Original Article

Validity, Reproducibility, and Clinical Significance of Noninvasive Brachial-Ankle Pulse Wave Velocity Measurement

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The present study was conducted to evaluate the validity and reproducibility of noninvasive brachial-ankle pulse wave velocity (baPWV) measurements and to examine the alteration of baPWV in patients with coronary artery disease (CAD). Simultaneous recordings of baPWV by a simple, noninvasive method and aortic pulse wave velosity (PWV) using a catheter tip with pressure manometer were performed in 41 patients with CAD, vasospastic angina, or cardiomyopathy. In 32 subjects (15 controls and 17 patients with CAD), baPWV was recorded independently by two observers in a random manner. In 55 subjects (14 controls and 41 patients with CAD), baPWV was recorded twice by a single observer on different days. baPWV were compared among 172 patients with CAD (aged 62±8 years); 655 age-matched patients without CAD but with hypertension, diabetes mellitus, or dyslipidemia; and 595 age-matched healthy subjects without these risk factors. baPWV correlated well with aortic PWV ($r=0.87$, $p<0.01$). Pearson's correlation coefficients of interobserver and intraobserver reproducibility were $r=0.98$ and $r=0.87$, respectively. The corresponding coefficients of variation were 8.4% and 10.0%. baPWV were significantly higher in CAD patients than in non-CAD patients with risk factors, for both genders ($p<0.01$). In addition, baPWV were higher in non-CAD patients with risk factors than in healthy subjects without risk factors. Thus, the validity and reproducibility of baPWV measurements are considerably high, and this method seems to be an acceptable marker reflecting vascular damages. baPWV measured by this simple, noninvasive method is suitable for screening vascular damages in a large population. (*Hypertens Res* 2002; 25: 359−364)

***Key Words*: pulse wave velocity, reproducibility, coronary artery disease**

Introduction

Pulse wave velocity (PWV) is known to be an indicator of arterial stiffness (*1*, *2*), and has been regarded as a marker reflecting vascular damages (*3*, *4*). Recent studies have demonstrated that PWV obtained by noninvasive automatic devices is not only a marker of vascular damages (*3*, *4*) but also a prognostic predictor (*5*, *6*). Therefore, PWV has a potential application for screening vascular damage in a large population (*2*, *7*). Recently, an instrument measuring brachial–ankle PWV (baPWV) using a volume-rendering method was developed. This instrument determines baPWV using pressure cuffs wrapped on the brachium and ankle, and is simpler than other noninvasive automatic devices. The technical simplicity and short sampling time of the new method make it more feasible for screening a large population than previous methods. However, the validity and the reproducibility of

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baPWV have not been confirmed. Furthermore, since baPWV is calculated using the distance between the brachium and ankle, as distinct from the other established method which generally measures PWV using the carotid–femoral distance (*1*, *8*), it is not clear whether baPWV, like the PWV measurements obtained by the established methods, is also altered in atheromatous diseases.

The present study was conducted to evaluate the validity and reproducibility of baPWV, and to examine the alteration of baPWV in patients with coronary artery disease (CAD) as a representative of atheromatous diseases.

Methods

Instruments

baPWV was measured using a volume-plethymographic apparatus (form PWV/ABI; Colin, Co., Ltd., Komaki, Japan). This instrument records PWV, blood pressure, electrocardiogram, and heart sounds simultaneously (*9*). The subject was examined in the supine position, with electrocardiogram electrodes placed on both wrists, a microphone for detecting heart sounds placed on the left edge of the sternum, and cuffs wrapped on both the brachia and ankles. The cuffs were connected to a plethymographic sensor that determines volume pulse form and an oscillometric pressure sensor that measures blood pressure. The pulse volume waveforms were recorded using a semiconductor pressure sensor (the sample acquisition frequency for PWV was set at 1,200 Hz). Volume waveforms for the brachium and ankle were stored, and the sampling time was 10 s with automatic gain analysis and quality adjustment.

Sufficient waveform data were obtained in this stored sample. McDonald reported that the mean value of the phase velocity above 2 to 2.5 Hz was very close to the wave front velocity (*10*). The characteristic points of waveforms were determined automatically according to this phase velocity theory. The components over 5 Hz were stored using a pass-filter and the wave front was determined. The time interval between the wave front of the brachial waveform and that of the ankle waveform was defined as the time interval between the brachium and ankle (ΔT_{ba}). The distance between sampling points of baPWV was calculated automatically according to the height of the subject. The path length from the suprasternal notch to the brachium (L_b) was obtained from superficial measurements and was expressed using the following equation: $L_b = 0.2195 \times$ height of the patient (in cm) $- 2.0734$. The path length from the suprasternal notch to the ankle (L_a) was obtained from superficial measurements and was expressed using the following equation: $L_a = (0.8129 \times$ height of the patient (in cm)$+ 12.328)$. Finally, the following equation was used to obtain baPWV: $\text{baPWV} = (L_a - L_b) / \Delta T_{ba}$. In all the studies, baPWV was obtained after at least 5-min rest.

In the following studies, all participants had no history or symptoms of peripheral artery diseases and had normal ankle/brachial pressure index values as determined by form PWV/ABI (>0.9). Informed consent was obtained from all subjects.

Assessment of Validity of baPWV

Forty-one consecutive patients (36 to 76 years old; mean age 62 ± 11 years; 34 males and 7 females) who underwent cardiac catheter examination including coronary angiography for a diagnosis of CAD or cardiomyopathy were recruited (37 patients were diagnosed with organic stenosis in the coronary artery, 2 patients were diagnosed with vasospastic angina, and 2 patients were diagnosed with non-obstructive hypertrophic cardiomyopathy). Coronary angiography was performed *via* a transfemoral approach using a 6 F catheter. After an at least 5-min rest, aortic PWV and baPWV were simultaneously recorded. For aortic PWV recording, pressure waveforms were recorded in the ascending aorta and at another point 50 cm distal to the descending aorta using a catheter tip manometer (Sentron; AC Roden, Amsterdam, the Netherlands). The foot of the aortic PWV was determined by the second derivative of the pressure wave method (the foot was defined as the maximum point) (*11*).

Assessments of Interobserver and Intraobserver Reproducibility

Thirty-two subjects (aged 24 to 80 years; mean age 53 $\pm$18 years; 22 males and 10 females; 15 controls and 17 patients with CAD) were recruited for the assessment of interobserver reproducibility. For each subject, baPWV was measured by two observers (an experienced observer: observer 1; and an inexperienced observer: observer 2) in a random order. A minimum of 5 min was allowed between measurements, and cuffs were rewrapped at the second measurement.

Fifty-five subjects (aged 24 to 81 years; mean age $55 \pm$ 17 years; 37 males and 18 females; 14 controls and 41 patients with CAD) were recruited for the assessment of intraobserver reproducibility. Observer 1 measured baPWV twice for each participant with an interval of at least 1 day between the two measurements. Both measurements were performed in the morning under a fasting condition. In patients with CAD, medications were not changed between the two measurements and were withheld on the morning of the measuring day.

Assessment of Alternation of baPWV in Patients with Coronary Artery Disease

Three groups of subjects were recruited for this study. The first group consisted of 172 patients with CAD as confirmed by coronary angiography, and with blood pressure controlled to below 140/90 mmHg. This group included 131 males and 41 females with an age range of 42 to 77 years and a mean

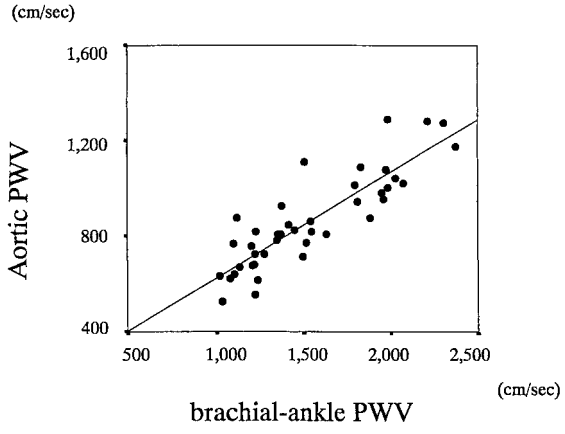

Fig. 1. *Relationship between aortic pulse wave velocity obtained using a catheter-tip manometer and brachial-ankle pulse wave velocity obtained by a noninvasive method. Aortic PWV, aortic pulse wave velocity obtained by a catheter-tip manometer; brachial-ankle PWV, noninvasive brachial-ankle pulse wave velocity.*

age of 62±8 years. Their risk factors consisted of hypertension alone (n=61), diabetes mellitus alone (n=9), dyslipidemia alone (n=30), or more than 2 of these risk factors (n=72).

The subjects in the second and the third groups were selected from either 7,025 subjects who took annual health examination or 415 subjects who were being followed as outpatients of the Tokyo Medical University Hospital for treatment of coronary risk factors. The second group consisted of 655 age-matched patients (aged 45 to 75 years; mean age 61±6 years; 485 males and 170 females) without CAD but with coronary risk factors such as hypertension (n=218), diabetes mellitus (n=79), dyslipidemia (n=189), hypertension+diabetes mellitus (n=50), hypertension+dyslipidemia (n=71), diabetes mellitus+dyslipidemia (n=31), or all three (n=17) (hypertensive subjects with blood pressure >140/90 mmHg were excluded).

The third group consisted of 595 age-matched healthy subjects without any of the above risk factors (aged 45 to 75 years; mean age 61±6 years; 373 males and 222 females). The healthy subjects satisfied the following criteria: blood pressure<140/90 mmHg, fasting blood glucose<110 mg/dl, total cholesterol<220 mg/dl, body mass index<25, and no history of smoking. All the patients with risk factors and age-matched healthy subjects had no medical history of atherogenic diseases, and their electrocardiograms were confirmed as within the normal limit. baPWV was obtained from all subjects.

Statistics

Data are expressed as the mean±SD. Statistical analysis was performed using the SPSS software package (SPSS, Chicago, USA). Pearson's correlation analysis, determination of coefficient of variation, and Bland–Altman plotting were performed for the assessments of validity and reproducibility (*12*). One-way analysis of variance was used for comparisons among groups. Values of $p<0.05$ were considered to indicate statistical significance.

Results

Figure 1 depicts the relationship between aortic PWV obtained by the catheter method and baPWV. A good correlation was observed between the two measurements (r=0.87, $p<0.01$). Figure 2 depicts the relationships of interobserver and intraobserver measurements, and Fig. 3 depicts their Bland–Altman plots. Pearson's correlation coefficient of in-

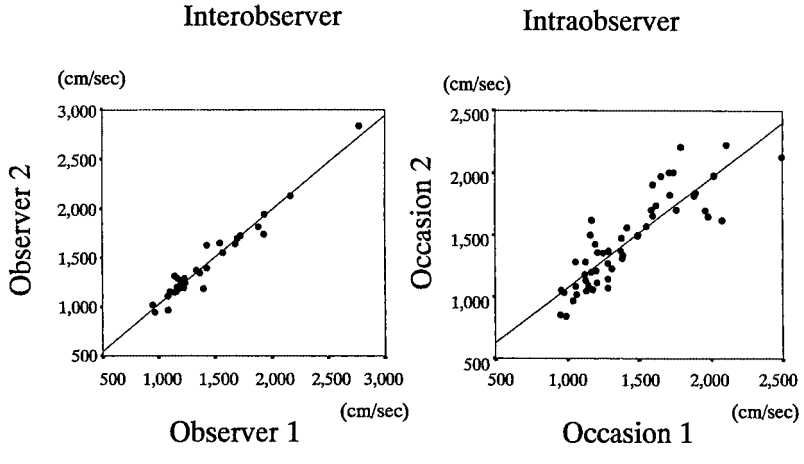

Fig. 2. *The left panel shows the relationship between two independent measurements by two observers, and the right panel shows the relationship between two occasionally different measurements by one observer.*

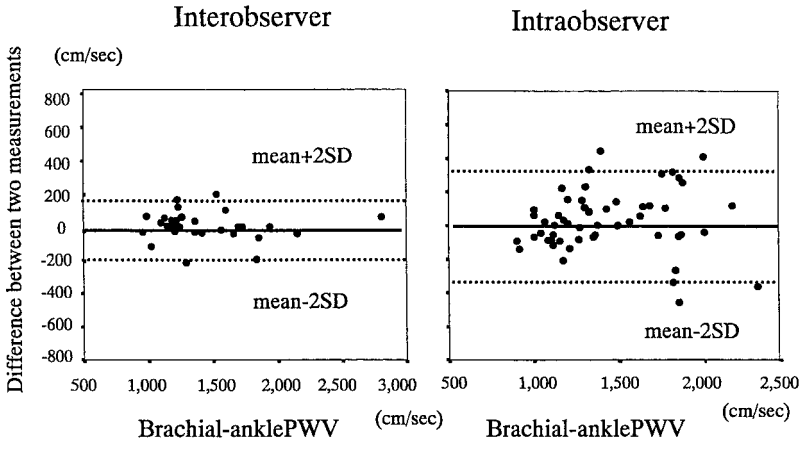

Fig. 3. *The left panel shows Bland–Altman plots depicting the difference between measurements by two observers, and the right panel shows Bland–Altman plots depicting the difference between two occasionally different measurements by one obsrever.*

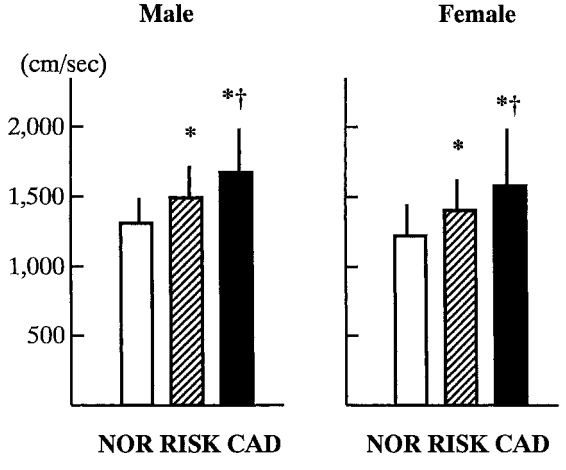

Fig. 4. *Brachial-ankle pulse wave velocity in patients with coronary artery disease, patients without coronary artery disease but with risk factors, and age-matched healthy subjects without risk factors. CAD, patients with coronary artery disease; RISK, patients with risk factors; NOR, age-matched subjects without risk factors.* $^{*}p<0.01$ *vs. NOR;* $^{\dagger}p<0.01$ *vs. RISK.*

terobserver reproducibility was 0.98 ($p<0.01$) and that of intraobserver reproducibility was 0.87 ($p<0.01$). The coefficient of variation of interobserver reproducibility was 8.4%, and that of intraobserver reproducibility was 10.0% (*13*). In the Bland–Altman plots of interobserver and intraobserver measurements, most of the values ranged within a mean$\pm$2 SD deviations (*12*).

Mean blood pressure was not different between the first and second measurements of baPWV in the interobserver (first measurement, 90$\pm$11 mmHg; second measurement, 92$\pm$10 mmHg) or intraobserver (first measurement, 91$\pm$12 mmHg; second measurement, 91$\pm$11 mmHg) measurements. In addition, changes in mean blood pressure did not correlate with changes in baPWV at the first or second measurements with respect to interobserver or intraobserver reproducibility.

Figure 4 depicts baPWV in patients with CAD, patients with coronary risk factors, and age-matched healthy subjects. baPWV was significantly higher in patients with CAD than in non-CAD patients with risk factors for both genders ($p<0.01$). In addition, baPWV was significantly higher in non-CAD patients with risk factors than in age-matched subjects without risk factors for both genders ($p<0.01$). Blood pressure in patients with CAD (male: 120$\pm$12/75$\pm$8 mmHg; female: 119$\pm$13/71$\pm$10 mmHg) was slightly but significantly lower than that either in non-CAD patients with risk factors (male: 127$\pm$9/82$\pm$8 mmHg; female: 123$\pm$9/76$\pm$8 mmHg) or in healthy subjects (male: 122$\pm$10/79$\pm$6 mmHg; female: 121$\pm$11/74$\pm$7 mmHg) ($p<0.01$).

Discussion

Ideally, when evaluating the validity of noninvasive baPWV measurements, the noninvasive baPWV should be compared with the baPWV obtained by the catheter method using a catheter tip manometer in the brachium and ankle. However, this procedure is too invasive for clinical application. Therefore, instead of invasive measurements of the brachial and ankle pressure waveforms, we compared the noninvasive baPWV with the PWV obtained by invasive measurements of the aorta across a distance of 50 cm using a catheter tip manometer. The noninvasive baPWV showed a good correlation with the aortic PWV obtained by invasive recording. This result provided an acceptable validation of the noninvasive baPWV measurement. In addition, a close relationship has been demonstrated between the aortic PWV obtained by

invasive methods and the carotid-femoral PWV determined by noninvasive methods (*14*). It has been well established that the carotid-femoral PWV is a useful marker for either vascular damage or prognosis. Thus, baPWV can be considered an acceptable marker with an efficacy equal comparable to that of carotid-femoral PWV.

The method that we used to measure baPWV does not require any specialized technique, and the examiner has only to wrap cuffs on the brachium and ankle. After these simple preparations, baPWV is automatically measured. The simplicity of this method makes it suitable for screening large populations. The present study also demonstrated considerably high Pearson's correlation coefficients of interobserver and intraobserver reproducibility. In the Bland−Altman plots, the deviation was greater at high baPWV values in the plots of intraobserver measurement. This phenomenon has also been recognized in the measurement of carotid-femoral PWV (*15*). In cases when the PWV values are high, confounding factors such as blood pressure, blood flow (*16*), and sympathetic tone (*17*) might increase the variability of PWV. In the present study, however, the deviation ranged within a mean$\pm$2.0 SD even in cases with high baPWV. Furthermore, the coefficients of variation for interobserver and intraobserver reproducibility were less than 20% (*13*). Thus, while an augmented variability of baPWV should be taken into account in cases of elevated baPWV, the reproducibility of the baPWV measurement is acceptable in clinical practice.

An increase of carotid-femoral PWV in patients with atheromatous diseases is a well recognized phenomenon (*18*, *19*), and mean carotid-femoral PWV correlates well with vascular damages (*3*, *4*). PWV is composed of a central elastic component and a peripheral muscular component, and the component of peripheral muscular arteries is larger in baPWV than in carotid-femoral PWV (*20*). The increase in PWV from the femoral to the tibial artery is greater than that from the aortic arch to the femoral artery. While age is an important determinant for PWV, its influence is more pronounced in the central elastic arteries than in the peripheral muscular arteries (*21*). Accordingly, it is important to determine whether baPWV reflects vascular damages in a manner similar to carotid-femoral PWV. Increased PWV are observed in patients with coronary risk factors such as hypertension, diabetes mellitus, or dyslipidemia (*16*). In the presence of these confounding factors, the elevation of blood pressure is a powerful determinant for baPWV (Yamashina and Tomiyama, in preparation). Therefore, to confirm the similarity between baPWV and carotid-femoral PWV as indices of vascular damage, patients with either CAD or hypertension whose blood pressure was under 140/90 mmHg were selected. Even when taking these confounding factors into consideration, baPWV was significantly higher in patients with CAD. Thus, baPWV seems to reflect vascular damage as effectively as carotid-femoral PWV.

Recently, the Rotterdam study directly demonstrated a close association between arterial stiffness assessed by carotid-femoral PWV and atherosclerosis evaluated by ultrasound examination of the carotid artery and aorta (*4*). On the other hand, functional vascular abnormality, which is thought to indicate an early stage of atherosclerosis, was demonstrated in subjects with coronary risk factors (*22*). Further studies are currently underway in our laboratory to examine the association of the noninvasive baPWV with both structural vascular abnormality as determined by ultrasound examination and functional vascular abnormality as determined by flow-mediated dilatation of the brachial arteries.

While blood pressure is an important determinant of PWV (*16*), blood pressure was not different between the first and second measurements in the present study. In addition, day-to-day variability of baPWV did not correlate with day-to-day variability of blood pressure. However, it has been well documented that high variability of blood pressure occurs in some cases (*23*). Further evaluations of the validity and reproducibility of baPWV in such cases are currently underway in our laboratory.

In conclusion, The present study confirms the validity and interobserver and intraobserver reproducibility of noninvasive baPWV measurement, and suggests that noninvasive baPWV is an acceptable marker of vascular damages comparable to the carotid-femoral PWV obtained by other established methods. Thus, baPWV has a potential application for screening vascular damages in a large population.

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