

## Clinical Factors Associated with Brachial-Ankle Pulse Wave Velocity in Patients on Maintenance Hemodialysis

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Pulse wave velocity (PWV) is a main parameter for arterial stiffness. In patients with end-stage renal disease (ESRD), PWV is known to be associated with increased mortality. But factors related to the increased PWV in ESRD patients are not well defined. In addition, the carotid-femoral PWV (cfPWV) measurement, which traditionally has been used to evaluate arterial stiffness, has low reproducibility. Recently, brachial-ankle PWV (baPWV) measurement, which can be performed more easily than cfPWV measurement, has become available as a means of measuring PWV. The aim of this study is to investigate the clinical factors associated with increased baPWV in ESRD patients. BaPWV was examined for 65 ESRD patients on maintenance hemodialysis during the period between the 7<sup>th</sup> to the 11<sup>th</sup> of February in 2005 using VP-1000. The clinical factors included age, sex, smoking history, blood pressure, diabetes, body mass index, interdialytic weight gain, duration of dialysis, lipid profile, uric acid, albumin, creatinine, C-reactive protein, calcium, phosphate, intact parathyroid hormone, and hematocrit were analyzed regarding associations (or to determine associations) with baPWV. The median age was 53.8±12.0, 31 males and 34 females. BaPWV was 18.9±5.2 m/s and there was no significant difference between gender (18.1±4.4 m/s vs 19.4±5.9 m/s, p=NS). In multiple regression models, age, predialysis systolic blood pressure, and diabetes were independent variables. In conclusion, age, systolic blood pressure, and diabetes were correlated with baPWV in ESRD patients. Thus baPWV measured by simple, noninvasive methods may become available for screening high risk groups in ESRD patients, although further longitudinal studies are necessary.

**Key Words :** atherosclerosis; renal dialysis; blood pressure

### Introduction

In end-stage renal disease (ESRD) patients, the most common cause of death is cardiovascular disease<sup>1)</sup>, because of advanced atherosclerosis in this population. Atherosclerosis progresses through two key elements, thickening (atherosis) and stiffening (sclerosis) of the arterial wall<sup>2)</sup>. Arterial thickening causes ischemia and/or infarction and

stiffening of arterial walls is associated with arterial dilatation and hypertrophy<sup>3)</sup>. Atherosclerosis of arterial wall has been considered as a risk factor of cardiovascular disease traditionally. Compared with atherotic change, sclerotic change of the arterial wall has only recently been studied. Arterial stiffness, a powerful independent predictor of all cause and cardiovascular mortality, can be examined by measurement of pulse wave velocity (PWV)<sup>4)</sup>. Therefore, through the identification of high risk groups of cardiovascular disease in ESRD patients is by PWV, mortality rates can be decreased through early intervention. PWV had been traditionally computed on the basis of pulse

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transit time and the distance traveled between the carotid artery and femoral artery, i.e., carotid-femoral PWV (cfPWV). However this technique is complex and inconvenient, particularly in screening large populations. BaPWV appears equal in the efficacy for determining mortality to cfPWV in ESRD patients<sup>5</sup>. Recently a device assessing brachial-ankle PWV (baPWV) was developed. This technique using the device is more feasible for screening a large population than previous methods because of technical simplicity and convenience<sup>6,7</sup>. Few studies have examined the baPWV and its influent factors in Korean ESRD patients. We conducted this study to evaluate the clinical factors associated with baPWV in patients on maintenance hemodialysis.

## Methods

### 1. Subjects

This study is a cross-sectional study. Sixty-five ESRD patients who were undergoing maintenance hemodialysis therapy in Hanyang University Guri Hospital were recruited between February 2005 and June 2005.

### 2. Data collection

Demographic and medical data, including smoking habits, medication history, and cause of ESRD, were obtained from medical records and interviews. We classified patients with a smoking history of more than 20 pack-years as the smoking group, taking renin angiotensin system (RAS) blockade for more than 6 months as the RAS blockade group, and statin for more than 1 month as the statin group.

### 3. Physiological data and blood pressure measurement

All participants measured their height and weight after hemodialysis. Dry weight was assessed in a normal albumin level and just prior to manifest hypotension, muscle cramps, and postural hypotension clinically<sup>8</sup>.

Body mass index (BMI) and body surface area (BSA) were calculated from measured height and body mass using the following equation:  $BMI = \text{body mass (kg)} / \text{height (m)}^2$ ,  $BSA (m^2) = 0.20247 \times \text{height (m)}^{0.725} \times \text{weight (kg)}^{0.425}$ . Inter-

dialytic weight gain was adjusted by BSA. Blood pressure (BP) was assessed after 15 minutes of resting in the arm contralateral to the arteriovenous fistula with a mercury sphygmomanometer and a cuff of appropriate size. The mean arterial pressure (MAP) was calculated as the following equation:  $MAP = DBP + [(SBP - DBP) / 3]$ , where DBP and SBP represent diastolic blood pressure and systolic blood pressure, respectively. A total of eight measurements were made at predialysis and postdialysis. Pulse pressure was defined as the difference between SBP and DBP.  $\Delta SBP$ ,  $\Delta DBP$ , and  $\Delta MAP$  were defined as the difference between predialysis and postdialysis measurements of SBP, DBP, and MAP.

### 3. Laboratory measurements

Plasma total cholesterol, high-density lipoprotein cholesterol, triglycerides, uric acid, blood sugar, and serum creatinine levels were measured enzymatically. All blood samples were obtained in a fasting state in the morning.

### 4. Echocardiography

Two-dimensional M-mode echocardiography was performed by an experienced echocardiographer using the HP sonos 2,500. Left ventricular internal diameter (LVID), septal wall thickness (SWT), and the posterior wall thickness (PWT) were made according to the recommendations of the American Society of Echocardiography. Left ventricular (LV) mass was calculated using Devereux's formula:  $LV \text{ mass (g)} = 0.80 \times [1.04 \times \{ (PWT + LVID + SWT)^3 - LVID^3 \}] + 0.6^9$ .

The LV mass index was performed by adjusting LV mass for BSA.

### 5. Measurement of baPWV

BaPWV and Ankle-brachial blood pressure index (ABPI) were assessed by using a Colin Waveform analyzer (form PWV/ABI; Colin, Co., Ltd., Komaki, Japan) which simultaneously records bilateral arm and ankle blood pressure, pulse volumes of brachial and posterior tibial arteries, heart sounds, and electrocardiogram. All patients were

**Table 1. Clinical characteristics of the study population**

Variables	Total (n=65)	Male (n=31)	Female (n=34)	p
Age (years)	53.9±12.0	52.6±14.1	55.1±9.8	NS
Duration of dialysis (years), median [25-75% quartile]	3.2 [1.4-4.9]	3.9 [1.3-5.2]	2.8 [1.4-4.9]	NS
Dry weight (kg)	55.7±8.2	58.3±7.4	53.3±8.2	NS
IDWG/BSA (kg/m <sup>2</sup> )	2.0±0.4	1.9±0.4	2.0±0.5	NS
BMI (kg/m <sup>2</sup> )	21.5±2.8	20.9±2.5	22.0±3.0	NS
Cause of ESRD, n (%)				NS
Diabetes	25 (38.5)	10 (32.3)	15 (44.1)	
Hypertension	9 (13.8)	5 (16.1)	4 (11.8)	
Chronic glomerulonephritis	3 ( 4.6)	2 ( 6.5)	1 ( 2.9)	
Cystic disease	2 ( 3.1)	0 ( 0 )	2 ( 5.9)	
Renal tuberculosis	1 ( 1.5)	1 ( 3.2)	0 ( 0 )	
Nephrotoxin etc.	1 ( 1.5) 5 ( 7.7)	0 ( 0 ) 5 (16.1)	1 ( 2.9) 0 ( 0 )	
Unknown	19 (29.2)	8 (25.8)	11 (32.4)	
Smoking history, n (%)	23 (35.9)	22 (71 )	1 ( 2.9)	<0.01
RAS blockades, n (%)	19 (29.2)	9 (29 )	10 (29.4)	NS
Statins, n (%)	18 (27.7)	7 (22.6)	11 (32.4)	NS

Values are expressed as mean±SD or number (%), except duration of dialysis. IDWG, interdialytic weight gain; BSA, body surface area; BMI, Body mass index; ESRD, end-stage renal disease; RAS, rennin angiotensin system; NS, not significant.

**Table 2. Blood chemistry of the study population**

Variables	Total (n=65)	Male (n=31)	Female (n=34)	p
Albumin (g/dL)	4.0±0.4	4.1±0.4	3.9±0.4	NS
Calcium (md/dL)	9.0±0.6	9.1±0.5	8.8±0.6	0.02
Phosphate (mg/dL)	6.1±1.7	6.2±1.6	6.0±1.9	NS
Intact PTH (pg/mL)	252.6±212.3	234.4±213.2	269.3±213.2	NS
Creatinine (mg/dL)	10.3±3.5	11.6±3.7	9.1±3.0	<0.01
Hematocrit (%)	29.4±3.5	29.6±4.0	29.2±2.9	NS
CRP (mg/dL)	0.6±1.0	0.7±1.0	0.6±1.0	NS
Uric acid (mg/dL)	8.0±1.8	8.3±1.7	7.8±1.9	NS
Fasting glucose (mg/dL)	117.8±70.0	104.2±38.7	130.1±88.4	NS
HDL cholesterol (mg/dL)	40.9±10.2	39.4±11.0	42.3±9.3	NS
Non-HDL cholesterol (mg/dL)	129.7±43.6	121.2±40.5	137.4±45.5	NS

Values are expressed as mean±SD or number (%). PTH, parathyroid hormone; CRP, C-reactive protein; HDL, high-density lipoprotein; NS, not significant.

examined on supine position after hemodialysis treatment and after resting for their BP stabilized for at least 5 minutes. Monitoring cuffs were placed around both the brachium without blood access and ankles.

## Results

The clinical characteristics of study patients are shown in Table 1. Mean age was 53.9±12.0 years and dialysis duration was 3.2 (25-75% quartile, 1.4-4.9) years. The causes of ESRD included diabetes, hypertension, chronic glomerulonephritis, etc. In 29.2% of the patients, the

cause was not identified. These characteristics were not different between both genders.

Table 2 shows the biochemical parameters. Mean serum calcium was 9.0 mg/dL and it was significantly higher in males than in females (male: 9.1 mg/dL; female: 8.8 mg/dL; p=0.02). Serum creatinine was 11.6 mg/dL and 9.1 mg/dL in the males and females (p<0.01). Mean fasting glucose was 117.8 mg/dL, which was higher in females than in males but didn't have statistic significance (male: 104.2 mg/dL; female: 130.1 mg/dL; p=NS)

Table 3 shows cardiac parameters. Pulse pressure at

**Table 3. Blood pressure and cardiac parameters of the study population**

Variables	Total (n=65)	Male (n=31)	Female (n=34)	p
Pulse pressure (mmHg)				
Predialysis	80.3±12.9	81.5±12.3	79.2±13.5	NS
Postdialysis	64.6±14.0	63.7±13.3	65.4±14.8	NS
Blood pressure (mmHg)				
Predialysis systolic	169.1±14.1	171.0±11.9	167.4±15.9	NS
Postdialysis systolic	150.3±16.0	150.2±15.2	150.5±16.8	NS
△ SBP	18.7±14.6	20.8±14.1	16.8±15.1	NS
Predialysis diastolic	88.8±6.1	89.5±7.1	88.2±5.1	NS
Postdialysis diastolic	85.8±6.2	86.5±7.1	85.2±5.2	NS
△ DBP	3.0±6.3	3.0±6.4	3.0±6.2	NS
Predialysis mean	171.4±12.2	173.1±10.6	169.8±13.4	NS
Postdialysis mean	158.1±12.8	158.0±12.9	158.1±12.9	NS
△ MAP	13.3±12.1	15.1±11.9	11.7±12.3	NS
LV mass index (g/m <sup>2.7</sup> )	71.6±13.2	73.7±15.8	70.1±11.1	NS
baPWV (m/s)	18.9±5.2	18.1±4.4	19.4±5.9	NS

Values are expressed as mean±SD. △SBP, predialysis systolic blood pressure-postdialysis systolic blood pressure; △DBP, predialysis diastolic blood pressure-postdialysis diastolic blood pressure; △MAP, predialysis mean arterial pressure-postdialysis mean arterial pressure; LV, left ventricular; baPWV, brachial-ankle pulse wave velocity; NS, not significant.

**Table 4. Correlation coefficients between baPWV and variables**

Variables	r	p
Age (years)	0.45	<0.01
Predialysis SBP (mmHg)	0.36	<0.01
Postdialysis SBP (mmHg)	0.46	<0.01
Predialysis DBP (mmHg)	0.11	NS
Postdialysis DBP (mmHg)	0.15	NS
△SBP (mmHg)	-0.16	NS
△DBP (mmHg)	-0.04	NS
△MAP (mmHg)	-0.15	NS
HDL cholesterol (mg/dL)	0.26	0.04
Non-HDL cholesterol (mg/dL)	0.19	NS
CRP (mg/dL)	-0.02	NS
Uric acid (mg/dL)	-0.24	0.05
Creatinine (mg/dL)	-0.34	0.01
Fasting glucose (mg/dL)	0.22	0.08
Albumin (g/dL)	-0.08	NS
Hematocrit (%)	-0.002	NS
Calcium (mg/dL)	0.15	NS
Phosphate (mg/dL)	-0.17	NS
Intact PTH (pg/dL)	-0.05	NS
Dialysis vintage (years)	-0.08	NS
Dry weight (kg)	-0.10	NS
BMI (kg/m <sup>2</sup> )	-0.01	NS
IDWG/BSA (kg/m <sup>2</sup> )	0.06	NS
LV mass index (g/m <sup>2.7</sup> )	-0.10	NS

baPWV, brachial-ankle pulse wave velocity; SBP, systolic blood pressure; DBP, diastolic blood pressure; △SBP, predialysis systolic blood pressure-postdialysis systolic blood pressure; △DBP, predialysis diastolic blood pressure-postdialysis diastolic blood pressure; △MAP, predialysis mean arterial pressure-postdialysis mean arterial pressure; HDL, high-density lipoprotein; CRP, C-reactive protein; PTH, parathyroid hormone; BMI, Body mass index; IDWG, interdialytic weight gain; BSA, body surface area; LV, left ventricular; NS, not significant.

**Table 5. Comparisons of baPWV according to categorical variables**

		Mean±SD	p
Gender	Male (n=31)	18.1±4.4	NS
	Female (n=34)	19.4±5.9	
Diabetes	Yes (n=26)	21.5±5.4	<0.01
	No (n=39)	17.0±4.3	
Smoking	Yes (n=23)	17.7±3.8	NS
	No (n=41)	19.4±5.9	
RAS blockades	Yes (n=19)	20.3±6.1	NS
	No (n=46)	18.2±4.8	
Statins	Yes (n=18)	21.5±5.7	<0.01
	No (n=47)	17.8±4.7	

baPWV, brachial-ankle pulse wave velocity; RAS, rennin angiotensin system; NS, not significant.

predialysis and postdialysis were 80.3±12.9 mmHg and 64.6±14.0 mmHg. Predialysis and postdialysis SBP were 169.1±14.1 mmHg and 150.3±16.0 mmHg, and predialysis and postdialysis DBP were 88.8±6.1 mmHg and 85.8±6.2 mmHg. LV mass index was 71.6±13.2 g/m<sup>2.7</sup>, and baPWV was 18.9±5.2 m/s. These parameters have no significant difference between both genders.

In simple regression analysis, baPWV was significantly correlated with age, predialysis SBP, postdialysis SBP, HDL cholesterol and creatinine, and marginally correlated with uric acid (Table 4). In the diabetic group, baPWV was significantly higher than in the nondiabetic group (21.5±5.4 m/s vs 17.0±4.3 m/s, p<0.01). baPWV was 21.5±

**Table 6. Multiple regression analysis of factors associated with baPWV**

Variables	Model 1 $\beta$	Model 2 $\beta$
Age (years)	12.6*	14.3*
Predialysis SBP (mmHg)	8.5*	8.8*
Diabetes	272.3*	279.0*
Statins	108.5	57.0
RAS blockades	204.3	222.4
HDL Cholesterol (mg/dL)	12.1	12.5
Creatinine (mg/dL)	-12.7	5.4
Uric acid (mg/dL)	-8.1	-21.1
Smoking	-	-214.7
IDWG/BSA (kg/m <sup>2</sup> )	-	-7.4
BMI (kg/m <sup>2</sup> )	-	-11.2
R <sup>2</sup>	0.46	0.49

baPWV, brachial-ankle pulse wave velocity; SBP, systolic blood pressure; RAS, rennin angiotensin system; HDL, high-density lipoprotein; IDWG, interdialytic weight gain; BSA, body surface area; BMI, Body mass index.

\* $p < 0.05$ .

5.7 m/s and 17.8±4.7 m/s in the statin group and in the nonstatin group (Table 5). There were no significant correlations in gender, smoking habits, and RAS blockades.

Factors associated with baPWV were evaluated by multiple regression analysis (Table 6). Increased baPWV was associated positively with age, predialysis SBP, and diabetes (model 1). In model 2, which included 11 variables, the result was similar to that of model 1.

## Discussion

In ESRD patients, cardiovascular mortality is due to atherosclerosis of large arteries. Atheroma of the vessel intima causes ischemia and/or infarction downstream from the lesions and fatal cardiovascular diseases. Sclerotic change of arterial walls, that is stiffening, attributes to an increase in systolic pressure and pulse pressure and a decrease in diastolic pressure. The outcomes of these changes are an increase of LV afterload, LV hypertrophy, and a decrease in coronary blood flow<sup>3, 10</sup>.

Arterial stiffness has been measured as aortic stiffness using the tonometric sensor on the carotid and femoral arteries. Increased aortic stiffness was associated with age, hypertension, diabetes, and ESRD, and well established as independent predictor of all-cause and cardiovascular mor-

tality in the general population as well as in ESRD patients<sup>4</sup>. CfPWV reflects aortic PWV. However this technique has low reproducibility because of technical difficulty.

On the other hand, baPWV is automatically measured by the oscillometric technique using blood pressure cuffs over arms and ankles, which is simple and reproducible as compared with the cfPWV measurement. While cfPWV assesses the stiffness of large, central arteries such as the aorta, baPWV reflects the both central and peripheral arteries. Therefore, it had been controversial whether baPWV can substitute for cfPWV in prediction of cardiovascular mortality. However, recent several studies reported that baPWV was the predictor of cardiovascular mortality in the general population as well as in ESRD patients<sup>5, 11</sup>) and associated with increasing age and blood pressure in the general population<sup>12</sup>), although a weaker predictor than ABPI in the prediction of cardiovascular mortality<sup>5</sup>).

In Korean ESRD patients on hemodialysis, few studies have investigated the factors associated with baPWV. Our study showed that baPWV was independently associated with age, systolic pressure, and diabetes, which is consistent with a previous Japanese study<sup>5</sup>). However, vascular calcification related factors such as a calcium-phosphate product and abdominal aortic calcium deposit index were also associated with baPWV in other reports<sup>5, 13</sup>). Aging induces the gradual replacement of the degenerated elastic fibers by collagenous fibers and calcification of the arterial wall. Also deterioration of endothelial function causes a decrease in nitric oxide secretion, an increase of endothelin secretion, and vascular smooth muscle growth. These changes promote arterial wall hypertrophy and stiffness and substantially increase PWV<sup>14</sup>). Tomiyama et al. reported that age is an important determinant independent of blood pressure in the healthy subject<sup>12</sup>). This association was remarkably strong in females compared with males, which suggests effect of gender on PWV. In contrast, Shoji et al. did not find any difference between both genders<sup>15</sup>) and this is similar to our present study (male 18.1±4.4 m/s vs female 19.4±5.9 m/s,  $p = \text{NS}$ ).

In accordance with many previous studies, diabetes was associated with increased PWV<sup>5, 11, 15, 16</sup>. The nonenzymatic glycosylation of matrix proteins caused by chronic hyperglycemia, increased intima-media thickness, or medial calcification is considered as the pathogenesis of arterial stiffness<sup>17</sup>. When combined with hypertension, these changes are amplified. Among local hormonal mediators, angiotensin II is particularly important, as it induces hypertrophy of vascular smooth muscle cells and increases collagen production by fibroblasts, mediated by the effects of this peptide on the AT1 receptors<sup>16</sup>. Theoretically arterial stiffness can be decreased by the direct effect of hypertension itself and indirect effect through angiotensin II. Guerin et al. reported that angiotensin converting enzyme inhibitor reduced arterial stiffness and improved survival regardless of antihypertensive effect<sup>8</sup>. Uchida found that telmisartan produced a significant decrease in baPWV at 3 months after telmisartan treatment in patients with mild to moderate hypertension<sup>18</sup>. However, as shown in the present study, angiotensin converting enzyme inhibitor didn't have any association with baPWV in ESRD patients. This result suggests ESRD patients have different vascular characteristics from uncomplicated hypertensive patients.

ESRD patients are persistently exposed to oxidative stress, which causes oxidation of LDL-cholesterol and acceleration of atherosclerosis<sup>19</sup>. Statin may improve arterial distensibility by inhibition of the cholesterol oxidation and promotion of nitric oxide production<sup>20</sup>. Ichihara et al. reported that baPWV was significantly reduced by 6-month administration of fluvastatin in ESRD patients<sup>21</sup>. Contrary to their result, in simple regression analysis of this present study, baPWV was higher in the statin group than in the nonstatin group (21.5±5.7 m/s vs 17.8±4.7 m/s,  $p < 0.01$ ). However, when adjusted for age, systolic pressure, diabetes, HDL-cholesterol, creatinine, and uric acid, the association disappeared.

This study contains some limitations. Number of subjects may be too small for other factors, but age and blood pressure were proven to have an influence on baPWV. Also, because we didn't evaluate the hemodialysis ad-

equacy, it may not be relevant to analyze the effect of some variables related with hemodialysis such as blood pressure, interdialytic weight gain, creatinine, calcium, and phosphorous. Finally, the equation coefficient used to calculate baPWV is based on the Japanese population, it is questionable whether we may apply the same equation to Koreans. Despite these limitations, it is meaningful that the present study suggests that baPWV measurement can be used to screen the high risk groups of cardiovascular mortality such as old age, hypertension, and diabetes.

In conclusion, the present study showed that age, systolic pressure, and diabetes were independently associated with baPWV. Although further longitudinal studies are necessary, baPWV can be applied to screen high risk patients as mentioned above and early intervention can reduce the cardiovascular mortality in ESRD patients.

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