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Availability of Cardio-Ankle Vascular Index (CAVI) as a Screening Tool for Atherosclerosis

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Background A novel index, the cardio-ankle vascular index (CAVI), which reflects the stiffness of the aorta, femoral artery, and tibial artery, was recently developed by measuring brachial–ankle pulse wave velocity and blood pressure.

Methods and Results In the present study 1,014 Japanese adults from the general population were screened to clarify the correlation between CAVI and other existing markers related to atherosclerosis, including carotid intima–media thickness (CIMT) and homocysteine (HCY). CAVI was strongly associated with age in both men and women. After adjustment for age and sex, CAVI was correlated with systolic and diastolic blood pressures. In addition, CAVI was significantly correlated with total cholesterol hemoglobin A_{1c} and total HCY, as well as CIMT.

Conclusion CAVI is an appropriate screening tool for atherosclerosis, but further studies are needed to establish a convenient and effective screening system using it. (*Circ J* 2008; **72:** 304–308)

Key Words: Atherosclerosis; Cardio-ankle vascular index (CAVI); Carotid intima–media thickness (CIMT); Homocysteine (HCY)

Appropriate assessment and prevention of cardiovascular disease (CVD) is 1 of the most important medical tasks worldwide. The World Health Organization has projected that the worldwide annual number of CVD Disability-adjusted life years (DAILYs: a measure that combines years of potential life lost due to premature death with years of productive life lost due to disability) will reach 153 million by 2010, 169 million by 2020, and 187 million by 2030, and that CVD death will reach 18.1 million by 2010, 20.5 million by 2020, and 24.2 million by 2030! Because atherosclerosis is a major contributor to CVD, accounting for much of the mortality and morbidity[2] the establishment of effective and accurate strategies for screening is very important.

Recent technological advances in medical equipment have allowed noninvasive assessment of atherosclerosis in its early stages[3] High-resolution B-mode ultrasonography provides a noninvasive method of quantifying arterial wall thickening, and it has been shown that the carotid intima–media thickness (CIMT) is a strong predictor of CVD[4] In addition, pulse wave velocity (PWV) has been developed as a noninvasive clinical index of aortic stiffness[5] and reportedly predicts cardiovascular events and all-cause mortality in hypertensive patients and in the general population[6,7] However, measurement of classic PWV is technically difficult and has low reproducibility, and the data obtained vary significantly between institutions and operators because of the technical difficulty[8] In order to overcome these problems, the brachial-ankle PWV (baPWV), which is simple to measure and has high reproducibility, was developed and has been shown to predict the presence of coronary disease[9] as well as correlating with CIMT![10] However, there are problems, because this method is influenced by changes in blood pressure (BP) during the examination and by the autonomic nervous system[8,11]

A novel index, the cardio-ankle vascular index (CAVI), which reflects the stiffness of the aorta, femoral artery, and tibial artery and involves measurement of baPWV and BP, was recently developed[8,12] CAVI is essentially independent of changes in BP during examination, but shows a strong correlation with systolic BP (SBP)![12] Although there are several reports of the evaluation of CAVI in patients on hemodialysis![12] those with hyperglycemia[13] and those who had undergone heart transplantation![14] there are few on the evaluation of CAVI as a screening tool for atherosclerosis in the general population![11] and none about the correlation between CAVI and CIMT. Although we recently evaluated the availability of CAVI as a screening tool for atherosclerosis in young Japanese adult (mean age 21.4 years, range 18–31 years), no correlation was observed with other existing markers, including CIMT![15]

Because we hypothesized that CAVI might be a useful screening tool for atherosclerosis in the general adult population, in the present study we screened a representative sample to evaluate the correlation between CAVI and other existing markers related to atherosclerosis, including CIMT and homocysteine (HCY), which is considered to be an inde-

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Table 1 Characteristics of the Study Participants

	Men (n=242)	Women (n=772)	All participants (n=1,014)
Age (years)	64.4±11.0	61.9±10.7	62.5±10.8
BMI (kg/m^2)	23.4±3.0	22.8±3.2	23.0±3.1
WC (cm)	84.9±8.8	80.5±10.1*	81.5±10.0
SBP (mmHg)	142±20	141±21	141±21
DBP (mmHg)	87±11	84±11	85±11
TC (g/L)	2.0±0.3	2.2±0.3	2.1±0.4
TG (g/L)	1.4±0.8	1.2±0.6**	1.3±0.7
HDL-C (g/L)	0.54±0.15	0.62±0.15	0.60±0.15
LDL-C (g/L)	1.1±0.3	1.3±0.3	1.3±0.3
HbA$_{1c}$ (%)	5.1±0.8	5.0±0.6**	5.0±0.6
Creatinine (mg/L)	10.9±2.3	8.4±1.6**	9.0±2.1
UA (g/L)	64±15	49±12**	53±15
tHCY (μmol/L)	10.3±4.7	8.3±3.8**	8.7±4.1
CIMT (mm)	0.8±0.2	0.7±0.2**	0.7±0.2
CAVI	8.5±1.4	8.0±1.3	8.1±1.3

*Values are mean±standard deviation. *p<0.05 and **p<0.01 vs men. BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total choles-terol; TG, triglyceride; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; HbA$_{1c}$, hemoglobin A$_{1c}$; UA, uric acid; tHCY, total homocysteine; CIMT, carotid intima media-thickness; CAVI, cardio-ankle vascular index.*

pendent risk factor for atherosclerosis![16]

Methods

Subjects

Prior to this study, ethical approval was obtained from the Special Committee of Nagasaki University (project registration number 0501120073). The study was conducted during a medical screening program for members of the general population aged over 40 years, living in Goto city (total population was 44,874 in 2007), Nagasaki Prefecture, Japan. The data were collected by the staff of Nagasaki University, in cooperation with that of Goto city. After obtaining informed consent, we enrolled 1,139 Japanese adults (285 men, 854 women); 38 participants with an apparent past or present history of cerebral infarction or hemorrhage or ischemic heart disease, and 71 participants with insufficient data were excluded from the study, as were 16 participants who showed severe hypertriglycemia (>4.0 g/L). Finally, 1,014 participants were included for further analysis (242 men, 772 women).

Data Collection and Laboratory Measurements

Height and weight were measured, and body mass index (BMI: kg/m^2) was calculated as an index of obesity. SBP and diastolic BP (DBP) were recorded at rest, simultaneously with the measurement of CAVI.

Blood samples were collected from each participant after overnight fast. Serum and plasma were separated and stored at –20°C and –80°C, respectively, until assay. Serum concentrations of total cholesterol (TC), triglyceride (TG), and high-density lipoprotein-cholesterol (HDL-C) were measured by standard laboratory procedures, and low-density lipoprotein-cholesterol (LDL-C) was calculated by the Friedwald equation. In addition to fasting blood sugar and hemoglobin A$_{1c}$ (HbA$_{1c}$), serum creatinine and uremic acid (UA) were measured by standard laboratory procedures. Plasma total HCY (tHCY) levels were measured using a high-performance liquid chromatographic method developed by Garcia and Apitz-Castro![17]

Table 2 Simple Correlation Analysis of CAVI and Other Variables

	Men	Women	All participants
BMI	–0.021	0.003	0.01
WC	0.062	0.16**	0.16**
SBP	0.21**	0.31**	0.28**
DBP	0.14*	0.17**	0.18**
TC	0.039	0.10**	0.042
TG	–0.036	0.14**	0.11**
HDL-C	0.031	–0.070	–0.080*
LDL-C	0.039	0.108**	0.050
HbA$_{1c}$	0.22**	0.18**	0.20**
Creatinine	0.12	0.14**	0.20**
UA	0.020	0.088*	0.13**
tHCY	0.11	0.11**	0.14**
CIMT	0.32**	0.37**	0.37**

**p<0.05 and **p<0.01. Abbreviations as in Table 1.*

Measurement of CAVI and CIMT

CAVI was recorded using a VaseraVS-1000 vascular screening system (Fukuda Denshi, Tokyo, Japan) with the participant resting in a supine position. The principles underlying CAVI have been described by Yambe et al[8] ECG electrodes are placed on both wrists, a microphone for detecting heart sounds is placed on the sternum, and cuffs are wrapped around both the arms and ankles. After automatic measurements, obtained data were analyzed using VSS-10 software (Fukuda Denshi), and the values of right and left CAVI were calculated. Averages of the right and left CAVI were used for analysis.

Measurement of CIMT by ultrasonography of the left and right carotid arteries was performed by 2 medical doctors (N.T. and M.N.), using a LOGIC Book XP with a 10-MHz linear array transducer (GE Medical Systems, Milwaukee, WI, USA). A detailed protocol has been described elsewhere![18] Averages of left and right CIMT were calculated and used in the analysis. Intra-observer variation of CIMT (N.T., n=32) was 0.91 (p<0.01), and interobserver variation (N.T. vs M.N., n=41) was 0.78 (p<0.01).

Statistical Analysis

Results are expressed as mean±standard deviation. Differences between women and men in the laboratory values were evaluated using the t-test. Multiple linear regression analysis was performed to evaluate CAVI and other existing parameters adjusted for confounding factors (age, sex, waist circumference (WC), SBP, TG, HDL-C, HbA$_{1c}$, creatinine, UA, tHCY and CIMT, Table 1), which showed significant correlations with CAVI by simple linear regression analysis in all subjects. Although DBP also showed a significant correlation with CAVI, it was not analyzed as a confounding factor, because of intercorrelation with SBP (r=0.80, p<0.01). Because TG and tHCY levels had a skewed distribution, logarithmic transformation was performed for the simple correlation analysis and multiple linear regression analysis. Probability values less than 0.05 were considered indicative of statistical significance. All statistical analyses were performed using SPSS v11.0 software (SPSS Japan, Tokyo, Japan).

Results

Characteristics of the study participants are shown in Table 1. The average age of the men was significantly older

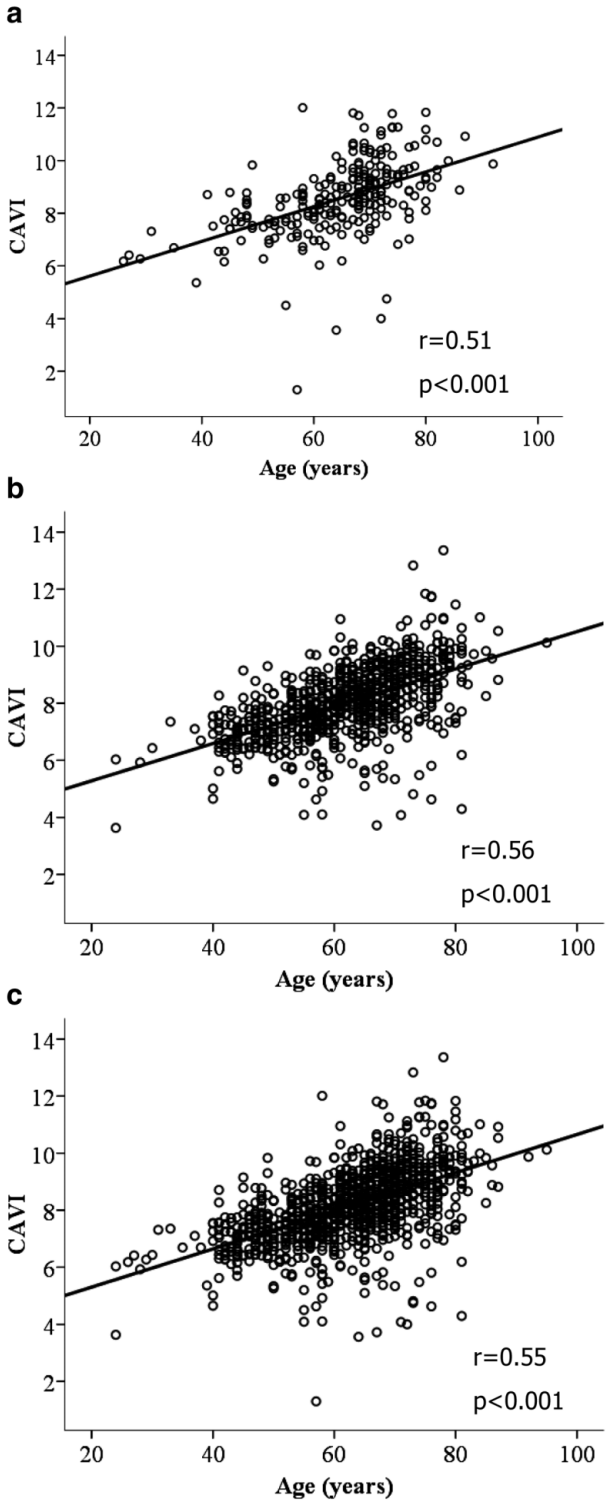

Fig 1. Relationship between cardio-ankle vascular index (CAVI) and age in (a) men (n=242), (b) women (n=772), and (c) all participants (n=1,014).

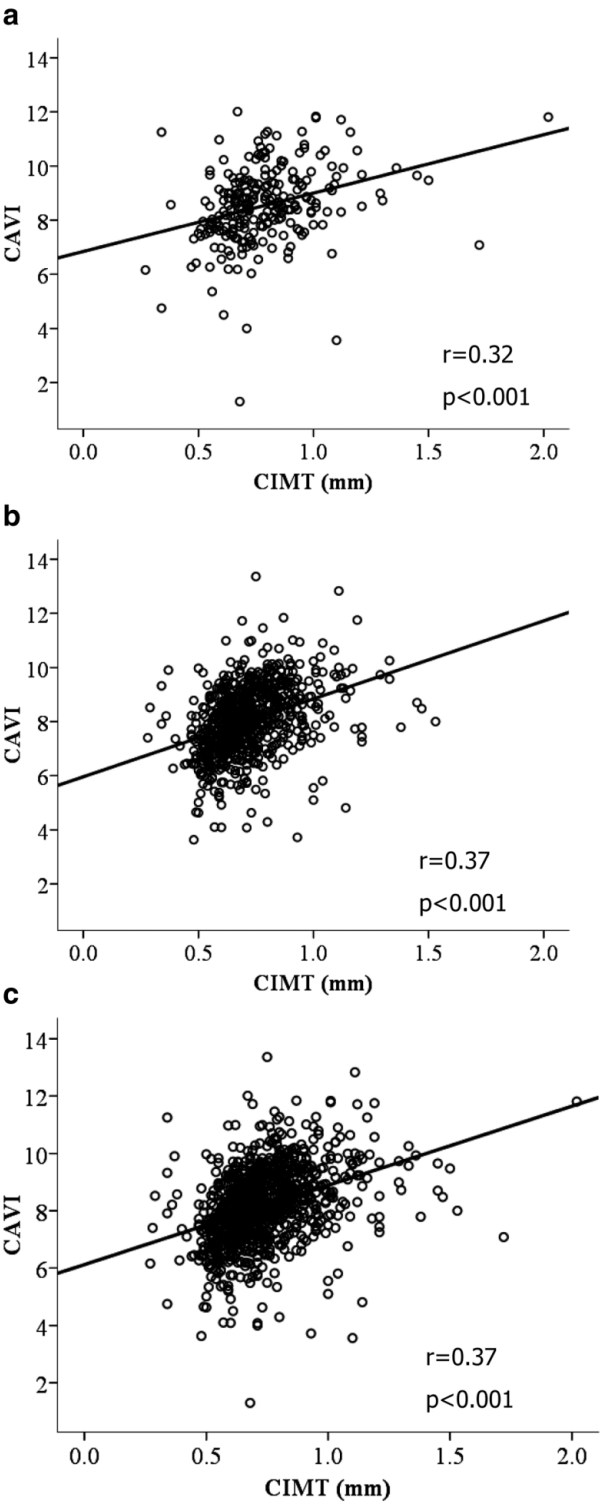

Fig 2. Relationship between cardio-ankle vascular index (CAVI) and carotid intima–media thickness (CIMT) in (a) men, (b) women, and (c) all participants.

than that of the women (64.2±11.1 years vs 61.9±10.7 years, p<0.01). Other than SBP and HbA_{1c}, all parameters showed significant differences between men and women.

By simple linear regression analysis, CAVI was significantly correlated with age in men (r=0.51, p<0.001), women (r=0.56, p<0.001), and all participants (r=0.55, p<0.001, Fig 1). It was also significantly correlated with CIMT in men (r=0.32, p<0.001) and in women (r=0.37, p<0.001) (Fig 2). Furthermore, CAVI was significantly correlated with SBP, DBP, HbA_{1c} and CIMT in men and with WC, SBP, DBP, TC, TG, LDL-C, HbA_{1c}, creatinine, UA, tHCY, and CIMT in women. In all participants, CAVI was signifi-

cantly correlated with WC, SBA, DBP, TG, HDL-C, HbA_{1c}, creatinine, UA, tHCY, and CIMT (Table 2).

By multiple linear regression analysis adjusted for confounding factors, CAVI was significantly correlated with age, SBP, DBP, HbA_{1c} tHCY in all subjects (Table 3). Also, CAVI was significantly correlated with CIMT. On the other hand, CAVI was not significantly correlated with TC, TG, HDL-C, and LDL-C.

Table 3 Multiple Linear Regression Analysis of CAVI With Relevant Factors Adjusted for Confounding Factors

	β	95%CI	p value
Age	*0.056*	*0.048, 0.063*	*<0.001*
Sex	*0.39*	*0.20, 0.59*	*<0.001*
WC	*–0.005*	*–0.012, 0.003*	*0.24*
SBP	*0.006*	*0.002, 0.009*	*0.002*
TG	*0.17*	*–0.20, 0.54*	*0.36*
HDL-C	*0.003*	*–0.002, 0.008*	*0.21*
HbA_{1c}	*0.18*	*0.062, 0.29*	*0.003*
Creatinine	*–0.27*	*–0.70, 0.15*	*0.21*
UA	*–0.012*	*–0.069, 0.044*	*0.67*
tHCY	*0.4*	*0, 0.80*	*0.05*
CIMT	*0.81*	*0.37, 1.26*	*<0.001*

β, *regression coefficient.*
CI, confidence interval. Other abbreviations as in Table 1.

Discussion

In this study, we screened CAVI in adults from the Japanese general population and showed that it is independently associated with age, sex, SBP, HbA_{1c}, tHCY and CIMT. Previous research has shown that in vivo aortic stiffness decreases sharply with age in the first decade of life, reaching a minimum at 10 years of age, and thereafter increases with age in both genders[19] The increase in central artery stiffness with age is responsible for earlier wave reflections and changes in pressure wave contours, and cross-sectional studies have shown that aortic PWV (aPWV) increases with age by approximately $0.1\,m \cdot s^{-1} \cdot year^{-1}$[20]. However, we demonstrated that CAVI increases with age about 0.066/year in this study, which suggests that CAVI, as with PWV, can serve as a marker for the increase in central artery stiffness with age.

CAVI is designed not to be affected by BP during measurement, but is probably affected by long-term hypertension. By simple linear regression analysis, Shirai et al recently reported that compared with baPWV, CAVI correlated weakly with SBP and did not correlate with DBP in patients on hemodialysis[12] However, we observed a significant correlation between CAVI and SBP/DBP in both men and women by simple linear regression analysis, and showed that CAVI independently correlated with SBP, after adjustment for confounding factors. In the general population, CAVI may reflect BP, whereas it is essentially independent of changes in BP during examination.

Although there is no doubt that LDL-C directly participates in atherosclerosis and is a major risk factor for CVD, we showed that CAVI was not significantly correlated with HDL-C or LDL-C. Previous reports also indicated a lack of association between baPWV and LDL-C;[21,22] suggesting that further evaluation of LDL-C, in combination with apolipoprotein B, which is a reasonable index of the number of LDL particles, might be appropriate to clarify the effect of lipid metabolism on CAVI.

We are the first to show that CAVI correlates with CIMT, after adjustment for confounding factors, in the general population. Currently, measurement of CIMT is widely used as a noninvasive method of quantifying arterial wall thickening and atherosclerosis progression, and increased CIMT has been shown to be a strong predictor of cardiovascular morbidity and mortality[4,23] Kobayashi et al reported that in patients with risk factors for atherosclerosis, CIMT was independently related to baPWV, and they suggested that the combination of CIMT and baPWV might give reliable information on clinical or subclinical atherosclerosis[10] Furthermore, Okura et al recently showed a significant positive correlation between CAVI and IMT by simple linear regression analysis in patients with hypertension[24] As with baPWV, the measurement of CAVI requires only a few minutes for the entire procedure. Our current results suggest that measurement of CAVI in combination with CIMT might be appropriate for screening of the general population, as well as for patients with atherosclerosis risk factors and for large-scale studies.

Interestingly, we observed that CAVI significantly correlated with HbA_{1c} in the general population after adjustment for confounding factors. It has been reported that baPWV is associated with fasting insulin levels and insulin-related factors, including HbA_{1c}, leading to reduced insulin sensitivity;[25] and our results suggest that, as with baPWV, CAVI may reflect glucose intolerance and possible insulin sensitivity. Further evaluation to clarify the relationship between CAVI and insulin sensitivity is needed.

After adjustment for confounding factors, CAVI was significantly correlated with tHCY, although we did not observe any differences in CAVI between the *CC* and *CT* vs *TT* genotypes of *C667T/MTHFR*. The association between baPWV and HCY is still controversial. Mayer et al evaluated the association between aPWV and tHCY in the general population and found a positive association, even after adjustment for conventional cardiovascular risk factors[26] On the other hand, de Bree et al conducted a similar cross-sectional analysis and concluded that tHCY concentration was not associated with arterial stiffness[27] In our study group, CIMT was significantly correlated with tHCY after adjustment for age and sex, which suggests that tHCY might be a marker relevant to atherosclerosis. However, we observed a complete lack of association of CAVI and *C667T/MTHFR* (data not shown), which suggests that careful elaboration is needed for the evaluation of HCY as a screening marker for atherosclerosis.

Study Limitations

First, we could not evaluate the current medication of participants, which might influence the values of CAVI and other markers, nor did we evaluate information about past/present history of coronary risk factors (hypertension, diabetes, hyperlipidemia and smoking). We also could not evaluate the relationship between CAVI and other atherosclerotic markers, such as high-sensitivity C-reactive protein and adipocytokines, including adiponectin and leptin.

Conclusion

We screened CAVI in adults from the Japanese general population, and our results indicate that it may be appropriate as a screening tool for atherosclerosis. Further studies are needed to establish a convenient and effective screening system for atherosclerosis using this technique.

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