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Screening Validity of Arterial Pressure−Volume Index and Arterial Velocity−Pulse Index for Preclinical Atherosclerosis in Japanese Community-Dwelling Adults: the Nagasaki Islands Study

Hirotomo Yamanashi[1, 2], Jun Koyamatsu[1], Mako Nagayoshi[3], Yuji Shimizu[3], Shin-ya Kawashiri[3], Hideaki Kondo[3], Shoichi Fukui[3], Mami Tamai[4] and Takahiro Maeda[1, 3]

[1] Department of Island and Community Medicine, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan
[2] Department of Clinical Medicine, Institute of Tropical Medicine, Nagasaki University, Nagasaki, Japan
[3] Department of Community Medicine, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan
[4] Department of Immunology and Rheumatology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan

Aim: The arterial pressure−volume index (API) and arterial velocity−pulse index (AVI) are novel measurement indices of arterial stiffness. This study was performed to examine the screening validity of the API and AVI for preclinical atherosclerosis in Japanese community-dwelling adults.

Methods: We conducted a cross-sectional study of 2,809 participants aged ≥40 years who underwent Japanese national medical check-ups from 2014 to 2016. Preclinical atherosclerosis was defined as a mean carotid intima−media thickness (CIMT) of ≥1.0 mm. Multivariable linear regression analysis was performed to investigate the association of CIMT with API and AVI, adjusting for body mass index, sex, and the Framingham−D'Agostino score. We also examined receiver operating characteristic curves, sensitivity, and specificity to predict preclinical atherosclerosis defined by the CIMT. The cardio-ankle vascular index was also measured for comparison with the API and AVI.

Results: Of 2,809 participants, 68 (2.4%) had preclinical atherosclerosis. In the multivariable linear regression analysis, the API and AVI maintained a positive association with the mean CIMT (B=2.6, P=0.009 and B=3.7, P=0.001, respectively). The cut-offs of the API and AVI that demonstrated better sensitivity and specificity for detection of subclinical atherosclerosis were 31 [area under the curve (AUC), 0.64] and 29 (AUC, 0.60).

Conclusions: The API and AVI were positively associated with preclinical carotid atherosclerosis independent of the participants' cardiovascular risk. The ability of these scores to predict carotid atherosclerosis could make them a useful screening tool for atherosclerosis.

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Key words: Arterial stiffness, Arterial pressure−volume index, Arterial velocity−pulse index, Carotid intima−media thickness

Introduction

The arterial pressure−volume index (API) and the arterial velocity−pulse index (AVI) are new oscillometric indices of arterial stiffness. Compared with conventional indices, they require shorter measurement times, have more comfortable postural requirements, and involve easier operation of the measurement devices. These merits make the use of these measurement indices fit for broad clinical settings and screening of large communities.

The carotid intima−media thickness (CIMT)

Address for correspondence: Hirotomo Yamanashi, Department of Island and Community Medicine, Nagasaki University Graduate School of Biomedical Sciences, 205, Yoshikugi, Goto, Nagasaki 853-8691, Japan E-mail: yamanashi@nagasaki-u.ac.jp

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measured by high-resolution B-mode ultrasound is a widely accepted method of assessing atherosclerosis[1]. An increased CIMT is a potent predictor of future cardiovascular and cerebrovascular events[2-6]. However, several methodological weaknesses must be considered when measuring the CIMT, such as the definition of carotid plaques, the choice of measurement sites, and assessment of the maximum or minimum CIMT[1].

The cardio-ankle vascular index (CAVI) and brachial-ankle pulse wave velocity are also measures of the overall arterial stiffness from the origin of the aorta to the ankle and can be used to estimate the risk of atherosclerosis[7-9]. In a prospective cohort of Japanese outpatients with metabolic disorders, the CAVI was an independent predictor of future cardiovascular events[8]. In a cross-sectional study of a Korean middle-aged population, arterial stiffness as measured by the brachial-ankle pulse wave velocity was associated with composite preclinical atherosclerosis[9].

Previous studies have revealed the clinical significance of these indices[10-13] and the correlation of the API and AVI with the CIMT or CAVI in healthy Japanese adults[14]. However, the screening validity of these indices for preclinical atherosclerosis has not been investigated.

Aim

The aim of this study was to evaluate the screening validity of the API and AVI for preclinical atherosclerosis in Japanese community-dwelling adults.

Methods

Study Setting and Participants

The Nagasaki Islands Study was a prospective cohort study performed in Goto city of the western islands of Japan. The participants were recruited upon medical check-ups, and members of the general population aged ≥40 years living in Goto city were targeted for enrollment. The recruitment process has been described elsewhere[15]. We enrolled 3,517 participants (1,355 men and 2,162 women) from 2014 to 2016. Of the 3,517 participants, we excluded those with an apparent past or present history of stroke (n=137) or ischemic heart disease (n=221). We also excluded those with missing data regarding their medical history (n=3), smoking status (n=5), API and AVI (n=146), CIMT (n=6), and cholesterol profile (n=200). In total, 2,809 participants with a mean age of 69.5 years (standard deviation, 9.6 years; range, 40−94 years) were evaluated.

The protocol for the Nagasaki Islands Study was approved by the Ethics Committee for the Use of Humans of Nagasaki University (project registration number: 14051404; Nagasaki, Japan). Written informed consent was obtained from all participants.

Data Collection and Laboratory Measurements

Body weight and height were measured with an automatic body composition analyzer (BF-220; Tanita, Tokyo, Japan) at the time of blood drawing, and the body mass index (BMI) was then calculated. Abdominal circumference was measured with an inelastic measuring tape placed over the skin at the level of the umbilical point. Trained medical technologists measured the API, AVI, systolic blood pressure, and diastolic blood pressure at rest using cuff oscillometry with a PASESA AVE-1500 (Shisei Datum, Tokyo, Japan). The cuff was wrapped around one side of the upper arm of seated participants[10]. Blood samples were obtained. After coagulation, each blood sample was centrifuged and the serum separated. The serum levels of low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, creatinine, and glycated hemoglobin were measured using standard laboratory procedures. Trained interviewers obtained information on the participants' smoking status, alcohol intake, medical history, and use of antihypertensive agents, hypoglycemic agents, and lipid-lowing drugs. The smoking status and drinking status were categorized as "never," "ex," or "current." The risk of atherosclerotic disease was estimated using the risk equation (D'Agostino scale) based on the Framingham study[16]. The D'Agostino scale includes age, total cholesterol, high-density lipoprotein cholesterol, and systolic blood pressure as quantitative variables and sex, drug treatment for hypertension, smoking, and a history of diabetes mellitus as dichotomous variables.

Measurements of CIMT and CAVI

Research doctors or laboratory technicians measured the CIMT by ultrasonographic examination of the left and right carotid arteries using a LOGIQ Book XP with a 10-MHz transducer (GE Healthcare, Milwaukee, WI, USA) that was programmed with the CIMT measurement software Intimascope (Cross Media Ltd., Tokyo, Japan)[17]. The protocol used in this study has been described in detail elsewhere[18]. The mean CIMT was calculated as the mean of the right and left CIMT measurements with carotid plaque excluded. Preclinical atherosclerosis was defined as a mean CIMT of ≥1.0 mm[2, 3].

The CAVI was recorded using a VaSera 1500 device (Fukuda Denshi, Tokyo, Japan) with the participant resting in the supine position. The CAVI measurement integrates cardiovascular elasticity derived from the aorta to the ankle pulse velocity through an oscillometric method, and it is used as an accurate measure of vascular stiffness that does not depend on blood pressure at the time of measurement[19]. The averages of the right and left CAVI were used for analysis. (The CAVI was only available in subsample of 1,753 participants because the measurement sites were restricted at the time of the medical check-ups.)

Statistical Analyses

We calculated correlation coefficients between the API or AVI and atherosclerosis risk factors as continuous variables. Simple and multivariable linear regression analysis was performed to investigate the association between the CIMT and API, AVI, or CAVI. The Framingham−D'Agostino score, sex, height, and BMI were included in the adjustment model[20]. We examined receiver operating characteristic curves, sensitivity, and specificity to predict preclinical atherosclerosis as defined by the CIMT. All *P*-values for statistical tests were two-tailed, and $P<0.05$ was considered significant. All statistical analyses were carried out using STATA v14 (StataCorp, College Station, TX, USA).

Table 1. Characteristics of the study participants ($n=2{,}809$)

Characteristics	Total
Age (years)	69.5 ± 9.6
Women	1,733 (61.7)
Height (cm)	155.5 ± 9.0
Body mass index (kg/m^2)	23.2 ± 3.4
Abdominal circumference (cm)	84.1 ± 9.3
Systolic blood pressure (mmHg)	136.9 ± 19.8
Diastolic blood pressure (mmHg)	75.8 ± 11.5
Pulse pressure (mmHg)	61.2 ± 17.4
Hemoglobin A1c (%)	5.7 ± 0.6
Total cholesterol (mg/dL)	201.4 ± 33.9
LDL cholesterol (mg/dL)	120.1 ± 29.1
HDL cholesterol (mg/dL)	59.9 ± 14.5
Triglycerides (mg/dL)	106.8 ± 66.2
Mean CIMT (mm)	0.70 ± 0.14
Mean CIMT > 1.0 mm	68 (2.4)
Maximum carotid intima-media thickness (mm)	0.87 ± 0.18
CAVI score[§]	8.41 ± 1.19
Hypertension	1,775 (63.2)
Antihypertensive Drug Use	1,168 (41.6)
Diabetes mellitus	284 (10.1)
Antidiabetic Drug Use	184 (6.6)
Dyslipidemia	1,435 (51.1)
Lipid Lowering Drug Use	527 (18.8)
Current Smoker	268 (9.5)
Framingham−D'Agostino	14.5 ± 4.5
API	30.7 ± 8.1
AVI	27.6 ± 8.8

Data are presented as mean ± standard deviation or n (%).
API, arterial pressure−volume index; AVI, arterial velocity−pulse index; CIMT, carotid intima−media thickness; CAVI, cardio-ankle vascular index; LDL, low-density lipoprotein; HDL, high-density lipoprotein.
[§] For data on CAVI: $n=1{,}753$.

Results

Table 1 shows the characteristics of the study participants. The mean API, AVI, and CAVI were 30.7, 27.6, and 8.41, respectively. A total of 2.4% of the participants had a mean CIMT of ≥ 1.0 mm.

The API was positively correlated with age, male sex, BMI, abdominal circumference, systolic blood pressure, pulse pressure, glycated hemoglobin, mean CIMT, maximum CIMT, CAVI, and the Framingham−D'Agostino score and negatively correlated with height (**Table 2**). The AVI was positively correlated with age, male sex, systolic and diastolic blood pressure, pulse pressure, mean CIMT, maximum CIMT, CAVI, and the Framingham−D'Agostino score but negatively correlated with height, BMI, abdominal circumference, and triglycerides.

In the multivariable linear regression analysis, the vascular structure and function parameters (API, AVI, and CAVI) maintained a positive association with the mean CIMT ($B=2.4$, $P=0.017$; $B=3.2$, $P=0.004$; and $B=1.3$, $P<0.001$, respectively) after adjusting for BMI, sex, height, and the Framingham−D'Agostino score (**Table 3**).

Like the mean CIMT, these indices also maintained a positive association with the maximum CIMT ($B=1.6$, $P=0.037$; $B=2.4$, $P=0.004$; and $B=0.8$, $P<0.001$, respectively) even after adjustments.

The cut-offs of the API, AVI, and CAVI that demonstrated better sensitivity and specificity for detection of subclinical atherosclerosis as defined by a mean CIMT of ≥ 1.0 mm were 31 [sensitivity, 0.67; specificity, 0.54; area under the curve (AUC), 0.64], 29 (sensitivity, 0.67; specificity, 0.54; AUC, 0.60), and 8.9 (sensitivity, 0.72; specificity, 0.68; AUC, 0.71), respectively (**Fig. 1**).

Discussion

The present study is the first to evaluate the relationships of the API and AVI with preclinical atherosclerosis as defined by the CIMT in Japanese healthy adults. The API and AVI were positively associated with the mean CIMT, independent of the participants' cardiovascular risk. The cut-offs of the API and AVI that were more sensitive and specific for predicting preclinical atherosclerosis with a mean CIMT of ≥ 1.0 mm were 31 and 29, respectively.

Table 2. Bivariate correlation of API or AVI with other variables

	API	AVI
API		0.26**
Age (years)	0.33**	0.37**
Sex (women)	0.17**	0.13**
Height (cm)	−0.26**	−0.27**
Body mass index (kg/m²)	0.14**	−0.10**
Abdominal circumference (cm)	0.12**	−0.07**
Systolic blood pressure (mmHg)	0.65**	0.55**
Diastolic blood pressure (mmHg)	−0.02	0.17**
Pulse pressure (mmHg)	0.75**	0.51**
Hemoglobin A1c (%)	0.06*	−0.01
Total cholesterol (mg/dL)	0.00	−0.02
LDL cholesterol (mg/dL)	0.01	−0.01
HDL cholesterol (mg/dL)	−0.03	0.02
Triglycerides (mg/dL)	0.03	−0.06*
Mean CIMT (mm)	0.19**	0.19**
Maximum CIMT (mm)	0.18**	0.18**
CAVI score §	0.22**	0.24**
Framingham−D'Agostino (dagscore)	0.46**	0.39**

API, arterial pressure−volume index; AVI, arterial velocity−pulse index; CIMT, carotid intima−media thickness; CAVI, cardio-ankle vascular index; LDL, low-density lipoprotein; HDL, high-density lipoprotein.
§For data on CAVI: n = 1,753.
**P < 0.001, *P < 0.05

Table 3. Linear regression analysis of the association between CIMT and API, AVI, or CAVI

	API		AVI		CAVI	
	B (95% CI)	*P*	B (95% CI)	*P*	B (95% CI)	*P*
Mean CIMT						
Crude	10.9 (8.7, 13.0)	< 0.001	11.9 (9.6, 14.2)	< 0.001	2.9 (2.5, 3.3)	< 0.001
Adjusted	2.4 (0.4, 4.3)	0.017	3.2 (1.0, 5.4)	0.004	1.3 (0.9, 1.7)	< 0.001
Maximum CIMT						
Crude	7.8 (6.2, 9.4)	< 0.001	8.7 (7.0, 10.5)	< 0.001	1.9 (1.6, 2.2)	< 0.001
Adjusted	1.6 (0.1, 3.0)	0.037	2.4 (0.8, 4.1)	0.004	0.8 (0.6, 1.1)	< 0.001

API, arterial pressure−volume index; AVI, arterial velocity−pulse index; CIMT, carotid intima−media thickness; CAVI, cardio-ankle vascular index.
n = 1,753.
Adjusted by Framingham−D'Agostino score, sex, height, and body mass index.

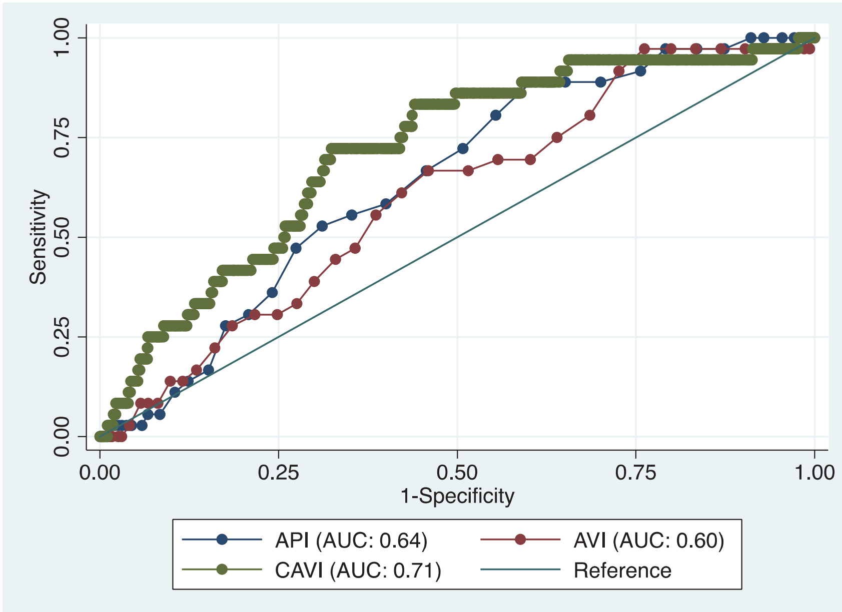
Screening Validity of API and AVI for Preclinical Atherosclerosis Compared with CAVI

In our previous study, we suggested using the CAVI as a screening tool for atherosclerosis based on our findings in a general population of 1,014 adults. Several other reports have also shown that the CIMT is positively correlated with the CAVI in patients with hypertension[21] and coronary artery disease[22]. In the current study, we investigated the validity of the API and AVI in screening for preclinical atherosclerosis as defined by a mean CIMT of ≥ 1.0 mm.

Although the API and AVI had a lower AUC, sensitivity, and specificity than the CAVI, evaluation is simple and convenient, can be performed in the sitting position, and takes less time. These merits made the API and AVI fit for use in screening preclinical atherosclerosis in broad clinical and public health settings.

Association between API and CIMT

An observational study of consecutive Japanese patients who underwent coronary angiography showed



Presence of a mean CIMT of ≥1.0 mm

	Cut-off value	Sensitivity	Specificity	AUC (95% CI)
CAVI	8.9	0.72	0.68	0.71 (0.63 - 0.79)
API	31	0.67	0.54	0.64 (0.56 - 0.72)
AVI	29	0.67	0.54	0.60 (0.51 - 0.69)

API, arterial pressure–volume index; AVI, arterial velocity–pulse index; CIMT, carotid intima–media thickness; CAVI, cardio-ankle vascular index; AUC, area under the receiver operating characteristic curve; CI, confidence interval.

Fig. 1. Receiver operating characteristic curve for predicting a mean CIMT of ≥1.0 mm using the API, AVI, and CAVI.

that the API was associated with the presence of significant coronary stenosis[12]. The authors suggested that the API might be associated with the brachial-ankle pulse wave velocity[10] and that a higher brachial-ankle pulse wave velocity is associated with the development of endothelial dysfunction and serves as a risk factor for coronary artery disease. Because a greater CIMT is a risk factor for coronary artery disease[23], the association between the API and mean CIMT in the current study was consistent with the findings of previous studies.

Association between AVI and CIMT

The AVI can reflect the central arterial stiffness[10], and the AVI is significantly associated with the central blood pressure[12, 24, 25]. One study showed that increased augmentation of the central blood pressure was associated with the CIMT in patients with type 2 diabetes[26]. Therefore, we speculated that the association between the AVI and CIMT may share a common background mechanism associated with the central blood pressure.

The Discrepancy in the Correlation of API or AVI with Other Parameters

The negative correlation of the AVI with the BMI, abdominal circumference, and triglycerides should be explained because these parameters are related to arterial stiffness or atherosclerosis. A discrepancy between the API and AVI in terms of their correlation with BMI, abdominal circumference, and triglycerides was seen in a large-scale cross-sectional study in Japan[14], although the correlation coefficient between the AVI and triglycerides was not a negative value but instead was not statistically significant. This might indicate that this discrepancy is based on the theoretical characteristic of AVI measurement[24]. The AVI is derived from the amplitude of oscillometric reflected waveforms. The value of these waveforms is influenced by age and peripheral arterial resistance[24]. Thus, the AVI is strongly correlated with age[14]. In the current study, the correlation coefficient between the AVI and age was larger than that between the API and age. We investigated the association between AVI and BMI in the linear regression analysis to determine the presence of a confounding effect by age. Attenuation of the beta coefficient after adjustment for age was found, suggesting the presence of partial confounding ($B = -0.25$, $P < 0.001$ to $B = -0.22$, $P < 0.001$). However, this does not fully explain the discrepancy.

We observed that the AVI was positively correlated with diastolic blood pressure, while the API was not. A possible explanation is that the API is theoretically derived using the collapsing behavior of the artery[27]. To derive the API, the slopes of the pressure−volume curve are calculated from the occlusive cuff pressure for pulse pressure and the amplitude of cuff oscillations[10]. In the present study, the pulse pressure was strongly correlated with the API (correlation coefficient, 0.75; $P < 0.001$) as well as with the systolic blood pressure (0.65, $P < 0.001$). According to the Framingham Heart Study, the diastolic blood pressure generally starts to decline after the age of 50 to 60 years while the pulse pressure continues to steeply rise[28]. Most of our study participants comprised older people aged ≥60 years (86%). Consequently, age-related hemodynamic patterns may affect calculation of the API, but not the AVI.

Further investigation is needed to clarify these differences between the API and AVI.

Limitations

The main limitation of this study was its cross-sectional design, which prevented us from establishing cause−effect relationships.

Another weakness of this study is that only 2.4% of the participants had a mean CIMT of ≥1.0 mm. However, we treated the mean and maximum CIMT as a continuous variable in the linear regression analysis. We also analyzed the data using a mean CIMT of ≥0.9 mm as the definition of atherosclerosis. The number of cases thus increased to 225 (8.0%), and the AUCs for predicting a mean CIMT of ≥0.9 mm using the API and AVI were 0.63 (95% confidence interval, 0.58−0.67) and 0.64 (95% confidence interval, 0.59−0.69), respectively. Therefore, the lower reliability due to the small number of cases (mean CIMT of ≥1.0 mm) did not seem to bias the results.

Conclusion

The API and AVI showed a positive association with preclinical carotid atherosclerosis independent of the participants' cardiovascular risk. The ability of these indices to predict carotid atherosclerosis is less sensitive than the CAVI in Japanese healthy adults. However, considering the several merits of evaluation using the API and AVI, these methods can be a useful tool to screen people for atherosclerosis.

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Disclosure Statement

The authors declare no conflict of interest.

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