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A novel method for evaluating human carotid artery elasticity: Possible detection of early stage atherosclerosis in subjects with type 2 diabetes

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Abstract

We recently developed a novel method for evaluating the elasticity of arterial walls, the phased tracking method. Herein, we evaluated atherosclerosis of the carotid artery with this method in 242 individuals with type 2 diabetes. In multiple regression analysis of subject status, age, systolic blood pressure and hyperlipidemia were found to be independently associated with carotid artery elasticity values. We also measured currently established values for atherosclerosis, carotid artery IMT and baPWV, in these subjects. Carotid artery elasticity correlated with max IMT ($r=0.291$, $p<0.01$), plaque score (PS) ($r=0.220$, $p<0.01$) and baPWV ($r=0.345$, $p<0.01$). Elasticity, max IMT and plaque score, all correlated with the number of risk factors for atherosclerosis, i.e. hypertension, hyperlipidemia and smoking, in addition to diabetes, consistent with the view that these values reflect atherosclerosis. Importantly, however, in subjects with IMT <1.1 mm, who are classified as not having atherosclerosis as defined by IMT criteria, only carotid artery elasticity correlated with the number of risk factors ($p<0.05$). These results suggest that (1) the measured carotid artery elasticity values reflect atherosclerosis and (2) our novel method has potential for detecting atherosclerosis in its early stage.
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Keywords: Human carotid artery elasticity; Atherosclerosis; Diabetes

1. Introduction

Individuals with type 2 diabetes are at very high risk for atherosclerosis [1]. Although many methods have been developed for detecting atherosclerosis, those currently available are mainly for detecting established atherosclerosis. Therefore, the disease process is well-advanced at the time of diagnosis. To reduce future cardiovascular complications in subjects with atherogenic disorders such as type 2 diabetes

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mellitus, detection of early stage atherosclerosis is urgently needed.

Carotid intima-media thickness (IMT) is a well-established surrogate marker for cardiovascular risk [2]. Measuring IMT with ultrasonography is non-invasive and relatively simple [3,4], and IMT is now commonly employed as an endpoint marker in clinical trials. Carotid IMT correlates with cardiovascular risk factors and indeed predicts macrovascular events such as myocardial infarction [5] and stroke [6]. Carotid IMT is greater in subjects with diabetes, both type 1 [7] and type 2 [8,9], than in non-diabetic subjects of the same age. When analyzed in diabetic patients, IMT correlates with glycemic control and the duration of diabetes. Interventions, such as blood glucose lowering [10], lipid lowering [11], ACE inhibition [12] and anti-platelet treatment [13], have been demonstrated to suppress IMT progression. However, it has also been reported that IMT is not affected by either therapeutic interventions [14] or glycemic control [15]. These conflicting results might be attributable to a very small change in IMT, a 0.1 mm increase per decade in normal subjects. Such a small change may mask actual change due to inter-assay variations in IMT measurement. Most importantly, it is not possible to make a diagnosis of atherosclerosis until the appearance of arterial wall thickening.

We recently developed a novel non-invasive method for evaluating the movement of multiple sites in cardiac and arterial walls (3.616 measurement sites/9.0 mm × 6.4 mm) during a single heartbeat [16,17]. This innovative phased tracking method enables us to evaluate regional characteristics; the softer the site, the more easily it deforms during one heartbeat. This reflects regional elasticity. This method has already been applied to the in vivo detection of regional changes in cardiac and arterial walls [18–20], and the interventricular septum [21]. Evaluation of plaque vulnerability has also been attempted [16]. It is theoretically possible to detect qualitative changes in the carotid arterial wall with this method. We therefore tested the possibility of being able to detect atherosclerosis in the early stage.

Herein, we show that carotid artery elasticity, as measured in Japanese subjects with type 2 diabetes, correlates well with results obtained with currently established methods for evaluating atherosclerosis. Most importantly, elasticity correlates with the number of risk factors for atherosclerosis in those with IMT <1.1 mm, who are classified as not having atherosclerosis as defined by IMT criteria [22,23]. These results strongly suggest that it is possible to detect early stage atherosclerosis with this novel method.

2. Methods

2.1. Study subjects

The study subjects were recruited from among patients followed at the diabetes clinic at Tohoku University Hospital. Patients with type 1 diabetes, renal failure (serum creatinine >2.0 mg/dl), severe heart failure (NYHA functional class 2–4), atrial fibrillation and peripheral arterial disease were excluded from the study. All participants analyzed were Japanese type 2 diabetes patients ($n = 242$) who met the WHO criteria for diabetes mellitus. The study protocol was approved by the Tohoku University Institutional Review Board. Informed consent was obtained from each patient. Subjects characteristics are shown in Table 1.

Table 1
Subject characteristics

Number	242
Age (years)	62.1 ± 12.4
Male (%)	54.1
Body weight (kg)	62.2 ± 13.6
BMI (kg/m^2)	24.2 ± 4.2
Duration of diabetes (years)	12.0 ± 9.70
Fasting blood glucose (mg/dl)	141 ± 32.1
HbA1c (%)	7.08 ± 1.33
Systolic blood pressure (mmHg)	130 ± 18.3
Diastolic blood pressure (mmHg)	75.8 ± 11.1
Total cholesterol (mg/dl)	191 ± 38.4
HDL cholesterol (mg/dl)	51.2 ± 14.6
LDL cholesterol (mg/dl)	115 ± 31.9
Triglyceride (mg/dl)	127 ± 94.1
Uric acid (mg/dl)	5.09 ± 1.37
High-sensitive CRP (mg/dl)	0.18 ± 0.23
Diabetic retinopathy (%)	30.2
Microalbumiuria or proteinuria (%)	38.8
Diabetic neuropathy (%)	46.4
Diet:OHA:insulin (%)	20.0:37.8:42.2
Hyperlipidemia (%)	37.2
Hypertension (%)	39.3
Current smoker (%)	30.6
BMI >25 (%)	38.0

Data are presented as means ± S.D.

We used the following criteria for atherogenic risk factors. Hyperlipidemia was defined as total cholesterol ≥5.7 mmol/dl (220 mg/dl) and/or triglyceride ≥1.7 mmol/l (150 mg/dl), based on the definition proposed by the Japan Atherosclerosis Society in 2002, or taking antihyperlipidemic drugs. The subjects whose systolic BP ≥140 mmHg and/or diastolic BP ≥90 mmHg (The Japanese Society of Hypertension guidelines in 2004) or who were taking antihypertensive drugs were defined as having hypertension. The subjects who currently smoked were classified as current smokers.

2.2. Measurement of ABI and baPWV

Ankle brachial pressure index (ABI) and brachial ankle pulse wave velocity (baPWV) were measured using an automatic waveform analyzer (BP-203RPE; Colin Co., Komaki, Japan) after a 5 min rest. This device was designed to simultaneously measure blood pressure levels in both arms (brachial arteries) and ankles (posterior tibial arteries), and to then calculate the ankle systolic BP/brachial systolic BP. Pulse waves were recorded on the right brachial artery and both posterior tibial arteries. The average baPWV was calculated by divid-

ing the arm–ankle distance by the pulse wave transmission time between these points.

2.3. Measurement of carotid artery intima-media thickness

Intima-media thickness of the carotid arteries was measured using ultrasound diagnostic equipment (EUB-450, Hitachi Medico, Tokyo, Japan) with an electrical linear transducer (mid-frequency of 7.5 MHz). The common carotid artery (CCA), carotid bulb and portions of the internal and external carotid arteries on both sides were scanned with the subject in the supine position. The scan encompasses the region between 30 mm proximal to the beginning of the dilation of the bifurcation bulb and 15 mm distal to the CCA flow divider. We defined the max IMT as the thickest IMT in the scanned regions [24] and a max IMT <1.1 mm was considered normal. We defined a plaque, a focal IMT thickening, as an area with IMT ≥1.1 mm and calculated the plaque score (PS) by totaling the maximal thickness values of all plaques in the scanned area [25]. The scans were performed by a trained sonographer and the scanning period averaged 20 min in each patient.

2.4. Measurement of arterial wall elasticity

Real-time measurement of regional elasticity in the carotid artery wall was achieved based on a previously described method [20] with ultrasound diagnostic equipment (prototype system by Panasonic). With this system, an ultrasound beam is used for sequential scanning at 32 positions with a linear type 7.5 MHz probe. Multiple points were preset from the luminal surface to the adventitia along each beam with constant intervals of 320 μm, and multiple layers were defined as being between two neighboring points. Then, the displacement of each point preset along each beam was obtained by applying the phased tracking method to the received echo. Minute changes in the thickness of each layer were determined by subtracting displacements of two neighboring points. The elasticity of each layer was obtained from the thickness change and the blood pressure measured at the upper arm. Since the reflected ultrasound was resampled at an interval of 107 ns (=80 μm along the depth direction) after quadrature demodulation, we further divided each layer with a thickness of 320 μm into four points, shifted the initial depth of each layer by one-fourth of 320 μm, and applied the above procedure to each depth. Thus, the elasticity was obtained at intervals of 80 μm in the depth direction and 200 μm in the axial direction of the artery. A cross-sectional image and the process of elasticity measurement are schematically depicted in Fig. 1.

2.5. Statistical analysis

Variables were compared using Pearson's regression analysis and Student's *t*-test as appropriate. Then, a multiple linear regression analysis was performed to evaluate the independent parameters that were significantly related to arterial elasticity. The relationships between number of risk factors and the values of atherosclerosis markers were examined by analysis of covariance (ANCOVA), adjusted with age as a covariate. A p value less than 0.05 was accepted as indicating statistical significance. All statistical analyses were performed using the Statistical Package for the Social Sciences Version 13.0 (SPSS Japan Inc., Tokyo, Japan).

3. Results

We assessed the associations of carotid artery elasticity with subject characteristics (Table 2). Elasticity correlated

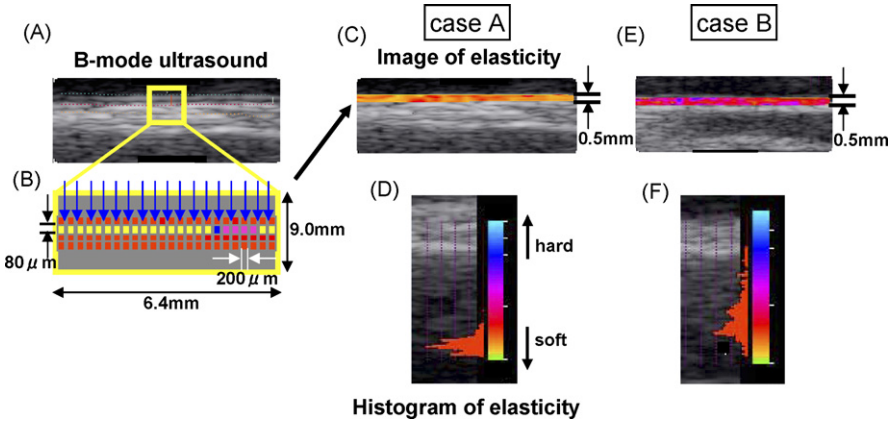

Fig. 1. The intima–media complex was visualized by conventional B-mode scanning (A), and minute thickness changes in the layers at each depth (113 depths × 32 beams per 9 mm × 6.4 mm scanned area) during one heart beat were then recorded by the phased tracking method (B). Thickness changes in each layer represent deformity, a reflection of elasticity. This elasticity is displayed as a 2D cross-sectional color image on B-mode scanning, and the image is updated at every heartbeat (C). The elasticity distribution is shown as a histogram (D). Representative results obtained from a normal subject, case A (male, age 40), are shown. Case B (male, age 45), in marked contrast, suffered from type 2 diabetes, hyperlipidemia and an old cerebral infarction, but had an IMT of only 0.5 mm, the same thickness as that of case A. The elasticity (E) was, however, extremely different from that of case A, as shown in the histogram (F).

Table 2
Associations between arterial elasticity and subject characteristics

Variables	*r*-Value	*p*-Value
Age	0.34	<0.01
Duration of diabetes	0.136	<0.05
Fasting blood glucose	−0.012	0.86
HbA1c	−0.003	0.97
Total cholesterol	0.103	0.10
HDL cholesterol	0.066	0.31
LDL cholesterol	0.089	0.17
Triglyceride	−0.064	0.32
Systolic blood pressure	0.443	<0.01
Diastolic blood pressure	0.147	<0.05
Uric acid	−0.03	0.65
High-sensitive CRP	0.037	0.56

Table 3
Mean arterial elasticity values in the presence and absence of cardiovascular risk factors

Variables	Elasticity (kPa)		*p*
	−	+	
Male	51.6 ± 12.6	51.0 ± 14.5	0.99
Hyperlipidemia	49.8 ± 12.3	54.7 ± 13.7	<0.01
Hypertension	49.6 ± 13.3	54.8 ± 13.6	<0.01
Current smoker	51.6 ± 13.3	51.8 ± 14.5	0.88
BMI >25	51.6 ± 13.7	51.6 ± 13.5	0.99
Diabetic retinopathy	52.3 ± 13.7	50.9 ± 14.1	0.67
Diabetic nephropathy	50.5 ± 13.6	53.9 ± 13.6	0.06
Diabetic neuropathy	50.8 ± 12.9	51.4 ± 14.4	0.65

Data are presented as means ± S.D.

Table 4
Multivariate adjustment for parameters related to arterial elasticity

Variables	Coefficient (β)	95% CI	*p*-Value
Age (years)	0.28	0.18–0.43	<0.01
Duration of diabetes (years)	−0.02	−0.18–0.14	0.77
Systolic blood pressure (mmHg)	0.39	0.21–0.38	<0.01
Hyperlipidemia	0.11	0.08–6.24	<0.05

with age ($r = 0.340$, $p < 0.01$), duration of diabetes ($r = 0.136$, $p < 0.05$) and blood pressure, both systolic ($r = 0.430$, $p < 0.01$) and diastolic ($r = 0.147$, $p < 0.05$).

We then examined whether or not cardiovascular risk factors affect arterial elasticity values (Table 3). Hyperlipidemic subjects had significantly higher arterial elasticity values than those with normal lipid profiles. Similarly, subjects with hypertension had higher values. However, arterial elasticity values did not depend on other risk factors, such as sex, obesity, smoking and diabetic complications.

To elucidate the independent variables affecting arterial elasticity, we performed multiple linear regression analysis with parameters related to elasticity. We employed four clinical parameters, age, duration of diabetes, systolic blood pressure and hyperlipidemia, based on the results shown in Tables 2 and 3. We found age, systolic blood pressure and hyperlipidemia to be independently associated with elasticity values (Table 4).

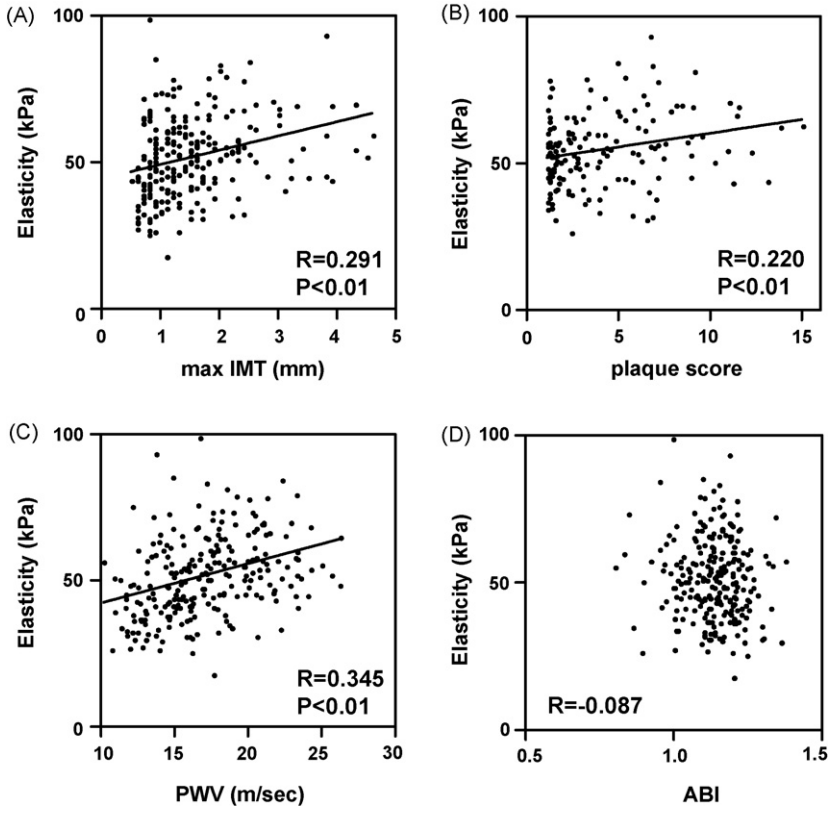

Fig. 2. Correlations between arterial elasticity values and max IMT (A), plaque score (B), baPWV (C) and ABI (D).

To assess the clinical relevance of carotid artery elasticity, we compared our elasticity values to those obtained with currently established methods for evaluating atherosclerosis: max IMT, plaque score, baPWV and ABI. Carotid artery elasticity showed significant positive correlations with max IMT ($r = 0.291$, $p < 0.01$) (Fig. 2A), the plaque score ($r = 0.220$, $p < 0.01$, $n = 160$) (Fig. 2B) and baPWV ($r = 0.345$, $p < 0.01$) (Fig. 2C) in subjects with type 2 diabetes. It should be kept in mind that the plaque score can be obtained only in subjects with IMT ≥ 1.1 mm ($n = 160$), such that the correlation was studied only in those having definite atherosclerosis based on IMT criteria [22,23]. Arterial elasticity showed no correlation with the ABI value ($r = -0.087$, $p = 0.176$) (Fig. 2D). However, when we performed multiple linear regression analysis adjusted with independent parameters, age, systolic blood pressure and hyperlipidemia (Table 4), the correlations between elasticity and atherosclerosis markers (max IMT, plaque score and baPWV) were no longer present.

In a subject with more than one risk factor, the atherosclerotic process would be accelerated and thus affect the values of atherosclerosis markers. Four modifiable risk factors, diabetes, hypertension, hyperlipidemia and current smoking,

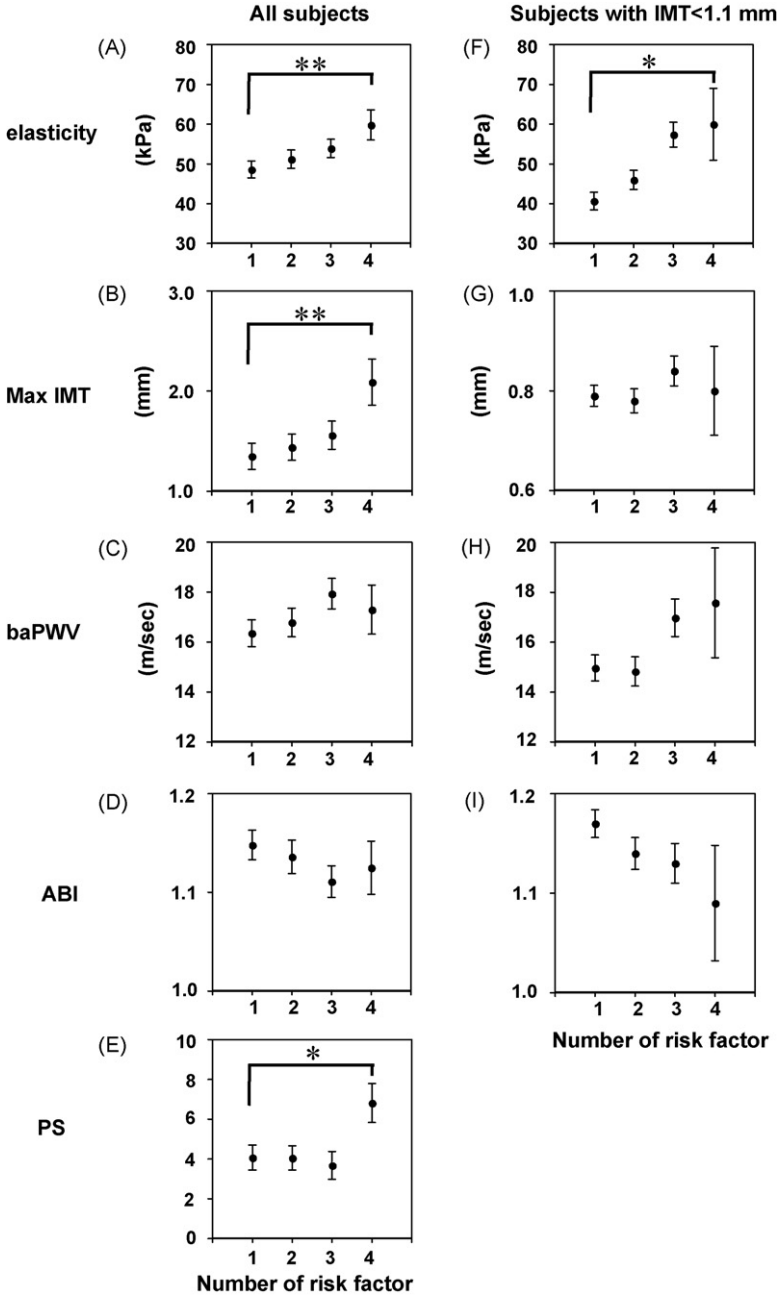

Fig. 3. Correlations of values reflecting atherosclerosis with the number of risk factors in all study subjects (A–E, $n = 242$) and subjects with max IMT <1.1 mm (F–I, $n = 82$). Data are presented as means ± S.E. $^{*}p < 0.05$, $^{**}p < 0.01$.

were taken into account in this study. All subjects had at least one risk factor, diabetes. When all the subjects were analyzed by ANCOVA, adjusted with age as a covariate, the higher the number of risk factors, the greater the attenuation of arterial elasticity values, max IMT and the plaque score (Fig. 3A, B, E). However, very interestingly, when subjects with max IMT <1.1 mm, who are regarded as not having atherosclerosis based on IMT criteria, were analyzed ($n = 82$), only age-adjusted carotid artery elasticity correlated with an increasing number of risk factors (Fig. 3F). Other age-adjusted parameters for evaluating atherosclerosis, max IMT, baPWV and ABI, showed no significant correlations with a greater number of risk factors in subjects with max IMT <1.1 mm (Fig. 3G–I).

4. Discussions

Our most important finding is that in subjects with max IMT <1.1 mm, who are regarded as being free of atherosclerosis based on IMT criteria [22,23], only carotid artery elasticity as measured with our novel non-invasive method correlated with an increasing number of risk factors. No other values obtained with the currently available methods showed correlations with the number of risk factors in these "non-atherosclerotic" subjects. Thus, our novel method of measuring arterial wall elasticity raises the possibility of detecting atherosclerosis in its early stage.

Carotid artery elasticity correlates well with results obtained with currently established methods for evaluating atherosclerosis in subjects with type 2 diabetes. These results strongly suggest that elasticity as measured with our current method reflects the severity of atherosclerosis. The measurement procedures are relatively simple, essentially the same as those of B-mode ultrasonography. In addition, arterial wall elasticity is shown as a color coded cross-sectional image with a side by side B-mode ultrasonogram, which is very practical in the clinical setting.

This novel ultrasonic method accurately tracks the movement of the arterial wall based on both the phase and the magnitude of demodulated signals, allowing instantaneous determination of the position of an object. With this method, it is possible to accurately detect small-amplitude velocity signals, less than a few micrometers, that are superimposed on arterial wall motion due to the heartbeat. This method thus allows the elasticity, a qualitative feature, of the arterial wall to be evaluated. In addition to detecting the early stage atherosclerosis, this method may enable us to evaluate progression or regression of atherosclerosis in a much shorter time than currently available methods. This possibility is extremely interesting because a means of evaluating whether or not a treatment is effective for preventing atherosclerosis is urgently needed. It usually takes years to detect the progression or regression of atherosclerosis, while it may take only months with our present method of qualitative arterial wall measurement. For example, it may be possible to detect an improvement in response to statin treatment within a few months. Similarly, we will be able to assess the effects on atherosclerosis of altering risk factors within months. These possibilities clearly merits further study.

A variety of methods are widely used for evaluating atherosclerosis. Measuring carotid IMT with ultrasound is one of the most well-established methods because it is safe, non-invasive, reproducible and easy to perform. IMT provides quantitative information, i.e. vessel-wall thickness. Depicting changes in IMT is thus generally thought to take a long time. baPWV is also a non-invasive method, which assesses atherosclerosis, as a reflection of arterial stiffness, and the usefulness of baPWV has been reported in clinical studies [26–28]. However, the pulse wave velocity depends on the ratio of the inner radius of the artery to wall thickness, which is not related to regional elasticity. It also reportedly depends on heart rate [29].

While the elasticity average of the intima and media of the carotid artery wall was calculated and used for evaluation of atherosclerosis in this study, another interesting aspect of elasticity is its distribution. The elasticity distribution, which is depicted in a histogram, might provide additional information regarding qualitative changes in atherosclerosis, and should be comprehensively studied in the future. In conclusion, our novel method for evaluating carotid artery wall elasticity holds promise for early detection of atherosclerosis.

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