

Carotid artery plaque assessment using quantitative expansive remodeling evaluation and MRI plaque signal intensity

Yoshitaka Kurosaki, MD,¹ Kazumichi Yoshida, MD, PhD,² Ryu Fukumitsu, MD,²
Nobutake Sadamasa, MD, PhD,¹ Akira Handa, MD, PhD,¹ Masaki Chin, MD,¹ and
Sen Yamagata, MD, PhD¹

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

OBJECT Plaque characteristics and morphology are important indicators of plaque vulnerability. MRI-detected intra-plaque hemorrhage has a great effect on plaque vulnerability. Expansive remodeling, which has been considered compensatory enlargement of the arterial wall in the progression of atherosclerosis, is one of the criteria of vulnerable plaque in the coronary circulation. The purpose of this study was risk stratification of carotid artery plaque through the evaluation of quantitative expansive remodeling and MRI plaque signal intensity.

METHODS Both preoperative carotid artery T1-weighted axial and long-axis MR images of 70 patients who underwent carotid endarterectomy (CEA) or carotid artery stenting (CAS) were studied. The expansive remodeling ratio (ERR) was calculated from the ratio of the linear diameter of the artery at the thickest segment of the plaque to the diameter of the artery on the long-axis image. Relative plaque signal intensity (rSI) was also calculated from the axial image, and the patients were grouped as follows: Group A = rSI $\geq$ 1.40 and ERR $\geq$ 1.66; Group B = rSI < 1.40 and ERR $\geq$ 1.66; Group C = rSI $\geq$ 1.40 and ERR < 1.66; and Group D = rSI < 1.40 and ERR < 1.66. Ischemic events within 6 months were retrospectively evaluated in each group.

RESULTS Of the 70 patients, 17 (74%) in Group A, 6 (43%) in Group B, 7 (44%) in Group C, and 6 (35%) in Group D had ischemic events. Ischemic events were significantly more common in Group A than in Group D ($p = 0.01$).

CONCLUSIONS In the present series of patients with carotid artery stenosis scheduled for CEA or CAS, patients with plaque with a high degree of expansion of the vessel and T1 high signal intensity were at higher risk of ischemic events. The combined assessment of plaque characterization with MRI and morphological evaluation using ERR might be useful in risk stratification for carotid lesions, which should be validated by a prospective, randomized study of asymptomatic patients.

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KEY WORDS carotid artery MRI; carotid artery disease; expansive remodeling; intraplaque hemorrhage; risk stratification; vascular disorders

CAROTID artery atherosclerosis is one of the important causes of ischemic stroke. The efficacy of carotid endarterectomy (CEA) for severe symptomatic stenosis of the carotid artery has been demonstrated in several multicenter, randomized, clinical trials.^{7,8,18} Currently, the therapeutic approach for preventing future ischemic events, including CEA, carotid artery stenting (CAS), and medical treatment, is decided primarily based

on the percentage of luminal narrowing of the vessel. However, it has been shown that thromboembolic mechanisms correlate strongly with ischemic events in carotid artery stenosis.^{16,36} Thus, a method for evaluating the risk of thromboembolism might improve the ability to identify the actual high-risk patients who would benefit most from intervention. In recent studies, some investigators have reported that plaque with a lipid-rich necrotic core

ABBREVIATIONS BB = black blood; CAS = carotid artery stenting; CE = contrast enhanced; CEA = carotid endarterectomy; ERR = expansive remodeling ratio; ICA = internal carotid artery; IPH = intraplaque hemorrhage; rSI = relative plaque signal intensity; VD = vessel diameter.

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and intraplaque hemorrhage (IPH), one of the features of vulnerable plaque, can be detected as high signal intensity on carotid T1-weighted MRI^{10,35,37} and is strongly associated with ipsilateral ischemic stroke.^{1,14} Other investigators have shown that geometrical change of the artery correlates with the risk of ischemic events, and that expansive remodeling may be particularly associated with plaque instability and a high risk for ischemic events.¹² This study aimed to provide more accurate risk stratification of carotid plaque through the evaluation of quantitative expansive remodeling and MRI plaque signal intensity.

Methods

Patient Population

A total of 89 consecutive carotid stenoses in 86 patients who were scheduled to undergo CEA or CAS due to atherosclerotic carotid stenosis were included in this study. Patients who did not undergo either carotid T1-weighted axial or long-axis MR images, had poor imaging quality, had near occlusion, or had a history of CEA on the ipsilateral side were excluded. Inclusion criteria for revascularization were $\geq 70\%$ carotid stenosis or $< 70\%$ symptomatic stenosis with recurrent infarcts in the ipsilateral hemisphere refractory to maximal medical therapy.

Patient characteristics were recorded retrospectively by reviewing medical records. Ischemic events ipsilateral to the carotid artery within the previous 6 months were recorded, including cerebral infarction, transient ischemic attack, and retinal ischemia (amaurosis fugax and retinal artery occlusion). The severity of carotid stenosis was evaluated by digital subtraction angiography using the North American Symptomatic Trial (NASCET) collaborators' criteria.¹⁸ The hospital ethics committee approved the study, and written informed consent was obtained from all patients.

Imaging Techniques

Carotid artery MRI was performed using a 1.5-T MRI machine (Gyrosan Intera; Philips Medical Systems) equipped with an 8-cm-diameter surface coil. A previously published standardized protocol was used to obtain black-blood (BB) T1-weighted axial and long-axis images of the carotid arteries, including the area with the highest stenosis on the index side.^{33,35} The parameters for the imaging sequences were as follows: 1) long-axis T1-weighted images (3D inversion recovery [IR] turbo field echo): TR 10 msec; TE 2.7 msec; inversion time (TI) 500 msec; flip angle (FA) 35°; 320 × 512 matrix; 1.6-mm section thickness; 150-mm FOV; 2) axial T1-weighted images (2D double IR-turbo spin-echo images): TR 700–1000 msec; TE 12 msec; FA 110°; 256 × 256 matrix; 3-mm section thickness; 150-mm FOV; and TR, 1 cardiac cycle. Fat suppression was used to reduce signals from subcutaneous fat. All patients underwent BB-MRI within 2 weeks before surgery.

MRI Signal Intensity

Signal intensities of plaque and the proximal sternocleidomastoid muscle on T1-weighted axial MR images were measured at a workstation by a colleague (K.Y. or R.F.)

who was blinded to patient information. Relative MRI signal intensity was calculated with the following formula (Fig. 1):³⁵ $rSI = SI_{\text{whole plaque}} / SI_{\text{SCM}}$, in which rSI represents relative plaque signal intensity, SI represents signal intensity, and SCM represents sternocleidomastoid muscle. With reference to the previous study,³⁵ an $rSI \geq 1.40$, which corresponds to the lipid core with IPH, was defined as hyperintense plaque.

Expansive Remodeling Ratio

We have previously reported about the expansive remodeling ratio (ERR).³⁴ The measurement technique for the ERR was developed by applying the method used in NASCET to evaluate stenosis.¹⁸ The ERR was calculated using long-axis BB-MRI and the following formula (Fig. 2): $ERR = \text{the maximum distance between the lumen and the outer borders of the plaque perpendicular to the axis of the internal carotid artery (ICA) (stenotic ICA vessel diameter [VD])} / \text{the maximal luminal diameter of the distal ICA at a region unaffected by atherosclerosis [distal ICA VD]}$.

In our previous study about the ERR, the control ERR measured in the contralateral nonatherosclerotic ICA in patients with unilateral carotid artery stenosis was reported.³⁴ The control ERR (mean $\pm$ SD) was 1.36 ± 0.15 . Two SDs of the mean control ERR, 1.66 or more, was defined as high ERR.

Relationships Between MRI Signal Intensity, ERR, and Symptoms

Based on whether patients had hyperintense plaque and high ERR, the patients were grouped as follows: Group A = $rSI \geq 1.40$ and $ERR \geq 1.66$; Group B = $rSI < 1.40$ and

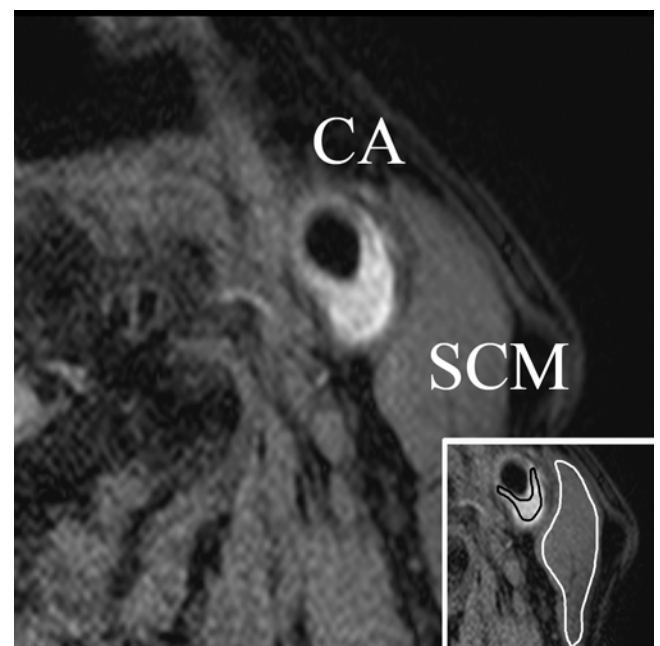


FIG. 1. Measurement of rSI in the carotid artery (CA) using axial, high-resolution MRI. The rSI is measured with the region of interest drawn over the whole plaque except for the lumen with reference to the sternocleidomastoid muscle (SCM). The rSI in this symptomatic patient is 1.73.

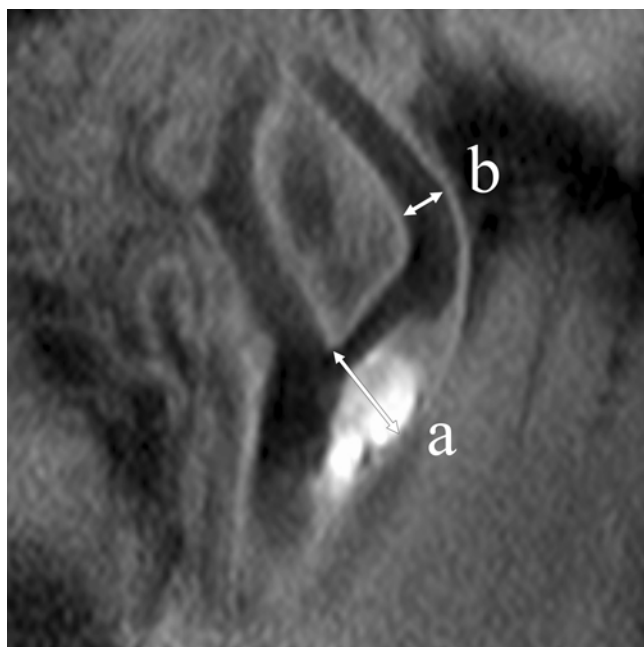


FIG. 2. Measurement of the ERR in the carotid artery using long-axis, high-resolution MRI. The ERR is calculated as the ratio of the maximal outside diameter of the atherosclerotic ICA near the carotid bulb (a) and the maximal outside diameter of the ICA well beyond the plaque (b). The ERR in this symptomatic patient is 2.79.

ERR ≥ 1.66 ; Group C = rSI ≥ 1.40 and ERR < 1.66 ; and Group D = rSI < 1.40 and ERR < 1.66 . Ipsilateral ischemic events within 6 months were retrospectively evaluated in each group.

Statistical Analysis

All statistical analyses were performed using SPSS for Windows (version 17.0, SPSS Inc.). Differences in the age of the baseline characteristics of each group were analyzed by the Kruskal-Wallis test, while differences in sex and risk factors were analyzed using the chi-square for independence test. The differences in the stenosis rate, rSI, and ERR between groups were analyzed using the Kruskal-Wallis test, using 1-way ANOVA for the distal ICA VD and stenotic ICA VD. The chi-square test for independence was used to assess the relationship between group and ischemic events within 6 months. The level of significance was established at $p < 0.05$.

Results

Of the 89 patients, 8 did not undergo MRI, 3 had studies of poor imaging quality, 5 had near occlusion, 2 had restenosis after CEA, and 1 had plaque confirmed in the common carotid artery, leaving 70 patients for evaluation. Of these 70 patients, Group A had 23 patients, Group B had 14, Group C had 16, and Group D had 17 (Fig. 3). Except for hypertension, no significant differences existed in baseline characteristics among the groups (Table 1).

The stenosis rate was $65.1\% \pm 25.1\%$ in Group A, $81.7\% \pm 9.4\%$ in Group B, $66.8\% \pm 17.6\%$ in Group C, and $74.5\% \pm 11.5\%$ in Group D (Table 2). The stenosis rate differed significantly among the 4 groups, with the lowest rate in

Group A. The rSI was 1.68 ± 0.24 in Group A; 1.22 ± 0.10 in Group B; 1.69 ± 0.21 in Group C; and 1.14 ± 0.15 in Group D. The rSI also differed significantly among the 4 groups. The ERR was 2.14 ± 0.31 in Group A; 1.96 ± 0.19 in Group B; 1.43 ± 0.16 in Group C; and 1.41 ± 0.98 in Group D. The ERR also differed significantly among the 4 groups (Table 2).

The relationship between group and patients with an ipsilateral ischemic event within 6 months was examined. The number of patients with ipsilateral ischemic events within 6 months was 17 (73%) in Group A, 6 (43%) in Group B, 7 (44%) in Group C, and 6 (35%) in Group D. There were significantly more ipsilateral ischemic events in Group A than in Group D ($p = 0.01$), and the number of patients with ipsilateral ischemic events was relatively higher in Group A than in Groups B ($p = 0.058$) and C ($p = 0.056$; Fig. 4).

Discussion

The results of the present study demonstrated a relationship between the extent of expansive remodeling and plaque signal intensity rSI and the presence of symptoms. In the present study, patients with a high degree of expansion of the vessel, a T1 high-signal-intensity plaque, and IPH were more likely to have ischemic events within 6 months. These results indicate the potential contribution of the combined assessment of morphological evaluation using ERR and plaque characterization with rSI for the prediction of a patient's risk for a future stroke. Patients with higher ERR and IPH may be at high risk for cerebral infarction. The combined assessment of ERR and plaque signal intensity rSI could be useful in risk stratification for carotid lesions.

Recent vascular biology studies have indicated that plaque vulnerability is an important risk factor for ischemic events.³ Various evaluation methods for plaque vulnerability have been reported;^{11,23,28} evaluation using signal intensity on carotid artery MRI is also used in clinical practice^{14,25} and is useful for identification of high-risk lesions.^{13,19} Recent technological developments in MRI equipment and imaging sequencing make it possible to assess the carotid plaque components.³⁵ In particular, IPH, which is a characteristic component of vulnerable plaque, was detected as high signal intensity on T1-weighted imaging, and it confers higher risk for ischemic events than its absence in both symptomatic¹ and asymptomatic²⁹ patients. However, plaque vulnerability depends on not only the plaque components, but also other factors, such as plaque volume and plaque morphology.¹⁷ Therefore, more accurate risk assessment would be possible by adding evaluation of these factors.

Expansive vascular remodeling is a morphological change in the artery⁹ and has been considered one of the criteria for vulnerable plaque in the coronary arteries.²⁰ Plaque with expansive remodeling has been shown to have a significantly larger lipid core and higher macrophage count than negatively or less positively remodeled plaque.³¹ Recent studies have also shown that expansive carotid remodeling was associated with low endothelial stress and plaque rupture^{4,5} and was significantly greater in patients

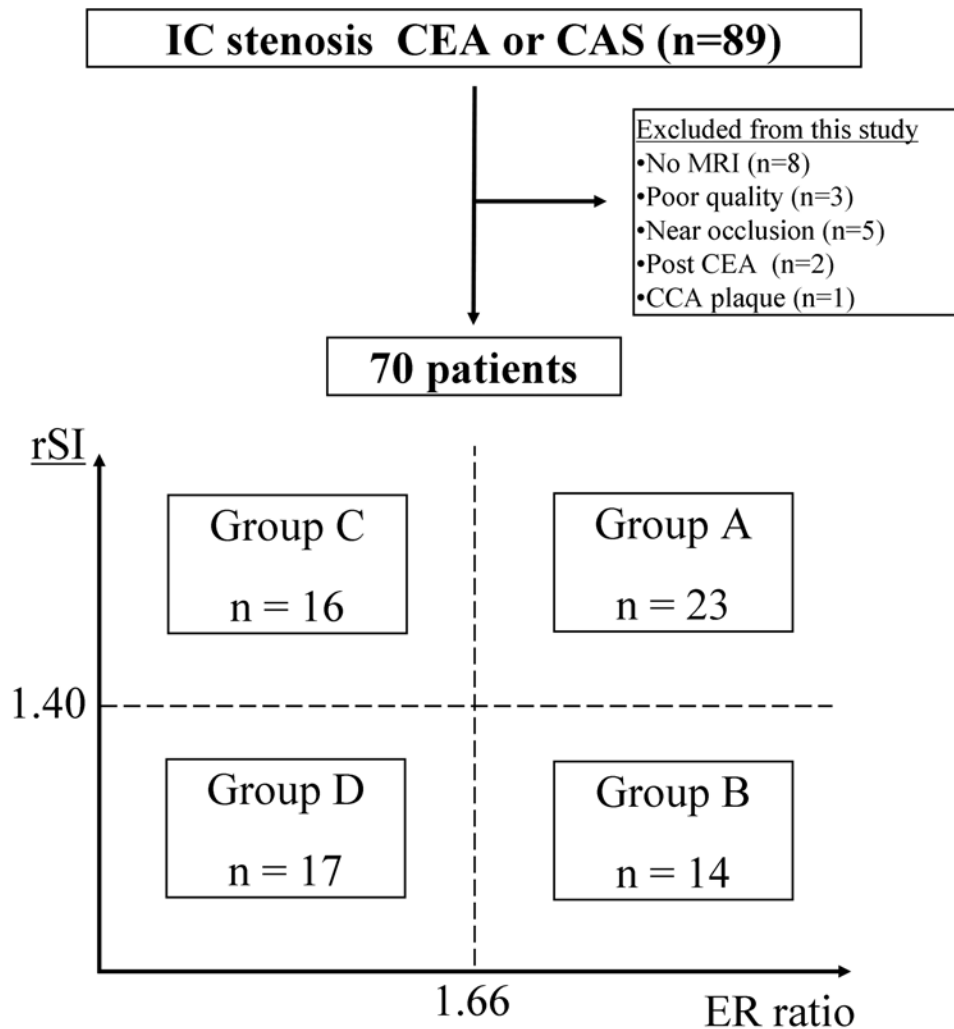


FIG. 3. Grouping based on rSI and ERR.

with cerebral ischemic symptoms than in asymptomatic patients.¹² Therefore, we hypothesize that evaluation with plaque signal intensity and expansive remodeling is useful for identifying higher-risk lesions. In fact, in the present series of patients scheduled for CEA and CAS, ischemic

events within 6 months were significantly higher in patients with IPH and expansive remodeling than in patients without IPH and expansive remodeling.

Concerning factors related to vulnerability of carotid plaque, other important markers are plaque cap thickness and inflammation.¹⁷ The fibrous cap is a layer of connective tissue separating the lipid-rich necrotic core (which includes IPH) of the atherosclerotic plaque from the carotid artery lumen. With rupture of fibrous caps, plaque components are exposed to flowing blood, which may result in arterial thrombus formation, thus leading to ischemic events.²⁷ A thin or ruptured fibrous cap is the strongest risk factor for ipsilateral ischemic events.⁸ Thus, an assessment method that includes evaluation of fibrous cap status may enable more accurate risk stratification. Noninvasive options including contrast-enhanced (CE) MRI,² ultrasonography,⁶ and CT³² have been investigated to assess fibrous cap integrity, but inadequate spatial resolution remains a problem. A combination of minimum cap thickness < 200 μ m and a representative cap thickness < 500 μ m identified ruptured plaques most reliably,²¹ but spatial resolution of CE MRI is 390 $\times$ 390 μ m and in-plane resolutions of ultrasonography and CT are 300

TABLE 1. Patient characteristics by group*

Characteristic	Group A	Group B	Group C	Group D	p Value
No. of patients	23	14	16	17	
Mean age (yrs)	74.4	72.9	72.7	72.2	0.3
Females	3 (13)	3 (21)	1 (6)	1 (5)	0.4
Hypertension	22 (95)	10 (71)	13 (81)	17 (100)	0.04
Diabetes mellitus	7 (30)	2 (14)	6 (37)	4 (23)	0.5
Hyperlipidemia	14 (60)	5 (35)	10 (62)	12 (70)	0.2
Smoking	6 (26)	6 (42)	9 (56)	8 (47)	0.2
Ischemic heart disease	7 (30)	4 (28)	3 (18)	7 (41)	0.5

* Data are shown as number (%) of patients unless otherwise indicated. Group A = rSI $\geq$ 1.40 and ERR $\geq$ 1.66; Group B = rSI < 1.40 and ERR $\geq$ 1.66; Group C = rSI $\geq$ 1.40 and ERR < 1.66; and Group D = rSI < 1.40 and ERR < 1.66.

TABLE 2. rSI and ERR by group*

Variable	Group A	Group B	Group C	Group D	p Value†
No. of patients	23	14	16	17	
Stenosis rate (%)	65.1 ± 25.1	81.7 ± 9.4	66.8 ± 17.6	74.5 ± 11.5	0.03
rSI	1.68 ± 0.24	1.22 ± 0.10	1.69 ± 0.21	1.14 ± 0.19	<0.001
ERR	2.14 ± 0.31	1.96 ± 0.19	1.43 ± 0.16	1.41 ± 0.15	<0.001
Distal ICA VD (mm)	4.07 ± 0.66	4.02 ± 0.80	4.64 ± 0.56	4.87 ± 0.98	0.002
Stenotic ICA VD (mm)	8.64 ± 1.27	7.95 ± 1.99	6.63 ± 1.08	6.83 ± 1.19	<0.001

* Values are presented as the mean ± SD.

† Boldface values are statistically significant ($p \leq 0.05$).

× 400 μm and 500 × 500 μm , respectively.¹⁵ Improved diagnostic technology offers the hope of more accurate prediction of carotid artery disease risk.

Inflammation of plaque may also play an important role in plaque vulnerability.²² Inflamed plaques may readily cause artery-to-artery thromboembolism through plaque rupture.¹⁵ Noninvasive options, including CE MRI²⁶ and 18F-fluorodeoxyglucose (FDG) PET,³⁰ have been investigated to assess the degree of inflammation. Tawakol et al.³⁰ demonstrated that FDG-PET can determine the macrophage content of carotid plaques in vivo. Furthermore, others demonstrated that a combination of FDG-PET and MRI is complementary in identifying high-risk carotid plaques with inflamed or hemorrhagic components.²⁴ FDG-PET may be useful for noninvasively identifying macrophage-rich carotid plaques. Furthermore, its combination with carotid artery MRI may provide more useful information on plaque composition. However, it would be difficult to routinely perform a dual PET/MRI examination because of cost. In addition, dual PET/MRI needs longer imaging time, because it involves different kinds of modalities. On the other hand, the present assessment of ERR and rSI can be obtained simply and rapidly from the same modality, carotid BB-MRI. Therefore, this combination method is a good candidate for routine imaging

evaluation of carotid disease, especially for asymptomatic patients, and it may make it possible to select truly nonstenotic high-risk lesions such as mild carotid stenosis with expansive remodeling and high-volume plaque,³⁶ which would not be identified for intervention by the current stenosis-based method.

Limitations of the Study

The limitations of this study include its small sample size and its retrospective nature. Some selection bias may have been introduced by having study patients who were scheduled to have CEA or CAS. Therefore, it appears that patients with a higher ERR and greater hyperintensity were more likely to have reported symptoms prior to revascularization, but this does not mean that expansive remodeling or rSI can be used to predict future events in an entirely asymptomatic and unselected population. In addition, because most studies about the relationship between expansive remodeling and ischemic events were retrospective, it is not clear that expansive remodeling truly causes ischemic events. A plaque with a high ERR in a symptomatic patient could merely represent fresh IPH. It is possible that expansive remodeling could be the result of rapid growth of IPH at the ischemic event. However, in the present study, even with IPH, the number of symptomatic plaques in Group A, accompanied by high ERR, was higher than that in Group C, which was not accompanied by high ERR. This result might demonstrate the potential predictive value of the ERR for ischemic events.

Next, one possible limitation is the threshold of ERR. A high value was defined as 2 standard deviations (1.66) or more of the mean control ERR (1.36), which was calculated from normal carotid arteries without stenosis in our previous study.³⁴ In the same previous study, the mean ERR of patients with carotid stenosis was 1.68 ± 0.40 , and the receiver-operating characteristic analysis found that when the cutoff value of ERR was set at 1.88, the sensitivity and specificity for the detection of ischemic symptom were 0.6 and 0.78, respectively. If the cutoff value of ERR was set at 1.88 in the present study, the number of patients with ischemic events within 6 months was also significantly higher in Group A ($rSI \geq 1.4$ and $ERR \geq 1.88$) than in Group D ($rSI < 1.4$ and $ERR < 1.88$; $p = 0.01$). Thus, assessment of dual plaque signal intensity and quantitative remodeling evaluation may be reasonable, but the cutoff value of ERR remains to be elucidated. To investigate the usefulness of the combined assessment of ERR

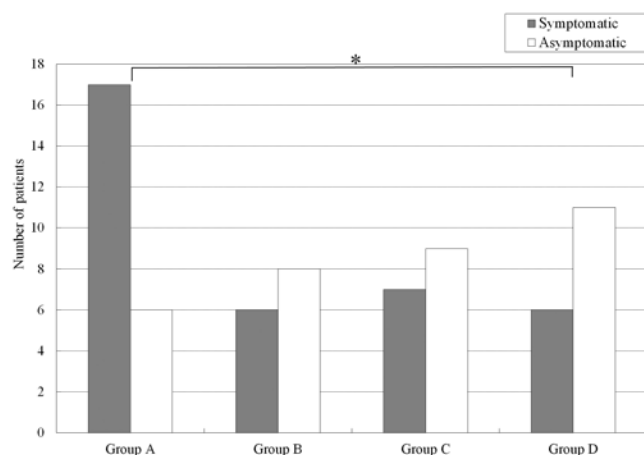


FIG. 4. Relationships among the 4 groups with respect to the numbers of patients with ipsilateral ischemic events within 6 months. The number of patients with ipsilateral ischemic events was significantly higher in Group A than in Group D ($p = 0.01$), and it was relatively higher in Group A than in Groups B ($p = 0.058$) and C ($p = 0.056$).

and plaque signal intensity for accurate stroke risk stratification, a long-term prospective study, including asymptomatic patients with early-stage carotid atherosclerosis, should be performed.

Conclusions

In the present series of carotid artery plaque scheduled for CEA or CAS, plaque with a high degree of expansion of the vessel and T1 high signal intensity was at higher risk of causing ischemic events. These findings suggest that the combination of quantitative expansive remodeling evaluation and rSI with MRI might noninvasively contribute to more accurate risk stratification, but this does not mean that expansive remodeling or plaque signal intensity can be used to predict future events in an entirely asymptomatic and unselected population. To investigate the predictive value of ERR and plaque signal intensity for future ischemic events, a prospective study, including asymptomatic patients with early-stage carotid atherosclerosis, should be performed.

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Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Kurosaki. Acquisition of data: Kurosaki, Yoshida, Fukumitsu, Handa. Analysis and interpretation of data: Kurosaki. Drafting the article: Kurosaki. Critically revising the article: Yoshida. Reviewed submitted version of manuscript: Yoshida, Sadamasa, Chin. Study supervision: Sadamasa, Chin, Yamagata.

Correspondence

Yoshitaka Kurosaki, Department of Neurosurgery, Kurashiki Central Hospital, 1-1-1 Miwa, Kurashiki City, Okayama 710-8602, Japan. email: kurosaki0106@gmail.com.

Asymptomatic Carotid T1-High-Intense Plaque as a Risk Factor for a Subsequent Cerebrovascular Ischemic Event

Yoshitaka Kurosaki^a Kazumichi Yoshida^b Hitoshi Fukuda^a Akira Handa^a
Masaki Chin^a Sen Yamagata^a

^aDepartment of Neurosurgery, Kurashiki Central Hospital, Kurashiki, and ^bDepartment of Neurosurgery, Kyoto University School of Medicine, Kyoto, Japan

Keywords

Carotid MRI · Carotid artery disease · Intraplaque hemorrhage

Abstract

Background: Intraplaque hemorrhage, detected as a high-signal intensity on carotid MRI, is also strongly associated with ischemic events in symptomatic patients. However, in asymptomatic patients, the relationship of the T1-high intense plaque and the subsequent stroke is not clear. The aim of this study is to test the hypothesis that asymptomatic carotid T1-high intense plaque is a risk factor for a subsequent cerebrovascular ischemic event. **Methods:** Of the 1,353 consecutive patients, who underwent head and carotid MRI as part of their annual medical check-up, the imaging quality of 13 was poor and 150 did not present for follow-up examination, thus leaving 1,190 subjects for evaluation. Of the 1,190 patients, 96 patients had findings of high-signal intensity on carotid MRI and 1,094 patients did not. Cerebrovascular events were retrospectively evaluated. **Results:** During a mean follow-up period of 53 months, 4 patients with high-signal intensities on carotid MRI (4%) and 3 with no findings (0.3%) had a cerebrovascular ischemic event, with the occurrences significantly higher in the high-signal-intensity group. ($p < 0.01$) Cox regression analysis indicated

that the presence of the high-intense plaque on carotid MRI (hazard ratio [HR] 4.2; 95% CI 1.0–17.1; $p = 0.04$), age (HR 1.1; 95% CI 1.0–1.2; $p = 0.003$), and diabetes mellitus (HR 7.2; 95% CI 1.8–27.4; $p = 0.004$) were associated with the occurrence of subsequent ischemic cerebrovascular events. **Conclusions:** Asymptomatic carotid T1-high-intense plaque might be a potential high-risk factor for a subsequent cerebrovascular ischemic event.

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Introduction

The risk assessment in primary prevention of stroke is widely considered to be important. Risk assessment is usually based on vascular risk factors, but these systematic factors have a limited predictive value [1].

Recent technological developments in MRI equipment and imaging sequencing make it possible to assess the plaque components [2]. The evaluation of local atherosclerotic plaque is gaining attention as a new approach to identify patients who are at high risk of ischemic events [3]. In particular, intraplaque hemorrhage (IPH), which is detected as a high-signal intensity on T1-weighted imaging, is a characteristic component of vulnerable plaque [4] and confers higher risk for ischemic events in symptomatic pa-

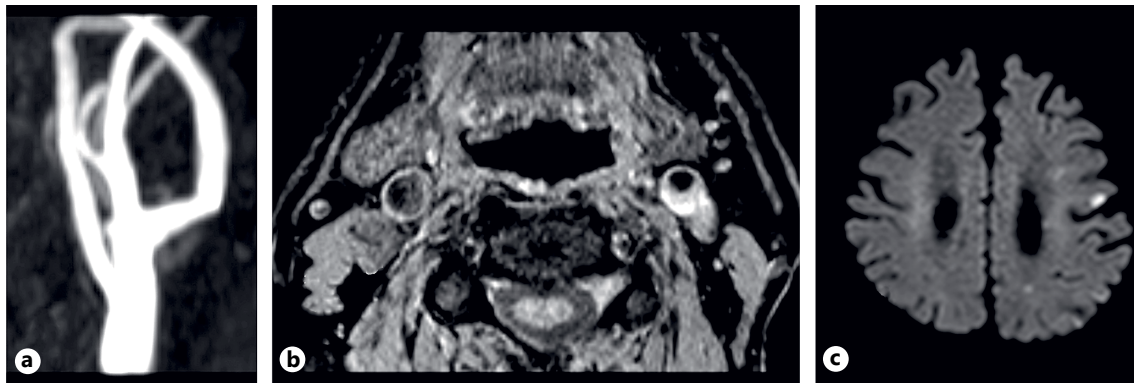


Fig. 1. An example of the carotid MRI. **a** Magnetic resonance angiography time-of-flight image through the carotid bifurcation reveals mild stenosis. **b** Axial carotid magnetic resonance image

demonstrates a hyperintense left carotid plaque. **c** Four years later, diffusion-weighted imaging revealed left-cerebral infarction.

tients [5]. If IPH is a risk factor for an ischemic event, we can hypothesize that the presence of IPH in asymptomatic patients indicates an advanced state of atherosclerosis. The aim of this study is to test the hypothesis that asymptomatic carotid T1-high-intense plaque is a risk factor for a subsequent cerebrovascular ischemic event.

Materials and Methods

We investigated 1,353 consecutive patients who underwent head and carotid MRI as part of an annual medical checkup, which is optional and not covered by public health insurance, in the Kurashiki Central Hospital. Patients with imaging of a poor quality, or those who had no follow-up history at the Kurashiki Central Hospital after medical checkup were excluded. Among these patients, subsequent cerebrovascular events (ischemic events, intracerebral hemorrhage, and subarachnoid hemorrhage) were retrospectively evaluated in patients with hyperintensities on carotid MRI (the high-signal-intensity group) and in those with no findings (the non-high-signal-intensity group) following the approval of the hospital ethics committee.

Risk Factors

The Kurashiki Central Hospital annual medical check-up program included an interview and physical examination performed by a physician, with venous blood samples obtained in the morning after a 12-h fast. All patients were given lifestyle advice based on the results by a physician and referred to the primary care physician for any needed treatment as clinically indicated.

Imaging

Carotid MRI was performed with a 1.5-T MRI scanner (Gyrosan Intera; Philips Medical Systems) using a Synergy neck/head coil and the following imaging parameters: field of view, 220 mm; matrix size, 179×256 ; repetition/echo time, 30/5.8 ms; flip angle, 20 degrees; and slice thickness, 3.0 mm. Carotid plaque sig-

nal intensity was evaluated using the proximal sternocleidomastoid muscle as a reference. A relative signal intensity of 1.25 or more was defined as positive (Fig. 1).

Statistical Analysis

Numerical data were expressed as means $\pm$ SD 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. Event-free survival rates in the high-signal-intensity and non-high-signal-intensity groups were calculated using the Kaplan-Meier analysis.

Cox proportional hazards modeling was performed to analyze the association of the time to a cerebrovascular event with carotid artery characteristics as ascertained by MRI and other risk factors. Only univariate analyses (using one independent variable) were included in the Cox regression model. The hazard ratios (HRs) with a 95% CI were determined using the Cox regression analysis. Decision-tree analysis was performed to effectively stratify the risk of cerebrovascular ischemic events by a combination of multiple predictors, using the chi-square automatic interaction detector (CHAID) method. The probability of freedom from ischemic events was estimated using the Kaplan-Meier method; comparisons of survival curves by the stratified risk groups were performed using the log-rank test. Differences were considered statistically significant at the *p* value <0.05 . Commercially available software (SPSS version 22, IBM Corp. Armonk, NY, USA) was used for all statistical analyses.

Results

Of the 1,353 patients, 13 had imaging of a poor quality and 150 had no history of follow-up consultation, leaving 1,190 patients for evaluation. Of the 1,190 patients, 96 patients had findings of high-signal intensity on carotid MRI (8.1%, right side 47, left side 43, bilateral 6) and 1,094 patients did not. There was no significant difference in

Table 1. Baseline characteristics of this study participants with and without carotid MRI hyperintense plaque

	Without MRI-IPH (<i>n</i> = 1,094)	With MRI-IPH (<i>n</i> = 96)	<i>p</i> value
Anthropometric variables			
Male	655 (60)	68 (71)	0.038
Age, years	55.6±9.7	58.9±9.5	0.0016
BMI, kg/m ²	23.2±3.2	23.0±3.0	0.4
Systolic blood pressure, mm Hg	122.2±17.5	124.0±17.5	0.4
Diastolic blood pressure, mm Hg	75.7±10.9	76.2±10.3	0.7
Biochemical markers			
HDL cholesterol, mmol/L	1.50±0.38	1.47±0.40	0.4
LDL cholesterol, mmol/L	3.10±0.74	3.00±0.72	0.1
Triglycerides, mmol/L	2.93±1.82	2.91±1.60	0.9
HbA1c, %	5.2±0.7	5.1±0.5	0.2
Creatinine, μmol/L	67±14	68±13	0.2
Personal history			
Hypercholesterolemia	589 (54)	45 (47)	0.2
Diabetes	96 (8)	8 (8)	1
Hypertension	363 (33)	38 (40)	0.2
Therapies			
Hypertension medication	237 (21)	27 (28)	0.2
Hypercholesterolemia medication	112 (10)	7 (7)	0.5
Diabetes medication	53 (5)	6 (6)	0.5

BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HbA1c, hemoglobin A1c.

the baseline characteristics between the high-signal-intensity group and non-high-signal-intensity group, except the mean age and number of males (Table 1).

The mean follow-up period of the high-signal-intensity group and non-high-signal-intensity group were 52.8 and 51.6 months, respectively. During the follow-up period, cerebrovascular events were observed in 16 patients (cerebral hemorrhage, 3; subarachnoid hemorrhage, 2; cerebral infarction, 10; transient ischemic attack, 1). Four patients with high-intense plaque on carotid MRI (4%) and 3 with no findings (0.3%) had a cerebrovascular ischemic event; the occurrence of ischemic event was significantly higher in the high-signal-intensity group than in the non-high-signal-intensity group ($p < 0.01$). Kaplan–Meier analysis showed a significantly lower event-free survival rate in the high-signal-intensity group (log-rank test = 11.2, $p = 0.0008$; Fig. 2). Ischemic event caused by a carotid lesion occurred in 3 patients. This included 2 high-signal-intensity patients and 1 non-high-signal-intensity patient.

Cox regression analysis indicated that the high-intense plaque on carotid MRI (HR 4.2; 95% CI 1.0–17.1; $p = 0.04$), age (HR 1.1; 95% CI 1.0–1.2; $p = 0.003$), and diabetes mellitus (HR 7.2; 95% CI 1.8–27.4; $p = 0.004$) were as-

sociated with the development of subsequent ischemic cerebrovascular events (Table 2). The CHAID method with ischemic event as the dependent variable revealed that diabetes mellitus was the primary risk factor. In cases with diabetes mellitus, the high-intense plaque on carotid MRI was the secondary risk factor for the ischemic event (Fig. 3a). Accordingly, the risk of ischemic event was stratified into 3 groups; low risk (without diabetes mellitus, $n = 1,086$), medium risk (carotid MRI non-high-signal intensity but with diabetes mellitus, $n = 96$), and high risk (with diabetes mellitus and carotid MRI high-signal intensity, $n = 8$). There was a significant difference in freedom from the ischemic event among these stratified groups (Fig. 3b, Kaplan–Meier method and log-rank test).

Discussion

The relation between carotid artery and subsequent stroke has several implications. Several studies have reported about carotid intima-media thickness (IMT) evaluated by carotid echography [6]. Some studies targeted patients with severe stenosis or high vascular risk factors,

Table 2. Relationship between risk factors and ischemic cerebrovascular event

	Risk of ischemic event	
	univariate, HR (95% CI)	multivariate, HR (95% CI)
With MRI-IPH	6.2 (1.8–21.4)	4.2 (1.0–17.1)
Male	6.0 (0.8–47.2)	
Age	1.1 (1.0–1.2)	1.1 (1.0–1.2)
BMI	0.9 (0.8–1.2)	
Hypertension	5.3 (1.4–20.1)	ns
Systolic blood pressure	1.0 (0.9–1.0)	
Diastolic blood pressure	1.0 (0.9–1.0)	
Hypertension medication	4.1 (1.3–13.7)	
Hypercholesterolemia	1.6 (0.5–5.3)	
HDL cholesterol	0.97 (0.92–1.01)	
LDL cholesterol	0.97 (0.95–0.99)	ns
Triglycerides	1.0 (0.9–1.0)	
Hypercholesterolemia medication	3.4 (0.8–12.6)	
Diabetes	13.5 (4.1–44.2)	7.2 (1.8–27.4)
HbA1c	1.8 (1.2–2.6)	
Diabetes medication	16.7 (5.1–55.0)	
Creatinine	2.3 (0.09–57.5)	

BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HbA1c, hemoglobin A1c; ns, not significant.

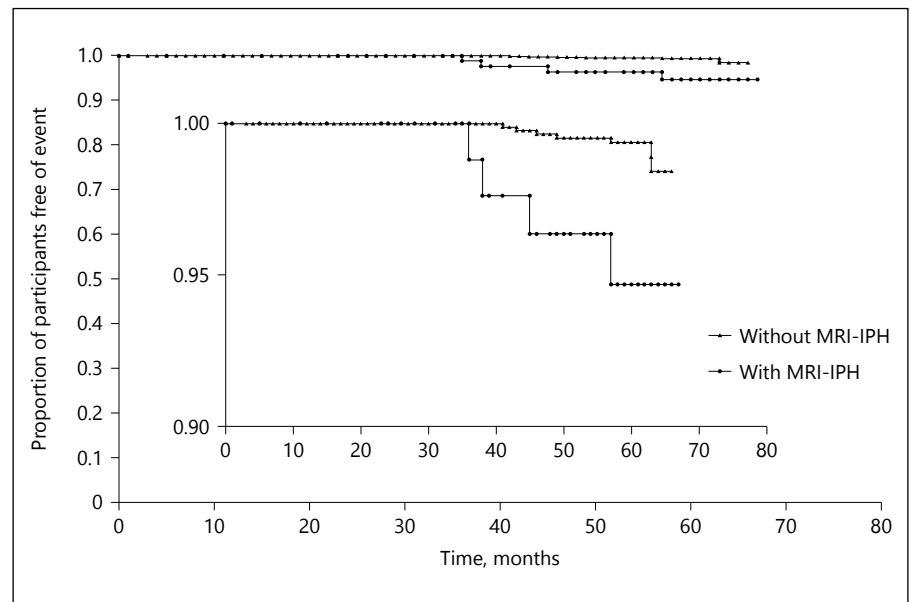


Fig. 2. Kaplan–Meier survival estimates of the proportion of participants remaining free of ischemic cerebrovascular events in the carotid MRI high-signal-intensity and non-high-signal-intensity group (log-rank test = 11.2, $p = 0.0008$).

demonstrating a relationship between IMT and subsequent stroke [7, 8]. However, another study that targeted those with a low vascular risk, could not demonstrate the predictive value of IMT [9]. Recently, plaque evaluation is of current interest as a different approach for the pre-

diction of the cerebrovascular events. IPH is a characteristic of vulnerable plaque [4], which is detected as a high-signal intensity on T1-weighted imaging [10, 11], and it confers a higher risk for ipsilateral ischemic events than its absence in both symptomatic and asymptomatic pa-

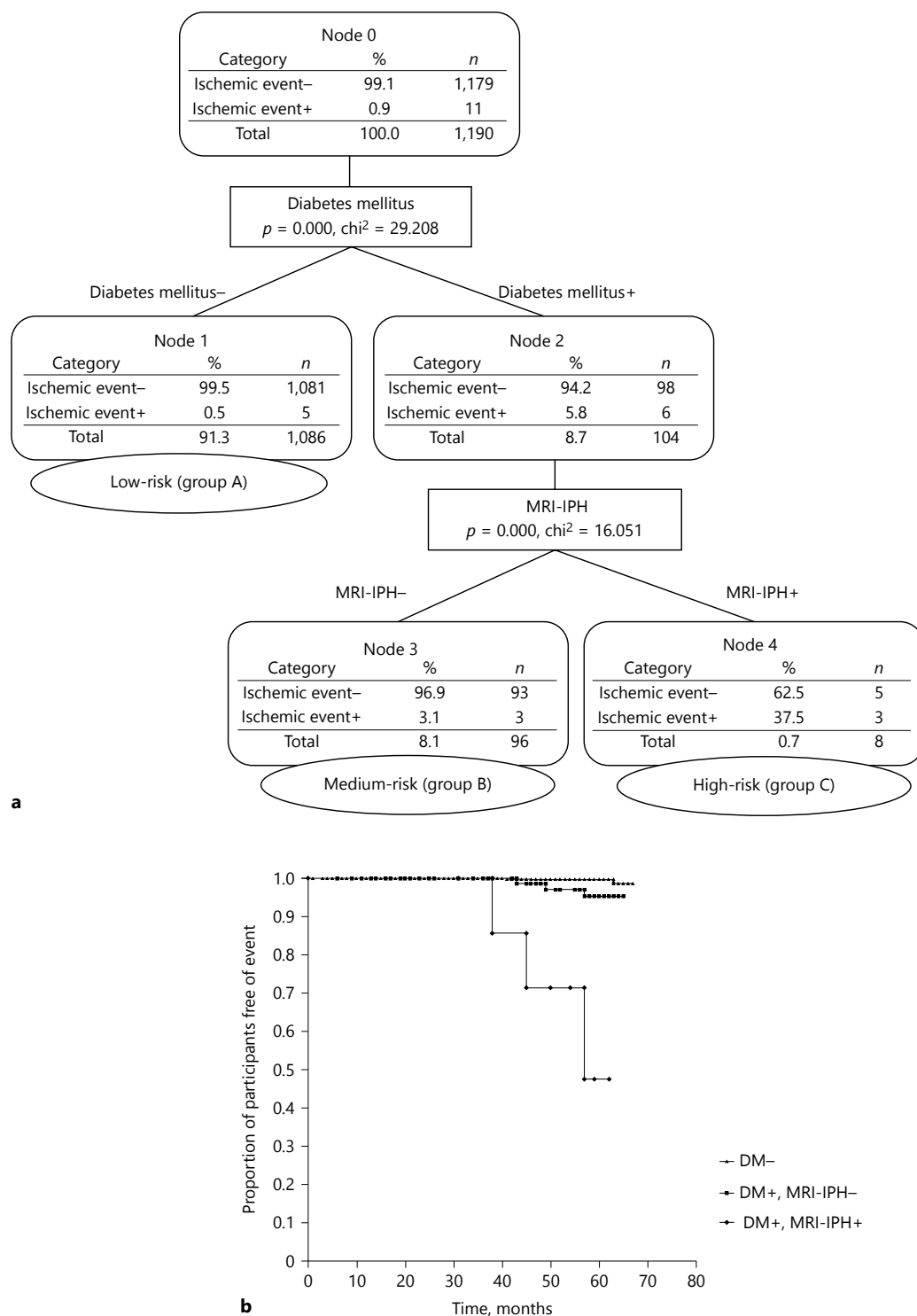


Fig. 3. a Decision-tree analysis to stratify the risk of subsequent ischemic event by a combination of multiple predictors. Those with neither diabetes mellitus nor carotid high-intense plaque, those without carotid high-intense plaque but with diabetes mellitus, and those with diabetes mellitus and carotid high-intense

plaque were categorized into low-risk (group A), medium-risk (group B), and high-risk (group C) groups, respectively. **b** Kaplan-Meier plot of cumulative freedom from cerebral ischemic event by the groups (A–C) stratified by the decision-tree analysis.

tients [5, 12]. Hellings et al. [13] have shown that the presence of IPH in the carotid endarterectomy specimen is independently associated with an increased risk of a future stroke (HR 2.1; 95% CI 1.1–4.4). They have confirmed that a local plaque can be an indicator of the cerebrovascular status of a patient. The results of our study support their argument and have the potential usefulness because carotid MRI can detect IPH noninvasively. In addition, several studies have also demonstrated a relationship between carotid IPH and coronary artery disease [13]. These facts suggest that carotid IPH might be a biomarker of clinical ischemic events due to the progression of atherosclerosis.

The source of plaque hemorrhage is considered to be a combination of plaque bleeding at the luminal site due to plaque disruption and IPH as a result of defective intraplaque vessels [14]. IPH may insudate into a preexisting necrotic core or into spaces between calcifications and matrix [15]. The accumulation of erythrocyte membranes in the necrotic core induces the formation of cholesterol crystals with the recruitment of macrophages and causes an abrupt increase in the levels of free cholesterol, resulting in an increase in plaque volume [16]. A large population-based study demonstrated that the risk factors for the presence of IPH were hypertension and current smoking. On the other site, the presence of lipid core, which is without high-signal intensity on T1-weighted imaging, relates with dyslipidemia but not with hypertension and current smoking [17]. Furthermore, the lipid core size in the dissected carotid plaque in another study showed no association with the ischemic events [13]. These facts might indicate that the systemic vascular status of the patients with IPH is different with that of the patients with lipid core. The presence of IPH may suggest advanced systematic atherosclerosis. The evaluation of the carotid plaque and detection of IPH might be useful for the risk stratification of asymptomatic patients.

In this study, the CHAID method, which is one of the methods of decision-tree analysis, showed that patients with both diabetes mellitus and carotid IPH are at a higher risk for a subsequent ischemic event. Although the number of patients with both diabetes mellitus and carotid IPH were small, the fact that half of the patients had subsequent ischemic event is a point to be noted. A relationship between diabetes mellitus and the presence of carotid IPH has not been demonstrated in a large population-based study [17]. Similarly, in our study, there was no significant difference in diabetes mellitus between the carotid MRI findings group and non-findings groups, and multivariate analysis demonstrated that diabetes

mellitus and IPH were independent risk factors for a subsequent ischemic event. From these results, we could hypothesize that the state of systematic atherosclerosis in patients with diabetes mellitus differed between those with and without IPH. Although a prospective study is needed to confirm this hypothesis, the detection of carotid IPH by MRI may have the potential for the risk stratification of subsequent ischemic event in diabetic patients. If diabetes mellitus and carotid IPH are both detected during the checkup, focused lifestyle advice and atherosclerosis risk factor control could be followed.

The limitations of this study include its retrospective nature and its small number of events. Although a major strength of our study is the large sample of middle-aged patients, some selection bias may have been introduced by having study patients who underwent annual medical checkup. The checkup procedures done in this study were optional and were not covered by public health insurance. Therefore, it could be said that the study population may contain a disproportionate amount of employed, wealthy, and health-conscious individuals. In fact, the prevalence of atherosclerotic risk factors such as hypertension, dyslipidemia, and diabetes mellitus as found in this study was lower than that found in another Japanese population-based study [18]. Thus, the natural history may have been worse than what our results suggest. To investigate the usefulness of detection of carotid IPH for accurate stroke risk stratification, a prospective population-based study should be performed.

Conclusion

In the present series of patients who underwent optional medical checkup, our analysis showed that those with carotid T1-high-intense plaque were at higher risk of a subsequent cerebrovascular ischemic event. These findings suggest that the detection of carotid IPH might contribute to the risk stratification assessment of a future stroke, but our results do not suggest that carotid T1-high-intense plaque can be used to predict future events in unselected population. To investigate the usefulness of detection of carotid IPH for accurate stroke risk stratification, a prospective population-based study should be performed.

Disclosure Statement

The authors have no conflicts of interests to declare.

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