ORIGINAL ARTICLE

Carotid arterial circumferential strain by two-dimensional speckle tracking: a novel parameter of arterial elasticity

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Recently, the development of two-dimensional speckle-tracking (2DST) technology has allowed the direct measurement of the elastic parameters of the carotid arterial wall. The aims of this study were to determine the feasibility of measuring peak circumferential strain (CS) of the carotid arterial wall using 2DST and to compare this value with conventional arterial stiffness parameters in subjects with and without hypertension. The study included 90 healthy subjects and 40 age- and sex-matched patients with hypertension. The short-axis view of the right common carotid artery was recorded. The CS in the posterior region of the carotid artery was calculated by 2DST using special software and corrected by the following equation: $\varepsilon_{\text{circ}} = \ln(\text{systolic blood pressure/diastolic blood pressure})/\text{CS}$. We simultaneously measured the stiffness index β (β) at the same location and the brachial-ankle pulse wave velocity (baPWV). Sixty randomly selected healthy subjects were used to assess the inter/intra-observer variability of $\varepsilon_{\text{circ}}$ and β . In healthy subjects, $\varepsilon_{\text{circ}}$ was significantly correlated with β , age and baPWV. These correlations were slightly better than the corresponding correlations of β with age and baPWV. The hypertensive patients had a significantly larger $\varepsilon_{\text{circ}}$ than the healthy subjects (0.112 ± 0.074 vs. $0.066 \pm 0.029\%$, $P < 0.001$). The inter/intra-observer variability for $\varepsilon_{\text{circ}}$ was significantly lower than that for β . Our data suggest that the measurement of carotid $\varepsilon_{\text{circ}}$ using 2DST is feasible and has better reproducibility than conventional carotid arterial stiffness.

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INTRODUCTION

Increased arterial stiffness is one of the early manifestations of adverse structural and functional changes within the vessel wall and an important independent predictor of future adverse cardiovascular events and all-cause mortality in various populations.^{1,2} In addition, several pharmacological and nonpharmacological interventions have been reported to improve arterial stiffness.² Therefore, the simple, accurate measurement of arterial stiffness with high reproducibility is very important. Thus far, various noninvasive parameters of arterial stiffness have been evaluated using various devices.² The stiffness index β (β) is one of the parameters of arterial stiffness determined by carotid ultrasound in the clinical setting. However, this parameter is estimated from the extension of the arterial wall based on the systolic and diastolic lumen diameter along with pulse pressure and does not take into account the expansion of the intima-media wall.

Recently, two-dimensional speckle-tracking (2DST) echocardiography has been shown to provide an angle-independent, well-validated method for strain measurement in human heart.^{3–9} Although this method can be applied to the human carotid arterial wall to directly

assess arterial elasticity, it has not been well assessed. Therefore, the aims of this study were to evaluate the feasibility of direct measurement of peak circumferential strain (CS) of the carotid arterial wall using 2DST, to compare the reproducibility of CS with conventional arterial stiffness parameters in healthy subjects, and to compare CS between subjects with and without hypertension.

METHODS

Study population

Ninety-four consecutive healthy subjects without risk factors for atherosclerosis such as hypertension, dyslipidemia, diabetes mellitus and current smoking were enrolled. In addition, 41 age- and sex-matched patients with hypertension were enrolled. The presence of risk factors for atherosclerosis were defined as follows: hypertension as systolic blood pressure ≥ 140 mm Hg and/or diastolic blood pressure ≥ 90 mm Hg measured at the time of ultrasound examination or current antihypertensive therapy; dyslipidemia as either serum low-density lipoprotein cholesterol ≥ 140 mg dl⁻¹, triglycerides ≥ 150 mg dl⁻¹, high-density lipoprotein cholesterol < 40 mg dl⁻¹ or current antilipid therapy; and diabetes mellitus as either serum fasting blood glucose ≥ 126 mg dl⁻¹, HbA1c $\geq 6.5\%$ or current antidiabetic therapy. All patients were required to

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Figure 1 The method used to measure peak circumferential strain (CS) by two-dimensional speckle-tracking echocardiography. The red arrowheads indicate the posterior region of the carotid artery. The white arrow indicates peak CS.

be in sinus rhythm at the time of the ultrasound examination. Exclusion criteria included subjects with known coronary artery disease, significant valvular heart disease, ejection fraction $\leq 60\%$ as assessed by echocardiography, renal disease, stroke, significant peripheral vascular disease (ankle to brachial blood pressure ratio ≤ 0.9) and other disease conditions such as fever and malaise. Four healthy subjects and one patient with hypertension were excluded because of speckle-tracking failure with poor two-dimensional images. The remaining 90 healthy subjects and 40 patients with hypertension were included in the analysis. Several metabolic variables, including fasting blood glucose, HbA1c, insulin, total cholesterol, high-density lipoprotein cholesterol, triglycerides and low-density lipoprotein cholesterol levels, were measured in all participants on the morning of the ultrasound studies. All drugs were discontinued at least 24 h before evaluation in the patients with hypertension. This study was approved by the ethics committee of Ehime University Graduate School of Medicine, and all patients and subjects gave informed consent before participation.

Routine carotid ultrasound and echocardiographic examination

Subjects were examined in the morning (0830–0900 hours) after a 12-h overnight fast in a quiet, temperature-controlled laboratory (22 °C after 15 min of rest in the supine position). The ultrasound examinations were performed by two vascular ultrasound experts who were blinded to the subject's identity and clinical profile. Ultrasound imaging was performed with a GE Vivid 7 ultrasound imaging system (GE Medical System, Milwaukee, WI, USA) with a high-resolution linear array transducer centered at 12 MHz (carotid) and a M4S probe (heart). All acquisitions were performed during short breath holding to minimize the effect of motion artifacts. The transducer was placed with the least possible pressure to avoid compressing the overlying jugular vein and to allow expansion of the carotid artery. The intima-media thickness (IMT) was obtained using B-mode imaging of the right common carotid artery in the longitudinal plane and calculated as the distance from the leading edge interface between lumen and intima to the leading edge interface between media and adventitia in the far wall of the artery. Five IMT measurements at 3-mm intervals were obtained starting 1 cm proximal to the bulb and moving proximally.¹⁰ The mean IMT was obtained from five IMTs in the final analysis. The internal luminal diameter during end-diastole (Dd) and end-systole (Ds) 1 cm proximal to the bulb were measured using M-mode ultrasound over five cardiac cycles and averaged. The inner lumen diameter was assessed as the

distance between the intima-lumen interface at the near wall and the lumen-intima interface at the far wall. In addition, three brachial artery blood pressure measurements were obtained in the right arm with an automated digital oscillometric sphygmomanometer (Omron Healthcare, Kyoto, Japan) and averaged to determine the resting blood pressure. The stiffness index β (β) was estimated according to the following equation: $\beta = \ln(Ps/Pd) \times Dd / (Ds - Dd)$, where Ps and Pd are the systolic and diastolic blood pressure in mm Hg, respectively.

In addition, several cardiac function parameters were also measured.¹¹ Left ventricular (LV) end-diastolic and end-systolic volumes and ejection fraction were estimated by a modified Simpson's rule from apical imaging planes and normalized to body surface area. The E/A ratio and early diastolic mitral annular velocity on the septal side (e') were obtained using pulse Doppler imaging and tissue Doppler imaging.

The measurement of CS

The short axial B-mode image at the same level of the right common carotid artery used for measuring β was acquired during three cardiac cycles with novel software developed for the 'rodent' heart.^{12,13} This application was capable of obtaining high-frame rate two-dimensional images. All images were recorded with a high frame rate (>100 frames s^{-1} ; mean frame rate: 143 ± 45 frames s^{-1}). Offline speckle-tracking analysis was performed on digitally stored gray scale images using custom software (EchoPAC PC BT08; GE Healthcare, Milwaukee, WI, USA). First, the endovascular border was manually traced at end-systole. The width of the region of interest (ROI) was reduced to a minimum by the software to avoid the mis-tracking of extravascular tissue, because it depends on the depth resolution (no fixed value). The software then automatically detected frame-to-frame movement of the natural ultrasound reflections (speckles) on standard ultrasonic images in two dimensions based on the block-matching and autocorrelation search algorithms.³ The carotid arterial wall was equally divided into six segments, and each segment was analyzed individually. CS, which is expressed as the circumferential stretch during systole, was automatically determined from each time-strain curve for all six segments. In the present study, CS only in the posterior region of carotid artery was analyzed because the measurement of IMT in the far wall has less discrepancy with histological findings.¹⁴ Figure 1 shows an example of CS measurement using 2DST. In addition, we corrected

CS because of the nonlinear stress–strain relationship using the following equation: $\varepsilon_{\text{circ}}(\%) = [\ln(P_s/P_d)/CS] \times 100$.¹⁵

Pulse wave analysis

The measurement of brachial-ankle pulse wave velocity (baPWV) was performed at the same position immediately after the ultrasound examination using the volume-plethysmographic method with previously validated equipment (from PWV/ABI; Colin Medical Technology, Komaki, Japan). A detailed description of this device has been reported previously.^{16,17} Cuffs were connected to both the plethysmographic and oscillometric sensors and wrapped around both arms and ankles while the patient was supine. Transit time (δT_{ba}) between the brachial and ankle pulse waves was automatically measured based on the time delay between the foot of the pressure increase (sharp initial systolic upstroke of the wave) in the arm and ankle. The distance between the two recording sites was calculated automatically based on the height of the subject (H) and anthropomorphic data for the Japanese population. The path length from the suprasternal notch to the brachium (L_b) and ankle (L_a) was calculated using the following equation: $L_b = 0.2195 \times H$ (cm) $- 2.0734$, $L_a = 0.8129 \times H$ (cm) $+ 12.328$. The baPWV was then calculated using the following equation: $\text{baPWV} = (L_a - L_b)/\delta T_{\text{ba}}$. The average of right and left baPWV was used in the final analysis. All measurements were carried out by the same trained investigator.

Table 1 Clinical characteristics of healthy subjects and patients with hypertension

Variable	Healthy subjects (N = 90)	Patients with hypertension (N = 40)	P
Age (years)	49 $\pm$ 12	52 $\pm$ 8	0.183
Male, n (%)	58 (64)	20 (50)	0.126
Body height (cm)	163 $\pm$ 8	163 $\pm$ 11	0.862
Body weight (kg)	62 $\pm$ 11	68 $\pm$ 17	0.007
Body mass index (kg m ⁻²)	23.0 $\pm$ 2.8	25.5 $\pm$ 5.0	<0.001
Systolic blood pressure (mm Hg)	123 $\pm$ 13	143 $\pm$ 19	<0.001
Diastolic blood pressure (mm Hg)	75 $\pm$ 10	85 $\pm$ 12	<0.001
Pulse pressure (mm Hg)	48 $\pm$ 7	58 $\pm$ 12	<0.001
Heart rate (per min)	66 $\pm$ 9	68 $\pm$ 8	0.444
Fasting blood glucose (mg dl ⁻¹)	97 $\pm$ 10	111 $\pm$ 25	<0.001
HbA1c (%)	5.5 $\pm$ 0.4	5.9 $\pm$ 0.9	<0.001
Insulin (μ U ml ⁻¹)	4.5 $\pm$ 3.0	6.9 $\pm$ 4.0	0.005
Total cholesterol (mg dl ⁻¹)	203 $\pm$ 34	194 $\pm$ 40	0.193
HDL cholesterol (mg dl ⁻¹)	62 $\pm$ 16	59 $\pm$ 19	0.478
Triglycerides (mg dl ⁻¹)	110 $\pm$ 73	118 $\pm$ 85	0.619
LDL cholesterol (mg dl ⁻¹)	120 $\pm$ 30	109 $\pm$ 33	0.083
Internal systolic diameter (mm)	6.4 $\pm$ 0.6	6.9 $\pm$ 1.0	0.002
Internal diastolic diameter (mm)	5.9 $\pm$ 0.6	6.4 $\pm$ 0.9	0.001
IMT (mm)	0.73 $\pm$ 0.17	0.81 $\pm$ 0.17	0.014
LV end-diastolic volume index (ml m ⁻²)	43 $\pm$ 8	43 $\pm$ 8	0.948
LV end-systolic volume index (ml m ⁻²)	26 $\pm$ 6	25 $\pm$ 6	0.542
LV ejection fraction (%)	65 $\pm$ 7	66 $\pm$ 7	0.555
E/A	1.38 $\pm$ 0.48	1.05 $\pm$ 0.32	<0.001
e' (cm s ⁻¹)	9.2 $\pm$ 2.4	7.3 $\pm$ 1.7	<0.001
Medical therapy, n (%)			
Calcium antagonists		26 (65)	
ACE inhibitors or ARB		19 (48)	
Beta blockers		5 (13)	
Diuretics		1 (3)	

Abbreviations: ACE, Angiotensin-converting enzyme; ARBs, Angiotensin receptor blockers; HDL, high-density lipoprotein; HT, hypertension; IMT, intima-media thickness; LDL, low-density lipoprotein; LV, left ventricular.

Data are expressed as the mean $\pm$ s.d.

Values of $P < 0.05$ were considered statistically significant.

Statistical analysis

All values are expressed as the mean $\pm$ s.d. The clinical and ultrasound parameters and baPWV were compared with an unpaired t -test between healthy subjects and patients with hypertension. Linear regression analysis was performed to evaluate the relationship of age or baPWV with the two stiffness parameters (β and $\varepsilon_{\text{circ}}$). The correlations between age and baPWV and the carotid stiffness parameters were compared using analysis of covariance. Multivariate logistic regression analysis that included all subjects was performed to determine the independent predictors of $\varepsilon_{\text{circ}}$. Age, gender, body mass index, the presence of hypertension, LV ejection fraction, metabolic variables, the use of each class of antihypertensive medications, Dd and IMT were used as dependent variables in the regression model. The inter-observer and intra-observer variability were assessed for measuring β and $\varepsilon_{\text{circ}}$ in 60 randomly selected healthy subjects and compared with a paired t -test. The inter-observer variability was calculated as the s.d. of the differences between the measurements of two independent observers who were unaware of the other data and expressed as a percentage of the average value. The intra-observer variability was calculated as the s.d. of the differences between the first and second determination (2-week interval) for a single observer and expressed as a percentage of the average value. All statistical analyses except for the Bland–Altman plot were performed using SPSS 15.0J software for Windows (SPSS, Chicago, IL, USA). The analysis for Bland–Altman plot was performed using Medcalc Version 12.1.3 for windows (Mariakerke, Belgium).

RESULTS

The overall baseline characteristics of healthy subjects and patients with hypertension are shown in Table 1. The patients with hypertension had significantly higher body weight, body mass index, blood pressure, pulse pressure, diabetic parameters, carotid diameter, IMT and lower LV diastolic parameters than those in healthy subjects.

The correlation between age and baPWV and carotid stiffness parameters in healthy subjects

In the healthy subjects, $\varepsilon_{\text{circ}}$ was significantly correlated with β ($r = 0.363$, $P < 0.001$). $\varepsilon_{\text{circ}}$ was positively correlated with age and baPWV, and these correlations were better than the corresponding correlations of β with age and baPWV, but the differences were not statistically significant (Figure 2).

Figure 2 Correlation between age and β (a) and $\varepsilon_{\text{circ}}$ (b) and the correlation between baPWV and β (c) and $\varepsilon_{\text{circ}}$ (d) in healthy subjects.

Comparison of stiffness parameters between healthy subjects and patients with hypertension

The stiffness parameters in both groups are displayed in Figure 3. The patients with hypertension had significantly higher baPWV, β and ϵ_{circ} than those in healthy subjects. Representative examples are shown in Figure 4.

The determinants of ϵ_{circ} in all subjects

Multivariate logistic regression analysis showed that age, heart rate and the presence of hypertension were significant independent predictors of ϵ_{circ} among the study parameters in all subjects (Table 2).

Figure 3 Comparison of stiffness parameters (a: baPWV, b: β , c: ϵ_{circ}) between healthy subjects and patients with hypertension.

Observer variability

The inter-observer and intra-observer variability for the measurement of ϵ_{circ} were significantly better than those for the measurement of β (Table 3, Figure 5).

DISCUSSION

To our knowledge, this is the first report of the measurement of a new stiffness parameter, ϵ_{circ} using high-frame 2DST in healthy subjects

Table 2 Multivariate logistic regression analysis of ϵ_{circ} among the study parameters in all subjects

Variables	β	<i>t</i>	P
Age	0.475	4.581	<0.001
Gender	-0.053	-0.505	0.615
Body mass index	0.160	1.534	1.282
Heart rate	0.240	2.593	0.011
HbA1c	-0.167	-1.649	0.102
HDL cholesterol	0.089	0.935	0.352
LDL cholesterol	0.095	1.039	0.301
Internal diastolic diameter	0.028	0.278	0.781
IMT	-0.118	-1.126	0.263
LV ejection fraction	0.011	0.121	0.904
Use of calcium antagonists	0.095	0.684	0.495
Use of ACE inhibitors or ARB	-0.199	-1.551	0.124
Use of beta blockers	0.060	0.541	0.590
Use of diuretics	-0.121	-1.162	0.248
Presence of hypertension	0.336	2.682	0.009

Abbreviations: ACE, Angiotensin-converting enzyme; ARBs, Angiotensin receptor blockers; β , stiffness index; ϵ_{circ} , corrected peak circumferential strain; HDL, high-density lipoprotein; HT, hypertension; IMT, intima-media thickness; LDL, low-density lipoprotein; LV, left ventricular. $R^2 = 0.371$ for the model, $P < 0.0001$.

Figure 4 Examples of circumferential strain curves of the right carotid artery by speckle-tracking imaging (left) and carotid echocardiographic data from B-mode and M-mode recordings (right) in a 44-year-old healthy subject (a) and a 48-year-old patient with hypertension (b). The red arrowheads indicate the posterior region of carotid artery. The white arrow indicates peak circumferential strain.

and patients with hypertension. The major findings of this study are the following: (1) there were significant correlations between ϵ_{circ} and age and between ϵ_{circ} and baPWV, and those correlations were slightly better than those between β and age, and between β and baPWV; (2) patients with hypertension had a significantly higher ϵ_{circ} than healthy subjects; (3) age, heart rate and the presence of hypertension were associated with ϵ_{circ} , even after adjustment for clinical data, metabolic variables, ultrasound parameters and antihypertensive medications; and (4) the reproducibility of ϵ_{circ} was significantly better than that of β .

Significance of ϵ_{circ} compared with the conventional parameter β

Increased arterial stiffness leads to worsening of myocardial ischemia as a result of increased after load and oxygen demand (elevated systolic blood pressure) or impaired coronary blood supply (decreased diastolic blood pressure).¹⁸ Furthermore, increased arterial stiffness is an independent prognostic predictor of cardiovascular events in several populations.¹ Thus, a non-invasive assessment of arterial stiffness is important in terms of an early stratification for future cardiovascular events. To date, several

ultrasound parameters of arterial elasticity have been reported.² Among them, carotid stiffness β is used to easily evaluate arterial stiffness in the clinical setting, because it was found to be independent of blood pressure within the normal physiological range and was associated with the severity of hypertension and coronary atherosclerosis.^{19,20} However, this parameter is based on the cyclic changes of the internal luminal diameter of the artery and does not take into account the expansion of the intima-media wall itself. Currently, 2DST is available to detect regional myocardial deformation in various cardiac diseases.^{3–9} Furthermore, the sensitivity of high-frame 2DST in the circumferential direction was recently assessed in rat and mouse models with very thin myocardial thickness,^{12,13} and this technique can be used in the clinical setting. Therefore, we applied it to the carotid arterial wall, because this technique enables the measurement of strain in very thin tissue segments with high reproducibility. Several studies have reported that aging is the most important determinant of arterial stiffness.¹ Actually, aging was one of the significant independent predictors of ϵ_{circ} in the present study. Thus, our results suggest that ϵ_{circ} reflects similar or slightly better associations between age and systemic stiffness compared with the conventional parameter β . We think that two main mechanisms may be responsible for this result. First, in general, reproducibility is correlated with the accuracy of the study parameter. In the present study, we manually measured the internal luminal diameter using M-mode rather than two-dimensional ultrasound. However, CS was semi-automatically measured using 2DST software with high reproducibility.^{3–9,12,13} The difference in measurement methods may account for the significantly better reproducibility of ϵ_{circ} compared with β . Second, ϵ_{circ} is a parameter

Table 3 Reproducibility of β and ϵ_{circ}

	β	ϵ_{circ} (%)	P
Inter-observer CV	18.8 ± 14.0	9.0 ± 9.4	<0.001
Intra-observer CV	16.1 ± 12.2	5.3 ± 6.4	<0.001

Abbreviations: β , stiffness index; CV, coefficient of variation; ϵ_{circ} , corrected peak circumferential strain.
Data are expressed as the mean ± s.d.

Figure 5 Bland–Altman plot of inter- and intra-observer variability for the analysis of β (a) and ϵ_{circ} (b). The horizontal solid line indicates the mean difference between the two measures, and the dashed lines indicate the 95% limits of agreement (mean difference ± 1.96 times the s.d. of the difference). A full color version of this figure is available at the *Hypertension Research* journal online.

that directly measures the elasticity of the carotid arterial wall in the circumferential direction, whereas β is an indirect parameter that measures the change of the internal luminal diameter of the artery in the radial direction.

The comparison of stiffness parameters between healthy subjects and patients with hypertension

Patients with hypertension have been reported to have higher arterial stiffness than healthy subjects, and this association is independent of age.^{20,21} Although the severity of hypertension was relatively mild in the present study and these patients did not have any other atherosclerotic risk factors, the patients with hypertension had significantly higher $\varepsilon_{\text{circ}}$ as well as conventional stiffness parameters compared with healthy subjects. In addition, the presence of hypertension was one of the independent predictors of $\varepsilon_{\text{circ}}$. These results support the concept that $\varepsilon_{\text{circ}}$ could serve as an early marker of increased arterial stiffness.

Clinical implications

The present study showed that $\varepsilon_{\text{circ}}$ was more reproducible and had a similar or slightly better correlation with age and systemic stiffness compared with β . This raises the possibility that $\varepsilon_{\text{circ}}$ could be used as a simple and more accurate index of arterial stiffness in clinical practice.

Study limitations

The present study has several limitations. First, the number of patients in this study was small and the variation of $\varepsilon_{\text{circ}}$ was relatively large. Therefore, more clinical studies in larger patient populations must be performed to confirm the accuracy of $\varepsilon_{\text{circ}}$ as an index of arterial stiffness. Second, the stiffness parameters β and $\varepsilon_{\text{circ}}$ were calculated at only a single site without plaque in the right common carotid artery, and this might have increased the variation of those parameters among subjects. In addition, it is unknown whether carotid stiffness parameters measured at a single site reflect arterial stiffness in patients with heterogeneous regional arterial stiffness due to diffuse plaques. Multiple site measurements in the entire carotid artery and the development of new software might reduce the variation in stiffness among subjects and improve the precision of the measurement. Third, this study was an observational study. The clinical significance of $\varepsilon_{\text{circ}}$ as a predictor of future events is still lacking. Thus, prospective studies in larger patient populations are definitely necessary to establish the validity of $\varepsilon_{\text{circ}}$ as a predictor of future events. Fourth, the precise blood pressure in the common carotid artery could not be measured, and we used brachial artery pressure to calculate stiffness β , as was done in previous studies. Finally, in this speckle-tracking software, manual adjustment of the ROI width is not allowed. Thus, it might be difficult to completely adjust the ROI width to the IMT. Future development of speckle-tracking software would be useful to improve the tracking of carotid artery deformation and to provide a better instrument for the study of arterial stiffness.

CONCLUSIONS

This study showed that the measurement of carotid $\varepsilon_{\text{circ}}$ using 2DST was feasible and that $\varepsilon_{\text{circ}}$ was more reproducible and had a similar or slightly better correlation with age and systemic stiffness than the conventional carotid arterial stiffness parameter β . Moreover, patients with hypertension had a significantly higher $\varepsilon_{\text{circ}}$ than healthy subjects. This clinically promising parameter might be used as a novel surrogate marker for early arteriosclerosis.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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