Validation of Ultrasound Parameters to Assess Collateral Flow via Ophthalmic Artery in Internal Carotid Artery Occlusion

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This study aimed to characterize the flow patterns using ultrasound (US) in the external carotid artery (ECA) in patients with total occlusion of internal carotid artery (ICA) and characterize collateral retrograde flow through the ophthalmic artery (OA, secondary collateral, internalization). This study was performed on 45 patients who were retrospectively selected with total occlusion of the ICA, who underwent digital subtraction angiography (DSA), magnetic resonance angiography (MRA), and US (43 men; mean age 68.1 ± 7.9 years). Collateral retrograde flow and collateral flow through the circle of Willis (primary collateral) were determined by DSA and MRA. We compared several US parameters such as ECA peak systolic velocity, mean velocity, end-diastolic (ED) velocity, pulsatility index (PI), and pulsatility transmission index (PTI). PTI was defined as the ratio of ipsilateral ECA PI to the ipsilateral common carotid artery (CCA). In this patient group, 27 patients showed retrograde flow through OA as assessed by DSA. The presence of primary collateral flow was significantly lower in patients with retrograde flow than without ($P < .05$). ECA ED velocity was significantly higher, and PI and PTI were significantly lower with retrograde flow through OA than without ($P < .05$). According to receiver operating characteristic analysis, PTI was the most highly correlated ultrasonologic parameter with internalization (cutoff value, .94; sensitivity, 92.6%; specificity, 94.5%). Using PTI was discriminative to determine internalization of ECA because a collateral pathway through OA in cases of ICA occlusion had less primary collateral pathways. **Key Words:** Carotid artery occlusion—collateral circulation—ophthalmic artery—carotid ultrasound—pulsatility transmission index.

Introduction

Annual stroke rates in patients with carotid artery occlusion range from 0% to 5%[1,2] in asymptomatic patients to 27% in symptomatic patients.[3,4] In patients with occlusion of the internal carotid artery (ICA), collateral circulation plays a pivotal role in the pathophysiology of cerebral ischemia.[5] The major collateral is the circle of Willis, including the anterior communicating artery (ACoA) and posterior communicating artery (PCoA), which can compensate for diminished blood flow (primary collateral). On the other hand, collateral pathways through the ophthalmic artery (OA) and leptomeningeal vessels may be recruited as secondary collateral when collateral flow through the circle of Willis is inadequate.[6] Some studies have shown that the presence of collateral circulation through the ipsilateral external carotid artery (ECA) and OA is associated with hemodynamic impairment in the ICA.[7,8] Therefore, secondary collateral circulation may be an indicator of increased risk of future ischemic events.

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To assess secondary retrograde flow in the OA, a conventional arteriography is the most accurate examination. However, arteriography is not suitable as a screening test because of the ever-present risk of a disabling stroke and systemic complications and also because of its high cost. Schneider et al[9] used transorbital Doppler (TOD) ultrasonography to assess OA as a source of collateral cerebral blood supply. However, evaluation of OA requires the use of specialized techniques, knowledge, and specific tools. Moreover, although there have been no reports of thermal hazards from TOD when using the orbital window, there is the possibility of potential effects on the retina.

Diagnosis of complete occlusion can be complicated by the presence of large ECA collaterals via OA, which can be mistaken for the ICA.[10,11] The conversion to a low-resistance Doppler sonography waveform in the ECA has been termed "internalization" because the abnormal spectral tracings in the ECA mimic the spectral tracings in a normal ICA.[12] This change is often because of complete occlusion of the ICA with subsequent development of low-resistance collateral pathways between the ipsilateral external and internal circulation, typically through the ophthalmic vascular bed.[13] Although it is easier to assess the collateral pathway with occlusion of the ICA, there are no published criteria for internalization using carotid ultrasound (US) measurements. Therefore, we determined the criterion for judgment of internalization based on ultrasonography of the neck.

Methods

Subjects

We retrospectively analyzed patients admitted to our institute with unilateral ICA occlusion who underwent digital subtraction angiography (DSA), magnetic resonance angiography (MRA), and carotid US between April 1999 and March 2009. In our study, the data were obtained using a standard of care clinical protocol. According to the standard ethical guidelines for clinical research in Japan, the requirement of informed consent was waived. We excluded patients with bilateral ICA occlusion and OA stenosis or occlusion in which the lesions affected the collateral circulation. We evaluated clinical features, carotid US parameters, MRA, and DSA data. The following underlying clinical features were examined: age, sex, ICA occlusion side, hypertension (blood pressure ≥ 140/90 mm Hg or history of antihypertensive medication), hypercholesterolemia (serum total cholesterol ≥ 5.7 mmol/L or history of antihypercholesterolemic medication), diabetes mellitus (fasting blood glucose 7.0 mmol/L, a positive 75-g oral glucose tolerance test, or history of antidiabetic medication), current smoking habit, and contralateral ICA stenosis (≥70% stenosis confirmed by carotid US, MRA, or DSA).

Digital Subtraction Angiography

Informed consent for DSA was obtained from both the patients and their family. Selective DSA was performed using a biplane, high-resolution angiography system (Angio Rex Super-G and DFP-2000A; Toshiba, Tokyo, Japan) with a matrix of 1024 × 1024 pixels. A catheter was inserted into the right brachial artery or femoral artery according to the Seldinger method and guided to the cerebral arteries. After a selective common carotid artery (CCA) injection on the side of the ICA occlusion, ECA collaterals were detected on the angiogram by the contrast filling of ECA, OA, carotid siphon, middle cerebral artery, or anterior cerebral artery. The degree of collateral flow via the OA observed in DSA was graded on a 3-point scale according to a previous report[14]: grade 0, slight collateral distribution (eg, no filling of OA); grade 1, small but definite collateral supply (eg, retrograde flow in OA with filling of carotid siphon); and grade 3, full collateral filling (eg, to the middle cerebral artery and/or anterior cerebral artery; Fig 1).

Magnetic Resonance Angiography

MRA was performed using a 1.5-T MR unit (Magnetom Sonata; Siemens, Erlangen, Germany). Previous studies have indicated that MRA provides a reliable method to assess the direction of flow in the circle of Willis[15,16]; therefore, we determined the collateral flow via the ACoA and PCoA using MRA. Stenosis of the A1 segment of the ACoA and PCoA of 70% or more was assessed as being incapable of fulfilling the collateral role.

Carotid Ultrasound

A carotid US examination was performed using a 7.5-MHz, linear-array transducer (SSA-270 A; Toshiba) within approximately 7 days before or after DSA (4.3 ± 3.6 days). One investigator with no previous knowledge of the patients' clinical information, including angiographic findings, measured several parameters of the carotid US (the flow velocities of ECA and CCA). The sample volume was set within two thirds of the diameter of the CCA or ECA, and care was taken to maintain an adequate angle of 60° or less between the beam and the wall of the CCA or ECA. The CCA flow was measured at 1-2 cm proximal to the bulb, and the ECA flow was measured before the bifurcation of the superior thyroid artery. The pulse repetition frequency was 3.0 or 3.5 Hz, and the low-pass filter was set at 70 Hz. We aimed to measure two thirds of the diameter in the center of the artery and actually measured mostly centerline velocity. We obtained the peak systolic flow velocity (PSV), the end-diastolic flow velocity (EDV), and the time-averaged peak mean flow velocity of the ipsilateral CCA and ECA. The pulsatility index (PI) was automatically calculated by the instrument as PSV − EDV/mean flow velocity (MV). The pulsatility transmission index (PTI)[17] was defined as a ratio of the PI of the ipsilateral ECA to a reference artery (CCA).

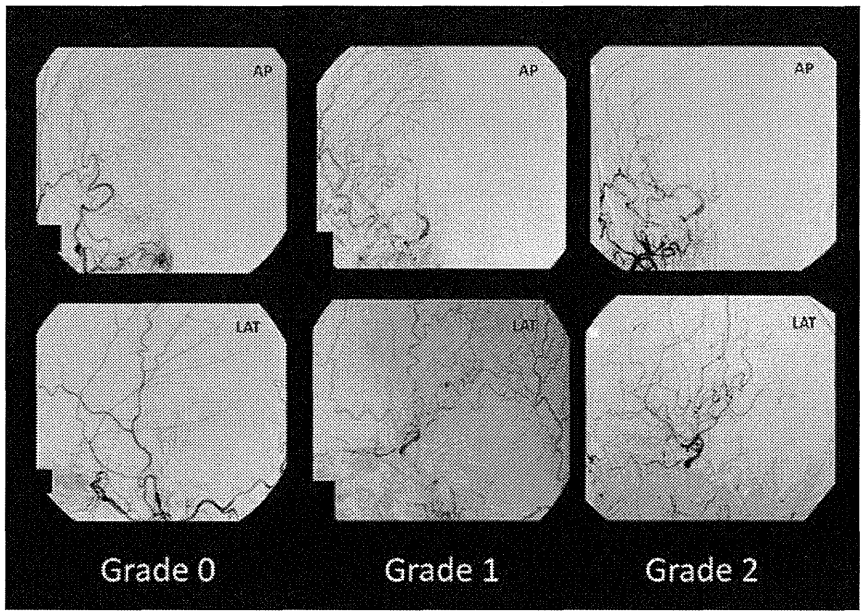

Figure 1. *Selective angiograms of the common carotid artery, demonstrating the degree of collateral flow from the ipsilateral external carotid artery (ECA) on the side of the internal carotid artery (ICA) occlusion. The degree of collateral flow via the ophthalmic artery (OA) observed on digital subtraction angiography (DSA) was graded into 3 groups: grade 0: no OA filling, grade 1: retrograde OA flow with carotid siphon filling, and grade 2: flow to middle cerebral artery and/or anterior cerebral artery.*

Statistical Analyses

The clinical characteristics of the 2 patient groups with retrograde flow via the OA and without retrograde flow via the OA were compared using the Student *t* test and the χ^2 test for categorical variables. Continuous baseline variables with normal distribution were expressed as mean ± SD and compared by Student *t* test. *P* value of .05 or less was considered statistically significant. To determine the predictive ability of parameters, those of the carotid US were compared using a Student *t* test, and receiver operating characteristic (ROC) analysis was performed to calculate sensitivities and specificities associated with each parameter. All statistical analyses were performed using the JMP 10 software package (SAS Institute Inc., Cary, NC).

Results

Study Population

A total of 45 patients were included (mean age 68.1 ± 7.9 years; 96% men and 4% women) in this retrospective study. All patients underwent DSA, MRA, and carotid US procedures. We divided the 45 patients with unilateral ICA occlusion into 2 groups: those with and without retrograde flow via the OA. A total of 27 patients had retrograde flow determined by DSA. There were no

Table 1. *Patient characteristics*

	Retrograde flow via the OA		
Patients (N = 45)	With (n = 27)	Without (n = 18)	*P* value
Mean age, y	67.5 ± 8.9	69.2 ± 6.3	.477
Gender, male (n = 43)	26 (96%)	17 (94%)	.768
Occlusion side (right sided) (n = 23)	15 (56%)	8 (44%)	.465
Hypertension (n = 35)	22 (81%)	13 (72%)	.467
Dyslipidemia (n = 27)	17 (63%)	10 (56%)	.619
Diabetes (n = 19)	11 (41%)	8 (44%)	.805
Current smoking (n = 35)	22 (82%)	13 (72%)	.464
Contralateral ICA stenosis (n = 12)	7 (26%)	5 (28%)	.891
Presence of ACoA (n = 26)	11 (41%)	15 (83%)	.005
Presence of PCoA (n = 15)	4 (15%)	11 (61%)	.001
Presence of ACoA or PCoA (n = 30)	12 (44%)	18 (100%)	<.001

Abbreviations: ACoA, anterior communicating artery; ICA, internal carotid artery; OA, ophthalmic artery; PCoA, posterior communicating artery.

Values are mean ± SD or n (%). *P* values determined by Student *t* test or the χ^2 test.

Table 2. *Ultrasound parameters between with and without retrograde flow via the ophthalmic artery on the occluded side*

Patients (N = 45)	Retrograde flow via the OA: With (n = 27)	Retrograde flow via the OA: Without (n = 18)	*P* value
ECA PSV (cm/s)	98.5 ± 35.1	102.7 ± 53.9	.750
ECA MV (cm/s)	38.2 ± 13.3	32.2 ± 17.7	.201
ECA EDV (cm/s)	19.3 ± 7.7	12.3 ± 7.8	.005
ECA PI*	2.03 ± .48	2.91 ± .88	<.001
CCA PI*	2.66 ± .65	2.57 ± .64	.643
PTI†	0.78 ± .13	1.14 ± .05	<.001

Abbreviations: CCA, common carotid artery; ECA, external carotid artery; EDV, end-diastolic flow velocity; MV, mean flow velocity; PSV, peak systolic flow velocity; PI, pulsatility index; PTI, pulsatility transmission index.

Values are mean ± SD. *P* values were determined by Student *t* test. Both ECA and CCA flow data were collected on the occluded side.

*PI = (PSV – EDV)/MV.

†PTI = ECA PI/CCA PI.

significant differences in the male/female ratio, age, occlusion side, contralateral ICA stenosis (≥70%), and carotid artery vascular risk factors between the 2 groups (Table 1). The patients with retrograde flow via the OA had fewer primary collateral pathways than those without retrograde flow determined by MRA (ACoA 11 [41%], PCoA 4 [15%], ACoA or PCoA 12 [44%]). We found the presence of primary collateral flow to be significantly different between the 2 groups ($P < .01$).

Distinguishing Those with Retrograde Flow via the OA from Those without Retrograde Flow Using Carotid Ultrasound

Carotid US parameters of all patients were obtained. Table 2 shows the adjusted mean values of carotid US parameters of the occlusive side. ECA PSV and MV were not associated with the presence of retrograde flow via the OA. The ECA EDV was higher, and PI and PTI were lower with retrograde flow via the OA than without significantly (ECA EDV 19.3 ± 7.7 cm/s versus 12.3 ± 7.8 cm/s; $P = .0025$, ECA PI: 2.03 ± .48 versus 2.91 ± .88; $P \leq .001$, PTI: .78 ± .13 versus 1.14 ± .05; $P \leq .001$).

Furthermore, to determine the prediction of retrograde flow, we examined the ROC by using the significant parameters associated with the presence of retrograde flow via the OA (ECA EDV, ECA PI, and PTI). PTI showed higher values than the other parameters, and we found that the best criterion to differentiate between cases with and without OA was PTI less than .94 (sensitivity and specificity of 92.6% and 94.5%, respectively). ROC curves are presented for the carotid US parameters in Figure 2

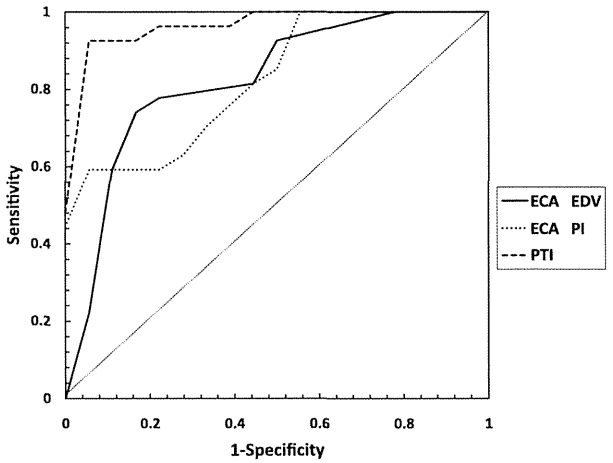

Figure 2. *Comparison of ROC curves of the parameters for the prediction of retrograde flow. According to ROC analysis, PTI was highly predictive of accuracy for these parameters (AUC: .95). The appropriate cutoff value of PTI was .94 (sensitivity 92.6%, specificity 94.5%). Abbreviations: AUC, area under the curve; ECA, external carotid artery; EDV, end-diastolic flow velocity; PI, pulsatility index; PTI, pulsatility transmission index; ROC, receiver operating characteristic.*

and demonstrate that the area under the curve of PTI is larger than the other parameters measured (area under the curve: ECA EDV .80, ECA PI .81, and PTI .95).

Comparison of PTI Values by Grading Retrograde Flow in DSA

The degree of collateral flow via the OA observed in DSA was divided into 3 grades (Fig 1). The largest proportion in this study was grade 0. The adjusted mean values of PTI based on grades are grade 0, 1.14 ± .21; grade 1, .77 ± .14; and grade 2, .78 ± .12. Comparing the groups by 1-way analysis of variance, grade 0 was higher than the others ($P < .0001$; Fig 3).

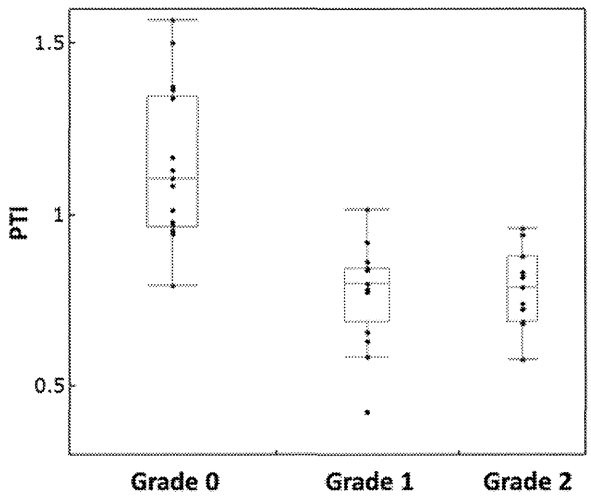

Figure 3. *Comparison of PTI values by grading retrograde flow via the OA. Using 1-way ANOVA, the PTI of grade 0 was significantly higher than the other grades (P < .01). Abbreviations: ANOVA, analysis of variance; OA, ophthalmic artery; PTI, pulsatility transmission index.*

Discussion

PTI was a significant predictor of carotid US parameters for distinguishing between the presence and absence of retrograde flow via the OA. To date, many studies of detection methods of retrograde flow via the OA have been completed; however, a method of detection using carotid US has not existed in the past. Carotid US is more widely used for patients with arterial sclerosis than TOD, MRA, and angiography. Moreover, carotid US is simple, safe, and cost effective compared with other techniques.

When the ICA is occluded, it has been shown previously that collateral flow via the circle of Willis compensates for deprived perfusion.[18,19] If the primary collaterals are insufficient to overcome cerebral blood flow deficiencies, the ECA can convert to a low-resistance system and serve as a major collateral through the OA. The low-resistance system of the ECA mainly consists of retrograde flow via the OA. In previous studies of patients with unilateral ICA occlusion, the proportion of those with collateral OA flow varied between 40% and 56%.[19-21] In our study, the prevalence of collateral OA flow detected by angiography was 60%. The presence of collateral flow through the ECA as assessed with TOD has been associated with relatively preserved cerebral hemodynamics.[22,23] However, secondary collaterals in ICA occlusion patients correlated with ipsilateral cerebral blood flow that suggests severe hemodynamic impairment.[6,24] This study shows that the patients with retrograde flow via the OA had significantly less primary collateral pathways. Moreover, there was a report that the presence of ophthalmic collaterals was a significant and independent predictor of increased oxygen extraction fraction as an index of hemodynamic impairment measured with positron emission tomography.[8] Therefore, patients with a prevalence of retrograde flow via the OA in unilateral ICA occlusion would be at a higher risk for infarction recurrence.

Within the parameters of carotid US, the EDV of ECA was also significantly correlated with the internalization of ECA, but its significance was weaker than that of PI and PTI. PI and PTI, considering that they represent the combined effect of each velocity change (PSV, EDV, MV), may reflect changes more sensitively in cerebrovascular resistance rather than velocity measurements. Moreover, although PI is affected by systemic cardiovascular characteristics (heart rate, blood pressure, vascular compliance, and arterial pCO_2) between individuals,[25,26] PTI may counteract individual variations. In this study, on comparing each carotid US parameter, PTI was found to be the most reliable for detecting the prevalence of retrograde flow via the OA. To obtain information regarding the amount of collateral flow via the OA, we graded the degree of collateral flow via the OA observed with DSA. PTI appears to permit grading of cerebral inflow conditions. We found no significant difference between grade 1 and grade 2 but found a difference between grade 0 and grade 1 or 2. This result may show that ordinary grading of retrograde flow is not very reliable as angiography may be inaccurate because reversal flow is possibly dependent on the pressure of contrast injection.

The present study has several limitations including possible bias related to patient selection. Only a relatively small number of subjects were analyzed because all patients needed to undergo DSA to determine precise retrograde flow via the OA. Small vessels in the circle of Willis and OA may have remained invisible on the images, but we speculate that collateral flow that was not detected on DSA did not substantially contribute to cerebral perfusion. Finally, because angiography and US were performed around the same time, the MRA data cannot be verified by follow-up data. However, results from previous longitudinal studies suggest that collateralization may develop slowly over months in patients with ICA occlusion.[27,28]

Conclusions

Carotid US PTI is the best indicator in patients with unilateral ICA occlusion to determine retrograde flow via OA. The pattern of collateral supply has significant influence on hemodynamic status. This technique easily provides an approximation of the level of cerebral collateral perfusion.

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Aortic Transgraft Hemorrhage after Intravenous Tissue Plasminogen Activator Therapy in Patients with Acute Ischemic Stroke

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Background: The safety of intravenous recombinant tissue plasminogen activator (IV tPA) therapy for patients with an aortic aneurysm or undergoing aortic graft replacement has not been established. We evaluated the incidence, bleeding site, coagulation factors, and clinical outcomes of patients treated with IV tPA for acute stroke. *Methods:* Between October 2005 and May 2013, 394 ischemic stroke patients were treated in our stroke center with IV tPA. Among these patients, we investigated those who had a history of aortic aneurysm with or without aortic graft replacement before IV tPA therapy and underwent computed tomography imaging. We compared the levels of D-dimer and hemoglobin (Hb) around IV tPA therapy between the patients with and without tPA-associated periaortic bleeding. *Results:* Seven patients with a history of aortic aneurysm (3 men; mean age: 80.4 years) were examined; 3 had undergone aortic graft replacement, and 2 had experienced tPA-associated bleeding around vascular grafts. The serum D-dimer levels in those with bleeding were only slightly higher before tPA than in those without (median: 10.5 vs. 1.5 μg/mL) but were elevated 1 day after tPA (107.4 vs. 8.6 μg/mL). The Hb levels 2 days after tPA were comparable with those before tPA (11.9 vs. 11.8 g/dL) but were lower in the patients with bleeding than in those without (8.5 vs. 11.7 g/dL). Surgical intervention was not required, although 1 patient required blood transfusion. *Conclusions:* Our analysis provides reassurance regarding the risk of IV tPA therapy in patients undergoing aortic graft replacement. **Key Words:** Intravenous thrombolysis—IV tPA therapy—acute ischemic stroke—aortic aneurysm—aortic graft replacement—aortic transgraft hemorrhage.

Intravenous recombinant tissue plasminogen activator (IV tPA) therapy improves functional neurologic outcome and reduces mortality in acute ischemic stroke.[1] In August 2012, the indication of IV tPA therapy for acute ischemic stroke was extended in Japan to 4.5 hours after stroke onset.[2] Because the benefit of IV tPA therapy rapidly declines over time from the initial symptom onset,[3] it is important to identify patients who are suitable for IV tPA therapy as early as possible. However, given that IV tPA therapy increases the risk of major bleeding, particularly in the brain, patients should be carefully selected for IV tPA therapy using valid eligibility criteria.

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Patients with stroke have been associated with a higher incidence of abdominal aortic aneurysm.[4] According to the Japanese guidelines for administering IV tPA therapy, patients with an aortic aneurysm require "careful administration" of tPA for acute ischemic stroke.[2] However, the safety of IV tPA therapy for patients with an aortic aneurysm or undergoing aortic graft replacement has not been established. Few studies have examined whether periprosthetic graft hemorrhages are associated with thrombolysis.[5-10] In those studies, the indications for thrombolysis were limb ischemia or myocardial infarction, and the thrombolytic agents used included tPA, streptokinase, or urokinase. There are no reports on IV tPA therapy for acute ischemic stroke in patients with a history of aortic aneurysm when the coagulation and fibrinolytic systems were sufficiently monitored.

In the present study, we evaluated the incidence, bleeding site, coagulation/fibrinolysis markers, and the clinical outcomes of consecutive patients treated with IV tPA for acute ischemic stroke who had a history of aortic aneurysm with or without aortic graft replacement.

Methods

Patients were selected from a prospective clinical registry of patients with acute ischemic stroke treated in our stroke center with IV tPA between October 2005 and May 2013. The study was approved by Medical Ethics Committee of National Cerebral and Cardiovascular Center, Japan. Inclusion and exclusion criteria for IV tPA (.6 mg/kg) therapy were used in accordance with the Japanese guidelines for administering IV tPA (alteplase) therapy. Based on these Japanese guidelines, the patients with acute ischemic stroke were treated with IV tPA within 3 hours of stroke onset between October 2005 and August 2012, and within 4.5 hours of stroke onset after August 2012.[2]

Patients meeting the following inclusion criteria were included in the study: (1) history of aortic aneurysm with or without aortic graft replacement before IV tPA therapy and (2) at least 1 body examination with computed tomography (CT) imaging (Aquilion TM, Toshiba Medical Systems Co., Ltd., Tokyo, Japan) during hospitalization for acute stroke.

An aortic aneurysm was defined by the Japanese guidelines for the diagnosis and treatment of aortic aneurysm and aortic dissection, which included a circumferential or local enlargement of part of the aortic wall that exceeded 45 mm in diameter in the thoracic region or 30 mm in the abdominal region in a fusiform manner.[11]

The baseline characteristics, stroke severity on admission and discharge, onset-to-needle time, risk factors, subtype of ischemic stroke, body CT images, blood examination including coagulation markers, and modified Rankin scale (mRS) score on discharge were collected for each patient.

The original Trial of ORG 10172 in Acute Stroke Treatment criteria were used to determine the subtype of ischemic stroke.[12] Symptomatic intracranial hemorrhage was defined as extravascular blood present in the brain or cranium that was associated with clinical deterioration and was accompanied by at least a 4-point increase in the National Institutes of Health Stroke Scale (NIHSS) score. Hemorrhagic transformations occurring within 36 hours of IV tPA therapy were classified according to the European Cooperative Acute Stroke Study (ECASS) morphologic definitions into the following 5 categories: no hemorrhagic transformation, hemorrhagic infarction (HI) types 1 and 2, and parenchymal hematoma types 1 and 2.[13] Body CT images were reviewed by an experienced radiologist (M.H.). Statistical analysis was not performed because only a small number of patients were examined.

Results

Between October 2005 and May 2013, 394 patients were treated in our hospital with IV tPA for acute stroke. During this period, 9 patients presented with a history of aortic aneurysm who were treated with IV tPA. Two of these patients, however, were not examined by body CT imaging during their hospitalization for acute stroke. Therefore, 7 patients (3 men and 4 women; mean age: 80.4 years) met the inclusion criteria and were enrolled in the study.

The clinical characteristics of these 7 patients are summarized in Table 1. The subtypes of ischemic stroke included 2 cases (28.6%) of large artery atherosclerosis and 5 cases (71.4%) of cardioembolism. The onset-to-needle time, which indicates the period between symptom onset and treatment initiation, ranged between 68-186 minutes with a median of 158 minutes.

Three patients (2 men and 1 woman; mean age, 80.3 years) had undergone an aortic aneurysm repair (Table 2). One patient had received a prosthetic graft for an abdominal aortic aneurysm with an InterGard graft (InterVascular, La Ciotat, France), and one patient had received a prosthetic graft for a thoracic aneurysm with a Gelweave graft (Vascutek Ltd, Renfrewshire, Scotland, United Kingdom). Another patient had received 2 prosthetic grafts, which included a thoracic aortic aneurysm with a UBE J-graft (Junken Medical Co, Ltd, Tokyo, Japan) and an abdominal aortic aneurysm with the InterGard graft. All 4 prosthetic grafts used Dacron grafts. In all 3 patients, the period between the operation and IV tPA therapy was at least 4 months, and according to their medical records, their postoperative courses were uneventful. Four patients (1 man and 3 women; mean age, 80.5 years) had a history of thoracic aortic aneurysm without surgical repair. The mean maximum diameter of thoracic aortic aneurysm was 46.5 mm (range, 45-48 mm).

Body CT examinations were performed between 1-24 days after tPA infusion, with a median of 5 days. Bleeding in a body cavity associated with IV tPA therapy was present in only 2 of the 7 patients. The basic clinical characteristics of bleeders and nonbleeders are presented

Table 1. *Baseline characteristics*

Baseline characterisitics	All patients (N = 7)	With bleeding (N = 2)	Without bleeding (N = 5)
Age, mean ± SD	80.4 ± 6.7	78.5 ± 9.2	81.2 ± 6.5
Male, n (%)	3 (43)	1 (50)	2 (40)
NIHSS on admission, median (range)	16 (7-21)	9.5 (7-12)	19 (14-21)
Onset-to-needle time, min, median (range)	158 (68-186)	180 (173-186)	150 (68-170)
Hypertension, n (%)	7 (100)	2 (100)	5 (100)
Diabetes mellitus, n (%)	0 (0)	0 (0)	0 (0)
Hyperlipidemia, n (%)	4 (57)	1 (50)	3 (60)
Use of antiplatelet therapy in the prehospital setting, n (%)	2 (29)	1 (50)	1 (20)
Use of anticoagulant therapy in the prehospital setting, n (%)	0 (0)	0 (0)	0 (0)
Systolic blood pressure, mm Hg, median (range)	158 (110-192)	174 (156-192)	158 (110-177)
Diastolic blood pressure, mm Hg, median (range)	86 (52-105)	69 (52-86)	95 (62-105)
Heart rate/min, median (range)	98 (52-141)	69 (52-86)	100 (79-141)
Stroke type, n (%)			
Cardioembolic stroke	5 (71.4)	1 (50)	4 (80)
Large artery disease	2 (28.6)	1 (50)	1 (20)

Abbreviations: NIHSS, National Institutes of Health Stroke Scale; SD, standard deviation.

in Table 1. As Table 1 indicates, the onset-to-needle time was longer in bleeders than in nonbleeders (median, 180; range, 173-186 minutes vs. median, 150; range, 68-170 minutes). The systolic blood pressure at initial presentation was higher in bleeders (median: 174, range: 156-192 mm Hg) than in nonbleeders (median, 158; range, 110-177 mm Hg). The NIHSS score on admission was lower in bleeders (median, 9.5; range, 7-12) than in nonbleeders (median, 19; range, 14-21). All patients who experienced bleeding in a body cavity associated with IV tPA therapy had undergone aortic graft replacement for aortic aneurysm. Bleeding associated with IV tPA therapy occurred in 2 of the 3 (67%) patients who had undergone aortic graft replacement for aortic aneurysm.

The bleeding sites were not located at an anastomosis but were identified around the grafts. As shown in Table 2, the periods between graft replacement and IV tPA therapy for the 2 patients with bleeding were 3.6 and 1.8 years. In both cases, the hematomas were gradually reabsorbed over time. One patient (Fig 1) had received a prosthetic graft for an abdominal aneurysm with the InterGard graft, which is a collagen-coated knitted Dacron graft. The other patient (Fig 2) had received a prosthetic graft for a thoracic aneurysm with the Gelweave graft, which is a gelatin-sealed woven Dacron graft.

The temporal profiles of D-dimer, fibrin degradation product (FDP), and hemoglobin (Hb) before and after IV tPA therapy are summarized in Figure 3. The increase in the mean serum D-dimer level 1 day after IV tPA therapy was greater in bleeders than in nonbleeders (+97.0 vs. +5.0 μg/mL). The serum FDP level was slightly higher in bleeders (median, 18.5; range, 11-26 μg/mL) than in nonbleeders (median, 6.0; range, 4-16 μg/mL) before and 1 day after IV tPA therapy (bleeders: median, 26; range, 26-26; nonbleeders: median, 11; range, 10-24 μg/mL) but was higher in bleeders (median, 64; range, 13-115 μg/mL) than in nonbleeders (median, 5; range, 5-5 μg/mL) 2 days after IV tPA therapy. Although Hb levels were comparable before IV tPA therapy between bleeders (median, 11.9; range, 10.8-13 g/dL) and nonbleeders (median, 11.8; range, 10.5-16.9 g/dL), they were lower in bleeders (median, 8.5; range, 8.5-8.5 g/dL) than in nonbleeders (median, 11.7; range, 10.5-16.3 g/dL) 2 days after IV tPA therapy. Other coagulation markers including activated partial thromboplastin time (APTT) and

Table 2. *Clinical data for 3 patients who underwent aortic aneurysm repair*

Case number	Age (Year)	Treatment	Site of aneurysm	Type of graft	Interval* (y)	Perigraft bleeding
1	85	Replacement	Abdominal aorta	Knitted dacron	3.6	+
2	72	Replacement	Thoracic aorta	Woven dacron	1.8	+
3	84	Replacement	Thoracic aorta	Woven dacron	0.3	−
		Replacement	Abdominal aorta	Woven dacron	2.8	−

*Interval between graft replacement and IV tPA therapy.

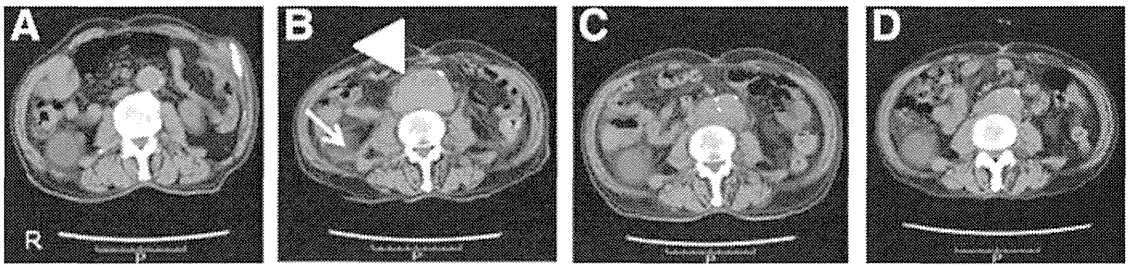

Figure 1. *An 85-year-old man who had received an aortic graft replacement for an abdominal aortic aneurysm presented with impaired consciousness and aphasia. (A, B) Body computed tomography (CT) images obtained just before intravenous recombinant tissue plasminogen activator (IV tPA) therapy (A) and 3 days after IV tPA therapy (B), when the patient experienced pain in his lower back. A hematoma was identified around the prosthetic graft (B; arrowhead) and in the retroperitoneal space (arrow). (C, D) Body CT images obtained 17 (C) and 28 days after IV tPA therapy (D) indicate that the hematoma was gradually reabsorbed.*

prothrombin time-international normalized ratio (PT-INR) were similar between the 2 groups around IV tPA therapy.

The clinical course and outcomes for the 7 patients following IV tPA therapy are summarized in Table 3. Although patients with perigraft bleeding associated with IV tPA therapy required blood transfusion therapy because of a worsening anemia, none of the patients required surgical treatment. No symptomatic intracranial hemorrhage occurred in either group. Asymptomatic intracranial hemorrhages occurred in 3 nonbleeders, which included HI-1, HI-2, and parenchymal hematoma type 1 hemorrhages. Both NIHSS and mRS scores on discharge were lower in bleeders (NIHSS: median, 2.5; range, 1-4; mRS: median, 1.5; range, 1-2) than in nonbleeders (NIHSS: median, 9; range, 1-144; mRS: median, 4; range, 2-5).

Discussion

The present study indicates that bleeding associated with IV tPA therapy occurred in 2 of the 3 (67%) patients who had undergone aortic graft replacement for aortic aneurysm. The increase in serum D-dimer levels after IV tPA therapy in patients with periprosthetic bleeding suggests that a coagulation marker may serve as a biomarker for monitoring abdominal bleeding after tPA therapy in patients with a history of aortic aneurysm. None of the patients required surgical treatment, and all patients experienced an uneventful course, which provides reassurance regarding the risk of IV tPA therapy in patients with a history of aortic aneurysm or aortic graft replacement.

Dacron and expanded polytetrafluoroethylene grafts are widely used grafts. Dacron grafts can be further categorized into 2 groups according to whether the fabric is knitted or woven. Knitted grafts have a loose weave, and their initial integrity depends on mural thrombus. After approximately 3 months, fibroblasts penetrate the fabric, and by approximately 6 months, the graft is incorporated into the tissue. Woven grafts have a tighter weave and do not rely on mural thrombus for their integrity. Thus, theoretically, it might be expected that thrombolysis might be more likely to cause bleeding through the interstices of knitted grafts than through the interstices of woven grafts. However, periprosthetic graft bleedings with thrombolysis have been reported in both knitted and woven Dacron grafts. Cable et al[10] discussed the possibility that bleeding with thrombolysis in cases with woven grafts might have been secondary to anastomotic incompetence or pseudoaneurysm. In our patients, there was no anastomotic incompetence or pseudoaneurysm before thrombolysis that was evident in the CT images. Nevertheless, the mechanisms underlying perigraft bleeding after thrombolysis remain unclear and require further study.

An early increase in FDP or D-dimer levels was observed in patients with myocardial or cerebral infarctions treated with systemic thrombolysis. Previous analyses have demonstrated that early increases in FDP or D-dimer after systemic thrombolytic therapy were associated with

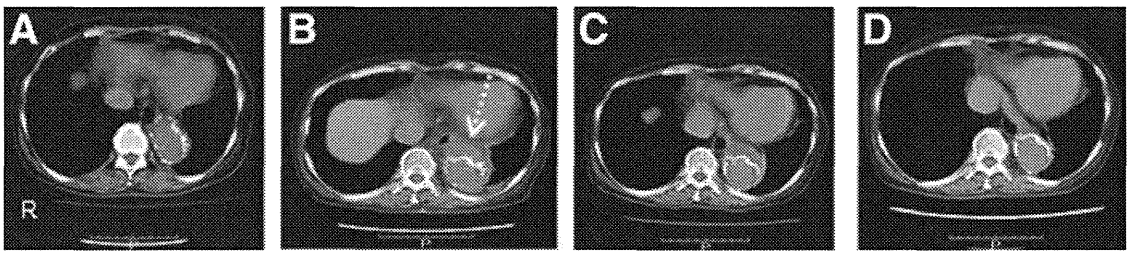

Figure 2. *A 72-year-old woman who had received an aortic graft replacement for a thoracic aortic aneurysm presented with right hemiparesis and aphasia. (A, B) Body computed tomography (CT) images obtained 9 months before IV tPA therapy (A) and 3 days after IV tPA therapy (B). Although she reported no pain, a hematoma was identified around the prosthetic graft (B; arrow). (C, D) Body CT images obtained 17 (C) and 36 days after IV tPA therapy (D) that indicate the hematoma was gradually reabsorbed.*

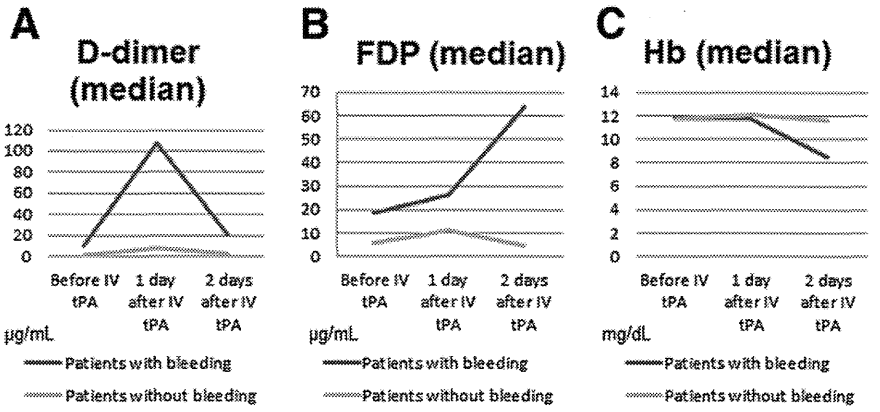

Figure 3. *Temporal profiles of D-dimer, FDP, and Hb around IV tPA therapy. (A) Temporal profile of the median serum D-dimer level around IV tPA therapy. (B) Temporal profile of the median serum FDP level around IV tPA therapy. (C) Temporal profile of the mean Hb level around IV tPA therapy.*

cerebral or general bleeding.[14-16] Trouillas et al[17] demonstrated that an increase in FDP greater than 200 mg/L 2 hours after the onset of thrombolysis could predict early cerebral hemorrhage. The D-dimer level also increases after recanalization occurs; however, the extensive increase in D-dimer or FDP levels is considered to include lysable fibrin from other systemic pools. D-dimer and FDP maybe useful biomarkers for monitoring perigraft hemorrhage in systemic thrombolytic therapy for acute ischemic stroke patients who had previously undergone aortic graft replacement, if they have no cerebral hemorrhage.

Among our 394 patients treated with IV tPA for acute ischemic stroke, none experienced an aortic aneurysm rupture after therapy. Hayashi et al[18] reported a case of an acute aneurysm rupture after systemic tPA infusion for acute stroke treatment that required surgical repair with endovascular stent grafts. Many studies have investigated the relationships between hemostatic markers and aneurysm geometrics or abdominal aneurysm growth, but they provide conflicting findings. Reilly et al[19] reported that the aortic wall in an abdominal aortic aneurysm is degraded by a synergistic combination of macrophages, plasminogen activators, and matrix metalloproteases. Lindholt et al[20] reported that tPA therapy had a positive correlation with the aneurysm growth rate, indicating that aortic matrix degradation and aneurysm expansion maybe partially caused by plasmin increases resulting from tPA. However, according to Siennicka et al,[21] there is a negative relationship between tPA and maximum abdominal aortic aneurysm diameter and intraluminal thrombus. Considering that the mechanisms of aortic aneurysm rupture after IV tPA therapy remain unclear, both the risks and benefits of tPA therapy should be carefully considered for patients with an aortic aneurysm.

Table 3. *Clinical course of patients with or without bleeding after IV tPA therapy*

Clinical course of patients	With bleeding (N = 2)	Without bleeding (N = 5)
Blood transfusion therapy, n (%)	1 (50)	0 (0)
Symptomatic ICH, n (%)	0 (0)	0 (0)
Hemorrhagic transformations in cranium within 36 h, n (%)	0 (0)	3 (60)*
NIHSS on discharge, median (range)	2.5 (1-4)	9 (1-14)
mRS on discharge, median (range)	1.5 (1-2)	4 (2-5)

Abbreviations: ICH, intracranial hemorrhage; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.

*HI-1-type hemorrhage (n = 1); HI-2-type hemorrhage (n = 1); PH-1-type hemorrhage (n = 1).

Our study has several limitations. First, the body CT images acquired shortly before IV tPA therapy were unavailable because of the life-threatening circumstances of acute ischemic stroke; there may not be sufficient time to undergo CT imaging in these situations. Thus, our findings provide only circumstantial evidence and do not exclude the possibility that periprosthetic bleeding was present before IV tPA therapy. However, Wyss et al[22] reported that there were no ruptures in the open repair of an abdominal aortic aneurysm during a mean follow-up of 4.8 years. Nevertheless, spontaneous perigraft hemorrhages are reported after successful aortic aneurysm repair on a case-report basis. Second, our sample size was relatively small because this was a retrospective, single-center study. A large prospective, multicenter study is needed to verify the relationship between IV tPA therapy and bleeding in aortic aneurysm or aortic graft replacement.

Conclusions

In summary, our data suggest that IV tPA therapy may induce bleeding around vascular grafts. When managing patients with acute ischemic stroke who have a history of aortic aneurysm or aortic graft replacement, physicians should consider both the risks and benefits of IV tPA therapy. If IV tPA therapy is initiated, then the physician must be vigilant and monitor for hemorrhage around an aortic aneurysm or vascular graft using FDP, D-dimer, and Hb levels, in addition to imaging the aorta with CT.

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Evaluation of carotid artery outward remodeling by T1-weighted magnetic resonance imaging in carotid endarterectomy and stenting

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Objective: We evaluated carotid artery outward remodeling and plaque relative signal intensity (rSI) using T1-weighted magnetic resonance imaging (T1-MRI) to investigate their clinical significance in carotid revascularization.
Methods: From 86 patients undergoing carotid endarterectomy (CEA) or carotid artery stenting (CAS), 88 lesions (51 lesions treated with CEA and 37 lesions treated with CAS) were analyzed retrospectively. We evaluated the preoperative carotid artery remodeling index (CRI), determined by a ratio of the external cross-sectional vessel area at maximum stenosis and the reference cross-sectional vessel area at the distal portion of the internal carotid artery, and the plaque rSI, which is quantified as the ratio between the signal intensities of plaque and adjacent muscle using T1-MRI. We divided carotid lesions into four groups using the median values of CRI and rSI: L/L (CRI < 1.8, rSI < 2.5), H/L (CRI ≥ 1.8, rSI < 2.5), L/H (CRI < 1.8, rSI ≥ 2.5), and H/H (CRI ≥ 1.8, rSI ≥ 2.5). The primary end point was detection of acute ipsilateral ischemia on diffusion-weighted imaging (DWI) within 72 hours of treatment.
Results: Mean CRI and rSI were significantly higher in lesions treated with CEA than in those treated with CAS. Postoperative DWI abnormalities were observed in 4 CEA cases (7.8%) and 10 CAS cases (27.0%) ($P = .01$). In the CAS group, the frequency of DWI abnormalities was 5.5% for the L/L, 40.0% for the H/L and L/H, and 55.5% for the H/H group ($P = .009$). Multivariate analysis showed that the degree of stenosis and H/H lesion were independent risk factors for cerebral embolism. No correlation was found between plaque parameters and postoperative DWI findings in the CEA group.
Conclusions: CRI and rSI provide complementary information for the prediction of high-risk plaques associated with CAS but not with CEA. Preoperative evaluation with T1-MRI facilitates the selection of a treatment strategy for carotid artery stenosis. (J Vasc Surg 2015;■:1-8.)

In the initial stages of atherosclerotic plaque formation, before luminal stenosis, arterial enlargement occurs to ensure an adequate luminal area.[1] This phenomenon is known as expansive, positive, or outward remodeling of the artery. In coronary arteries, this process plays an important role in plaque vulnerability.[2-6] Outward remodeling of the carotid artery has also been documented,[7,8] as has a high rate of stroke recurrence with low-grade (<50%) stenosis[9] and the association of symptoms with high-grade (≥50%) stenosis.[10,11]

Carotid plaque imaging using a T1-weighted magnetic resonance imaging (T1-MRI) technique, such as magnetization-prepared rapid acquisition with gradient-echo (MPRAGE) or cardiac-gated black-blood MRI, is widely used to predict vulnerability.[12-15] It helps predict further ischemic events[16-18] and complications of carotid endarterectomy (CEA) or carotid artery stenting (CAS).[19-21] A recent report suggested that a high-intensity signal in the plaque on screening with time-of-flight (TOF) magnetic resonance (MR) angiography can discriminate plaques that are at higher risk for cerebral embolism during CAS procedures.[22]

Few studies have evaluated both carotid remodeling and plaque signal intensity simultaneously,[11] and no study to date has investigated their relationship with outcomes after surgical intervention. We previously demonstrated that the degree of carotid remodeling and plaque signal intensity correlate with plaque vulnerability, as confirmed by clinical and histologic examinations.[23] On the basis of these results, we hypothesized that carotid remodeling might be associated with ipsilateral cerebral embolism during surgical revascularization. The aim of this study was to investigate the clinical significance of arterial outward remodeling in patients who had undergone either CEA or CAS for atherosclerotic carotid artery stenosis. We also aimed to clarify any association with plaque relative signal intensity (rSI) using T1-MRI.

METHODS

Study population. This was a single-center, retrospective cohort study. We enrolled 93 consecutive patients who had undergone CEA or CAS for atherosclerotic carotid

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artery stenosis (95 lesions) at the National Cerebral and Cardiovascular Center in Japan between January 2011 and April 2012. Exclusion criteria for the study were (1) lesions whose maximum area of stenosis was in a common carotid artery (n = 4), (2) lesions that caused near-occlusion (n = 1), (3) restenosis after CEA or CAS (n = 1), and (4) preoperative evaluation using 1.5 T MRI (n = 1).

Finally, we investigated 88 lesions (51 treated with CEA and 37 treated with CAS) from 86 patients. The patients' baseline characteristics were obtained by reviewing medical records. Patients were considered symptomatic if they had experienced a stroke, amaurosis fugax, or transient ischemic attacks involving the ipsilateral carotid area within 180 days of the initial assessment.[24] Measurements of carotid stenosis (percentage determined on the basis of the diameter) were obtained using the North American Symptomatic Carotid Endarterectomy Trial methodology, based on angiography or computed tomography angiography.[25] Symptomatic patients with >70% stenosis and asymptomatic patients with >80% stenosis of the carotid artery were considered for revascularization. CEA was considered the first-line therapy; CAS was indicated mainly in high-risk patients with unfavorable neck anatomy for arterial surgery or with comorbidities that increased the risk of general anesthesia.[26] In older patients (>80 years), both procedures were considered, and the choice was based on the characteristics of the lesion and the patient's general condition.

The study protocol was in accordance with the Declaration of Helsinki and was approved by the local Institutional Review Board. All patients provided written informed consent before participating.

MRI procedures. MRI was performed using a standard neck array and spine array coils in a Verio 3T system (Siemens, Munich, Germany). Three-dimensional, inversion recovery-based T1-MRI (MPRAGE) was used to examine the carotid artery structure, including the external vessel wall and the vascular lumen, transaxially in the null blood condition (effective inversion time, 660 milliseconds; repetition time, 1400 milliseconds). The water excitation technique was used to suppress fat signals. Other scanning parameters were as follows: echo time, 2.68 milliseconds; field of view, 250 × 250 mm; matrix, 256 × 256; section thickness, 1.5 mm; 56 partitions, covering 70 mm around the carotid bifurcation; and data acquisition time, 3 minutes 46 seconds. Multislab three-dimensional TOF MR angiography was also performed to delineate the luminal shape (echo time, 3.69 milliseconds; repetition time, 25 milliseconds; same spatial resolution as in MPRAGE).

The same MRI system was used for diffusion-weighted imaging (DWI). The echoplanar method was applied under the following conditions: repetition time, 6000 milliseconds; echo time, 80.0 milliseconds; slice thickness, 5 mm; spacing, 1.5 mm; level of diffusion weighting (b value), 1000 s/mm^2; and field of view, 23 cm.

Quantitative evaluation of carotid remodeling and plaque rSI. Plaque imaging data were transferred to a personal computer running open-source OsiriX imaging software (version 5.6 32-bit; http://www.osirix-viewer.com/) to assess the carotid artery remodeling. The degree of luminal stenosis in the carotid arteries was evaluated by analysis of an axial image and curved multiplanar reconstruction to produce a two-dimensional image showing the cross-sectional profile of a vessel along its length. Atherosclerotic lesions were identified on axial images, and serial cross-sectional images were obtained by changing the orientation of the z-axis. We evaluated the carotid remodeling index (CRI), the ratio of external cross-sectional vessel area (CSVA) at maximum stenosis to the distal portion of the internal carotid artery (Fig 1).[6]

Using MPRAGE, for each image, the signal intensity of plaques and of the adjacent muscle (typically the sternocleidomastoid muscle) was measured at 5-mm intervals from the common carotid bifurcation to the internal carotid artery.[18] MR rSI of the atherosclerotic plaque was quantified as the ratio between the signal intensities of plaque and adjacent sternocleidomastoid muscle. A single, blinded investigator (D.M.) obtained all measurements. The reproducibility of CRI was assessed by measurements performed by a second investigator (Y.K.) in all patients.

Evaluation of postoperative cerebral embolism. All patients underwent MRI including DWI within 72 hours of the revascularization procedures. We retrospectively evaluated the presence of acute ipsilateral ischemic lesions using postprocedural DWI. The results were compared with those of the baseline imaging performed before the operation, and only new, hyperintense ipsilateral lesions were recorded.

Therapeutic procedures. CEA was performed under general anesthesia using an operating microscope and somatosensory evoked potential monitoring to selectively place the shunt.[27]

For CAS, patients were administered antiplatelet agents (clopidogrel [75 mg daily] and aspirin [100 mg daily], or clopidogrel [75 mg daily] and cilostazol [200 mg daily], given in combination) at least 4 days before the procedure. With the patient under local anesthesia, a sheath was placed in the femoral artery or, in some cases, in the brachial artery. Heparin was administered to achieve an activated coagulation time >275 seconds, and a guiding catheter was placed in the common carotid artery. The distal protection device was passed through the lesion and deployed distally in the vessel. In most cases, predilation was performed with an undersized balloon. A stent of appropriate size was selected and deployed. Postdilation with a larger balloon was performed when the minimum diameter of the stenotic lesion was <3 mm, as determined by intravascular ultrasound. The distal protection device was then collapsed and withdrawn. Embolic filter devices used were FilterWire EZ (Stryker, Kalamazoo, Mich) in 36 cases and Angioguard XP (Johnson & Johnson, Cordis, Miami, Fla) in 1 case. For the stents, Precise Pro RX (Johnson & Johnson) was used in 35 cases, and Carotid Wallstent Monorail (Stryker) was used in 2 cases. All CEA and CAS procedures were managed by the same surgeon (K.I.).

Statistical analysis. Continuous variables are presented as mean ± standard deviation. Categorical data are reported as frequencies (percentages). Categorical variables were compared by Fisher exact test. The two-sided

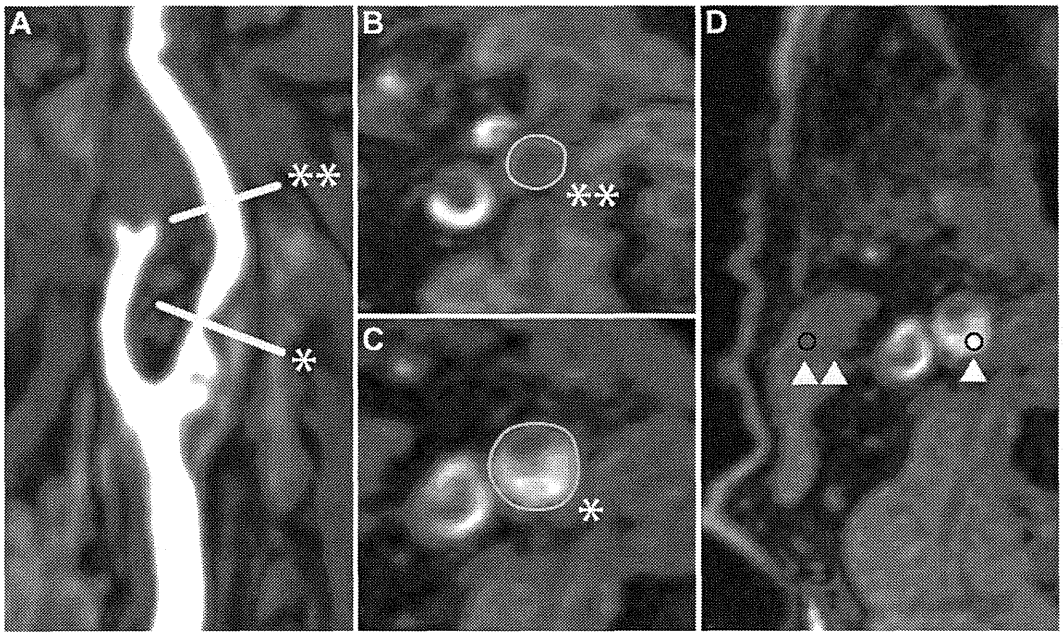

Fig 1. Representative images of carotid lesions. **A**, Sagittal section of carotid stenosis on time-of-flight (TOF) magnetic resonance (MR) angiography (*maximum stenosis of the internal carotid artery; **unaffected part of the distal internal carotid artery). **B** and **C**, *Encircled regions* show the external cross-sectional areas of the distal internal carotid artery (**B**, **) and maximum stenosis of the internal carotid artery (**C**, *) by a three-dimensional inversion recovery-based T1-weighted magnetic resonance imaging (T1-MRI) technique (magnetization-prepared rapid acquisition with gradient-echo [MPRAGE]). **D**, Zoomed source image of MPRAGE. The signal intensity of plaques (*circle with arrowhead*) and of the adjacent muscle (*circle with double arrowheads*) was measured.

unpaired *t*-test and the Mann-Whitney *U* test were used to analyze normally and non-normally distributed continuous variables, respectively. Cases of acute cerebral embolism during revascularization were analyzed, and statistical tests for trend were performed for study groups segregated using the median of both CRI and rSI values. The occurrence of acute ipsilateral ischemic lesions was tested with univariate and multivariable analyses by logistic regression for age, sex, degree of stenosis, symptoms, hypertension, diabetes, dyslipidemia, peripheral vascular disease, coronary artery disease, CRI, and rSI. Stepwise logistic regression with backward elimination for *P* values > .10 was used to select the most significant predictors. Statistical significance was defined as a *P* value < .05. Analysis was performed with the JMP software package (version 9.0.2; SAS Institute, Cary, NC) and Stata 13 (StataCorp, College Station, Tex).

The Cohen κ value was calculated to quantify the level of agreement regarding CRI between observers. A κ value ≥ 0.75 was used to indicate a high level of agreement.

RESULTS

Table I summarizes the baseline characteristics of the study cohort. Symptoms were present in 45 patients (51.1%) in the entire patient group, 28 patients (54.9%) in the CEA group and 17 patients (45.9%) in the CAS group. There was no significant difference between the two groups. The frequency of comorbid dyslipidemia was 84.3% in the CEA group and 64.8% in the CAS group ($P = .03$). The frequency of coronary artery disease was 17.6% in the CEA group and 59.4% in the CAS group ($P < .0001$).

Quantitative evaluation of carotid remodeling and plaque rSI. In the entire group of patients, the mean and median values of CRI were 1.86 ± 0.57 and 1.82, and those of rSI were 2.48 ± 1.01 and 2.54. A mild positive correlation was observed between the values of CRI and rSI ($r = 0.35$; $P = .0006$). No significant correlation was observed between the degree of stenosis and the values of CRI ($r = -0.03$; $P = .72$) or rSI ($r = -0.11$; $P = .27$). The mean value of CRI was significantly higher in the CEA group (2.02 ± 0.58) than in the CAS group (1.64 ± 0.49) ($P = .002$). The mean value of rSI was also significantly higher in the CEA group (2.78 ± 1.01) than in the CAS group (2.06 ± 0.86) ($P = .0007$) (Fig 2, *A* and *B*). However, there was no difference between symptomatic and asymptomatic lesions in terms of mean CRI and rSI (Fig 2, *C* and *D*).

Interobserver agreement of CRI was excellent ($\kappa = 0.79$; $P < .0001$).

Postoperative cerebral embolism. Ipsilateral, small, hyperintense lesions on DWI within 72 hours of the operation were observed in 4 lesions (7.8%) in the CEA group and 10 lesions (27.0%) in the CAS group ($P = .01$). In the perioperative period, no ipsilateral strokes or myocardial infarctions occurred in the study cohort. Only one death

Table I. Baseline clinical characteristics of the study cohort

	CEA (n = 51)	*CAS (n = 37)*	P *value*
Age, years	71.7 ± 6.9	71.6 ± 4.6	.96
Male sex	44 (86.2)	35 (94.5)	.20
Symptomatic lesion	28 (54.9)	17 (45.9)	.46
Medical history			
Hypertension	44 (86.2)	33 (89.1)	.96
Diabetes mellitus	14 (27.4)	6 (16.2)	.21
Dyslipidemia	43 (84.3)	24 (64.8)	.03
Peripheral vascular disease	3 (5.9)	4 (10.8)	.39
Coronary artery disease	9 (17.6)	22 (59.4)	<.0001
Medication			
Aspirin	42 (82.4)	34 (91.9)	.19
Clopidogrel	17 (33.3)	37 (100)	<.0001
Cilostazol	6 (11.8)	3 (8.1)	.57
Statins	36 (70.6)	25 (67.6)	.76
CCBs	26 (50.9)	19 (51.4)	.97
ARBs	19 (37.3)	12 (32.4)	.64
Laboratory parameters			
Total cholesterol, mg/dL	160.8 ± 32.8	168.8 ± 31.6	.28
Triglycerides, mg/dL	137.9 ± 77.4	127.2 ± 66.3	.50
HDL cholesterol, mg/dL	43.8 ± 10.8	47.4 ± 12.7	.16
LDL cholesterol, mg/dL	92.9 ± 26.1	98.9 ± 22.9	.26
C-reactive protein, mg/dL	0.46 ± 1.5	0.28 ± 0.3	.45
Plaque parameters			
Degree of stenosis, %	74.7 ± 11.7	79.0 ± 8.5	.06
Ulceration	8 (15.7)	2 (5.4)	.13
Calcification	25 (49.0)	21 (56.8)	.47

ARBs, Angiotensin II receptor blockers; *CAS,* carotid artery stenting; *CCBs,* calcium channel blockers; *CEA,* carotid endarterectomy; *HDL,* high-density lipoprotein; *LDL,* low-density lipoprotein.
Continuous data are presented as mean ± standard deviation and categorical data as number (%).

(1.9%) occurred in the CEA group, caused by severe ileus and pneumonia.

Univariate analysis of the risk factors for postoperative ischemic lesions showed no significant factor in the CEA group (Supplementary Table I, online only). In the CAS group, both CRI and rSI were significant predictors for cerebral embolism as continuous variables in univariate and multivariable analyses. However, after both variables were included in the model simultaneously to determine which was more important, both variables became marginally significant (Supplementary Table II, online only). Therefore, we subdivided the patients into four groups according to high (H) and low (L) CRI in lesions with high (H) and low (L) rSI, based on their median values: L/L (CRI < 1.8, rSI < 2.5), H/L (CRI ≥ 1.8, rSI < 2.5), L/H (CRI < 1.8, rSI ≥ 2.5), and H/H (CRI ≥ 1.8, rSI ≥ 2.5) (Fig 3, *A*). In the CAS group, the observed frequency of DWI abnormalities was 5.5% in group L/L, 40.0% in H/L, 40.0% in L/H, and 55.5% in H/H (trend, $P = .009$). On the other hand, no significant trend was observed in the CEA group ($P = .901$) (Fig 3, *B* and *C*).

In the CAS group, the degree of stenosis, L/L lesion, and H/H lesion were all identified as significant factors (Table II). In multivariable logistic regression analysis using stepwise selection, degree of stenosis and H/H lesion were found to be independent risk factors (Table II).

Defining high-risk plaques as non-L/L lesions provided a sensitivity of 90%, specificity of 62.9%, positive predictive value of 47.3%, and negative predictive value of 94.4%. If rSI or CRI was used alone, it provided a sensitivity of 70.0%, specificity of 74.1%, positive predictive value of 50.0%, and negative predictive value of 87.0%.

DISCUSSION

This study demonstrated that (1) both CRI and rSI were significantly higher in the CEA group than in the CAS group, but no difference was seen between those with symptoms and those without symptoms; (2) in the CAS group, the frequency of postoperative ipsilateral cerebral embolism was highest in carotid lesions when both CRI and rSI were high, and lowest when both were low; (3) on multivariable analysis, for both CRI and rSI, high plaque markers (H/H lesion; CRI ≥ 1.8, rSI ≥ 2.5) and the degree of stenosis were independent risk factors for postoperative ipsilateral ischemic lesions in the CAS group; and (4) no association was observed between plaque imaging parameters and postoperative ischemic events in the CEA group.

Glagov et al[1] first reported expansive vessel remodeling to maintain an adequate luminal area in response to early-stage formation of atherosclerotic plaques. Since then, several studies have used a range of imaging modalities to show a relationship between this process and coronary artery vulnerability to plaque formation.[2-6]

The method for calculating the CRI was based on an earlier work by Varnava et al,[6] who evaluated plaque remodeling in the coronary artery using the cross-sectional area at the plaque and reference segments. Unlike the coronary artery, the internal carotid artery does not taper in a uniform or predictable fashion, and the location of a segment that is notably normally expanded (ie, the carotid bulb) is considerably variable. This could be a major limitation for the evaluation of carotid artery remodeling. In theory, however, any significant variability would be accounted for, because any natural variance would be similar in the study group. In addition, any variance in the location of plaque within the vessel would be likely again accounted for, because in all patients, plaques occur almost exclusively near the bulb region. In our previous study, to evaluate the effect of this natural variance, we analyzed 20 lesions (20 patients having lacunar infarction without any carotid artery stenosis; 18 men; mean age, 66.8 ± 6.4 years) as normal controls for validation. The results revealed that the study group (36 patients with symptomatic carotid stenosis [32 men; mean age, 70.5 ± 8.7 years] and 25 patients with asymptomatic carotid stenosis [22 men; mean age, 66.4 ± 6.5 years]) showed a significantly higher CRI and larger external CSVA at

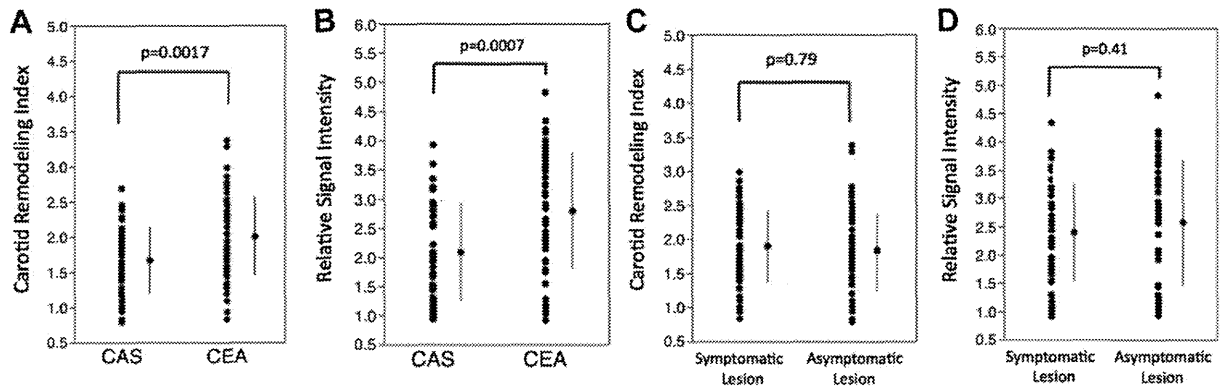

Fig 2. Carotid remodeling index (CRI) and relative signal intensity (rSI) between carotid endarterectomy (*CEA*) and carotid artery stenting (*CAS*) groups (**A** and **B**) and symptomatic and asymptomatic lesions (**C** and **D**).

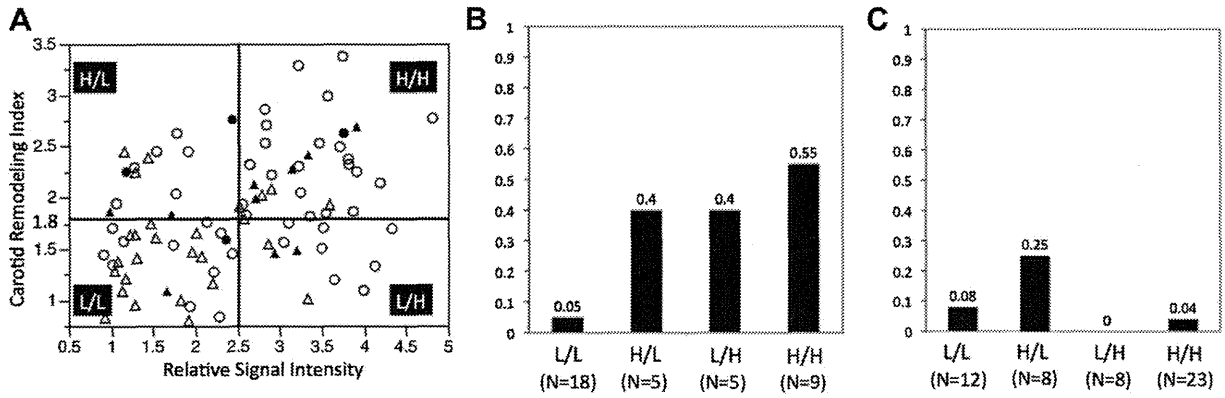

Fig 3. A, Division of carotid lesions using the median values of carotid remodeling index (CRI) and relative signal intensity (rSI): L/L (CRI < 1.8, rSI < 2.5), H/L (CRI ≥1.8, rSI < 2.5), L/H (CRI < 1.8, rSI ≥ 2.5), and H/H (CRI ≥ 1.8, rSI ≥ 2.5). Carotid lesions were divided into four groups: carotid endarterectomy (CEA) with cerebral embolism (*filled circle*), CEA without cerebral embolism (*open circle*), carotid artery stenting (CAS) with cerebral embolism (*filled triangle*), and CAS without cerebral embolism (*open triangle*). **B,** In the CAS group, the observed frequencies of diffusion-weighted imaging (DWI) abnormalities in groups L/L, H/L, L/H, and H/H were 5.5%, 40.0%, 40.0%, and 55.5%, respectively (*P* for trend = .009). **C,** In the CEA group, no significant trend was observed ($P = .901$).

the maximum stenosis of the internal carotid artery than the control group. However, the external CSVA at the distal internal carotid artery was almost identical in these groups. Therefore, we believe that our assumption for calculating CRI does not misrepresent the presence of arterial outward remodeling in this study group.

Hardie et al[10] used multidetector computed tomography angiography in a series of subjects with high-grade (≥50%) internal carotid artery stenosis and found significantly greater expansive carotid remodeling in patients with cerebral symptoms than in asymptomatic patients. Yoshida et al,[9] using T1-MRI, reported that symptomatic, low-grade (<50%) carotid stenosis with both high-signal plaque and expansive remodeling was associated with a high rate of stroke recurrence that was refractory to aggressive medical treatment. However, no difference was observed in CRI between symptomatic and asymptomatic lesions in this study. This finding, which contradicts other results, including our previous study, may be due to the evolution of medical therapy and the decrease in the use of surgical intervention for asymptomatic carotid stenosis[28]; thus, selection bias for asymptomatic lesions may have occurred in these studies.

In the present study, both CRI and rSI were significant predictors for cerebral embolism as continuous variables in univariate and multivariable analyses in the CAS group. However, after both variables were included in the model simultaneously to determine which was more important, both variables became marginally significant (Supplementary Table II, online only). In considering these two independent parameters simultaneously, patients who showed high CRI and high rSI were thought to be at the

Table II. Univariate and multivariable analyses of factors for ipsilateral cerebral embolism during carotid artery stenting (CAS)

	Univariate analysis		*Multivariable analysis*	
	OR (95% CI)	P *value*	*OR (95% CI)*	P *value*
Age	1.10 (0.93-1.31)	.24		
Male sex	0.34 (0.012-9.35)	.47		
Symptomatic lesion	3.96 (0.88-21.84)	.07		
Medical history				
Hypertension	1.12 (0.12-24.37)	.92		
Diabetes mellitus	0.48 (0.02-3.63)	.51		
Dyslipidemia	0.75 (0.16-3.56)	.70		
Coronary artery disease	1.86 (0.41-10.12)	.42		
Medication				
Aspirin	NA	.16		
Cilostazol	NA	.16		
Statins	0.85 (0.15-3.94)	.84		
CCBs	0.34 (0.06-1.52)	.16		
ARBs	1.16 (0.25-6.40)	.84		
Laboratory parameters				
Total cholesterol	1.01 (0.97-1.03)	.67		
Triglycerides	1.01 (0.99-1.02)	.13		
HDL cholesterol	1.01 (0.94-1.07)	.76		
LDL cholesterol	0.98 (0.95-1.02)	.49		
C-reactive protein	4.36 (0.54-43.79)	.16		
Plaque parameters				
Degree of stenosis	1.21 (1.05-1.43)	.002	1.21 (1.03-1.42)	.019
Ulceration	1.36 (0.12-8.15)	.99		
Calcification	0.69 (0.16-3.02)	.61		
Plaque subgroups[a]				
L/L	0.055 (0.0027-0.36)	.0013	Reference	
H/L	1.43 (0.17-8.97)	.70	28.41 (0.80-1002.08)	.066
L/H	3.12 (0.33-29.75)	.29	14.19 (0.84-238.33)	.065
H/H	8.0 (1.50-51.30)	.014	27.01 (1.63-444.99)	.021

ARBs, Angiotensin II receptor blockers; *CCBs,* calcium channel blockers; *CI,* confidence interval; *HDL,* high-density lipoprotein; *LDL,* low-density lipoprotein; *NA,* not applicable; *OR,* odds ratio.
[a]The designations of the plaque parameters are described in Results.

highest risk of cerebral embolism; therefore, we subdivided the patients into four groups according to high and low CRI in lesions with high and low rSI. Importantly, the rate of cerebral embolism in the group with high CRI with low rSI was intermediate but comparable with that in the group with low CRI with high rSI. Although the number of lesions in these subgroups was rather small (Fig 3), our results indicate that there is a possible important subgroup at a high risk for cerebral embolism that may be undetected when only plaque signal intensity is used. Concerning the cut-off values of CRI and rSI, we used the median values of these parameters to analyze both the CEA and CAS groups. In the CAS group, by using receiver operating characteristic curve analysis, the optimal cutoff values of CRI and rSI for predicting cerebral embolism were noted to be 1.83 (area under the curve, 0.72; 95% confidence interval, 0.53-0.90) and 2.69 (area under the curve, 0.74; 95% confidence interval, 0.54-0.94), being nearly identical to the cut-off values obtained in this analysis.

Only a few studies have evaluated both carotid remodeling and plaque signal intensity. Miura et al[13] showed a significant positive correlation between the extent of remodeling (defined as the ratio between maximum stenosis and reference distal portion) and the plaque rSI. To our knowledge, no report to date has investigated the clinical importance of both CRI and rSI in surgical intervention. The present study is the first to show that CRI and rSI can be used as complementary parameters to identify high-risk plaques for cerebral embolism after CAS. Detection of vulnerable plaques using the MR signal intensity of the carotid plaque tends to vary by the MRI technique used.[29] In histopathologic analysis, Hishikawa et al[15] demonstrated that in patients with high-grade carotid artery stenosis, high signal intensity on MPRAGE sequences indicates larger necrotic cores and a more severe degree of intraplaque hemorrhage than lower signal intensity. However, they discussed that the signal hyperintensity may not be related to fresh thrombi or hemorrhages. Similarly, Yoshimura et al[22] revealed that high-intensity signals in the plaques on TOF MR angiography were associated with intraplaque hemorrhage, based on glycoprotein A levels, and macrophage infiltration but not with the thickness of the fibrous cap. In a previous study, Fukuda et al[23] showed that higher CRI is associated with a high necrotic core proportion and intraplaque hemorrhage score as well as with a high prevalence of fresh intraplaque hemorrhage,

mural thrombus, and inflammatory cells (macrophages and lymphocytes); further, CRI is negatively correlated with fibrous cap thickness. Although the direct histopathologic comparison of plaques with these plaque parameters has not yet been reported, these findings support our conclusion that CRI and rSI could provide complementary information to improve the predictive value for events after CAS.

The clinical implications of our findings are that CRI and rSI can be used to predict cerebral embolisms in patients who have had CAS, but not after CEA. Using these two variables together provides a positive predictive value of 50% and a negative predictive value of about 95% for CAS. Thus, we can identify approximately 50% of plaques at low risk for embolism after CAS. In cases in which the risk is higher, a CEA procedure should be performed, or if this is not possible, CAS should be performed with a different type of embolic protection or stents. MPRAGE imaging may be used in the clinic to evaluate plaque vulnerability using both CRI and rSI.

This study has several limitations. First, selection bias may exist because of the nonrandom choice of treatment and retrospective nature of the study. Although our treatment strategy for carotid stenosis is not simply based on the preoperative diameter ratio, a marginally significant difference was noted in the degree of stenosis between the CEA and CAS groups. However, our findings suggest that embolic complications after CEA procedures can be prevented because both CRI and rSI were significantly higher in the CEA group than in the CAS group. Second, the sample size was small, and Fig 2 shows a wide spread of values for both CRI and rSI. A study involving a larger sample is needed. However, the present study was conducted in a single center, and all procedures were managed by a single surgeon; thus, good reproducibility among procedures was achieved. Third, carotid plaque volume is reported to be an important indicator for distal embolism related to CAS,[30] but the relationship between CRI and plaque volume remains unclear. The relationship between carotid plaque volume, CRI, and distal embolism attributable to CAS remains to be elucidated in future studies.

CONCLUSIONS

CRI and rSI provide complementary information for the identification of high-risk plaques associated with CAS but not with CEA. Preoperative evaluation with T1-MRI facilitates the selection of a treatment strategy for carotid artery stenosis.

AUTHOR CONTRIBUTIONS

Conception and design: DM, KF, KI
Analysis and interpretation: DM, HK, YM
Data collection: DM, YK
Writing the article: DM
Critical revision of the article: KN, KI
Final approval of the article: KI
Statistical analysis: KN
Obtained funding: Not applicable
Overall responsibility: KI

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