Original Article

Brachial-Ankle Pulse Wave Velocity as a Marker of Atherosclerotic Vascular Damage and Cardiovascular Risk

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The measurement of brachial-ankle pulse wave velocity (baPWV) is simple and applicable for general population studies. The present study was conducted to evaluate the applicability of baPWV for screening cardiovascular risk as well as for use as a marker of the severity of atherosclerotic vascular damage in a general population. baPWV was measured in a cross-sectional study involving two cohorts constituting a total of 10,828 subjects who underwent annual health screening check up examinations (6,716 males and 4,112 females; age 30 to 74 years). The Framingham risk score and Pocock's score were obtained. Multivariate analysis demonstrated that baPWV was associated with both scores, independently from conventional atherosclerotic risk factors. The receiver-operator characteristic curve demonstrated that a baPWV of 14.0 m/s is useful for risk stratification by Framingham score and to discriminate patients with either stroke or coronary heart disease (n=143), but the likelihood ratios were less than 5.0. Logistic regression analysis demonstrated that a baPWV>14.0 m/s is an independent variable for the risk stratification by Framingham score and for the discrimination of patients with atherosclerotic cardiovascular disease. Thus, baPWV has potential as a new marker of cardiovascular risk and may be more useful than other conventional markers; in addition, baPWV is easy to obtain and serves as an indicator of either atherosclerotic cardiovascular risk or severity of atherosclerotic vascular damage; thus it is useful to screen the general population. While the discriminating powers are not sufficiently high, a cutoff value of 14.0 m/s serves to screen subjects, especially in middle-aged ones, of either gender. (*Hypertens Res* 2003; 26: 615–622)

***Key Words*: atherosclerosis, pulse wave velocity, risk factors, cardiovascular diseases**

Introduction

To prevent cardiovascular diseases, the management of atherogenic diseases, such as hypertension, diabetes mellitus, and dyslipidemia, is crucial (*1*, *2*). However, subjects having these disorders account for a large segment of the population (*1*, *2*). A simple marker of cardiovascular risk or of the severity of atherosclerotic vascular damage may allow us to screen a population and to select the subjects requiring intensive management for these diseases (*1*, *3*). Pulse wave velocity (PWV) reflects arterial stiffness, and it is a marker of both the severity of vascular damage (*4*) and the prognosis of cardiovascular diseases in selected subjects, such as patients with hypertension (*5*) or with abnormal glucose metabolism (*6*). However, PWV has seen limited use, mostly because it is generally measured as the carotid-femoral PWV (*4*–*6*), and this parameter cannot be obtained simply enough for screening of a general population.

Recently, brachial-ankle PWV (baPWV) measurement, which can be performed more easily than carotid-femoral PWV measurement, has become available as a means of measuring PWV (*7*–*10*). baPWV can be obtained simply by wrapping the four extremities with blood pressure cuffs, and

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Received March 11, 2003; Accepted in revised form April 23, 2003.

it serves as a simple marker of the severity of vascular damage (*7*). This simple method can be applied for a large population study. While carotid-femoral PWV is mostly used to assess the stiffness of large, central arteries such as the aorta, baPWV reflects the stiffness of both central and peripheral muscular arteries (*7–9*). Therefore, it is necessary to evaluate the applicability of baPWV both as a marker of cardiovascular risk and as a marker of the severity of atherosclerotic vascular damage in a general population.

The present study measured baPWV in a cross-sectional analysis of two cohorts involving more than 10,000 subjects at the time of their annual health check up. We then evaluated the cutoff value of baPWV as a marker of cardiovascular risk as assessed by the Framingham risk score, which is applicable for Japanese (*11*), and the cutoff value of baPWV as a marker of severity of atherosclerotic vascular damage for evaluating patients with either stroke or coronary heart disease.

Methods

Subjects

The present study was conducted in two cohorts. Both cohorts were made up of subjects who had annual health check ups (including baPWV measurement) at either of two institutions affiliated with Tokyo Medical University (where more than 4,000 subjects are screened annually) from April 2001 to the end of March 2002. The medical history and symptoms of each subject were confirmed by the consulting doctors. In these cohorts, patients having diseases (except for atherosclerotic cardiovascular diseases) requiring medical treatment and subjects who had an abnormal ankle/brachial pressure index of less than 0.9 as determined using plethysmography were excluded. In addition, patients with a medical history of arteriosclerosis obliterans or aortic aneurysm were excluded, because these diseases are known to reduce PWV. A total of 10,828 consecutive subjects (age range: 30 to 74 years; 6,716 men and 4,112 women) including 143 patients with either stroke or coronary heart disease and 2,644 patients with hypertension, dyslipidemia, diabetes mellitus, or two or three of these diseases in combination were included in this study. Informed consent was obtained from all subjects.

Instruments

baPWV was measured using a plethysmography (form PWV/ABI; Colin Co., Ltd., Komaki, Japan), which simultaneously records PWV, blood pressure, an electrocardiogram, and heart sounds (*7–10*). Subjects were examined in the supine position. Electrodes of the electrocardiograph were placed on both wrists, a microphone was placed on the left edge of the sternum to detect heart sounds, and pneumatic cuffs were placed on both the brachia and ankles. The cuffs were connected to a 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, with the sample acquisition frequency for PWV set at 1,200 Hz.

Volume waveforms for the brachium and ankle were stored for a sampling time of 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 (*12*). 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 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 heart to the brachium (L_b) was measured externally and was expressed using the following equation: $L_b = 0.2195 \times \text{height of the patient (cm)} - 2.0734$. The path length from the heart to the ankle (L_a) was expressed using the following equation: $L_a = 0.8129 \times \text{height of the patient (cm)} + 12.328$. Finally, baPWV was calculated from the following equation: $\text{baPWV} = (L_a - L_b)/\Delta T_{ba}$.

In all the studies, baPWV was obtained after at least 5 min of rest. The validity and reproducibility of the measurement of baPWV were previously reported elsewhere (*7*).

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.

Risk Scoring and Confirmation of Atherosclerotic Diseases

The experience of the Framingham population study was used to develop an algorithm for calculating a score predictive of the 10-year risk of coronary heart disease in persons aged 30 to 74 years without atherosclerotic cardiovascular diseases (coronary heart disease or stroke) (*13*). Using this score, risk was stratified according to Grundy's criteria, and the high risk group and high risk+moderately above average risk group were defined (*14*). In addition, the risk score proposed by Pocock *et al*. was also obtained in all participants (including patients with atherosclerotic cardiovascular disease) (*15*).

Atherosclerotic cardiovascular diseases were described according to the criteria of the International Classification of Diseases (10th revision) for coronary heart disease and cerebrovascular disease. These diseases were validated from the clinical questionnaires and findings of the physical check-up.

Table 1. Clinical Characteristics of the Subjects Distributed by Gender

	Males (n=6,716)	Females (n=4,112)
Age		
30–39	1,913	1,221
40–49	1,760	1,080
50–59	2,083	1,152
60–69	803	538
70–	157	121
SBP (mmHg)	126±15	119±18
DBP (mmHg)	81±10	73±11
BMI (kg/m^2)	23.8±2.8	21.2±2.9
FBS (mmol/l)	5.5±1.1	5.2±0.8
TC (mmol/l)	5.2±0.9	5.3±0.9
TG (mmol/l)	1.4±1.0	0.9±0.5
HDL (mmol/l)	1.4±0.3	1.9±0.4
High blood pressure	1,722	572
Diabetes mellitus	503	98
Dyslipidemia	847	724
Smoking	2,371	450
CAD	82	37
Stroke	19	4
CAD+stroke	1	0
LVH	30	11
Framingham score	3.6±3.5	0.5±6.9
Framingham score risk		
High	250	4
Moderate	648	109
Pocock's score	32.5±8.2	19.3±10.6

SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; FBS, fasting blood sugar; TC, total cholesterol; TG, triglycerides; HDL, high density lipoprotein cholesterol; CAD, coronary artery disease; LVH, subjects having electrocardiographic left ventricular hypertrophy; High, subjects with high risk in Framingham score; Moderate, moderately above average risk.

High blood pressure was defined as a systolic blood pressure (SBP)≧140 mmHg and/or diastolic blood pressure (DBP) ≧90 mmHg as measured by an oscillometric method during the measurement of baPWV, or the use of antihypertensive drugs; diabetes mellitus was defined as a fasting blood glucose≧6.9 mmol/l or the use of hypoglycemic agents, and dyslipidemia was defined as total cholesterol≧6.2 mmol/l or the use of hypocholesterolemic drugs. Electrocardiographic left ventricular hypertrophy was defined according to Framingham's criteria (*16*).

Statistics

Data are expressed as the mean±SD. Statistical analysis was performed using the SPSS software package (SPSS, Chicago, USA). Linear regression analysis was performed to evaluate the association between baPWV and other clinical variables. Then, step-wise multiple regression analysis was performed to determine the correlation and independent variables for baPWV. To compare the sensitivity and specificity of baPWV for risk stratification using the Framingham score, areas under the receiver operating characteristic (ROC) curve of the association between baPWV and high risk or more than moderate risk stratifications were compared. A ROC curve was also used to discriminate patients with stroke or coronary heart disease by baPWV. Then, the values with the highest sum of sensitivity and specificity were identified as the cutoff values. The independence of the influence of baPWV>14.0 m/s both on the risk stratification using the Framingham score and on the discrimination of patients with either stroke or coronary heart disease was assessed by logistic regression analysis. Values of $p<0.05$ were considered to indicate statistical significance.

Results

The clinical characteristics, including data derived from the medical history, are summarized in Table 1. In the present study, the Framingham score of 10,685 subjects without overt atherosclerotic cardiovascular diseases was calculated. As shown in Fig. 1, baPWV was significantly correlated with both the Framingham score and Pocock's score in both genders (*13*, *15*). The multivariate analysis demonstrated that baPWV was significantly correlated with both scores, and that these associations were independent of conventional risk factors (Table 2). Figure 2 shows the ROC curves of the association between baPWV and high risk stratification or more than moderate risk stratification by the Framingham score in both genders (*14*). The area under the curve was larger in the high risk stratification (0.79) than in the more than moderate risk stratification (0.62) in males. In females, the area under the curve was also larger in the high risk stratification (0.83 *vs.* 0.77); however, only 4 subjects belonged to the high risk group. Therefore, baPWV may be most applicable for screening males at high risk and females at a more than moderate risk of developing atherosclerosis. The highest discriminating sensitivity and specificity were 83% and 63% (likelihood ratio=2.2) at baPWV=14.0 m/s for males and 73% and 70% (likelihood ratio=2.4) at baPWV=14.0 m/s for females.

baPWV in patients with either stroke or coronary heart disease [male (n=102): 1,503±282 cm/s; female (n=41): 1,489±304 cm/s] was higher than that in subjects without these diseases [male (n=6,614): 1,331±242 cm/s; female (4,071): 1,207±245 cm/s] in both genders ($p<0.01$). Figure 3 shows the ROC curves of the association between baPWV and the discrimination of patients with either stroke or coronary heart disease in both genders. The area under the curve was 0.69 in males and 0.77 in females, and the highest discriminating sensitivity and specificity were 68% and 62%

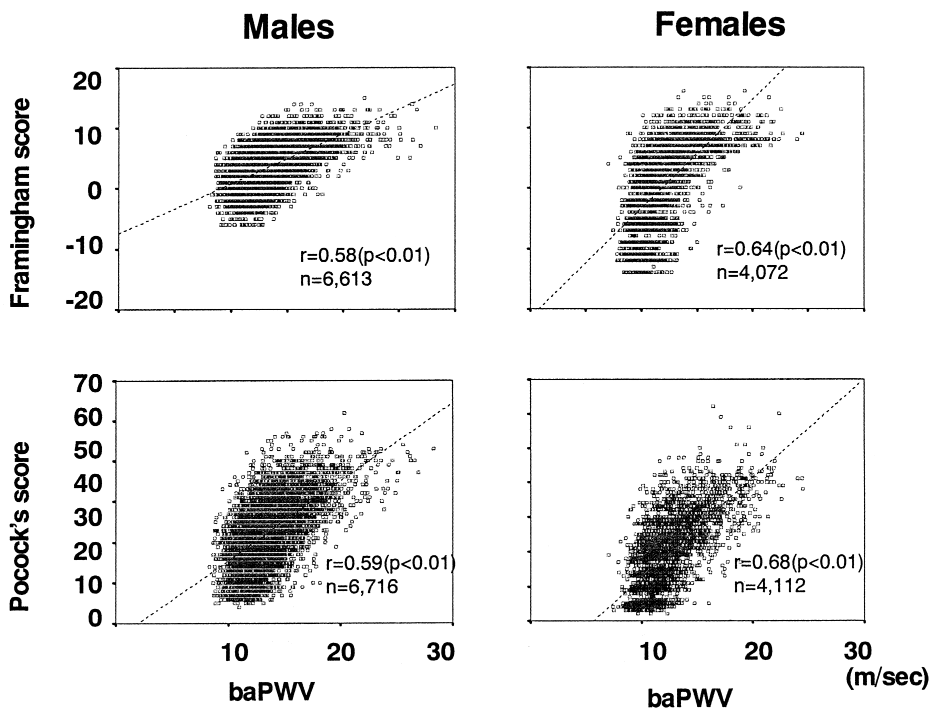

Fig. 1. *Correlations of baPWV with the Framingham score and Pocock's score. baPWV, brachial-ankle pulse wave velocity.*

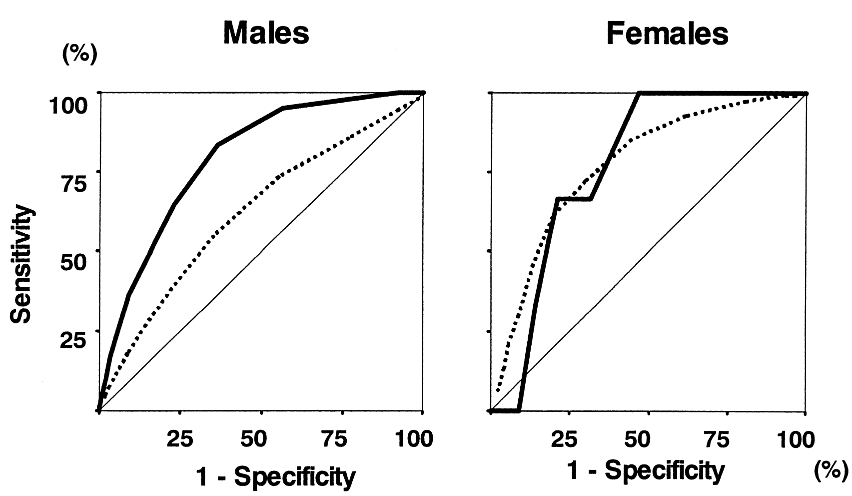

Fig. 2. *Receiver operating characteristic curve between brachial-ankle pulse wave velocity and high risk stratification or more than moderate risk stratification by Framingham score. Continued lines represent high risk stratification and hatched lines represent more than moderate risk stratification.*

(likelihood ratio = 1.8) at baPWV = 14.0 m/s for males and 53% and 85% (likelihood ratio = 3.5) at baPWV = 14.0 m/s for females.

Tables 3 and 4 show the results of logistic regression analysis to assess the independence of the influence of baPWV > 14.0 m/s on the risk stratification by Framingham score and on the discrimination of patients with either stroke or coronary heart disease, respectively. These analyses demonstrated that baPWV > 14.0 m/s is an independent variable for assessing the risk stratification by Framingham score and for discriminating patients with either stroke or coronary heart disease in both genders.

Discussion

The Framingham risk score is a conventional means of predicting the risk of coronary heart disease in a general population (*13*, *14*). This score is usually applied for screening sub-

Table 2. Results of Multiple Regression Analysis to Assess the Correlation of Risk Scores with baPWV or Conventional Risk Factors

	Male			Female		
	β	t	p value	β	t	p vale
Framingham score	$r^2=0.90$			$r^2=0.89$		
baPWV	0.04	5.8	<0.01	0.13	12.5	<0.01
Age	0.62	124.0	<0.01	0.81	103.9	<0.01
Smoking	0.29	70.4	<0.01	0.11	19.6	<0.01
MBP	0.20	31.1	<0.01	0.16	18.5	<0.01
PP	0.02	4.8	<0.01			ns
BMI	0.02	4.2	<0.01	0.02	2.6	<0.01
TC	0.31	70.5	<0.01	0.15	21.6	<0.01
HDL	−0.28	−59.4	<0.01	−0.11	−17.0	<0.01
TG			ns	0.04	6.0	<0.01
FBS	0.08	19.4	<0.01	0.06	10.9	<0.01
Pocock's score	$r^2=0.93$			$r^2=0.96$		
baPWV	0.03	5.9	<0.01	0.03	4.3	<0.01
Age	0.80	186.8	<0.01	0.83	167.9	<0.01
Smoking	0.37	102.9	<0.01	0.33	91.5	<0.01
MBP	0.11	19.2	<0.01	0.08	12.7	<0.01
PP	0.09	19.2	<0.01	0.06	11.6	<0.01
BMI			ns			ns
TC	0.17	47.7	<0.01	0.04	8.7	<0.01
HDL	−0.02	−3.5	<0.01	−0.02	−3.0	<0.01
TG			ns			ns
FBS	0.03	7.0	<0.01	0.06	16.7	<0.01

baPWV, brachial-ankle pulse wave velocity; MBP, mean blood pressure; PP, pulse pressure; BMI, body mass index; TC, total cholesterol; HDL, high density lipoprotein cholesterol; TG, triglycerides; FBS, fasting blood sugar; ns, not significant.

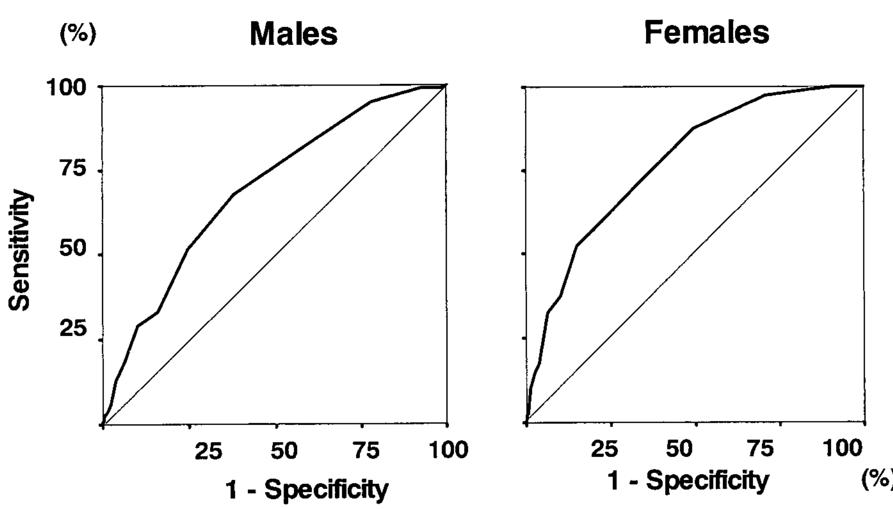

Fig. 3. *Receiver operating characteristic curve between brachial-ankle pulse wave velocity and the presence/absence of either stroke or coronary heart disease.*

jects without an overt coronary heart disease. In addition, Pocock *et al*. reported a new risk-predicting score that can be applied for screening subjects with or without cardiovascular diseases (*15*). In the present study, therefore, we evaluated the association of baPWV with both scores. The good correlation of baPWV with both scores suggested baPWV also reflects cardiovascular risk. Recently, the clinical importance of a global estimation of cardiovascular risk has been widely

Table 3. Results of Logistic Regression Analysis to Assess the Independence of the Influence of baPWV>14.0 m/s on Risk Stratification (High or More than Moderate) Determined Using Framingham Score

Parameter	Odds	CI	*p* value
High risk stratification (males)			
Diabetes mellitus	11.7	7.9–17.2	<0.01
Hypercholesterolemia	15.4	8.7–27.4	<0.01
Hypertension	13.3	8.8–20.2	<0.01
Obesity	2.4	1.7–3.3	<0.01
Smoke	27.9	18.1–43.1	<0.01
baPWV>14.0 m/s	2.3	1.6–3.6	<0.01
More than moderate risk stratification (females)			
Diabetes mellitus	38.4	21.3–69.3	<0.01
Hypercholesterolemia	3.3	1.6–6.8	<0.01
Hypertension	6.2	3.6–10.8	<0.01
Obesity	1.9	1.2–3.2	<0.01
Smoke	6.1	3.4–10.7	<0.01
baPWV>14.0 m/s	2.2	1.3–3.9	<0.01

Obesity: body mass index>25 kg/m^2 ; Smoke: with/without active smoking; baPWV>14.0 m/s: baPWV less than/over 14.0 m/s. baPWV, brachial-ankle pulse wave velosity; CI, confidence interval.

Table 4. Results of Logistic Regression Analysis to Assess the Independence of the Influence of baPWV>14.0 m/s on the Discrimination of Patients with Either Stroke or Coronary Heart Disease

Parameter	Odds	CI	*p* value
Male			
Diabetes mellitus	3.0	1.9–4.8	<0.01
Hypercholesterolemia	0.3	0.1–2.2	ns
Hypertension	1.0	0.7–1.6	ns
Obesity	1.0	0.7–1.6	ns
Smoke	0.4	0.2–0.7	<0.01
baPWV>14.0 m/s	2.9	1.8–4.6	<0.01
Female			
Diabetes Mellitus	4.7	1.9–11.8	<0.01
Hypercholesterolemia	1.2	0.3–5.2	ns
Hypertension	1.8	0.8–3.8	ns
Obesity	1.1	0.5–2.5	ns
Smoke	0.1	0.0–0.1	ns
baPWV>14.0 m/s	3.1	1.4–6.9	<0.01

Obesity: body mass index>25 kg/m^2; Smoke: with/without active smoking; baPWV>14.0 m/s: baPWV less than/over 14.0 m/s. baPWV, brachial-ankle pulse wave; CI, confidence interval; ns, not significant.

discussed (*1*, *2*). Major risk factors (homocystines, high-sensitive C-reactive protein, interleukin-6, and so on) other than conventional risk factors have been defined, and they are important for the estimation of risk for developing atherosclerosis (*1*, *2*, *17*).

Multivariate analysis showed that baPWV correlated with both scores independent of other conventional atherosclerotic risk factors. Therefore, the present results suggest that baPWV may have potential as a new risk marker for the general population.

Using the Framingham score, Blacher *et al*. demonstrated that a carotid-femoral PWV of >13.0 m/s was a marker of cardiovascular risk in hypertensive patients (*18*). Although blood pressure is known to be an important determinant of PWV (*19*), the mean SBP among the subjects of Blacher *et al*. was 144 mmHg (*18*). This cutoff point cannot be applied to the general population, because blood pressure is much lower in the general population. Because gender also influences the PWV (*20*), it might be appropriate to determine the individual cutoff values of PWV in both genders. Furthermore, Asmar used the Moens-Korteweg's equation to demonstrate that PWV is inversely correlated with the square root of the diameter of a vessel (*21*). Compared with the carotid-femoral PWV, the assessment of baPWV includes smaller arteries (*7–10*). It is thus important to determine the baPWV cutoff values for screening subjects at risk of developing cardiovascular diseases in the general population. Thus, a ROC curve based on baPWV was used to identify and discriminate among patients at risk of developing cardiovascular diseases based on the Framingham risk score (*14*), with a baPWV of 14.0 m/s found to be the most effective discriminating value to screen male subjects at high risk of developing cardiovascular diseases, as well as female subjects at a more than moderate risk of developing such diseases.

Several studies have demonstrated that an increased carotid-femoral PWV reflects the presence of cardiovascular disease (*18*, *22*, *23*). The results of our previous study also demonstrated that baPWV was increased in patients with coronary heart disease (*7*). The present study demonstrated that an increased baPWV (baPWV>14.0 m/s) serves to discriminate the patients with either stroke or coronary heart disease independent from conventional atherosclerotic risk factors in both genders. Using the carotid-femoral PWV, Blacher *et al*. performed similar analyses (*18*). While the clinical background of subjects differed between the two studies [in particular, the number of subjects with atherosclerotic cardiovascular disease was higher in Blacher's study (25% of total subjects) than in the present study (1% of total subjects)], Blacher *et al*. also reported that the two values (cardiovascular risk prediction and screening for the presence of atherosclerotic diseases) were similar. While baPWV>14.0 m/s is a cutoff value for risk prediction and for screening, their likelihood ratios were less than 5.0. Therefore, their discriminating powers were not particularly high for either purpose.

Although in the present study we did not investigate the underlying mechanisms that increased baPWV, several mechanisms have been discussed (*22*, *24*, *25*). Increased PWV reflects increased arterial stiffness. Conventional atherosclerotic risk factors, which are used to determine the Framingham risk score, have been linked to arterial stiffness (*24*, *25*). The plural complication of these risk factors. Complication by one or more of these risk factors may have a synergetic influence on increased arterial stiffness. Increased arterial stiffness leads to an increase of cardiac ventricular load, thereby reducing cardiac systolic performance and increasing myocardial oxygen demand (*22*, *25*, *26*), and it also contributes to the progress of atherosclerosis, probably through the effect of increased cycle stress on arterial wall thickening (*27*).

In the present study, 70% of subjects aged more than 60 years showed a baPWV of over 14.0 m/s. This result suggests that a baPWV cutoff value of 14.0 m/s is applicable for middle-aged subjects rather than the elderly. Age is known to be one of the major determinants of PWV (*9*, *19*). In future studies, it will be important to establish a chronological cutoff value of baPWV as a marker of cardiovascular risk over a wide age-range of subjects, including elderly patients, and to carefully assess the applicability of this cutoff.

In conclusion, baPWV has potential as a new marker of cardiovascular risk over conventional markers, it is easy to obtain and serves as an indicator of either atherosclerotic cardiovascular risk or severity of atherosclerotic vascular damage; thus it is useful to screen the general population. While the discriminating powers are not sufficiently high, a cutoff value of 14.0 m/s serves to screen subjects, especially in middle-aged subjects, of either gender. To confirm the applicability of baPWV as an index of cardiovascular risk, a prospective study has been planned and is underway in our Tokyo Medical University.

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