

# Evaluation of the Time-Dependent Changes and the Vulnerability of Carotid Plaques Using Contrast-Enhanced Carotid Ultrasonography

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*Background:* The association of carotid plaque enhancement on contrast-enhanced carotid ultrasound (CEUS) and plaque vulnerability evaluated by magnetic resonance imaging (MRI) was to be determined. *Materials and methods:* The 103 patients underwent CEUS from May 2013 until June 2016. CEUS images of the carotid plaque were obtained offline. Plaque images obtained at 1, 3, 5, and 10 minutes were compared with the reference image, defined as the image obtained at 0 minute. Plaque brightness was assessed using the gray-scale median during contrast enhancement (GSM-C). Plaque vulnerability was evaluated using T1- and T2-weighted MRI and Volume ISotropic TSE Acquisition (VISTA), with a VISTA cutoff value for the plaque muscle ratio (PMR) of 1.5. Time-dependent changes in the GSM-C were evaluated, and those between 0 and 1 minute were compared with the PMR values determined on MRI. *Findings:* GSM-C decreased significantly over time, from 32.0 at 0 minute to 28.0 at 1 minute, 25.0 at 3 minutes, and 19.0 at 10 minutes. The greater the increase in the changes in the GSM-C from 0 to 1 minute, the more significant the association with a PMR higher than the median on T1 (GSM-C: 0 minute: 29.0, 1 minute: 24.0,  $P = .015$ ), a PMR less than or equal to the median on T2 (0 min: 35.0, 1 min: 28.0,  $P = .003$ ), and a PMR more than 1.5 determined on VISTA (GSM-C: 0 minute: 29.0, 1 minute: 24.0,  $P = .005$ ). *Conclusions:* Early changes in the GSM-C evaluated with CEUS indicate significant plaque vulnerability on MRI. **Key Words:** Carotid plaque—CEUS—MRI—vulnerability.

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## Introduction

Contrast-enhanced carotid ultrasound (CEUS) has been shown to correlate with the pathological findings of carotid plaque.<sup>1-7</sup> This imaging modality can also be used to evaluate intraplaque vessels and the vasa vasorum. Both are important determinants of plaque vulnerability, given that the presence of intraplaque vessels correlates significantly with the frequency of cardiovascular risk factors and the development of cardiovascular disease.<sup>8</sup> A CEUS study demonstrated that the density of the plaque shoulder is more significantly associated with plaque vulnerability than that of the area of the plaque core.<sup>7</sup>

In a previous report,<sup>9</sup> we showed that CEUS reveals plaque-surface irregularities, intraplaque hemorrhage, and

fibrous cap disruption. Ulceration of the carotid arteries is also more effectively detected by CEUS than with standard carotid ultrasound. The addition of magnetic resonance imaging (MRI) to the pathological findings can confirm the vulnerability of carotid-artery plaques.<sup>10</sup> A high signal intensity on T1-weighted MRI is a definitive finding indicating the vulnerability of carotid plaques.<sup>11-13</sup> However, whether plaque findings on MRI are associated with those determined using CEUS has not been investigated. As plaque brightness that is ultrasonographically evaluated is implicated in the vulnerability of carotid plaque, plaque brightness during CEUS study may also give us some information about its vulnerability. The purpose of this study was to determine the association between plaque brightness on MRI and the CEUS results.

## Methods

### Materials

From May 2013 to June 2016, 126 patients with carotid stenosis were prospectively investigated. All the patients had significant carotid stenosis whose degree of stenosis measured by the method of the European Carotid Endarterectomy trial was more than 50% in computed tomography (CT) angiography or ultrasonography and their modified Rankin Scale (mRS) was 0-2. The patients were excluded when they did not agree to the CEUS study (N = 20) or were not able to obtain MRI (N = 3). Thus, a total of 103 patients were registered in this study. The characteristics of the study patients and plaque sections are shown in Table 1. The patients had a high frequency of hypertension and hyperlipidemia.

The images were acquired offline by capturing them at the start of contrast enhancement (0 minute) and then 1, 3, 5, and 10 minutes thereafter. The acquired CEUS

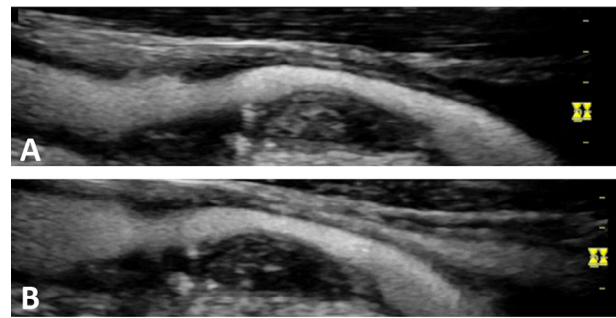
**Table 1.** Background and characteristics of the study patients (n = 103)†

Characteristics of patients	
Age* (y)	72.2 ± 7.5
Male, n (%)	92 (89.3%)
Hypertension, n (%)	72 (69.9%)
Hyperlipidemia, n (%)	81 (78.6%)
Diabetes mellitus, n (%)	39 (37.9%)
Smoking, n (%)	27 (26.2%)
Antithrombotic agents, n (%)	83 (80.6%)
Degree of stenosis (ECST, %)*	73.3 ± 13.2%
Interval from MRI to ultrasonography (days)†	6 (2-14)
Symptom, n (%)	49 (47.6%)

Abbreviations: ECST, European Carotid Stenosis Trial; MRI, magnetic resonance imaging.

\*Mean ± SD.

†Median (interquartile range).



**Figure 1.** Carotid-artery findings in a 68-year-old male with right carotid artery stenosis. (A) Longitudinal view of the carotid plaque on contrast-enhanced carotid ultrasound 0 minute after contrast enhancement shows increased contrast. (B) At 1 minute, there is a decrease in enhancement.

images were analyzed by 2 experienced observers (H.S. and T.O.) blinded to the patients' clinical characteristics. The research protocol was approved by the Human Subjects Committee at Fukuoka University Hospital (number 13-9-03). All patients provided written consent to participate in the study.

### Ultrasonographic Study

After carotid ultrasound with a GE LOGIQ 7 (GE Healthcare, Milwaukee, WI) to screen patients for enrollment, CEUS was performed using a 7-MHz linear transducer, as described in our previous paper.<sup>9</sup> Long-axis images, in which the plaque features were clearly visible, were captured from each patient. First, the boundary of the plaque was drawn with reference to the CEUS image obtained at 0 minute, just after the arrival of contrast medium, which allowed the brightness of the plaque within its boundary to be measured using Photoshop CS6 (Adobe Corp., CA, USA) (Fig 1, A). The median plaque brightness was defined as the gray-scale median during contrast (GSM-C). The GSM-C was similarly determined from the images acquired at 1 (Fig 1, B), 3, 5, and 10 minutes after the injection of contrast.

### MRI Protocol

The carotid plaques of all patients were imaged by MRI within 2 weeks of the CEUS. Scans were obtained using a 1.5-T scanner (ACHIEVA; Philips Medical Systems, Best, the Netherlands) and a SENSE head/neck coil (Philips Medical Systems), in which the quadrature head element had 2 neck elements. The carotid plaque was evaluated, as described previously.<sup>14,15</sup> Short-axis 2D turbo spin echo (2D-TSE) T1- and T2-weighted images and Volume ISotropic Turbo spin echo Acquisition (VISTA) were applied using the same equipment.

### Image Review

Plaque signal intensity was measured with reference to the adjacent sternocleidomastoid muscle. The values

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