Inflammation, Left Ventricular Hypertrophy, and Mortality in End-stage Renal Disease

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Introduction. The aim of this study was to evaluate ventricular geometry, its relationship with the inflammatory markers, and mortality of patients with end-stage renal disease on peritoneal and hemodialysis treatment.
Materials and Methods. We enrolled adult patients on long-term dialysis (hemodialysis and peritoneal dialysis) for more than 3 months. Two-dimensional echocardiography was performed by an experienced cardiologist who was blinded to all clinical details of patients. Cardiovascular mortality was assessed during a 2-year follow-up period.
Results. There were 129 participants, of whom 86 (66%) were on hemodialysis. Left ventricular hypertrophy was present in 86.7%; concentric hypertrophy was found in 64 (49.1%) and eccentric hypertrophy in 48 patients (37.2%). Patients with left ventricular hypertrophy were further divided into tertiles according to their left ventricular mass index. Logistic regression found pulse pressure as an independent risk factor associated with left ventricular mass index (odds ratio [OR], 1.04; 95% confidence interval (CI), 1.01 to 1.19; P = .047). Cardiovascular mortality rate was 15.5%. Multivariable analysis showed that C-reactive protein (OR, 1.06; 95% CI, 1.01 to 1.10; P = .01), pulse pressure (OR, 1.01; 95% CI, 1.0 to 1.26; P = .046), and left ventricular mass index (OR, 1.03; 95% CI, 1.01 to 1.21; P = .03) were independent risk factors for cardiovascular mortality.
Conclusions. Concentric hypertrophy is the most frequent left ventricular geometry model in patients with chronic kidney disease. Inflammation, pulse pressure, and left ventricular hypertrophy are interrelated and all contribute to mortality and cardiovascular death risk among dialysis patients.

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INTRODUCTION

Cardiovascular disease is responsible for at least 40% of all deaths in patients with end-stage renal disease receiving maintenance dialysis therapy. This prevalence is higher compared with the general population. The Framingham study showed that the presence of left ventricular hypertrophy (LVH) is associated with increased mortality. Left ventricular hypertrophy is a frequent complication and a risk factor of mortality in patients with dialysis.[1] Apart from the traditional risk factors for cardiovascular disease, there is increasing evidence

that these patients are at increased risk as a result of potential specific uremic risk factors that are responsible for the presence and progression of cardiovascular disease, as volume overload by hypertension, anemia, abnormal phosphocalcic metabolism, accumulation of specific uremic toxins (advanced glycation end products, asymmetric dimethylarginine, homocysteine, etc), and the chronic inflammatory progress. All these risk factors can lead to left ventricular damage, hypertrophy, or ischemia which predispose to cardiac dilatation or dysfunction of cardiac pump.[2-5] Myocardial hypertrophy leads to intermyocardial fibrosis,[2,6,7] which can cause dysfunction of cardiac electric system and ventricular arrhythmia,[8] progressive damage of contractility, and rise of myocardial stiffness, resulting in congestive heart failure.[5]

Inflammation is one of the earliest events in cardiac stress situations such as pressure and volume overload, and it involves elevated levels of endothelial adhesion molecules as well as increased production and release of inflammatory cytokines and chemokines in the tissue.[9] C-reactive protein (CRP) is an important marker of inflammation and is associated with cardiovascular morbidity and left ventricular hypertrophy.[4,10] Bo and coworkers showed that high levels of CRP were twice higher in patients with LVH compared to patients with normal left ventricular mass independently from other cardiovascular risk factors diseases.[11] Several studies have reported that inflammation is an independent risk factor for cardiovascular mortality and all-cause mortality in patients treated with both hemodialysis and peritoneal dialysis (PD).[12-15] A persistent inflammatory status is characteristic of this population.[16] The aim of this study was to evaluate the geometry of the left ventricle and its relationship with inflammation and mortality in patients with chronic kidney disease treated with hemodialysis and PD.

MATERIALS AND METHODS

Participants

This study enrolled all patients older than 18 years who were on long-term dialysis (hemodialysis or PD) for more than 3 months. The study protocol was approved by the local ethics committees and was performed in accordance with the ethics principles of the Declaration of Helsinki, and all included patients gave their written informed consent. Patients with moderate to severe valve pathology and with an unsuitable echocardiographic view were not included. Hemodialysis patients had native fistulas or arteriovenous grafts, and were on hemodialysis 3 times per week, 4 hours per treatment, with standard bicarbonate-containing dialysate bath, using high-flux dialysis membrane. The PD patients were on continuous ambulatory PD, 4 to 5 exchanges per day with 2000 mL of conventional lactate-buffered glucose-based PD solutions (Dianeal PD4; 40 mmol/L lactate; pH 5.3 to 5.5; containing 1.36%, 2.27%, or 3.86% dextrose as appropriate; Baxter Healthcare).

Measurements

Demographic data including age at study, duration on dialysis, and presence of underlying diabetes mellitus were collected. All samples for laboratory data were obtained from all patients in the morning after 12 hours fasting (for hemodialysis patients before midweek session) up 2 weeks before echocardiography. Blood pressure of the PD patients was measured in the PD clinic using a standard mercury sphygmomanometer with the patient in the supine position 3 times with a 3-minute rest between each measurement. Blood pressure of the hemodialysis patients was measured 30 minutes after midweek hemodialysis session was finished, using the nonarteriovenous fistula or shunt arm. The mean of blood pressure was measured during 3 last visits for PD patients or 3 last weeks for hemodialysis patients prior echocardigraphy was registered. Pulse pressure was calculated as the difference between systolic and diastolic pressures. The residual kidney function was calculated by standart measurement.

The examination was perfomed with 2-dimensional echocardiography (HDI 5000 Sono CT machine with a tranducer 2.5 mHz). The patients on hemodialysis were examined 2 to 24 hours after hemodialysis session. The echocardiographic technique, calculation of dimensions, and different cardiac volumes were realized according to recommendations of the American Society and European Association of Echocardiography. The echocardiographic evaluation included endocavitary dimensions of the left ventricle and other cardiac chambers. The left ventricular mass was calculated according to Devereux formula[17]:

$$1.04 \times [(LVID + PWT + IVST)^3 - LVID^3] \times 0.8 + 0.6$$

where LVID indicates left ventricular internal diameter; PWT, posterior wall thickness; and IVST, intraventricular septal thickness. Left ventricular hypertrophy was determined as left ventricular mass index (LVMI) greater than 115 g/m² for men and greater than 95 g/m² for women. The relative wall thickness was calculated as posterior wall thickness plus septal thickness, divided by the left ventricular internal diameter; the limit value was considered 0.42 and greater. According to left ventricular mass and relative wall thickness, the prevalence of 4 geometrical models of the left ventricle was evaluated for the patients: normal geometry (LVMI, ≤ 95 g/m² for women and ≤ 115 g/ m² for men; relative wall thickness [RWTH], ≤ 0.42); concentric remodeling (LVMI ≤ 95 g/m² for women and ≤ 115 g/ m² for men; RWTH, > 0.42); concentric hypertrophy (LVMI > 95 g/m² for women and > 115 g/ m² for men; RWTH, > 0.42); eccentric hypertrophy (LVMI > 95 g/m² for women and > 115 g/ m² for men; RWTH, ≤ 0.42).

Cardiovascular mortality within 2 years of follow-up was defined as sudden death; death associated with an ischemic myocardial event when the patient experienced angina with new changes on electrocardiography (ST elevation, ST depression, and negative T waves), or associated with risen cardiac enzyme levels; death from heart failure (refractory to ultrafiltration); and vascular cerebral accidents confirmed with computed tomography.

Statistical Analysis

All the statistical analyses were performed with the SPSS software (Statistical Package for the Social Sciences, version 19.0, SPSS Inc, Chicago, IL, USA). Results were expressed as mean ± standard deviation. Categorical data were compared between groups by the chi-square test and the mean values, by the *t* test. Significance for trend effect was tested across the four groups of patients with increasing LVMI. Factors predictive of cardiovascular mortality were identified by a logistic regression model. *P* values less than .05 were considered significant.

RESULTS

There were 129 participants, of whom 86 (66%) were on hemodialysis. The mean age was 51.9 ± 13.5 years and the mean time on therapy 43.1 ± 35.3 months. The clinical and laboratory data of the patients are showed in Table 1.

Table1. Characteristics of the Study Population

Characteristic	Value*
Age, y	51.9 ± 13.5
Sex	
Male	71 (55)
Female	59 (45)
Dialysis vintage, mo	43.1 ± 35.3
Diabetes mellitus	28 (21.8)
Body mass index, kg/m²	24.05 ± 4.32
Calcium, mg/dL	8.37 ± 0.91
Phosphate, mg/L	5.15 ± 1.43
Calcium-phosphate product, mg²/dL²	43.33 ± 13.54
Intact parathyroid hormone, pg/mL	591.9 ± 557.5
Alkaline phosphatase, UI/mL	149.4 ± 175.4
Righ renal flow, mL/min	1.34 ± 1.2
Uricemia, mg/dL	6.23 ± 4.21
Blood urea nitrogen, mg/dL	75.32 ± 34.12
Serum creatinine, mg/dL	8.23 ± 1.92
Low-density lipoprotein cholesterol, mg/dL	112.1 ± 37.7
Trygliceride, mg/dL	156.0 ± 83.8
Pulse pressure, mm Hg	55.27 ± 14.45
Urine output, mL/d	552.1 ± 583.9
Serum albumin, g/dL	3.57 ± 0.46
Fibrinogjen, mg/dL	453.0 ± 149.2
C-reactive protein, mg/dL	8.84 ± 17.06
Hemoglobin, g/dL	10.72 ± 1.12

*Values are mean ± standard deviation and frequency (percentage).

Left ventricular hypertrophy was present in 86.7% of the patients, whereas only 6.2% of the patients had a normal model of left ventricle geometry. Concentric hypertrophy was found in 64 patients (49.1%) and eccentric hypertrophy in 48 patients (37.2%), with a significant difference between groups (*P* = .02). Patients with LVH were further divided into tertiles according to their LVMI. The clinical characteristics of the four groups of patients are shown in Table 2.

Higher pulse pressure, lower levels of hemoglobin, and higher CRP levels showed a significant trend across the four groups of patients with increasing LVMI. Logistic regression analysis found only pulse pressure as an independent risk factor associated with LVMI (odds ratio [OR], 1.04; 95% confidence interval (CI), 1.01 to 1.19; *P* = .047). Cardiovascular mortality during the follow-up was 15.5% (19 events). The main causes of cardiovascular death were sudden deaths (31.5%) followed by deaths from ischemic heart disease and stroke (26.3%). In 15.7% of the patients, heart failure was found the cause of death.

The association of fatal cardiovascular events with demographic, laboratory factors, and important

Table 2. Clinical and Laboratory Data by Left Ventricular Mass Index (LVMI) Category*

Variable	LVMI category				*P* for Trends
	Normal LVMI	Tertile I (Lowest)	Tertile II (Middle)	Tercile III (Highest)	
Male sex, %	75.0	51.4	61.1	65.8	.39
Age, y	51.19 ± 13.04	51.20 ± 12.93	52.67 ± 13.88	52.63 ± 11.71	.94
Dialysis vintage, mo	44.75 ± 38.97	52.94 ± 39.06	47.75 ± 35.49	39.13 ± 43.88	.52
Diabetes mellitus, %	12.5	8.6	19.4	31.6	.08
Death, %	6.3	8.6	9.8	23.7	.07
Body mass index, kg/m^2	25.66 ± 4.85	24.30 ± 3.15	25.44 ± 25.44	24.93 ± 4.36	.62
Pulse pressure, mm Hg	48.75 ± 12.58	52.86 ± 14.87	52.78 ± 15.60	59.74 ± 12.63	.04
Righ renal flow, mL/min	1.53 ± 1.75	1.36 ± 1.51	1.69 ± 1.97	1.36 ± 2.11	.85
Serum albumin, g/dL	3.73 ± 0.55	3.58 ± 0.40	3.52 ± 0.41	3.61 ± 0.49	.49
C-reactive protein, mg/dL	6.34 ± 6.92	7.79 ± 7.18	5.23 ± 4.38	13.70 ± 31.81	.05
Calcium-phosphate product, mg^2/dL^2	43.26 ± 15.45	45.14 ± 12.19	37.30 ± 13.31	43.18 ± 13.62	.08
Hemoglobin, g/dL	11.05 ± 1.37	11.54 ± 1.19	11.39 ± 1.29	10.62 ± 1.51	.01
Peritoneal dialysis modality, %	25.0	31.4	52.8	28.9	.10

*Values are mean ± standard deviation and percentage.

cardiac echocardiographic indexes are presented in Table 3. Logistic regression analysis showed that CRP (OR, 1.06; 95% CI, 1.01 to 1.10; *P* = .01), pulse pressure (OR, 1.01; 95% CI, 1.0 to 1.26; *P* = .046), and LVMI (OR, 1.03; 95% CI, 1.01 to 1.21; *P* = .03) were independent risk factors for cardiovascular mortality.

DISCUSSION

In our study, 87% of the patients were found to have LVH. Concentric hypertrophy was found the most frequent left ventricular geometry model (64 patients, 49.1%) followed by eccentric hypertrophy (48 patients, 37.2%). These data correlate with data presented by Foley and collegaues[18] and London and colleagues[19] who showed that more than 75% of patients with end-stage kidney disease had LVH. We also found that higher pulse pressure, lower hemoglobin levels, and higher CRP levels showed significant trending effect across the four groups of patients with increasing LVMI.

Wang and coworkers[20] described the relationship between CRP and LVH in patients with PD. A similar relationship was reported also in hemodialysis patients.[12,21,22] We found a trend of higher CPR levels in the last tertile of LVMI compared to the

Table 3. Association of Fatal Cardiovascular Events With Demographic Factors, Laboratory Results, and Cardiac Echocardiographic Indexes

Variable	Univariable Analysis		Multivariable Analysis	
	Odds Ratio (95% Confidence Interval)	*P*	Odds Ratio (95% Confidence Interval)	*P*
Male sex	1.28 (0.41 to 4.01)	.67	2.01 (0.22 to 18.08)	.54
Age, y	1.01 (0.95 to 1.03)	.45	1.01 (0.93 to 1.10)	.78
Dialysis vintage, mo	1.01 (0.99 to 1.02)	.28	1.02 (0.99 to 1.05)	.19
Diabetesmellitus	1.64 (0.47 to 5.67)	.44	1.74 (0.14 to 21.55)	.67
Body mass index , kg/m^2	1.03 (0.91 to 1.18)	.62	1.08 (0.88 to 1.32)	.46
Pulse pressure, mm Hg	1.04 (1.00 to 1.09)	.04	1.01 (1.0 to 1.26)	.05
Residual kidney function, mL/min	0.97 (0.72 to 1.31)	.86	0.96 (0.68 to 2.03)	.50
Serum albumin, g/dL	0.44 (0.14 to 1.43)	.17	0.08 (0.01 to 2.32)	.14
C-reactive protein, mg/L	1.02 (1.01 to 1.24)	.04	1.06 (1.01 to 1.10)	.01
Hemoglobin, g/dL	0.65 (0.44 to 0.96)	.03	0.51 (0.25 to 1.03)	.06
Left ventricular mass index	1.01 (1.01 to 1.02)	.05	1.03 (1.01 to 1.21)	.03
Left atrial volume index	0.98 (0.90 to 1.05)	.52	1.01 (0.99 to 1.03)	.17
Shortening fraction, %	1.02 (0.91 to 1.14)	.76	1.00 (0.99 to 1.44)	.65
E/E' ratio	1.10 (0.98 to 1.24)	.10	1.02 (0.80 to 1.29)	.87
Hemodialysis modality	1.63 (0.48 to 5.47)	.43	5.16 (0.13 to 200.30)	.38

others (P = .05). The explanation of that may relate to increased oxidative stress, which is a widely recognized phenomenon in chronic kidney failure and is closely related to systemic inflammation, which is referred to be very high in dialysis patients, and also to fluid overload and loss of kidney function.[23] Blood pressure spreads through the arterial tree as a repetitive continuous wave and is more accurately described as consisting of a pulsatile component and a steady component.[24] Pulse pressure as a difference between systolic and diastolic blood pressure is an index of the pulsatile component of the cardiac cycle and is determined by the relationship between ventricular ejection and the elastic properties of large arteries (arterial stiffness),[12] as well as the indirect effect of arterial-wave reflection from periphery back to central conduit arteries. Arterial stiffness causes a lower compliance, and a higher wave pressure results in a higher pulse pressure. Atherosclerosis and vascular calcifications in dialysis have a very important role in pulse pressure too. It was reported that the relationship between pulse pressure and atherosclerosis is bi-directional in that elevated pulse pressure is both a cause and a consequence of atherosclerosis.[25,26] Patients with end-stage renal disease present vascular abnormalities that contribute to elevated pulse pressure, especially medial vascular calcification, which leads to increased arterial stiffness, increased pulse-wave velocity, and early wave reflection. An increase in pulse pressure leads to left ventricular hypertrophy, congestive heart failure, ventricular arrhythmias, acute myocardial infarction, and cerebrovascular events, and affects the incidence of sudden deaths.[26] It was shown that pulse pressure has a consistent association with higher mortality in patients on maintenance hemodialysis. We found pulse pressure as an independent risk factor of cardiovascular mortality and the only independent risk factor for LVMI.

Anemia has been associated with left ventricular hypertrophy in most echocardiographic studies of renal patients.[19] Anemia is considered to be a risk factor in developing left ventricular hypertrophy. It was also reported as a major contributor in cardiac morbidity and mortality, and in all causes of mortality in patients in dialysis.[27,28] Hemoglobin levels are observed to predict the grade of LVH, every 1 unit decrease of hemoglobin (g/dL) levels was reported to be associated with 50% increased risk for dilatation and left ventricular systolic dysfunction.[27,29] In our study we found lower hemoglobin level in the last tertile of LVMI.

Cardiovascular diseases have high prevalence at patients in dialysis and are the main cause of death in this population of chronic patients evolving over 50% of causes.[30] Chronic kidney disease now is considered as a risk prevalence equivalent with coronary artery disease.[31-33] Based on the data of American and European large registries of chronic kidney disease, the risk evaluation for cardiac events as acute myocardial infarct is 3.5 to 50 higher in patients on dialysis treatment compared with the general population.[14] During this period of follow-up, we had 19 (15.2%) fatal events. Sudden death was the most frequent cause of mortality followed by ischemic disease and cerebrovascular accidents. Analyzing the association of fatal cardiovascular event (death compared to survival) with clinical factors, laboratory ones and important echocardiographic indexes according to the logistic binary regression model, we observed an increase of risk for cardiovascular mortality of 6% for every unit increase of CPR, of 3% for every unit increase of left ventricular mass, and of 1% for every unit of pulse pressure.

There is a sufficient evidence for the relationship between left ventricle hypertrophy and myocardial fibrosis. As it is known concentric hypertrophy, leads to decreased diastolic compliance and may place the myocardium at risk of ischemia, even without coronary artery disease. Independently from causal mechanisms of the myocardial hypertrophy, an ischemia lead to activation of cell apoptosis and activation of mechanisms that cause the creation of extracellular matrix that produces intermyocardial fibrosis[2,6,7]; progressive damage of contractility and myocardial stiffness, resulting in systolic and diastolic dysfunction, dilated cardiomyopathy and chronic heart failure.[5] Myocardial fibrosis also leads to heart electric system dysfunction and ventricular arrhythmias (ventricular fibrillation).[8] Many studies have reported that CRP is an independent predictor of acute myocardial infarction and cardiovascular heart disease incidence, demonstrating that patient who were in the last quartile had a five time higher cardiovascular risk compared with the patients with CRP level in the lowest quartile.[21,34] As mentioned

above, CRP in our study was found as an important independent risk factor for cardiovascular mortality. C-reactive protein is being tight related to the cardiovascular disease and atherosclerosis and is suggested to be not only a protein derived from liver that serves as a marker, but also as a mediator of vascular disease.

However, it is worth considering some limitations our study has encountered. First, a single measurement of CRP was taken at the time of echocardiography and did not reflect changes over time. Second we didn't measure the volume status of our patients and the effect on LVMI. Third the follow up of our patients was relatively short.

CONCLUSIONS

Our study showed once again the high prevalence of LVH by a left ventricular geometry in patients on dialysis treatment, with concentric hypertrophy as the most frequent left ventricular geometry model. Inflammation, arterial stiffness, and LVH are interrelated and both contribute to increase mortality and cardiovascular death risk of dialysis patients.

CONFLICT OF INTEREST

None declared.

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