Original Article

Evaluation of the Cardio-Ankle Vascular Index, a New Indicator of Arterial Stiffness Independent of Blood Pressure, in Obesity and Metabolic Syndrome

Noriko SATOH[1)], Akira SHIMATSU[1)], Yasuhisa KATO[2)], Rika ARAKI[3)], Kazunori KOYAMA[4)], Taiichiro OKAJIMA[5)], Makito TANABE[5)], Mariko OOISHI[6)], Kazuhiko KOTANI[1),7)], and Yoshihiro OGAWA[8)], for the Japan Obesity and Metabolic Syndrome Study (JOMS) Group

Aortic stiffness is predictive of cardiovascular diseases (CVD) and mortality in lifestyle-related diseases. The cardio-ankle vascular index (CAVI), a new index of arterial stiffness, was recently developed by measuring of pulse wave velocity (PWV) and blood pressure (BP). CAVI is adjusted for BP based on stiffness parameter β and is less influenced by BP, suggesting its superiority over brachial-ankle PWV (baPWV). However, there are currently no reports on the usefulness of CAVI as an atherogenic index in obesity and metabolic syndrome (MS). Among the 325 obese Japanese outpatients enrolled in the multi-centered Japan Obesity and Metabolic Syndrome Study, 216 patients (67%) met the criteria of MS according to the modified National Cholesterol Education Program–Adult Treatment Panel III. CAVI values were significantly higher in MS than in non-MS patients, whereas there was no significant difference in body mass index, total cholesterol, and low-density lipoprotein-cholesterol between both groups. CAVI values were weakly correlated with BP but closely correlated with the severity of MS and MS-related parameters such as hypoadiponectinemia, relative to baPWV. Furthermore, weight-reduction therapy through diet and exercise over a 3-month period significantly decreased CAVI values in parallel with increasing adiponectin. This study demonstrates for the first time that CAVI is a good indicator of arterial stiffness. It is closely correlated with the severity of MS and CVD risks in obesity and independent of BP, and is thus superior to baPWV. Therefore, the determination of arterial stiffness by CAVI may be useful for evaluating and managing the CVD risks of MS patients. (*Hypertens Res* 2008; 31: 1921–1930)

***Key Words*: arterial stiffness, obesity, metabolic syndrome, cardiovascular risk, blood pressure**

From the [1)]Clinical Research Institute for Endocrine Metabolic Diseases, Kyoto Medical Center, Kyoto, Japan; [2)]Diabetes Center, National Hospital Organization, Nagoya Medical Center, Nagoya, Japan; [3)]Internal Medicine, National Hospital Organization, Mie Hospital, Tsu, Japan; [4)]Internal Medicine, National Hospital Organization, Tokyo Medical Center, Tokyo, Japan; [5)]Department of Internal Medicine and Department of Clinical Research, National Hospital Organization, Kokura Hospital, Kitakyushu, Japan; [6)]Ooishi Clinic, Kyoto, Japan; [7)]Department of Clinical Laboratory Medicine, Jichi Medical University, Shimotsuke, Japan; and [8)]Department of Molecular Medicine and Metabolism, Medical Research Institute, Tokyo Medical and Dental University, Tokyo, Japan.

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Address for Reprints: Noriko Satoh, M.D., Ph.D., Clinical Research Institute for Endocrine Metabolic Diseases, National Hospital Organization, Kyoto Medical Center, 1–1 Fukakusa Mukaihata-cho, Fushimi-ku, Kyoto 612–8555, Japan. E-mail: nsato@kyotolan.hosp.go.jp

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Introduction

Metabolic syndrome (MS) is characterized by multiple risk factors of atherosclerosis such as obesity, elevated blood pressure (BP), elevated glucose, and dyslipidemia (*1*). Several epidemiological studies have demonstrated that MS increases the risk of all-cause mortality and cardiovascular morbidity and mortality (*2*, *3*). It is therefore important to predict and prevent the onset or progression of cardiovascular disease (CVD) in MS patients.

Aortic stiffness, a direct indicator of arterial distensibility, has been highly predictive of CVD mortality in type 2 diabetic patients (*4*). We previously demonstrated that treatment with pioglitazone, an insulin-sensitizing agent, significantly decreases brachial-ankle pulse wave velocity (baPWV), suggesting that it has an anti-atherogenic effect in type 2 diabetic patients (*5*). However, baPWV is affected by BP and even by the activity of the autonomic nervous system (*6*–*8*). Recently, a new index of arterial stiffness, the cardio-ankle vascular index (CAVI), was developed. The index is calculated from the heart-ankle PWV (haPWV), adjusted for BP based on stiffness parameter β (*8*). Indeed, CAVI has been reported to be correlated with other CVD risks, thus reflecting the degree of atherosclerotic change with good reproducibility in patients having routine health checkups, those with type 2 diabetes and hemodialysis patients with atherosclerotic diseases (*9*, *10*). In addition, in patients with a high risk of CVD and cardiac diseases, the accuracy and usefulness of CAVI have also been reported to be comparable with other parameters of atherosclerosis, suggesting the utility of CAVI as a long-term predictor of the risk of CVD (*11*–*13*). However, there have been no large population-based studies on the usefulness of CAVI in obesity and MS, a precursor of CVD. Moreover, no prospective study of CAVI has reported on its interventional therapeutic effect in other areas, such as weight-reduction therapy, which contributes to a decrease in the risk of atherosclerotic disease (*14*, *15*).

It is important to establish the clinical relevance of CAVI in relation to MS and to understand its superiority over other known indicators of arterial distensibility such as baPWV. This study was designed to examine 1) the relationship of CAVI to CVD risk in obesity and MS and 2) the effect of diet- and exercise-induced weight reduction on CAVI. To properly examine these issues, we conducted a multi-center study with a large sample size and with both cross-sectional and prospective designs.

Methods

Subjects

A total of 325 obese Japanese outpatients (135 men and 190 women, mean age 52.5 years) were consecutively enrolled in a multi-center study (Japan Obesity and Metabolic Syndrome Study [JOMS]) that involved five National Hospital Organization hospitals (Kyoto, Tokyo and Nagoya Medical Centers and Kokura and Mie Hospitals) and the Ooishi Clinic in Japan as part of a study conducted by the Policy Based Medical Service Network for Endocrine and Metabolic Diseases during the period from October 2005 to March 2007. Each institution's ethical committee approved this study, and all patients gave written informed consent. The JOMS study has been registered in the University Hospital Medical Information Network (UMIN) system (UMINStudyID: UMIN000000559), which is open to the public. The study was designed to assess the characteristics of MS and the success rate and effect of weight-reduction therapy with diet and exercise guidance for preventing CVD in obese Japanese patients. We recruited obese subjects who had a body mass index (BMI) of $\geq$25 kg/m^2. Exclusion criteria were previous history of CVD, other vascular diseases, apparent renal disease, or severe liver dysfunction. In this study, the data on CAVI were obtained from the JOMS study.

Diagnostic Criteria of MS

Obese patients were classified as having MS or not (non-MS) according to the criteria proposed by the U.S. National Cholesterol Education Program–Adult Treatment Panel III (NCEP-ATPIII) (*16*). Accordingly, those who had at least three of the following factors were judged as having MS and those with fewer than three were judged as being non-MS subjects. The factors were as follows: 1) raised concentration of triglycerides (TG)$\geq$150 mg/dL; 2) reduced concentration of high-density lipoprotein-cholesterol (HDL-C) $<$40 mg/dL for men and $<$50 mg/dL for women; 3) raised BP: systolic BP (SBP)$\geq$130 mmHg or diastolic BP (DBP)$\geq$85 mmHg or previously diagnosed cases of hypertension (HT); 4) raised fasting plasma glucose concentration (FPG)$\geq$110 mg/dL or previously diagnosed cases of diabetes mellitus (DM); and 5) raised threshold for waist circumference (WC) to define central adiposity as $\geq$85 cm for men and $\geq$90 cm for women. Since the Japanese are less obese than those in the United States and have relatively low WCs, we employed as diagnostic criteria for central adiposity those proposed by the National Metabolic Syndrome Criteria Study Group of Japan in 2005 (*17*).

Data Collection and Laboratory Assay Methods

Height and weight were measured, and BMI was calculated as weight in kg divided by the square of height in m as an index of obesity. WC was measured at the level of the umbilicus in the standing position. SBP and DBP were measured twice with an automatic electronic sphygmomanometer (BP-103i II; Nippon Colin, Komaki, Japan). Blood was taken from the antecubital vein in the morning after a 12-h fast without the intake of medication to determine FPG, hemoglobin A1c (HbA1c), immunoreactive insulin (IRI), total cholesterol

Table 1. Baseline Characteristics with and without MS According to the Criteria Proposed by the NCEP-ATPIII for Metabolic Syndrome

	Non-MS	MS	*p* value
Male/female	35/74	100/116	0.014
Age (years)	49.4±1.4	53.9±0.9	0.006
BMI (kg/m^2)	30.8±0.7	30.8±0.3	0.999
Waist circumference (cm)	96.4±1.6	101±0.8	0.008
Systolic blood pressure (mmHg)	131±1.4	143±1.1	<0.001
Diastolic blood pressure (mmHg)	78.7±1.1	84.5±0.9	<0.001
Fasting plasma glucose (mmol/L)	5.84±0.18	7.77±0.22	<0.001
HbA1c (%)	5.99±0.12	6.86±0.09	<0.001
IRI (pmol/L)	92.9±10.4	142±14.8	0.030
HOMA-R	4.40±0.71	9.56±1.67	0.034
Total cholesterol (mmol/L)	5.31±0.08	5.49±0.13	0.377
Triglyceride (mmol/L)	1.33±0.06	2.26±0.13	<0.001
HDL-C (mmol/L)	1.54±0.03	1.33±0.02	<0.001
LDL-C (mmol/L)	3.20±0.07	3.22±0.06	0.845
Leptin (ng/mL)	14.9±1.15	14.9±0.87	0.807
Adiponectin (μg/mL)	8.05±0.49	7.06±0.30	0.048
CRP (μg/mL)	1.05±0.12	1.46±0.12	0.030
baPWV (cm/s)	1,318±23	1,448±21	<0.001
CAVI	7.41±0.13	8.13±0.11	<0.001
Proportion of			
Hypertension (%)	40.4	81.9	0.003
Diabetes (%)	23.9	83.7	<0.001
Dyslipidemia (%)	22.0	77.2	<0.001
Taking calcium antagonist (%)	13.8	34.4	<0.001
Taking ACE/ARB (%)	16.5	49.3	<0.001
Taking anti-diabetic medications (%)	20.2	58.3	<0.001
Taking statins (%)	13.7	30.7	<0.001
Current smoker (%)	12.8	20.9	0.075

Data are expressed as the mean±SEM. BMI, body mass index; IRI, immunoreactive insulin; HOMA-R, homeostasis model assessment; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; CRP, high-sensitive C-reactive protein; baPWV, brachial-ankle pulse wave velocity; CAVI, cardio-ankle vascular index; ACE, angiotensin-converting enzyme; ARB, angiotensin II type 1 receptor blocker.

(TC), low-density lipoprotein-cholesterol (LDL-C), HDL-C, TG, high-sensitive C-reactive protein (CRP), leptin, and adiponectin levels. FPG, HbA1c, TC, LDL-C, HDL-C, and TG levels were determined according to standard procedures. IRI was measured by an enzyme immunoassay (Tosoh, Tokyo, Japan). The insulin resistance index was assessed by the homeostasis model assessment (HOMA-R) (*5*). The CRP and adiponectin levels were measured with enzyme-linked immunosorbent assays (ELISA) (Assay Pro, St. Charles, USA, and Otsuka Pharmaceutical, Tokyo, Japan, respectively). The leptin levels were determined using a radioimmunoassay (Linco Research, St. Charles, USA) (*5*).

Measurements of CAVI and baPWV

CAVI and baPWV were determined using a Vasera VS-1000 vascular screening system (Fukuda Denshi, Tokyo, Japan) (*8*, *10*, *18*). The ECG, phonocardiograph, and pressures and waveforms of brachial and ankle arteries were measured, and the cardio-ankle PWV and CAVI values were automatically calculated by the Vasera VS-1000. CAVI values were obtained by substituting the stiffness parameter β in the following equation for detecting vascular elasticity and PWV: stiffness parameter $\beta = 2\rho \times 1/(P_s - P_d) \times \ln(P_s/P_d) \times PWV^2$ (ρ is blood density, P_s and P_d are SBP and DBP in mmHg, respectively, and PWV was measured between the aortic valve and the ankle) (*8*, *10*). Therefore, CAVI, which represents the stiffness of the aorta, is not affected by BP. The principles underlying CAVI have been described in detail by Yambe *et al*. (*8*) and Shirai *et al*. (*10*). The average coefficient of variation of CAVI is less than 5%, which is small enough for clinical use and confirms that CAVI has good reproducibility (*10*).

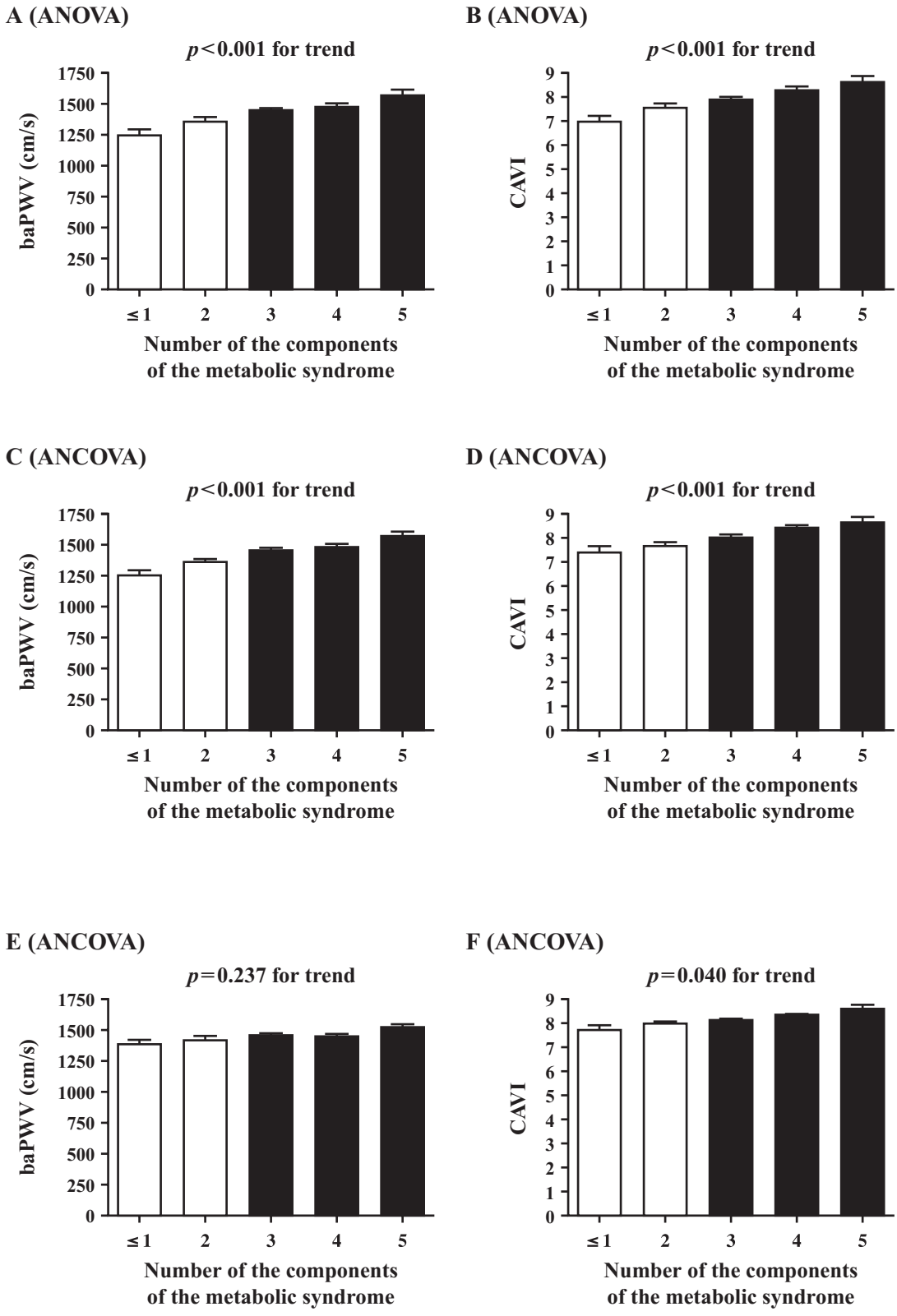

Fig. 1. *The values of baPWV (A), CAVI (B), age-adjusted baPWV (C), age-adjusted CAVI (D), age- and SBP-adjusted baPWV (E), and age- and SBP-adjusted CAVI (F), stratified by number of components of metabolic syndrome according to the criteria proposed by the NCEP-ATPIII. Data are mean±SEM. Differences between groups were assessed by ANOVA and ANCOVA. Non-metabolic syndrome and metabolic syndrome are indicated by open and closed bars, respectively.*

Table 2. Baseline Correlations Related to baPWV and CAVI

	baPWV			CAVI		
	Partial correlation coefficients	Partial correlation coefficients (age-adjusted)	Partial correlation coefficients (age- and SBP-adjusted)	Partial correlation coefficients	Partial correlation coefficients (age-adjusted)	Partial correlation coefficients (age- and SBP-adjusted)
Age	0.582**	—	—	0.726**	—	—
BMI	−0.131**	−0.078	−0.109*	−0.191†	−0.142**	−0.150**
Waist circumference	−0.108*	−0.039	−0.086*	−0.192†	−0.115**	−0.142**
Systolic blood pressure	0.340†	0.290†	—	0.176**	0.112*	—
Diastolic blood pressure	−0.022	0.196†	−0.025	−0.036	0.069	−0.025
Fasting plasma glucose	0.142**	0.135**	0.123*	0.180†	0.136**	0.133**
HbA1c	0.027	0.043	0.021	0.112*	0.089*	0.078*
IRI	0.075	0.078	0.077	0.065	0.039	0.038
HOMA-R	0.075	0.069	0.067	0.123*	0.102*	0.099*
Total cholesterol	0.049	0.035	0.037	0.081	0.053	0.058
Triglyceride	0.101*	0.095*	0.076	0.113*	0.079*	0.078*
HDL-C	−0.060	−0.066	−0.050	−0.134**	−0.104**	−0.096*
LDL-C	0.083	0.082	0.073	0.016	0.014	0.020
Leptin	−0.046	0.020	−0.027	−0.076	−0.011	−0.031
Adiponectin	−0.085	−0.084	−0.085	−0.211†	−0.147**	−0.154**
CRP	0.001	0.015	0.005	−0.029	−0.019	−0.017

SBP, systolic blood pressure; other abbreviations used in this table are the same as in Table 1. *$p<0.05$, **$p<0.01$, †$p<0.001$.

Weight-Reduction Therapy

Of the patients enrolled in this study, 166 obese patients (71 men and 95 women, mean age 53.4 years, mean BMI 30.4) were subjected to weight-reduction therapy through lifestyle modifications to reduce energy intake and increase physical activity for 3 months. The prescribed diet consisted of 25 kcal/kg of ideal body weight per day, and subjects were instructed to exercise for at least 30 min at a moderate intensity at least 3 d/week (*19*). Before and 3 months after the end of the weight-reduction therapy, we measured MS-related data such as BMI, WC, BP, and blood variables and calculated CAVI values for each patient. Intake of antihypertensive, diabetic, and anti-hyperlipidemic agents was unchanged. To confirm subjects' compliance, we also monitored their diet and exercise records. We defined those who were able to reduce their body weight by 5% or more and as successful in weight reduction, and those who reduced their body weight less than 5% as unsuccessful. Presumably the unsuccessful patients did not follow the diet and exercise therapy instructions.

Statistical Analysis

Data are presented as the mean±SEM, and $p<0.05$ was considered statistically significant. The χ^2 test was used for making a baseline comparison between categorical variables, and when the comparison involved continuous variables, a Student's two-tailed *t*-test was used. Pearson's correlation coefficients were used to investigate the correlation of CAVI with baPWV, age and SBP, and to assess the partial correlation of CAVI with metabolic parameters, with successive adjustment for 1) age and 2) age and SBP. The mean CAVI values were stratified by the number of components of MS using ANOVA and ANCOVA, adjusted for the covariates of age and SBP. A stepwise multivariate regression analysis was performed to elucidate factors related to the CAVI values in all subjects. Two-way repeated measures ANOVA was performed to compare changes in CAVI values over 3 months between those successful and unsuccessful in weight reduction. Pearson's correlation coefficients were used to investigate the correlation of the changes in CAVI values with the changes in metabolic parameters during weight reduction. All statistical analyses were performed using Stat View version 5.0 for Windows (SAS Institute Inc., Cary, USA).

Results

Baseline Clinical Characteristics of Patients with and without MS

Table 1 summarizes the characteristics of the study cohort, comparing those with and without MS. The prevalence of MS among patients in this study was 66.5% according to the NCEP-ATPIII guidelines (Table 1). Age, the percentage of males, WC, SBP, DBP, FPG, HbA1c, IRI, HOMA-R, TG,

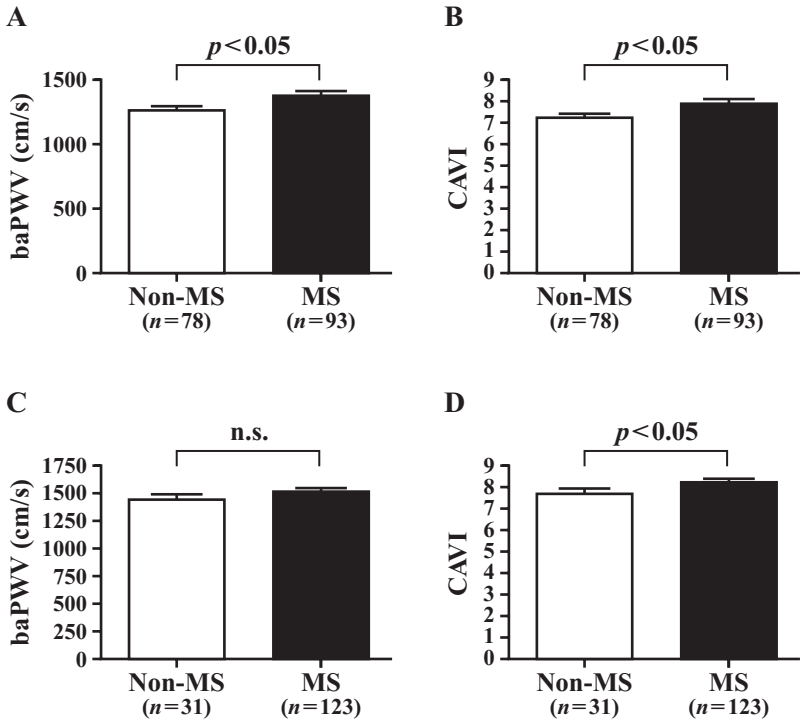

Fig. 2. *Comparision between the means of baPWV and CAVI after dividing all patients into classes with and without high blood bressure (BP). baPWV (A) and CAVI (B) in non-MS and MS patients without high BP (SBP < 140 mmHg and DBP < 90 mmHg). baPWV (C) and CAVI (D) in non-MS and MS patients with high BP (SBP ≥ 140 mmHg or DBP ≥ 90 mmHg). Data are means ± SEM. Differences between groups were assessed by Student's two-tailed t-test.*

and CRP levels and baPWV were significantly higher in the MS group than in the non-MS group, while BMI, TC, LDL-C and leptin levels did not differ between the groups. HDL-C and adiponectin levels were significantly lower in the MS groups than in the non-MS groups. CAVI values were also significantly (11%) higher in MS patients than in non-MS patients (Table 1). When we analyzed the data separately for men and women, it was found that gender was not an influential factor, as demonstrated in Online Table 1.

We also examined the mean of CAVI values and the mean of age- and SBP-adjusted CAVI stratified by the number of risk factors for MS in all subjects. The means of CAVI and age-adjusted CAVI were increased according to the number of risk factors ($p<0.001$) (Fig. 1B and D). Even after adjusting for both age and SBP, the higher the number of risk factors, the higher the CAVI values ($p<0.05$) (Fig. 1F).

Correlation between MS-Related Parameters and CAVI

A linear regression analysis of all the enrolled patients demonstrated that CAVI values were strongly correlated with age ($r=0.726$) and weakly with SBP ($r=0.176$, Table 2 and Online Fig. 2B, D), as in previous studies (*9*, *10*). The CAVI values and those of age-adjusted CAVI had significant positive correlations with SBP, FPG, HbA1c, HOMA-R and TG and negative correlations with BMI, WC, HDL-C and adiponectin (Table 2). In this study, age- and SBP-adjusted CAVI also showed significant positive correlations with FPG, HbA1c, HOMA-R, and TG and negative correlations with BMI, WC, HDL-C, and adiponectin (Table 2). FPG, HbA1c, IRI and HOMA-R levels had significant positive correlations with CAVI values in women, but the levels of these factors were not correlated with CAVI in men. However, the serum levels of TG and HDL-C were significantly correlated with CAVI in men, although these were not correlated with CAVI in women (Online Tables 2 and 3).

Comparison between CAVI and baPWV

There was a close correlation between CAVI and baPWV in all the patients enrolled ($r=0.784$) (Online Fig. 1). Both CAVI and baPWV were significantly correlated with age (Online Fig. 2A, B). In this study, baPWV was strongly correlated with SBP ($r=0.340$) (Table 2, Online Fig. 2C), whereas CAVI showed a weak correlation with SBP ($r=0.176$) (Table 2, Online Fig. 2D). In these analyses, baPWV and CAVI values were significantly correlated with age and SBP; therefore we also analyzed the correlations of metabolic and proatherogenic factors with age-adjusted

Table 3. Effect of Weight Reduction in Obese Patients on the Metabolic Variables, baPWV and CAVI

	Group unsuccessful in weight reduction		Group successful in weight reduction	
	Before	3 months	Before	3 months
Male/female	50/67		21/28	
Age (years)	53.6±1.3		53.0±2.0	
Body weight (kg)	77.5±1.5	77.7±1.6	80.2±2.5	73.8±2.2**
BMI (kg/m^2)	30.0±0.4	30.1±0.5	31.4±0.7	28.9±0.7**
Waist circumference (cm)	97.6±1.2	97.1±1.1	98.1±1.4	94.6±1.4**
Systolic blood pressure (mmHg)	138±1.2	138±1.4	134±2.5	129±2.2
Diastolic blood pressure (mmHg)	81.6±1.0	81.5±1.0	78.9±1.9	76.9±1.4
Fasting plasma glucose (mmol/L)	7.11±0.2	6.88±0.3	7.93±0.6	6.83±0.4**
HbA1c (%)	6.59±0.1	6.60±0.1	6.71±0.2	6.41±0.2
IRI (pmol/L)	127±18	130±18	110±22	85.2±14
HOMA-R	7.06±1.2	6.23±0.9	7.93±2.1	4.56±0.8
Total cholesterol (mmol/L)	5.28±0.1	5.30±0.1	5.15±0.1	5.02±0.1
Triglyceride (mmol/L)	1.80±0.1	1.78±0.1	1.79±0.1	1.67±0.1
HDL-C (mmol/L)	1.46±0.03	1.46±0.04	1.41±0.05	1.43±0.05
LDL-C (mmol/L)	3.15±0.07	3.18±0.07	3.03±0.12	2.90±0.11
Leptin (ng/mL)	12.7±1.0	13.1±0.9	13.0±1.7	10.2±1.0**
Adiponectin (μg/mL)	7.34±0.3	7.64±0.3	6.61±0.5	7.90±0.5**
CRP (μg/mL)	1.21±0.1	1.12±0.1	1.38±0.2	1.03±0.1
baPWV (cm/s)	1,419±25	1,416±25	1,400±46	1,344±40 **
CAVI	8.07±0.1	7.98±0.1	7.84±0.3	7.62±0.2**

Abbreviations used in this table are the same as in Table 1. *$p<0.05$, **$p<0.01$, $^{\dagger}p<0.001$ *vs*. before.

baPWV or CAVI, and age- and SBP- adjusted baPWV or CAVI (Table 2). In this study, age-adjusted baPWV showed significant correlations only with SBP, DBP, FPG, and TG, and age- and SBP-adjusted baPWV showed significant correlations only with FPG, whereas age-adjusted CAVI or age- and SBP-adjusted CAVI showed significant positive correlations with many variables, including hypoadiponectinemia (Table 2). Interestingly, in a stepwise multivariate linear regression analysis, the independent variables contributing to increased CAVI values were not only the increases in age, SBP, and FPG but decreases in WC, HDL-C, and adiponectin, although the independent variables contributing to the increase in baPWV were only increases in age, SBP, and FPG (Online Table 4).

Furthermore, both CAVI and age-adjusted CAVI were significantly associated with the number of risk factors (Fig. 1B, D), as were baPWV and age-adjusted baPWV (Fig. 1A, C). However, when both age and SBP were adjusted, CAVI was significantly associated with the number of risk factors, whereas baPWV was not (Fig. 2E, F).

We also compared the mean values of CAVI and baPWV in patients with or without high BP according to the guidelines of the Japanese Society of Hypertension (*20*). When BP was low (SBP<140 mmHg and DBP<90 mmHg), both CAVI and baPWV were higher in MS patients than in non-MS patients ($p<0.05$) (Fig. 2A, B). However, when BP was high (SBP≥140 mmHg or DBP≥90 mmHg), CAVI showed a significantly higher correlation with MS than non-MS patients ($p<0.05$) (Fig. 2D). In fact, in these patients, there was no significant difference in baPWV between MS and non-MS patients ($p=0.11$) (Fig. 2C). Incidentally, in both the low and high BP groups, MS patients had higher levels of CRP, a marker of inflammation and an independent predictor for the development of CVD (*3*, *5*), than those in non-MS patients (low BP group: non-MS 1.03±0.10 μg/mL, MS 1.40±0.14 μg/mL, $p<0.05$; high BP group: non-MS 1.06±0.13 μg/mL, MS 1.49±0.15 μg/mL, $p<0.05$) (data not shown).

Effect of Body Weight Reduction on CAVI Values of Obese Subjects

Of 166 patients, 49 (30%) successfully reduced body weight more than 5%. In those patients, BMI, WC, FPG, and leptin decreased and adiponectin increased. CAVI values, as well as those for baPWV, were significantly lower 3 months after the start of the period of diet and exercise (Table 3). Of the patients who were unsuccessful in reducing their weight ($n=117$), the above variables did not change throughout the observation period. Importantly, by repeated measures ANOVA, CAVI values declined significantly only in those successful in weight reduction ($p=0.015$). The decrease in CAVI values was strongly correlated with the decrease in BMI and the increase in adiponectin, whereas the decrease of baPWV was not significantly correlated with increase in adiponectin (Online Table 5). Multivariate regression analysis ($r^2=0.12$) also revealed that the decrease in BMI and the

increase in adiponectin were independent determinants of the changes in CAVI (β=0.171, −0.162, p=0.029, 0.039) (data not shown).

Discussion

This investigation is the first to examine the clinical relationship between metabolic syndrome and CAVI, a newly developed indicator of arterial stiffness. This study is the first to demonstrate that CAVI values are higher in obese MS patients than in obese non-MS patients. Because we recruited patients with a BMI of ≥25 kg/m^2 for this study, higher levels of MS-related variables were found even in the non-MS group, perhaps explaining why no marked differences in adipocytokines such as leptin were observed between the groups. Nonetheless, CAVI values were substantially higher in the MS than the non-MS group. An increase in the number of MS components has been reported to be related to worsening pathophysiology and to an increased risk of atherosclerotic diseases (*3*, *21*). There is also a significant positive correlation between CAVI values and the number of components of MS, even after adjustments for age and SBP. These observations clearly indicate that CAVI values are tightly correlated with the development of MS.

Our data demonstrate the significant correlation between CAVI and MS-related parameters other than BP, all of which are known to contribute to atherogenesis. Multivariate regression analysis revealed that increased SBP and FPG and decreased HDL-C and adiponectin are the important determinants of age-adjusted CAVI. Adiponectin, the only established adipocytokine with anti-atherogenic and anti-inflammatory properties, is recognized to be an important mediator linking adiposity and atherosclerosis in the adipovascular axis of the MS patients (*22*, *23*). These observations suggest that an increased CAVI is related to hypoadiponectinemia, a predictor of the onset of diabetes and future adverse cardiac events. It was recently reported that CAVI was significantly correlated with the number of stenotic vessels found by coronary angiography and that only CAVI, not intima-media thickness (IMT) and plaque score, was associated with severity of coronary atherosclerosis (*13*). Taken together, these findings suggest that CAVI provides a more sensitive predictor of CVD in MS patients.

In this study, we demonstrated that CAVI shows a good correlation with baPWV (r=0.784), which also suggests that CAVI similarly serves as a predictor of CVD. Previous studies showed that baPWV is correlated with MS and its components in healthy subjects, patients with impaired fasting glucose or those with a risk of CVD (*24–26*). However, there have been no reports on arterial stiffness in obese patients, even as assessed by baPWV. Our finding in obese patients is consistent with recent studies about the accuracy and usefulness of CAVI with patients in groups at high risk for CVD and cardiac diseases, as compared with other representative parameters of atherosclerosis and coronary events, such as the aortic stiffness parameter β, IMT, and left ventricular diastolic function. Thus, CAVI appears to be a long-term indicator for CVD risk (*11–13*).

This study showed the advantages of CAVI, which is only weakly correlated with SBP and shows no correlation with DBP in obese patients, as is the case with healthy subjects and hemodialysis patients (*9*, *10*). These characteristics of CAVI are in contrast to those of baPWV, which is highly correlated with SBP and DBP even after age adjustment. Indeed, age-adjusted CAVI had a markedly weak correlation with SBP compared with age-adjusted baPWV. These data correspond with the report that CAVI is less influenced by changes in BP during exercise stress, showing the reliability and advantage of CAVI as an index of atherosclerosis in obese or MS patients with labile BP (*27*). Furthermore, probably because of its independence of BP, we found that CAVI was more useful than baPWV in obese patients with high BP. Of the enrolled patients with low BP, both CAVI and baPWV were higher in MS than non-MS patients. However, in patients with high BP, CAVI values in MS patients were higher than in non-MS patients, unlike baPWV values, which showed no difference between MS and non-MS patients. The reason may be the inability of baPWV to detect slight differences in arterial stiffness in non-MS patients compared with MS patients who had significantly higher levels of CRP, independent of the risk of CVD (*3*). However, CAVI seemed to be able to estimate the differences in development of atherosclerosis between non-MS and MS patients in the high BP group, since it is not affected by high BP. Because high BP is a component of MS and is a major risk factor for CVD (*28*), the data in this study suggest the superiority of CAVI over baPWV as an atherogenic index in MS and obese patients.

In this study, age- and SBP-adjusted CAVI increased according to the number of risk factors of MS, while age- and SBP-adjusted baPWV were unchanged. Since baPWV is affected by BP, baPWV may not be as sensitive in detecting mild vascular dysfunction. Thus, CAVI, and not baPWV, may be more closely associated with MS-related parameters such as hypoadiponectinemia. In this regard, in obese subjects who have a tendency toward HT, CAVI can successfully detect the presence of subclinical atherosclerosis as risk factors pile up. Taken together, CAVI, rather than baPWV, may be associated with atherosclerotic changes in obesity and MS, possibly as a result of the dysregulation of adipocytokine production and chronic intravascular inflammation. It is conceivable that CAVI may help assess the progression of atherosclerosis even during its early phase in patients with obesity and MS.

We noted several sex-related differences in the relationship between CAVI level and MS variables. In contrast to men, there was a significant relationship between CAVI and impaired glucose tolerance in women. Interestingly, the increase in CAVI was significantly correlated with TG and HDL-C in men but not in women. This result might represent a difference in the pathophysiological mechanisms of

impaired glucose tolerance or dyslipidemia between men and women. Further studies are needed on the precise mechanisms of such sex differences.

Interestingly, our longitudinal study is the first to show that successful short-term weight reduction dramatically reduces CAVI. Until now, clinical evidence linking improvement in MS state by weight loss and vascular destiffening was lacking (*29*), and there are few papers showing the effect of weight reduction on baPWV over a long period in obese individuals (*30*). Therefore, the effect of short-term weight-reduction therapy on arterial stiffness has not been reported. Our data are consistent with the notion that modest weight reduction through short-term lifestyle modification alleviates insulin resistance and vascular impairments such as endothelial activation and adhesion molecules (*15*, *31*), thereby highlighting the beneficial effect of weight reduction on vascular function in obesity. In this study, low CAVI values were significantly correlated with increased adiponectin, whereas baPWV values had no such correlation. Given that CAVI sensitively reflects slightly improved vascular function, it will help evaluate how successful therapy intervention of any kind may be with respect to the reduction of atherosclerotic risk.

In conclusion, this study demonstrates for the first time that CAVI is a good atherogenic index. Because it is unaffected by BP, it is superior to baPWV. Our longitudinal study also shows that CAVI is a sensitive index for detecting slightly improved arterial distensibility caused by short-term weight-reduction therapy. The data of this study should stimulate future research as to whether CAVI can provide an enhanced diagnosis index, risk stratification, therapeutic intervention effect, and possibly prognostic information regarding MS and the CVD associated with it.

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References

1. Eckel RH, Grundy SM, Zimmet PZ: The metabolic syndrome. *Lancet* 2005; **365**: 1415–1428.
2. Isomaa B, Almgren P, Tuomi T, *et al*: Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care* 2001; **24**: 683–689.
3. Ridker PM, Buring JE, Cook NR, Rifai N: C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events: an 8-year follow-up of 14 719 initially healthy American women. *Circulation* 2003; **107**: 391–397.
4. Cruickshank K, Riste L, Anderson SG, Wright JS, Dunn G, Gosling RG: Aortic pulse-wave velocity and its relationship to mortality in diabetes and glucose intolerance: an integrated index of vascular function? *Circulation* 2002; **106**: 2085–2090.
5. Satoh N, Ogawa Y, Usui T, *et al*: Antiatherogenic effect of pioglitazone in type 2 diabetic patients irrespective of the responsiveness to its antidiabetic effect. *Diabetes Care* 2003; **26**: 2493–2499.
6. Matsui Y, Kario K, Ishikawa J, Eguchi K, Hoshide S, Shimada K: Reproducibility of arterial stiffness indices (pulse wave velocity and augmentation index) simultaneously assessed by automated pulse wave analysis and their associated risk factors in essential hypertensive patients. *Hypertens Res* 2004; **27**: 851–857.
7. Ito N, Ohishi M, Takagi T, *et al*: Clinical usefulness and limitations of brachial-ankle pulse wave velocity in the evaluation of cardiovascular complications in hypertensive patients. *Hypertens Res* 2006; **29**: 989–995.
8. Yambe T, Yoshizawa M, Saijo Y, *et al*: Brachio-ankle pulse wave velocity and cardio-ankle vascular index (CAVI). *Biomed Pharmacother* 2004; **58**: S95–S98.
9. Kubozono T, Miyata M, Ueyama K, *et al*: Clinical significance and reproducibility of new arterial distensibility index. *Circ J* 2007; **71**: 89–94.
10. Shirai K, Utino J, Otsuka K, Takata M: A novel blood pressure–independent arterial wall stiffness parameter; cardio-ankle vascular index (CAVI). *J Atheroscler Thromb* 2006; **13**: 101–107.
11. Mizuguchi Y, Oishi Y, Tanaka H, *et al*: Arterial stiffness is associated with left ventricular diastolic function in patients with cardiovascular risk factors: early detection with the use of cardio-ankle vascular index and ultrasonic strain imaging. *J Card Fail* 2007; **13**: 744–751.
12. Takaki A, Ogawa H, Wakeyama T, *et al*: Cardio-ankle vascular index is a new noninvasive parameter of arterial stiffness. *Circ J* 2007; **71**: 1710–1714.
13. Nakamura K, Tomaru T, Yamamura S, Miyashita Y, Shirai K, Noike H: Cardio-ankle vascular index is a candidate predictor of coronary atherosclerosis. *Circ J* 2008; **72**: 598–604.
14. Esposito K, Pontillo A, Di Palo C, *et al*: Effect of weight loss and lifestyle changes on vascular inflammatory markers in obese women: a randomized trial. *JAMA* 2003; **289**: 1799–1804.
15. Dengel DR, Kelly AS, Olson TP, Kaiser DR, Dengel JL, Bank AJ: Effects of weight loss on insulin sensitivity and arterial stiffness in overweight adults. *Metabolism* 2006; **55**: 907–911.
16. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults: Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panal III). *JAMA* 2001; **285**: 2486–2497.
17. The Examination Committee of Criteria for Metabolic Syndrome: Definition and criteria of metabolic syndrome. *J Jpn Soc Int Med* 2005; **94**: 794–809.
18. Yamashina A, Tomiyama H, Takeda K, *et al*: Validity, reproducibility, and clinical significance of noninvasive brachial-ankle pulse wave velocity measurement. *Hypertens Res* 2002; **25**: 359–364.
19. Japan Atherosclerosis Society: Japan Atherosclerosis Society Guidelines for Diagnosis and Treatment of Atherosclerotic Cardiovascular Diseases. Tokyo, Japan Atherosclerosis Society, 2002, pp 24–26.
20. Japanese Society of Hypertension: Japanese Society of

Hypertension Guidelines for the Management of Hypertension (JSH 2004). *Hypertens Res* 2006: **29**: S1–S105.
21. Safar ME, Thomas F, Blacher J, *et al*: Metabolic syndrome and age-related progression of aortic stiffness. *J Am Coll Cardiol* 2006; **47**: 72–75.
22. Kadowaki T, Yamauchi T, Kubota N, Hara K, Ueki K, Tobe K: Adiponectin and adiponectin receptors in insulin resistance, diabetes, and the metabolic syndrome. *J Clin Invest* 2006; **116**: 1784–1792.
23. Matsuzawa Y, Funahashi T, Kihara S, Shimomura I: Adiponectin and metabolic syndrome. *Arterioscler Thromb Vasc Biol* 2004; **24**: 29–33.
24. Sipila K, Koivistoinen T, Moklanen L, *et al*: Metabolic syndrome and arterial stiffness: the Health 2000 Survey. *Metabolism* 2007; **56**: 320–326.
25. Ohnishi H, Saitoh S, Takagi S, *et al*: Pulse wave velocity as an indicator of atherosclerosis in impaired fasting glucose: the Tanno and Sobetsu study. *Diabetes Care* 2003; **26**: 437–440.
26. Mattace-Raso FU, van der Cammen TJ, Hofman A, *et al*: Arterial stiffness and risk of coronary heart disease and stroke: the Rotterdam Study. *Circulation* 2006; **113**: 657–663.
27. Ibata J, Sasaki H, Kakimoto T, *et al*: Cardio-ankle vascular index measures arterial wall stiffness independent of blood pressure. *Diabetes Res Clin Pract* 2008; **80**: 265–270.
28. Takeuchi H, Saitoh S, Takagi S, *et al*: Metabolic syndrome and cardiac disease in Japanese men: applicability of the concept of metabolic syndrome defined by the National Cholesterol Education Program–Adult Treatment Panel III to Japanese men—the Tanno and Sobetsu Study. *Hypertens Res* 2005; **28**: 203–208.
29. Zieman SJ, Melenovsky V, Kass DA: Mechanisms, pathophysiology, and therapy of arterial stiffness. *Arterioscler Thromb Vasc Biol* 2005; **25**: 932–943.
30. Barinas-Mitchell E, Kuller LH, Sutton-Tyrrell K, *et al*: Effect of weight loss and nutritional intervention on arterial stiffness in type 2 diabetes. *Diabetes Care* 2006; **29**: 2218–2222.
31. Rector RS, Turk JR, Sun GY, *et al*: Short-term lifestyle modification alters circulating biomarkers of endothelial health in sedentary, overweight adults. *Appl Physiol Nutr Metab* 2006; **31**: 512–517.