The association between expansive arterial remodeling detected by high-resolution MRI in carotid artery stenosis and clinical presentation

Kazumichi Yoshida, MD, PhD,¹ Ryu Fukumitsu, MD,¹ Yoshitaka Kurosaki, MD,² Takeshi Funaki, MD,¹ Takayuki Kikuchi, MD, PhD,¹ Jun C. Takahashi, MD, PhD,¹ Yasushi Takagi, MD, PhD,¹ Sen Yamagata, MD, PhD,² and Susumu Miyamoto, MD, PhD¹

¹Department of Neurosurgery, Kyoto University Graduate School of Medicine, Kyoto; and ²Department of Neurosurgery, Kurashiki Central Hospital, Okayama, Japan

OBJECT The purpose of the present study was to investigate the association between carotid artery (CA) expansive remodeling (ER) and symptoms of cerebral ischemia.

METHODS One hundred twenty-two consecutive CAs scheduled for CA endarterectomy (CEA) or CA stent placement (CAS) were retrospectively studied. After excluding 22 CAs (2 were contraindicated for MRI, 8 had near-occlusion, 6 had poor image quality, and 6 had restenosis after CEA or CAS), there were 100 CAs (100 patients) included in the final analysis. The study included 50 symptomatic patients (mean age 73.6 ± 8.9 years, 6 women, mean stenosis $68.5\% \pm 21.3\%$) and 50 asymptomatic patients (mean age 72.0 ± 5.9 years, 5 women, mean stenosis $79.4\% \pm 8.85\%$). Expansive remodeling was defined as enlargement of the internal carotid artery (ICA) with outward plaque growth. The ER ratio was calculated by dividing the maximum distance between the lumen and the outer borders of the plaque perpendicular to the axis of the ICA by the maximal luminal diameter of the distal ICA at a region unaffected by atherosclerosis using long-axis, high-resolution MRI.

RESULTS The ER ratio of the atherosclerotic CA was significantly greater than that of normal physiological expansion (carotid bulb; $p < 0.01$). The ER ratio of symptomatic CA stenosis (median 1.94, interquartile range [IQR] 1.58–2.23) was significantly greater than that of asymptomatic CA stenosis (median 1.52, IQR 1.34–1.81; $p = 0.0001$). When the cutoff value of the ER ratio was set to 1.88, the sensitivity and specificity to detect symptoms were 0.6 and 0.78, respectively. The ER ratio of symptomatic patients was consistently high regardless of the degree of stenosis.

CONCLUSIONS There was a significant correlation between ER ratio and ischemic symptoms. The ER ratio might be a potential indicator of vulnerable plaque, which requires further validation by prospective observational study of asymptomatic patients.

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KEY WORDS atherosclerosis; carotid stenosis; expansive remodeling; magnetic resonance imaging; vulnerable plaque; vascular disorders

CAROTID artery (CA) stenosis is a major cause of cerebral infarction and can be treated with medical therapy alone or in combination with interventions such as CA endarterectomy (CEA) or CA stent placement (CAS). While the benefits of CEA or CAS for moderate- to high-grade CA stenosis have been established in several previous large clinical trials,^{4,6,9,32} multifaceted medical treatment for atherosclerotic vascular disease has improved

dramatically in recent years, and the role of CEA/CAS for stroke prevention, particularly in asymptomatic CA stenosis, needs to be redefined based on more accurate stroke risk stratification.

Therefore, accurate stroke risk stratification for future ischemic events using diagnostic imaging is useful for stroke prevention. Accumulating evidence from recent vascular biology studies demonstrates that the qualitative and

ABBREVIATIONS CA = carotid artery; CAE = CA endarterectomy; CAS = CA stent placement; CI = confidence interval; ER = expansive remodeling; ICA = internal CA; IQR = interquartile range; NASCET = North American Symptomatic Carotid Endarterectomy Trial; OR = odds ratio; ROC = receiver operating characteristic.

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morphological characteristics of plaque influence the risk of ischemic events,²² as well as the luminal narrowing of the CA. However, the selection of treatment modalities for patients with CA stenosis is based mostly on degree of stenosis, symptomatic status, and general physical condition of the patients.

The CA can change its geometry in response to the development of atherosclerosis either by negative remodeling or expansive remodeling (ER), and such arterial remodeling has been extensively investigated in the coronary circulation. Expansive remodeling is enlargement of the atherosclerotic artery with outward plaque growth, was first described in a postmortem histological study, and was initially considered a compensatory response that retarded luminal narrowing and prevented ischemic events.¹² However, subsequent studies with the advent of intravascular ultrasonography demonstrated that compensatory ER may also be associated with plaque instability and increase the risk of ischemic events.^{2,14,23} Matsuo et al. investigated plaque characteristics and arterial remodeling using intravascular ultrasonography in coronary and peripheral arteries such as the carotid, renal, and iliac arteries, and reported that arteries with ER, compared with those with negative remodeling, demonstrated more characteristics of fibroatheroma, which is one of the most significant features of vulnerable plaque regardless of its location.²⁰

There have been 2 previous studies that used multi-detector CT angiography to investigate the association between ER in the CA and clinical presentation.^{13,21} The purpose of this study was to assess the feasibility of long-axis CA MRI³³ for quantitative assessment of ER and to evaluate the association between the extent of ER and cerebral ischemic events.

Methods

Patient Population

Based on prospectively collected data for patients with CA stenosis who were scheduled for CEA or CAS at Kurashiki Central Hospital, a total of 122 consecutive CAs in 119 patients were retrospectively analyzed. Inclusion criteria for CEA/CAS included $\geq 70\%$ asymptomatic CA stenosis and $\geq 50\%$ symptomatic stenosis. For symptomatic low-grade stenosis ($< 50\%$), we considered CEA when patients presented with more than 2 recurrences despite maximal medical therapy and no other general problems, and consented to surgical intervention. Two CAs were contraindicated for MRI due to pacemaker implantation, 8 CAs had near-occlusion, 6 CAs had MR images graded as inadequate for diagnosis due to poor image quality, and 6 CAs had restenosis after CEA ($n = 3$) or CAS ($n = 3$). These 22 CAs were excluded and 100 CAs in 100 patients were included in the final analysis. Symptomatic patients were defined as those who experienced amaurosis fugax, a transient ischemic attack, or stroke in the territory of the ipsilateral internal CA (ICA) within 6 months. There were 50 symptomatic patients and 50 asymptomatic patients. The severity of CA stenosis was evaluated by digital subtraction angiography using criteria from the North American Symptomatic Carotid Endarterectomy Trial (NASCET) Collaborators.⁴

Age, sex, percentage of luminal stenosis, and risk factors for ischemic stroke (hypertension, hyperlipidemia, diabetes mellitus, ischemic heart disease, and smoking habit) were analyzed based on symptoms, and only the percentage of luminal stenosis ($p = 0.0011$) and method of revascularization ($p = 0.0001$) were significantly different between symptomatic and asymptomatic patients (Table 1). Hypertension and hyperlipidemia were by definition restricted to those cases using blood pressure-lowering drugs and statins, respectively. Diabetes mellitus was defined as use of insulin or oral glucose inhibitors. Ischemic heart disease was defined as angina or prior myocardial infarction. These patient characteristics are summarized in Table 1.

The local institutional review board of Kurashiki Central Hospital approved this study, and all patients provided written informed consent to participate in all procedures associated with the study.

Imaging Techniques

A 1.5-T, whole-body MRI machine (Gyrosan Intera, Philips Medical Systems) with an 8-cm surface coil was used to image the CAs. T1-weighted images of sagittal sections parallel to the long axis of the CA at 1-mm intervals were obtained using the double inversion recovery technique to suppress the blood flow signal. The fat suppression method was applied to suppress marked signal hyperintensity due to subcutaneous fat tissue by using the chemical shift-selective fat suppression technique of spectral presaturation with inversion recovery. The parameters of black-blood MRI were as follows: 3D inversion-recovery turbo field echo, field of view 150 mm, matrix 320×512 , TR/TE/TI 10/2.7/500 msec, flip angle 35° , slice thickness 1.6 mm, and reconstructed voxel size $0.29 \times 0.29 \times 0.8$ mm.

Definition of ER and Measurement of the ER Ratio

In this study, ER was defined as enlargement of the ICA with outward plaque growth more than 3-mm thick

TABLE 1. Characteristics of the patients with CA stenosis scheduled for CEA or CAS

Variable	Lesions ($n = 50$ each group)		p Value
	Symptomatic (%)	Asymptomatic (%)	
Mean age $\pm$ SD (yrs)	73.6 ± 8.9	72.0 ± 5.9	0.3173
Females	6 (12)	5 (10)	0.7493
Mean % stenosis $\pm$ SD*	68.5 ± 21.3	79.4 ± 8.85	0.0011†
CEA	34 (68)	15 (30)	0.0001†
CAS	16 (32)	35 (70)	0.0001†
Hypertension	44 (88)	44 (88)	1
Hyperlipidemia	26 (52)	30 (60)	0.4203
Diabetes	12 (24)	20 (40)	0.0863
Ischemic heart disease	19 (38)	23 (46)	0.4177
Smoking habit	23 (46)	22 (44)	0.8407

* According to NASCET criteria.

† Significant difference between the two groups.

on long-axis high-resolution MRI. The measurement technique for the ER ratio was developed by applying the method used in NASCET to evaluate stenosis.¹⁰ The ER ratio in the CA was calculated using the long-axis, black-blood MRI³³ and the following formula:

ER ratio = the maximum distance between the lumen and the outer borders of the plaque perpendicular to the axis of the ICA/the maximal luminal diameter of the distal ICA at a region unaffected by atherosclerosis (Fig. 1).

When the plaque with maximal outside diameter and the normal distal ICA with maximal outside diameter could not be observed on the same image, 2 separate long-axis images that included the maximal outside diameter of the affected ICA and the distal unaffected ICA were selected for the calculation. The control ER ratio was measured in the contralateral nonatherosclerotic ICA in patients with unilateral CA stenosis and the following formula was used:

ER ratio (control) = the maximal luminal diameter at the normal bulb/the maximal luminal diameter of the ICA well beyond the bulb.

Image Review

Expansive remodeling ratio measurements were performed by 2 experienced investigators blinded to the clinical information (R.F. and Y.K.). The interobserver reproducibility of the ER ratio was assessed in 25 consecutive patients by determining the intraclass correlation coefficient, which varies from 0 (no agreement) to 1 (perfect agreement).

Statistical Analysis

Numerical data are expressed as means $\pm$ standard

deviations and were compared using Welch's t-test or the Wilcoxon rank-sum test as appropriate. Categorical data were evaluated by using the chi-square test. Multiple logistic regression analysis was performed to adjust for other predictors of ischemic symptom (age, sex, percentage of stenosis, hypertension, hyperlipidemia, diabetes, ischemic heart disease, and smoking habit). The results are expressed as odds ratios (ORs) with 95% confidence intervals (CIs). Values of the ER ratio to differentiate between the 2 groups were calculated from receiver operating characteristic (ROC) curves. All data were statistically analyzed using SPSS (version 12.0 for Windows, SPSS Inc.) and probability values < 0.05 were considered statistically significant.

Results

Interobserver Agreement

The intraclass correlation coefficient value was 0.782 (95% CI 0.449–0.909), which indicated substantial to good interobserver agreement.

Normal Carotid Bulb and ER of Atherosclerotic ICA

In 25 patients with unilateral CA stenosis, the ER ratio in the affected ICA was 1.68 ± 0.40 and significantly greater than the control ER ratio of 1.36 ± 0.15 in the non-affected ICA ($p < 0.01$, Fig. 2).

Expansive Remodeling Ratio and CA Ischemic Symptoms

The ER ratio in symptomatic patients (median 1.94, interquartile range [IQR] 1.58–2.23) was significantly greater than that in asymptomatic patients (median 1.52, IQR 1.34–1.81, $p = 0.0001$; Fig. 3). In multiple logistic

FIG. 1. Long-axis, black-blood MR images. **A:** Illustration of the measurement of the ER ratio. The ER ratio is calculated as the ratio of the maximum distance between the lumen and the outer borders of the plaque perpendicular to the axis of the ICA (a) and the luminal diameter of the distal ICA (b). The solid lines indicate the luminal surface at a region unaffected by atherosclerosis and the plaque-adventitia interface at an atherosclerotic region. The dotted line indicates the long axis of the ICA. **B:** Illustrative case of asymptomatic CA stenosis in a 68-year-old male patient. The ER ratio and stenosis percentage were 1.5 and 75%, respectively. **C:** Illustrative case of symptomatic CA stenosis in a 73-year-old male patient. The ER ratio and stenosis percentage were 2.29 and 20%, respectively. In B and C, the short arrows represent the luminal diameter of the distal ICA, and the long arrows the maximum distance between the lumen and the outer borders of the plaque perpendicular to the axis of the ICA.

FIG. 2. Comparison between the ER ratio of the atherosclerotic ICA (ICS, or CA stenosis) and the nonatherosclerotic normal ICA (Control) in 25 patients with unilateral CA stenosis. The mean ER ratio in the stenotic ICA (1.68 ± 0.40) was significantly greater than normal physiological expansion (1.36 ± 0.15 , $p < 0.01$). * $p < 0.01$.

regression analysis, only ER ratio was positively associated with ischemic symptoms (OR 10.683, 95% CI 2.613–43.674; $p = 0.001$; Table 2). ROC curve analysis found that the ER ratio could accurately discriminate symptomatic from asymptomatic patients (area under the ROC curve = 0.721). When the cutoff value of the ER ratio was 1.88, the sensitivity and specificity to discriminate symptomatic patients were 0.6 and 0.78, respectively.

When patients were classified into 4 groups depending on the luminal stenosis rate (CA stenosis < 50%, 50%–70%, 71–80%, and > 81%), the mean ER ratios for symptomatic patients were 1.93 ± 0.54 (CA stenosis < 50%),

FIG. 3. Comparison of the ER ratio between symptomatic ($n = 50$) and asymptomatic ($n = 50$) patients. The median ER ratio of symptomatic patients (median 1.94, IQR 1.58–2.23) was significantly greater than that of asymptomatic patients (median 1.52, IQR 1.34–1.81; $p = 0.0001$). * $p < 0.001$.

TABLE 2. Multivariate logistic regression analysis of factors associated with ischemic symptoms

Factor	OR	95% CI	p Value
ER ratio	10.683	2.613–43.674	0.001*
Age	1.033	0.967–1.102	6.759
Sex (female)	1.347	0.269–10.301	0.717
% stenosis	0.002	0.000–0.117	0.003*
Hypertension	1.593	0.386–6.573	0.520
Hyperlipidemia	0.687	0.242–1.952	0.482
Diabetes	0.721	0.262–1.989	0.528
Ischemic heart disease	0.742	0.279–1.976	0.551
Smoking habit	1.644	0.557–4.849	0.368

* Statistically significant ($p < 0.05$).

1.93 ± 0.54 (50%–70%), 1.90 ± 0.139 (71%–80%), and 1.93 ± 0.33 (> 81%). The ER ratios in symptomatic patients were consistently elevated, regardless of the stenosis rate. In contrast, the mean ER ratios in asymptomatic patients were 1.54 ± 0.27 (50%–70%), 1.56 ± 0.37 (71%–80%), and 1.67 ± 0.30 (> 81%), and the ER ratio had a tendency to be positively associated with the luminal stenosis rate, although the relationship did not reach statistical significance (Fig. 4).

Discussion

To our knowledge, this is the first report to confirm the feasibility of MRI to quantitatively assess carotid artery ER and to demonstrate a relationship between the extent of ER and ischemic symptoms. The role of ER in atherosclerotic arterial disease has been extensively investigated

FIG. 4. Expansive remodeling ratios of symptomatic and asymptomatic patients according to the percentage of luminal stenosis of the ICA. The ER ratios for symptomatic patients were 1.93 ± 0.54 (CA stenosis < 50%), 1.93 ± 0.54 (50%–70%), 1.90 ± 0.139 (71%–80%), and 1.93 ± 0.33 (> 81%), whereas those for asymptomatic patients were 1.54 ± 0.27 (50%–70%), 1.56 ± 0.37 (71%–80%), and 1.67 ± 0.30 (> 81%). It should be noted that the ER ratio of symptomatic patients was consistently high, regardless of the CA stenosis rate.

in the coronary circulation, and quantification of ER has been performed predominantly using intravascular ultrasonography.^{2,14,23} However, few studies pertaining to carotid artery ER have been reported and the clinical significance of carotid artery ER remains to be established.^{13,21} Long-axis, high-resolution MRI³³ was applied to measurement of the carotid artery ER ratio in the present study using the method of stenosis assessment in NASCET,¹⁰ because a simple, minimally invasive screening modality is needed for the detection of CA vulnerable plaque. There is an inherent difference between coronary artery and CA vasculature, namely, the CA has a normally expanded segment of the carotid bulb, and we first compared the ER ratio of the atherosclerotic ICA with physiological expansion (control ER ratio) in patients with unilateral ICA stenosis and confirmed that the ER ratio of the affected ICA was significantly larger than the control ER ratio (Fig. 2).

The ER ratio in this study was significantly higher in symptomatic than asymptomatic patients, while there was some overlap between them (Fig. 3). Our results agree with those of Hardie et al.¹³ and Miura et al.²¹ who both reported a relationship between ER and symptoms in CA atherosclerosis evaluated by multidetector CT angiography. Moreover, we demonstrated that the ER ratio in symptomatic patients was consistently elevated regardless of stenosis rate, whereas that of asymptomatic patients tended to increase accordingly with the luminal stenosis rate (Fig. 4). Our data suggest that there is an essential difference in the mechanism for plaque progression when comparing vulnerable with stable plaques, and the ER ratio is more important than the stenosis rate for the early diagnosis of high-risk plaque requiring CA intervention. Postmortem histological studies in the coronary circulation have demonstrated that plaques with ER have a significantly larger lipid core, contain more macrophages, and have an enhanced activity of matrix metalloproteinases compared with negative remodeling plaques.^{19,24,31} Also, in a basic study of macrophage-rich CAs that developed in apolipoprotein E knockout mice, Ivan et al.¹⁵ found that macrophages facilitate ER through increased matrix degradation by matrix metalloproteinases. Although the precise mechanism responsible for ER remains to be elucidated, the results of these previous studies have consistently shown that there is a close relationship between ER and an inflamed plaque at high risk of rupture.

The benefit of CEA for moderate- to high-grade stenosis in patients with symptomatic and asymptomatic CA stenosis has been established in several previous multicenter trials.^{4,9,32} The effectiveness of CAS has also been established as a useful alternative to CEA in a recent large clinical trial.⁶ However, risk stratification for stroke and the need for CA intervention in these randomized trials was based merely on the percentage of luminal stenosis, whereas recent progress in vascular biology^{7,22} and the development of vessel wall imaging^{3,18,26} have proven that plaque characteristics and morphology, as well as the severity of stenosis, have a significant influence on the ischemic event rate. For example, Takaya et al. conducted a prospective study in asymptomatic patients with 50%–79% CA stenosis and examined the relationship between baseline CA plaque features identified by MRI and the subse-

quent CA ischemic events.²⁹ This prospective assessment with MRI demonstrated that thinned or ruptured fibrous caps, intraplaque hemorrhage, larger maximum lipid-rich necrotic cores, and larger maximum wall thickness were associated with the development of subsequent ischemic events. In addition to technical innovations for the diagnosis of vascular lesions, multifaceted medical treatment for atherosclerotic vascular disease has improved dramatically in recent years, and this has led some to call for redefining the role of CEA/CAS for stroke prevention in CA stenosis.¹ Therefore, there is a growing need for accurate detection of truly high-risk patients. The ER ratio in the CA determined by MRI might contribute to more rigorous risk stratification of patients for cerebral ischemic events. As plaque instability is not merely a local vascular occurrence, but also exists simultaneously at multiple sites in the systemic vascular beds, the carotid artery ER ratio could be useful also for predicting other ischemic events in coronary or peripheral arteries.

In addition to MRI, there are other modalities that can be used for quantitative assessment of carotid artery ER, and one of these is catheter-based intravascular ultrasonography.²⁷ However, CA ultrasonography, multidetector CT angiography,^{13,21} and MRI are better suited for screening patients for unstable plaque in the clinical setting because they are less invasive. Ultrasonography has many methodological advantages such as noninvasiveness, ease of use, and suitability for repeated imaging. However, for the evaluation of CA circulation, ultrasonography has some limitations. Plaque with dense calcification, a CA with marked meandering, and a stenosis at a high position cannot be fully imaged on CA ultrasonography. The feasibility of CA ultrasonography for assessing the ER ratio should be tested in the future. Compared with multidetector CT angiography, MRI is superior in that it does not deliver radiation⁵ and there are no contrast-induced adverse effects.^{8,11,25} Moreover, MRI could be more accurate in demonstrating the tissue surrounding the vessel wall with high-contrast resolution and measurement of the ER ratio. In addition to the accuracy of carotid artery ER measurement, MRI—which is the only vascular imaging technique capable of detecting the presence and the age of CA intraplaque hemorrhage²⁸—can provide more precise information on the plaque components. Carotid artery ER evaluation in combination with MRI plaque characterization could reliably detect the presence of vulnerable plaque, which is subject to future investigation. On the other hand, MRI has several limitations. First, MRI requires more time for imaging and is more susceptible to motion artifacts. The spatial resolution of MRI is not as good as that of multidetector CT angiography. Second, MRI cannot be performed in patients with medical devices such as a pacemaker, or in patients who cannot lie still, as often occurs with an acute stroke. Third, MRI cannot provide an evaluation of vessel diameter due to poor image quality because of motion artifacts in approximately 5% of patients. Moreover, although the accuracy of high-resolution MRI for CA plaque characterization has been firmly established,³⁰ such accuracy has not yet been established for evaluating the vessel outer wall. Expansive remodeling assessment with MRI requires further valida-

tion by comparison studies with intraoperative vessel wall measurements and preoperative assessment of the ER ratio in patients undergoing CEA. However, the limitations in current MRI diagnosis should be overcome with technological developments such as surface coil design and stronger magnetic fields.^{16,17}

Our results have limitations inherent in the retrospective design of the study. First, it is possible that the elevated ER ratios that we found in symptomatic patients could be the result, rather than the cause, of ischemic events. A plaque with a high ER ratio in a symptomatic patient could have merely represented fresh intraplaque hemorrhage. Although this plaque may have been the embolic source, the imaging may only be a representation of previously ruptured plaque, which would undermine the potential predictive value of the ER ratio for ischemic events. Second, our results were based on a comparison between patients known to be symptomatic and those not yet symptomatic, and could not be simply used for the prediction of stroke in a prospective analysis of asymptomatic patients. Studies correlating the histology of plaque excised in CEA with the ER ratio in asymptomatic patients, and more importantly, long-term prospective studies in asymptomatic patients with early-stage CA atherosclerosis, are needed to prove the value of the ER ratio for accurate stroke risk stratification.

Conclusions

In our series of patients with CA stenosis scheduled for CEA or CAS, the degree of ER in the CA measured with long-axis, high-resolution MRI was significantly greater in symptomatic than asymptomatic patients. Moreover, the elevated ER ratio in symptomatic patients was independent of the severity of stenosis. The ER in atherosclerotic CAs might be an important indicator of vulnerable plaque, which should be validated by prospective observational study for asymptomatic patients.

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Author Contributions

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Correspondence

Kazumichi Yoshida, Department of Neurosurgery, Kyoto University Graduate School of Medicine, 54 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto 606-8507, Japan. email address: kazuy@kuhp.kyoto-u.ac.jp.