Original Article

Clinical Usefulness and Limitations of Brachial-Ankle Pulse Wave Velocity in the Evaluation of Cardiovascular Complications in Hypertensive Patients

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The goal of this study was to clarify the clinical usefulness and limitations of brachial-ankle pulse wave velocity (PWV) to evaluate hypertensive complications, in comparison with carotid-femoral PWV. Patients with essential hypertension (n=296, male/female=161/135; age=61.1±0.7 years) were enrolled. We measured brachial-ankle PWV, femoral-ankle PWV and carotid-femoral PWV simultaneously, and evaluated target organ damage and associated clinical conditions (cerebrovascular and cardiovascular disease) using the World Health Organization classification modified in 1999. Carotid-femoral PWV (p<0.0001; r=0.521) and brachial-ankle PWV (p<0.0001; r=0.478) but not femoral-ankle PWV were significantly correlated with age. Carotid-femoral PWV was significantly higher in patients with associated clinical conditions compared with that in patients with target organ damage (p<0.05) and those with no complications (p<0.0001). Brachial-ankle PWV was significantly higher in patients with associated clinical conditions (p<0.05) and target organ damage (p<0.05) compared to those with no complications, but there was no significant difference in brachial-ankle PWV between these two groups. Moreover, femoral-ankle PWV was significantly lower in patients with associated clinical conditions compared with that in patients with target organ damage (p<0.05). These data suggest that brachial-ankle PWV could underestimate arterial stiffness in hypertensive patients with a history of cardiovascular events. (*Hypertens Res* 2006; 29: 989–995)

***Key Words*: brachial-ankle pulse wave velocity, carotid-femoral pulse wave velocity, hypertensive complication**

Introduction

Arterial stiffness measured by pulse wave velocity (PWV) has been identified as an independent cardiovascular risk and related with mortality and morbidity. These conclusions were reached using PWV measured between the carotid and femoral arteries (cfPWV). To measure PWV using this procedure, the placement of pressure-sensitive transducers on the carotid and femoral arteries requires much skill and more than 20 min. Moreover, placement of a transducer on the femoral artery can be psychologically invasive, especially for women. To overcome these drawbacks, an easier approach for determining brachial-ankle PWV (baPWV) has been developed in Japan, and use of this procedure has been widespread there for a short time. In the last several years, many reports have been published using the baPWV procedure. For example, the use of baPWV as an indicator of atherosclerosis in patients

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with impaired fasting glucose (*1*) and hypertension (*2*), its correlation with aortic calcification (*3*), and its relation to the severity of hypertensive organ damages (*4*, *5*) have all been investigated. Moreover, clinical trials have been performed to clarify the influences of baPWV on metabolic syndrome (*6*) and microalbumineria (*7*). This procedure might be more widely adopted as clinical evidence of its usefulness accumulates. However, these two procedures measure PWV between very different sites—*i.e.*, the ankle to brachium *vs.* the carotid to femur. Previous reports have suggested that muscular arteries such as the femoral or brachial artery shows different stiffness responses than elastic arteries such as the aorta (*8*), and that cfPWV reflects vascular aging more accurately than carotid-radial PWV (*9*). These data indicate that baPWV might not be accurate because of including muscular arteries of lower limbs, which were indicated by femoral-ankle PWV (faPWV). Moreover, there has been no direct comparison of cfPWV, baPWV and faPWV in complicated hypertensive patients. The goal of this study was to clarify the clinical usefulness and limitations of baPWV in the evaluation of hypertensive complications (as a model of clinical atherogenic complications) in comparison with cfPWV and faPWV.

Methods

Study Population

The present clinical investigation was designed as a hospital-based and cross-sectional study to compare the efficacies of baPWV, faPWV and cfPWV in the evaluation of hypertensive complications in patients with essential hypertension. Hypertension was defined as systolic blood pressure (SBP) of more than 140 mmHg and/or diastolic blood pressure (DBP) of more than 90 mmHg and/or administration of antihypertensive drugs. The subjects were 296 patients with essential hypertension, all of whom underwent serial simultaneous measurements of baPWV, faPWV and cfPWV as indices of arterial stiffness in our hospital. We only included patients who had undergo echocardiography, ECG, brain MRI and carotid ultrasonography. We excluded patients whose ankle-brachial index (ABI) was less than 0.9, those who had suffered a cerebrovascular or cardiovascular event within 1 month, and those who had congestive heart failure of grade 3 or higher on the New York Heart Association scale. The protocol was approved by the hospital ethics committee, and written informed consent was obtained from all the subjects. Among the 296 subjects, 130 were not being treated with any antihypertensive drugs, and 166 patients were being treated with one or more antihypertensive drugs. Among the 166 patients being treated with antihypertensives, 101 were taking a calcium antagonist, 73 an angiotensin II receptor antagonist, 50 an angiotensin-converting enzyme (ACE) inhibitor, 26 a β-blocker, 26 a diuretic and 3 an α-blocker.

Table 1. Patients' Characteristics

	Total	No treatment
Number	296	130
Male/female	161/135	70/60
Age (years old)	61±0.7	58±1.2
Height (cm)	160±0.5	161±0.8
Weight (kg)	62.9±0.7	63.9±1.2
BMI (kg/m^2)	24.4±0.2	24.5±0.3
Hyperlipidemia (%)	61	58
Diabetes (%)	19	19
SBP (mmHg)	148±1.4	153±2.3
DBP (mmHg)	85±0.9	87±1.4
TC (mmol/l)	5.37±0.05	5.49±0.09
TG (mmol/l)	3.79±0.16	3.89±0.30
HDL-C (mmol/l)	1.43±0.02	1.48±0.04
FBG (mmol/l)	5.91±0.10	5.67±0.12
No complications (%)	55	62
Target organ damage (%)	30	28
Associated clinical condition (%)	15	10
CAD (%)	7.4	1.6
Stroke (%)	6.6	5.5
PAD (%)	4.7	1.6

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; FBG, fasting blood glucose; CAD, coronary artery disease; PAD, peripheral artery disease.

Target Organ Damage and Associated Clinical Conditions

We evaluated organ damage due to hypertension according to the World Health Organization (WHO)–International Society of Hypertension (ISH) classification modified in 1999 (*10*). We evaluated the target organ damages (TOD) according to the 1999 WHO-ISH guidelines—*i.e.*, left ventricular hypertrophy (LVH), retinal artery narrowing, proteinuria (more than 20 mg/l), increased plasma creatinine concentration (1.2–2.0 mg/dl) and carotid plaque. LVH was considered to be present in patients with a septal and/or posterior wall thickness of more than 12 mm (the Sokolow and Lyon criterion) as determined by ECG and/or echocardiography. Carotid plaque was determined by carotid ultrasonography as a score of 5 or more as previously reported (*11*). Retinal artery narrowing was determined as grade 2, 3, or 4 of the Scheie classification by an independent ophthalmologist. A specially trained technician examined the echocardiograms and carotid ultrasonograms (Power Vision 6000; Toshiba, Tokyo, Japan) and took the mean of three examinations as representative data for this study.

We also evaluated the associated clinical conditions (ACC) according to the 1999 WHO-ISH guidelines—*i.e.*, cerebrovascular disease by brain MRI, computed tomography,

Table 2. Each PWV Correlated with Age

	cfPWV (m/s)	baPWV (m/s)	faPWV (m/s)
Total			
Mean±SEM	9.35±0.10	17.08±0.20	11.45±0.10
Correlation with age			
C.C.	0.521	0.478	0.073
p value	<0.0001	<0.0001	0.2188
No treatment			
Mean±SEM	9.11±0.15	17.12±0.30	11.55±0.14
Correlation with age			
C.C.	0.585	0.567	0.178
p value	<0.0001	<0.0001	0.0495
Treatment			
Mean±SEM	9.53±0.13	17.04±0.27	11.37±0.14
Correlation with age			
C.C.	0.449	0.431	0.019
p value	<0.0001	<0.0001	0.8124

C.C., correlation coefficient.

Table 3. Clinical Background Classified by Hypertensive Complications

	No complication	TOD	ACC
Number	164	88	44
Male/female	77/87	50/38	34/10**
Age (years old)	60±0.9	61±1.5	66±1.3**,#
Height (cm)	159±0.7	160±1.0	161±1.0
Weight (kg)	62.1±1.0	64.6±1.3	62.3±1.6
BMI (kg/m^2)	24.3±0.3	25.0±0.4	24.0±0.6
Hyperlipidemia (%)	64	55	59
Diabetes (%)	16	16	34*
SBP (mmHg)	148±1.8	150±2.7	147±3.8
DBP (mmHg)	86±1.1	86±1.7	81±2.2#
TC (mmol/l)	5.49±0.08	5.21±0.09*	5.10±0.15*
TG (mmol/l)	3.85±0.23	3.82±0.27	3.55±0.31
HDL-C (mmol/l)	1.49±0.04	1.37±0.04	1.35±0.06
FBG (mmol/l)	5.77±0.12	5.77±0.12	6.89±0.49**,##
ABI	1.13±0.01	1.14±0.01	1.07±0.02**,##

TOD, target organ damage; ACC, associated clinical condition; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; FBG, fasting blood glucose; ABI, ankle-brachial index. *$p<0.05$, **$p<0.01$ *vs*. No complication; #$p<0.05$, ##$p<0.01$ *vs*. TOD.

neurological findings; coronary artery disease (CAD) by ECG, echocardiogram, typical symptoms; congestive heart failure; and peripheral artery disease (PAD) without ulceration and gangrene. Moreover, we evaluated lacunar infarction by brain MRI.

Pulse Wave Velocity Measurement

For the PWV measurements, participants visited the hospital in the morning; they were instructed not to take any antihypertensive drugs, nitrate, or aspirin for the 8 h preceding their visit. Measurements were performed in the morning with each patient in the supine position after 30 min of rest. After baPWV measurement, cfPWV measurement was performed in a controlled environment at 22±2°C. Three measurements taken 2 min apart were averaged. The intra-observer coefficient of variation (CV) was calculated using 3 measurements from each of 7 healthy men. The intra-observer CV for baPWV was 3.4±1.8% and the intra-observer CV for cfPWV was 2.8±1.2%.

We determined cfPWV using a model FCP-4731 (Fukuda Denshi Co., Tokyo, Japan), which allowed on-line pulse wave

recording and automatic calculation, using the previously reported method (*12*). Briefly, the pulse waveforms of the right carotid and femoral artery were recorded noninvasively using a TY-306-Fukuda pressure-sensitive transducer (Fukuda Denshi Co.), and heart sound was recorded at the same time. We directly measured the distance between the second intercostal portion of the right sternum and right femoral artery sensor in place of the aortic length from the aortic valve and femoral artery. A preprocessing algorithm automatically analyzed the gain in each waveform and adjusted it for equality of the two signals.

To evaluate baPWV, we used a device (AT-form PWV/ABI; Nippon Colin, Komaki, Japan) that can simultaneously monitor bilateral brachial and ankle pressure wave forms by the volume plethysmographic method, with optional tonometry sensors for carotid arterial wave measurements (*13*). We also placed the plethysmographic sensor on the left femoral artery to determine faPWV. This procedure automatically calculates the distances of these sensors from the height of each subject. To evaluate baPWV, the time duration between brachial wave form and ankle wave form was automatically calculated as the heart-ankle time duration minus the heart-brachial time duration.

Statistical Analysis

Data were analyzed with JMP ver. 4 software (SAS Inc., Cary, USA) and presented as the mean±SEM. When 3 groups were compared, overall probability values were derived from 1-way ANOVA. We also used unpaired Student's *t*-test to make comparisons between 2 groups. A value of $p<0.05$ was taken as statistically significant. We used receiver operating characteristic (ROC) methodology, which is an effective tool for determining the overall accuracy and efficiency of a diagnostic test. Accuracy is the ability of the test to discriminate between health and disease over the complete spectrum of operating conditions (*14*).

Results

Background

The clinical characteristics of the subjects are shown in Table 1. TOD was identified in 30% of the total subject group and in 28% of the untreated group. Of the total subjects, 15% ($n=44$) had ACC, including CAD ($n=20$), stroke ($n=19$) and/or PAD ($n=14$), and of the untreated subjects, 10% ($n=13$) also had ACC. Four patients with CAD suffered from PAD, and four patients with stroke also suffered from PAD.

The correlations between each type of PWV and age are shown in Table 2. cfPWV and baPWV were strongly correlated with age in the total group, the no treatment group, and the treatment group. However, faPWV was weakly correlated with age in the no treatment group ($p=0.0495$), but not correlated with age in the total group and the treatment group.

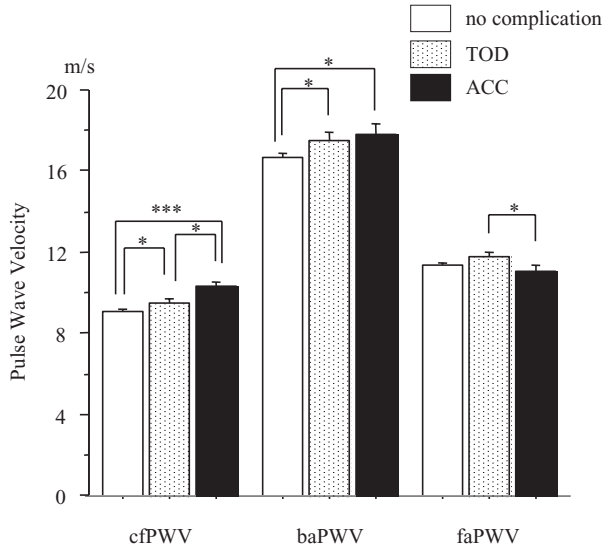

Fig. 1. *Relationship between PWV and hypertensive complications.* *p < *0.05;* **p < *0.005;* ***p < *0.0001.*

Relation of cfPWV, baPWV and faPWV to Hypertensive Complications

Clinical background classified by hypertensive complications is shown in Table 3. Patients with ACC were more likely to be male and diabetic, tended to be older, and showed higher levels of fasting blood glucose and lower levels of diastolic blood pressure and total cholesterol. ABI in patients with ACC was significantly lower than in patients with no complications and patients with TOD. In the ACC group, ABI in patients with PAD was 0.959±0.030, that in patients with CAD was 1.076±0.024 and that in patients with stroke was 1.103±0.020. ABI in patients with PAD ($p<0.0001$) or CAD ($p=0.0175$) was lower than that without either disease (data not shown). The comparison of cfPWV, baPWV and faPWV in patients with TOD and ACC is presented in Fig. 1. As measured by cfPWV, PWV was significantly higher in patients with ACC compared to that in patients with TOD or patients without complications. baPWV was significantly higher in patients with ACC and TOD compared with that in patients with no complications, but there was no significant difference between the groups with TOD and ACC. Moreover, faPWV was significantly lower in patients with ACC compared with that in those with TOD.

Relation of cfPWV, baPWV and faPWV to Associated Clinical Conditions

To assess whether or not an association existed between the different types of PWV and the different types of CV events, we compared cfPWV, baPWV and faPWV in patients with different types of cardiovascular disease, such as CAD, stroke

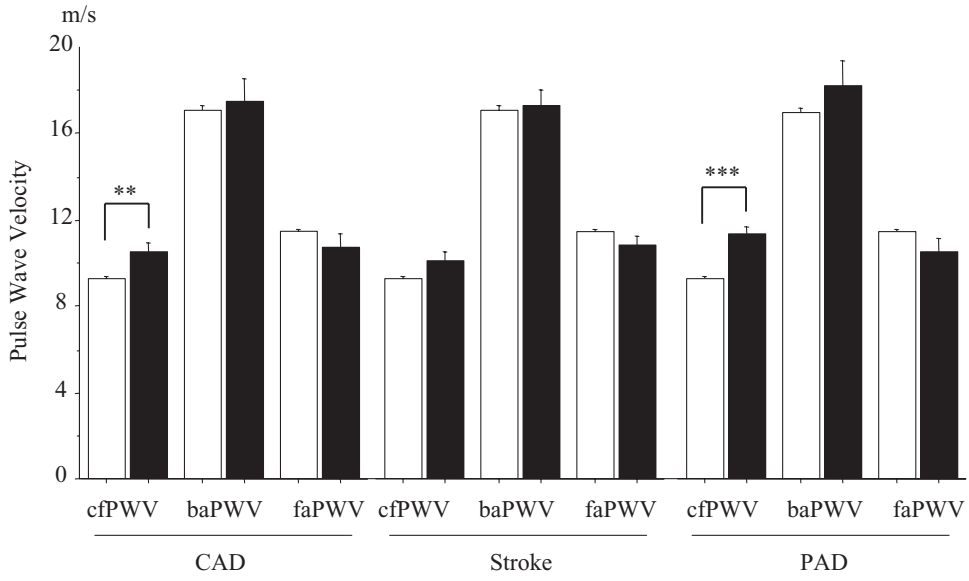

Fig. 2. *Relationship between PWV and severe organ damage. TOD, target organ damage; ACC, associated clinical condition. The open bars represent patients without any associated clinical condition, and the closed bars represent patients with an associated clinical condition,* i.e.*, coronary artery disease (CAD), stroke, or peripheral artery disease (PAD).* **p < *0.005;* ***p < *0.0001.*

and PAD. The results are presented in Fig. 2. With respect to CAD, cfPWV was significantly higher in patients with this complication than in patients without it ($p<0.005$), however, baPWV was not different between patients with and those without CAD ($p=0.596$). Moreover, faPWV in patients with CAD tended to be lower than in those without CAD ($p=0.0768$). cfPWV in patients with PAD was also significantly higher compared with that in patients without PAD ($p<0.0001$), but baPWV showed no significant difference between the group with and that without PAD ($p=0.178$). faPWV tended to be lower in patients with PAD than in those without it ($p=0.0576$). With respect to stroke, cfPWV tended to be lower in patients who had had a stroke than in those who had not ($p=0.0587$), but baPWV and faPWV were not significantly different between these two groups.

ROC Curve for baPWV and cfPWV

The ROC curves for TOD and ACC are presented in Fig. 3. The ROC curve for TOD identified by baPWV was quite similar to that for TOD identified by cfPWV (Fig. 3A). This result suggested that baPWV and cfPWV are equally accurate in discriminating between hypertensive patients with TOD and hypertensive patients without any complication. On the other hand, the ROC curve for ACC as identified by cfPWV was shifted left and upwards compared with that for baPWV (Fig. 3B). This suggests that cfPWV is a more accurate for identifying patients with ACC compared with the other PWV measurements.

Discussion

This study revealed that baPWV is as effective as cfPWV for evaluating the severity of hypertension in patients without cardiovascular events; on the other hand, only cfPWV was useful in evaluating cardiovascular complications in patients with essential hypertension.

The cfPWV is a well-established index of arterial stiffness. Recently, baPWV was developed as a new index to evaluate arterial stiffness through the convenient measurement of PWV between the brachial and ankle arteries. These two measurements of arterial stiffness, which showed a strong correlation with age in the present study, are based on the PWV measured between different sites. cfPWV evaluates arterial stiffness as PWV between the carotid and iliac artery, which mostly involves the aorta, whereas baPWV measures PWV between the brachial and ankle arteries, including the aorta and femoral artery. The structure of the aorta and arteries are quite different, and a previous report suggested that cfPWV was different from femoral-dorsalis pedis PWV (*15*). It is also apparent that different arterial segments respond differently to aging. This is probably related to differences in the proportions of elastin-collagen smooth muscle, with most studies showing a much more pronounced relationship of stiffness to age in the more proximal, more elastic, and less muscular arteries (*8*). Another study reported a non-significant and small decrease in PWV in the carotid to radial segment with aging, possibly associated with a decrease in arterial stiffness.

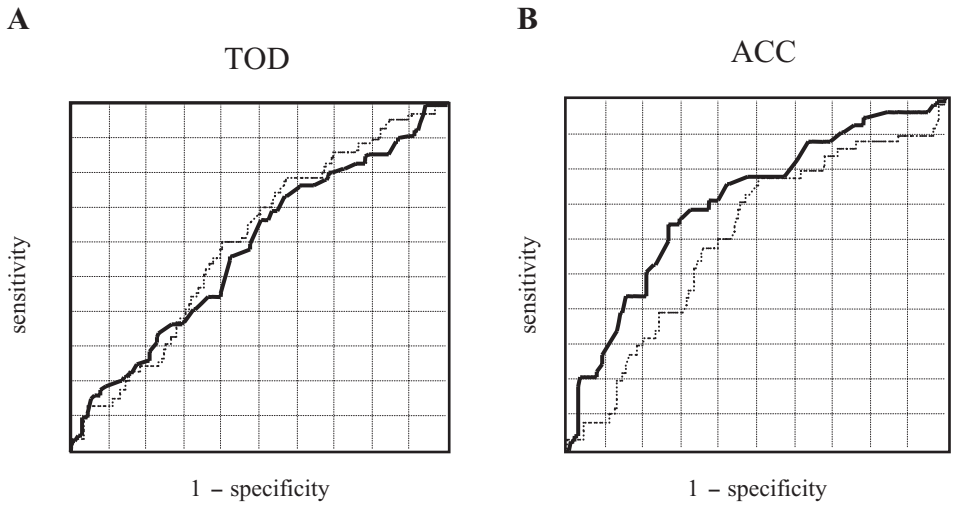

Fig. 3. *ROC curves for baPWV and cfPWV evaluation of hypertensive complications. A: ROC curves for baPWV (dotted line) and cfPWV (solid line) for target organ damage (TOD) after adjustment for age. The total area under the ROC curve is 0.59 for baPWV and 0.58 for cfPWV. B: ROC curves for baPWV (dotted line) and cfPWV (solid line) for associated clinical conditions (ACC) after adjustment for age. The total area under the ROC curve is 0.60 for baPWV and 0.71 for cfPWV.*

Conversely, the predominantly elastic aorta demonstrated a considerable age-related increase in PWV (*9*). Moreover, two reports have suggested that femoral arterial distensibility (*16*) and femoral-ankle arterial stiffness (*17*) gradually increase with age. In the present study, only faPWV in patients not taking antihypertensive agents was correlated with age, and this correlation was quite weak. We recruited patients with ABI >0.9, but the ABI in patients with PAD was lower than those in the patients with CAD or stroke. This finding suggests that patients with PAD might show latent impaired circulation in the femoral artery even if ABI is higher than 0.9. Although only a small number of patients with CAD or stroke suffered from PAD, patients with CAD or stroke without PAD might show impaired femoral arterial flow because atherosclerosis is a systemic disorder of the arteries. In light of all of the above, it is easy to understand why faPWV was lower in patients with ACC than in those with TOD. Thus the fact that baPWV was not significantly higher in patients with ACC than in those with TOD was due to underestimation of the PWV between the femoral and ankle artery.

Note

In a previous report, Munakata *et al*. reported that baPWV was strongly correlated with cfPWV in normotensive and untreated hypertensive patients (*5*). Our results are in agreement with this previous study, in that baPWV was strongly correlated with cfPWV in our patients without complications ($p<0.0001$; $r=0.401$). Moreover, the earlier study revealed that the use of baPWV resulted in a higher WHO classification score. In this regard as well, our results are in partial agreement with theirs; baPWV was particularly higher in patients with TOD. However, Munakata *et al*. (*5*) did not directly compare baPWV and cfPWV in patients with different stages of organ damage. We directly compared baPWV and cfPWV among patients with TOD, ACC, and no complications, and our results revealed that cfPWV was more effective in evaluating hypertensive patients with organ damages.

Finally, we emphasize that a further cohort study with a large number of patients who are not receiving treatment for hypertension is required to confirm our hypothesis. However, we should be more cautious in using baPWV to evaluate arterial stiffness in hypertensive patients who have experienced cardiovascular diseases.

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