Original Article

Left Ventricular Hypertrophy Is Associated with Arterial Stiffness and Vascular Calcification in Hemodialysis Patients

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Left ventricular hypertrophy (LVH) is the most frequent cardiac abnormality in patients with end-stage renal disease (ESRD). Recent studies have shown that arterial stiffness is associated with mediacalcinosis in these patients. However, whether arterial stiffness and vascular calcification are associated with the LVH in patients with ESRD has not been well established. Forty-nine patients on chronic hemodialysis participated in this study. 1) To better understand the mechanism underlying the increased incidence of LVH, we studied the relation between LVH and each of arterial wall stiffness, aortic calcification, and numerous clinical parameters in 49 patients on chronic hemodialysis. 2) To evaluate the contribution of arterial stiffness and arterial calcification to LVH in hemodialysis patients, we performed the present clinical analysis on 49 patients on chronic hemodialysis. We used an automatic device to measure arterial pulse wave velocity (PWV) as an index of arterial wall stiffness. The aortic calcification index (ACI) was quantified morphometrically by CT scan. The left ventricular mass index (LVMI) was estimated by M-mode echocardiography. To understand the mechanism underlying the increased incidence of LVH, we examined the factors contributing to LVMI in these patients. The correlation between each of the study parameters and LVMI as an indicator of LVH was then examined. The LVMI value was correlated positively with PWV ($r = 0.439$, $p = 0.0014$), systolic blood pressure ($r = 0.421$, $p = 0.0023$), and ACI ($r = 0.467$, $p = 0.0006$). A stepwise linear regression analysis showed that PWV, systolic blood pressure, and ACI were independently associated with LVH in our subjects. These results suggest that LVH is associated with hypertension, increased arterial stiffness, and the extent of vascular calcification in hemodialysis patients, with vascular calcification being the most important contributor to the development of LVH. Alteration of pulsatile dynamics contributes to an increase in left ventricular load and thus is also related to the LVH in these patients. These results suggest that LVH is associated with hypertension, increased arterial stiffness, and the extent of vascular calcification in hemodialysis patients. Vascular calcification, which alters the pulsatile dynamics and thereby contributes to an increase in left ventricular load, is the most important contributor to the development of LVH in patients undergoing hemodialysis. *(Hypertens Res 2004; 27: 47–52)*

Key Words: renal dialysis, pulse wave velocity, vascular calcification, hypertension, arterial stiffness
Introduction

The cardiovascular mortality rate is higher in hemodialysis patients than in the non-uremic population. In a previous epidemiological study, damage to large arteries was shown to be a major factor contributing to the high cardiovascular morbidity and mortality of patients with end-stage renal disease (ESRD) (1). Previous clinical studies (2, 3) have found that sclerosis of the abdominal aorta reflects early atherosclerosis and is significantly correlated with coronary atherosclerosis. Arteriosclerosis involves two important changes: thickening and stiffening of the arterial wall (4). The increased stiffness raises systolic blood pressure (BP) and pulse pressure while decreasing diastolic BP, thereby causing increased left ventricular afterload and altered coronary perfusion. Thus, increased arterial stiffness may be associated with left ventricular hypertrophy (LVH) in patients with ESRD.

It has been reported that patients with ESRD have stiffer arteries than age- and BP-matched non-uremic subjects (5). Moreover, arterial hypertrophy is accompanied by an incremental increase in elastic modulus value and a large increase in pulse-wave velocity (PWV) in these patients (6, 7). Recently, Blacher et al. (8) reported that aortic stiffness predicts all-cause and cardiovascular mortality in patients with ESRD, suggesting that arterial wall stiffness may be a good predictor of cardiovascular mortality in ESRD patients. In hemodialysis patients, aortic PWV was found to be associated with mediacaclinosis of the aorta and an elevation of calcium-phosphate (Ca-P) (6, 9). However, the relationship among LVH, arterial stiffness, and vascular calcification has not been fully elucidated.

The purpose of the present study was to evaluate the contribution of arterial stiffness and arterial calcification to LVH in hemodialysis patients.

Methods

Patient and Study Design

The study subjects were 49 (27 men and 22 women) maintenance haemodialysis patients enrolled in the Dialysis Unit of Minami Senju Hospital. The underlying diseases were type 2 diabetes mellitus (DM) in 17 patients and chronic glomerulonephritis (CGN) without DM in 32. We excluded patients with severe illnesses such as liver cirrhosis and congestive heart failure or apparent acute inflammatory symptoms.

Hemodialysis was performed three times weekly (4 h/day) using hollow-fiber dialyzers such as cellulose triacetate (FB, Nipro, Osaka, Japan) and polysulfone (PS, Fresenius, Bad-Homburg, Germany). These patients had undergone dialysis for at least six months prior to the study, using the same membrane and the same dialysis procedure for at least three months. Their mean dialysate potassium concentration was 2.0 mEq/l, the mean calcium concentration was 3.0 mEq/l, the mean blood flow rate was 200 ml/min, and the mean dialysate flow rate was 500 ml/min. Residual urine volumes of the hemodialysis patients were less than 100 ml/day.

BP was measured with a standard mercury sphygmomanometer and cuffs adapted to arm circumference. BP was recorded after the subjects had been recumbent for at least 10 min.

Blood was drawn in the morning after an overnight fast of at least 12 h before starting a dialysis session. Whole blood was used for measuring hematocrit, EDTA-plasma for measuring fasting plasma glucose and lipids, and serum for the other biochemical assays, including the assay of albumin, which was measured using a commercially available kit (IATRONE Co., Tokyo, Japan). C-reactive protein (CRP) was determined by a latex-aggregation method (IATRONE). Intact parathyroid hormone (iPTH) was measured by radioimmunoassay (normal range: 10–65 pg/ml), as previously described (10). Other measurements were made by routine methods.

Investigations were performed in the morning before the first weekly dialysis session. Each subject gave informed consent to participate in the study. This study was approved by the ethics committee of our hospital.

Echocardiography

M-mode echocardiography was performed with an ACUSON XP10 using a 2.25 MHz transducer. Measurements were performed blindly by the same investigator according to the methods of the American Society of Echocardiography (11), as previously described (12). M-mode measurements included left ventricular end-diastolic diameter (LVED), left ventricular posterior wall thickness (PWT), and interventricular septal thickness (IVST). Left ventricular mass (LVM) was calculated according to the Penn convention (13) using the formul: \[ \text{LVM} = 1.05 \times [(\text{PWT} + \text{IVST} + \text{LVED})^2 - \text{LVED}^2] - 13.6. \] The LVM index (LVMi) was calculated as LVM divided by body surface area. Inter- and intraobserver reproducibilities were less than 5%. Forty (81.6%), 32 (65.3%), and 15 (30.6%) of the 49 patients were given Ca antagonists, angiotensin-converting enzyme inhibitors, and β-blockers, respectively. No patient was given α-blockers. No drugs were discontinued before the echocardiographic evaluations.

Assessment of Arterial PWV

Occulsion and monitoring cuffs were placed snugly around both sides of the upper and lower extremities, with patients in the supine position. Then, pressure waveforms of the brachial and tibial arteries were recorded after 15 min of bed rest using an automatic waveform analyzer (BP-203RPE; Colin, Komaki, Japan). Electrocardiographic monitoring was performed with electrodes placed on both wrists. Heart
sounds, S1 and S2, were detected by a microphone set on the left edge of the sternum at the fourth intercostal space. The pressure waveforms obtained at two different sites were simultaneously recorded to determine the time interval between the initial rise in the brachial and tibial pressure waveforms (ΔT). The path length from the suprasternal notch to the elbow (ΔD_b) was obtained from superficial measurements and was expressed using the following equation: ΔD_b = 0.2195 H - 2.0734, where H (in cm) is the height of the patient. The path length from the suprasternal notch to the femur to the ankle (ΔD_a) was calculated as follows: ΔD_a = (0.5643 H - 18.381) + (0.2486 H + 30.709). The following equation was used as a surrogate index of PWV in the lower extremities: PWV (cm/s) = (ΔD_a - ΔD_b)/ΔT. The best 10 consecutive pulses were analyzed, and the average PWV from the heart to the posterior tibial artery was calculated by dividing the distance by the time interval. Two measurements were performed in each leg and the average value was used for the analysis. PWV was expressed in cm/s. The coefficient of variation of the PWV was less than 5%. This method has been validated by the time interval. Two measurements were performed in each leg and the average value was used for the analysis. PWV value correlated positively with age (r = 0.435, p = 0.0016). To assess the combined influence of variables on arterial PWV, we used a stepwise linear regression analysis with forward and backward elimination procedures. Statistical analyses were performed using the Stat View statistical software package (Stat View 5; SAS Institute, Cary, USA). Values of p < 0.05 were considered to indicate statistical significance.

Results

Baseline Characteristics in Hemodialysis Patients

Clinical parameters of the hemodialysis patients in the present study are summarized in Table 1. Their mean age was 60.4 ± 1.6 years, and the mean duration of dialysis therapy was 9.6 ± 0.8 years. Twenty-seven patients (55.1%) were men, and 17 patients (34.7%) had diabetes.

Analysis of Arterial Stiffness

To examine the relationships between arterial stiffness and clinical parameters, univariate analysis was performed. The PWV value correlated positively with age (r = 0.438, p = 0.0015) and serum triglycerides (r = 0.32, p = 0.0247), but negatively with serum albumin levels (r = - 0.435, p = 0.0016). To assess the combined influence of variables on arterial PWV, we used a stepwise linear regression analysis. The model included the following variables: age, BP, duration of dialysis, blood lipids, fasting plasma glucose, hematocrit, Ca × P product, CRP, and ACI. Three of these factors—age, triglyceride, and albumin—were independently associated with PWV values.

Analysis of Vascular Calcification

To examine the relationship between vascular calcification and clinical parameters, univariate analysis was performed. The ACI value correlated positively with age (r = 0.421, p = 0.0023) and iPTH (r = 0.318, p = 0.0255). To assess the combined influence of variables on ACI, a stepwise linear regression analysis was performed. The model included the following variables: age, BP, duration of dialysis, blood lipids, fasting plasma glucose, hematocrit, Ca × P product, CRP, and ACI. Three of these factors—age, triglyceride, and albumin—were independently associated with PWV values.

Table 1. Characteristics of the Hemodialysis Patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>49</td>
</tr>
<tr>
<td>Age (years)</td>
<td>60.4 ± 1.6</td>
</tr>
<tr>
<td>Male (%)</td>
<td>55.1</td>
</tr>
<tr>
<td>Duration of dialysis (years)</td>
<td>9.6 ± 0.8</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>156.7 ± 16.3</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>87.9 ± 9.5</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>10.9 ± 2.9</td>
</tr>
<tr>
<td>Serum albumin (mg/dl)</td>
<td>3.5 ± 0.4</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>159.8 ± 32.4</td>
</tr>
<tr>
<td>Triglyceride (mg/dl)</td>
<td>129.9 ± 92.4</td>
</tr>
<tr>
<td>Fasting plasma glucose (mg/dl)</td>
<td>126.5 ± 52.6</td>
</tr>
<tr>
<td>C-reactive protein (mg/dl)</td>
<td>0.3 ± 0.4</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>30.2 ± 2.0</td>
</tr>
<tr>
<td>Pulse wave velocity (cm/s)</td>
<td>2,124.3 ± 61.6</td>
</tr>
<tr>
<td>Aortic calcification index (%)</td>
<td>30.3 ± 26.3</td>
</tr>
<tr>
<td>Left ventricular index (g/m²)</td>
<td>185.6 ± 35.7</td>
</tr>
</tbody>
</table>

ACI was independently checked by two observers. Reproducibility was absolute for the patients studied. The sequence of CT scans and their orientation were standardized, and the qualities of scans were primarily dependent on the hardware used. To optimize reproducibility, all scans from the cross-sectional study were done by the same investigator using the same CT equipment as previously described (17).
Assessment of the Factors Related to LVH

As shown in Fig. 1, LVMI values correlated positively with PWV values (r = 0.439, p = 0.0014, Fig. 1), systolic BP (r = 0.421, p = 0.0023, Fig. 2) and ACI (r = 0.467, p = 0.0006, Fig. 3). A stepwise linear regression analysis was performed to adjust for the influences of different pathogenic factors on LVH in all patients. The clinical parameters of age, duration of dialysis, diastolic BP, serum levels of albumin, cholesterol, and triglyceride, and fasting plasma glucose, CRP, Ca \( \times \) P product, iPTH, and hematocrit were not independently associated with LVH. Stepwise regression analysis indicated that ACI (coefficient \( \beta = 0.401, p < 0.0001 \)), systolic BP (coefficient \( \beta = 0.345, p < 0.0001 \)), and arterial PWV (coefficient \( \beta = 0.342, p < 0.0001 \)) were independently associated with LVH (Table 2).

Table 2. Stepwise Regression Analysis for LVMI and Related Parameters

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>Coefficient ( \beta )</th>
<th>Probability (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACI</td>
<td>0.401</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>0.345</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Arterial PWV</td>
<td>0.342</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

\( r^2 = 0.332 \)
\( F \) value = 11.4
Root mean square (RMS) = 29.8

LVMI, left ventricular mass index; ACI, aortic calcification index; BP, blood pressure; PWV, pulse wave velocity.

Discussion

LVH is the most frequent cardiac abnormality in patients starting ESRD therapy (18), and is a strong and independent risk factor for cardiovascular morbidity and mortality in these patients (19). LVH in ESRD patients is principally due to an increased demand in left ventricular minute work resulting from volume/flow and pressure overload (20).

Hypertension is present in approximately 80–90% of ESRD patients and is an important factor in the development of LVH in these patients (21–23). The presence of hypertension in ESRD patients implies pressure and/or volume overload. However, a previous study reported discrepancies between BP values and the degree of LVH in dialysis patients (21). In the present study, systolic BP correlated significantly with LVH in univariate analysis, and systolic BP was a strong contributor to the development of LVH in stepwise linear re-
Arterial stiffness increases with age and hypertension (6, 24). In patients with ESRD, arterial stiffness has been shown to be increased in comparison to age- and BP-matched non-uremic subjects. This increase in arterial stiffness is certainly of multifactorial origin, but the exact mechanisms are not clear. In hemodialysis patients, aortic PWV has been associated with mediacalcosis of the aorta and an elevation in uremic subjects. This increase in arterial stiffness is certainly to be increased in comparison to age- and BP-matched non-uremic subjects. This increase in arterial stiffness is certainly related to the LVH in these patients.

In the present study, a stepwise linear regression analysis revealed that several factors, i.e., age, higher serum triglyceride levels, and lower serum levels of albumin, were significantly associated with PWV in hemodialysis patients. The susceptibility of ESRD patients to oxidative stress might be attributable to increased free radical and reactive oxygen metabolite production and to increased levels of oxidizable substances, especially triglycerides with unsaturated fatty acids (25). On the other hand, Kaysen (26) reported that serum albumin concentration was inversely proportional to that of either CRP or serum amyloid A protein, suggesting that hypoalbuminemia was primarily a response to inflammation, although malnutrition might also have made a contribution. As a result of hypertension in addition to increased oxidative stress and inflammation, arterial stiffness is apparently altered in hemodialysis patients. The positive correlation between LVMI and PWV in the present study suggests that arterial stiffness may contribute to the development of LVH in these patients. However, PWV was not a significant contributor to LVH in the stepwise linear regression analysis.

Vascular calcification is also strongly associated with an increased risk of cardiovascular events and mortality in uremic patients (27, 28). As in non-uremic patients, calcification in those with ESRD occurs in the arterial intima in association with atherosclerotic plaques (29). However, medial calcification can also occur and probably increases arterial stiffness and ventricular afterload (30). Goodman et al. (31) recently demonstrated a high prevalence of coronary artery calcification among young adults receiving dialysis, especially those who had been on dialysis for more than 10 years. Multiple risk factors have been implicated in the development of arterial calcifications. In previous studies, cardiovascular calcification in patients with ESRD has been variably associated with age, duration of dialysis, race, DM, serum P, Ca, HDL-cholesterol and triglyceride concentrations, and markers of inflammation (28–34). However, no consistent and/or constant associations could be established between arterial remodeling and common vascular risk factors. In the present study, several factors, including age and iPTH, were independently associated with ACI. Moreover, ACI was an independent variable contributing to the development of LVH according to stepwise linear regression analysis. Therefore, the extent of vascular calcification may be associated with the progression of LVH in patients with ESRD.

In conclusion, we have shown clearly that LVH is associated with hypertension, increased arterial stiffness, and the extent of vascular calcification in hemodialysis patients, with vascular calcification making the most important contribution to the development of LVH. Alteration of pulsatile dynamics contributes to an increase in left ventricular load and is related to the LVH in these patients.

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References


