Original Article

Higher Brachial-Ankle Pulse Wave Velocity Is Associated with More Advanced Carotid Atherosclerosis in End-Stage Renal Disease

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Brachial-ankle pulse wave velocity is a new measure of arterial stiffness. We examined whether higher brachial-ankle pulse wave velocity is associated with more advanced carotid atherosclerosis and left ventricular hypertrophy in patients with end-stage renal disease, and whether this effect would be mediated by the influence of wave reflection on central arterial pressure. In 68 patients with end stage renal disease, we examined blood pressures, brachial-ankle pulse wave velocity and the augmentation index of the left common carotid artery, a measure of the impact of wave reflection on the systolic peak in central arteries. The degree of carotid atherosclerosis was quantified by a plaque score and maximum intimal-medial thickness. Echocardiography was used to determine the left ventricular mass index. In simple regression analysis, brachial-ankle pulse wave velocity was correlated with both plaque score and maximum intimal-medial thickness (r=0.420, p<0.001 and r=0.452, p<0.0005, respectively) but not with left ventricular mass index. Multiple regression analysis was performed with the plaque score or maximum intimal-medial thickness as the dependent variable and brachial-ankle pulse wave velocity and known clinical risk factors as the independent variables. The brachial-ankle pulse wave velocity was an independent risk factor for both plaque score (β=0.006, p=0.004) and maximum intimal-medial thickness (β=0.008, p=0.04). Independent risk factors for left ventricular mass index were left ventricular diastolic dimension (β=3.509, p=0.000007) and augmentation index (β=0.580, p=0.04). The brachial-ankle pulse wave velocity was unrelated to augmentation index in patients with end stage renal disease. In conclusion, higher brachial-ankle pulse wave velocity was found to be a risk factor for carotid atherosclerosis in patients with end-stage renal disease; this effect was independent of the influence of wave reflection on central arterial pressure. The brachial-ankle pulse wave velocity was unrelated to left ventricular structure. (*Hypertens Res* 2005; 28: 9–14)

***Key Words*: end-stage renal disease, atherosclerosis, left ventricular hypertrophy, augmentation index, pulse wave velocity**

Introduction

The risk of cardiovascular death is 10 times higher in patients with end-stage renal disease (ESRD) than in the general population (*1*). The higher cardiovascular death rate may be attributable to pathophysiologic causes leading to advanced atherosclerotic changes of the arterial wall and left ventricular

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hypertrophy (LVH).

One of the most important factors commonly contributing to atherosclerosis and LVH in ESRD may be increased end-systolic stress, which has been shown to result from increased stiffness of large arteries and augmentation of systolic pressure in central arteries by wave reflection (*2*, *3*). Some studies have linked presence of vascular calcification in ESRD patients to increased aortic stiffness as assessed by pulse wave velocity (PWV) (*4*). Increased influence of arterial wave reflection in uremic patients has been found to be directly related to LVH (*5*). Moreover, both aortic stiffness and arterial wave reflection in the central arteries have been shown to independently predict cardiovascular death in patients with ESRD (*6*–*8*). Therefore, repeated evaluation of arterial pathophysiologic characteristics is critical for an improved understanding of altered cardiovascular function in ESRD, and ultimately for the formulation of more specific prevention strategies.

PWV has been examined most often in the carotid and femoral arteries. Recently, however, a new PWV measurement based on analysis of brachial and ankle sites was developed (*9*, *10*). Since brachial-ankle PWV (baPWV) reflects the properties of lower limb arteries as well as the aorta, it does not necessarily agree with carotid-femoral PWV (*9*). However, hypertensive patients with more advanced organ damage have been shown to have higher baPWV (*9*). Nakamura *et al*. have found that the length of abdominal aorta affected by calcification, a known risk factor for cardiovascular morbidity and mortality, also independently predicted baPWV (*11*). Accordingly, baPWV could be used as a new measure of vascular damages predisposing to cardiovascular events.

The aim of this study was to examine the clinical significance of baPWV measurements in ESRD. We examined the relationship between baPWV and carotid atherosclerosis as well as LVH in patients undergoing maintenance hemodialysis. To further clarify whether increased arterial stiffness as assessed by baPWV affects vascular or cardiac alterations through modulation of central arterial pressure, we simultaneously measured the augmentation index (AI) in the common carotid artery.

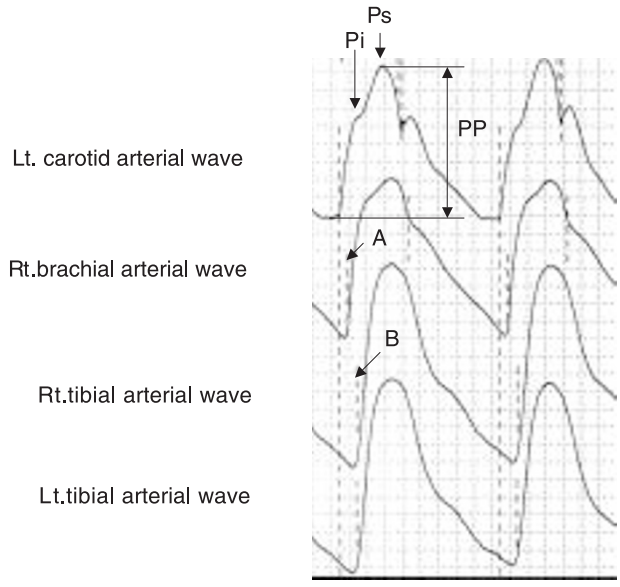

Fig. 1. *Simultaneous recording of arterial waves at left common carotid and right brachial and bilateral tibial sites in a 70-year-old man with end-stage renal disease. Lines A and B denote the foot of the right brachial arterial wave and that of the right tibial arterial wave, respectively. Ps and Pi indicate the late systolic peak of the left common carotid arterial wave and the inflection point separating the late and early systolic peaks. The ratio of (Ps – Pi) to PP was defined as an augmentation index.*

Methods

Subjects

Sixty-eight ESRD patients (age, 59.6±1.6 years; range, 32 to 81 years) who were undergoing maintenance hemodialysis therapy were studied. All participants were given a standardized questionnaire concerning demographic data, past medical history, current medications, and personal habits such as cigarette smoking. A self-reported personal history of cardiovascular symptoms also was recorded. Patients with peripheral arterial disease who had an ankle pressure index below 0.9 were not included, as this would preclude determination of the baPWV (*9*). Blood was drawn in the morning after overnight fasting for at least 12 h. Fasting blood sugar, total cholesterol, high density lipoprotein (HDL)-cholesterol, and triglyceride concentrations were measured.

Duration of dialysis therapy ranged from 1 to 26 years (mean, 4.4 years). Seven patients had a past history of coronary artery disease, while 2 had a history of cerebrovascular disease and 3 had a history of aortic aneurysm. None had a clinical cardiovascular event during the 6 months preceding the study. Causes of renal failure were diabetes in 22 patients and nondiabetic etiology in 46. Fifty-seven ESRD patients (87%) were taking antihypertensive medications. Medication for hypertension included calcium-channel blockers (77%), angiotensin-converting enzyme inhibitors (33%), angiotensin II receptor blockers (54%), β- or αβ-receptor blockers (7%), sympatholytic agents (30%), and diuretics (26%). Five patients (7%) took statins for treatment of dyslipidemia. Patients underwent dialysis three times weekly, all *via* an arteriovenous shunt. For ethical reasons, subjects with antihypertensive medications were studied without "washing out" antihypertensive medications. This study was approved by the Ethics Committee of Tohoku Rosai Hospital. The purpose of this study was fully explained, and all patients gave informed consent.

Table 1. Clinical Characteristics of Patients with End-Stage Renal Disease

Age (years)	59.6±1.6	(32–82)
Male/female	46/22	
Smoking (%)	41 (60%)	
Body mass index (kg/m^2)	22.0±2.8	(14.7–28.1)
Fasting blood sugar (mg/dl)	116±5	(64–278)
Total cholesterol (mg/dl)	166±4	(106–244)
Triglyceride (mg/dl)	116±9	(30–548)
HDL (mg/dl)	42±2	(21–86)
Systolic blood pressure (mmHg)	154±2.4	(114–198)
Diastolic blood pressure (mmHg)	88±1.3	(57–117)
Pulse pressure (mmHg)	66±1.8	(38–107)
Heart rate (bpm)	70±1.4	(49–110)
baPWV (cm/s)	1,836±48	(1,217–3,070)
Augmentation index (%)	24.6±1.8	(−24–57)
Left atrial dimension (mm)	42.6±0.8	(26.8–61.2)
Left ventricular diastolic dimension (mm)	51.5±0.9	(37.0–69.5)
Left ventricular mass index (g/m^2)	148±5.1	(64.9–268.7)
Ejection fraction	0.65±0.01	(34.0–79.0)
E/*A* ratio	0.92±0.05	(0.39–2.76)
max IMT (mm)	2.0±0.9	(0.50–3.50)
Plaque score	6.2±5.4	(0.0–19.2)

HDL, high density lipoprotein; baPWV, brachial-ankle pulse wave velocity; max IMT, maximum intimal-medial thickness.

Brachial-Ankle PWV and Carotid AI

The baPWV and carotid AI were studied using a new device, the AT-form PWV/ABI (Colin, Komaki, Japan), which has been described in detail elsewhere (*9*, *10*). In brief, the instrument simultaneously records right and left brachial and tibial arterial pressure wave forms, lead I of the electrocardiogram, and a phonocardiogram. A carotid tonometry sensor also was coupled with this device for analysis of the common carotid arterial wave (Fig. 1). Occlusion cuffs, which were connected to both plethysmographic and oscillometric sensors, were placed around both arms and ankles for pulse wave analysis and blood pressure measurements. The time difference between the brachial and ankle arterial pressure wave (ΔT) was determined by the wave front velocity theory (*12*). The distance between the arm and ankle (D) was calculated based on anthropometric data for the Japanese population. Finally, the baPWV was calculated as $D/\Delta T$. In ESRD patients, pulse wave analysis of the brachial artery was carried out only on the non-shunt side.

The AI was examined by analysis of the left common carotid arterial wave (Fig. 1). The carotid arterial wave was analyzed using a multielement tonometry sensor (*13*). The common carotid arterial wave was digitized at 1,200 Hz. After identification of the early and late systolic peaks and the inflection point that separated them, we measured the height of the shoulder and the height above the shoulder (ΔP) of the late systolic peak attributable to the return of wave reflections from reflecting sites (*14*, *15*). The ratio of ΔP to the carotid pulse pressure defined the augmentation index (%), which was used to estimate the effect of wave reflections in central arteries.

Echocardiography

Two-dimensional M-mode echocardiography was performed by an experienced echocardiographer using a commercially available instrument (Nemio 30; Toshiba, Tokyo, Japan) equipped with a 2.5 to 3.75-MHz sector probe. Left ventricular internal diameters and parietal thickness were calculated from two-dimensional guided M-mode tracing and measured in three to five consecutive cardiac cycles according to the recommendations of the American Society of Echocardiography. Left ventricular mass was calculated according to the Penn convention and normalized with respect to body surface area. The ejection fraction (EF) was estimated as the ratio of left ventricular end-systolic to diastolic volume. The early diastolic peak flow velocity (E), late diastolic peak flow velocity (A), and ratio of E to A (E/A) were recorded using a sample volume at the mitral leaflet tips. The intra- and inter-observer coefficients of variation for the left ventricular mass index (LVMI) were 7.9% and 8.4%, respectively (*16*).

Carotid Ultrasonography

The degree of carotid atherosclerosis was evaluated ultrasonographically. Ultrasound examinations were performed by an experienced sonographer using an 8 to 15 MHz scanner

Table 2. Correlation Coefficients Determined by Simple Regression Analysis between max IMT or Plaque Score and Other Variables in Patients with End-Stage Renal Disease

Variable	max IMT		Plaque score	
	r	*p*	*r*	*p*
Age	0.438	0.0005	0.476	<0.0001
BMI	0.300	0.02	0.203	0.09
T-Chol	−0.138	0.316	0.032	0.795
HDL	−0.267	0.04	−0.179	0.142
Systolic blood pressure	0.296	0.02	0.242	0.05
Pulse pressure	0.443	0.0004	0.4185	0.0004
LVMI	0.188	0.149	0.288	0.02
baPWV	0.420	0.0008	0.4518	0.0001
AI	0.254	0.05	0.255	0.04

BMI, body mass index; T-Chol, total cholesterol; HDL, high density lipoprotein; LVMI, left ventricular mass ndex; baPWV, brachial-ankle pulse wave velocity; AI, augmentation index.

Table 3. Correlation Coefficients Determined by Simple Regression Analysis between LVMI and Clinical Variables in Patients with End-Stage Renal Disease

	r	*p*
Age	0.217	0.07
BMI	−0.075	0.543
Systolic blood pressure	0.188	0.124
Pulse pressure	0.239	0.04
baPWV	0.063	0.608
AI	0.268	0.02
LVDd	0.606	<0.0001

BMI, body mass index; baPWV, brachial-ankle pulse wave velocity; AI, augmentation index; LVDd, left ventricular diastolic dimension.

(Nemio 30; Toshiba). The protocol involved scanning of both near and far walls of the common carotid artery, the carotid bulb and each of the internal and external carotid arteries (*17*). These arteries were scanned longitudinally and transversely to determine the presence of plaques, defined as localized echo structures encroaching into the vessel lumen for which the distance between the media-adventitia interface and the internal side of the lesion was ≥1.1 mm. We studied the maximum intimal-medial thickness (max IMT) and plaque score as indices of carotid atherosclerosis (*17*) because both parameters have been reported to have prognostic significance (*18*, *19*). The max IMT indicates the maximum wall thickness of the whole carotid arteries, including the plaque lesion. The plaque scores were calculated by summing the maximum thickness in millimeters of plaques in both carotid systems. The details of the method used to calculate the plaque score have been reported previously (*17*, *18*).

Statistical Analysis

All data are expressed as the mean±SD. Correlation coefficients were calculated by Pearson's product-moment or Spearman's rank-order procedures when appropriate. Multiple regression analysis was used to assess independent associations between one dependent and two or more independent variables. A p value less than 0.05 was considered to indicate significance. All analyses were performed using commercially available software for Windows (Stat Flex version 5.0; Stat Flex, Osaka, Japan).

Results

The clinical characteristics of the 68 patients with ESRD are depicted in Table 1. Table 2 shows the correlation coefficients of possible risk factors with max IMT or plaque score in patients with ESRD. Age, systolic pressure, and pulse pressure were positively correlated with both max IMT and plaque score. Body mass index (BMI) was significantly and positively correlated with max IMT. The HDL concentration was negatively correlated with max IMT. The LVMI was positively correlated with the plaque score. Higher baPWV was associated with greater max IMT or plaque score. Similarly, larger AI was associated with a higher value of max IMT or plaque score. The max IMT and plaque score of diabetic patients tended to be greater than those of non-diabetic patients (2.3±0.8 *vs*. 1.9±0.9 mm and 7.4±4.9 *vs*. 5.7±5.7, respectively), but these differences did not reach a statistically significant level.

Since the above risk factors are expected to interfere with each other, multiple regression analysis was performed to explore the independent impact of baPWV on carotid atherosclerosis. The baPWV was found to be an independent contributor to max IMT (β=0.008, p=0.04) along with BMI (β=0.145, p=0.0002) and AI (β=0.02, p=0.008). Similarly, the baPWV was a significant contributor to plaque score (β=0.006, p=0.004) along with BMI (β=0.635, p=0.005), AI (β=0.108, p=0.02) and LVMI (β=0.627, p=0.05). The determination coefficients of these models were 0.420 for max IMT and 0.432 for plaque score, respectively. The max IMT was well correlated with plaque score (r=0.810, p<0.000001) in the 68 patients with ESRD. Figure 2 shows a scatter plot for baPWV and plaque score. As shown in Fig. 3, the baPWV was unrelated to the AI (r=0.008, n.s.), suggesting that higher baPWV was not associated with greater wave reflection in the central arteries.

In simple regression analysis, the LVMI was significantly correlated with left ventricular diastolic dimension, augmentation index, and pulse pressure, and marginally correlated with age in ESRD patients (Table 3). Multivariate regression analysis indicated that LVDd (β=3.509, p=0.000007) and AI (β=0.580, p=0.04) were independent contributors to LVMI in ESRD patients. The determination coefficient of this model was 0.445.

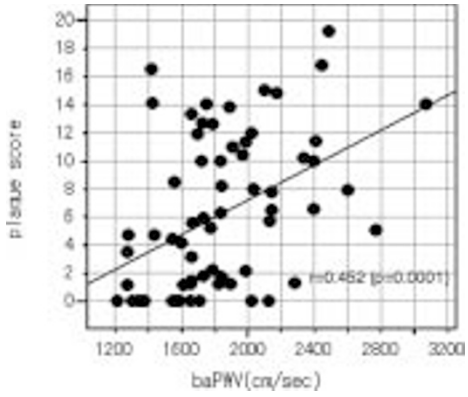

Fig. 2. *Scatter plot of the baPWV and plaque score in 68 patients with ESRD.*

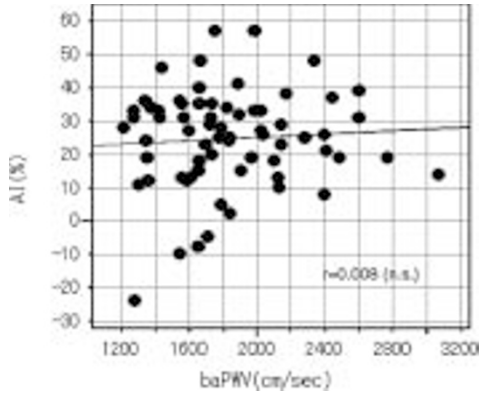

Fig. 3. *Scatter plot of the baPWV and the augmentation index in 68 patients with ESRD.*

Discussion

The baPWV is a new measure of arterial stiffness that takes account of the properties of both the aorta and lower limb arteries. Accordingly, baPWV reflects arterial stiffness in a different arterial territory than carotid-femoral PWV (cfPWV), which is determined mainly by properties of the aorta. We have shown that baPWV does not agree with the cfPWV (*9*), although they correlated with each other. Thus, results for cfPWV cannot be taken as equivalent to the baPWV. The cfPWV has shown clinical and prognostic significance in patients with ESRD (*2*, *4*, *6*), but these matters have not been addressed for baPWV. We therefore examined whether baPWV is related to the degree of carotid atherosclerosis or LVH in patients with ESRD.

Both carotid plaque score and max IMT were significantly and positively associated with baPWV, independently of other risk factors such as BMI, LVMI, and AI. Thus, higher baPWV was associated with more marked atherosclerotic changes in patients with ESRD. Our data are consistent with recent reports showing a significant association between higher baPWV and atherosclerotic vascular lesions in nonuremic patients. Nakamura *et al*. have reported that length of abdominal aortic calcification independently predicted baPWV (*11*). Moreover, high baPWV has been shown to independently predict the presence of significant coronary artery occlusion in male patients (*20*). Taken together, these findings indicate that baPWV could be used as a marker of atherosclerotic changes of the arterial walls that predispose to cardiovascular events.

Two likely explanations could link baPWV and carotid atherosclerosis in ESRD. First, atherogenic changes in the arterial wall include smooth muscle cell proliferation, deposition of lipid, and accumulation of collagen, elastin, and proteoglycans (*21*). These changes often are associated with thickening as well as stiffening of the arterial wall. Chronic renal failure and/or metabolic alterations secondary to renal failure have been suggested to promote atherosclerosis (*22*). A high prevalence of diabetes among ESRD patients also may explain coexistence of carotid atherosclerosis and systemic arterial stiffening, since diabetes contributes to the severity of atherosclerosis and arterial stiffening in ESRD (*23*).

Our data are consistent with previous reports in some points. First, a higher AI was associated with greater max IMT or plaque score and LVMI in ESRD patients, meaning that an increased impact of wave reflection in the central arteries could promote both carotid atherosclerosis and cardiac hypertrophy. These data support the finding that increased arterial wave reflection independently predicts cardiovascular mortality in ESRD (*8*). Second, LVMI was an independent contributor to carotid plaque score in ESRD patients. These results agree well with reports showing LVH to be a risk factor for carotid atherosclerosis (*24*, *25*) or ischemic stoke (*26*) in patients with essential hypertension. Our data further extended this finding to ESRD.

Although the cfPWV has been reported to be an independent contributor to AI in the common carotid artery (*3*), the baPWV was not related to this measure. This means that baPWV may have much less influence on the wave reflection in the central artery than cfPWV. The different hemodynamic influence on central arterial pressure may be explained in terms of the different arterial territories examined. The arterial wave generated by ventricular ejection travels along the arterial wall, and may return at the level of aortic bifurcation (*27*). Therefore, the PWV in the aorta would critically influence the timing and intensity of the reflected wave. The absence of a correlation between baPWV and AI suggests that baPWV may reflect a much shorter length of aorta than the cfPWV. In this context, baPWV was less influenced by the cushioning properties of the aorta, weighing against the use of baPWV as a marker of cardiac afterload in ESRD. This hypothesis is further supported by the fact that baPWV was unrelated to LVH.

Our data are inconsistent with the recent report showing that baPWV was significantly and positively correlated with

LVH in patients maintained on hemodialysis (*28*). The reason for the discrepancy is unclear, but the differences in organ damage among the subjects may have played a role. Compared with our data, the baPWV was higher (2,124 cm/s) and the LVMI was greater (186 g/m^2) in the previous report, although there was no difference in the age and blood pressures of subjects between the two studies. Thus, we cannot rule out the possibility that left ventricular structure may be influenced by baPWV in hemodialysis patients with stiffer arterial trees.

In conclusion, higher baPWV was associated with more advanced carotid atherosclerosis in ESRD, and this effect was independent of the influence of wave reflection on central arterial pressure. The greater AI, but not the higher baPWV, was a significant contributor to LVH. Thus simultaneous evaluation of the baPWV and AI of the common carotid artery is recommended for proper analysis of arterial function in patients with ESRD.

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