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Aortic Distensibility is Closely Related to the Progression of Left Ventricular Hypertrophy in Patients Receiving Hemodialysis

Yuji Matsumoto, MD
Mareomi Hamada, MD, FACA*
and Kunio Hiwada, MD, FACA*

EHIME, JAPAN

ABSTRACT

Aortic stiffening and left ventricular hypertrophy are believed to be major determinants for the prognosis of patients with end-stage renal disease. However, the relationship between left ventricular hypertrophy and aortic stiffness remains to be determined. Echocardiographically determined parameters and aortic distensibility determined with cine magnetic resonance were evaluated in 21 patients undergoing chronic hemodialysis. Hemodynamic variables measured at the beginning of the study were compared with those measured after 28 months. Aortic distensibility determined at the descending aorta was markedly lower in patients undergoing hemodialysis than in healthy control subjects. During the follow-up period, blood pressure and hemodynamic variables, including left ventricular mass index, remained unchanged. However, multiple regression analysis indicated that aortic distensibility independently contributed to the left ventricular mass index and to the change in left ventricular mass index between baseline and after 28 months. Baseline left ventricular mass index negatively correlated to aortic distensibility ($r = -0.74$, $p < 0.0001$), and the changes in left ventricular mass index positively correlated to aortic distensibility ($r = 0.52$, $p < 0.05$). Our study demonstrates that aortic distensibility at the descending aorta is a predictable marker for the development or regression of left ventricular hypertrophy. Therefore, patients with end-stage renal disease must be treated with appropriate drugs to improve aortic distensibility.

From the Department of Internal Medicine, Saijo Central Hospital; and the *2nd Department of Internal Medicine, Ehime University School of Medicine, Ehime Japan.

Introduction

Cardiovascular disease is the most frequent cause of death in patients with end-stage renal disease. Left ventricular hypertrophy (LVH) develops in large populations of patients with end-stage renal disease who are undergoing maintenance hemodialysis. In addition, LVH is known to be an independent risk factor related to mortality in patients with end-stage renal disease.[1,2] Thus, the regression of LVH is indispensable to improve the prognosis in patients with end-stage renal disease. In patients without end-stage renal disease, hypertension may be the major determinant factor of LVH, and usually LVH associated with hypertension can be reversed with antihypertensive treatment. However, previous studies have suggested that the development of LVH in patients with end-stage renal disease is related to multiple factors.[3-7] London et al showed that the alteration of aortic input impedance determined by arterial tone was related to cardiac afterload and myocardial hypertrophy in patients with end-stage renal disease.[8-10] This suggests that the damage of large arteries is closely related to the LVH in patients with end-stage renal disease.

A recent study has shown that increased aortic stiffness is a strong independent predictor of cardiovascular mortality in end-stage renal disease.[11] Aortic stiffness can be assessed directly by the measurement of aortic distensibility (AD). However, it is difficult to determine AD noninvasively, because of the difficulty in the determination of the size of aorta. Cine magnetic resonance can facilitate determination of the size of aorta at any level. We evaluated AD using cine magnetic resonance since 1994[12-17] and have already reported the low AD in patients with essential hypertension,[12,15,17] coronary artery disease and in those undergoing hemodialysis.[14,16]

The purposes of this study are to elucidate the relationship between AD, determined with cine magnetic resonance, and LVH in patients undergoing hemodialysis and to investigate factors related to the change of LVH during the long-term follow-up period in patients undergoing hemodialysis.

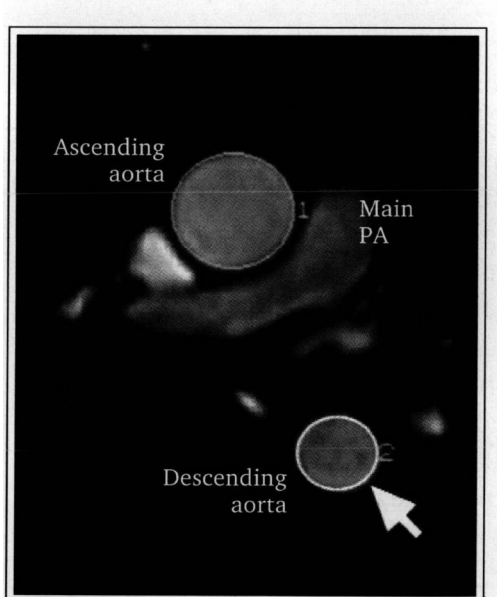

Figure 1. The tracing area of descending aorta (arrow) on cine MR. This transverse image was acquired with the following parameters: field of view, 35 cm; section thickness, 10 mm; flip angle, 60 degrees; repetition time, 50 msec; echo time, 22 msec; number of excitation, twice; matrix, 128 × 256. PA: pulmonary artery.

Methods

Study Patients

Twenty-one patients undergoing hemodialysis, 12 men and nine women (mean age, 63 ±9 years; range 46 to 79 years) participated in this study. All patients had been undergoing hemodialysis for 4 to 5 hours three times a week. The mean duration of hemodialysis at the start of the study was 74 ±46 months (range, 20 to 165 months). The cause of renal failure was chronic glomerulonephritis in eight patients, nephrosclerosis in five patients, interstitial nephritis in one patient, polycystic kidney in one patient, and systemic lupus erythematosus in one patient. The cause of renal failure in the other five patients was unknown. All patients had been treated with antihypertensive drugs before the commencement of hemodialysis. After hemodialysis, the blood pressure of eight pa-

tients was controlled with hemodialysis alone; 13 patients received antihypertensive drugs. Eight patients were treated with calcium channel blockers; three with a combination therapy of calcium channel blockers and angiotensin-converting enzyme inhibitors; one with a combination therapy of the calcium channel blocker, angiotensin-converting enzyme inhibitor and β-blocker; and one with α_1-blocker. Seven patients were current or former smokers. Nine men and six women without a history of chronic illness participated as healthy control subjects (mean age, 59 ±9 years). The patients who had coronary artery disease, valvular heart disease, left ventricular dysfunction, atrial fibrillation, or diabetes mellitus were excluded from this study. All subjects participated after giving informed consent.

Study Protocol

First, echocardiographically determined hemodynamic parameters including left ventricular mass (LVM), risk factors relating to cardiovascular diseases, and AD were measured at the beginning of the study. With use of these measurements, we examined the parameters relating to the LVM. Second, after at least 24 months (mean follow-up period: 28 ±4 months) identical parameters were measured. In addition, a difference in LVM index was determined between the start and the end of the study (dLVMI), and the relationships between dLVMI and various parameters were examined.

Determination of Aortic Distensibility

To evaluate AD, cine magnetic resonance was performed with a 0.5 T magnetic resonance system using a Toshiba MRT 50 (Tokyo, Japan). Aortic distensibility of the ascending and descending aorta was measured as reported previously.[12-17] After observation of aortic wall movement, we chose the cine frames of the maximum and minimum transverse areas of aorta for the measurements of AD. After determinations of maximum and minimum transverse areas of descending aorta, their areas were measured by tracing as shown in Figure 1. Then, AD was calculated with the following formula:

$$AD = (\text{max. area} - \text{min. area}) / (\text{min. area} \times \Delta P) \quad (1)$$

where ΔP means pulse pressure.

Determination of Echocardiographic Parameters

Two-dimensional and M-mode echocardiograms were obtained according to the recommendation of the American Society of Echocardiography[18] using an Aloka SSD system 860 (Tokyo, Japan). Interventricular septal thickness (IVST), left ventricular posterior wall thickness (LVPWT), left ventricular end-diastolic and end-systolic dimensions (LVDd and LVDs) were measured using M-mode echocardiographic recordings. Percent fractional shortening of the left ventricle (%FS) was calculated with the following formula:

$$\%FS = 100 \times (LVDd - LVDs) / LVDd \quad \textbf{(2)}$$

Left ventricular mass was estimated from the following formula by Devereux and Reichek[19]:

$$LVM\ (g) = 1.04 \times [(IVST + LVPWT + LVDd)^3 - LVDd^3] - 13.6 \quad (3)$$

Left ventricular mass was divided by body surface area to derive the left ventricular mass index (LVMI).

Determinations of Risk Factors for Cardiovascular Disease

The following information was collected from the charts at the beginning and the end of observation period: age, sex, weight gains between hemodialysis, duration of hemodialysis, original disease, and status of smoking. The following blood measurements were obtained before hemodialysis: hemoglobin, intact parathyroid hormone (intact PTH), total cholesterol, HDL-cholesterol, and triglyceride level. In addition, plasma concentration of brain natriuretic peptide (BNP) was measured before hemodialysis as reported previously.[20]

Statistical Analysis

All values are shown as mean ± SD. The significance of differences within the same group was analyzed with the paired Student's *t* test, and two groups comparing healthy subjects and hemodialysis patients were analyzed with the unpaired Student's *t* test. To evaluate the relationship between two variables, linear regression analysis was used. To determine the relationship between the risk factors and AD and to examine the influence of risk factors on LVH, multiple re-

gression analysis was performed. In the former analysis, dependent variables were AD of the descending aorta, and independent variables were gender, age, duration of hemodialysis, mean blood pressure, smoking, total cholesterol, HDL-cholesterol and triglyceride level. In the latter analysis, LVMI or dLVMI was the dependent variable, and independent variables were gender, age, blood pressure, smoking, and AD. A value of $p < 0.05$ was considered statistically significant. These procedures were performed on a Macintosh computer using the Stat View IV Statistical System.

Results

As shown in Table I, there were significant differences in systolic, diastolic, and mean blood pressure between healthy subjects and patients undergoing hemodialysis at baseline. In addition, pulse pressure was greater in hemodialyzed patients than in healthy subjects. Hemoglobin was significantly lower, and intact PTH and BNP was significantly higher in hemodialyzed patients than in healthy subjects. At baseline, IVST, PWT, and LVMI were significantly higher in hemodialyzed patients than in healthy subjects. There was a significant relationship between plasma level of BNP and LVMI in hemodialyzed patients at baseline and at 28 months, respectively ($r = 0.66$, $p < 0.001$ and $r = 0.67$, $p < 0.001$). There were no significant changes in all parameters in Table I between baseline and 28 follow-up months.

As shown in Table II, AD at the descending aorta in hemodialyzed patients was a lower value than that in healthy subjects. There was no significant change of maximum area, minimum area, and AD at the descending aorta between baseline and at 28 months.

Table III shows the relationship between AD at the descending aorta and risk factors that seem to be related to AD. Multiple regression analysis indicated that age independently contributed to AD at the descending aorta. However, no significant correlation was observed between the other risk factors and AD.

Table IV shows results of multiple regression analysis to determine the risk factors influencing the baseline LVMI or dLVMI in hemodialyzed patients. Aortic distensibility of the descending aorta was found to contribute independently to both baseline LVMI and dLVMI, whereas no significant correlation was observed between baseline LVMI or dLVMI and the other risk factors.

Figure 2 shows the relationship between baseline LVMI and AD at the descending aorta. A negative significant correlation was found between baseline LVMI and AD ($r = -0.74$, $p < 0.0001$). In addition, as shown in Figure 3, a positive correlation was found between dLVMI and AD ($r = 0.52$, $p < 0.05$).

Discussion

The most important finding in this study was a good correlation between LVMI and AD in patients undergoing hemodialysis. In addition, we found that the extent of LVH during the follow-up period in these patients was also significantly influenced by the extent of AD.

Aortic stiffness has been studied with pulse wave velocity,[21] angiography,[22] Doppler echocardiography,[23,24] and ultrasonography.[25,26] To decrease patient stress, it is very important that the method of examination is highly noninvasive. Magnetic resonance imaging (MRI) is an excellent choice. Magnetic resonance imaging can easily depict any location of the aorta and demonstrate a luminal cross-sectional area. Arterial compliance was first measured with MRI by Mohiaddin et al.[27] In their report, MRI was performed with a spin-echo sequence that acquired two images at end-diastole and end-systole. Cine magnetic resonance enables acquisition of more accurate maximum and minimum areas of the aorta during the cardiac cycle, so we used cine magnetic resonance to determine AD.[12-17]

Left ventricular hypertrophy is present in 40 to 70% of patients with renal failure undergoing chronic hemodialysis, and is an important determinant factor of survival in these patients.[1,2] In this study, LVMI of hemodialyzed patients was greater than that of healthy subjects, which seemed to be high considering their blood pressure. In addition, LVMI of hemodialyzed patients remained unchanged during the 2-year follow-up period. These findings suggest that LVH in hemodialyzed patients cannot be explained only by

Table I

Clinical and Echocardiographic Data

Parameters	Healthy Subjects (n=15)	Hemodialyzed Patients (n = 21)			
		Baseline	p*	Follow-up	p†
Systolic BP (mm Hg)	125.1 ±15.7	152.7 ±15.5	<0.0001	151.1 ±20.1	0.81
Diastolic BP (mm Hg)	71.9 ±9.4	81.8 ±7.9	0.0013	81.8 ±6.9	0.58
Mean BP (mm Hg)	92.3 ±7.5	105.6 ±8.8	<0.0001	104.9 ±8.3	0.64
Pulse pressure (mm Hg)	53.2 ±15.1	70.9 ±14.1	0.0009	69.3 ±20.9	0.73
Total cholesterol (mg/dL)	186.5 ±36.2	176.3 ±25.2	0.64	163.2 ±28.4	0.88
HDL cholesterol (mg/dL)	42.3 ±11.8	38.3 ±13.3	0.53	42.6 ±20.2	0.72
Triglyceride level (mg/dL)	169.9 ±19.8	143.0 ±54.0	0.33	131.8 ±60.5	0.84
Hemoglobin (g/dL)	14.3 ±1.1	8.4 ±0.9	<0.0001	8.9 ±1.1	0.90
Intact PTH (pg/dL)	12.3 ±2.5	66.13 ±72.8	<0.0001	56.13 ±70.8	0.71
BNP (pg/mL)	15.2 ±8.9	291.0 ±271.0	<0.0001	260.1 ±449.4	0.35
LVDd (mm)	48.3 ±1.3	48.0 ±4.5	0.78	49.4 ±4.1	0.06
LVDs (mm)	29.2 ±3.6	32.8 ±8.0	0.10	30.8 ±4.2	0.21
IVST (mm)	8.1 ±0.9	11.2 ±2.2	<0.0001	11.8 ±2.3	0.17
PWT (mm)	8.3 ±0.7	11.1 ±2.2	<0.0001	11.0 ±1.9	0.67
%FS (%)	39.8 ±6.2	31.7 ±15.5	0.065	34.7 ±6.0	0.70
LVMI (g/m^2)	103.3 ±21.2	154.6 ±49.9	0.0007	167.1 ±56.2	0.11

Values are means ± SD. BP: blood pressure; HDL: high-density lipoprotein; PTH: parathyroid hormone; LVDd: left ventricular end-diastolic dimension; LVDs: left ventricular end-systolic dimension; %FS: percent fractional shortening; IVST: interventricular septal wall thickness; PWT: left ventricular posterior wall thickness; LVMI: left ventricular mass index; BNP: brain natriuretic peptide. *Probability value for baseline compared with healthy subject; †Probability value for follow up compared with baseline.

elevated blood pressure. In fact, we often find that LVH is associated in normotensive hemodialyzed patients. In addition to hypertension,[3] the extent of LVH may be related to persistent volume overload, oversecretion of PTH,[4] uremic toxemia and anemia.[5] High cardiac output associated with arteriovenous shunt may be one of the important factors of LVH in hemodialysis patients. In our study, gender, duration of hemodialysis, and mean blood pressure showed no significant risk factors for LVM. Hemoglobin and PTH remained unchanged during the follow-up period. However, the availability of recombinant human erythropoietin permitted us to prevent the development of anemia and to improve LVH in hemodialyzed patients.[28] Thus, we can alleviate the various risk factors that seem to be related to the progression of LVH in hemodialyzed patients.[29,30]

Table II

Aortic Areas and Distensibilities in Hemodialyzed Patients

Parameters	Healthy Subjects (n=15)	Hemodialyzed Patients (n = 21)			
		Baseline	p*	Follow-up	p†
Max area of descending aorta (cm^2)	424.1 ±64.7	438.2 ±103.2	0.58	408.3 ±93.8	**0.73**
Min area of descending aorta (cm^2)	334.4 ±54.4	371.8 ±102.1	0.613	349.8 ±88.6	**0.83**
Aortic distensibility of descending aorta ($\times 10^{-3}$/mm Hg)	4.52 ±1.42	2.87 ±1.23	0.0007	2.59 ±1.17	0.77

Values are means ± SD. *Probability value for baseline compared with healthy subject. †Probability value for follow-up compared with baseline.

Table III

Risk Factors Affecting Aortic Distensibility in Hemodialyzed Patients

Independent Variables	Dependent Variables: Aortic Distensibility at Descending Aorta	
	β	p
Gender	0.200	0.464
Age	-0.514	0.023
Duration of dialysis	-0.179	0.415
Smoking	-0.523	0.602
Mean blood pressure	-0.140	0.537
R^2	0.567	

β: standard regression coefficient; R^2: multiple coefficient of determination.

In this study, although the degree of blood pressure, anemia, and secretion of PTH showed no significant change during the long-term follow-up period, LVMI was decreased in some patients. To the contrary, in patients with reduced AD, the degree of LVH could not be attenuated. A significantly positive correlation was observed between the change in LVMI and AD. These results showed that the regression and progression of LVH in hemodialyzed patients were significantly affected by AD. In view of the suggestion that the increased cardiovascular complications of hemodialyzed patients would be related to reduced AD, the improvement of AD is the most important factor for

Table IV

Risk Factors Affecting LVMI and dLVMI in Hemodialyzed Patients

Independent Variables	Dependent Variables			
	LVMI		dLVMI	
	β	p	β	p
Gender	0.161	0.369	−0.173	0.435
Age	0.720	0.738	0.341	0.208
Duration of dialysis	−0.055	0.779	−0.024	0.921
Mean blood pressure	0.084	0.714	0.188	0.511
Aortic distensibility of descending aorta	−0.612	0.021	0.798	0.016
R^2	0.593		0.373	

β: standard regression coefficient; R^2: multiple coefficient of determination.

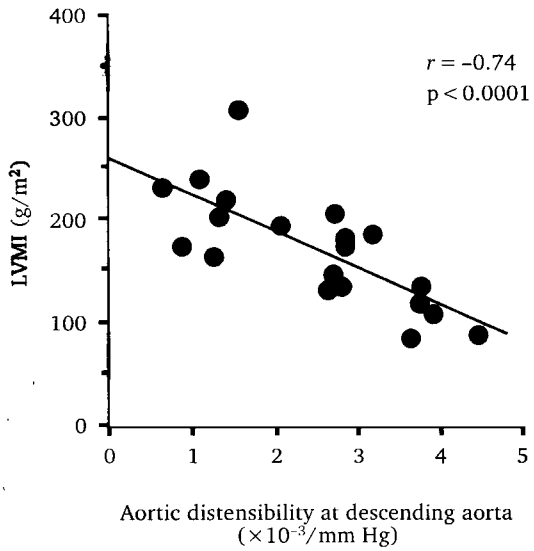

Figure 2. The relationship between aortic distensibility at the descending aorta and LVMI.

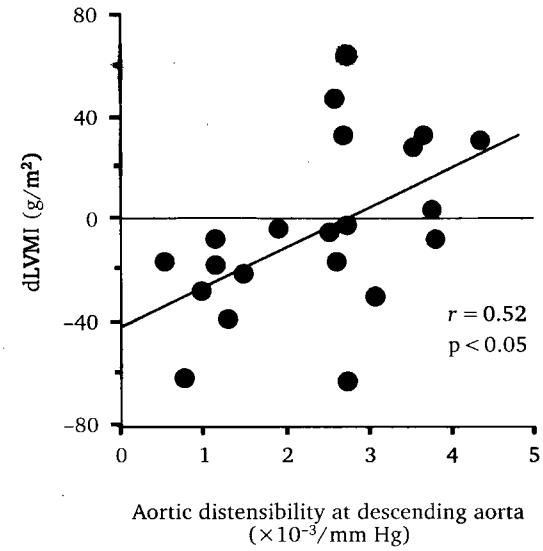

Figure 3. The relationship between aortic distensibility at the descending aorta and dLVMI.

a good prognosis in patients with end-stage renal disease. It appears that aging, smoking, and some factors related to the advancement of renal disease exert opposing effects on large arteries.[27,28] For this reason, LVH could not be improved in patients with reduced AD. It is important to prevent the reduction of AD at the earlier stage of renal failure. Before the establishment of structural changes of aortic wall, it is important to improve the functional abnormalities of large arteries with use of drugs.[31-33] Several studies have presented the effects of antihypertensive treatment on arterial function. London et al demonstrated that angiotensin-converting enzyme inhibition induced the reduction in arterial wave reflections in distal parts of arterial tree, resulting from the decrease in pulsatile pressure load and the increased AD in hemodialyzed patients.[38] We recently reported that antihypertensive therapy improved AD in hypertensive patients and its effect was greater with use of nicardipine and alacepril than with trichlormethiazide.[17] Therefore, we must treat patients with end-stage renal disease with appropriate drugs to improve AD.

Plasma concentration of BNP is known to be a marker of LVH,[34] as well as heart failure,[35,36] and BNP level decreases according to the regression of LVH associated with antihypertensive treatment.[37] In our study, plasma concentration of BNP was very high, and its level was significantly related to the extent of LVMI. The plasma level of BNP in our patients was extraordinary high for the levels of LVMI, compared to data previously reported.[38,39] This may be mainly responsible for their renal dysfunction, which disturbs clearance from the blood.[38,39] Our study also showed no significant relationship between the regression of LVH and the reduction of plasma concentration of BNP level. The reason for this discrepancy remains to be determined. Left ventricular hypertrophy in end-stage renal disease is related to multiple factors, and thus, plasma BNP level may not reflect only the change of LVMI.

Yuji Matsumoto, MD
Department of Internal Medicine
Saijo Central Hospital
Tsuitachi 804 Saijo
Ehime 793-0027, Japan

E-mail: yumatsum@shikoku.ne.jp

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