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**CLINICAL STUDY**

# Prevalence and Risk Factors of Myocardial Remodeling in Hemodialysis Patients

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*Background.* Left ventricular hypertrophy (LVH) is an independent risk factor for morbidity/mortality in patients with end stage renal disease (ESRD). Our study aimed to identify prevalence as well as independent risk factors that contribute to the development of LV geometric remodeling in our HD patients. *Methods.* The left ventricles of 116 HD patients were classified echocardiographically into four different geometric patterns on the basis of LV mass and relative wall thickness. Furthermore, we measured inferior vena cava (IVC) diameter and its collapsibility index (CI) by echocardiography. Finally, we modeled a stepwise multiple regression analysis to determine the predictors of LV geometry. *Results.* Our study provides evidence that HD patients had a prevalence of abnormal LV geometry in 92% and LVH in 81%. We found all four geometric models of LV. Most dominant were eccentric LVH. Concentric LVH was observed in 37, normal geometry (NG) in 9, and concentric remodeling (CR) in 13 of HD patients. Mean arterial blood pressure was significantly higher in the cLVH group (95 ± 10 mmHg) than in the NG and CR groups (81.6 ± 12.3 and 80 ± 11.8, respectively, $p < 0.001$). The cLVH and eCLVH groups had significantly lower mean hemoglobin (10.3 ± 1.4g/dL and 10.6 ± 1g/dL, respectively) compared with the NG group (11.9 ± 1.4g/dL), $p < 0.001$. Furthermore, interdialytic weight gain (kg) was significantly higher in eCLVH group (3.13 ± 0.8) than in NG group (2.3 ± 1.1), $p < 0.001$. Mean IVC index of the eLVH group (10.83 ± 2.07 mm/m$^2$) was significantly higher than corresponding indexes of NG (10.83 ± 2.07 mm/m$^2$), CR (8.31 ± 1.32 mm/m$^2$) and cLVH (8.12 ± 2.06 mm/m$^2$) groups ($p < 0.001$ for each comparisons). *Conclusion.* Mean arterial pressure, hemoglobin, IVC index, and interdialytic weight gain were found to be independent predictors of LV geometry ($R^2 = 0.147$; $p < 0.001$) in HD patients.

**Keywords** hemodialysis, inferior vena cava, left ventricular hypertrophy, geometric remodeling

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## INTRODUCTION

Despite the progress made over the past decades in the field of renal care, cardiovascular disease (CVD) remains a major cause of morbidity and mortality in patients with end stage renal disease (ESRD). It is accounting for about 50% of deaths,[1,2] and the rate of cardiovascular mortality in these patients is 20 times greater compared with that in the general population.[3] Left ventricular hypertrophy (LVH) is present in a majority of HD patients and is accompanied in the long term by cardiac myocyte apoptosis, fibrosis, capillary rarefaction and, consequently, ischemic heart disease.[4] It is considered a predictor of both cardiovascular events and deaths in patients with ESRD, regardless of age, diabetes mellitus, hypertension, hyperlipidemia, smoking, and coronary heart disease.[5–9]

However, apart from myocardial mass gain, abnormal left ventricular (LV) geometry is also associated with poor outcome in chronic dialysis patients,[10] and different geometric models (concentric or eccentric hypertrophy as well as concentric remodeling) play an important role as well.[11–15] Risk of cardiovascular events is the highest in patients with concentric LVH (cLVH). It is smaller in cases of eccentric LVH (ecLVH) and minimal in patients with concentric remodeling (C remodeling).[10,12,16] The data of the prevalence of LVH in chronic renal failure (CRF) are controversial. It was shown in 25–87% of predialysis patients and 50–97% of dialysis patients.[17–24] There is no agreement about the frequency of LVH geometric models in ESRD. While most studies demonstrate a predomination of cLVH (40–63% versus 20–30% of ecLVH),[20,24,25] some authors report the higher prevalence (63–79.6%) ecLVH.[22,26,27]

The aim of this study was to determine the prevalence of the left ventricular hypertrophy and its geometric models in patients with ESRD and to investigate the risk factors of myocardial remodeling in hemodialysis patients in our center.

## MATERIALS AND METHODS

In all, 129 patients who were on HD for at least 12 months at Institute of Nephrology and Hemodialysis, Clinical Center Nis, Serbia, were enrolled in the study (see Table 1). Exclusion criteria were multisystem disease, previous history of myocardial infarction, severe cardiac valvular disease, congestive cardiac failure, and poor echocardiographic window.

The mean age of the study group was 41±13 years, which ranged from 19 to 71 years. The etiologies of chronic renal failure of the final 116 HD patients were diabetes mellitus in 12, chronic glomerulonephritis in 22, chronic PN in 14, hypertensive nephrosclerosis in 31, ADPKD in 14, miscellaneous in 6, and unknown in 17 patients.

Their HD sessions were performed with controlled ultrafiltration machines and polysulfone hollow-fiber dialyzers. Duration of dialysis (3–4 hours) and blood and dialysate flow (500 mL/min) was prescribed to a Kt/V > 1.3. Ultra-filtration volume and concentration of dialysate were adjusted individually.

Echocardiography was performed within 18 to 24 hours after routine dialysis and according to the guidelines of the American Society of Echocardiography, using a Toshiba Powervision 6000 (Toshiba Co, Tokyo, Japan) ultrasound machine with a broadband 2.0–4.8 MHz transducer allowing M-mode and two-dimensional measurements. Left ventricular end diastolic diameter (EDD), end systolic diameter (ESD), interventricular wall thickness during diastole (IVST), and posterior wall thickness during diastole (PWT) were measured by M-mode. From these measurements, the left ventricular mass (LVM) was calculated according to the Devereux formula.[27]

LVM index (LVMI) was calculated as the ratio between LVM and body surface area (BSA) (normal values 110 g/m$^2$ for women and 130 g/m$^2$ for men).[20] The relative wall thickness (RWT) was calculated with the following formula:

$$RWT = (IVST + PWT)/(IVST + PWT + EDD).$$

Furthermore, because a significant proportion of HD patients demonstrate latent overhydration, we performed measurement of the diameter of inferior vena cava (IVC) and its decrease on deep inspiration [collapsibility index (CI)] by echocardiography to achieve assessment of volume status in dialysis patients.[28] It is a non-invasive and fast method that reflects well the plasma but not the interstitial volume. Using the parameters LVMI and relative

***Table 1***
Comparisons of clinical and laboratory characteristics of HD patients with four different LV geometric patterns

| | Normal LV (n = 9) | Concentric remodeling (n = 13) | Concentric LVH (n = 37) | Eccentric LVH (n = 57) | *p* |
|---|---|---|---|---|---|
| Age (years) | 47 ± 5,8 | 52 ± 19 | 56 ± 12 | 55 ± 10 | NS |
| Sex (male/female) | 6/3 | 8/5 | 22/15 | 35/22 | NS |
| Duration of HD (months) | 59 ± 54 | 63,5 ± 63 | 60 ± 52 | 64 ± 50 | NS |
| Body mass index (kg/m$^2$) | 22,4 ± 1,8 | 24 ± 3,81 | 23,3 ± 3,2 | 24 ± 3,5 | NS |
| Kt/v | 1,21 ± 0,12 | 1,25 ± 0,15 | 1,19 ± 0,15 | 1,22 ± 0,14 | NS |
| Interdialytic weight gain (kg) | 2.3 ± 1.1 | 2.94 ± 1 | 2.64 ± 0.9 | 3.13 ± 0.8 | 0.001 |
| SBP (mmHg) | 102.5 ± 23.5 | 109 ± 16 | 128.5 ± 15.6 | 122.8 ± 20 | 0.02 |
| DBP (mmHg) | 61.6 ± 13.2 | 65.6 ± 10 | 73.2 ± 7.8 | 72 ± 9.5 | 0.02 |
| MAP (mmHg) | 81.6 ± 12.3 | 80 ± 11.8 | 95 ± 10 | 89 ± 12.5 | 0.001 |
| Hemoglobin (g/dL) | 11.9 ± 1.4 | 10.9 ± 1.7 | 10.3 ± 1.4 | 10.6 ± 1 | 0.001 |
| Haematocrit (%) | 33.4 ± 4.1 | 31.3 ± 5.1 | 28.9 ± 3.9 | 30.5 ± 3 | 0.02 |
| Serum calcium (mmol/L) | 2.53 ± 0.26 | 2.59 ± 0.2 | 2.35 ± 0.21 | 2.42 ± 0.34 | NS |
| Serum phosphorus (mmol/L) | 1.57 ± 0.49 | 1.42 ± 0.46 | 1.37 ± 0.38 | 1.58 ± 0.46 | NS |
| Ca × P | 4.02 ± 1.49 | 3.62 ± 0.9 | 3.23 ± 1 | 3.75 ± 1 | NS |
| Parathormone (pg/mL) | 323 ± 268 | 367 ± 413 | 445 ± 428 | 386 ± 386 | NS |
| Serum albumin (g/dL) | 40.3 ± 0.6 | 38.7 ± 5.1 | 36.8 ± 7.5 | 36.7 ± 9 | NS |
| Total cholesterol (mmol/L) | 4.4 ± 0.98 | 4.16 ± 0.96 | 4.64 ± 1.3 | 4.86 ± 1.2 | NS |
| Triglyceride (mmol/L) | 2.63 ± 0.9 | 2.08 ± 1.66 | 2.04 ± 1.23 | 2.13 ± 1.3 | NS |
| LDL cholesterol (mmol/L) | 1.68 ± 0.2 | 2.37 ± 0.8 | 2.68 ± 1.07 | 3.32 ± 0.9 | NS |
| Patients on rHuEpo (%) | 88 | 87 | 91 | 92 | NS |
| Dose of rHuEpo (IU/week) | 4500 ± 2664 | 4666 ± 2065 | 4920 ± 1847 | 4600 ± 1850 | NS |
| Dose of rHuEpo (IU/kgTT/week) | 70.5 ± 42 | 65.9 ± 30.4 | 80.1 ± 27.4 | 65 ± 35.5 | NS |

wall thickness (RWT = 2* wall thickness / end-diastolic diameter), four classes of LV geometry may be recognized: normal geometry (normal LVMI and normal RWT), concentric remodeling (normal LVMI and increased RWT), eccentric LVH (increased LVMI and normal RWT), and concentric LVH (increased LVMI and increased RWT).[29]

The role of age, anemia, hypertension, serum albumin level, hyperphosphatasemia, and secondary hyperparathyroidism were investigated. Average interdialytic weight gain has been analyzed as well. Hemoglobin (Hb), serum electrolytes, serum creatinine (Cr), albumin, calcium, phosphate, calcium-phosphate product, as well as alkaline phosphatase and intact parathyroid hormone (iPTH) were evaluated.

Whole blood counts and blood chemistry were analyzed by standard laboratory procedures. Intact parathyroid hormone (PTH) levels were determined using radioimmunoassay (Sigma-Aldrich Laboratories, The Woodlands, Texas, USA).

### Statistical Analysis

All calculations were done using SPSS program. Data were expressed as mean ± SD. Comparisons between clinical, laboratory, and echocardiographic characteristics of HD patients with different LV geometric patterns were done using one-way ANOVA test. Post hoc comparisons between pairs of means were made by using Dunns with a downward adjustment of the alpha level to compensate for multiple comparisons. Stepwise multiple regression analysis was performed to define the predictors LV geometric patterns. The LV geometric adaptation was included into the multiple regression equation by assigning numerals to represent geometric models. The LV geometric changes were dummy coded as 0 for concentric remodeling (CR and cLVH) and 1 for eccentric remodeling (eLVH) according to RWT, with the exclusion of NG. A $p$ value of less than 0.05 was considered to represent statistical significance.

## RESULTS

We identify all four geometric models of LV in our group of 116 HD patients. Most dominant were eccentric LVH (52 patients or 45%). Concentric LVH was observed in 37 (32%), normal geometry (NG) in 9 (7%), and concentric remodeling (CR) in 13 (11%) of our HD patients.

Clinical and laboratory characteristics of the patients with four different LV geometric patterns were presented in Table 1. Age, sex, BMI, duration of HD, serum albumin level, and Kt/V did not differ significantly between groups. On the other hand, mean arterial BP (MAP), hemoglobin, and interdialytic weight gain were different between the groups. Mean arterial blood pressure (MAP) was significantly higher in the cLVH group (95±10 mmHg) than in the NG and CR groups (81.6±12.3 and 80±11.8, respectively, $p < 0.001$). The cLVH and eCLVH groups had significantly lower mean hemoglobin (10.3±1.4g/dl and 10.6±1g/dl) compared with the NG group (11.9±1.4g/dl, $p < 0.001$). Furthermore, interdialytic weight gain (kg) was significantly higher in eCLVH group (3.13±0.8) than in NG group (2.3±1.1, $p < 0.001$).

Echocardiographic data of four groups were presented in Table 2. Mean LVMI index of the eLVH and cLVH groups were significantly higher than indexes of NG and CR groups ($p < 0.001$). Mean IVC index of the eLVH group

***Table 2***
Echocardiographic comparisons between four different LV geometric patterns in HD patients

| | NG (n = 9) | CR (n = 13) | cLVH (n = 37) | eLVH (n = 57) |
|---|---|---|---|---|
| LVID at end-diastole (cm) | 4.75 ± 0.59 | 4.37 ± 0.52 | 4.89 ± 0.59 | 5.48 ± 0.48[a] |
| IVST at end-diastole (cm) | 0.88 ± 0.14 | 1.17 ± 0.20 | 1.21 ± 0.11 | 1.25 ± 0.19[b] |
| RWT (cm) | 0.34 ± 0.07[c] | 0.53 ± 0.06 | 0.62 ± 0.10 | 0.44 ± 0.02 |
| PWT at end-diastole (cm) | 0.83 ± 010 | 1.14 ± 0.09 | 1.13 ± 0.12[b] | 1.13 ± 0.12 |
| LVMI ($g/m^2$) | 100.78 ± 17.74 | 104 ± 19.4 | 192.18 ± 44.8[d] | 185.6 ± 41.7[d] |
| IVC diameter (mm) | 13.6 ± 2.73 | 14.8 ± 3.18 | 13.9 ± 2.24 | 19.6 ± 3.1[a] |
| IVC index ($mm/m^2$) | 10.83 ± 2.07 | 8.31 ± 1.32 | 8.12 ± 2.06 | 10.83 ± 2.07[a] |
| CI | 0.52 ± 0.13 | 0.60 ± 0.10 | 0.56 ± 0.08 | 0.47 ± 0.12[e] |

$p < 0.001$ for [a]eLVH vs. NG, CR, and cLVH; [b]eLVH vs. NG, CR, and cLVH; [c]NG vs. CR and cLVH; [d]cLVH and eLVH vs. NG and CR.

$p < 0.01$ for [e]eLVH vs. CR and cLVH.

***Table 3***
Multiple regression analysis for the determination of predictors of the LV geometric stratification in HD patients

| Independent variables | ß (coefficient) | t-test value | *p* |
|---|---|---|---|
| IVC index | 0.34 | 3.11 | 0.002 |
| MAP | 0.383 | 3.447 | 0.001 |
| Interdialytic weight gain | 0.36 | 3.18 | 0.047 |
| Hemoglobin (g/dL) | –0.201 | –2.192 | 0.048 |

($10.83 \pm 2.07$ mm/m$^2$) was significantly higher than indexes of NG ($7.81 \pm 1.46$ mm/m$^2$), CR ($8.31 \pm 1.32$ mm/m$^2$), and cLVH ($8.12 \pm 2.06$ mm/m$^2$) groups ($p < 0.001$ for each comparisons). The eLVH group also had a significantly lower mean CI value ($0.47 \pm 0.12$) than CR ($0.60 \pm 0.10$) and cLVH ($0.56 \pm 0.08$) groups (ANOVA $p = 0.009$).

Stepwise multiple regression analysis was modeled to define the independent determinants of LV geometry. MAP, hemoglobin, hematocrit, interdialytic weight gain, parathormone were included into the model. MAP, hemoglobin, IVC index and interdialytic weight gain were found to be independent predictors of LV geometry ($R^2 = 0.147$; $p < 0.001$; see Table 3).

## DISCUSSION

Our study provides evidence that HD patients had a prevalence of abnormal LV geometry in 92% and LVH in 81%. Furthermore, hypervolemia, assessed by IVC index, mean arterial pressure, and anemia, were independent factors that contribute to LV geometric stratification in HD patients.

Dialysis patients have many risk factors for both volume and pressure overload. In ESRD patients treated by dialysis, fluid overload and arterial hypertension often contribute to a combination of eccentric and concentric hypertrophy. Classifying LVH into eccentric or concentric types is sometimes difficult in these patients, as cyclic variations in extracellular fluid volume and electrolyte balance mean that steady-state conditions are not achieved. Although hemodynamic factors cannot account entirely for increased LV mass, we previously mentioned that LVH in ESRD is due principally to a chronic increase in stroke work and LV minute work, resulting from an association of volume and pressure overload.[25] Studies of hypertensive patients with primary hypertension implicate blood pressure load in the development of concentric LVH (increased wall thickness with increased LV mass) and, in addition, increased plasma volume in those with eccentric LVH (normal wall thickness with increased LV mass).[16,30] The heterogeneity of the LV geometry in HD patients was a consequence of volume factors and anemia, according to our study. As with previous reports in the ESRD population,[31] our patients had primarily eccentric LVH, which probably means inadequate volume control.

Reports from Framingham study have demonstrated that LVM has a deep impact on cardiovascular outcomes.[7] The standard geometric classification was shown to be independently associated with cardiac death in chronic dialysis patients without symptomatic heart disease, with the adjusted relative risk of 1.26.[10] According to an echocardiographic prognostic classification system proposed by Foley et al.,[10] in dialysis patients with LV dilatation and normal systolic function, high cavity volume (>120 mL/m$^2$) was independently associated with late mortality (> 2 years after starting dialysis therapy), with the adjusted relative risk being 17.14. LVMI was of no prognostic significance in this group. LVMI was associated with late mortality only in patients with normal cavity volume and high LVM in the mentioned study. Paoletti et al. found eccentric LVH in dialysis patients to be less responsive to ACE inhibition and to be associated with a greater cardiovascular risk during a three-year follow-up period than concentric LVH.[32] It is therefore thought that factors other than hemodynamics, such as growth factors and signaling pathways, may codetermine the LV geometry.

Studies of arterial BP and LVH showed an extensively differing relation between the two, which may be attributed to the type (predialysis BP, clinic BP, or 24-hour ABPM), standardization, and number of BP measurements. In a cross-sectional analysis, Zoccali et al.[33] showed that the predictive value of predialysis BP for left ventricular mass was as strong as that of 24-hour ABPM.

Anemia is a frequent finding in ESRD patients and influences both the pathogenesis of adverse outcomes from cardiovascular disease.[34] In chronic anemia, prolonged volume overload and increased cardiac work lead to progressive cardiac enlargement and LVH,[35–38] and its influence on LV structure has been demonstrated previously by a variety of studies. It also contributed independently to LV geometry in our study. Low hemoglobin was also shown to be an independent risk factor for LV hypertrophy and predicts death in patients with ESRD.[39,40] There was a tendency toward more severe anemia in the group who developed eLVH in our group of patients. Amelioration of anemia with erythropoietin has been reported to reduce cardiac size and wall thickness and improve cardiac function in chronic hemodialysis patients.[41] However, the normalization of hemoglobin did not induce regression of overt LV dilatation or cLVH in hemodialysis patients in the prospective study conducted by Foley et al.[42] The combined treatment of anemia and hypertension did result in regression of LVH in some dialysis patients. In these patients, there was a concomitant

favorable effect on cardiovascular and all-cause survival.[43] The exact role of parathormone (PTH) as a cause of LVH in CKD patients is yet to be determined. Various theories proposed include vascular and visceral calcification, arteriolar wall thickening, myocardial interstitial fibrosis, and promotion of hyperlipidemia and hypertension due to the effect of PTH as possible etiologies for the development of LVH in CKD patients. However, we did not find a positive correlation between PTH level and LVH in our study group.

In conclusion, volume factors such as IVC index, MAP, and anemia contribute to LV geometric stratification in our HD patients. Correction of hypervolemia as well as reversal of anemia may reduce echocardiographic disease and improve prognosis in HD patients. Further prospective studies that will examine effects of volume removal and amelioration of anemia on LV geometry are warranted.

## ACKNOWLEDGMENTS

No conflict of interest has been reported.

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