Comparative Evaluation of Angioscopy and Intravascular Ultrasound for Assessing Plaque Protrusion During Carotid Artery Stenting Procedures

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BACKGROUND: Evaluation of plaque protrusion after carotid artery stenting (CAS) is important for predicting periprocedural ischemic complications. In contrast to intravascular ultrasound (IVUS), angioscopy allows direct visualization of the plaque. The aim of this study was to evaluate utility and safety of angioscopy during CAS and compare it with IVUS.

METHODS: The study included 13 carotid artery stenosis lesions in 11 consecutive patients (mean age 70.5 years; 10 men) at a single center. During CAS procedure, poststenting plaque protrusion was evaluated with angioscopy and IVUS.

RESULTS: Mean level of internal carotid artery stenosis was 79.2%. Eight lesions were symptomatic, and 5 lesions were predicted to have vulnerable plaque by preprocedural magnetic resonance imaging. A carotid WALLSTENT was placed in all cases. After stenting, angioscopy provided good visualization in all cases. Plaque protrusions were observed in 1 case by IVUS and in 8 cases by angioscopy. Diffusion-weighted imaging showed positive lesions in 3 cases (23%). For 2 of these lesions, plaque protrusions were observed by angioscopy but not by IVUS. All lesions associated with positive diffusion-weighted imaging findings were observed to have yellow plaque on angioscopy.

CONCLUSIONS: Angioscopy provided direct visualization of stent lumens after CAS. Angioscopy detected more plaque protrusion than IVUS and allowed clearer observation of plaque characteristics. Angioscopy may be more useful than IVUS for examination of plaque protrusion and plaque evaluation after CAS, especially for plaque identified as potentially vulnerable by preprocedural examination.

INTRODUCTION

In carotid artery stenting (CAS), plaque assessment is extremely important for identifying patients at risk of ischemic complications, such as patients with protruding, mobile, or vulnerable plaque, who may need additional treatment. A plaque assessment is usually performed before the CAS procedure using carotid artery ultrasound and magnetic resonance imaging (MRI). Intraprocedural evaluations are also important, in which intravascular ultrasound (IVUS) or optical coherence tomography (OCT) is often used. However, IVUS and OCT provide only an indirect view of the plaque. In contrast, angioscopy can directly visualize the vascular lumen, showing the color of its surface, small thrombi, plaque protrusion, and morphology. Since the 1980s, endoscopy and then angioscopy have been recognized as useful for identifying arteriosclerosis-related plaque in coronary disease. However, there have been few reports about the use of angioscopy for investigating carotid artery disease. In this study, we observed vascular and stent lumens on angioscopy during CAS procedures and evaluated the risk of ischemic complication during the periprocedural period, comparing the utility and safety of angioscopy in CAS with that of IVUS.

Key words
- Angioscopy
- Carotid artery stenting
- Plaque protrusion

Abbreviations and Acronyms
- CAS: Carotid artery stenting
- CEA: Carotid artery endarterectomy
- CREST: Carotid Revascularization Endarterectomy versus Stenting Trial
- DWI: Diffusion-weighted imaging
- ECA: External carotid artery
- ICA: Internal carotid artery
- IVUS: Intravascular ultrasound
- MRI: Magnetic resonance imaging
- OCT: Optical coherence tomography
- PAES: Parodi antiemboli system
- SAPPHIRE: Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy

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MATERIALS AND METHODS

Patients
The study included 13 carotid artery stenosis lesions in 11 consecutive patients (mean age 70.5 years; 10 men) between February and September 2015. The angioscopy system used in this study is recognized by insurance companies in Japan for use in coronary artery disease, but not in carotid artery disease. The ethical review board of our hospital approved its use for this study, and written informed consent was obtained from all patients. The study was conducted in accordance with the principles of the Declaration of Helsinki. The inclusion criteria were as follows: asymptomatic internal carotid artery (ICA) stenosis >80% of the lumen diameter or symptomatic ICA stenosis >50% of the lumen diameter was present; a high risk for endarterectomy existed according to the criteria of the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) study; ICA stenosis suddenly progressed in the follow-up course and the need of CAS was considered.

Plaque morphology and character were evaluated before the procedure by black blood imaging and time-of-flight angiography on MRI. Vulnerable plaque was defined as plaque exhibiting high signal on T1-weighted or T2-weighted imaging compared with the intensity of the parotid and maxillary glands or the existence of high signal in the plaque on time-of-flight imaging. During the CAS procedure, IVUS and angioscopy were performed and evaluated before and after stenting. All patients underwent neurologic examinations before and after the CAS procedure, and MRI diffusion-weighted imaging (DWI) was acquired the day after CAS to evaluate ischemic changes. The CAS, IVUS, and angioscopy procedures were based on procedures reported in a previous study.

Carotid Artery Stenting
CAS procedures were performed according to our standard technique with the modified Parodi antiemboli system (PAES) and distal protection of the ICA by FilterWire EZ (Boson Scientific, Marlborough, Massachusetts, USA) to prevent any distal embolic complications under the condition of local anesthesia. For at least 2 weeks before the procedure, patients received dual (1 patient) or triple (10 patients) antiplatelet therapy combining aspirin (100 mg/day) with clopidogrel (75 mg/day) and/or cilostazol (200 mg/day). Ten patients were also taking statins.

The procedure was as follows. After placing a 9-F long sheath introducer in the femoral artery and a 4-F short sheath in the femoral vein at the opposite side as a flow reversal system, the patient was systemically heparinized with a heparin bolus, followed by continued intravenous heparin throughout the CAS procedure to maintain an activated clotting time >275 seconds. A 9-F guiding catheter with an occlusion balloon (OPTIMO; Tokai Medical Products, Inc., Aichi, Japan) was guided into the common carotid artery with a coaxial system using a 6-F inner catheter (JB2; Medikit Co. Ltd., Tokyo, Japan) and a 0.035-inch stiff guidewire (Radifocus Guidewire M Stiff type; Terumo Corporation, Tokyo, Japan). The OPTIMO balloon was then connected to a 4-F short sheath, which was placed in the femoral vein through a filter for blood transfusion as a flow reversal system. To prevent the backflow of blood from the external
A carotid artery (ECA), a carotid GuardWire (Medtronic, Minneapolis, Minnesota, USA) was placed in the ECA at the proximal side of the bifurcation of the superior thyroid artery. Under the flow reversal condition with the OPTIMO balloon and carotid GuardWire inflated, a FilterWire EZ was gently passed through the stenotic lesion and deployed in the petrous portion of the ICA to provide distal protection. Before stenting, the OPTIMO balloon was deflated to allow IVUS to be performed and then reinflated to prevent the inflow of blood while angiography was performed with a saline flush to wash out blood. Then under the flow reversal condition, predilation for percutaneous transluminal angioplasty was performed with a balloon selected according to the size of a normal portion of the ICA. A carotid WALLSTENT (Boston Scientific) was placed to completely cover the plaque. After stenting, postdilation with the percutaneous transluminal angioplasty balloon was followed by blood aspiration using an aspiration catheter (Medtronic) until all debris had been removed. The aspirated blood was infused via a filter through the sheath at the femoral vein. After aspiration, IVUS and angiography were performed again.

**Intravascular Ultrasound**

IVUS was performed using an Eagle Eye Platinum IVUS catheter (Philips Corporation, San Diego, California, USA) with a Volcano 95 IVUS imaging system (Philips Corporation). Plaque protrusion was detected by ChromaFlo (Philips Corporation) IVUS, which colorizes the flow, as defects in the flow.

**Angioscopy**

Angioscopy was performed using a VISIBLE Fiber angioscope (FiberTech Co., Ltd., Tokyo, Japan) (external diameter of the inserted part, 0.75 mm; effective length, 1620 mm) with an imaging system, FT-203F (FiberTech Co., Ltd.), based on 3 charge-coupled devices (Figure 1). Once the modified PAES and distal protection were in place, as described under Carotid Artery Stenting, the angioscope was inserted into the aspiration catheter and guided to the distal side of the carotid lesion. With the blood flow to the ICA interrupted by the OPTIMO balloon in the common carotid artery and the carotid GuardWire in ECA, intraluminal blood was expelled by flushing approximately 50 mL of physiologic saline through the OPTIMO balloon, allowing the vascular and stent lumens to be clearly observed (Figure 2).

**Statistical Analysis**

JMP Version 10 software (SAS Institute Inc., Cary, North Carolina, USA) was used for statistical analysis. Data were compared by using \( \chi^2 \) test with Fisher exact test. \( P \) values < 0.05 were considered statistically significant. Factors with \( P < 0.3 \) in \( \chi^2 \) tests were included in multivariate logistic regression analysis.
RESULTS

This study enrolled 11 patients. Two patients had bilateral lesions; thus, 13 lesions were analyzed. In the preprocedural plaque evaluations, the mean level of ICA stenosis was 79.2%. Of lesions, 8 were symptomatic, and 5 were asymptomatic; 5 were identified as potentially having vulnerable plaque on preprocedural MRI. All lesions were treated with a carotid WALLSTENT, and additional stenting was needed in only 1 case (Table 1). No patient exhibited any new neurologic deficit after CAS.

After stenting, angioscopy provided good visualization in all cases with no difficulties. IVUS revealed plaque protrusion in only 1 lesion in case 4, whereas angioscopy showed plaque protrusions in 8 lesions (Figure 3 and Table 2); this difference in detection rate was statistically significant (P = 0.011). In case 4, fluttering plaque protrusion in the stent was observed by angioscopy but was not recognized by IVUS (Videos 1 and 2). The plaque protrusion pointed out by IVUS was described more clearly by angioscopy (Figure 3). In 4 lesions, yellow plaques were observed on angioscopy, but not on IVUS.

DWI in the postprocedural MRI showed high-intensity spots in the ipsilateral cerebral hemisphere with 3 of the lesions (23%). Two of these lesions had been identified as potentially having vulnerable plaque on preprocedural MRI. In 2 of the 3 lesions, DWI-positive plaque protrusions could not be observed by IVUS; however, in these lesions, plaque protrusion could be observed by angioscopy (Table 2). All DWI-positive lesions after CAS were observed on angioscopy to have yellow plaque protrusions. The only factor to show a statistically significant relationship with the DWI-positive lesions was the existence of yellow plaque observed by angioscopy (P = 0.014) (Table 3). Multivariate logistic regression analysis revealed that the existence of yellow plaque was the only factor that had a significant relationship with DWI-positive lesions, as observed using postprocedural MRJ (P = 0.033) (Table 3).

DISCUSSION

Since the SAPPHIRE report in 2004 and the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) in 2010, CAS has been performed to treat patients with evidence for high risk and standard risk for carotid artery endarterectomy (CEA).16,17 However, the risk of periprocedural ischemic complications is higher with CAS than with CEA. The CREST study reported more frequent periprocedural cerebral ischemic complications in the CAS group than in the CEA group (4.1% vs. 2.3%).17 Various studies have reported DWI-positive findings after CAS in 17, 36 to 64% of cases18-22; however, these studies differed in the technique used for the CAS procedure, such as embolic protection, the type of stent used, and whether there was predilation or postdilation. In a systematic review, Schnaudigel et al.23 reported that the rate of DWI-positive findings was significantly higher with CAS than with CEA (57% vs. 10%). In CAS using dual protection, the modified Parodi method, and distal protection with a filter wire in the ICA, the DWI-positive rate was reported as 17.3%;21 a lower rate than with other protection techniques; for this reason, we used the dual protection technique in the present study. Angioscopy was used in our study, and the DWI-positive rate was 23%, a level regarded as tolerable compared with rates in past reports.

DWI-positive lesions after CAS have been reported to be associated with ischemic events.24 In addition, a relationship between the character of the plaque and the risk of periprocedural ischemic complications with CAS has been

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (Years)/Sex</th>
<th>Symptoms</th>
<th>Side</th>
<th>Stenosis Rate</th>
<th>Plaque Appearance</th>
<th>APT</th>
<th>Stent</th>
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<td>A + Cl + Ci</td>
<td>CW</td>
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<td>CW</td>
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<tr>
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<td>Right</td>
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<td>Soft</td>
<td>A + Cl + Ci</td>
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<tr>
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<td>Soft</td>
<td>Cl + A + Ci</td>
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APT, antiplatelet therapy; M, male; A, aspirin; Cl, clopidogrel; Ci, cilostazol; CW, carotid WALLSTENT; F, female.
Figure 3. Plaque protrusion findings detected by angioscopy and intravascular ultrasound. White arrows point to white plaque protrusions (cases 1, 3, 6, 8, and 11). Yellow arrows point to yellow plaque protrusions (case 4 bilaterally and case 10). Red arrow points to a fluttering plaque protrusion (case 4, right side C). The plaque protrusion detected by intravascular ultrasound in case 4 on the right side (case 4, right side B) as shown more clearly by angioscopy (case 4, right side A). AS, angioscopy; IVUS, intravascular ultrasound.
observed. Therefore, the preprocedural assessment of plaque morphology is considered to be important. In reports of the preprocedural evaluation of plaque morphology by carotid ultrasound and MRI, the presence or absence of vulnerable plaques, which are a risk factor for periprocedural cerebral ischemic complication, has been proposed as an index. In addition, it has been reported that there was a relationship between plaque volume measured with three-dimensional T1-weighted gradient echo sequence on MRI and the rate of DWI-positive at postprocedural MRI. In the present study, 3 of 5 lesions that had been identified as having potentially vulnerable plaque before CAS showed DWI high-intensity spots in the ipsilateral hemisphere on postprocedural MRI.

Although in this report there was no significant relationship between the vulnerable plaque in preprocedural MRI and postprocedural DWI-positive lesions, as indicated in some past reports, the preprocedural evaluation of plaque is thought to be important to help avoid ischemic complication after CAS.

The intraprocedural evaluation of plaque protrusion and thrombus is also considered to be important in CAS. If findings associated with a high risk for ischemic complications, such as plaque protrusion and vulnerable plaque, can be detected during the procedure, additional treatment can be provided to avoid these complications. Although there have been various reports of the intraprocedural observation and evaluation during CAS procedures of plaque protrusions in the stent lumen by IVUS and OCT, there have been only a few reports about the use of angioscopy in CAS. Conversely, there have been several reports since the 1980s of use of angioscopy in coronary artery diseases. Uchida reviewed the angioscopic features of plaque, especially vulnerable plaque, and evaluated the neointimal coverage of stents in the coronary artery.

IVUS, OCT, and angioscopy allow real-time evaluation of plaque properties before stent placement and the detection of plaque protrusions after stent placement. The most significant difference between IVUS or OCT and angioscopy is that angioscopy can directly visualize the lumen of the vessel and stent. However, a search of the literature found no previous study that compared the evaluation of plaque protrusions by angioscopy with that by IVUS or OCT in CAS. Using IVUS, the frequency of detecting plaque protrusions after CAS has been reported as 2.6%–7.8%. The rate of plaque prolapse detected by OCT after CAS has been reported as 17.6%–40.2%. In comparison, Tanemura et al. reported the frequency of plaque protrusion identified by angioscopy after CAS to be 25%. Thus, the rate of detection of plaque protrusion after CAS was higher with angioscopy than with IVUS. This was consistent with the findings of the present study, with angioscopy detecting 8 plaque protrusions and IVUS detecting only 1. Of the 3 patients with DWI-positive lesions on MRI after CAS, plaque protrusion was detected by IVUS in only 1, whereas it was observed in all 3 patients on angioscopy. The relationship between plaque protrusions detected by both IVUS and angiography, DWI-positive lesions, and ischemic complications has been reported. However, in the present study, 2 of 3 lesions with DWI-positive lesions were not observed as plaque protrusion with IVUS. There was no statistically significant relationship between plaque protrusion detected by IVUS,
angiography, and DWI-positive lesions. However, all of the DWI-positive lesions were observed to be yellow plaque protrusions on angioscopy. In this study, only the yellow plaque protrusions showed a statistically significant relationship with the DWI-positive lesions. In coronary disease, there is an association between a yellow plaque and the thickness of the fibrous cap of the plaque; hence, yellow plaque detected by angioscopy has been considered to be vulnerable.11 In coronary disease, an association between yellow plaque and distal embolization of plaque debris has been shown.12 It therefore appears that IVUS alone is insufficient for evaluating plaque protrusion in CAS as well as in coronary stenting. Thus, it may be better to evaluate the plaque protrusion with angioscopy rather than IVUS alone when a lesion is considered to be vulnerable plaque on preprocedural MRI.

The first problem of angioscopy is to obtain a clear view. Tanemura et al.13 reported that a clear view was not obtained in one third (6) of the lesions investigated, with insufficient washout of blood experienced in 4 of those 6 lesions. It is necessary to use a physiologic saline flush to expel the blood almost completely from the vessel lumen. In that report, embolic protection was provided by distal balloon protection alone or PAES without distal protection from a filter device in the ICA. Therefore, in the present study, the CAS procedure and angioscopy were performed under proximal and distal protection, modified PAES, and distal protection with a filter device. The common carotid artery and ECA were occluded by balloon, on the proximal side to the superior thyroid artery where possible, allowing the blood flow to be reduced enough to expel the blood with a saline flush. This allowed a clear view to be obtained for all the lesions.

The second problem associated with angioscopy is the increase in DWI-positive lesions from flushing saline to expel the blood in the stent lumen. Tanemura et al.15 reported a relatively high DWI-positive rate of 47%. Flushing saline to expel blood is thought to involve the risk of transporting vulnerable plaques and debris protruding into the stent lumen to the distal side, resulting in ischemic complications during the periprocedural period. In the present study, in addition to the modified PAES, a filter device in the ICA was used for distal protection. The DWI-positive rate was lower than in the previous report (23% vs. 47%). Sakamoto et al.21 reported that proximal and distal protection can reduce the DWI-positive rate. Using a similar method may therefore reduce the DWI-positive rate even when angioscopy is used.

The next problem for angioscopy is the visual field. Tanemura et al.13 reported that they were unable to obtain 360° observation of the wall of the vessel. Although nearly the entire vessel wall and stent could be observed in the present study, the narrow angle of the visual field may restrict the absorbable area in the lumen, especially in tortuous lesions.

The final problem related to angioscopy is decision making with regard to the need for additional treatment. In the present study, 3 lesions were associated with DWI-positive findings on postprocedural MRI, and 8 lesions were observed to have plaque protrusion on angioscopy, with 4 observed to have yellow plaque. Only 1 lesion required an additional stent, and there were no new neurologic deficits in any patient in the periprocedural period. It is unclear which findings by angioscopy after stenting require additional treatment to avoid periprocedural complications; this needs further consideration. From the results of this study, for the lesion considered as a vulnerable plaque in preoperative evaluation, when the property of plaque protrusion after CAS using angioscopy confirmed as a vulnerable plaque, such as a yellow plaque protrusion or a fluttering plaque, additional treatment may be necessary. A limitation of this study is that the results cannot be generalized because of the limited number of lesions. To establish the utility and safety of angioscopy, it is necessary to repeat this investigation with a larger number of cases.

CONCLUSIONS

Angioscopy allowed direct evaluation of the stent lumens, providing clearer visualization of the lumens of vessel and stent than with IVUS. As a consequence, angioscopy detected more plaque protrusion and yellow, potentially vulnerable, plaque than was possible with IVUS. Thus, angioscopy may be more useful than IVUS for examination of plaque protrusion and plaque evaluation after CAS, especially when plaque has been predicted to be vulnerable by MRI before CAS.

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Conflict of interest statement: The authors declare that the article content was composed in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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