Original Article

Impact of Lifestyle-Related Diseases on Carotid Arterial Wall Elasticity as Evaluated by an Ultrasonic Phased-Tracking Method in Japanese Subjects

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***Aim*: We investigated the relationship between coronary risk factors and the intima-media thickness (IMT) and wall elasticity of carotid arteries. A new real-time ultrasonic measurement system that allows measurement of the elasticity of the carotid arterial intima-media complex was applied to 350 subjects, who were also checked for the presence/absence of hypertension, dyslipidemia, diabetes mellitus and regular smoking. Simultaneous measurement of the elastic modulus and IMT was conducted at four sites in the bilateral carotid arteries.**

***Methods and Results*: In the group with maximum IMT (max IMT) <1.1 mm, the IMT, as well as the mean elastic modulus in the circumferential direction (Eθ), showed positive correlations with age and coronary risk factors. Multiple regression analysis showed that age, systolic blood pressure and pulse rate remained independent determinants of Eθ. The number of criteria fulfilling the diagnosis of metabolic syndrome showed a good positive correlation with the value of Eθ in the group with max IMT values <1.1 mm.**

***Conclusion*: Measurement of carotid arterial wall elasticity together with IMT is useful to detect distortions in intramural elasticity distribution occurring in the early stages of atherosclerosis.**

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Key words; Elastic modulus, Carotid arteries, Intima-media thickness, Metabolic syndrome, Atherosclerosis

Introduction

Carotid arterial intima-media thickness (IMT) is one of the established indices of chronic atherosclerotic arterial disease[1-5]; however, IMT is not a direct measure of the stiffness of the arterial wall. Recently, a new ultrasonic system that can measure regional elasticity in the arterial wall utilizing a phased tracking method has been developed[6-10]. The modulus of elasticity has also been successfully derived from measuring change in arterial wall thickness during one cardiac cycle as an index of the "stiffness/softness" of the arterial wall. In a previous study, we reported the usefulness of measuring the elastic modulus of common carotid arteries (CCAs) by ultrasound imaging to detecting early-stage atherosclerotic lesions caused by cigarette smoking[9].

The main aim of the present study was to determine whether early-stage atherosclerotic changes, caused by hypertension, diabetes mellitus, dyslipidemia and obesity, could also be detected using the ultrasound-based tissue characterization system for the arterial wall. Another objective of the study was to assess the relationship between the IMT and the elastic modulus, especially using a cutoff value of the max IMT of 1.1 mm in various lifestyle-related diseases,

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including metabolic syndrome.

Methods

Study Population

Three hundred fifty healthy volunteers and untreated outpatients (209 men and 141 women; mean age, 49.9 years old) with and without lifestyle-related diseases were enrolled in this study. The clinical and demographic characteristics of the study population are shown in **Table 1**. Subjects were assessed for the presence of atherosclerotic risk factors as defined by the guidelines of the Japanese Societies of Hypertension[11], Atherosclerosis[12] and Diabetes Mellitus[13]. Hypertension was defined as a systolic BP ≥140 mmHg and/or diastolic BP ≥90 mmHg. Hyperlipidemia was defined as serum low-density lipoprotein cholesterol (LDL-C) ≥140 mg/dL and/or serum triglyceride (TG) ≥150 mg/dL. Diabetes mellitus was defined as a fasting plasma glucose (FPG) ≥126 mg/dL. Smoking was assessed using a self-administered questionnaire and was classified as current vs. never. None of the subjects had secondary hypertension, hypertension complicated by recent cardiovascular events, atrial fibrillation, or arteriosclerosis obliterans (ASO), defined as an ankle/brachial blood pressure index (ABI) <0.9.

The subjects provided informed consent and the study was approved by the Institutional Ethics Committees of Tohoku Kosai Hospital and Panasonic Shikoku Electronics Co., Ltd.

Risk Factor Evaluation

A detailed history of the risk factors and medical conditions of each subject was obtained. The subjects were requested to fast overnight without medication until blood samples were drawn. Venous blood samples were then drawn for analysis of FPG and serum concentrations of TC, TG, high-density lipoprotein cholesterol (HDL-C) and HbA1C by standard laboratory methods. Serum LDL-C was calculated by Friedewald's equation. None of the patients had a TG >400 mg/dL, at which the Friedewald equation is known to yield unreliable results. Body mass index (BMI) was calculated as the weight [kg]/height^2 [m^2].

Metabolic Syndrome

Metabolic syndrome was defined as a waist circumference ≥85 cm in men and ≥90 cm in women, along with two or more of the following three risk factors: hypertension (blood pressure ≥130/85 mmHg), dyslipidemia (HDL-C <40 mg/dL or TG ≥150 mg/dL), and glucose intolerance (FPG ≥110 mg/dL)[14].

Table 1. Characteristics of the study population

	Risk Factor (−) (n = 101)	Risk Factor (+) (n = 249)
Age (y.o.)	38.3 ± 8.9	54.7 ± 11.6***
Male	65 (63.1%)	143 (58.1%)
BMI (kg/m^2)	22.0 ± 2.7	23.7 ± 3.3***
Waist (cm)	76.4 ± 10.0	82.6 ± 9.0***
SBP (mmHg)	113.1 ± 10.5	128.2 ± 16.3***
DBP (mmHg)	71.9 ± 8.5	77.9 ± 10.2***
PP (mmHg)	41.2 ± 8.1	50.3 ± 12.5***
PR (bpm)	69.4 ± 9.4	70.3 ± 10.2
TC (mg/dL)	178.8 ± 27.5	227.2 ± 42.4***
TG (mg/dL)	82.4 ± 52.1	142.5 ± 82.2***
HDL-C (mg/dL)	58.2 ± 13.2	54.6 ± 14.6***
LDL-C (mg/dL)	98.3 ± 23.3	135.4 ± 35.3***
FPG (mg/dL)	86.7 ± 8.3	103.1 ± 29.8***
HbA1c (%)	4.6 ± 0.4	5.5 ± 1.0***
UA (mg/dL)	5.0 ± 1.5	5.5 ± 1.3
Hypertension (%)	0	47.6
Hyperlipidemia (%)	0	73.0
Diabetes mellitus (%)	0	17.7
Smoking (%)	0	49.0
Smoking Index	0	622.7 ± 388.4
Hyperuricacidemia (%)	0	11.3
Metabolic syndrome (%)	0	17.6
Mean IMT (mm)	0.50 ± 0.09	0.73 ± 0.15***
Mean Eθ (kPa)	144.3 ± 39.6	165.1 ± 52.9***
Plaque occurrence (%)	2.0	68.6
baPWV (cm/sec)	1093.8 ± 248.5	1506.4 ± 310.4***

***p < 0.001 vs risk factor (−)

RF: Risk factor (hypertension, diabetes mellitus, hyperlipidemia and smoking), BMI: Body mass index, Waist: waist circumference, SBP: Systolic blood pressure, DBP: diastolic blood pressure, PP: pulse pressure, PR: pulse rate, TC: total cholesterol, TG: triglyceride, HDL-C: high density cholesterol, LDL-C: low density cholesterol, FPG: fasting plasma glucose, UA: uric acid, baPWV: brachio-ankle pulse wave velocity.

Carotid IMT and Elasticity Measurements

The subjects were studied after having abstained from caffeine, alcohol, and smoking for the previous 12 hours. The subjects rested in a supine position for 15 min in a quiet room before the baseline hemodynamic measurements were obtained. Brachial blood pressure and pulse rate (PR) (mean of three readings) were measured in the right arm with an automated digital oscillometric sphygmomanometer (EW-3110; Matsushita Electric Works, Osaka, Japan). Imaging study of the bilateral CCAs was performed using a newly developed high-resolution ultrasonic measurement system (prototype; Panasonic Shikoku Electron-

ics,) with a center frequency of 7.5 MHz. One well-trained ultrasound technologist who regularly participates in quality control measurement sessions performed all the ultrasound examinations[9].

IMT can only be determined accurately in the far arterial wall because only far wall IMT is defined by leading edges, which allows correct ultrasonographic representation. Therefore, the far wall at the following sites was measured: 1) the distal 3 cm of the straight part of both CCAs, 2) the distal 1 cm of both carotid bulbs. As in several previous studies, we defined a plaque as a focal raised lesion using an IMT cutoff value of 1.1 mm. The mean IMT was determined as the average of the IMT values measured at four locations on the CCAs bilaterally, not including the bulb. The max IMT was determined as the maximum value of the IMT measured at six locations on the CCAs bilaterally, including the bulb, in order to assess for the presence of plaques.

The novel ultrasound system employed in this study measures radial strain of the arterial wall during one cardiac cycle and calculates the elasticity from the radial strain and the pulse pressure. The distribution of elasticity is displayed as a 2D cross-sectional color image on B-mode images, and the image is updated every heartbeat. For the measurement of minute changes in thickness, the system uses the phased tracking method[5-10]. The elasticity parameter was estimated at intervals of 80 μm in the depth direction and 400 μm in the axial direction. From the maximum change in thickness during one heartbeat, the radial strain ε_r of each assigned layer in the arterial wall was calculated as follows:

$$\varepsilon_r = (h_{max} - h_{min})/h_{max}, \quad (1)$$

where h_{max} and h_{min} are the maximum and minimum thicknesses, respectively, of an assigned layer in the wall.

The elastic modulus in the radial direction (Er) and that in the circumferential direction (Eθ) were calculated as follows:

$$Er = \text{Pulse Pressure}/\varepsilon_r, \quad (2)$$
$$E\theta = (1/2) \times (r_0/h_0 + 1) \times Er, \quad (3)$$

where pulse pressure is the difference between the brachial systolic and diastolic blood pressure (carotid blood pressure would be more accurate but is not easy to measure), and $h_0 = h_{max}$ and r_0 are the initial wall thickness and radius of the vessel in end diastole, respectively. Radial strain ε_r is caused by radial compression and circumferential stretching due to the increase of blood pressure Δp when the longitudinal strain is neglected. Circumferential stretching produces radial strain due to the incompressibility of the arterial wall. Therefore, both the radial and circumferential stresses should be considered to evaluate elasticity; however, as shown in Eq. (2), Er is defined as the ratio of pulse pressure (which corresponds to radial stress) to radial strain. Circumferential stress acting on the cylindrical shell is not the same as pulse pressure and also depends on r_0/h_0; therefore, Er is apparent elasticity in the radial direction and depends on r_0/h_0 as well as on the elasticity of the arterial wall. Alternatively, Eθ was introduced to evaluate the elasticity of the arterial wall by suppressing the influence of r_0/h_0[7]. The measurement reproducibility has been reported previously[11]. In the present study, the reproducibility of the elastic modulus was assessed in 49 patients. There were no significant differences between the first and second visits in the SBP ($p = 0.21$), PR ($p = 0.59$), IMT ($p = 0.95$) or Eθ ($p = 0.69$). **Fig. 1A** shows the level of agreement of Eθ. The correlation coefficients for SBP, PR, IMT and Eθ were 0.73, 0.90, 0.87 and 0.91 ($p < 0.0001$), respectively. The coefficients of variation (CV) of SBP, PR, IMT and Eθ were 12.4%, 17.0%, 33.7% and 38.6%, respectively. As shown by the Bland-Altman plots in **Fig. 1B**, the mean intraobserver-intersession difference was 4.8 kPa with an SD of 25.0 kPa for Eθ. In the graph, most of the data points fell within the 2 SD range.

Pulse Wave Velocity (PWV) Measurements

Brachial-ankle PWV (baPWV) was measured using volume-plethysmographic apparatus (Form/ABI; Colin Co., Ltd., Komaki, Aichi, Japan) by simultaneous BP and waveform measurements of all four limbs along with ECG and phonogram tracings. PWV was automatically calculated by time-phasic analysis using the following formula: distance between two sites divided by the pulse wave transit time. The baPWV was measured from the ascending point of the right brachial pulse volume recorder to the ascending point of each ankle pulse volume recorder. The distance between the right brachium and ankle was estimated as described previously[15].

Statistical Analysis

Data are expressed as the mean ± SD. Statistical analysis was performed using the JMP® software package (JMP 7.0.1; SAS Institute, USA), and p values < 0.05 were considered to denote significance. Differences among groups were analyzed by one-way analysis of variance (ANOVA) or analysis of covariance (ANCOVA). Linear regression analysis was performed to evaluate the associations among the IMT, elastic modulus and other clinical variables. Multiple linear

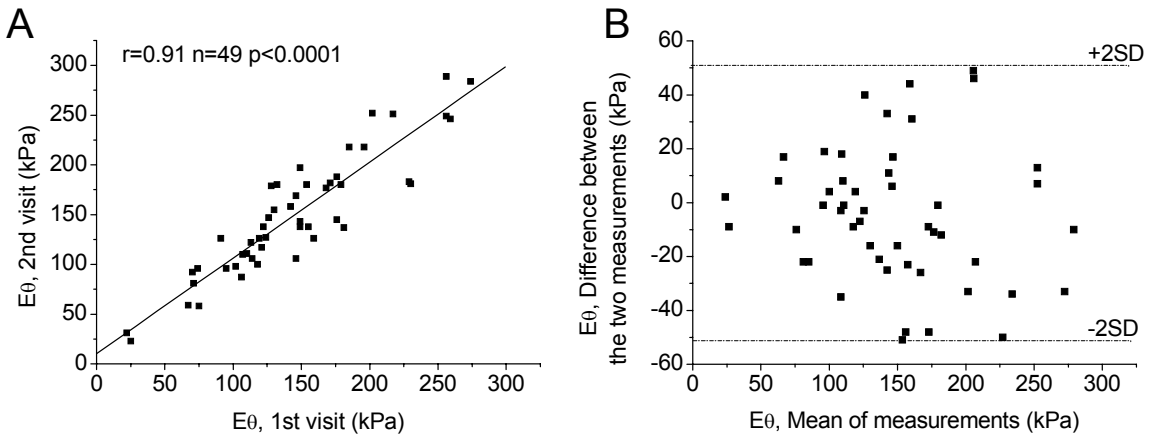

Fig. 1. (A) Reproducibility of the elastic modulus, Eθ. Correlation between the measurements of Eθ values at the 1st and 2nd visits.

(B) Bland-Altman plots showing the differences between the Eθ values at the 1st and 2nd visits plotted against their mean values. Lines represent the mean difference and the limits of agreement, that is, ± 2 SD.

regression analysis was applied to evaluate whether the relationship between any two parameters was independent of other related factors.

Results

Associated Risk Factors

We conducted measurements at four locations in the bilateral carotid arteries and obtained the mean values of IMT and Eθ. As shown in **Table 1**, the mean IMT and mean Eθ in the group with at least one risk factor (Risk Factor (+)), i.e., hypertension, hyperlipidemia, diabetes mellitus and/or smoking, were significantly larger than those in the healthy group (Risk Factor (−)). As shown in **Fig. 2**, the mean IMT and mean Eθ values were correlated with age in all patients. The strength of the correlation was in the order of mean IMT (r=0.74, **Fig. 2A**) > mean Eθ (r=0.30, **Fig. 2B**); however, the mean IMT was slightly correlated with the mean Eθ (r=0.19, p=0.0006), as shown in **Fig. 2C**, indicating that the elastic modulus does not always increase with thickening of the IMT. The results of simple regression analysis (**Table 2**) revealed that the mean IMT was significantly positively correlated with age, BMI, waist circumference, SBP, DBP, TC, TG, LDL-C, FPG, HbA1c and baPWV, and negatively correlated with the HDL-C; the mean Eθ was significantly positively correlated with age, BMI, waist circumference, SBP, DBP, PR, FPG, HbA1c and baPWV.

The results of multiple regression analysis for all the subjects, shown in **Table 3**, revealed age, SBP and HbA_{1C} to be independent determinants of the mean IMT; however, age, SBP and PR remained independent determinants of the mean Eθ.

Analysis Using a Cutoff Value of the Max IMT

Since it has been reported that native Japanese reach an IMT of 1.1 mm at age 70 and subjects with max IMT < 1.1 mm are often classified as not having atherosclerosis[5], we divided the participants into the two groups divided by a cutoff value of the max IMT, i.e., a group with max IMT values less than 1.1 mm (max IMT < 1.1 mm) and a group with max IMT values equal to or more than 1.1 mm (max IMT ≥ 1.1 mm). As shown in **Table 4**, the mean Eθ was significantly larger in the group with max IMT ≥1.1 mm (n=173) than in that with max IMT < 1.1 mm (n=177).

In the group with max IMT < 1.1 mm, as shown in **Table 5**, in simple regression analysis of the mean IMT and mean Eθ, the correlation coefficients, except those for the lipid levels, that is, TC, TG, HDL-C and LDL-C, showed a similar tendency in all participants; however, in the group with max IMT ≥ 1.1 mm, the correlation coefficients between the mean IMT and mean Eθ with risk factors were weaker than the results obtained from analysis of the whole subject population. A negative correlation was observed between the PR and the mean IMT.

In regard to lipid levels, the mean Eθ did not show a significant correlation with lipid levels in the

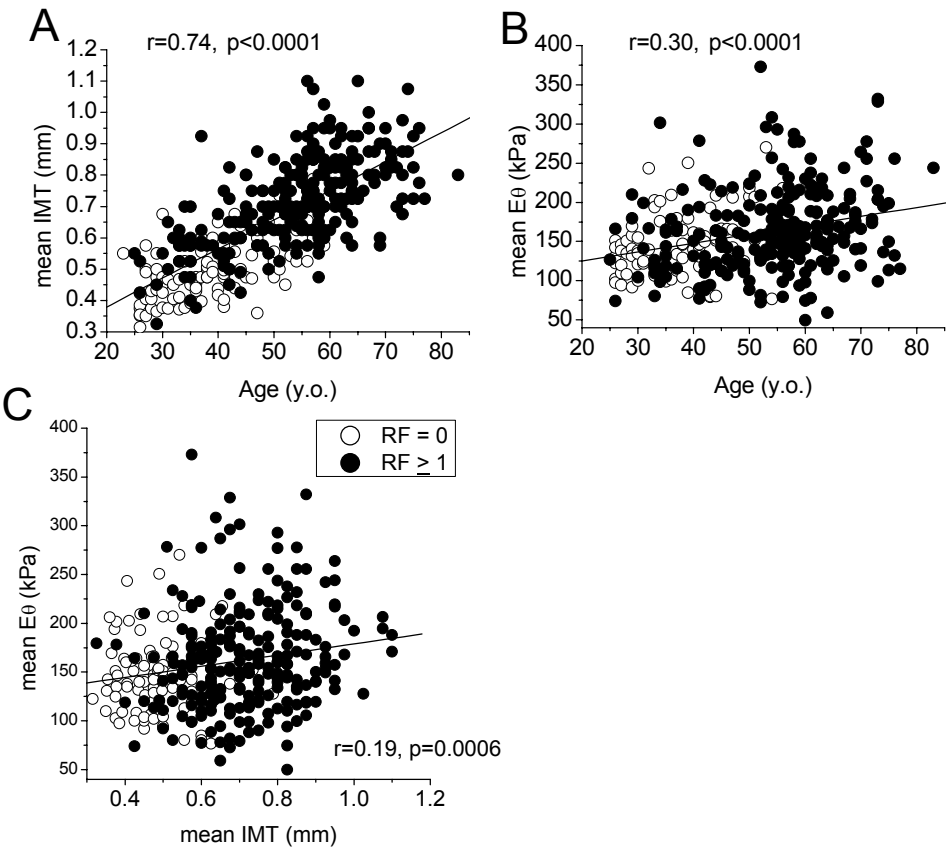

Fig. 2. Correlation of age with mean IMT (A) and mean Eθ (B). Correlation of mean IMT with mean Eθ (C). RF = 0, group with no risk factors; RF ≥1, group with at least one risk factor.

Table 2. Correlation coefficients of mean IMT and mean Eθ with risk factors obtained by simple regression analysis

	Mean IMT	Mean Eθ
Age	0.74***	0.30***
BMI	0.23***	0.13*
Waist	0.29***	0.18**
SBP	0.52***	0.49***
DBP	0.28***	0.23***
PR	−0.09	0.16**
TC	0.35***	−0.02
TG	0.25***	0.10
HDL-C	−0.16**	−0.07
LDL-C	0.32***	−0.01
FPG	0.27***	0.18**
HbA1C	0.27***	0.18**
UA	0.01	0.05
baPWV	0.57***	0.39***

*$p<0.05$, **$p<0.01$, ***$p<0.001$

Table 3. Multiple regression analysis for all subjects

	Mean IMT		Mean Eθ	
	β	p	β	p
Age	0.53	<0.0001	0.15	0.0133
Gender	−0.03	NS	0.10	NS
BMI	0.06	NS	0.01	NS
SBP	0.21	0.001	0.48	<0.0001
PR	−0.10	NS	0.13	0.0112
HDL-C	−0.09	NS	0.05	NS
HbA1C	0.12	0.017	0.05	NS

Table 4. Statistics of mean IMT and mean Eθ in the two groups with max IMT < 1.1 mm and with max IMT ≥ 1.1 mm

	Max IMT < 1.1 mm (n = 177)	Max IMT ≥ 1.1 mm (n = 173)	p
Mean IMT	0.54 ± 0.11	0.78 ± 0.14	<0.0001
Mean Eθ	150.6 ± 45.8	167.9 ± 53.3	0.0017

Table 5. Correlation coefficients of mean IMT and mean Eθ with risk factors in the two groups with max IMT <1.1 mm and with max IMT ≥ 1.1 mm obtained by simple regression analysis

	Max IMT <1.1 mm		Max IMT ≥ 1.1 mm	
	Mean IMT	Mean Eθ	Mean IMT	Mean Eθ
Age	0.64^{***}	0.33^{***}	0.46^{***}	0.18^{*}
BMI	0.38^{***}	0.17^{*}	-0.02	0.04
Waist	0.42^{***}	0.24^{**}	-0.03	0.06
SBP	0.41^{***}	0.41^{***}	0.30^{***}	0.50^{***}
DBP	0.26^{**}	0.19^{*}	0.02	0.18^{*}
PR	0.04	0.27^{**}	-0.17^{*}	0.13
TC	0.46^{***}	0.10	-0.02	-0.23^{*}
TG	0.41^{***}	0.21^{*}	-0.03	-0.02
HDL-C	-0.26^{**}	-0.03	-0.09	-0.08
LDL-C	0.43^{***}	0.08	0.15	-0.17^{*}
FPG	0.35^{***}	0.19^{*}	0.09	0.14
HbA_{1C}	0.44^{***}	0.24^{*}	0.14	0.11
UA	0.11	0.21^{*}	0.09	-0.04
baPWV	0.47^{***}	0.39^{***}	0.41^{***}	0.29^{**}

$^{*}p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$

analysis of the whole subject population (**Table 2**). On the other hand, in the group with max IMT ≥ 1.1 mm, while no significant correlation of the mean IMT with the lipid levels was observed, the mean Eθ showed a significant negative correlation with the LDL-C and TC (**Table 5** and **Fig. 3**). In the group with max IMT <1.1 mm, the mean IMT showed a positive correlation with TC, TG and LDL-C, and a negative correlation with HDL-C, while the mean Eθ showed a significant positive correlation with only the TG.

Correlation with the Number of Risk Factors and Metabolic Syndrome

As shown in **Fig. 4A**, in the group with max IMT <1.1 mm, both the mean IMT and mean Eθ increased significantly with the number of cardiovascular risk factors (hypertension, hyperlipemia, diabetes mellitus, and smoking) (ANOVA, $p<0.0001$).

In addition, as shown in **Fig. 4B**, the mean IMT and mean Eθ were significantly increased in metabolic syndrome subjects with max IMT <1.1 mm (Mets, $n=41$, male 34, female 7) than in non-Mets subjects with max IMT <1.1 mm ($p<0.05$).

As shown by the horizontal axis in **Fig. 5**, the subjects were classified into six groups based on waist circumference and the number of risk factors. The sex- and age-adjusted means of the mean IMT, mean Eθ and baPWV were all elevated in subjects with full-blown metabolic syndrome as well as in those with pre-metabolic syndrome ($p<0.05$).

Discussion

In this study, the relationships between the risk factors and the elastic modulus values Eθ were examined by comparing healthy volunteers and patients with lifestyle-related diseases.

First, good reproducibility of the measurement of Eθ was shown for the same examiner. Assessment of the elastic modulus is easy and the parameter is as accurate as the IMT in reflecting arterial wall elasticity. We did not recognize any difference in reproducibility at any locations.

In general, carotid IMT is conventionally reported to be correlated with age, blood pressure, FPG and serum cholesterol levels, and the degree of obesity[1-5, 16, 17]. Similar to previous studies, our results

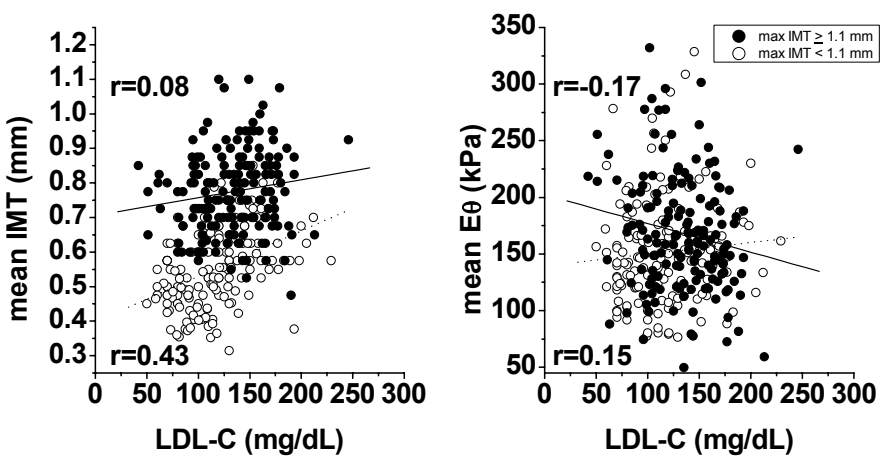

Fig. 3. Correlation of LDL-C with mean IMT and mean Eθ.

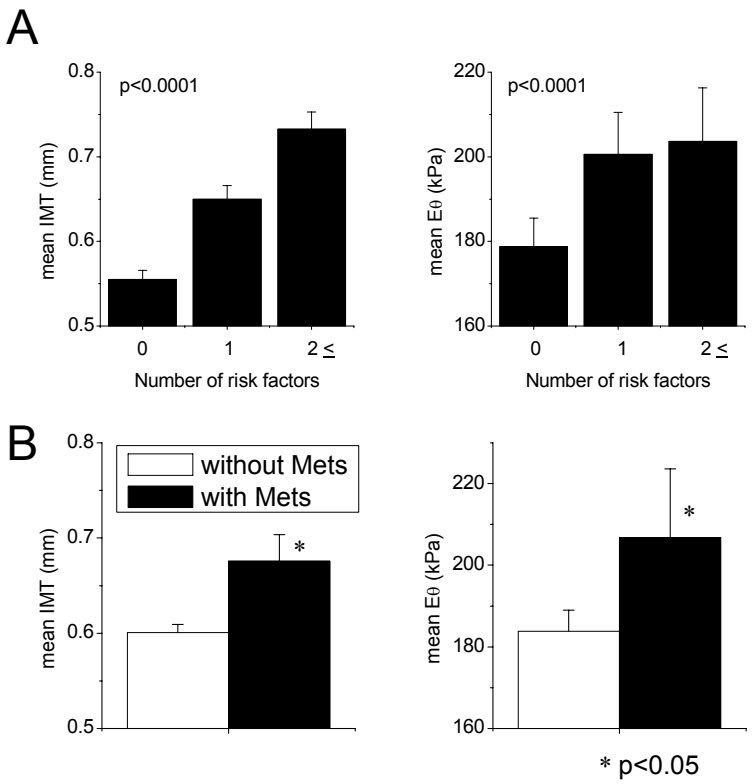

Fig. 4. (A) Relationships between the number of risk factors and mean IMT and mean Eθ in the group with max IMT <1.1 mm.

(B) Mean IMT and mean Eθ in the absence and presence of metabolic syndrome (Mets) in the group with max IMT <1.1 mm.

in **Table 3** show that age, SBP and HbA1c were independent determinants of the mean IMT by multiple regression analysis. On the other hand, only age, SBP and PR were independent risk factors of an increase of Eθ.

We demonstrated that the IMT and elastic modulus might reflect different aspects of the atherosclerotic process. The conventional ultrasonic B-mode method, including carotid IMT measurement, shows morphological changes such as thickening and calcification. Studies with conventional integrated backscatter (IBS) analysis[18-20] only reflect a difference in echogenicity and do not directly show the elasticity of the arterial wall. In the present study, our method enabled qualitative evaluation of the carotid arterial wall with simultaneous measurement of the elastic modulus and the IMT. As shown in **Fig. 2C**, an increased IMT is not always associated with an increased elastic modulus. As shown in **Table 5**, with max IMT values less than 1.1 mm, positive correlations were observed between Eθ and most of the risk factors (**Table 5**); however, these correlations were found to be weaker with max IMT values equal to or greater than 1.1 mm. It would seem that mural thickness is an important consideration in assessing the correlation of the elastic modulus with coronary risk factors. This was particularly true for TG and LDL-C, that is, in the group with max IMT <1.1 mm, only TG in the serum showed a positive correlation with Eθ. On the other hand, in the group with max IMT ≥ 1.1 mm, serum LDL-C showed a negative correlation with Eθ (**Table 5** and **Fig. 3**). It has been reported that carotid stiffness, which is commonly considered as an early indicator of vascular damage, is not increased in cases of hypercholesterolemia[21]. Assessment of advanced plaques by transmission electron microscopy revealed intact, but attenuated, endothelium overlying the cellular deposits, lipid-containing smooth muscle cells, partially absent basement membrane, macrophages filled with small cytoplasmic lipid droplets, and an extracellular matrix composed of elastic tissue, myelin figures, necrotic debris and cholesterol clefts[22]. Variations in the elastic modulus of the arterial wall occurring with changes in the relative ratios of these com-

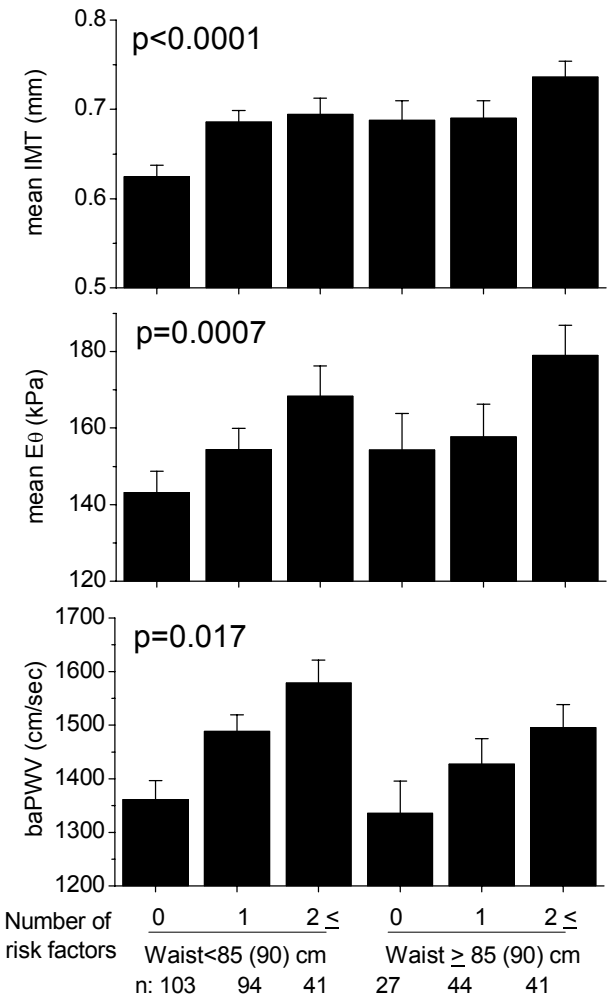

Fig. 5. Sex- and age-adjusted means of the mean IMT and mean Eθ and baPWV stratified by the waist circumference and number of risk factors of metabolic syndrome (hypertension, dyslipidemia, and glucose intolerance). The diagnosis of metabolic syndrome in Japanese subjects is based mainly on a waist circumference of ≥85 cm in men and ≥90 cm in women. Error bars indicate the SEM. *P*-values were obtained by ANCOVA.

ponents may explain the weak correlations of Eθ with coronary risk factors in the group with max IMT ≥1.1 mm. The inverse correlation of Eθ with LDL-C in the group with max IMT ≥1.1 mm may be explained by the similar phenomenon of the pathogenesis of vulnerable or unstable lipid-rich lesions in acute coronary artery syndrome[23-25]. Thus, the combination of IMT and elastic modulus of the carotid arterial wall may help to detect atherosclerotic lesions effectively.

In the group with max IMT <1.1 mm, an accumulation of risk factors is associated with elevation of Eθ as well as IMT and has been reported previously in patients who smoke[9] and have diabetes mellitus[26]. In subjects with normal intima-media thickness, the correlations of the overall elasticity of the common carotid artery with coronary risk factors have been reported to be stronger than those of conventional IMT[27]. In the present study, it was found that other risk factors contributed to an increase of Eθ, especially in the group with max IMT <1.1 mm. In early atherosclerotic lesions, impaired local availability of nitric oxide and endothelium-dependent vasodilatation may result from either short- or long-term exposure to several risk factors. Recurrent or persistent exposure to the risk factors may result in a state of persistent endothelial dysfunction and altered vascular wall milieu that might promote progression of the structural changes associated with atherosclerosis[28]. These changes are proposed as one possible explanation for the increases in elastic modulus values in association with various risk factors in the group with max IMT <1.1 mm observed in this study.

In lifestyle diseases, including metabolic syndrome, PWV is an established marker of atherosclerosis[29-31]. It is correlated with the IMT and mainly reflects the functional changes of the blood vessels, but is not related to regional elasticity[26]; in the present study, as shown in **Table 2**, **5**, the Eθ and IMT were correlated with baPWV. As shown in **Fig. 5**, we also found that an increase in the number of risk factors for metabolic syndrome was correlated with the elastic modulus as well as IMT and the baPWV. Tsubakimoto *et al.* showed a similar correlation of baPWV with an increase in the number of risk factors for metabolic syndrome[31].

The present study has the following limitations. Eθ may be a better marker to show the elasticity of the arterial wall itself because Er (apparent elasticity) is influenced not only by increased elasticity, but also by thickening of the arterial wall at the same location, especially in areas with marked thickening. Eθ also seems to be relatively unaffected by age, as shown in **Fig. 2**. In **Fig. 3**, LDL-C was weakly but significantly correlated with Eθ in the group with max IMT ≥1.1 mm. Eθ showed a decrement of elasticity, which is thought to cause the accumulation of lipid deposits. However, a limitation of the measurement of Eθ by the current technique is that echoic determination of the borders of the anterior wall and the adventitia of the posterior wall of the carotid artery is imprecise, especially at curved boundaries such as in the bulb and severely atherosclerotic regions. Without an accurate measurement of h_0/r_0 as described in the Methods section, Eθ cannot provide an accurate estimate of elasticity.

In summary, determination of the elastic modulus of the carotid arterial wall as well as IMT measurement could be useful for assessing the local state in the carotid artery and the systemic clinical condition associated with the accumulation of risk factors. A combination of the measurements of both elasticity and IMT yields more information and opens up the possibility of evaluating various arteriosclerotic lesions in lifestyle-related disorders such as metabolic syndrome.

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