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Original Article

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Usefulness of Carotid Arterial Strain Values for Evaluating the Arteriosclerosis

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Aim: We investigated the clinical usefulness of carotid arterial strain and the strain rate for evaluating the progression of arteriosclerosis measured using a two-dimensional speckle-tracking method in carotid ultrasonography.

Methods: We enrolled 259 participants (age: 64 ± 12 years; men: 149; women: 110) in this retrospective analysis. The circumferential strain and the strain rate were measured in bilateral common carotid arteries, and the lowest values were used for the analyses. To assess the characteristics of strain and the strain rate, we investigated the associations between the strain values and gender, age, body mass index (BMI), blood pressure (BP), and the presence of hypertension, diabetes mellitus, and hyperlipidemia. We also examined the explanatory factors for the strain values using clinical parameters along with the intima-media thickness (IMT), the ankle brachial index (ABI), and the cardio-ankle vascular index (CAVI) as possible candidates. Finally, we investigated whether the strain values might be an independent predictor for vascular diseases using multivariate logistic regression analyses.

Results: The carotid circumferential strain and the strain rate were significantly correlated with age, IMT, and the CAVI, but not with the BMI, BP, or ABI. Strain and the strain rates were lower in participants with hypertension or cerebrovascular disease and were selected as significant predictive factors for the presence of cerebrovascular diseases, together with diabetes and the CAVI.

Conclusions: Strain and the strain rate of carotid arteries, which could represent local arterial stiffness, might be associated with atherosclerosis and could possibly be used to predict cerebrovascular disease.

Key words: Common carotid artery, Strain, Strain rate, Speckle-tracking, Aortic stiffness

Introduction

Atherosclerotic diseases are the leading causes of death and disability in the world. Arterial stiffening is an early marker of atherosclerosis that can predict cardiovascular morbidity and mortality in the future. Therefore, the development of accurate and non-invasive methods for the early diagnosis of atherosclerotic vascular stiffness is expected in the field of clinical physiological laboratory medicine. Regarding physiological indicators of atherosclerosis, flow-mediated dilation (FMD)[1-3], pulse wave velocity (PWV)[4-7], the cardio-ankle vascular index (CAVI)[8], and the ankle brachial index (ABI)[9, 10] are widely used at present and have been proven, at least to some extent, to be useful predictors of vascular diseases.

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In addition to these physiological tests, carotid ultrasonography can be performed to assess atherosclerotic changes non-invasively. This ultrasonography test uses the carotid artery as a representative vessel of the systemic vasculature and measures the intima-media thickness (IMT) as a non-invasive parameter for evaluating atherosclerosis. Recent studies and a recent meta-analysis have proposed some limitations of IMT; for example, IMT changes cannot accurately predict the benefits of therapeutic interventions for cardiovascular risk factors[11-13]. Therefore, the development of a new, non-invasive, more accurate method to evaluate atherosclerotic changes is needed.

Along with the IMT values, arterial wall stiffness is another candidate parameter related to carotid ultrasonography, because local mechanical changes in the arterial wall during atherosclerotic progression can theoretically occur earlier than structural changes, which can be detected as an increased IMT. In the past decade, methods for assessing arterial wall motion and strain as measured using two-dimensional speckle-tracking have been developed to evaluate arterial stiffness. Two-dimensional speckle-tracking involves the application of pattern matching technology to the field of ultrasonography to estimate where the local area in a template image is shifted in the consequent image. The continuous repetition of such tracking enables the tracking of a specific point. Strain is derived from the relative movement of the speckles, representing deformation such as contraction or expansion, and the strain rate is the speed of speckle movement, representing the deformation rate. Currently, this technique is more commonly used in echocardiography: two-dimensional speckle-tracking echocardiography can measure the cardiac strain in an angle-independent and well-validated manner and has been demonstrated to be useful for the assessment of myocardial deformation[14, 15].

As well as echocardiography, two-dimensional speckle-tracking can be applied to carotid ultrasonography to assess arterial elasticity, which would provide another clinical parameter related to carotid ultrasonography in addition to IMT. Actually, two-dimensional speckle-tracking of the carotid artery, which is non-invasive, simple, and feasible, has been shown to reflect atherosclerotic changes in previous studies[16-18]. Its application to carotid ultrasonography, however, has been less established than its application to echocardiography.

Aim

In this study, we aimed to investigate the clinical usefulness of carotid arterial strain as determined using the two-dimensional speckle-tracking method in carotid ultrasonography by examining the association between strain or the strain rate and clinical parameters, including the presence of atherosclerotic diseases, or the physiological laboratory test results that are commonly performed at present.

Methods

Participants

In this study, we enrolled 259 participants (age: 64 ± 12 years; men: 149; women: 110) who had undergone carotid ultrasonography in the Department of Clinical Laboratory (August to December 2012) or a health check-up clinic (October 2013 to May 2014) at The University of Tokyo Hospital.

The presence of cardiovascular risk factors such as hypertension, diabetes mellitus, and hyperlipidemia were evaluated based on the past history and medical records; we assumed the presence of hypertension when the participants were prescribed a antihypertensive medication or their blood pressure (BP) was >140/90 mmHg, the presence of diabetes mellitus when they were prescribed a antidiabetic medication or their HbA1c was >6.5%, and the presence of hyperlipidemia when they were prescribed a antihyperlipidemia medication or their low-density lipoprotein cholesterol levels were >140 mg/dL or their high-density lipoprotein cholesterol levels were <40 mg/dL. The participants were assumed to have cerebrovascular disease (CVD) based on a medical history of ischemic stroke or transient ischemic attack; cardiovascular disease (CAD) based on a medical history of percutaneous coronary intervention, coronary artery bypass graft surgery, or previous myocardial infarction; and peripheral arterial disease (PAD) based on an ABI of ≤0.90 or a past history of lower limb arterial reconstruction or amputation because of lower limb ischemia.

This study was approved by the Ethics Committee of The Graduate School of Medicine, The University of Tokyo (3683).

Carotid Ultrasonography

Images were acquired by four experts in carotid imaging using an Aplio 300 TUS-A300 or Xsario SSA-660A ultrasound system (Toshiba Medical Systems, Otawara, Tochigi, Japan) equipped with a 7.5-MHz linear probe. The common carotid ultrasound examination was performed with the patients in a supine position. Their necks were hyperextended, and their heads were turned contralateral to the test side. The left common carotid arteries were visualized from a fixed lateral transducer angle. The measurement of the strain was performed bilaterally from the images of the short axis of the common carotid artery at 1 cm

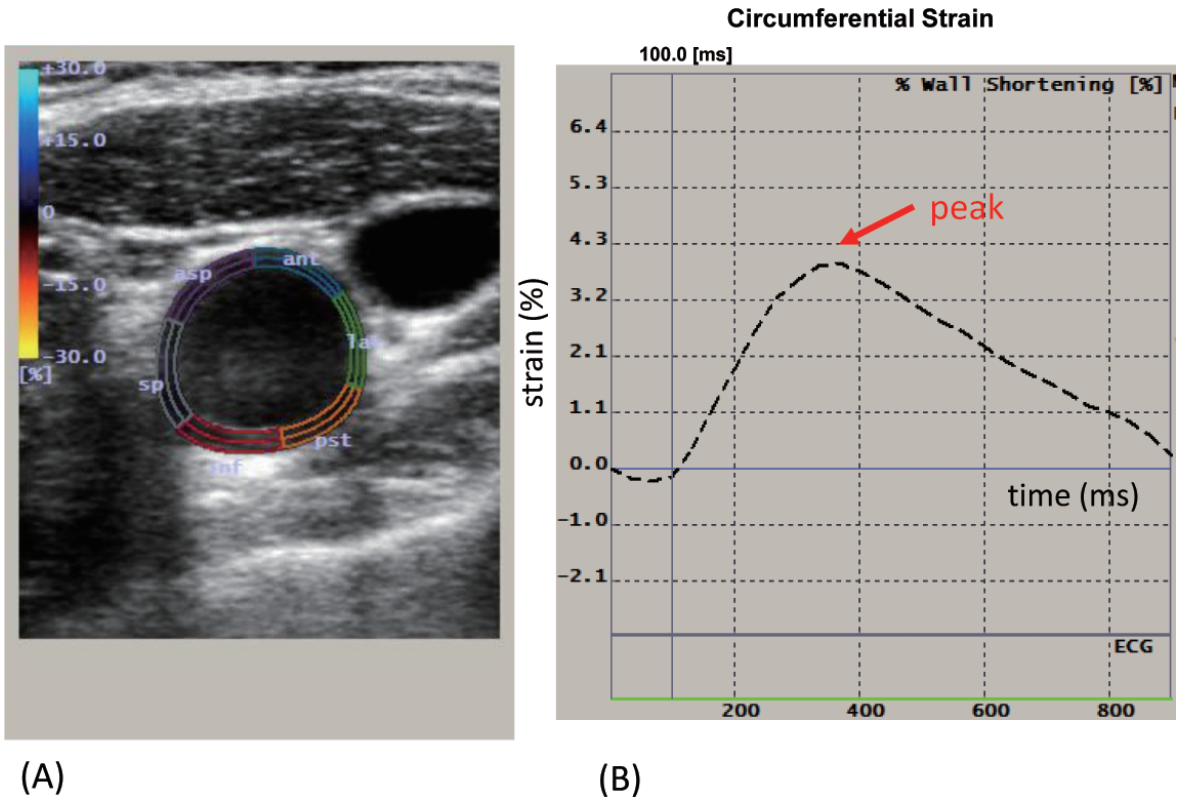

Fig. 1. Speckle-tracking analysis.

(A) Representative speckle-tracking imaging showing the short axis of the common carotid artery. (B) An example of the curve for the mean strain of the six splits in the short axis.

inferior to the carotid bulb. At least two consecutive beats were stored with a frame rate of 29–53 frames/s. The maximum IMT was defined as the distance between the leading edge of the luminal ultrasound and media/adventitia ultrasound. The IMT of the common carotid artery was measured as the maximum thickness between the proximal and the common carotid bulb, and plaques were deemed as an IMT ≥1.0 mm.

Other Physiological Measurements

The BPs were measured at the bilateral brachial and ankle arteries, and the ABI and CAVI[19] were analyzed using a VaSera VS-1500ATN device (Fukuda Denshi Co. Ltd., Tokyo, Japan) with the subject in a supine position. The examinations were performed after the subject had rested for 5 min. Height and weight were also recorded, and the body mass index (BMI) was calculated as the weight (kg) divided by the height-squared (m^2). We analyzed the CAVI values, which were taken immediately after carotid ultrasonography or within 1 year. Regarding the right and left data, the higher values for BP, CAVI, and maximum IMT and the lower values for ABI were adopted for the analysis. In patients with an ABI of ≤0.90, the CAVI values were assessed as missing values.

Speckle-Tracking Analysis

The data analysis was performed using an external computer installed with 2-D speckle-tracking offline software (Toshiba Medical Systems, Tokyo, Japan). A motion picture of the axial view of the common carotid artery at the site of the largest diameter pulsating in one cardiac cycle was obtained from each subject. The pictures were recorded from the end-diastolic phase (the point just before the beginning of the QRS-wave), where the common carotid artery is most contracted. In this picture, we manually plotted six points along the inner rim of the carotid intima, starting at the 8 O'clock position. Then, the computer system recognized the common carotid artery and automatically provided the circumferential strain and strain rates for six equally divided segments, as shown in **Fig. 1**. For the segments that were judged to have poor tracking by the system, the investigators manually adjusted the vessel edges in each frame to make them more appropriate. Based on the values obtained above, we deemed the maximal absolute values of strain and the strain rate in each segment as the "peak" strains and strain

Table 1. Clinical characteristics of the study population

Characteristics	All subjects (n=259)
Age, years	64.2 ± 12.3
Female, n (%)	110 (42.5)
Height, cm	161.0 ± 13.2
Weight, kg	62.7 ± 14.6
Body mass index, kg/m^2	23.9 ± 4.0
Blood pressure, mm Hg	
Systolic	131.3 ± 16.6
Diastolic	80.9 ± 11.7
IMT, mm	1.3 ± 0.6
Left	1.2 ± 0.5
Right	1.2 ± 0.5
CAVI	8.4 ± 1.3
ABI	1.1 ± 0.2
Strain, %	2.92 (2.03−3.78)
Left	3.19 (2.28−4.10)
Right	3.59 (2.66−4.65)
Strain rate, 1/s	0.23 (0.17−0.30)
Left	0.26 (0.19−0.34)
Right	0.28 (0.20−0.40)
Medical history, n (%)	
Hypertension	129 (53.0)
Diabetes	83 (34.0)
Hyperlipidemia	111 (45.3)
Cardiovascular disease (CAD)	30 (12.2)
Cerebral vascular disease (CVD)	26 (10.7)
Peripheral arterial disease (PAD)	25 (10.0)
Current or ex-smoking, n (%)	113 (48.7)

Data are expressed as the mean ± SD or the number (%) or median (interquartile range).

Table 2. Clinical characteristics of the control subjects (i.e., absence of hypertension, diabetes, subjects without CAD, CVD and PAD)

Characteristics	control (n=73)
Age, years	59.3 ± 11.2
Female, n (%)	37 (50.7)
Height, cm	161.2 ± 19.5
Weight, kg	61.9 ± 13.0
Body mass index, kg/m^2	23.0 ± 3.1
Blood pressure, mm Hg	
Systolic	127.1 ± 15.3
Diastolic	82.2 ± 10.0
IMT, mm	1.1 ± 0.5
Left	1.0 ± 0.4
Right	1.0 ± 0.4
CAVI	7.9 ± 1.1
ABI	1.1 ± 0.1
Strain, %	3.14 (2.54−4.14)
Left	3.36 (2.66−4.29)
Right	4.08 (2.98−5.02)
Strain rate, 1/s	0.25 (0.19−0.32)
Left	0.27 (0.23−0.35)
Right	0.31 (0.26−0.41)

rates, respectively. We used the peak of the mean circumferential strain curve of the strain or the strain rate in the right or left carotid artery as the left or right strain or the strain rate and adopted the lower values of the right and left strains or the strain rates for the analysis.

Although the reproducibility of the measurements has been previously shown to be excellent[16, 20], we confirmed their reproducibility using our method: strain values were measured twice by a single investigator at different times in 30 left and right images from 15 subjects to investigate the intraobserver variability, and the strain values were also measured by another trained investigator at an independent time to obtain the interobserver variability. The reproducibility of the strain measurements was evaluated as the intraclass correlation coefficient (ICC). The results of the interobserver and intraobserver variabilities showed excellent reproducibility for the strain measurements (strain: intraobserver ICC: 0.95, interobserver ICC: 0.96; strain rate: intraobserver ICC: 0.95, interobserver ICC: 0.94).

Statistical Analysis

All the data were statistically analyzed using SPSS 22 (Chicago, IL). The results were expressed as the mean ± SD or median (interquartile range). Correlations were investigated using the Spearman correlation test. The difference among unpaired groups was evaluated using a Mann−Whitney U test, and the difference among the three groups was investigated using the Kruskal−Wallis test followed by the Games Howell test as a post-hoc test. The independent effects of several clinical parameters on strain and the strain rate were evaluated using a stepwise multiple regression analysis, using age, gender, BMI, systolic BP, CAVI ≥ 9.0, IMT ≥ 1.0, ABI ≤ 0.9, current or ex-smoking, and the presence of hypertension, diabetes mellitus, hyperlipidemia, CAD, CVD, and PAD as candidate explanatory factors. The significant predictive factors for the presence of CAD, CVD, or PAD were investigated using a multivariate logistic regression analysis with strain or the strain rate, age, gender, BMI, systolic BP, CAVI ≥ 9.0, IMT ≥ 1.0, ABI ≤ 0.9, current or ex-smoking, and the presence of hypertension, diabetes mellitus, or hyperlipidemia as possible candidate factors. A P-value of <0.05 was regarded as statistically significant in all the analyses.

Table 3. Strain values according to risk factors for atherosclerosis

Variable	Strain			Strain rate		
	Yes (n)	No (n)	*P* value	Yes (n)	No (n)	*P* value
Age ≧60	2.79 (1.95−3.64) (175)	3.18 (2.46−4.26) (84)	0.005**	0.22 (0.16−0.28) (175)	0.28 (0.21−0.37) (84)	0.000**
Male sex	3.01 (2.17−3.87) (149)	2.75 (2.00−3.54) (110)	0.076	0.25 (0.17−0.34) (149)	0.22 (0.15−0.27) (110)	0.011*
BMI ≧25	2.66 (1.74−3.73) (82)	2.97 (2.33−3.78) (168)	0.069	0.20 (0.15−0.30) (82)	0.25 (0.19−0.30) (168)	0.061
Systolic BP >140	2.85 (1.81−3.72) (67)	2.92 (2.17−3.78) (188)	0.355	0.21 (0.16−0.28) (67)	0.24 (0.17−0.31) (188)	0.169
IMT ≧1.0	2.80 (1.95−3.67) (185)	3.26 (2.50−4.26) (73)	0.008**	0.22 (0.16−0.29) (185)	0.27 (0.21−0.34) (73)	0.000**
CAVI ≧9.0	2.53 (1.88−3.56) (70)	2.96 (2.40−3.80) (147)	0.039*	0.21 (0.15−0.28) (70)	0.25 (0.18−0.33) (147)	0.020*
ABI ≦0.9	3.03 (1.52−3.76) (21)	2.90 (2.16−3.79) (222)	0.617	0.23 (0.14−0.32) (21)	0.23 (0.17−0.31) (222)	0.726
Hypertension	2.72 (1.86−3.69) (129)	3.02 (2.40−3.80) (116)	0.025*	0.22 (0.15−0.29) (129)	0.24 (0.18−0.32) (116)	0.043*
Diabetes	2.72 (1.93−3.78) (83)	2.91 (2.16−3.73) (161)	0.405	0.21 (0.15−0.30) (83)	0.24 (0.17−0.30) (161)	0.299
Hyperlipidemia	2.90 (1.95−3.75) (111)	2.89 (2.19−3.74) (134)	0.351	0.23 (0.15−0.30) (111)	0.24 (0.18−0.31) (134)	0.122
Current or ex-smoking	3.10 (2.31−3.82) (113)	2.65 (1.95−3.53) (119)	0.008**	0.25 (0.18−0.34) (113)	0.22 (0.15−0.29) (119)	0.009**

Data are expressed as the median (interquartile range).
BMI: body mass index; BP: blood pressure; IMT: intima-media thickness; CAVI: cardio-ankle vascular index; ABI: ankle brachial index
*: $P<0.05$, **: $P<0.01$

Results

Study Population

Of the 259 participants, 113 visited the Department of Clinical Laboratory and 146 attended the health check-up clinic. Among the participants, the tracking qualities of the images obtained from either the right or left carotid artery were unsatisfactory for analysis in 18 cases. In these cases, only the images obtained on one side were used for the analyses. The characteristics of the participants are summarized in Table 1 and Table 2.

Association between Strain or Strain Rate and the Presence of Risk Factors for Atherosclerosis or the Results of Other Physiological Measurements

Strain and the strain rate ranged from 0.61% to 11.69% and from 0.06 to 1.02 1/s, respectively. The median value (interquartile range) of the strain in all the participants was 2.92% (2.03%−3.78%), whereas that of the strain rate was 0.23 (0.17−0.30) 1/s.

First, we investigated the characteristics of strain and the strain rate. Table 3 shows the strain values according to the presence of risk factors for atherosclerosis or the clinical thresholds of other physiological laboratory tests. No difference in the strain was observed between male and female participants, whereas the strain rate was lower in female than in male participants. Strain and the strain rate were significantly lower in participants aged ≥60 years compared with those aged <60 years, among participants with hypertension compared with those without hypertension, among participants with an IMT of ≥1.0 mm compared with those with an IMT of <1.0 mm, and among participants with a CAVI of ≥9.0 compared with those with a CAVI of <9.0. Strain and the strain rate were significantly higher in participants with current or ex-smoking than in those without current or ex-smoking. There were no significant differences between those with and those without other comorbidities or physiological measurements.

Regarding the correlation between strain or the strain rate and clinical parameters or other physiological measurements, strain and the strain rate were inversely correlated with age (strain: $r=-0.21$, $P=0.001$; strain rate: $r=-0.30$, $P<0.001$), IMT (strain: $r=-0.20$, $P=0.001$; strain rate: $r=-0.26$, $P<0.001$), and CAVI (strain: $r=-0.16$, $P=0.022$; strain rate: $r=-0.21$, $P=0.002$) (Fig. 2). By contrast, strain and the strain rate were not significantly correlated with the BMI (strain: $r=-0.11$, $P=0.098$; strain rate: $r=-0.08$, $P=0.190$), systolic BP (strain: $r=-0.09$, $P=0.162$; strain rate: $r=-0.10$, $P=0.103$), diastolic BP (strain: $r=-0.10$, $P=0.125$; strain rate: $r=-0.10$, $P=0.122$) or ABI (strain: $r=0.04$, $P=0.525$; strain rate: $r=0.05$, $P=0.475$). Regarding the association between medications and the strain values, we observed that the participants taking angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) had significantly lower values of strain and strain rate (Table 4).

These results suggested that the strain and strain rate were associated with some atherosclerotic risk factors, implying that they might somehow reflect arterial stiffness in clinical practice.

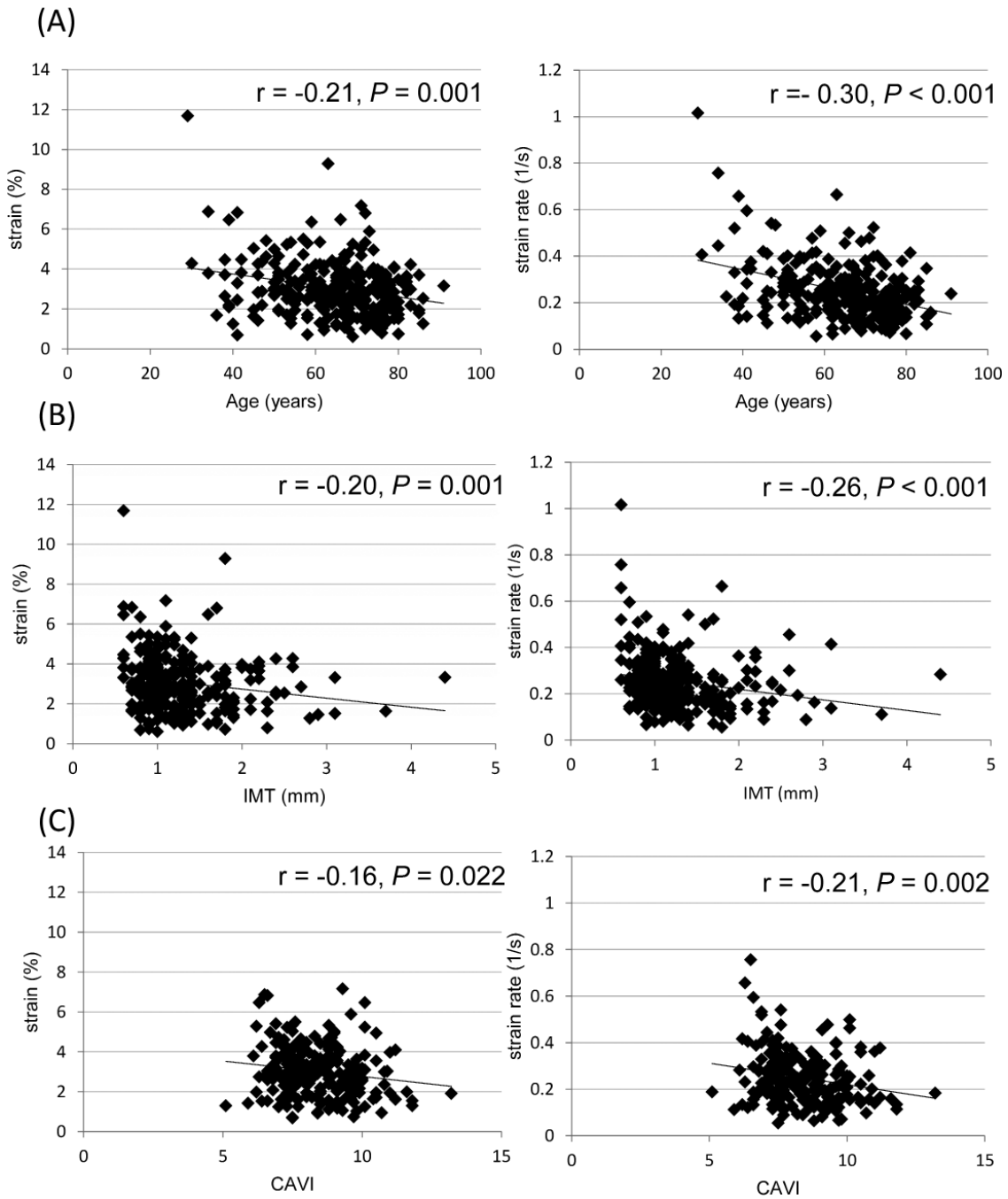

Fig. 2. Correlation between strain values and clinical parameters.

Correlations were investigated between the strain values and age (A), IMT (B), and CAVI (C).

Association between Strain or Strain Rate and Vascular Diseases

Next, we investigated the association between the strain or strain rate and the past history of vascular diseases. As shown in **Fig. 3**, strain and the strain rate were significantly lower in participants with CVD (strain: 2.22% [1.62%−3.33%] in CVD vs. 2.93% [2.15%−3.80%] in non-CVD, P=0.024; strain rate: 0.17 [0.14−0.26] 1/s in CVD vs. 0.24 [0.17−0.31] 1/s in non-CVD, P=0.012). We observed no significant differences in CAD or PAD.

Because other factors such as age and the presence of atherosclerotic risk factors might be confounding factors for the association between strain or the

Table 4. Strain values according to medications.

Variable	Strain			Strain rate		
	Yes (n)	No (n)	*P* value	Yes (n)	No (n)	*P* value
Calcium antagonists	2.73 (1.91−3.57) (72)	2.94 (2.09−3.85) (167)	0.113	0.25 (0.16−0.29) (72)	0.23 (0.17−0.31) (167)	0.793
ACE inhibitors or ARB	2.60 (1.65−3.73) (84)	2.95 (2.24−3.78) (155)	0.040*	0.20 (0.14−0.30) (84)	0.24 (0.18−0.30) (155)	0.025*
Beta blockers	3.15 (1.94−3.89) (26)	2.87 (2.04−3.73) (214)	0.722	0.23 (0.16−0.31) (26)	0.23 (0.17−0.30) (214)	0.921
Diuretics	3.33 (2.88−4.04) (9)	2.88 (2.02−3.74) (231)	0.179	0.29 (0.24−0.34) (9)	0.23 (0.17−0.30) (231)	0.063

Data are expressed as the median (interquartile range).
Abbreviations: ACE, Agiotensin-converting enzyme; ARBs, Angiotensin receptor blockers
*: $P<0.05$

strain rate and CVD, we performed multivariate logistic regression analyses for the presence of CVD using the presence of atherosclerotic risk factors and physiological measurements other than strain and the strain rate, as well as strain or the strain rate. As shown in **Table 5**, strain and the strain rate were selected as significant independent risk factors of CVD along with the presence of diabetes mellitus and CAVI, but not for CAD or PAD (data not shown).

Discussion

In the present study, we investigated the characteristics of strain and the strain rate, a possible parameter representing arterial wall viscoelasticity, and found that both parameters were associated with some atherosclerotic risk factors, suggesting that they might somehow reflect early atherosclerosis in clinical practice. Moreover, we also observed that the parameters were associated with a past history of CVD.

We have assessed the strain and the strain rate with circumferential measurement, in this study, for the following reasons: (1) Arterial smooth muscle cells are aligned primarily in the circumferential direction in the media of artery as described previously[21-23]. (2) To the best of our knowledge, no study has compared the circumferential strain and the longitudinal strain in human carotid artery, whereas most studies have chosen circumferential (and radial in some studies) strain assessment[16, 17, 24-26], may be because the longitudinal motion of the artery might be difficult to assess because of the low amplitudes combined with the intrinsic lower spatial resolution in the azimuth direction. Regarding the difference between circumferential strain and radial strain, Bjallmark *et al.*[17] demonstrated that, compared with circumferential strain variables, the radial strain variables evaluated did not appear to be sufficiently sensitive in the assessment of carotid arterial stiffness. (3) The circumferential strain assessment is averaged over a larger number of tracking points. Therefore, we thought that the circumferential strain assessment might reduce the amount of noise in the data and the circumferential variables might possess lower variability and overall better performance, compared with the axial strain.

Regarding the strain values of the control participants, in this study, strain and the strain rate were 3.14% (2.54%−4.14%) and 0.25 (0.19−0.32) 1/s, respectively, which were lower than the previous studies; Yang *et al.*[27] reported that strain was 5.48% ± 0.30% in 20 healthy subjects (10 females) with a mean age of 56.6 ± 1.9 years and Bjallmark *et al.* observed that strain was 4.5% ± 1.0% and the strain rate was 0.60 ± 0.1 1/s in 10 healthy individuals (4 females) with a mean age of 54.6 ± 3.3 years. The reason for the discrepancy between the present study and previous studies might be the higher mean of age in the present study's control participants (**Table 2**).

Regarding the association with atherosclerotic risk factors, we found that strain and the strain rate were inversely correlated with age and hypertension. These results were concordant with the results of previous studies, which demonstrated that common carotid artery strain measures were significantly and inversely correlated with increasing age[16, 17, 20, 25, 28] and hypertension[26, 29], and that these results were reasonable because arterial stiffness can be accelerated by the presence of hypertension[30, 31]. However, strain and the strain rate were not significantly associated with diabetes, hyperlipidemia, or BMI, which are regarded as atherosclerotic risk factors. These results were partly reproduced by previous reports[29, 32]. Although strain and the strain rate are associated with the presence of hypertension, significant correlations with systolic or diastolic BP were not observed at the time of measurement, suggesting the possibility that strain or the strain rate reflects the past cumulative hypertensive stress, rather than temporary stress. These results may reflect the presence of hysteresis, a well-known signature of viscoelasticity, in the stress−strain relations[33]. When assessing vascular remodeling from a material mechanics aspect, it is important to assume that the artery is viscoelastic, rather than

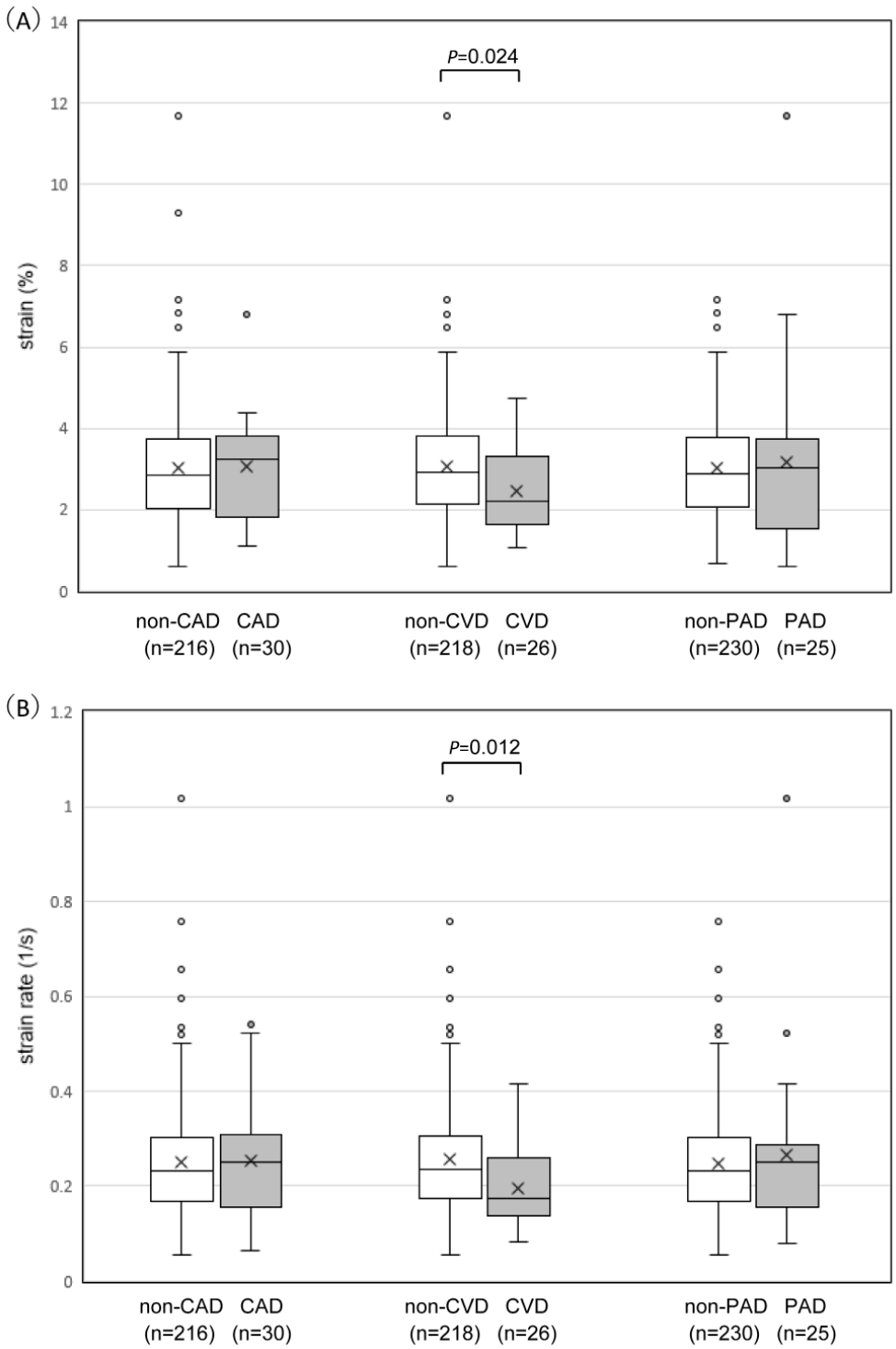

Fig. 3. Strain values of the participants with artery diseases.

Median and average of strain (A) and the strain rate (B) in patients with or without artery disease.
CAD: cardiovascular disease; CVD: cerebrovascular disease; PAD: peripheral arterial disease.
The tops and bottoms of each box represent 1st quartile and 3rd quartile of the samples, respectively. The line in the middle of each box represents the sample median. The whiskers are lines extending above and below each box and they are drawn from the ends of the interquartile ranges to the furthest observations within the whisker length. Observations beyond the whisker length are marked as outliers (○=open circles, responses to outlier). ×=closed circles, responses to average.

simply an elastic material; smooth muscles are known to have a viscous effect, whereas elastin fibers exert an elastic effect. Considering these results together with those from a previous article demonstrating that the elasticity and viscosity of the carotid artery were altered in hypertensive patients[34], strain and the strain rate are thought to reflect mainly past adverse viscoelastic effects of continuous stress caused by hypertension, suggesting the importance of controlling BP. We also investigated the association between the use of antihypertensive medications and the strain values and found that the strain values were lower in those who used ACE inhibitors or ARBs (**Table 4**). Because of the observational design of this study, it is unclear whether strain and the strain rate were lowered by the use of ACE inhibitors or ARBs or the participants with lower strain values were more frequently prescribed ACE inhibitors or ARBs by physicians because of increased atherosclerotic risk factors.

In this study, however, we observed that the strain rate was significantly lower in female than in male participants and in non-smokers than in those with current or ex-smoking. These results seem to contradict the established association between gender or smoking and atherosclerotic diseases. Although at present we cannot determine the underlying mechanisms, one possible explanation is that most of the female participants included in this study were >50 years of age, and after menopause, the decrease in estrogen is known to predispose women to atherosclerosis[35]. Because most of the female participants in the present study were non-smokers, gender might be a confounding factor influencing the lower strain rate in non-smokers.

We also observed that strain and the strain rate had very weak or no correlations with IMT or CAVI. These associations have been reproduced in previous studies: Yuda *et al.*[20] also reported no significant correlation between strain and CAVI in relatively young healthy subjects, and Tsai *et al.*[36] and Catalano *et al.*[16] also demonstrated that strain and the strain rate were not or were only weakly correlated with IMT. These poor correlations might be explained by the fact that strain merely reflects local carotid stiffness, whereas IMT and CAVI reflect systemic vascular stiffness. The weak correlation between strain values and CAVI can also be explained by the limited availability of data, because CAVI cannot be measured in subjects with an ABI ≤0.9 who have advanced arteriosclerosis, which is a limitation of CAVI. Overall, these results might provide unique information, in addition to other physiological laboratory tests.

When we investigated the association between strain values and the presence of vascular diseases, we observed a significant association between the abnormality in strain values and CVD. Regarding this association, Van Sloten *et al.*[37] reported that stiffening of the carotid arteries impairs their cushioning function and increases the pressure and flow pulsatility, which are transmitted into the cerebral circulation and can increase the risk of stroke[38, 39]. Carotid stiffening can also lead to stroke through the development of (rupture-prone) atherosclerotic carotid plaques[40]. Actually, Tsai *et al.* demonstrated that circumferential strain and the strain rate were associated with previous ischemic stroke in elderly individuals[36]. Contrary to CVD, the reasons for the absence of the relationship between the abnormality in strain values and CAD remain unclear. Regarding this issue, Wierzbowska-Drabik *et al.* demonstrated that circumferential strain, unlike IMT, did not allow for differentiation between patients with three-vessel CAD and control subjects[41], whereas Kim *et al.* reported that the CAD severity and extent were correlated with strain and the strain rate, but were not correlated with IMT[24]. Further studies are needed to investigate the association between strain values and CAD.

Regarding the difference between strain and the strain rate, the strain, not strain rate, has been widely used to evaluate the usefulness of the speckle-tracking method in echocardiography. However, the usefulness of the strain rate remains to be elucidated in the field of carotid ultrasonography. Therefore, in this study, we compared the clinical characteristics between strain and the strain rate and found no obvious significant differences. However, the possibility exists that the strain rate might possess some characteristics that differ from those of strain in carotid ultrasonography, considering the differences between the heart and vessels including differences in the types of myocytes and the presence of elastic fibers. Further studies are needed to elucidate the usefulness of the strain rate.

Table 5. Multivariate logistic regression analysis for CVD

(A) Model A.			
Variables	odds ratio	(95% CI)	*P* value
CAVI	5.80	(1.68−19.97)	0.005
Diabetes	4.17	(1.28−13.58)	0.018
strain	0.48	(0.27−0.88)	0.018
(B) Model B			
variables	odds ratio	(95% CI)	*P* value
CAVI	5.68	(1.64−19.65)	0.006
Diabetes	4.34	(1.33−14.15)	0.015
strain rate	0.00	(0.00−0.19)	0.016

CVD: cerebrovascular disease; CAVI: cardio-ankle vascular index

There are some limitations to this study. First, we excluded 18 images (3%) because of inadequate image quality. The recording of high-quality images during carotid ultrasonography is essential for the measurement of strain and the strain rate. Second, in the present study, we did not calibrate the strain or strain rate by BP. Although many previous studies did not correct by BP and it remains controversial whether it is proper to calibrate strain and strain rate by BP, some studies demonstrated possible usefulness of strain and strain rate corrected with BP[16, 26]. Third, because we used Toshiba machine for the assessment of carotid strain and the strain rate, there was the possibility of inter-vendor variability of carotid strain parameters.

However, considering the unique characteristics of strain and the strain rate compared with IMT or CAVI together with the excellent reproducibility as described in the Methods section, strain values could be useful in clinical physiological tests, because they can provide a simple and more accurate index of local arterial stiffness. Considering that strain and the strain rate were significantly correlated with CVD and carotid arteries are anatomically near cerebral arteries, further studies might elucidate that the strain values could provide useful information on CVD, for example, lower carotid arterial strain values might predict the present existence or the future complication of CVD.

Conclusions

Our method of measuring strain and the strain rate using two-dimensional speckle-tracking, which is a non-invasive, simple, and reproducible method that can be used for clinical physiological laboratory testing, provides an index of viscoelastic deterioration of the vascular wall. Strain and the strain rate might reflect local arterial stiffness, which cannot be evaluated using other physiological tests such as IMT or CAVI, and may be associated with cerebrovascular diseases.

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Conflicts of interest

None.

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