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ORIGINAL ARTICLE

Brachial-ankle pulse wave velocity as a marker of subclinical organ damage in middle-aged patients with hypertension

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KEYWORDS
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Summary
Objective: This study was conducted to clarify whether the brachial-ankle pulse wave velocity (baPWV) might serve as a marker of target organ damage in middle-aged hypertensive subjects.
Methods and results: Multivariate linear regression analysis demonstrated that while the baPWV showed a significant relationship to the intima-media thickness of the carotid artery (IMT), no such relationship was observed between the baPWV and the left ventricular mass index as assessed by echocardiography or the estimated glomerular filtration rate in either the 162 hypertensive patients who had never previously received antihypertensive medication or the 269 hypertensive patients who were under antihypertensive medication for at least 1 year. Receiver—operator characteristic (ROC) curve analysis suggested that a baPWV = 18 m/s was the best cutoff value to identify increased IMT in hypertensive patients who had never previously received antihypertensive medication (area under curve = 0.77). Binary logistic regression analysis demonstrated that the odds ratio (OR) of a baPWV of $\geq$18 m/s for identifying increased IMT {OR = 7.38 (1.94—28.05)} was significant, even after adjustments. In hypertensive patients who had been under antihypertensive medication for at least 1 year, however, the area under the curve and OR were only modest.

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Conclusion: The baPWV may be a marker of carotid atherosclerosis, rather than of left ventricular hypertrophy or renal insufficiency, especially in middle-aged hypertensive subjects (subjects in their 30s to 60s), not only in those who have never previously received antihypertensive medication, but also in those who are under antihypertensive medication.

Introduction

Recent studies have demonstrated that increased arterial stiffness is an independent risk factor for cardiovascular disease [1—5]. In Japan, the brachial-ankle pulse wave velocity (baPWV) is frequently used as a marker of arterial stiffness [6,7]. However, it has not yet been clarified whether baPWV might also be a marker of subclinical organ damage. Left ventricular hypertrophy (LVH), increased intima-media thickness (IMT) of the common carotid artery, and low estimated glomerular filtration rate (eGFR) are recognized as signs of subclinical target organ damage in hypertension [8—10]. The present cross-sectional study was conducted to clarify whether the baPWV might serve as a marker of subclinical target organ damage (i.e., LVH, increased IMT of the common carotid artery, and/or low eGFR) in middle-aged hypertensive subjects. With this objective, we attempted to evaluate the associations separately in hypertensive subjects who had never previously received antihypertensive medication and those who had been on antihypertensive medication for at least 1 year, because blood pressure is one of the major determinants of the baPWV [11].

Methods

Subjects and protocol

From September 2001 to June 2007, 431 consecutive middle-aged subjects (in their 30s to 60s) with hypertension (of which 162 had never previously received antihypertensive medication and 269 consecutive hypertensive subjects who had been under treatment with antihypertensive medication for at least a year) who were seen at the outpatient department of Tokyo Medical University Hospital were enrolled in this study. Informed consent was obtained from all of the participants. None of the subjects had a history of atherosclerotic cardiovascular diseases, including of symptoms or electrocardiographic evidence of ischemic heart disease, or of arrhythmias. Patients with serious medical problems requiring specific medical treatment were excluded from this study. Furthermore, subjects meeting the following exclusion criteria were also excluded an ankle/brachial systolic blood pressure index (ABI) of less than 0.95, atrial fibrillation and serum creatinine $\geq$2.0 mg/dl [6,7,12]. Blood pressure was measured at the outpatient clinic by the conventional cuff method. Measurement of the baPWV, echocardiography, ultrasonography of the carotid artery, and blood sampling were performed in the morning after the subjects had fasted overnight for 12 h. The study protocol was approved by the Ethics Committee of Tokyo Medical University.

Pulse wave velocity

The baPWV was measured using a volume-plethymographic apparatus (Form/ABI, Colin, Co. Ltd., Komaki, Aichi, Japan). Details of the methodology have been described elsewhere [6,7,12,13]. In brief, the subjects were examined while resting in the supine position. Electrocardiographic electrodes were attached to both wrists, and cuffs were wrapped around both upper arms and ankles. The pulse-volume waveform in the upper arm and ankle were recorded using a semiconductor pressure sensor after the subject had rested for at least 5 min. This method has been validated previously [6]. Usually, the brachial-ankle PWV is represented in the unit of cm/s. In this study, however, the unit was changed to m/s to simplify determination of the cutoff value of the brachial-ankle PWV. Then, the measured value was rounded off to the nearest 1000 (i.e., 1500—1599 cm/s was represented as 15 m/s).

Ultrasonographic examination of the heart and carotid arteries

The left ventricular mass was calculated by transthorachic echocardiography by Devereux's method [14]. The left ventricular mass index (LVMI) was calculated as the left ventricular mass divided by the body surface area. After the echocardiographic examination, both carotid arteries were imaged using an ultrasonographic system equipped with a 10.0-MHz transducer. The inter-observer

Table 1 Clinical characteristics of the hypertensive subjects who had never previously received antihypertensive medication and subjects who had received antihypertensive medication for at least a year

	Never-treated	Medication	*p*-Value
Number of subjects	162	269	
Age (years)	56 ± 10	60 ± 10	$p < 0.01$
Gender (male/female)	93/69	157/112	ns
BMI (kg/m^2)	23.8 ± 3.8	24.0 ± 3.3	ns
Smoking (number of subjects)	36	73	ns
SBP (mmHg)	148 ± 19	130 ± 14	$p < 0.01$
DBP (mmHg)	88 ± 12	77 ± 9	$p < 0.01$
baPWV (m/s)	16.5 ± 3.6	15.5 ± 3.1	$p < 0.01$
LDL (mg/dl)	124 ± 27	119 ± 28	$p < 0.01$
HDL (mg/dl)	59 ± 15	54 ± 24	ns
TG (mg/dl)	115 ± 67	126 ± 67	ns
FPG (mg/dl)	107 ± 23	105 ± 12	ns
LVMI (g/m^2)	120 ± 23	121 ± 27	ns
LVH (%)	90 (55.5)	123 (45.7)	$p < 0.05$
IMT (mm)	0.80 ± 0.14	0.83 ± 0.16	ns
IMT > 0.9 mm (%)	24 (14.8)	67 (24.9)	$p < 0.01$
eGFR (ml/min/1.73 m^2)	76 ± 19	74 ± 20	ns
eGFR < 60 ml/min/1.73 m^2 (%)	24 (14.8)	62 (23.0)	$p < 0.01$
Medication			
CCA	0	191	—
ARB	0	137	—
ACEi	0	28	—
BB	0	39	—
Diuretic	0	54	—
Statin	0	30	—
Oral anti-diabetics	0	4	—

Abbreviations: never-treated = hypertensive subjects who had never previously received antihypertensive medication; medication = hypertensive subjects who had received antihypertensive medication for at least a year; BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; baPWV = brachial-ankle pulse wave velocity; LDL = serum low-density lipoprotein cholesterol; HDL = serum high-density lipoprotein cholesterol; TG = serum triglycerides; FPG = fasting plasma glucose; LVMI = left ventricular mass index; LVH = number of subjects with left ventricular hypertrophy; IMT = intima-media thickness of the common carotid artery as assessed by ultrasound examination; IMT > 0.9 mm = number of subjects with increased intima-media thickness of the common carotid artery; eGFR = estimated glomerular filtration rate; eGFR < 60 ml/min/1.73 m^2 = number of subjects with renal insufficiency; CCA = number of subjects prescribed a calcium channel antagonist; ARB = number of subjects prescribed an angiotensin II receptor blocker; ACEi = number of subjects prescribed an angiotensin converting enzyme inhibitor; BB = number of subjects prescribed a beta-blocker; diuretic = number of subjects prescribed a diuretic; statin = number of subjects prescribed a statin; oral anti-diabetics = number of subjects prescribed oral anti-diabetic medication.

and intra-observer coefficients of variation for the measurement of the left ventricular mass at our institute were 7.2% and 13.5% [15].

Using guided two-dimensional ultrasonography, longitudinal B-mode images, approximately 1 cm proximal to the carotid sinus, were obtained with simultaneous electrocardiographic recordings. The intima-media thickness (IMT) was measured at a site free of any discrete plaques along a 10 mm-long segment of the far wall of the common carotid artery and measured as the distance between the lumen-intima interface and the media—adventitia interface at two points in the right and left common carotid arteries. The means of these four measurements were used for the analysis. The inter-observer and intra-observer coefficients of variation for the measurement of the IMT at our institute were 6.2% and 6.0%.

Laboratory measurements

The plasma levels of high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), triglycerides (TG) and glucose were measured enzymatically. All blood samples were obtained after the subjects had fasted overnight. The eGFR was estimated using the modified modification of diet in renal disease (MDRD) equation; i.e., $0.741 \times 175 \times \text{serum creatinine}^{-1.154} \times \text{age}^{-0.203}$ ($\times 0.724$ in female) [16].

Table 2 Results of univariate linear regression analysis to assess the relationship of the brachial-ankle pulse wave velocity to the parameters of target organ damage in the entire study population, in subjects who had never previously received antihypertensive medication and in subjects who had been under treatment with antihypertensive medication for at least a year

Variable	*r*	*p*-Value
Entire study population ($n = 431$)		
IMT	0.28	<0.01
LVMI	0.13	<0.01
eGFR	−0.21	<0.01
Never received antihypertensive medication ($n = 162$)		
IMT	0.38	<0.01
LVMI	0.22	<0.01
eGFR	−0.19	0.02
Under treatment with antihypertensive medication for at least a year ($n = 269$)		
IMT	0.25	<0.01
LVMI	0.08	0.20
eGFR	−0.24	<0.01

Abbreviations: IMT = intima-media thickness of the common carotid artery as assessed by ultrasound examination; LVMI = left ventricular mass index; eGFR = estimated glomerular filtration rate.

Statistics

Data were expressed as mean ± S.D. Statistical analysis was performed using the SPSS software for Windows, Version 11.0J (SPSS, Chicago, IL). For assessment of the differences between groups, an un-paired *t*-test was applied for continuous variables, and the Chi-square test was applied for categorical variables. Univariate linear regression analysis was performed to evaluate the association between the brachial-ankle PWV and other clinical variables. Multivariate linear regression analysis was applied to evaluate whether the relationships between the brachial-ankle PWV and other parameters of organ damage were independent from other related factors. A receiver—operating characteristic (ROC) curve was used to discriminate patients with target organ damage based on the value of the brachial-ankle PWV. Then, the value with the highest sum of sensitivity + specificity was identified as the cutoff value. Using these cutoff values, the odds ratios for the presence of target organ damage were calculated by binary logistic regression analysis with and without adjustments.

Results

The clinical characteristics of the hypertensive subjects who had never previously received antihypertensive medication and the subjects who had been under treatment with antihypertensive medication for at least a year are shown in Table 1. We defined target organ damage as follows: LVH:LVMI $\geq 125\,g/m^2$ in males and $\geq 110\,g/m^2$ in females; increased IMT:IMT > 0.9 mm; renal insufficiency:eGFR < 60 ml/min/1.73 m^2. The mean age was higher and the blood pressure and baPWV were lower in the subjects who had never previously received antihypertensive medication than in the subjects who had been under treatment with antihypertensive medication for at least a year. While the LVMI, IMT and eGFR were similar in both groups, the prevalence rates of LVH, increased IMT and renal insufficiency were higher in the latter group than in the former group (Table 1).

Univariate linear regression analysis demonstrated significant correlations between the brachial-ankle PWV and the IMT, LVMI and eGFR in each of the entire study population, subjects who had never previously received antihypertensive medication and the subjects who had been under treatment with antihypertensive medication for at least a year (Table 2). Multivariate linear regression analysis demonstrated a significant relationship of the brachial-ankle PWV to the IMT, but not to the LVMI or eGFR, after the adjustments using Model 1 (adjusted for age, gender, body mass index, systolic and diastolic blood pressure, smoking status and the plasma levels of LDL, HDL, TG and glucose) in the group of subjects who had never previously received antihypertensive medication (Table 3). It also demonstrated a significant relationship between the brachial-ankle PWV and IMT after adjustment using Model 2 [adjusted for age, gender, body mass index, systolic and diastolic blood pressure, smoking status, plasma levels of LDL, HDL, TG and glucose and medication {for diabetes

Table 3 Results of multivariate linear regression analysis with adjustments to assess the relationship of the brachial-ankle pulse wave velocity to the parameters of target organ damage in the entire study population, in subjects who had never previously received antihypertensive medication and in subjects who had been under treatment with antihypertensive medication for at least a year

Variable	R^2	Beta	*t*-Value	*p*-Value
Entire study population ($n = 431$)				
IMT	0.21	0.15	2.39	<0.01
LVMI	0.18	0.09	1.39	0.17
eGFR	0.14	−0.06	−1.01	0.32
Adjusted using Model 2 (see text)				
Never previously received antihypertensive medication ($n = 162$)				
IMT	0.29	0.16	1.81	0.04
LVMI	0.27	0.12	1.24	0.22
eGFR	0.13	−0.17	−1.56	0.12
Adjusted using Model 1 (see text)				
Under treatment with antihypertensive medication for at least a year ($n = 269$)				
IMT	0.24	0.11	2.14	0.04
LVMI	0.21	0.07	1.03	0.30
eGFR	0.15	−0.06	−0.86	0.39
Adjusted using Model 2 (see text)				

Abbreviations: IMT = intima-media thickness of the common carotid artery as assessed by ultrasound examination; LVMI = left ventricular mass index; eGFR = estimated glomerular filtration rate.

mellitus, hypercholesterolemia and/or hypertension (calcium channel antagonist, angiotensin II receptor blocker, angiotensin converting enzyme inhibitor, beta-blocker and diuretic)}] in the entire study population and the subjects who had been under treatment with antihypertensive medication for at least a year (Table 3).

Fig. 1 shows the ROC curve of the brachial-ankle PWV to identify subjects with increased IMT in the entire study population, the subjects who had never previously received antihypertensive medication, and the subjects who had been under treatment with antihypertensive medication for at least a year. The best cutoff points were as follows: entire study population (area under curve = 0.68): brachial-ankle PWV = 17 m/s, sensitivity = 57% and specificity = 70%; subjects who had never previously received antihypertensive medication (area under curve = 0.77): brachial-ankle PWV = 18 m/s, sensitivity = 75% and specificity = 74%; subjects who had been under treatment with antihypertensive medication for at least a year (area under curve = 0.66): brachial-ankle PWV = 16 m/s, sensitivity = 63% and specificity = 64%.

The results of a binary logistic regression analysis demonstrated that the odds ratio of the cutoff value of the brachial-ankle PWV for identifying increased IMT was significant in the subjects who had never previously received antihypertensive medication adjusted using Model 1 and in the entire study population and the subjects who had been under treatment with antihypertensive medication for at least a year adjusted using Model 2 (Table 4). The highest odds ratio was found for the subjects that had never previously received antihypertensive medication (Table 4).

Discussion

Atherosclerotic plaques play a key role in the onset of cardiovascular events [17]. The IMT reflects the severity of the atherosclerotic changes in the common carotid artery and is known as a useful parameter to predict future cardiovascular events [9,18]. Arterial endothelial damage causes plaque formation, and abnormalities of the arterial medial layer are thought to be a major determinant of increased arterial stiffness [1—5]. Progression of atherosclerosis produces abnormalities of the arterial medial layer (i.e., vascular smooth muscle hypertrophy and its proliferation and proliferation of connective tissue), and contributes, at least in part, to further increase of the arterial stiffness. In turn, increased arterial stiffness enhances atherogenicity via disturbed endothelial shear stress [1—3]. Thus, atherosclerosis and increased arterial stiffness have a mutual cause—consequence relationship. In the present study, the results of the multivariate linear regression analysis demonstrated a significant relationship of the brachial-ankle PWV to

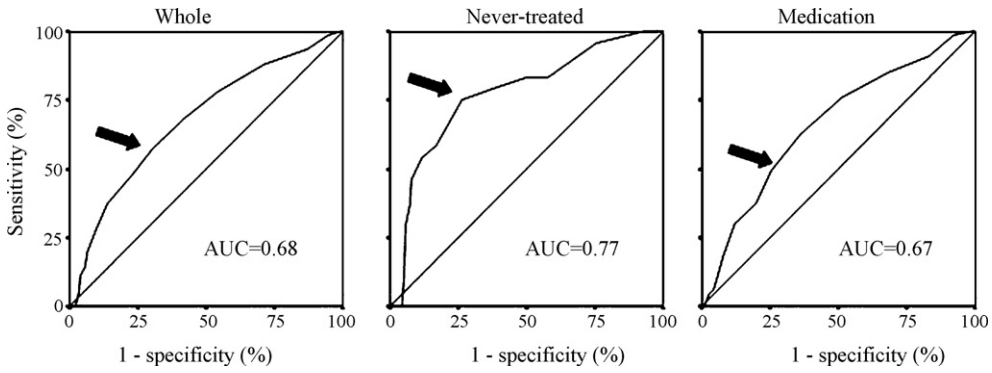

Figure 1 Receiver—operator characteristic curve between brachial-ankle pulse wave velocity and increased intima-media thickness of the common carotid artery in the entire study population, in the group of subjects who had never previously received antihypertensive medication, and in the group of subjects who had received antihypertensive medication for at least a year. *Abbreviations*: whole = entire study population; never-treated = hypertensive subjects who had never previously received antihypertensive medication; medication = hypertensive subjects who had received antihypertensive medication for at least a year; arrow represents the best discriminating point; AUC = area under curve.

the IMT, independent of confounding variables, in not only hypertensive subjects who had never previously received antihypertensive medication, but also in those who had been under treatment with antihypertensive medication for at least a year.

Taking into consideration the results of the ROC curve analysis and binary logistic regression analysis in this study, the brachial-ankle PWV = 18 m/s seemed to be an appropriate cutoff value to identify increased IMT of the common carotid artery in hypertensive subjects who had never previously received antihypertensive medication. Based on the results of this study, it is proposed that a brachial-ankle PWV = 16 m/s might be a suitable cutoff value to identify residual carotid atherosclerosis in hypertensive patients under antihypertensive treatment. However, the area under the curve in the ROC analysis was not large and the odds ratio to identify increased IMT was not sufficiently high. Therefore, the usefulness of the cutoff value may only be modest in patients under treatment.

The European Society of Hypertension and European Society of Cardiology 2007 Guidelines for the Management of Arterial Hypertension has proposed that the PWV be also considered as one of the markers of subclinical target organ damage, and a threshold of the carotid—femoral PWV (cfPWV)

Table 4 Results of binary logistic regression analysis to identify increased intima-media thickness of common carotid artery by the cutoff value of the brachial-ankle pulse wave velocity with and without adjustments in the entire study population, in subjects who had never previously received antihypertensive medication and in subjects who had been under treatment with antihypertensive medication for at least a year

	OR	95% CI	*p*-Value
Entire study population (cutoff value of the baPWV $\geq$17 m/s: n = 431)			
Crude	3.11	1.93—5.01	<0.01
Adjusted	2.33	1.2—4.42	0.01
Adjusted using Model 2 (see text)			
Never previously received antihypertensive medication (cutoff value of the baPWV $\geq$ 18 m/s: n = 162)			
Crude	8.49	3.13—23.06	<0.01
Adjusted	7.38	1.94—28.05	<0.01
Adjusted using Model 1 (see text)			
Under treatment with antihypertensive medication for at least a year (cutoff value of the baPWV $\geq$ 16 m/s: n = 269)			
Crude	2.97	1.68—5.26	<0.01
Adjusted	2.02	1.00—4.37	0.05
Adjusted using Model 2 (see text)			

Abbreviations: OR = odds ratio; CI = confidential interval; baPWV = brachial-ankle pulse wave velocity.

of >12 m/s as a conservative estimate of significant alterations of aortic function [10]. The next logical step would be to confirm the threshold value of the brachial-ankle PWV to predict future cardiovascular events by conducting prospective studies in patients with hypertension.

Increased arterial stiffness causes LVH via increased cardiac afterload and impairment of eGFR via microvascular damage via increased pulse pressure [1,19,20]. After the adjustments, the brachial-ankle PWV showed no significant association with the LVMI or eGFR in this study. The absences of these associations might be partially explained as follows. While central blood pressure estimated by the augmentation index has been reported to be closely correlated with the LVMI [21], the PWV does not show a close correlation with this index [22]. Thus, PWV is not a direct marker of the cardiac afterload. The eGFR in 78—85% of the study subjects in this study was over 60 ml/min/1.73 m^2. The MDRD equation underestimates the eGFR in this range [23], and such underestimation might have contributed, at least in part, to the blunting of the association of the brachial-ankle PWV with the eGFR.

Study limitations

This study had two major limitations, as follows: firstly, in addition to blood pressure, age is also a major determinant of arterial stiffness [11]. In our previous study subjects, age showed a closer correlation with the brachial-ankle PWV ($r = 0.59$, $p < 0.01$) than the systolic blood pressure ($r = 0.42$, $p < 0.01$) or diastolic blood pressure ($r = 0.41$, $p < 0.01$) [24]. In the present study, we have proposed the target brachial-ankle PWVs for hypertensive patients in their 30s to 60s, and the mean age of the subjects in the present study was 55 years. Therefore, the usefulness of the brachial-ankle PWV as a marker of subclinical organ damage in hypertensive patients aged 70 years or older should be examined. Secondly, microalbuminuria is another marker of target organ damage [10], but was not examined in this study.

In conclusion, the brachial-ankle PWV may not be a useful marker to identify LVH and/or low eGFR in subjects with hypertension. On the other hand, the parameter seems to reliably reflect the severity of carotid atherosclerosis in middle-aged subjects (in their 30s to 60s) who have never previously received antihypertensive medication rather than in those who are under antihypertensive medication.

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