ORIGINAL ARTICLE

Oscillometric measurement of brachial artery cross-sectional area and its relationship with cardiovascular risk factors and arterial stiffness in a middle-aged male population

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An enlarged arterial diameter is associated with an increased risk for cardiovascular disease. This study examined the relationship of noninvasively measured brachial artery cross-sectional area with cardiovascular risk factors and arterial stiffness in a middle-aged male population. Absolute volumetric changes of the brachial artery were measured with a newly developed oscillometric method during a general health examination in 387 men (mean age: 38 ± 9 years) without known cardiovascular disease. Based on the measurement, the estimated area (eA) of the brachial artery at end-diastole was obtained. Brachial artery volume elastic modulus (V_E) and brachial–ankle pulse wave velocity (baPWV) were simultaneously measured as indices of arterial stiffness by the same device. The relationships of eA with cardiovascular risk factors, including age, obesity, hypertension, dyslipidemia, impaired fasting glucose/diabetes mellitus (IFG/DM), hyperuricemia, smoking and their associated continuous variables, as well as V_E and baPWV, were examined. Overall, the mean eA was 12.9 ± 2.9 mm². The eA was significantly higher in subjects with obesity, hypertension or IFG/DM than in those without each of these risk factors. In a multiple linear regression analysis, body mass index ($\beta = 0.31$, $P < 0.001$), age ($\beta = 0.25$, $P < 0.001$), systolic blood pressure ($\beta = 0.16$, $P = 0.004$) and pulse rate ($\beta = -0.13$, $P = 0.005$) were independent determinants of eA. In contrast, neither V_E nor baPWV were selected as independent determinants of eA. In conclusion, enlarged brachial artery cross-sectional area was significantly associated with cardiovascular risk factors such as age, body mass index and systolic blood pressure, but it was not associated with increased arterial stiffness.

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INTRODUCTION

Enlargement of arterial diameter is thought to be an initial step toward the progression of atherosclerosis.^{1,2} Previous studies have shown the relationship between the diameter of the brachial artery and conventional cardiovascular risk factors,³ including metabolic syndrome.⁴ Brachial artery diameter is also positively associated with brachial intima–media thickness⁵ and negatively associated with brachial flow-mediated vasodilation.^{6–8} Interestingly, enlargement of brachial artery diameter is shown in subjects with coronary artery calcification⁸ and in those with increased carotid intima–media thickness.^{3,9} In a population-based cohort study, brachial artery diameter predicted the risk of cardiovascular disease (CVD).¹⁰ Taken together, these observations suggest the usefulness of measuring brachial artery diameter in clinical and epidemiological settings for identifying individuals with impaired arterial function,

those with atherosclerosis and those at high-risk for CVD. However, one major limitation of measuring brachial artery diameter is that, to date, ultrasonography has been almost the sole noninvasive method and, in fact, it requires particular examination techniques.¹¹

Recently, a new device based on an oscillometric method has been developed for the measurement of brachial artery cross-sectional area, which is virtually identical to the diameter. This measurement does not require any particular expertise, indicating the potential for wider application of measuring brachial artery cross-sectional area using this oscillometric device. However, clinical and epidemiological data on the relevance of the measurement has been lacking so far. The objective of this study was to measure the brachial artery cross-sectional area using the oscillometric device and to examine its relationship with cardiovascular risk factors in a middle-aged male population without known CVD. This study also examined the

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relationship between brachial artery cross-sectional area and arterial stiffness, which is a well-known risk marker for CVD independent of conventional cardiovascular risk factors.¹²

METHODS

Study population

This study was conducted during an annual health examination at a semiconductor manufacturing plant in Kanagawa, Japan, in 2011. Out of 403 male workers who underwent a complete health examination, 15 were excluded because the oscillometric measurements did not succeed. An individual with ankle-brachial blood pressure (BP) index ≤ 0.9 was also excluded. We initially intended to exclude subjects with CVD, but there were no such subjects. Finally, this included 387 subjects (mean age: 38 ± 9 years; range: 20–62 years). There were 36 female workers who also underwent the health examination, and oscillometric measurement was successful in 33 female workers. However, to obtain statistical results for a more homogeneous population and because of their relatively small number, we did not include the results of the female workers in the main analysis. The study was approved by the Ethics Committee of Nippon Medical School, and all participants gave written informed consent.

Data collection

All participants underwent anthropometric and BP measurements and blood sampling in a temperature-controlled room maintained at $22 \pm 2^\circ\text{C}$. Body weight and height were measured and body mass index (BMI) was calculated as the weight (kg) divided by the square of the height (m^2). Obesity was defined as $\text{BMI} \geq 25.0 \text{ kg m}^{-2}$.

The brachial systolic and diastolic BP were measured by well-trained staff members with mercury sphygmomanometers and an optimal cuff size for the arm circumference. BP measurements were taken on the right arm with the subject seated after at least 5 min of rest. Hypertension was defined as systolic BP ≥ 140 mm Hg, diastolic BP ≥ 90 mm Hg or current use of antihypertensive medications.

Blood samples were obtained from the antecubital vein after overnight fasting. White blood cell counts were measured using an automatic cell counter. Standard enzymatic methods were used to measure the serum low-density lipoprotein (LDL) cholesterol, triglycerides, uric acid and plasma glucose levels and hemoglobin A1c (HbA1c). The serum high-density lipoprotein (HDL) cholesterol level was measured using a direct method. Dyslipidemia was defined as LDL cholesterol $\geq 140 \text{ mg dl}^{-1}$, HDL cholesterol $< 40 \text{ mg dl}^{-1}$, triglycerides $\geq 150 \text{ mg dl}^{-1}$ or current use of antidiabetic medications. Hyperuricemia was defined as uric acid $\geq 7.0 \text{ mg dl}^{-1}$ or current use of uric acid-lowering medications. Impaired fasting glucose (IFG) was defined as fasting plasma glucose $\geq 110 \text{ mg dl}^{-1}$ and diabetes mellitus (DM) was defined as fasting plasma glucose $\geq 126 \text{ mg dl}^{-1}$, HbA1c $\geq 6.5\%$ or current use of glucose-lowering medications.

A self-reported questionnaire was used to check subjects' smoking status, which was categorized as current or no smoking. Current smoking was defined as cigarette smoking on a regular basis (at least once daily) at the time of study participation.

The 30-year risk of incident CVD according to the Framingham CVD risk prediction algorithm¹³ was calculated on the basis of age, BMI, systolic BP, smoking and DM status and use of antihypertensive medication. The estimated risk is shown as a percentage and categorized as low ($< 10\%$), intermediate ($10\text{--}20\%$) and high ($> 20\%$).

Oscillometric measurement

Brachial artery absolute volume was measured using a newly developed device, the Health Chronos TM-2771 prototype (A&D Company, Tokyo, Japan). This device consists of a main unit and four cuffs for oscillometric BP measurement and plethysmography at the right and left brachial and tibial arteries. The outsides of the occlusive cuffs are composed of a hard material to avoid expansion with increases in arterial volume, so that the changes in the cuff pressure (CP) accurately reflect volumetric changes of the artery.

To measure brachial artery absolute volume, the device initially sought the lowest CP that indicated complete collapse of the brachial artery (volume = 0) at end-diastole. The brachial artery plethysmogram was recorded at this CP.

Figure 1 (a) A brachial artery plethysmogram with calibration (arrow). (b) A representative pressure (blood pressure (BP)–cuff pressure (CP) difference)–area (cross-sectional area) curve. Estimated area (eA) of the brachial artery is obtained when the BP–CP difference is identical to diastolic BP (DBP). Volume elastic modulus (V_E) of the brachial artery is calculated as the change in the BP–CP difference (ΔP_1) per 1% increase in cross-sectional area at P_1 (A_{P_1}), where P_1 is defined as $P_0 + 40$ mm Hg and P_0 is defined as the point with the lowest CP indicating complete collapse of the brachial artery.

During the measurement, air for calibration flowed from the main unit into the cuff. This calibration makes it possible to determine the absolute volumetric changes of the brachial artery from the plethysmogram under the condition of cuff inflation (Figure 1a). Thereafter, the CP was gradually decreased and the calibrated plethysmogram was recorded several times at regular CP intervals.

The main unit next described a pressure (BP–CP difference)–area (brachial artery cross-sectional area) curve as an approximate logarithmic curve (Figure 1b), using the data obtained from the plethysmogram. The brachial artery cross-sectional area was calculated as the brachial artery volume divided by the brachial cuff length. Estimated cross-sectional area and volume elastic modulus (V_E) of the brachial artery were obtained from the pressure–area curve. The eA was defined as the cross-sectional area at the point where the BP–CP difference was identical to the diastolic BP (that is, end-diastolic cross-sectional area). The lowest CP indicating complete collapse of the brachial artery is usually a little higher than BP; therefore, the corresponding point (P_0) on the pressure axis of the curve was set at less than zero. V_E was defined as the change in the BP–CP difference (ΔP_1) per 1% increase in cross-sectional area at P_1 , where $P_1 = P_0 + 40$ mm Hg. We previously reported that eA closely correlated with the brachial artery diameter measured with ultrasonography ($r = 0.93$) in healthy subjects.¹⁴ In the previous report, we also showed that the coefficients of variation of eA and V_E for two consecutive measurements were 3.6% and 8.3%, respectively.¹⁴

Before the above measurements, brachial–ankle pulse wave velocity (baPWV) was measured by nearly the same methods described elsewhere with another commercially available device.¹⁵

The values of eA, V_E and baPWV for the right and left sides were, respectively, averaged and used in the subsequent statistical analysis.

Statistical analysis

All statistical tests were performed using SPSS software version 19.0.0 (IBM Corporation, Somers, NY, USA). Continuous variables with and without a skewed distribution were expressed as the median (interquartile range) and the

mean $\pm$ s.d., respectively. Categorical data were expressed as the percent of total. The unpaired Student's *t*-test and an analysis of variance with the *post hoc* Bonferroni multiple comparisons were used to examine the difference between the two groups and among the three groups, respectively. Pearson's correlation coefficient was analyzed to determine the simple correlation between variables. A multiple linear regression analysis was conducted to examine the independent determinants of eA among cardiovascular risk factors and the indices of arterial stiffness. In the analysis, variables that showed a *P*-value <0.2 by the Pearson's correlation coefficient were used as explanatory variables. All statistical tests were two-sided, and a *P*-value <0.05 was considered significant.

RESULTS

The characteristics of the study participants are described in Table 1. The means or the medians of cardiovascular risk parameters were found to be within acceptable ranges. The prevalence of participants who were taking medications for hypertension, dyslipidemia, DM and hyperuricemia was 3.9%, 2.1%, 0.8% and 2.1%, respectively.

Overall, the mean eA, V_E and baPWV were 12.9 ± 2.9 mm², 0.98 ± 0.19 mmHg per % and 1277 ± 181 cm s⁻¹, respectively. The scatter plots between eA and V_E or baPWV are shown in Figure 2. A significant but weak correlation was found between eA and V_E ($r=0.16$, $P=0.002$) as well as eA and baPWV ($r=0.20$, $P<0.001$).

As shown in Figure 3, eA was significantly higher in subjects with obesity, hypertension, dyslipidemia or IFG/DM than in those without each of these risk factors. In contrast, eA was found to be similar between subjects with and without hyperuricemia or current smoking.

A significant correlation was observed between eA and the Framingham CVD risk ($r=0.32$, $P<0.001$). When the subjects were

divided according to the Framingham CVD risk category, eA gradually increased across the categories and significant differences in eA were found among all combinations of the categories (all $P<0.001$; Figure 4).

As noted in Table 2, eA significantly and positively correlated with age, BMI, systolic and diastolic BP, log-transformed triglycerides, fasting plasma glucose, HbA1c and uric acid, while it tended to correlate negatively with pulse rate in a univariate analysis. In a multiple linear regression analysis, Model 1 (V_E and baPWV-excluded model) showed that age, BMI, systolic BP and pulse rate were independent determinants of eA. In Model 2 (V_E and baPWV-included model), the same independent determinants as those seen in Model 1 were observed, while neither V_E nor baPWV were selected as independent determinants of eA.

Sensitivity analyses were next conducted. When diastolic BP was substituted for systolic BP as an explanatory variable in the multiple linear regression analysis (Model 2), age, BMI and pulse rate remained as independent determinants of eA (data not shown). However, diastolic BP did not reach a statistically significant level as an independent determinant ($\beta=0.10$, $P=0.064$). Next, when the multiple linear regression analysis (Model 2) was conducted in the 372 subjects who were not taking antihypertensive medications (that

Table 1 Characteristics of the study subjects ($n=387$)

Age (years)	38 $\pm$ 9
Height (cm)	171.9 $\pm$ 6.1
BMI (kg m ⁻²)	23.1 $\pm$ 3.5
Obesity, <i>n</i> (%)	95 (24.5)
Systolic BP (mm Hg)	123 $\pm$ 11
Diastolic BP (mm Hg)	71 $\pm$ 9
Antihypertensive medication use, <i>n</i> (%)	15 (3.9)
Hypertension, <i>n</i> (%)	34 (8.8)
Pulse rate (b.p.m.)	66 $\pm$ 10
LDL cholesterol (mg dl ⁻¹)	118 $\pm$ 29
HDL cholesterol (mg dl ⁻¹)	57 $\pm$ 13
Triglycerides (mg dl ⁻¹) ^a	84 (60, 127)
Antidyslipidemic medication use, <i>n</i> (%)	8 (2.1)
Dyslipidemia, <i>n</i> (%)	142 (36.7)
Fasting plasma glucose (mg dl ⁻¹)	87 $\pm$ 9
HbA1c (%)	5.2 $\pm$ 0.3
Glucose-lowering medication use, <i>n</i> (%)	3 (0.8)
IFG/DM, <i>n</i> (%)	8 (2.1)
DM, <i>n</i> (%)	5 (1.3)
Uric acid (mg dl ⁻¹)	5.9 $\pm$ 1.2
Uric acid-lowering medication use, <i>n</i> (%)	8 (2.1)
Hyperuricemia, <i>n</i> (%)	80 (20.7)
White blood cell count ($\times 10^3/\mu$ l)	6.0 $\pm$ 1.5
Current smoking (%)	133 (34.4)
eA (mm ²)	12.9 $\pm$ 2.9
V_E (mm Hg per %)	0.98 $\pm$ 0.19
baPWV (cm s ⁻¹)	1277 $\pm$ 181

Abbreviations: baPWV, brachial-ankle pulse wave velocity; BMI, body mass index; BP, blood pressure; DM, diabetes mellitus; eA, estimated area; Hb, hemoglobin; HDL, high-density lipoprotein; IFG, impaired fasting glucose; LDL, low-density lipoprotein; V_E , volume elastic modulus.

^aMedian (interquartile range).

Figure 2 Scatter plots for the correlation between (a) estimated area (eA) and volume elastic modulus (V_E) of the brachial artery, and (b) eA and brachial-ankle pulse wave velocity (baPWV).

Figure 3 Comparison of estimated area (eA) of the brachial artery in subjects with and without each cardiovascular risk factor. IFG/DM, impaired fasting glucose/diabetes mellitus.

is, vasoactive drugs), all of the same independent determinants as those seen in the main analysis (age, BMI, systolic BP and pulse rate) were observed (data not shown). Finally, when the multiple linear regression analysis (Model 2) was repeated in only the 357 subjects who were not taking any medications for hypertension, dyslipidemia, DM or hyperuricemia, the results were substantially maintained, except that fasting plasma glucose was further selected as an independent determinant of eA (data not shown).

In regard to the indices of arterial stiffness, V_E significantly correlated with age ($r = 0.29$, $P < 0.001$) and pulse rate ($r = -0.22$, $P < 0.001$), but did not correlate with any other cardiovascular risk parameters used in this study (data not shown). Similarly, baPWV significantly correlated with age ($r = 0.53$, $P < 0.001$) and pulse rate ($r = 0.25$, $P < 0.001$), and further correlated with a number of

cardiovascular risk parameters, such as BMI, systolic and diastolic BP, white blood cell count, fasting plasma glucose and HbA1c, triglycerides and LDL cholesterol and uric acid (data not shown).

The characteristics and tentative results of the correlation analysis between eA and cardiovascular risk parameters in 33 female workers are listed in Supplementary Tables S1 and S2, respectively.

DISCUSSION

This study showed that eA was independently associated with age, BMI, systolic BP and pulse rate in a population of middle-aged men without known CVD. In contrast, no independent association was observed between eA and either V_E or baPWV. To our knowledge, this is the first study to focus on the extent of brachial artery enlargement

evaluated by the oscillometric method and to examine its relationship with cardiovascular risk factors and arterial stiffness.

In a multivariate analysis, age was an independent determinant of eA in this study. Arterial diameter has been reported to increase with advancing age.⁴ The present findings are therefore in line with earlier observations. Among other cardiovascular risk factors considered in this analysis, BMI and systolic BP were independent determinants of eA, which also supports the findings in this study that eA is larger in subjects with obesity or hypertension than in those without each of these risk factors. These results are also consistent with previous observations of the significant associations of BP or obesity indices with brachial or carotid artery diameters.^{3,16} From a clinical

perspective, these observations suggest that eA may be a useful marker for evaluating the effects of these risk factors on brachial artery enlargement. Earlier studies have reported that matrix metalloproteinases, a family of zinc-dependent endopeptidases capable of degrading all of the components of the extracellular matrix, have a crucial role in vascular remodeling.¹⁷ It has also been reported that matrix metalloproteinases, in particular matrix metalloproteinase-9, are increased in patients with hypertension and/or obesity.^{18–20} Matrix metalloproteinases, while not measured in this study, may be involved in the association of eA with BMI and systolic BP.

This study showed that eA gradually increased as the CVD risk category, as determined by the Framingham CVD risk prediction algorithm, increased.¹³ These are convincing results, because the Framingham CVD risk prediction algorithm incorporates variables that also showed a significant correlation with eA in this study, including age, BMI and systolic BP. These findings are further supported by the previous reports of the positive association between the enlargement of brachial artery diameter and increased risk of CVD.¹⁰ The usefulness of eA as a risk marker for future cardiovascular event is anticipated.

Unexpectedly, eA was not significantly associated with lipid profiles, uric acid levels, white blood cell counts or current smoking status, all of which have been reported elsewhere to be associated with impaired arterial properties.^{11,21–24} One possible reason for this finding is that the duration of exposure to these risk factors could not be evaluated because of the cross-sectional nature of this study. Alternatively, it is possible that brachial artery enlargement is not intrinsically influenced by these risk factors in this study population. Further longitudinal investigations would be needed to address this issue.

Although eA significantly correlated with both V_E and baPWV in a univariate analysis, independent associations were not observed in a multivariate model that included cardiovascular risk factors as

Figure 4 Comparison of estimated area (eA) of the brachial artery among the low (<10%), intermediate (10–20%) and high (>20%) cardiovascular disease (CVD) risk categories according to the Framingham CVD risk prediction algorithm. * $P<0.001$ vs. low category, † $P<0.001$ vs. low and intermediate category.

Table 2 Pearson's correlation coefficient and multiple linear regression analysis for the association between eA with each of the studied variables, including cardiovascular risk factors and indices of arterial stiffness

Variables	Pearson's correlation coefficient		Multiple linear regression analysis (Model 1) ^a		Multiple linear regression analysis (Model 2) ^a	
	R	P-value	β	P-value	β	P-value
Age	0.35	<0.001	0.26	<0.001	0.25	<0.001
Height	0.04	0.44	—	—	—	—
BMI	0.37	<0.001	0.31	<0.001	0.31	<0.001
Systolic BP	0.29	<0.001	0.13	0.007	0.16	0.004
Diastolic BP	0.29	<0.001	— ^b	—	— ^b	—
Pulse rate	−0.09	0.06	−0.16	0.001	−0.13	0.005
LDL cholesterol	0.07	0.16	−0.06	0.22	−0.06	0.26
HDL cholesterol	−0.05	0.37	—	—	—	—
Triglycerides ^c	0.15	0.004	−0.02	0.70	−0.02	0.75
Fasting plasma glucose	0.20	<0.001	0.07	0.14	0.07	0.14
HbA1c	0.21	<0.001	— ^b	—	— ^b	—
Uric acid	0.11	0.037	−0.01	0.85	−0.01	0.85
White blood cell count	0.01	0.83	—	—	—	—
Current smoking (Yes = 1)	0.04	0.41	—	—	—	—
V_E	0.16	0.002	—	—	0.08	0.10
baPWV	0.20	<0.001	—	—	−0.04	0.48
			(Model adjusted $R^2=0.25$)		(Model adjusted $R^2=0.25$)	

Abbreviations: β , Standardized regression coefficient; baPWV, brachial-ankle pulse wave velocity; BMI, body mass index; BP, blood pressure; eA, estimated area; Hb, hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; V_E , volume elastic modulus.

Model 1, does not include V_E or baPWV in the analysis; Model 2, includes V_E and baPWV in the analysis; —, not included in the analysis.

^aVariables with a $P<0.2$ by the Pearson's correlation coefficient were entered into the multiple linear regression analysis.

^bNot included to avoid multicollinearity with systolic BP or fasting plasma glucose.

^cLog-transformed value.

explanatory variables. These findings suggest the existence of some confounding factors for the relationship of eA with V_E or baPWV. Similar to the positive correlation between eA and age, V_E significantly and positively correlated with age in this study. It is also well known that baPWV is increased with advancing age²⁵ and, in fact, baPWV also significantly and positively correlated with age in this study. These results suggest that age is at least one of the potential confounding factors. Taken together, the lack of independent association of eA with V_E or baPWV seen in this study raises the possibility of a different clinical significance of eA from that of V_E or baPWV. This point may merit further investigation.

Another important finding of this study was the negative association of eA with pulse rate. This indicates that caution is needed when evaluating eA in subjects with bradycardia or tachycardia. However, the association with pulse rate is not specific to eA, but is shown in other noninvasive measures of arterial properties as well, including PWV and augmentation index.¹¹

There are limitations to this study. First, as noted above, this was a cross-sectional investigation. Therefore, the causal relationship between eA and cardiovascular risk factors could not be clarified. Second, the study participants included only middle-aged Japanese men at a single site. Therefore, it is unclear whether these results can be extrapolated to other populations, including female subjects, the elderly and other ethnic groups. In particular, female workers were not included in the main analysis because their number was relatively small. In fact, the results of the correlation analysis in female workers (Supplementary Table S2) appeared to be inconsistent with those in male workers, thus suggesting that a larger sample size may be needed to further discuss the relationship of eA with cardiovascular risk parameters in female workers.

In conclusion, this study showed that eA was significantly associated with age, BMI and systolic BP in a population of middle-aged men. These results suggest that eA may be a useful marker for evaluating the effects of these risk factors on brachial artery enlargement. In addition, eA was not independently associated with the indices of arterial stiffness, V_E or baPWV, thus suggesting a different clinical significance of eA from that of V_E or baPWV. To date, ultrasonography, which requires a skilled examiner, has been almost the sole noninvasive method to measure brachial artery diameter. In this regard, the oscillometric measurement technique presented here offers a simple and more operator-independent method to evaluate noninvasively brachial artery cross-sectional area. Further studies to examine the usefulness of this measurement in various clinical and epidemiological settings are anticipated.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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