Left ventricular mass and hemodynamic overload in normotensive hemodialysis patients

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Background. It remains uncertain whether the hemodynamic parameters are important determinants of left ventricular mass (LVM) in normotensive chronic hemodialysis (NTHD) patients, as has been found in their hypertensive counterparts.

Methods. Forty NTHD patients (mean age, 53.7 ± 14.4 years; male/female, 18/22) without the requirement of antihypertensive drugs for at least six months were studied. Controls were 41 hypertensive hemodialysis patients (HTHD) and 46 normotensive subjects with normal renal function (NTNR). The influence of anthropometrics, cardiovascular structure and function, and volume status on LVM (by two-dimensional echocardiography) was analyzed by steps of multiple linear regression.

Results. As compared with the NTNR and NTHD group, the HTHD group had obvious pressure and volume/flow overload, and greater LV wall thickness, chamber size and mass. In contrast, NTHD subjects had similar blood pressure, large artery function, LV chamber size and stroke volume as the NTNR subjects. However, the NTHD patients still had greater wall thickness and LVM, along with greater cardiac output, lower total peripheral resistance and lower end-systolic meridional stress to volume ratio (ESSV) than the NTNR group. LVM in the NTHD group was significantly positively related to averaged systolic blood pressure (SBPavg), body surface area, extracellular fluid (ECF), carotid intima-media thickness (IMT), aortic pulse wave velocity (PWV), and negatively related to ESSV and Kt/V. The independent significant noncardiac structural determinants of LVM in NTHD subjects were ESSV, SBPavg, PWV and SV (model $r^2 = 0.617$, $P < 0.001$).

Conclusions. The NTHD patients, without significant pressure and volume overload, still had increased LVM that was partially explained by the persistent flow overload and subclinical LV dysfunction.

Despite considerable advances in the medical care and dialysis facility, cardiovascular disease remains the major cause of death among end-stage renal disease (ERSD) patients [1]. Increased left ventricular mass (LVM), that is, LV hypertrophy (LVH), is the most frequent cardiac abnormality in patients starting ESRD therapy [2]. LVH is a strong and independent risk factor for cardiovascular morbidity and mortality in both normal population [3] and the ESRD patients [4]. In ESRD patients, LVH is principally due to an increased demand in LV minute work resulting from volume/flow and pressure overload [5].

Hypertension is present in approximately 80 to 90% of the ESRD patients and is an important factor for the development of LVH in ESRD patients [6]. The presence of hypertension in ESRD patients implies a status of pressure and/or volume overload. Consequently, normalization of hypertension by either the use of antihypertensive agents [7] or adequate ultrafiltration [8] indicates a substantial reduction of the hemodynamic overload [9]. Although pharmacological reduction of high blood pressure has been associated with the reduction of the hemodynamic overload and the regression of LVH in ESRD patients [9], it remains to be demonstrated whether normalization of hypertension by adequate dialysis alone is similarly effective in reducing hemodynamic loads and the extent of LVH [10].

In the present study we comprehensively evaluated the hemodynamic determinants of LVM in chronic hemodialysis (HD) patients whose blood pressures were normalized with good fluid control and without the requirement of antihypertensive medication. This is in contrast to the majority of previous studies about the determinants of LVM or LVH, which were conducted in ESRD patients with various degrees of hypertension [11].

METHODS

Study population

Eighty-one chronic HD patients were enrolled. Patients were considered eligible for inclusion when they

(*a*) had been on HD for at least 6 months; (*b*) had had history of hypertension before or after starting HD therapy; (*c*) had no previous history of cardiovascular disease, and (*d*) had LV ejection fraction (EF) of 55% or higher as estimated by M-mode echocardiography. Among the 81 HD patients, 40 attained clinical dry weight and normotension (NTHD) without receiving antihypertensive agents for at least six months, and 41 remained hypertensive (HTHD) under antihypertensive agent treatment. Dry weight was defined as the lowest body weight in the absence of overt fluid overload that a patient could tolerate without intradialytic symptoms and hypotension [12]. The etiologies responsible for the ESRD included chronic glomerulonephritis (17 NTHD and 19 HTHD subjects), nephrosclerosis (6 NTHD and 4 HTHD subjects), interstitial nephropathy (5 NTHD and 4 HTHD subjects), diabetic nephropathy (4 NTHD and 4 HTHD subjects), polycystic kidney (2 NTHD subjects), systemic lupus erythematosus (4 HTHD subjects), gout (1 NTHD and 1 HTHD subject) and unknown (5 NTHD and 5 HTHD subjects). In HTHD, 51.2% of patients received combined antihypertensive medications of calcium channel blockers plus angiotensin converting enzyme inhibitors or angiotensin II receptor blockers. The remaining received monotherapy of calcium channel blockers or angiotensin-converting enzyme inhibitors. All antihypertensives were temporarily discontinued on the day of cardiovascular examination. Another 46 age-matched normotensive subjects with normal renal function (NTNR) and without history of cardiovascular disease also were enrolled.

The hemodynamic examinations were performed on a mid-week non-dialysis day for the ESRD patients. The study was approved by the Institutional Review Board of Taipei Veterans General Hospital and written informed consent was obtained from each patient and normal control at enrollment.

Hemodialysis procedures

Hemodialysis patients received a four-hour dialysis session thrice-weekly using 1.6 m² surface area dialyzers with bicarbonate-based dialysate (Na⁺ 140 mEq/L, HCO_3^- 39 mEq/L, K⁺ 2.0 mEq/L, Ca²⁺ 3.0 mEq/L and Mg²⁺ 1.0 mEq/L). The ideal dry weight was assessed via meticulous bedside evaluation, which comprises of physical examinations and cardiac-thoracic ratio estimated by chest x-ray and echocardiography. If symptoms and signs of fluid overload were noted, the exceeded volume was ultrafiltrated during the dialysis session or via additional sessions. All patients were treated with subcutaneous recombinant human erythropoietin (rHuEPO) (Exprex®, Janssen-Cilag, Schaffhausen, Switzerland) at a mean dosage of 20,000 U per month with an aim to keep their levels of hematocrit up to 30%.

Anthropometric and volume status measurements

Body mass index (BMI) and body surface area (BSA) were calculated from weight and height. Waist-to-hip ratio (WHR) was calculated from waist and hip circumferences [13]. Fat-free mass (FFM), and extracellular fluid (ECF) and intracellular fluid (ICF) volumes were measured by the multifrequency bioimpedance (Model 4200; Xitron Technologies, San Diego, CA, USA) method [14].

Vascular structure and function

Supine brachial artery systolic (SBP) and diastolic blood pressures (DBP) were measured with an oscillometric device. Pulse pressure (PP) was the difference between SBP and DBP. Mean blood pressure (MBP) was PP/3 + DBP. End-systolic pressure was defined as (2SBP + DBP)/3 [13]. Common carotid SBP (SBPc) and PP (PPc), which closely reflect the pressure values in the ascending aorta [15], were calculated from the common carotid waveform calibrated by the brachial MBP and DBP [16]. Echocardiography was carried out by the same experienced cardiologist (C.H.C.). Each echocardiographic parameter was the mean value from four consecutive measurements. Aortic root diameter was determined by M-mode echocardiography (HP sonos 2500 or 5500, Agilent Technology, Andover, MA, USA). The carotid systolic and diastolic diameters and the intima-media thickness (IMT) of the posterior wall (distance from the leading edge of the lumen-intima interface to the leading edge of the media-adventitia interface [17]) were measured on-line from the digitized frozen longitudinal images with a 7-MHz vascular probe incorporated in the ultrasonographic unit. Carotid incremental elastic modulus was calculated according to the equation: elastic modulus = $(4a^2b\Delta P)/[(b^2-a^2)\Delta D]$ [18], where a is the internal radius and b is the external radius of the wall obtained from the echocardiogram, and ΔP and ΔD are the pressure and diameter changes over the cardiac cycle. Of note, ΔP was calculated by use of PPc.

The wall property of the aorta was indexed by the truncal pulse wave velocity (PWV). PWV was measured by recording pulse waves at the right common carotid artery and the right femoral artery sequentially using tonometry and a simultaneous ECG [19]. Carotid augmentation index (AGI) was analyzed from the right common carotid arterial pressure wave contour [20]. Total arterial compliance (AC) was estimated according to the diastolic area method [21] that requires a central aortic pressure wave and a known stroke volume (SV). In this study, the central aortic pressure wave was mathematically reconstructed from a tonometer-derived radial pressure wave [22]. Total peripheral vascular resistance (TPR) was calculated as the ratio of MBP to cardiac output (CO).

LV parameters

Two-dimensional (2-D) guided M-mode echocardiograms were obtained for measurements including interventricular septum thickness (IVS), posterior wall thickness (PWT), and LV internal dimensions in the diastole and systole [23]. LVM was calculated from both the 2-D echocardiographic measurements according to the truncated ellipsoidal formula [24] and the M-mode measurements [25]. The two independent calculations were significantly correlated in the following regression equation: LVM (M-mode) = 1.18 × LVM (2-D) + 30 ($r = 0.81$, $P < 0.001$). Since some cardiac indexes were derived from the same M-mode measurements and this might cause inherent interdependency between the M-mode derived LVM and other cardiac indices, we used only the 2-D derived LVM for all correlation and regression analyses. LV EF was calculated from the M-mode measurements according to Teichholz et al's formula [26].

Stroke volume (SV) was derived from the aortic annular cross-sectional area multiplied by the velocity integral of LV outflow, and CO from the SV multiplied by heart rate. Cardiac index was calculated as CO/BSA. LV end-diastolic volume (LVEDV) and end-systolic volume were directly measured from a frozen 2-D image of the apical four-chamber view according to the single plane area-length method [24]. Therefore, LVM, LVEDV, LV end-systolic volume and EF were all independent measurements or calculation. End systolic meridional stress to volume ratio (ESSV), an index of LV contractility [27], was calculated as:

$$\frac{\text{End-systolic pressure} \times \text{LV end-systolic dimension}}{\text{LV wall thickness} \times \text{LV end-systolic volume}}$$

(Eq. 1)

Inferior vena cava diameter (IVCD) at the level just below the diaphragm in the hepatic segment was measured by 2-D guided M-mode echocardiography when patients were in a supine position. With simultaneous electrocardiographic recording, IVCD was measured before the P wave of ECG during expiration and was expressed as index to BSA in mm/m^2 [28].

Uremia related modulators and laboratory evaluation

The interdialytic weight gain (IWG) was the average of the 25 consecutive differences of the patient's body weight at the beginning of HD minus the weight after the previous HD session prior to the comprehensive hemodynamic examination, and was expressed both as absolute value and percentage of the dry body weight. The averages of the SBP (SBPavg) and DBP (DBPavg) at the beginning of HD from the 25 consecutive HD sessions also were calculated. The adequacy of hemodialysis dosage was calculated with the formula Kt/V [29].

Hemoglobin and hematocrit measurements were performed with CELL-DYNE 1400 (Abbot Laboratories, Abbott Park, IL, USA). Serum calcium and inorganic phosphate were measured by automated enzymatic methods with a Hitachi auto-analyzer 7600 (Hitachi Ltd, Tokyo, Japan) and Boerhringer Mannheim Diagnostics reagents (Mannheim, Germany). Plasma intact parathyroid hormone levels were determined using the IRMA assay (DiaSorin Inc. Stillwater, MN, USA).

Statistical analysis

Data were expressed as mean ± SD for continuous variables and as proportions for categorical variables. Between-group comparisons were performed by one-way analysis of variance (ANOVA) with Duncan post-hoc test for continuous variables and by the Chi-square test for categorical variables. Pearson's correlation coefficients between LVM and other parameters were calculated. Only parameters with significant correlation with LVM were included in the subsequent multiple regression models. Multiple linear regression analysis was performed to identify the independent determinants of LVM in each category, namely, the blood pressure and heart rate, antropometrics, volume status, cardiac structure, cardiac function, arterial structure, arterial function and others, respectively. The independent determinants of LVM in each category (except for the parameters of the cardiac structure) were subjected to further forward stepwise multiple regression analysis. By calculating the ratios of individual partial r^2 to the full model r^2, the relative importance of each independent variable in the full model was determined. All statistical tests were two-tailed with a P value <0.05 to indicate statistical significance.

RESULTS

Clinical and cardiovascular parameters in hemodialysis patients and normal controls

The characteristics of the study groups are shown in Table 1. The three groups were comparable in age, gender and anthropometric indices. As compared with the NTNR and NTHD groups, the HTHD group had obvious pressure and volume overload along with greater LV wall thickness, chamber size and mass. The HTHD group had significantly higher brachial and carotid blood pressure, greater LVEDV, IVS, PWT, LVM, SV, CO, cardiac index and lower ESSV than the NTNR group. The HTHD group also had greater aortic diameter, carotid diameter, carotid IMT, carotid elastic modulus, AGI and PWV than the NTNR subjects.

In contrast, the NTHD group had similar brachial and carotid blood pressure, large artery function, LV chamber size and SV as the NTNR group. However, the NTHD subjects still had greater wall thickness and LVM, along with greater CO, lower TPR, lower ESSV and

Table 1. Characteristics of normal controls and hemodialysis (HD) subjects

	NTNR N = 46	NTHD N = 40	HTHD N = 41
Age *years*	53.7 ± 15.3	53.7 ± 14.4	54.6 ± 13.1
Sex *M/F*	18/28	18/22	25/16
HD duration *days*		1659 ± 1432	1249 ± 1525
Blood pressure and heart rate			
SBP *mm Hg*	115 ± 14	109 ± 19[b]	146 ± 23[c]
SBPc *mm Hg*	107 ± 14	100 ± 16[b]	134 ± 22[c]
DBP *mm Hg*	70 ± 10	65 ± 12[b]	81 ± 13[c]
MBP *mm Hg*	85 ± 11	80 ± 13[b]	103 ± 14[c]
PP *mm Hg*	45 ± 8	44 ± 11[b]	65 ± 19[c]
PPc *mm Hg*	34 ± 8	34 ± 8[b]	52 ± 17[c]
SBPavg *mm Hg*		122.3 ± 13.9[b]	150.3 ± 8.4
DBPavg *mm Hg*		73.5 ± 6.3[b]	85.0 ± 4.6
Heart rate *bpm*	61 ± 8	71 ± 12[a]	71 ± 11[c]
Anthropometrics			
Height *cm*	160 ± 8	158 ± 7	161 ± 9
Weight *kg*	62.7 ± 13.2	58.8 ± 9.0	59.1 ± 11.0
Body surface area *m²*	1.65 ± 0.19	1.59 ± 0.14	1.62 ± 0.18
Body mass index *kg/m²*	24.3 ± 4.2	23.6 ± 3.0	22.6 ± 3.2
Waist-to-hip ratio	0.84 ± 0.08	0.87 ± 0.07	0.85 ± 0.06
Volume status			
Fat free mass *kg*	38.8 ± 9.6	33.5 ± 7.7	35.7 ± 11.9
Extracellular fluid *L*	13.3 ± 2.6	12.0 ± 2.4	12.5 ± 2.6
Intracellular fluid *L*	16.0 ± 5.0	13.3 ± 3.6	14.6 ± 6.9
IVCD *mm/m²*	8.9 ± 2.1	6.9 ± 2.2[a]	8.0 ± 2.8
Cardiac structure			
LVM (by 2-D) *g*	111 ± 24	134 ± 35[a,b]	173 ± 41[c]
LVM (by M-mode) *g*	152 ± 44	188 ± 47[a,b]	243 ± 55[c]
IVS *cm*	0.97 ± 0.22	1.11 ± 0.15[a]	1.19 ± 0.17[c]
PWT *cm*	0.89 ± 0.12	1.02 ± 0.12[a,b]	1.12 ± 0.14[c]
LVEDV *mL*	88 ± 9	93 ± 11[b]	106 ± 13[c]
Cardiac function			
Stroke volume *mL*	66 ± 12	66 ± 17[b]	77 ± 13[c]
Cardiac output *L/min*	3.9 ± 0.7	4.6 ± 1.1[a,b]	5.4 ± 1.1[c]
Cardiac index *L/min/m²*	2.4 ± 0.4	2.9 ± 0.8[a,b]	3.3 ± 0.7[c]
Ejection fraction *%*	74 ± 7	75 ± 6[b]	71 ± 8
ESSV *mm Hg/mL*	13.1 ± 4.2	9.2 ± 3.0[a]	9.5 ± 4.0[c]
Arterial structure			
Aortic diameter *cm*	2.9 ± 0.3	3.1 ± 0.3[b]	3.3 ± 0.4[c]
Carotid diameter *cm*	0.56 ± 0.07	0.61 ± 0.09[a,b]	0.67 ± 0.08[c]
Carotid IMT *cm*	0.078 ± 0.012	0.088 ± 0.022[a]	0.089 ± 0.016[c]
Arterial function			
Elastic modulus *KPa · 10³*	0.26 ± 0.09	0.28 ± 0.15[b]	0.47 ± 0.43[c]
Augmentation index *%*	22 ± 11	17 ± 20[b]	31 ± 17[c]
Pulse wave velocity *cm/s*	824 ± 208	909 ± 240[b]	1156 ± 414[c]
AC *mL/mm Hg*	1.18 ± 0.39	1.32 ± 0.63	1.25 ± 0.49
TPR *mm Hg/L*	22 ± 5	18 ± 4[a]	20 ± 5
Others			
Hematocrit *%*	40.3 ± 3.0	30.8 ± 3.6[a]	30.0 ± 3.4[c]
Hemoglobin *g/dL*	13.4 ± 0.9	10.3 ± 1.3[a]	10.0 ± 1.2[c]
Kt/V		1.52 ± 0.25	1.48 ± 0.28
Interdialytic weight gain *kg*		3.26 ± 3.26	2.84 ± 0.95
Interdialytic weight gain *%*		5.6 ± 4.7	4.9 ± 1.5
Calcium *mg/dL*		9.3 ± 0.9	9.3 ± 0.7
Phosphate *mg/dL*		5.1 ± 1.1	5.2 ± 1.2
Intact-parathyroid hormone *pg/dL*		265 ± 388	145 ± 146

Abbreviations are: NTNR, normotensive normal renal function; NTHD, normotensive hemodialysis; HTHD, hypertensive hemodialysis; AC, total arterial compliance; DBP, diastolic blood pressure; DBPavg, pre-dialysis DBP from 25 consecutive dialysis sessions; ESSV, end-systolic meridional stress to volume ratio; HD, hemodialysis; IMT, intima-media thickness; IVCD, inferior vena cava diameter; IVS, interventricular septum thickness; LVEDV, left ventricular end-diastolic volume; LVM, left ventricular mass; MBP, mean blood pressure; PP, pulse pressure; PPc, carotid pulse pressure; PWT, posterior wall thickness; SBP, systolic blood pressure; SBPavg, pre-dialysis systolic blood pressure averaged from 25 consecutive hemodialysis sessions; SBPc, carotid systolic blood pressure; TPR, total peripheral resistance.
[a] NTNR vs. NTHD, $P < 0.05$
[b] NTHD vs. HTHD, $P < 0.05$
[c] NTNR vs. HTHD, $P < 0.05$

Table 2. Univariate relations of LVM with anthropometrical, cardiac and vascular indices in the normal controls and HD subjects

	NTNR N = 46	NTHD N = 40	HTHD N = 41
Age *years*	0.19 (0.200)	0.17 (0.290)	0.17 (0.295)
Blood pressure and heart rate			
SBP *mm Hg*	0.39 (0.008)[a]	0.33 (0.038)[a]	0.25 (0.117)
SBPc *mm Hg*	0.23 (0.136)	0.36 (0.021)[a]	0.24 (0.137)
DBP *mm Hg*	0.45 (0.002)[a]	0.32 (0.043)[a]	−0.02 (0.921)
MBP *mm Hg*	0.45 (0.002)[a]	0.34 (0.031)[a]	0.13 (0.435)
PP *mm Hg*	0.10 (0.527)	0.20 (0.216)	0.31 (0.049)[a]
PPc *mm Hg*	0.06 (0.677)	0.25 (0.118)	0.32 (0.039)[a]
SBPavg *mm Hg*		0.39 (0.014)[a]	0.18 (0.267)
DBPavg *mm Hg*		0.36 (0.025)[a]	0.02 (0.905)
Heart rate *bpm*	−0.20 (0.183)	−0.18 (0.264)	0.08 (0.632)
Anthropometrics			
Height *cm*	0.52 (<0.001)[a]	0.36 (0.024)[a]	0.16 (0.322)
Weight *kg*	0.68 (<0.001)[a]	0.37 (0.018)[a]	0.15 (0.335)
Body surface area *m²*	0.69 (<0.001)[a]	0.41 (0.009)[a]	0.17 (0.300)
Body mass index *kg/m²*	0.55 (<0.001)[a]	0.18 (0.269)	0.11 (0.509)
Waist-to-hip ratio	0.64 (<0.001)[a]	0.28 (0.081)	0.36 (0.020)[a]
Volume status			
Fat free mass *kg*	0.63 (<0.001)[a]	0.19 (0.239)	0.12 (0.446)
Extracellular fluid *L*	0.77 (<0.001)[a]	0.36 (0.025)[a]	0.35 (0.026)[a]
Intracellular fluid *L*	0.52 (0.001)[a]	0.10 (0.556)	0.03 (0.840)
IVCD *mm/m²*	−0.31 (0.039)[a]	−0.14 (0.405)	0.003 (0.986)
Cardiac structure			
IVS *cm*	0.71 (<0.001)[a]	0.44 (0.005)[a]	0.53 (<0.001)[a]
PWT *cm*	0.79 (<0.001)[a]	0.59 (<0.001)[a]	0.48 (0.002)[a]
LVEDV *mL*	0.68 (<0.001)[a]	0.54 (<0.001)[a]	0.45 (0.003)[a]
Cardiac function			
Stroke volume *mL*	0.54 (<0.001)[a]	0.33 (0.036)[a]	0.49 (0.001)[a]
Cardiac output *L/min*	0.43 (0.003)[a]	0.26 (0.107)	0.46 (0.002)[a]
Cardiac index *L/min/m²*	−0.01 (0.971)	0.10 (0.553)	0.39 (0.011)[a]
Ejection fraction *%*	0.26 (0.080)	−0.33 (0.037)[a]	−0.44 (0.004)[a]
ESSV *mm Hg/mL*	−0.69 (<0.001)[a]	−0.47 (0.002)[a]	−0.37 (0.018)[a]
Arterial structure			
Aortic diameter *cm*	0.47 (0.001)[a]	0.29 (0.061)	0.18 (0.258)
Carotid diameter *cm*	0.36 (0.014)[a]	0.29 (0.067)	0.49 (0.001)[a]
Carotid IMT *cm*	0.50 (<0.001)[a]	0.52 (0.001)[a]	0.11 (0.515)
Arterial function			
Elastic modulus *KPa · 10³*	0.15 (0.330)	−0.10 (0.539)	0.41 (0.009)[a]
Augmentation index *%*	−0.19 (0.212)	0.12 (0.452)	0.01 (0.943)
Pulse wave velocity *cm/s*	0.35 (0.021)[a]	0.41 (0.008)[a]	0.34 (0.031)[a]
AC *mL/mm Hg*	0.56 (<0.001)[a]	0.09 (0.618)	0.01 (0.941)
TPR *mm Hg/L*	−0.11 (0.453)	−0.03 (0.847)	−0.37 (0.017)[a]
Others			
Hematocrit *%*	0.34 (0.046)[a]	0.08 (0.636)	−0.23 (0.147)
Hemoglobin *g/dL*	0.38 (0.024)[a]	0.11 (0.493)	−0.27 (0.092)
Kt/V		−0.37 (0.017)[a]	−0.29 (0.066)
Interdialytic weight gain *kg*		0.07 (0.676)	0.25 (0.110)
Interdialytic weight gain *%*		0.04 (0.793)	0.21 (0.188)
Calcium *mg/dL*		0.09 (0.578)	−0.23 (0.146)
Phosphate *mg/dL*		0.08 (0.623)	0.07 (0.646)
Intact parathyroid hormone *pg/dL*		−0.04 (0.819)	−0.01 (0.971)

Numbers are correlation coefficients, and numbers in parentheses are *P* values. Abbreviations are: NTNR, normotensive normal renal function; NTHD, normotensive hemodialysis; HTHD, hypertensive hemodialysis; AC, total arterial compliance; DBP, diastolic blood pressure; DBPavg, pre-dialysis DBP from 25 consecutive dialysis sessions; ESSV, end-systolic meridional stress to volume ratio; HD, hemodialysis; IMT, intima-media thickness; IVCD, inferior vena cava diameter; IVS, interventricular septum thickness; LVEDV, left ventricular end-diastolic volume; LVM, left ventricular mass; MBP, mean blood pressure; PP, pulse pressure; PPc, carotid pulse pressure; PWT, posterior wall thickness; SBP, systolic blood pressure; SBPavg, pre-dialysis systolic blood pressure averaged from 25 consecutive hemodialysis sessions; SBPc, carotid systolic blood pressure; TPR, total peripheral resistance.

[a] Statistically significant

smaller IVCD than the NTNR group. On the other hand, the NTHD subjects had comparable aortic diameter, carotid elastic modulus, AGI and PWV, but greater carotid diameter and carotid IMT as compared with the NTNR group.

In terms of HD parameters, the NTHD and HTHD patients had similar Kt/V, IWG, hematocrit, hemoglo-bin, serum calcium, phosphate and intact-parathyroid hormone values.

Determinants of LVM

Blood pressure and heart rate. Left ventricular mass was significantly related to SBP, DBP and MBP (Table 2), and DBP was the significantly independent deter-

Table 3. Multiple regression models of LVM in each category of variables

	NTNR $N = 46$	NTHD $N = 40$	HTHD $N = 41$
Blood pressure	Model $r^2 = 0.202$	Model $r^2 = 0.149$	Model $r^2 = 0.105$
DBP *mm Hg*	0.450 (0.002)		
PPc *mm Hg*			0.324 (0.039)
Averaged SBP *mm Hg*		0.386 (0.014)	
Anthropometrics	Model $r^2 = 0.553$	Model $r^2 = 0.166$	Model $r^2 = 0.130$
Body surface area *m²*	0.475 (0.001)	0.408 (0.009)	
Waist-to-hip ratio	0.349 (0.010)		0.361 (0.020)
Volume status	Model $r^2 = 0.590$	Model $r^2 = 0.126$	Model $r^2 = 0.121$
Extracellular fluid *L*	0.768 (<0.001)	0.355 (0.025)	0.348 (0.026)
Cardiac structure	Model $r^2 = 0.808$	Model $r^2 = 0.575$	Model $r^2 = 0.467$
IVS *cm*	0.310 (0.001)		0.512 (<0.001)
PWT *cm*	0.408 (<0.001)	0.537 (<0.001)	
LVEDV *mL*	0.395 (<0.001)	0.484 (<0.001)	0.429 (0.001)
Cardiac function	Model $r^2 = 0.576$	Model $r^2 = 0.303$	Model $r^2 = 0.513$
Stroke volume *mL*		0.290 (0.043)	0.453 (<0.001)
Ejection fraction *%*			−0.440 (<0.001)
ESSV *mm Hg/mL*	−0.636 (<0.001)	−0.440 (0.003)	−0.271 (0.026)
Cardiac output *L/min*	0.313 (0.003)		
Arterial structure	Model $r^2 = 0.250$	Model $r^2 = 0.271$	Model $r^2 = 0.245$
Carotid diameter *cm*			0.495 (0.001)
Carotid IMT *cm*	0.500 (<0.001)	0.521 (0.001)	
Arterial function	Model $r^2 = 0.517$	Model $r^2 = 0.171$	Model $r^2 = 0.290$
Elastic modulus *KPa·10³*			0.392 (0.007)
Pulse wave velocity *cm/s*	0.453 (<0.001)	0.413 (0.008)	
AC *mL/mm Hg*	0.636 (<0.001)		
TPR *mm Hg/L*			−0.355 (0.013)
Others	Model $r^2 = 0.146$	Model $r^2 = 0.140$	
Hemoglobin *g/dL*	0.382 (0.024)		
Kt/V		−0.374 (0.017)	

Numbers are standardized regression coefficients, and numbers in parentheses are *P* values, Abbreviations are: NTNR, normotensive normal renal function; NTHD, normotensive hemodialysis; HTHD, hypertensive hemodialysis; AC, total arterial compliance; DBP, diastolic blood pressure; ESSV, end-systolic meridional stress to volume ratio; IMT, intima-media thickness; IVS, interventricular septal thickness; LVEDV, left ventricular end-diastolic volume; PPc, carotid pulse pressure; PWT, posterior wall thickness; PWV, pulse wave velocity; TPR, total peripheral resistance.

minant of LVM in this category in the NTNR subjects ($r^2 = 0.202$; Table 3). In the NTHD subjects, LVM was significantly related to SBP, SBPc, DBP, MBP, SBPavg and DBPavg (Table 2), and SBPavg was the significantly independent determinant ($r^2 = 0.149$; Table 3). In contrast, LVM was significantly related PP and PPc (Table 2), and PPc was the significantly independent determinant in the HTHD patients ($r^2 = 0.105$; Table 3).

Anthropometrics. Left ventricular mass was significantly related to height, weight, BSA, BMI, and WHR (Table 2), and BSA and WHR were significantly independent determinants of LVM in this category in the NTNR subjects ($r^2 = 0.553$; Table 3). LVM was significantly related to height, weight and BSA (Table 2), and BSA was the significantly independent determinant in the NTHD group ($r^2 = 0.166$; Table 3). In contrast, WHR was the only anthropometric parameter (Table 2) that was significantly related to LVM in the HTHD group ($r^2 = 0.130$; Table 3).

Volume status. The LVM was significantly positively related to FFM, ECF and ICF, and was significantly negatively related to IVCD (Table 2), and ECF was the only significantly independent determinant in the NTNR group ($r^2 = 0.590$; Table 3). On the other hand, LVM was only significantly related to ECF among the volume

status parameters (Table 2) in both NTHD ($r^2 = 0.126$) and HTHD groups ($r^2 = 0.121$; Table 3).

Cardiac structure. Left ventricular mass was significantly related to IVS, PWT and LVEDV in the NTNR, NTHD and HTHD groups (Table 2). In the NTNR subjects, all three parameters were significantly independent determinants of LVM ($r^2 = 0.808$; Table 3). In the NTHD group, PWT and LVEDV were significantly independent determinants ($r^2 = 0.575$; Table 3), while in the HTHD group, IVS and LVEDV were significantly independent determinants ($r^2 = 0.467$; Table 3).

Cardiac function. In the NTNR group, LVM was significantly positively related to SV and CO, and was significantly negatively related to ESSV (Table 2); ESSV and CO were the significantly independent determinants ($r^2 = 0.576$; Table 3). In the NTHD group, LVM was significantly positively related to SV, and was significantly negatively related to EF and ESSV (Table 2), and ESSV and SV were the significantly independent determinants ($r^2 = 0.303$; Table 3). In the HTHD group, LVM was significantly positively related to SV, CO and cardiac index, and was significantly negatively related to EF and ESSV (Table 2), and SV, EF and ESSV were the significantly independent determinants ($r^2 = 0.513$; Table 3).

Arterial structure. Left ventricular mass was significantly related to aortic diameter, carotid diameter and carotid IMT (Table 2), and IMT was the only significantly independent determinant in the NTNR group ($r^2 = 0.250$; Table 3). On the other hand, IMT and carotid diameter were the only significant determinant of LVM among arterial structure parameters (Table 2) in the NTHD ($r^2 = 0.271$) and HTHD ($r^2 = 0.245$) groups (Table 3), respectively.

Arterial function. Left ventricular mass was significantly related to PWV and AC (Table 2), and both were significantly independent determinants in the NTNR group ($r^2 = 0.517$; Table 3). On the other hand, PWV was the only significant determinant of LVM among the arterial function parameters (Table 2) in the NTHD group ($r^2 = 0.171$; Table 3). LVM was significantly related to carotid incremental elastic modulus, PWV and TPR (Table 2), and incremental elastic modulus and TPR were significantly independent determinants in the HTHD patients ($r^2 = 0.290$; Table 3).

Others. Left ventricular mass was significantly related to hematocrit and hemoglobin levels (Table 2), and hemoglobin was the significantly independent determinant among the two in the NTNR group ($r^2 = 0.146$; Table 3). On the other hand, LVM was not related to IWG, hematocrit, hemoglobin, or serum levels of calcium, phosphate or intact parathyroid hormone in both the NTHD and HTHD subjects. However, LVM was significantly negatively related to Kt/V in the NTHD group ($r^2 = 0.140$; Table 3) but not in the HTHD group. The relationship between Kt/V and LVM was partly related to the gender effect (Kt/V for NTHD men and women: 1.40 ± 0.22 vs. 1.61 ± 0.23, $P = 0.007$). However, Kt/V remained significantly related to LVM when sex was accounted for (data not shown).

Full models

The significant independent determinants of LVM in the categories of blood pressure, anthropometrics, volume status, cardiac function, arterial structure, arterial function, and others were selected for generation of full models of regression analysis. The parameters in the category of cardiac structure were not included because of the strong inherent relationship with LVM, even though all were independent measurements. In the NTNR subjects, the significantly independent determinants of LVM in the full model were ECF (standardized regression coefficient $\beta = 0.319$, $P = 0.014$), WHR ($\beta = 0.242$, $P = 0.031$), DBP ($\beta = 0.304$, $P = 0.002$) and ESSV ($\beta = -0.334$, $P = 0.005$). These four parameters explained 77.2% of the total variance of LVM ($P < 0.001$). In the NTHD group, the significantly independent determinants of LVM in the full model were ESSV ($\beta = -0.530$, $P < 0.001$), SBPavg ($\beta = 0.373$, $P = 0.002$), PWV ($\beta = 0.314$, $P = 0.008$) and SV ($\beta = 0.285$, $P = 0.010$). These

four parameters explained 61.7% of the total variance of LVM ($P < 0.001$). In the HTHD patients, the significantly independent determinants of LVM in the full model were carotid diameter ($\beta = 0.404$, $P < 0.001$), SV ($\beta = 0.404$, $P < 0.001$), EF ($\beta = -0.391$, $P < 0.001$) and ESSV ($\beta = -0.282$, $P = 0.006$). These four parameters explained 67.2% of the total variance of LVM ($P < 0.001$). The relative contribution of each of the determinants to the variance of LVM in each group is shown in Figure 1.

DISCUSSION

Previous studies of the determinants of LVM in uremic or non-uremic subjects were universally based on LVM calculated from M-mode echocardiographic measurements. When some independent variables, such as EF, LVEDV and ESSV, also were calculated from the same M-mode measurements, the interdependency between the dependent variable and the independent variables may raise serious concern. The present study used the independently measured 2-D–derived LVM for analysis that should substantially reduce such interdependency. The major findings in this study are (*1*) optimal HD alone can normalize arterial blood pressure and large artery function to levels equivalent to the non-uremic normotensive controls, indicating the effective reduction of pressure overload; (*2*) optimal HD also can effectively reduce volume overload as reflected in the measurements of ECF, LVEDV, SV, and IVCD in the NTHD group; (*3*) persistent flow overload and subclinical LV dysfunction were noted in the NTHD subjects; (*4*) effective reduction of pressure and volume overload by optimal HD alone may partially improve the changes of the cardiac and vascular structure secondary to hemodynamic overload; (*5*) while the LVM in the NTNR group is mainly determined by volume status, body size, blood pressure, and the structural and functional coupling between heart and large arteries (77.2% of the total variance of LVM), the LVM in the NTHD subjects is only partially determined by the hemodynamic factors (61.7% of the total variance of LVM), implying the significance of non-hemodynamic factors (neurohumoral) in the development of LVH in these patients.

Determinants of LVM in the normal renal function population

In the NTNR subjects, LVM is largely determined by body size and stroke work, which is a simple summary of LV workload and represents an approximate measure of the interaction between the two hemodynamic components (pressure and volume) [30]. Appropriateness of LVM to loading condition and body size can be assessed by relating observed LVM to levels predicted by an equation including sex, body height, SBP, and SV [30]. In the
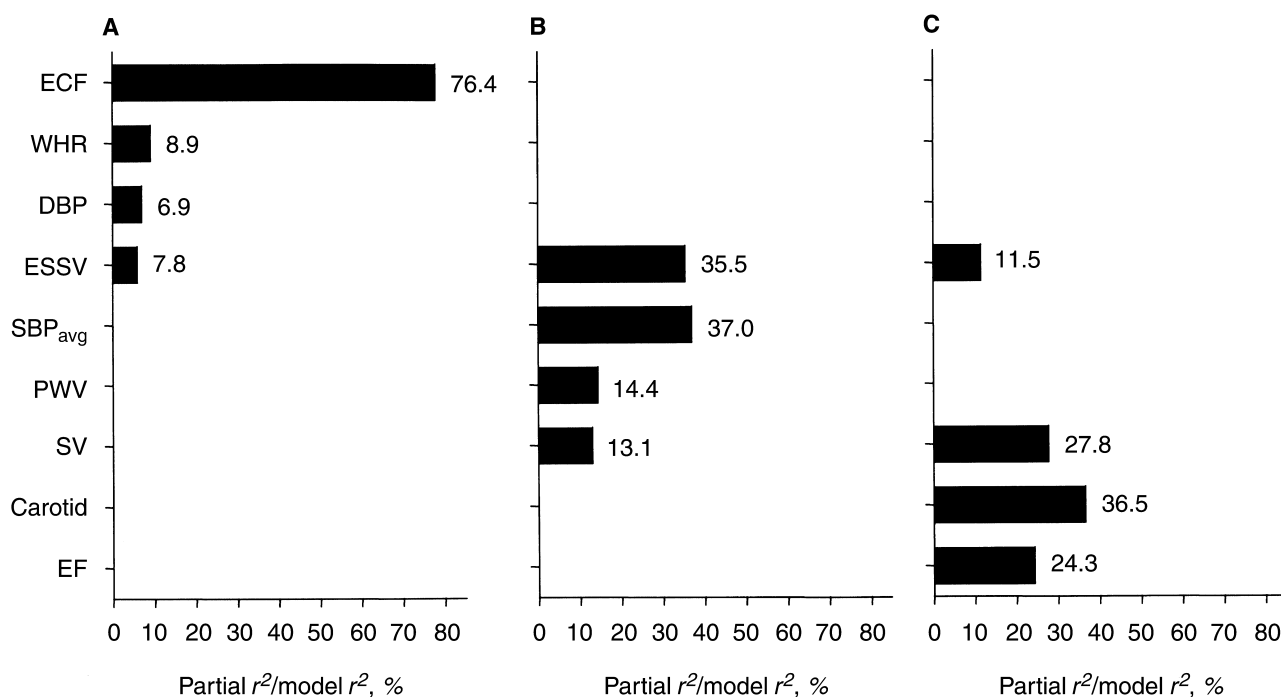
Fig. 1. Relative importance of each independent noncardiac structural variable in the final main effects multiple regression model is shown for the NTNR subjects (A), NTHD patients (B) and HTHD patients (C). Model r^2 is the proportion of variance of LVM that can be explained by the full model. Partial r^2 of each individual variable was calculated from the stepwise multiple regression approach. Ratio of partial r^2 to model r^2 is the proportion of the model variance that can be explained by the independent variable. Abbreviations are: NTNR, normotensive normal renal function; NTHD, normotensive hemodialysis; HTHD, hypertensive hemodialysis; Carotid, carotid diameter; DBP, diastolic blood pressure; ECF, extracellular fluid; EF, ejection fraction; ESSV, end-systolic meridional stress-to-volume ratio; SBPavg, averaged systolic blood pressure from 25 consecutive sessions; SV, stroke volume; WHR, waist-to-hip ratio.

Framingham study of 2226 men and 2746 women, age, height, SBP and BMI were statistically significant and independent correlates of LVM in both sexes [31]. In a population of 1315 Chinese subjects, the optimum multivariate linear regression main effects model for LVM had an adjusted model r^2 of 0.740, with 98% of the model variance accounted for by the five independent determinants: SV (49.6%), SBP (30.7%), ESSV (14.7%), BMI (1.8%) and aortic root diameter (1.6%) [13].

In the present study of 46 NTNR subjects, ECF, WHR, DBP and ESSV were identified as independent determinants of LVM, when the parameters of cardiac structure were not included. ECF is mainly determined by volume status and body size (correlation coefficient between ECF and BSA = 0.89, $P < 0.001$). Blood pressure is a parameter of cardiac and vascular function [13]. The importance of ESSV in determining LVM confirms previous findings [27]. Our results are compatible with the notion that body size, and the structural and functional coupling between heart and arteries are the principal determinants of LVM in the normal population.

Determinants of LVM in the hypertensive uremic patients

Both pressure and volume components of the hemodynamic load are evident in the hypertensive ESRD patients [16]. Conditions such as anemia [32], arteriovenous shunts, interdialytic weight change and overhydration induce a state of chronic flow overload. Hypertension, stiffening of the aorta and major arteries, and increased arterial wave reflection are the documented causes for the chronic pressure overload [33]. On the other hand, various non-hemodynamic factors responsible for LVH in the ESRD patients are recognized also, including hyperparathyroidism [34], increased plasma endothelin [35], renin-angiotensin system [9], hypoalbuminemia [36], and the uremic internal milieu [37]. In the present study, serum calcium, inorganic phosphate, and intact-parathyroid hormone were not significantly related to LVM, implying a minor role of hyperparathyroidism in the development of LVH in HTHD patients.

The 41 HTHD patients in our study were characterized by significantly higher central and peripheral SBP and PP, stiffer carotid artery and aorta, and stronger arterial wave reflection than either the NTNR or the NTHD subjects, implying the presence of obvious pressure overload. In addition, the greater LVEDV, SV, CO and CI in the HTHD patients indicated the presence significant volume/flow overload.

Since the HTHD patients were asymptomatic and without a previous history of heart disease, the lower ESSV in the presence of normal EF and LV dilation as

compared to the NTNR subjects indicates the presence of subclinical LV dysfunction. In the full model, carotid artery diameter, SV, EF and ESSV were identified as independent determinants of LVM. Since arterial structure is significantly correlated with arterial function (between carotid diameter and elastic modulus, $r = 0.32$, $P = 0.043$; between carotid diameter and PWV, $r = 0.51$, $P = 0.001$), the full model might further emphasize the importance of pressure overload (carotid diameter), volume/flow (SV) overload and subclinical LV dysfunction (EF and ESSV) in the development of LVH in HTHD patients [11].

It has been demonstrated that the calculated LVMI by echocardiography increases with ECF volume expansion and the calculated LVMI could decrease by approximately 26 g/m^2 during a dialysis session, as a result of fluid removal [38]. As shown in Tables 2 and 3, ECF was highly related to LVM ($r = 0.77$) and accounted for 55.5% of the total variance of LVM in the NTNR subjects. In contrast, ECF was only weakly related to LVM in both NTHD and HTHD patients. The results partly may be due to problems with the bioimpedance measurements [39], or may suggest that the role of salt and water overload in the pathogenesis of LVH in both NTHD and HTHD patients may not be as important as previously thought.

Determinants of LVM in the normotensive uremic patients

Although the hemodynamic overload is responsible for the development of LVH in most ESRD patients, it remains to be determined whether substantial hemodynamic overload is present in the ESRD patients with blood pressure normalized to the optimal levels.

London et al found an enlargement of the LV end-diastolic diameter in 57 normotensive HD patients (averaged SBP 137 mm Hg) in comparison to 40 healthy controls matched for sex, age and blood pressure [40]. Enlargement of the ventricle was related to anemia, the hemodynamic effect of arteriovenous fistula and secondary hyperparathyroidism [40].

In the present study, serum calcium, inorganic phosphate and intact-parathyroid hormone were not significantly related to LVM in the NTHD. Furthermore, the NTHD subjects (averaged SBP 109 mm Hg) had comparable LVEDV and SV but greater LVM in comparison with the NTNR subjects. IVCD has been shown in previous studies to be a simple and reliable tool to estimate 'dry weight' in chronic hemodialysis patients [28]. An IVCD of less than 8 mm/m^2 indicates under-hydration [28, 41], but significant bioelectrical impedance analysis changes only appear in major under-hydration (IVCD < 6.5 mm/m^2) [42]. While the NTHD patients had smaller IVCD (6.9 mm/m^2) than the NTNR subjects (8.9 mm/m^2), their ICF and ECF values were not significantly different.

Therefore, we cannot rule out the possibility that the NTHD patients were slightly dehydrated, nor were we certain whether the equilibration of intra- and extravascular volume status had been reached on the non-dialysis day. In any case, the normal LVEDV and SV along with small IVCD argues against the presence of volume overload in NTHD patients. On the other hand, the NTHD group still had greater CO and CI than the NTNR subjects, implying the presence of flow overload. The increased CO and CI in the NTHD group were responsible for the decreased TPR and were directly related to the faster heart rate as compared to the NTNR subjects. The flow overload in the absence of volume overload in the NTHD group was likely due to the inherent arteriovenous fistulae and anemia that may not be subject to aggressive fluid removal [5].

The NTHD patients had similar blood pressure and large artery function as the NTNR subjects, indicating the substantial reduction of pressure overload with optimal HD alone. However, the NTHD patients still had greater wall thickness and LVM, and lower ESSV than the NTNR subjects. The residual or persistent cardiovascular structural abnormalities in the NTHD group suggest a limitation of adequate HD in the reversal of abnormal cardiovascular adaptation. In the full model, ESSV, SBPavg, PWV and SV were identified as independent determinants of LVM in the NTHD group and ESSV contributed 35.5% of the variance explained by the model (Fig. 1B), implying the importance of subclinical LV dysfunction in the development of LVH similar to that in the HTHD group. The persistent subclinical LV dysfunction might be due to the persistent flow overload and/or the intrinsic uremic factor responsible for the LV dysfunction in the ESRD patients [40].

Limitations of the study

The present study was not an interventional study evaluating the effect of optimal HD on the hemodynamic overload and the changes of cardiovascular structure and function. Instead, this was a prospectively conducted case-control study with its inherent limitations in the interpretation of results. Although the levels of blood pressure in the NTHD group before the blood pressure was controlled were not available, the inclusion of two control groups, namely, the NTNR and HTHD groups, enabled us to speculate reasonably on the potential limitations of the optimal HD by aggressive fluid removal alone on the reverse remodeling of cardiovascular structure and function. All HD patients in this study were maintained a hemoglobin level of around 10 g/dL as recommended by our National Health Insurance System, which is lower than 11 to 12 g/dL, a range considered currently to be the lower limit of adequacy in terms of LV damage. This less than ideal level of hemoglobin

might partially be responsible for the flow overload observed in both the NTHD and HTHD patients.

The HTHD patients received regular antihypertensive medication that might have had favorable effects on the cardiovascular function and structural remodeling [43], and this might explain the failure of arterial wave reflection (as indexed by AGI) as an important determinant of LVM, as demonstrated in the HTHD patients who were withdrawn from antihypertensive medications in previous studies [44]. Since AGI is highly pressure dependent [20], our results also indicate that arterial wave reflection is only important when blood pressure is not under control.

Clinical implications

The hemodynamic overload and subclinical LV dysfunction are major determinants of the abnormal cardiovascular remodeling and future cardiovascular risk in patients with ESRD. The results from the present study further suggest that optimal HD by adequate fluid removal, which may be sufficient for the reduction of pressure and volume overload, may not be sufficient for the correction of flow overload, subclinical LV dysfunction and the cardiovascular structural abnormalities. Interventions in addition to maintaining optimal HD may be required to reduce the future cardiovascular risk in the NTHD patients.

In conclusion, the NTHD patients did not appear have significant pressure and volume overload as compared to the NTNR subjects. However, they still had increased LVM that was partially explained by the persistent flow overload and subclinical LV dysfunction.

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APPENDIX

Abbreviations used in this study are: AC, aortic compliance; AGI, carotid augmentation index; AGIh, carotid augmentation index normalized by height; BMI, body mass index; BSA, body surface area; CO, cardiac output; DBP, diastolic blood pressure; DBPavg, averaged diastolic blood pressure from 25 consecutive sessions; ECF, extracellular fluid; EF, ejection fraction; ESSV, end systolic meridional stress to volume ratio; FFM, fat-free mass; HD, hemodialysis; HTHD, hypertensive hemodialysis group; ICF, intracellular fluid; IMT, carotid artery intima-media thickness; IVCD, diameter of inferior vena cava; IVS, intraventricular septum thickness; IWG, interdialytic weight gain; LV, left ventricular; LVEDV, left ventricular end-diastolic volume; LVH, left ventricular hypertrophy; LVM, left ventricular mass; NTHD, nor-

motensive hemodialysis group; NTNR, normotensive normal renal function group; MBP, mean blood pressure; PP, pulse pressure; PPc, pulse pressure in the common carotid artery; PWT, posterior wall thickness; PWV, pulse wave velocity; SBP, systolic blood pressure; SBPavg, averaged systolic blood pressure from 25 consecutive dialysis sessions; SBPc, systolic blood pressure in the common carotid artery; SV, stroke volume; TPR, total peripheral vascular resistance; WHR, waist-to-hip ratio.

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