Contrast-enhanced carotid ultrasonography and MRI plaque imaging to identify patients developing in-stent intimal hyperplasia after carotid artery stenting

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Abstract

Aim: In-stent intimal hyperplasia (ISH) observed after carotid artery stenting (CAS) may lead to in-stent restenosis. We aimed to investigate whether contrast-enhanced carotid ultrasonography (CEUS) and magnetic resonance imaging (MRI) plaque imaging prior to CAS are predictive for ISH at 6 months after CAS. **Material and method:** A total of 14 patients (13 men, 1 woman; mean age, 74.2 years) were prospectively enrolled. CEUS and MRI plaque imaging were performed before CAS. ISH was diagnosed by carotid angiography at 6 months after CAS. Patients were divided into two groups based on the thickness of ISH and age, risk factors, enhancement in CEUS, MRI plaque imaging and number of replaced stents were compared between groups. **Results:** Carotid angiography at 6 months after CAS revealed ISH in 10 patients. Plaque enhancement on CEUS was observed in 6 patients, all of whom showed ISH. A significant association was seen between plaque enhancement on CEUS and development of ISH (χ^2 test, CEUS enhancement (+) 100% vs. CEUS enhancement (-) 50% $p=0.040$). Carotid plaques in 12 patients were diagnosed as unstable by MRI plaque imaging. Presence of ISH was significantly associated with unstable plaque diagnosed by MRI plaque imaging (χ^2 test, unstable 83% vs. stable 0%; $p=0.016$). **Conclusion:** Carotid plaque MRI and CEUS may be useful to predict ISH after CAS.

Keywords: in-stent intimal hyperplasia; contrast-enhanced carotid ultrasonography; carotid artery stenting

Introduction

In-stent restenosis (ISR) may occur several years after carotid artery stenting (CAS) and may require re-treatment [1-4]. The frequency of ISR was reported as 6.0% at 2 years after CAS in the CREST study [5], 10.7% at 2 years in the SPACE study [6] and 3.3% at 3 years in the EVA-3S study [7]. ISR is thought to be related to

neointimal hyperplasia due to proliferation of smooth muscle cells, suggesting that in-stent intimal hyperplasia (ISH) may be a risk marker for ISR [8].

We evaluated carotid plaque instability using contrast-enhanced carotid ultrasonography (CEUS) and magnetic resonance imaging (MRI), investigations performed prior to CAS and 6 months later, in order to investigate the predictive value of these imaging for ISH developing.

Material and methods

A total of 14 patients (13 men, 1 woman; mean age, 74.2 years) who underwent preoperative assessment between April 2014 and March 2015 with cerebral angiography, MRI plaque imaging and CEUS, prior to CAS, were prospectively enrolled. Lumen diameter at the point of maximum stenosis and the diameter of the normal distal internal carotid artery (ICA) were measured using

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conventional cerebral angiography, then percent stenosis was calculated using the method described in the North American Symptomatic Carotid Endarterectomy Trial (NASCET) study [9]. The presence of a stenotic lesion in the ICA responsible for the ipsilateral ischemic stroke was defined as symptomatic ICA stenosis.

Follow-up conventional cerebral angiography was planned for all patients at 6 months after CAS and the presence of ISH was diagnosed based on the angiographic findings. ISH was defined as any defect of contrast agent adjacent to the contour of a carotid stent with a length ≥ 1.0 mm (fig 1). We diagnosed no ISH as absent in patients in whom angiography exhibited no or only a small length of defect (<1.0 mm) of contrast agent adjacent to the contour of the carotid stent. Diagnosis of ISH was performed by two neurologists. When no consensus decision could be reached, the diagnosis of another neurologist was added to reach the final diagnosis. This study was conducted in a single hospital, and the study protocol was approved by the St. Marianna University Bioethics Committee.

Carotid artery stenting

All procedures were performed via the femoral approach using the Seldinger method. All patients were on long-term antiplatelet therapy using aspirin, clopidogrel, or cilostazol either as monotherapy or in combination. Unfractionated heparin (10,000 units) was administered before starting the procedure. The procedures used included proximal balloon protection using Optimo (Tokai Medical Products, Aichi, Japan) and distal balloon protection using Carotid Guardwire PS (Medtronic, Santa Rosa, CA). After predilatation of the stenotic lesion, an appropriate stent for the stenotic lesion was implanted and then dilated. Pre-dilatation was performed in all patients using a balloon catheter, 4.0 mm or 4.5 mm in diameter. Post-dilatation was performed only in patients with placement of a single closed-cell stent using a balloon catheter, 5.0 mm in diameter. After the CAS proce-

dures, all patients were on dual antiplatelet therapy using aspirin, clopidogrel, or cilostazol in combination for 6 months.

Ultrasonography

All carotid ultrasound (US) exams were performed by the same examiner certified by the Japan Academy of Neurosonology. Carotid US was performed using a 7.5-MHz linear probe (SSA-770A Aplio; Toshiba Medical, Tokyo, Japan). B-mode imaging and color and power Doppler imaging and CEUS were performed using Sonazoid® (perfluorobutane microbubbles; Daiichi Sankyo Pharmaceutical, Tokyo, Japan). A total of 16 μ L of Sonazoid® was dissolved in 2 mL of water, and an intravenous bolus injection of 0.15 mL/kg body weight of the contrast agent suspension was injected into the antecubital vein. The acoustic power of harmonic US was set with a mechanical index (MI) of 0.2–0.3, a depth of 3 cm, and focus set at 2.5 cm. The presence of enhanced lesions was identified as the echogenic reflection of microbubbles in the plaque. Carotid plaque was evaluated from longitudinal and transverse views for about 5 min after contrast injection.

MRI plaque imaging

Black-blood carotid artery MRI (BB-MRI) was performed using a 1.5-T scanner (Achieva Nova Dual; Philips Healthcare, Best, the Netherlands) using a 16-channel NV coil. To identify the position of greatest wall thickness, standard imaging protocols were used; i.e., time-of-flight (TOF), T1-weighted, and T2-weighted imaging. For short-axis T1-weighted images (2-dimensional turbo spin-echo), parameters were: recovery time (TR), 1 cardiac cycle (1 R-R interval); echo time (TE), 15 ms; matrix, 153×192 ; thickness, 3 mm; field of view (FOV), 150 mm; number of samples (NSA), 6; and fat saturation (+). For short-axis T2-weighted images (2D-TSE), parameters were: TR, 2 cardiac cycles (2 R-R intervals); TE, 80 ms; matrix, 153×192 ; thickness, 3 mm; FOV, 150 mm; NSA, 8; and fat saturation (+). For TOF

Fig 1. In-stent hyperplasia on carotid angiogram. Follow-up conventional cerebral angiography at 6 months after the CAS. In-stent intimal hyperplasia (ISH) was defined as any defect of contrast agent adjacent to the contour of carotid stent with a length ≥ 1.0 mm. ISH was observed in 10 of 14 patients.

2D-TSE, parameters were: TR, 23 ms; TE, 6.9 ms; matrix, 120 × 240; thickness, 1.25 mm; number of excitations, 1; and fat saturation (+). For the characterization of carotid plaque, TOF, T1-weighted, and T2-weighted images were used. The signal intensity ratio relative to the ipsilateral sternocleidomastoid muscle (i.e., plaque/muscle ratio; P/M ratio) was calculated, and high intensity was defined as a plaque/muscle ratio >1.5 [10]. Unstable plaque was defined as the presence of a high-intensity signal (HIS) in the carotid plaque on TOF imaging or high intensity of the carotid plaque on T1-weighted imaging [11-13].

Statistical analyses

Subject characteristics are reported as mean and standard deviation (SD) unless otherwise indicated. Comparisons between plaque enhancement on CEUS and ISH were performed using the chi-square test. Comparisons between unstable plaque findings on MRI and ISH were also performed with chi-square tests for categorical data. Values of $P < 0.05$ were considered statistically significant. All statistical analyses were performed using SPSS Statistics for Windows version 22 software (IBM, Armonk, NY).

Results

Patient demographics and intraoperative findings are shown in Table I. ISH on carotid angiography at 6 months after CAS was observed in ten patients. Plaque enhancement on CEUS was observed in 6 patients (fig 2). All 6 patients with plaque enhancement on CEUS showed ISH. Significant associations were seen between plaque

enhancement on CEUS and ISH (χ^2 test, $p=0.040$). The 12 patients were diagnosed with unstable plaque by MRI plaque imaging. ISH was observed in 10 of the 12 patients with unstable plaque on MRI. A significant association was also observed between a diagnosis of unstable plaque on MRI and ISH (χ^2 test, $p=0.016$). No significant correlation was seen between the number of stents and ISH, patient age and ISH, risk factors and ISH, and symptomatic lesion and ISH (Table II).

Discussions

Assessment of carotid artery plaques prior to CAS is typically performed using TOF magnetic resonance angiography (MRA), BB-MRI, or carotid ultrasonography [10-13]. In recent years, CEUS using an ultrasound contrast agent has become a viable modality for diagnosing intraplaque neovascularization in the carotid artery and has attracted attention as a useful technique for plaque imaging [13].

The present study showed significant associations between plaque enhancement on CEUS performed before CAS and development of ISH at 6 months after CAS, implying that neovascularization may be a risk marker for ISH development. The source of neovascularization is direct branching from the vasa vasorum or intimal surface. These areas are very fragile, and plaque hemorrhage can easily occur [14]. Evaluation of neovascularization is therefore important in assessing plaque instability. Neovascularization is a sign of incipient plaque growth, and plaque continues to grow by nutrition from neovascularization [15].

Table I. Patients' demographics and intraoperative findings

Case	Age (y)	Sex	Symptomatic/asymptomatic stenosis	Lesion on DSA (side, %)	MRI stability	MRI T1-BB P/M ratio	MRI TOF HIS	CEUS enhancement	Number of Stents	ISH (mm on DSA)	ISH (≥ 1.0 mm)
1	71	M	asymptomatic	L, 73	stable	0.99	-	-	1	-	-
2	81	M	asymptomatic	R, 70	unstable	0.98	+	-	1	1.3	+
3	81	M	symptomatic	L, 78	unstable	1.78	+	+	2	1.2	+
4	73	M	asymptomatic	R, 72	stable	0.98	-	-	2	-	-
5	76	M	asymptomatic	L, 65	unstable	1.83	+	+	2	1.2	+
6	57	M	asymptomatic	R, 83	unstable	2.01	-	+	4	2.0	+
7	87	M	asymptomatic	R, 55	unstable	1.56	+	+	1	1.8	+
8	83	M	asymptomatic	L, 60	unstable	1.43	+	-	2	-	-
9	76	M	symptomatic	R, 85	unstable	1.46	+	-	2	1.9	+
10	79	M	asymptomatic	R, 85	unstable	1.08	+	-	1	2.2	+
11	62	M	symptomatic	R, 95	unstable	1.81	-	+	3	1.5	+
12	70	M	symptomatic	L, 77	unstable	2.02	+	-	1	-	-
13	73	F	asymptomatic	R, 72	unstable	1.88	+	-	1	1.1	+
14	70	M	symptomatic	R, 80	unstable	1.76	-	+	2	1.4	+

DSA; digital subtraction angiography, T1-BB P/M ratio; plaque/muscle ratio on T1-black blood, TOF; time of flight, HIS; high intensity signal, ISH; in-stent intimal hyperplasia

Table II. Factors associated with in-stent intimal hyperplasia

	ISH(+) n = 10	ISH(-) n = 4	p value
Age (mean±SD)*	74.3±6.0	74.2±9.1	0.839
Hypertension	9	3	0.469
Smoking	4	2	0.237
Diabetes	4	2	0.733
CEUS enhancement	6	0	0.040
MRI findings	10	2	0.016
Number of stents (2 stent and over)	6	2	0.733
Symptomatic lesion	4	1	0.597

ISH; in-stent intimal hyperplasia, CEUS; Contrast-enhanced carotid ultrasound, *Mann-Whitney U test

The atheromatous plaque existed even after the CAS. If neovascularization would be present in the atheromatous plaque, such intraplaque vessels might act as nutrient vessels for intimal growth under the stent. This may be why a significant association between plaque enhancement on CEUS exhibiting neovascularization and ISH development was observed in the present study.

The present study showed significant associations between unstable findings on MRI and ISH at 6 months after CAS. T1-weighted BB-MRI and TOF MRA have been reported as an indicator of plaque stability [11-14]. Unstable findings with high intensity on BB-MRI and TOF MRA were considered as the presence of intraplaque hemorrhage developing from the rupture of incompetent neovascularization [12]. Areas of neovascularization are very fragile, and plaque hemorrhage can easily arise. Thus, it is reasonable that MRI plaque imaging correlated with the development of ISH in this study.

In-stent restenosis (ISR) has been considered to involve the same mechanisms seen in whole arteries, including coronary arteries, and ISH is thought to be the cause of ISR [8,16]. When the artery is loaded by stent placement or balloon expansion, damage to the intima occurs and inflammatory cytokines and interleukin are released. These events promote invasion of macrophages and monocytes into damaged tissues. Moreover, platelet-derived growth factor is released from platelets aggregating in the damaged area. These events are thought to lead to intimal hyperplasia and restenosis in the stent [17,18]. Our study demonstrated that the use of CEUS and MRI plaque imaging may be useful to select patients developing ISH after CAS. The diagnosis of ISH early after CAS could thus be useful to identify patients developing ISR.

Our study has some limitations. First, only a small number of patients were studied. Thus, we were unable to demonstrate the superiority of ultrasonography over MRI for predicting ISH in this study. However, our findings are useful for hypothesis generation and further studies to compare the diagnostic accuracy of MRI and CEUS

Fig 2. Enhancement of carotid plaque on contrast-enhanced ultrasonography. The images show the findings of contrast enhancement of carotid plaque in each of these.

are warranted. Second, the technical methods and type of stent were optimized for each patient, which might have affected the development of ISH. Third, the definition of ISH used in this study was provisional. ISH needs to be investigated by further increasing the number of patients and setting a clear definition for ISH in a further study.

In **conclusion** carotid plaque MRI and CEUS may be useful imaging techniques to predict ISH after CAS.

Conflict of interest: none

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