g/m2 for women (10-12). LV concentric hypertrophy was defined as IVSd >11mm, LVEDD >11mm, LVEDD <4.7 mm and LVMi >131 g/m2 in males and >100 g/m2 in females, with normal fractional shortening and relative LV wall thickness >45% (10-12). Eccentric LV hypertrophy is present when LVMi >131 g/m2 in males and >100 g/m2 in females, LVEDD >57 mm, with normal fractional shortening and relative LV wall thickness ≤45% (10-12). LV dilatation was defined as LVEDD >57 mm and iEDV >90 mL/m2, with normal systolic function and LVMi (10-12). Impaired systolic function was defined as LVFS ≤25% and LVEF ≤50% (10-12).

Arterial blood pressure (pre-dialysis pressure) was calculated as the average value of 12 measurements (3/week) taken during the month preceeding the study. Mean arterial pressure was calculated as diastolic blood pressure + 1/3x(systolic blood pressure minus diastolic blood pressure).

Shunt blood flow (QAV) was determined with colour-flow Doppler ultrasound just before echocardiographic examination, on a SHIMADZU-2200 machine, using the 7.5 MHz probe. Blood flow was calculated as the average value of three measurements on an efferent vein, 2-4 cm proximally to anastamosis. Adequate dialysis requires blood flow of 300 to 800 mL/min.

Haemodialysis adequacy was assessed by the Kt/Vsp index, calculated based on Daugridas' second-generation formula:

$$\text{Kt/Vsp} = -\ln(C_2/C_1 - 0.008 \times T) + (4 - 3.5 \times C_2/C_1) \times UF/W,$$

where C_1 stands for predialysis serum urea (mmol/L), C_2 - postdialysis serum urea (mmol/L), T - treatment time (h), UF - ultrafiltration (L) and W - body weight after dialysis (kg). Serum urea was determined with a complete enzymatic method (urease-glutamate-dehydrogenase), with the reference range being 3.5 - 7.5 mmol/L. According to K/DOQI guidelines, the Kt/V delivered should be ≥1.2.

Causes of death in the examined HD patients were defined as cardiovascular events (acute myocardial infarction, congestive hart failure and sudden cardiac death) and non-cardiovascular events (infection/sepsis, neoplasm, unknown) (7).

Statistical analysis

Data are expressed as mean ± SD. Results were statistically analysed with the t test, Mann-Whitney U test, one-factorial ANOVA, Kruskal-Wallis test, Bonferroni test, univariate and multivariate logistic regression analysis, Kaplan-Meier and Log-Rank tests for survival analysis. Values <0.05 and <0.01 were considered significant.

RESULTS

General patients' data are shown in Table 1. LVH was present in 82 (71.31%) patients on regular HD. Concentric LVH was present in 33 patients (28.70%) and eccentric hypertrophy in 49 (42.61%) patients. LV dilatation was found in 16 (13.91%) patients. Seventeen patients (14.78%) had normal echocardiographic finding (Table 1).

Hyperhomocysteinaemia as a risk factor for LVH was present in 86.09% of all patients, anaemia in 76.52%, hypertension in 36.52% and microinflammation in 34.78%. Increased shunt flow (QAV >1000 mL/min) had the lowest prevalence of all LVH risk factors (9.57%), as shown in Figure 1.

Table 1. Demographic and clinical data of patients classified in relationship to left ventricular (LV) remodelling status (echocardiographic assessment)

*PI, II <0.05, **PI,IV <0.01,***PI,IV <0.05, ****PII,IV <0.01
ANOVA, Kraskal-Wolis-ov test

Univariate logistic regression analysis showed a significant negative correlation between HDL-cholesterol, haemoglobin, haematocrit and LVMi ($p<0.05$) (Table 2). A statistically significant correlation was found between arterial blood pressure, mean arterial blood pressure and LVMi ($p<0.05$) (Table 2).

Table 2. Univariate logistic regression analysis of risk factors for left ventricular hypertrophy

Multivariate logistic regression analysis showed anaemia to be an independent risk factor for LVH development (Table 3).

Table 3. Multivariate logistic regression analysis of risk factors for left ventricular hypertrophy

Figure 1. Prevalence of risk factors for left ventricular hypertrophy in haemodialysis patients

Patients with concentric LVH had a significantly higher dialysis adequacy index than patients with eccentric LVH ($p<0.05$), and significantly higher serum homocysteine ($p<0.01$) and cTnT ($p<0.05$) than patients with normal LV (Table 1).

Serum cTnT concentration was significantly higher ($p<0.01$) in patients with eccentric LVH than in those with normal LV mass (Table 1).

HD patients with poor outcome had significantly lower serum albumin ($p<0.01$), higher serum homocysteine ($p<0.05$) and higher LVMi, cTnT and cTnI ($p<0.01$), than patients with good outcome (Table 4).

The average two-year all-cause mortality rate in our study group was 13.74%. The average two-year cardiovascular mortality rate was 8.51%.

During the two-year follow-up period, patients with LVMi >120 g/m2 and iEDV >90 mL/m2 had a significantly higher all-cause mortality rate then patients with LVMi ≤120 g/m2 and iEDV ≤90 mL/m2 (Log-Rank 4.72,

p <0.05) (Figure 2). Patients with LVMi >120 g/m2 and iEDV ≤90 mL/m2 had a significantly higher cardiovascular mortality rate then patients with LVMi≤120 g/m2 and iEDV ≤90 mL/m2 in the same period of time (Log Rank 4.07, p <0.05) (Figure 3).

Table 4. Demographic, clinical and echocardiographic data in relationship to outcome in the two-year study period

Chi-Square tests, Mann-Whitney U test, Student-ov T test

Figure 2. Survival rate from all causes of death in haemodialysis patients in relationship to left ventricular mass index (LVMi) and end-diastolic left ventricular volume (iEDV) during the two-year follow-up period

Figure 3. Survival rate from cardiovascular causes of death in haemodialysis patients in relationship to left ventricular mass index (LVMi) and end-diastolic left ventricular volume (iEDV) during the two-year follow-up period

DISCUSSION

The risk of cardiovascular complications in patients with end-stage renal disease (ESRD) is by far greater than in the general population (13, 14). An increased incidence of cardiovascular disease in HD patients is correlated with a high prevalence of traditional (hypertension, disturbed lipid metabolism, diabetes, smoking) and non-traditional (microinflammation, oxidative stress, hyperhomocysteinaemia, secondary hyperparathyroidism) risk factors, which lead to increased atherosclerosis, characteristic of ESRD patients, plaque destabilization, myocardial fibrosis and valvular heart disease (15-17). The average two-year cardiovascular mortality rate in our study group was 8.51%. Similar results were reported by other authors who found a one-year mortality rate of 9% (1).

Left ventricular hypertrophy was present in 71.31% of patients on regular HD. A similar rate was reported by other authors (18-21). The prevalence of LVH in chronic renal failure patients is approximately 40%, reaching 75% in ESRD (11). Timely identification of risk factors and adequate treatment results in LVH regression in HD patients (22).

Anaemia is present in over 90% of HD patients and represents an important risk factor for LVH. Haemoglobin ≤100 g/L was present in 76.52% of our patients. Multivariate logistic regression analysis identified anaemia as an independent risk factor for LVH in our study group. Similar results were reported by other authors (23).

Hypertension is present in 50-80% of patients on regular HD (24, 25). The prevalence of hypertension (predialysis blood pressure ≤140/90 mmHg) in our study group was 36.52%. Univariate and multivariate logistic regression analysis showed that high blood pressure, together with other risk factors, contributes significantly to

the development of LVH. Target arterial blood pressure values for patients on regular HD are ≥140/90 mmHg, or ≥160/90 mmHg in elderly patients (24, 25).

Hyperhomocysteinaemia (tHcy >15 μmol/L) is an independent risk factor for atherosclerosis in HD patients (26). Over 80% of HD patients have increased plasma homocysteine. The prevalence of hyperhomocysteinaemia in our study group was 86.09%. A statistically significant positive correlation exists between plasma homocysteine and LVMi in HD patients (26). Univariate logistic regression analysis showed a non statistically significant correlation between homocysteine concentration and LVMi in our study group (R=0.0001, p=0.1600).

Inflammation (CRP >5.0 mg/L) is present in 30-50% of patients on regular HD (27). In our study group, microinflammation was present in 34.78% of patients. Some authors have reported a statistically significant positive correlation between CRP concentration and LVMi (28), but our results have not confirmed a statistically significant positive correlation between CRP levels and the echocardiographic parameters of LVH (R=0.0001, p=0.6559).

Hyperlipidaemia is an independent risk factor for atherosclerosis in HD patients (2). Hypertriglyceridaemia and low HDL-cholesterol are present in 30 - 50% of HD patients (2). In our study group, HDL-cholesterol <1.0 mmol/L was present in 20% of patients. Multivariate logistic regression analysis showed that decreased HDL-cholesterol together with other risk factors contributes to LVH development.

Secondary hyperparathyroidism (SHPTH) is often present in HD patients (19). The prevalence of SHPTH (iPTH >500 pg/mL) in our study group was 20%. No statistically significant correlation was found between serum iPTH and LVMi in our study group (R=0.0001, p=0.8884).

Left ventricular hypertrophy is an exceedingly frequent complication and represents the strongest predictor of adverse cardiovascular events in HD patients (3, 4). An increase of LVMi ≥1.0 g/m2/month is associated with an increased risk of cardiovascular complications (30). In patients with normal LV volume (iEDV ≤90 mL/m2) and systolic function (LVFS >25%, LVEF >50%), LVMi >120 g/m2 and LVMi/iEDV >2.2 g/mL are independently associated with late mortality (mortality rate >2 years following the start of regular HD treatment). Patients on chronic HD with LV volume >120 mL/m2 and LVMi/EDVi <1.8 also have a high cardiovascular mortality risk (31-33). Patients in our study group with LVMi >120 g/m2 and iEDV >90 mL/m2 had a significantly higher all-cause mortality rate then patients with LVMi ≤120 g/m2 and iEDV ≤90 mL/m2. Furthermore, patients with LVMi >120 g/m2 and iEDV ≤90 mL/m2 had a significantly higher cardiovascular mortality rate then patients with LVMi ≤120 g/m2 and iEDV ≤90 mL/m2. Other authors reported similar findings, suggesting that LV remodelling significantly influences outcome in HD patients (32, 33). Patients with LVH (LVMi >125 g/m2) have a significantly higher five-year mortality rate then patients with LVMi <125 g/m2 (34). Left ventricular hypertrophy is an independent predictor of cardiovascular mortality in patients on regular HD (34).

Echocardiographic assessment of LV remodelling enables identification of patients with increased risk for cardiovascular complications. Determining the most sensitive parameters for identifying patients at risk for cardiovascular complications enables timely and adequate treatment, thus providing a higher survival rate and better quality of life for HD patients (35-43).

ABBREVIATIONS:

HD - hemodialysis
LVH - left ventricular hypertrophy
LVMi - left ventricular mass index
LVEDVi - left ventricular end-diastolic volume index
QAV - arteriovenous fistula blood flow
cTnT - cardiac troponin T
cTnI - cardiac troponin I
PCD - percutaneous implantation of cardioverter defibrillator
MAP - mean arterial blood pressure
iPTH - intact parathyroid hormone
Ca x PO4 - calcium-phosphorus product
IVSd - interventricular septal wall thickness in diastole
LVPWd - left ventricular posterior wall thickness in diastole
LVEDD - left ventricular end-diastolic diameter
LVESV - left ventricular end-systolic volume
LVEDV - left ventricular end-diastolic volume
LVFS - left ventricular fractional shortening
LVEF - left ventricular ejection fraction
ESRD - end-stage renal disease
SHPTH - secondary hyperparathyroidism
BMI - body mass index
Kt/Vsp - dialysis adequacy index
BP - blood pressure
MAP - mean arterial blood pressure
IDWG - interdialysis weight gain
CRP - C-reactive protein
GN - glomerulonephritis
PN - pyelonephritis

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