Use of Contrast-enhanced Carotid Ultrasonography in Preoperative Assessment for Carotid Artery Stenting

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Objective: Contrast-enhanced carotid ultrasonography (CEUS) is a new technique for assessing carotid artery plaques. The present study attempted to demonstrate the association between the findings of CEUS performed prior to carotid artery stenting (CAS) and plaque debris caught during CAS.

Methods: This study was conducted with 16 patients (15 men, 1 woman; mean age: 74.8 years) who had undergone evaluation of carotid plaque vulnerability followed by CAS. The carotid plaque evaluation consisted of CEUS and MRI. The amount of debris retrieved during CAS was semi-quantitatively classified into three grades (large, moderate, and small) by three independent physicians based on inspection of photographs of retrieved debris. The existence of a correlation between CEUS findings and the amount of debris was examined.

Results: Enhanced plaque on CEUS was observed in 7 of 16 patients. A large amount of debris was observed during CAS in four of the seven patients with CEUS-enhanced plaques that were also assessed as unstable on MRI, while two patients had a moderate amount and one patient had a small amount of debris. There were significant correlations between the amount of debris and plaque enhancement on CEUS, unstable plaque on MRI, and enhancement of plaque on CEUS with unstable plaque on MRI (p = 0.036, p = 0.029, p = 0.036, respectively). For the prediction of moderate to large amount of debris occurring in CAS, enhancement of plaque demonstrated by CEUS had a sensitivity of 66.7% and a specificity of 85.7%, unstable plaque determined by MRI had a sensitivity of 100% and a specificity of 42.9%, and enhancement of plaque by CEUS and unstable plaque determined by MRI had a sensitivity of 100% and a specificity of 75%.

Conclusion: Plaque vulnerability assessment using the combination of CEUS and MRI can predict the amount of debris retrieved during CAS, while using CEUS alone proved to be insufficient.

Keywords ▶ contrast-enhanced ultrasonography, carotid ultrasonography, carotid artery stenting

Introduction

In carotid artery stenting (CAS), the occurrence of cerebral embolism due to plaque debris during stent deployment is not uncommon. There is currently no established method for predicting the onset of cerebral embolism due to plaque debris. Assessment of carotid artery plaques prior to CAS is typically done with carotid ultrasonography (US), T1-weighted black-blood MRI (BB-MRI), or time-of-flight MRA (TOF MRA).1–3) In recent years, however, contrast-enhanced carotid ultrasonography (CEUS) using an ultrasound contrast agent has become a viable modality for diagnosing intra-plaque neovascularization in the carotid artery, and it has attracted attention as a novel plaque imaging technique.4) In the present study, the validity of CEUS in evaluation of plaque vulnerability was investigated by analyzing the relationship between the findings of preoperative plaque imaging including CEUS and the amount of debris retrieved during CAS.

Materials and Methods

A total of 16 patients (15 men, 1 woman; mean age: 74.8 years) who underwent preoperative assessment
between April 2014 and March 2015 with cerebral angiography, carotid US, carotid plaque MRI, and CEUS prior to CAS to treat severe stenosis of the carotid artery were prospectively enrolled in this study.

The rate of carotid artery stenosis was measured using the North American Symptomatic Carotid Endarterectomy Trial (NASCET) method based on conventional carotid angiography. All patients underwent diagnostic angiography to verify the characteristics of the stenotic lesion. The presence of a stenotic lesion of the internal carotid artery (ICA) responsible for an ipsilateral ischemic stroke was defined as symptomatic ICA stenosis. The aspiration frequency, number of stent placements, and amount and size of debris caught during CAS were recorded and studied for correlations with the preoperative test findings. This study was conducted in a single hospital, and the study protocol was approved by the St. Marianna University Bioethics Committee.

**Carotid artery stenting**

All procedures were performed via the femoral approach using the Seldinger method. All patients were on long-term antiplatelet therapy using aspirin, clopidogrel, or cilostazol monotherapy or in combination. Unfractionated heparin (10000 units) was administered before starting the procedure. The procedures included proximal balloon protection using Optimo (Tokai Medical Products, Aichi, Japan) and distal balloon protection using Carotid Guardwire PS (Medtronic, Santa Rosa, CA, USA). After predilatation of the stenotic lesion, an appropriate stent for the stenotic lesion was implanted and then dilated. Predilatation was performed in all patients using a balloon catheter, 4 mm or 4.5 mm in diameter. Postdilatation was performed only in patients with placement of a single closed-cell stent using a balloon catheter, 5 mm in diameter.

**Debris**

After deploying the stent, aspiration of the blood was started while occluding distal blood flow. The debris was removed from the aspirated blood using a filter, and then the blood was returned to the veins via a venous sheath. Aspiration of blood was performed repeatedly using a 20 mL syringe. Visual inspection of the filter was performed at every 4th, 8th, 12th, and 16th aspirations. If any debris was observed at the 16th aspiration, further aspiration was continued until the debris was completely removed. The amount of debris captured by the filter when returning the blood to the veins was also included in the assessment.

All debris was collected in a cell strainer (Medtronic, Minneapolis, MN, USA) and recorded by a digital camera (Fig. 1). The size of the debris was classified into three categories, that is, small (<1 mm), medium (≥1 mm and <3 mm), and large (≥3 mm). The amount of debris was classified into three grades based on the amount of small debris, that is, small amount (<10 pieces of debris), medium amount (11–30 pieces of debris), and large amount (>30 pieces of debris). When one medium-sized piece of debris was found, it was counted as three small-sized pieces of debris. Whenever large-sized debris was found, the amount of debris was categorized as a large amount. Based on these definitions, the amount and size of debris were determined by agreement between two neurologists. When there was no agreement, the amount and size were graded by consensus after re-assessment of the photographs.

**Ultrasonography**

All US examinations were performed by a single doctor qualified by the Japan Academy of Neurosonology. Carotid US with a 7.5-MHz linear probe (SSA-770A Aplio; Toshiba Medical Co., Tokyo, Japan) was used. B-mode imaging and color and power Doppler imaging and CEUS were performed using Sonazoid (perfluorobutane microbubbles; Daiichi Sankyo Pharmaceutical, Tokyo, Japan). A total of 16 μL of Sonazoid were dissolved in 2 mL of water, and an intravenous bolus of 0.15 mL per kg of the contrast agent suspension was injected into the antecubital vein. The acoustic power of the harmonic US was set with a mechanical index (MI) of 0.2–0.3, depth of 3 cm, and focus set at 2.5 cm. The presence of enhanced lesions was identified as the echogenic reflections of microbubbles in the plaque. Carotid plaque was evaluated from the longitudinal and transverse views for about 5 min after contrast injection. The evaluation of enhancement on CEUS was made by two neurologists; the kappa coefficient for diagnostic concordance of plaque enhancement between them was 0.875. According to the echogenicity on B-mode imaging, plaque was categorized as high-echoic, iso-echoic, and low-echoic by the two neurologists. Any sites with variation in plaque echogenicity were regarded as mixed plaques, and they were classified in descending order as having mixed high-, mixed iso-, or mixed hypo-echogenicity.

**MRI imaging**

Carotid artery BB-MRI was performed with a 1.5 T scanner (Achieva Nova Dual; Philips Healthcare, Best, The Netherlands) using a 16-channel NeuroVascular (NV) coil.
For positioning of the greatest wall thickness, a standard imaging protocol was used, that is, TOF, T1-weighted and T2-weighted. For short-axis T1-weighted images (two dimensional [2D] turbo spin echo [TSE]), the parameters were as follows: recovery time (TR) 1 cardiac cycle (1 R-R interval), echo time (TE) 15 ms, matrix 153 × 192, thickness 3 mm, field of view (FOV) 150 mm, number of samples (NSA) 6, and fat saturation (+). For short-axis T2-weighted images (2D-TSE), the parameters were as follows: TR 2 cardiac cycles (2 R-R intervals), TE 80 ms, matrix 153 × 192, thickness 3 mm, FOV 150 mm, NSA 8, and fat saturation (+). For TOF 2D-TSE, the parameters were as follows: TR 23 ms, TE 6.9 ms, matrix 120 × 240, thickness 1.25 mm, number of excitations 1, and fat saturation (+).

For the characterization of carotid plaque, TOF, T1-weighted, and T2-weighted images were used. The signal intensity ratio relative to the ipsilateral sternocleidomastoid muscle, the plaque/muscle ratio (P/M ratio), was calculated, and high intensity was defined as a plaque/muscle ratio >1.5. Unstable plaque was defined as the...
presence of a high-intensity signal (HIS) in the carotid plaque on TOF imaging or high intensity of the carotid plaque on T1-weighted imaging.\(^1\)\(^2\)

### Statistical analyses

The subjects’ characteristics are reported as means and standard deviation (SD), unless otherwise indicated. Comparisons between plaque enhancement on CEUS and the amount of debris among large, moderate, and small were performed with chi-squared tests. Comparisons between unstable plaque findings on MRI and the amount of debris among large, moderate, and small were also performed with chi-squared tests for categorical data. A p-value less than 0.05 was considered significant. All statistical analyses were performed using SPSS version 22 (IBM SPSS Statistics for Windows; IBM Corp, Armonk, NY, USA).

### Results

Patients’ demographics and intraoperative findings are shown in Table 1. Plaque enhancement on CEUS was observed in seven patients. Figure 1 shows the correlation between CEUS findings and the amount of debris in these seven patients with enhanced plaque. Among these seven patients with enhanced plaque, a large amount of debris was observed in four patients, while two patients had a moderate amount, and one patient had a small amount of debris. In the remaining nine patients without plaque enhancement on CEUS (not shown in the figure), the amount of debris was as follows: a large amount in two patients, a moderate amount in one patient, and a small amount in six patients.

For the prediction of a moderate to large amount of debris, enhancement of plaque demonstrated on CEUS had a sensitivity of 66.7% and a specificity of 85.7%. There was a significant association between plaque enhancement on CEUS and the amount of debris (\(\chi^2\) test, \(p = 0.036\)).

In all, 13 patients, including all patients with plaque enhancement on CEUS, were diagnosed as having unstable plaque by carotid plaque MRI. Among these 13 patients with unstable plaque on MRI, a large amount of debris was observed in six patients, while three patients had a moderate amount, and four patients had a small amount of debris. For the prediction of a moderate to large amount of debris, unstable plaque determined by MRI had a sensitivity of 100% and a specificity of 42.9%. There was a significant association between a diagnosis of unstable plaque on MRI and the amount of debris (\(\chi^2\) test, \(p = 0.029\)).
using the Parodi Anti-Emboli System and distal protection using balloon occlusion, and predicting the amount of debris likely to be encountered during surgery is a key to selecting the right procedure. Depending on the estimated amount of debris, the surgeon can also decide in advance whether it would be more appropriate to use an open-cell or closed-cell stent.

T1-weighted BB-MRI and TOF MRA have been reported as indicators of plaque stability. Unstable findings with high intensity on BB-MRI and TOF MRA were considered to indicate the presence of intra-plaque hemorrhage and neovascularization. Plaque enhancement on CEUS has also been reported as an indicator of intra-plaque neovascularization, fibrous cap degradation, and plaque inflammation, leading to the increased adoption of this new imaging modality in the assessment of plaque stability. CEUS has recently been used to visualize intra-plaque neovascularization as an element of vulnerability. The source of neovascularization is direct branching from the vasa vasorum or the intimal surface. These areas are very fragile, and plaque hemorrhage can easily occur. Evaluation of neovascularization is therefore important in assessing plaque instability. While CEUS shows neovascularization, intra-plaque hemorrhage and large lipid cores are evaluated as unstable plaque on MRI. Hypo-echoic plaques seen on carotid US are also pathologically associated with large lipid cores and intra-plaque hemorrhage, and they are widely recognized as plaques that confer a high risk of cerebral infarction.

The difference between neovascularization and intra-plaque hemorrhage is that neovascularization is a sign of plaque starting to grow; plaque then continues to grow and finally collapses, causing intra-plaque hemorrhage. The difference between these two imaging modalities is considered to be one of the reasons that the combination of these two may allow greater diagnostic accuracy for the prediction of amount of debris. Six of seven patients with CEUS-enhanced plaque had a moderate to large amount of debris, and there was a significant correlation between plaque enhancement on CEUS and the amount of debris in the present study. Plaque enhancement on CEUS is a potential indicator of the amount of debris during CAS and should therefore be considered prior to surgery.

According to the results of the present study, the sensitivity of plaque enhancement on CEUS was 66.7% and the specificity was 85.7% for a moderate to large amount of debris occurring in CAS. The sensitivity of a diagnosis of unstable plaque

All seven patients with plaque enhancement on CEUS showed unstable plaque on MRI. The amount of debris with plaque enhancement on CEUS was as described above. All three patients with no plaque enhancement on CEUS and a diagnosis of stable plaque on MRI had only a small amount of debris.

The scattergram in Fig. 2 provides the relationship between plaque characteristics and amount of debris during the procedure of CAS. For the prediction of a moderate to large amount of debris, plaque characteristics with enhancement of plaque on CEUS and unstable plaque on MRI had a sensitivity of 100% and a specificity of 75% ($\chi^2$ test, $p = 0.036$). CEUS: contrast-enhanced carotid ultrasonography; ○: enhancement (−) on CEUS, ●: enhancement (+) on CEUS.

**Discussion**

Cerebral infarction due to plaque fragmentation and debris during stent deployment is a common occurrence in CAS. This is a major complication, so diagnostic imaging should be used prior to surgery to properly assess plaque stability. Measures to prevent plaque debris from flowing into peripheral regions during surgery include flow reversal...
on MRI was 100%, with specificity of 42.9% for a moderate to large amount of debris occurring in CAS.

As a cause of the low sensitivity of CEUS in this study, it is thought that CEUS mainly evaluates neovascularization seen in the early phase of plaque growth. Thus, CEUS may overlook unstable plaque, such as intra-plaque hemorrhage, in the late phase of plaque growth.

As a cause of the low specificity of MRI in this study, the use of cardiac-gated BB-MRI for plaque evaluation may have been involved. Sato et al reported that the plaque/muscle ratio is higher for cardiac-gated BB-MRI than for noncardiac-gated MRI. Therefore, MRI often shows plaque as unstable, which lowers the specificity.

The sensitivity of plaque enhancement on CEUS and unstable plaque determined by BB-MRI was 100%, and the specificity was 75% for a moderate to large amount of debris occurring in CAS. According to the results, the combination of MRI and CEUS can improve both of the sensitivity and specificity.

The present study has some limitations. First, subjective evaluation was used for the categorization of the amount of debris, enhancement on CEUS, and MRI findings. Second, a small number of patients were studied. Third, the technical methods and type of stent were optimized for each patient. These differences might affect the amount of debris. However, the present findings serve for hypothesis generation, and further prospective studies are warranted.

## Conclusion

While CEUS alone is currently inadequate for assessing plaque stability prior to CAS, combining this modality with carotid plaque MRI enables a more reliable assessment for the prediction of embolic risk due to debris in CAS. We expect to see an increase in the use of CEUS in the development of therapeutic strategies for CAS in the future.

## Disclosure Statement

The authors have no conflicts of interest to declare.

## References