Original Article

Age-Associated Increase in Arterial Stiffness Measured According to the Cardio-Ankle Vascular Index without Blood Pressure Changes in Healthy Adults

Su-Yeon Choi¹, Byung-Hee Oh², Jeong Bae Park³, Dong-Ju Choi⁴, Moo-Yong Rhee⁵ and Sungha Park⁶

¹Department of Internal Medicine, Seoul National University Hospital, Healthcare System Gangnam Center, Seoul, Korea

²Department of Internal Medicine, Seoul National University Hospital, Seoul, Korea

³Department of Internal Medicine, Kwandong University College of Medicine, Cheil General Hospital, Seoul, Korea

⁴Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam-si, Gyeonggi-do, Korea

⁵Department of Internal Medicine, Dongguk University Ilsan Hospital, Goyang-si, Gyeonggi-do, Korea

⁶Department of Internal Medicine, Yonsei University College of Medicine, Cardiovascular Hospital, Seoul, Korea

Aim: The cardio-ankle vascular index (CAVI) reflects arterial stiffness from the aorta to the ankle, independent of blood pressure (BP). We investigated the age-stratified CAVI in healthy, normotensive individuals to evaluate the effects of age on arterial stiffness.

Methods: The CAVI and peripheral BP were determined in healthy, normotensive Koreans 20 to 79 years of age. The subjects had no history of cardiovascular disease and did not take any medications for hypertension, diabetes mellitus or dyslipidemia (N=1,380; 44.1% in men).

Results: The mean systolic blood pressure (SBP), diastolic blood pressure (DBP) and pulse pressure (PP) were 117, 75 and 42 mmHg, respectively. The CAVI increased linearly with age and was determined using the following equation: $CAVI = 5.0 + 0.048 \times \text{age (year)}$ in men ($r^2 = 0.395$, $p < 0.001$), $CAVI = 4.8 + 0.045 \times \text{age (year)}$ in women ($r^2 = 0.450$, $p < 0.001$). However, SBP, DBP and PP did not change progressively with age. Age emerged as the major determinant of the CAVI in a stepwise multiple regression analysis (r^2 change=43.1%).

Conclusions: The CAVI scores increased with age in the healthy, normotensive individuals, whereas SBP, DBP and PP did not. Age was the dominant risk factor for the progression of arterial stiffness. These data suggest that the CAVI is a sensitive marker of the arterial aging process, above and beyond conventional upper arm BP.

J Atheroscler Thromb, 2013; 20:911-923.

Key words: Cardio-ankle vascular index, Arterial stiffness, Vascular aging, Blood pressure

Introduction

Age is an important risk factor for cardiovascular disease (CVD). The age-associated changes in the arterial structure and function that occur in apparently healthy humans include luminal dilatation and stiffening of the large arteries¹. Arterial stiffening is attributed to repeated cycles of distension and elastic

recoiling of the arterial wall, which accelerates the fragmentation and depletion of elastin and the deposition of collagen².

Arterial stiffness, which is evaluated according to various methods, such as the pulse-wave velocity (PWV), augmentation index (AIx) and beta-stiffness index, has been established to be a marker of CVD and a risk factor for the progression of atherosclerosis³. However, most of these parameters are affected by blood pressure at the time of measurement. The cardio-ankle vascular index (CAVI) reflects the stiffness of all arterial segments, including the aorta, femoral artery and tibial artery. This index was originally derived from Bramwell-Hill's equation and stiffness

Address for correspondence: Byung-Hee Oh, Internal Medicine/ Cardiology, Seoul National University College of Medicine, 101 Daehak-ro, Jongno-gu, Seoul 110-744, Korea
E-mail: ohbhmed@snu.ac.kr

Received: February 19, 2013

Accepted for publication: June 16, 2013

Fig. 1. Flow chart showing patient selection.

parameter β^4 . Therefore, the CAVI is not affected by blood pressure during measurement⁵. The CAVI has been reported to be related to cardiovascular risk factors, such as hypertension⁶, diabetes mellitus⁷, hyperlipidemia⁸, smoking⁹ and epicardial adipose tissue¹⁰. The CAVI may also play a role as a surrogate marker of subclinical atherosclerosis, and emerging data have shown associations between the CAVI and components of CVD, such as coronary atherosclerosis^{7, 11}, the cardiac function^{12, 13}, carotid atherosclerosis¹⁴, stroke¹⁵, the cognitive function¹⁶ and kidney disease¹⁷.

However, most previous studies have been conducted in subjects with CVD risk factors. There is a paucity of studies assessing the CAVI in healthy subjects. Moreover, no existing studies have investigated the association between age and arterial stiffness measured by the CAVI in healthy Koreans.

Aim

We investigated the age- and gender-stratified CAVI values in healthy, normotensive individuals without CVD risk factors in order to evaluate the effects of age on arterial stiffness.

Methods

Study Subjects

The study population consisted of 1,489 volunteers 20 years of age or older without a history of CVD, including angina, myocardial infarction, stroke and peripheral artery disease, or chronic kidney disease who were not taking any medications for hypertension, diabetes mellitus or dyslipidemia, as assessed using a medical questionnaire and physician interviews, and who underwent a routine health checkup for screening purposes at their request. All subjects were enrolled between July 2010 and March 2012 at five university hospitals in Seoul and Gyeonggi province in Korea.

We measured the blood pressure and performed blood tests in 1,489 healthy volunteers. Subjects with a blood pressure of $\geq 140/90$ mmHg, a fasting blood glucose level of ≥ 126 mg/dL, a glycated hemoglobin (HbA1c) level of $\geq 6.5\%$ or a serum total cholesterol level of ≥ 240 mg/dL were excluded from the analysis ($n=104$). The subjects with a measured ankle-brachial index of < 0.9 and those with clinically significant valvular heart disease or arrhythmias were excluded from the analysis because the CAVI could not be accurately measured in these patients ($n=5$). Therefore, a total of 1,380 subjects (men: $n=608$, women: $n=772$) were

Table 1. Baseline characteristics and the average values of the hemodynamic parameters

Parameters	Total (<i>n</i> = 1,380)	Male (<i>n</i> = 608)	Female (<i>n</i> = 772)	<i>p</i>
Age, years	47 ± 12	49 ± 11	45 ± 12	< 0.001
Age range, years	20-79	22-78	20-79	
Age group, <i>n</i> (%)				
20-29 years	144 (10.4)	39 (6.4)	105 (13.6)	
30-39 years	250 (18.1)	91 (15.0)	159 (20.6)	
40-49 years	374 (27.1)	167 (27.5)	207 (26.8)	
50-59 years	418 (30.3)	213 (35.0)	205 (26.6)	
60-69 years	158 (11.4)	73 (12.0)	85 (11.0)	
70-79 years	36 (2.6)	25 (4.1)	11 (1.4)	
Height, cm	165 ± 8	171 ± 6	159 ± 5.1	< 0.001
BMI, kg/m ²	22.9 ± 2.9	24.3 ± 2.5	21.8 ± 2.7	< 0.001
Waist circumference, cm	81.0 ± 9.2	86.8 ± 7.1	76.4 ± 8.0	< 0.001
Waist-hip ratio	0.82 ± 0.07	0.87 ± 0.06	0.80 ± 0.06	< 0.001
Fasting glucose, mg/dL	93 ± 10	96 ± 10	90 ± 10	< 0.001
HbA1c, %	5.6 ± 0.3	5.6 ± 0.3	5.6 ± 0.3	0.766
Total cholesterol, mg/dL	194 ± 30	195 ± 28	192 ± 31	0.057
Triglyceride, mg/dL	107 ± 71	133 ± 84	86 ± 50	< 0.001
HDL cholesterol, mg/dL	56 ± 13	51 ± 11	61 ± 13	< 0.001
LDL cholesterol, mg/dL	116 ± 27	119 ± 26	114 ± 28	0.001
Smoking*				< 0.001
Non-smoker, <i>n</i> (%)	1,099 (81.2)	351 (60.3)	748 (96.9)	
Ex-smoker, <i>n</i> (%)	69 (5.1)	63 (10.8)	6 (0.8)	
Current smoker, <i>n</i> (%)	186 (13.7)	168 (28.9)	18 (2.3)	
SBP, mmHg	117 ± 12	120 ± 12	115 ± 12	< 0.001
DBP, mmHg	75 ± 9	78 ± 9	73 ± 9	< 0.001
PP, mmHg	42 ± 9	42 ± 9	42 ± 8	0.986
MAP	89 ± 10	92 ± 9	87 ± 10	< 0.001
HR, beat/minute	70 ± 10	69 ± 11	70 ± 10	0.039
ABI				
Rt. ABI	1.14 ± 0.08	1.16 ± 0.07	1.12 ± 0.08	< 0.001
Lt. ABI	1.13 ± 0.08	1.16 ± 0.08	1.11 ± 0.07	< 0.001
CAVI, average	7.1 ± 0.9	7.3 ± 0.9	6.9 ± 0.8	< 0.001
CAVI Q1	4.5-6.5	4.8-6.8	4.5-6.3	
CAVI Q2	6.6-7.0	6.9-7.2	6.4-6.9	
CAVI Q3	7.1-7.5	7.3-7.8	7.0-7.4	
CAVI Q4	7.6-11.8	7.9-11.4	7.5-11.8	

The values are presented as the mean ± standard deviation or numbers (%). ABI: ankle-brachial index, BMI: body mass index, CAVI: cardio-ankle vascular index, DBP: diastolic blood pressure, HbA1c: glycated hemoglobin, HR: heart rate, HDL: high-density lipoprotein, LDL: low-density lipoprotein, MAP: mean arterial pressure, PP: pulse pressure, Q: quartile, SBP: systolic blood pressure, MAP = (SBP + 2DBP)/3.

*Information regarding exposure to smoking was missing in 26 subjects.

enrolled in this study (**Fig. 1**). The study protocol was approved by the local institutional review board of each university hospital and was in accordance with the Declaration of Helsinki. Written informed consent was obtained from each participant.

Cardiovascular Risk Factors

Baseline information on demographic and cardiovascular risk factors was collected. Body weight, body height, waist circumference, hip circumference and blood pressure were measured.

After a 15-minute rest with the subject in a seated position, the brachial blood pressure was mea-

Table 2. Baseline hemodynamic and clinical parameters according to age category in men and women

Age, year	Gender	20-29	30-39	40-49	50-59	60-69	70-79
Number	M	39	91	167	213	73	25
	F	105	159	207	205	85	11
CAVI	M [†]	6.2±0.6	6.8±0.6*	7.1±0.6*	7.5±0.7*	8.0±0.9	8.8±0.8
	F [†]	6.1±0.6	6.5±0.6	6.8±0.6	7.2±0.6	7.8±0.7	8.8±1.3
SBP, mmHg	M [†]	128±11*	123±12*	119±12*	118±11*	121±12	122±12
	F [†]	115±11	112±12	115±13	115±13	119±12	123±7
DBP, mmHg	M	77±8*	78±9*	78±10*	79±8*	78±8*	75±8
	F	72±8	72±9	73±10	73±9	75±8	74±8
PP, mmHg	M [†]	51±9*	45±8*	41±8	39±8*	42±10	47±9
	F [†]	43±7	40±7	41±8	41±9	44±10	49±7
MAP, mmHg	M	94±8*	93±10*	92±10*	92±9*	92±8*	91±9
	F [†]	86±9	85±10	87±10	87±10	89±8	91±7
HR, beat/min	M [†]	72±12	71±10	70±11	68±11	67±12	70±13
	F [†]	74±10	73±10	70±10	68±10	67±9	72±8
Height, cm	M [†]	175±5*	174±5*	172±6*	170±6*	170±5*	168±6*
	F [†]	162±5	161±4	159±5	158±5	157±5	154±4
BMI, kg/m ²	M [†]	23.4±3.0*	24.5±3.1*	24.6±2.3*	24.5±2.3*	23.8±2.2	24.0±2.8
	F [†]	20.2±2.1	21.1±2.6	22.2±2.6	22.4±2.5	23.0±2.7	23.2±2.9
Waist circumference, cm	M [†]	81.3±8.1*	86.4±8.0*	87.1±6.2*	87.4±6.7*	87.0±6.6*	89.0±8.0*
	F [†]	70.1±5.8	73.4±7.8	77.2±7.2	78.4±7.2	82.3±8.1	82.3±9.7
Waist-hip ratio	M [†]	0.82±0.05*	0.86±0.04*	0.89±0.04*	0.90±0.06*	0.91±0.04*	0.97±0.06
	F [†]	0.77±0.04	0.79±0.06	0.82±0.05	0.83±0.06	0.86±0.06	0.93±0.07
Fasting glucose, mg/dL	M [†]	89±7*	94±11*	97±10*	98±10*	96±10*	98±10
	F [†]	86±7	89±9	90±11	93±9	92±9	92±14
HbA1c, %	M	5.5±0.2	5.5±0.3	5.6±0.3	5.6±0.3	5.7±0.3	5.6±0.2
	F [†]		5.4±0.2	5.5±0.2	5.6±0.3	5.7±0.3	5.7±0.2
Total cholesterol, mg/dL	M [†]	185±30	191±28*	199±29*	198±28*	194±27*	185±24
	F [†]	177±27	179±29	190±29	206±29	205±27	198±37
Triglyceride, mg/dL	M [†]	107±61*	148±115*	141±86*	133±79*	116±58*	98±43
	F [†]	74±45	79±47	86±54	94±50	94±46	108±48
HDL cholesterol, mg/dL	M [†]	59±14*	49±10*	50±11*	50±12*	52±11*	51±13
	F [†]	66±12	61±13	60±13	60±13	59±10	61±15
LDL cholesterol, mg/dL	M [†]	104±24	115±27*	121±27*	122±25*	119±26	115±22
	F [†]	96±24	102±23	113±26	128±27	127±24	118±31
Smoking Status*, ‡							
Non-smoker, %	M	56.4	43.3	55.4	68.1	68.1	73.9
	F	98.1	96.2	95.2	98.0	97.6	100
Ex-smoker, %	M	15.4	6.7	14.6	9.3	7.2	17.4
	F	1.0	1.3	0.5	0.5	1.2	0
Current-smoker, %	M	28.2	50.0	29.9	22.5	24.6	8.7
	F	1.0	2.5	4.3	1.5	1.2	0

The data are presented as the mean ± SD. Student's t-test was used for comparisons between genders for each decile, and significant results are represented by * $p < 0.05$. [†] $p < 0.05$ was calculated using a one-way analysis of variance for the age category in each gender. [‡] $p < 0.05$ was calculated using the test for trend for the age category in men. The abbreviations are as in Table 1.

sured using an automatic cuff oscillometric device (HEM-780, Omron Corp., Kyoto, Japan). The average of two readings was used to determine the systolic blood pressure (SBP), diastolic blood pressure (DBP)

and pulse pressure (PP). The mean arterial pressure (MAP) was determined using the following equation: $\text{MAP} = (\text{SBP} + 2\text{DBP})/3$.

All study subjects fasted for 12 hours or longer

Fig. 2. Simple linear regression between CAVI and age.

Fig. 3. Differences in the average CAVI scores according to age between men (blue line) and women (green line) among the CVD risk-free Koreans based on the results shown in **Table 2**. The vertical bars indicate the standard deviation.

before the blood tests. The levels of total cholesterol, triglycerides (TGs), high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, fasting blood glucose and HbA1c were measured.

Measurement of the CAVI

The CAVI was measured using a VaSera VS-1000

(Fukuda Denshi Co. Ltd., Tokyo, Japan) according to the methods described previously^{10, 18}. Cuffs were applied to all four extremities at both upper arms and ankles with the subject lying supine. The measurements were obtained after the subject rested for 10 minutes. A phonocardiogram was placed firmly over the sternum between the second intercostal space, and

Fig. 4. Peripheral blood pressure values averaged for deciles of age.

Student's *t*-test was used for comparisons between genders for each decile. Significant results are represented by **p* < 0.05.

electrocardiogram leads were attached to both wrists. The PWV was calculated by dividing the vascular length (L) by the time (T) taken for the pulse wave to propagate from the aortic valve to the ankle. Since it is difficult to identify the starting time of the blood stream from the aortic valve based on the valve's opening sound, it is difficult to obtain the *T* value; thus, the *T* value was calculated by summing the time between the rise of the brachial pulse wave and the rise of the ankle pulse wave and the time between the aortic valve's closing sound and the notch of the brachial pulse wave. The CAVI was determined using the following equation:

$$\text{CAVI} = a[(2\rho/\Delta P) \times \ln(P_s/P_d) \times \text{PWV}^2] + b$$

Where P_s and P_d are SBP and DBP, respectively, ΔP is $P_s - P_d$, ρ is the blood density and *a* and *b* are constants. The average value of the right and left CAVI was used for the analysis.

Statistical Analysis

The data are expressed as the mean $\pm$ standard deviation, with frequencies and percentages for categorical variables. For continuous variables, the *t*-test and an analysis of variance (ANOVA) were used to make comparisons, depending on the number of groups to be assessed. For the TG levels, the distribution of which was highly skewed, we used the nonparametric Mann-Whitney *U* test for the statistical analysis. Categorical variables were compared using a chi-square

analysis.

Bivariate Pearson correlation analyses and partial correlations adjusted for age were used for the evaluation of the relationships between the CAVI and the other variables. Regression equations were derived for each gender to explore the effects of age on arterial stiffness using simple linear regression analyses. To determine the factors influencing arterial stiffness, a stepwise multiple linear regression analysis was performed. Variables entered into the regression model were chosen from simple correlation analyses and variables known or likely to be associated with arterial stiffness. All statistical analyses were performed using a statistical software package (SPSS 19.0, SPSS Inc., Chicago, Ill), and a *p*-value of less than 0.05 was considered to be statistically significant.

Results

The basal characteristics and average values of the hemodynamic parameters of the 1,380 subjects free from CVD risk factors are presented in **Table 1**. Among the 1,380 participants, 608 (44.1%) subjects were men. The mean SBP, DBP and PP were 117, 75 and 42 mmHg, respectively. The mean CAVI was 7.1. The cutoff values for the quartiles of the CAVI were 6.5, 7.0 and 7.5. **Table 2** shows the hemodynamic parameters according to the age categories (10-year intervals) for men and women. As expected, in both genders, the CAVI increased progressively from the

Table 3. Bivariate analysis showing the correlations between the CAVI and various parameters using Pearson correlation and partial correlation coefficients adjusted for age

	Pearson correlation		Pearson correlation adjusted by age	
	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>
Age	0.657	<0.001		
Height	0.111	<0.001	0.220	<0.001
Weight	0.108	<0.001	0.032	0.405
BMI	0.057	0.035	-0.140	<0.001
Waist circumference	0.237	<0.001	0.032	0.405
Length	0.109	<0.001	0.223	<0.001
SBP	0.059	0.031	0.048	0.204
DBP	0.124	<0.001	0.027	0.476
PP	-0.050	0.068	0.039	0.308
MAP	0.105	<0.001	0.038	0.318
HR	-0.135	<0.001	0.083	0.029
Total cholesterol	0.143	<0.001	-0.017	0.661
Triglyceride	0.087	0.002	0.065	0.087
HDL cholesterol	-0.151	<0.001	-0.036	0.349
LDL cholesterol	0.181	<0.001	-0.029	0.444
Fasting glucose	0.225	<0.001	0.078	0.041
HbA1c	0.139	<0.001	0.019	0.612

r refers to the correlation coefficient determined according to the Pearson bivariate correlation analysis.

The abbreviations are as in **Table 1**.

first to the last age group according to a one-way ANOVA with multiple comparison tests and a linear by linear association for test for trend, whereas SBP, DBP and PP did not change progressively with the increasing age groups (**Table 2**, **Fig. 2**, **3**, and **4**). The age-specific average CAVI scores in men were significantly greater than those in women in 30-59 years of age. Among the subjects 20-29 and 60-79 years of age, the differences in the age-specific average CAVI scores were statistically insignificant. The age-specific average SBP values in men were significantly greater than those in women among the subjects 20-59 years of age, and a similar trend was observed for DBP among the subjects 20-69 years of age and MAP among the subjects 20-69 years of age. **Supplemental Table 1** provides the percentile CAVI scores according to deciles of age by gender.

Table 2 shows the differences in the other CVD risk factors according to age group and gender. Most of the CVD risk factors differed significantly for each age category in both genders according to a one-way ANOVA with multiple comparison tests. BMI, waist circumference, the waist-hip ratio and the levels of TGs, fasting glucose and HbA1c had a tendency to increase with age in women, while waist circumference, the waist-hip ratio and the LDL cholesterol level

increased with age in men. The percentage of participants with a current smoking habit tended to decrease with age in men (*p* for trend <0.001 in men), although it was not significantly different in women. BMI and the levels of fasting glucose, total cholesterol, TGs and LDL cholesterol were higher and the HDL cholesterol levels were lower in men than in women in each age group <50 years. However, the total cholesterol and LDL cholesterol levels were higher in women than in men in the age groups ≥50 years. The BMI values did not significantly differ between men and women in the age groups ≥60 years, and the fasting glucose, TG and HDL cholesterol levels did not differ between the age groups ≥70 years.

The results of the regression analyses of the CAVI values in the men and women are provided in **Fig. 2**. The CAVI was determined using the following equation with a simple linear regression: CAVI = 5.0 + 0.048 × Age (year) in men (*r* = 0.629, *r*² = 0.395, *p* < 0.001), CAVI = 4.8 + 0.045 × Age (year) in women (*r* = 0.671, *r*² = 0.450, *p* < 0.001).

We investigated the correlations between various parameters and the CAVI scores (**Table 3**). Age, height, weight, BMI, waist circumference, length, SBP, DBP, MAP, heart rate (HR), total cholesterol, TG, HDL cholesterol, LDL cholesterol, fasting glucose and

Table 4. Stepwise regression analysis

Model	Regression Coefficient	SE	Beta	<i>p</i>	<i>r</i> ² change (%)
Total, CAVI, adjusted <i>r</i> ² =0.534, <i>p</i> =0.009					
Age	0.048	0.002	0.679	<0.001	44.9
Height	0.010	0.004	0.090	<0.001	3.2
BMI	-0.095	0.012	-0.321	<0.001	3.1
Current smoker	0.238	0.054	0.097	<0.001	1.2
Female gender	-0.186	0.060	-0.109	0.002	0.4
Waist circumference	0.011	0.004	0.119	0.008	0.3
Fasting glucose	0.005	0.002	0.058	0.009	0.3
Male, CAVI, adjusted <i>r</i> ² =0.451, <i>p</i> =0.012					
Age	0.046	0.003	0.614	<0.001	37.7
BMI	-0.117	0.018	-0.342	<0.001	3.7
Current smoker	0.212	0.064	0.112	0.001	1.9
Waist circumference	0.019	0.006	0.161	0.003	1.1
ln Triglyceride	0.154	0.061	0.089	0.003	0.7
Female, CAVI, adjusted <i>r</i> ² =0.544, <i>p</i> =0.017					
Age	0.051	0.002	0.779	<0.001	47.9
BMI	-0.072	0.009	-0.237	<0.001	5.3
Height	0.014	0.005	0.089	0.002	0.8
Fasting glucose	0.006	0.002	0.067	0.017	0.4

Variables, including age (year), gender, height (cm), BMI (kg/m²), waist circumference (cm), SBP (mmHg), PP (mmHg), HR (beat/min), fasting glucose (mg/dL), triglyceride (mg/dL), LDL cholesterol (mg/dL) and current smoking status, were entered in the model with stepwise selection. The abbreviations are as in **Table 1**. The triglyceride level was log transformed.

HbA1c exhibited significant associations with the CAVI. However, the strength of the correlations with the variables, except age, was weak (*r* for age=0.657, and *r* for other variables; $0 < |r| < 0.3$). Pearson bivariate partial correlation coefficients adjusted for age were used to evaluate the relationship between the CAVI and the other variables (**Table 3**). After adjusting for age, BMI remained negatively correlated and height remained positively correlated with the CAVI; however, the strength of the correlations was weak (*r*=-0.140 and *r*=0.220, respectively). **Supplemental Table 2** shows the CAVI values according to the classification of obesity with respect to BMI for adult Asians based on the modified WHO criteria Asia-Pacific guidelines¹⁹: normal (<23 kg/m²), overweight (23-24.9 kg/m²), obese I (25-29.9 kg/m²) and obese II (≥30 kg/m²). There were no significant differences in the CAVI values among the BMI categories in either men or women based on a one-way ANOVA.

Stepwise multiple regression models were constructed to determine the factors influencing the CAVI. Variables, including age, gender, height, BMI, waist circumference, SBP, PP, HR, fasting glucose, TG, LDL cholesterol and a current smoking status, were entered in the model with stepwise selection. The

TG level was log transformed (ln TG) because the distribution was skewed. As expected, age emerged as the major determinant of the CAVI. BMI and height were also found to be influencing factors for the CAVI (**Table 4**).

Discussion

We investigated the age- and gender-stratified baseline CAVI values in CVD risk-free healthy Koreans. In both genders, the CAVI increased progressively with age, whereas SBP, DBP and PP did not increase linearly with age. The age-specific average CAVI scores in men were significantly greater than those in women among the subjects 30-59 years of age. In our study, the CAVI as a marker of arterial stiffness reflected arterial aging above and beyond conventional upper arm blood pressure measurements, and age was the dominant cardiovascular risk factor influencing arterial stiffness.

Arterial Aging

The most consistent changes that occur in the arterial wall with age are luminal enlargement with wall thickening and a reduction in elastic properties

(stiffening) in large elastic arteries²⁰). Longstanding arterial pulsation in the central artery causes elastin fiber fatigue and fracture. Endothelial dysfunction²¹), the accumulation of advanced glycation end products on proteins²²), the calcium content of the arterial wall²²), changes in the extracellular matrix expression^{23, 24}) and increased stiffness of vascular smooth muscle cells^{23, 24}) have been reported to mediate age-associated vascular stiffness.

Age-associated changes in the arterial structure and function are thought to be part of normal aging; however, emerging evidence demonstrates that age-associated arterial stiffness is accelerated in the presence of CVD and that arterial aging is a risk factor for the development and progression of CVD and adverse cardiovascular outcomes¹).

In this study, the CAVI increased with age in the healthy, normotensive individuals, whereas SBP, DBP and PP did not increase progressively with age. Because age-related arterial changes occur at the level of large elastic arteries, the peripheral blood pressure obtained in the upper arm may not reflect arterial aging, especially in normotensive populations. However, the CAVI may be a sensitive arterial stiffness marker of the arterial aging process, even in CVD risk-free subjects.

A number of studies have investigated the effects of age on blood pressure. Most reports have indicated that peripheral SBP increases progressively with age, whereas DBP increases until 50 years of age then declines, or the rate of change in DBP begins to reduce with age after 45-50 years^{25, 26}). However, this association between age and blood pressure was not observed in the present study. This could be because the participants included only a small young population, especially in men, and a small geriatric population. Moreover, we enrolled only normotensive subjects at inclusion to establish the baseline CAVI scores according to age and gender among CVD risk-free persons.

The CAVI as an Index of Arterial Stiffness and Atherosclerosis

Recently, arterial stiffness has been implicated to contribute to the development of atherosclerosis³). Several noninvasive methods are used to assess arterial stiffness²⁷). The carotid-femoral PWV is considered to be the gold standard for evaluating central arterial stiffness²⁸). However, a relatively high level of skill and the need to expose the inguinal region are barriers to its clinical use. The brachial-ankle PWV is easy to measure and exhibits a close correlation with the carotid-femoral PWV; however, the main limitation of PWV

interpretation is the significant influence of blood pressure²⁹). The stiffness index, β , represents the blood pressure change required to expand the diameter of the artery and can be calculated without the influence of blood pressure³⁰); however, β is a marker of regional, not segmental, arterial stiffness³). The CAVI is determined by measuring the PWV, then adjusted according to the stiffness parameter β and a modification of Bramwell-Hill's equation, which reflects the stiffness of a considerable length of artery, and is not affected by blood pressure at the time of measurement^{5, 18}). Therefore, the CAVI has been demonstrated to be a superior index of arterial stiffness compared to the brachial-ankle PWV. Indeed, early results show easy measurement¹⁸) with good reproducibility³¹) and risk predictability⁴). The CAVI has been reported to be related to hypertension⁶), diabetes mellitus⁷), hyperlipidemia⁸), smoking⁹) and epicardial adipose tissue¹⁰) and consistently shows a good correlation with components of atherosclerotic disease, such as coronary artery disease^{7, 11, 32}), the cardiac function^{12, 13}), cerebrovascular disease^{14, 15, 33}), the cognitive function¹⁶) and kidney disease¹⁷). Recent studies have reported that the CAVI is decreased by controlling hypertension⁶) and diabetes mellitus³⁴) and abstaining from smoking³⁵). Further studies to compare CAVI scores between CVD risk-free groups and CVD high-risk groups in Koreans should be conducted to evaluate the impact of cardiovascular risk factors on arterial stiffness measured by the CAVI.

Age-Specific CAVI Scores in the CVD Risk-Free Healthy Subjects

As mentioned above, several studies have consistently shown that the CAVI is associated with traditional cardiovascular risk factors and atherosclerosis, and the usefulness of the CAVI has been evaluated in different population subsets, including hypertensive, diabetic and dialysis patients. However, there is a paucity of studies assessing the CAVI in asymptomatic healthy, normotensive subjects. In this study, we investigated the effects of age on arterial stiffness measured according to the CAVI and enrolled subjects with no history of CVD who were not taking any medications for hypertension, diabetes mellitus or dyslipidemia. The CAVI increased linearly with age. In association with an increase of 10 years of age, the CAVI increased by 0.48 in men and 0.45 in women according to the regression equation of the CAVI and age. Comparing the CAVI scores between genders stratified by age group, the age-specific average CAVI scores in men were higher than those in women among the subjects 30-59 years of age. However, the differences in the

average CAVI scores between the genders were insignificant among the subjects over 60 years of age.

According to the data of a nationwide survey, the Korean National Health and Nutrition Examination Survey conducted in 2007, men have a higher prevalence of metabolic syndrome than women among individuals < 50 years of age³⁶. In contrast, the prevalence of metabolic syndrome in women increases significantly from the age of 50 years and surpasses that of men thereafter³⁶. It is likely that menopause and the increasing pattern of abdominal obesity in women account for this dramatic change. In our study, the average SBP, DBP, MAP, BMI, fasting glucose and cholesterol values were higher in men than in women in each age group < 50 years. Among the subjects 70-79 years of age, the differences in average CAD risk factors between the genders were insignificant. Therefore, the increasing trend in CVD risk factors after menopause in women is a possible explanation for the gender differences in the CAVI according to age.

In this study, BMI exhibited a weakly negative correlation with the CAVI. However, there were no significant differences in the CAVI between the BMI categories among either men or women. In a study by Park *et al.*, the amount of visceral adipose tissue and epicardial adipose tissue (EAT) and the subcutaneous to visceral adipose tissue ratio (SVR) exhibited significant correlations with the CAVI. The volume of EAT demonstrated the strongest independent correlation with the CAVI after adjusting for covariables in a multivariable correlation analysis. However, BMI was negatively correlated with the CAVI, without statistical significance. The volume of EAT and SVR demonstrated significant differences according to the quartiles of the CAVI, despite the lack of significant differences in BMI¹⁰. Schillaci *et al.* reported that abdominal adiposity as measured by waist circumference is strongly and adversely associated with aortic PWV, whereas BMI as a measure of general adiposity is not in untreated essential hypertension patients³⁷. These studies support the concept that obesity is a heterogeneous disorder and body fat in different locations has different functions. Visceral obesity, rather than general obesity per se, is a possible risk factor for increased arterial stiffness. Therefore, further studies with a larger number of obese subjects are needed to evaluate the association between BMI and CAVI.

We provided the baseline CAVI values in healthy Koreans. It is helpful to establish the baseline CAVI scores in each ethnic and geographic group in order to understand the effects of CVD risk factors on arterial stiffness and evaluate the efficacy of treatment for

CVD. Although we were unable to statistically compare our results with those of previous studies, we tried to compare the average CAVI scores of the Korean population with those of a Japanese population comprising a CVD risk-free group³⁸. When the age- and sex-specific average CAVI scores were simply compared, the CAVI scores in the Koreans tended to be lower in all age groups. Other studies have compared the CAVI values in different races and geographic areas. Yambe *et al.* reported that the brachial-ankle PWV values were higher in a Russian group than in a Japanese group, suggesting that more rapid progression of atherosclerosis took place in the former³⁹. Hirasada *et al.* evaluated the CAVI values in a healthy Japanese population assessed during health checkups in two areas of Japan⁴⁰. Their results demonstrated that the CAVI values in the Amami residents were lower than those in the mainland residents, without differences in lifestyle or clinical characteristics. This result suggests that there are geographic differences in the mean CAVI values.

A large cohort of healthy, normotensive individuals in the Anglo-Cardiff Collaborative Trial (ACCT) was investigated for the effects of age on aortic PWV and AIx²⁵. In that study, the aortic PWV was significantly correlated with age. However, the age-related changes in aortic PWV and AIx did not appear to be linear, with AIx increasing more significantly in younger individuals and changes in aortic PWV being more prominent in older individuals over 50 years of age. Age-related changes in central PP are also more marked in subjects over 50 years of age. The authors reported that age, MAP and a male gender emerged as the major determinants of aortic PWV. Therefore, further studies with a larger sample size are needed to evaluate the associations between CAVI and aortic PWV and between AIx and central hemodynamic parameters.

Limitations

This study is associated with some limitations due to its cross-sectional design and limited sample size. Furthermore, the localization of enrollment of the subjects in an urban area may limit generalizations of the results. Furthermore, studies are needed to analyze the CAVI in association with central hemodynamic parameters, including central SBP, central DBP and AIx. Because the prognostic value of a high CAVI score in asymptomatic individuals is not yet clear, long-term prospective studies to properly address clinical outcomes based on the CAVI are warranted.

Conclusion

In conclusion, in this study, the CAVI score increased with age in both genders, whereas SBP, DBP and PP did not increase progressively with age in the healthy, normotensive Koreans. The CAVI as a marker of arterial stiffness reflects arterial aging. We would also like to establish the baseline CAVI scores in Koreans. Further studies comparing the CAVI scores in subjects with CVD risk factors may help to further understanding of the effects of these risk factors on arterial stiffness. In order to verify the potential clinical role of the CAVI, the predictive value of the CAVI for CVD should be assessed in long-term prospective studies.

Notice of Grant Support

This study was supported by a grant funded by Fukuda Denshi Co. Ltd. and Eujin med-electronic Co. Ltd.

Conflicts of Interest

None.

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Supplemental Table 1. CAVI percentiles according to age category for men and women

Male	20-29 yrs	30-39 yrs	40-49 yrs	50-59 yrs	60-69 yrs	70-79 yrs
Number	39	91	167	213	73	25
Mean $\pm$ SD	6.2 $\pm$ 0.6	6.8 $\pm$ 0.6	7.1 $\pm$ 0.6	7.5 $\pm$ 0.7	8.0 $\pm$ 0.9	8.8 $\pm$ 0.8
10 percentile	5.45	5.9	6.2	6.6	7.1	7.8
25 percentile	5.65	6.4	6.8	7.0	7.4	8.1
50 percentile	6.35	6.9	7.1	7.5	8.0	8.7
75 percentile	6.55	7.2	7.5	7.9	8.5	9.5
90 percentile	6.85	7.4	7.9	8.4	9.0	10.0
Female	20-29 yrs	30-39 yrs	40-49 yrs	50-59 yrs	60-69 yrs	70-79 yrs
Number	105	159	207	205	85	11
Mean $\pm$ SD	6.1 $\pm$ 0.6	6.5 $\pm$ 0.6	6.8 $\pm$ 0.6	7.2 $\pm$ 0.6	7.8 $\pm$ 0.7	8.8 $\pm$ 1.3
10 percentile	5.4	5.9	6.0	6.5	6.9	7.3
25 percentile	5.7	6.1	6.3	6.8	7.4	7.6
50 percentile	6.1	6.6	6.8	7.2	7.8	8.7
75 percentile	6.4	6.9	7.2	7.6	8.3	9.2
90 percentile	6.9	7.2	7.6	8.0	9.0	11.1

Supplemental Table 2. CAVI scores according to the classification of obesity based on BMI

BMI, kg/m ²	Classification [†]	Male		Female		<i>p</i> [*]
		n	CAVI	n	CAVI	
<22.9	Normal	175	7.4 $\pm$ 1.0	542	6.9 $\pm$ 0.8	<0.001
23.0-24.9	Overweight	189	7.4 $\pm$ 0.8	133	6.9 $\pm$ 0.8	<0.001
25.0-29.9	Obese I	231	7.2 $\pm$ 0.8	90	6.9 $\pm$ 0.9	0.002
30.0-	Obese II	13	6.8 $\pm$ 0.9	7	6.6 $\pm$ 0.9	0.614

BMI: body mass index, CAVI: cardio-ankle vascular index. The data are presented as the mean $\pm$ SD. * Student's *t*-test was used for comparisons between genders for each BMI group. [†] Classification of obesity according to BMI in adult Asians based on the modified WHO criteria Asia-Pacific guidelines. There were no significant differences in the CAVI among the BMI categories based on a one-way analysis of variance in either men or women.