High-Intensity Signal in Carotid Plaque on Routine 3D-TOF-MRA Is a Risk Factor of Ischemic Stroke

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Key Words
Ischemic stroke · Moderate carotid artery stenosis · Intraplaque hemorrhage · Time of flight MR angiography

Abstract
Background: Carotid atherosclerotic disease is recognized as an important risk factor for brain ischemic events. However, high-grade stenosis does not always cause ischemic strokes, whereas moderate-grade stenosis may often cause ischemic strokes. It has been reported that there is an association between carotid intraplaque hemorrhage (IPH) and new cerebral ischemic events. The purpose of this study was to elucidate the relationship between high-intensity signals (HIS) on maximum intensity projection (MIP) images from routine 3-dimensional time-of-flight magnetic resonance angiography (3D-TOF-MRA) and prior ischemic strokes in the patients with moderate carotid stenosis. Materials and Methods: Sixty-one patients with moderate carotid artery stenosis (50–69% stenosis based on North American Symptomatic Carotid Endarterectomy Trial criteria) were included. Carotid IPH was defined as the presence of HIS in carotid plaques on MIP images detected by 3D-TOF-MRA using criteria we previously reported. We analyzed the relationship between the presence of HIS in plaques and prior ischemic strokes defined as ischemic lesions on diffusion-weighted brain images. Results: HIS in carotid plaques were present in 27 (44%) of 61 patients. Prior ipsilateral ischemic strokes occurred more frequently in the HIS-positive group than the HIS-negative group (67 vs. 9%, p < 0.001). Furthermore, there were more smokers in the group with ischemic stroke than without it (62 vs. 25%, p = 0.005). In multivariate logistic regression analysis, HIS in carotid plaque (OR 23.4, 95% CI 4.62–118.3, p < 0.001) and smoking (OR 5.44, 95% CI 1.20–24.6, p = 0.028) were independent determinants of prior ischemic strokes after adjustment for age. Conclusions: HIS in carotid plaques on 3D-TOF-MRA MIP images are independent determinants of prior ischemic strokes in patients with moderate carotid artery stenosis, and they can potentially provide a reliable risk stratification of patients with moderate carotid artery stenosis.

Introduction
Carotid artery stenosis is one of the major causes of cerebral ischemic events. Previous large randomized controlled trials have established that carotid endarterectomy or carotid artery stenting significantly reduces ischemic...
stroke risk compared with medical therapy in patients with high-grade carotid artery stenosis, but does not reduce ischemic stroke risk in those with low- to moderate-grade stenosis [1–5]. The assessment of stroke risk and the criterion for surgical intervention in these randomized controlled trials have been based on the degree of stenosis [6, 7]. However, high-grade stenosis does not always cause cerebrovascular events, whereas moderate-grade stenosis may often cause cerebrovascular ischemic events [7–9]. Recently, some researchers reported the importance of imaging-based risk stratification strategies that take into account factors beyond luminal stenosis measurement, such as plaque composition [10, 11]. Especially, it was reported that intraplaque hemorrhage (IPH) is associated with accelerated plaque growth, luminal narrowing and development of symptomatic ischæmic events [12, 13]. Therefore, it is important to highlight the relationship between carotid IPH and ischemic events in patients with moderate carotid artery stenosis.

Maximum intensity projection (MIP) images from 3-dimensional time-of-flight magnetic resonance angiography (3D-TOF-MRA) are widely used for screening carotid arteries for stenosis [14]. This method allows for rapid determination of the degree of stenosis and other anatomical findings using rotational views. We and other investigators reported that MRI of carotid plaques has a good sensitivity with a moderate-to-good specificity for the detection and quantification of carotid IPH, using histology as a gold standard [15–18]. According to these methods, IPH can be seen as HIS on 3D-TOF-MRA MIP images of carotid plaques.

The purpose of this study was to elucidate the association between the presence of high-intensity signals (HIS) in the plaque on 3D-TOF-MRA MIP images of carotid plaques and prior ischemic strokes.

**Materials and Methods**

**Subjects**

We retrospectively reviewed consecutive MRAs that were scanned for carotid artery screening in patients who had at least one cardiovascular risk factor from January 2011 to November 2014. Inclusion criteria were (1) carotid artery stenosis from 50 to 69% assessed with MRAs as recommended by the North American Symptomatic Carotid Endarterectomy Trial collaborators [19]; and (2) no contraindications for MRI. Prior ischemic stroke was defined if the patients experienced neurological deficits and their diffusion-weighted images (DWI) of MRI of the brain showed an acute ischemic lesion caused by carotid stenosis within 180 days [19, 20]. Cardiovascular risk factors were evaluated in all patients at the same time. Hypertension was defined as systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≤ 90 mm Hg or the prior use of medications for hypertension. Hyperlipidemia was defined as serum LDL cholesterol ≥ 140 or the prior use of medications for hyperlipidemia. Diabetes mellitus was defined as HbA1C (NGSP) ≥ 6.5% or the prior use of medications for diabetes mellitus. The experimental protocol was approved by the institutional ethics committee, and informed consent for MR imaging as part of routine clinical procedure was obtained from all patients.

**MR Evaluation of Carotid Plaques and Cerebral Ischemic Lesions**

MRI was performed using a 1.5 T system (Magnetom Avanto, Siemens, Munich, Germany) equipped with a Neck-Matrix Coil. MIP images from 3D-TOF-MRA were obtained using the following parameters: repetition time, 26 ms; echo time, 7 ms; flip angle, 20 degrees; field of view, 220 × 165 mm; matrix, 256 × 180; and slice thickness, 1.0 mm.

The presence of HIS located in plaque but without connection to the lumen in all 18 projections was defined as HIS-positive (fig. 1) based on criteria we previously published [9, 16, 18]. Two reviewers, who were blinded to all clinical information, independently read the 3D-TOF-MRA MIP images of the carotid plaques. The 2 reviewers discussed their separate readings and arrived at a consensus opinion on the presence/absence of HIS for all arteries.

The same MRI system that was used for 3D-TOF-MRA was also used for DWI-MRI of the brain, applying the echo planar method under the following conditions: repetition time, 5,000 ms; echo time, 92.0 ms; slice thickness, 5.5 mm; spacing, 1.1 mm; b value, 1,000 s/mm²; and field of view, 22 cm. A positive ischemic lesion was evaluated by DWI and apparent diffusion coefficient maps [21].

**Statistical Analysis**

Continuous values are expressed as the mean ± SD. Categorical data are summarized as percentages and were compared using Fisher’s exact test. Comparisons of continuous variables between cohorts were performed using an unpaired Student’s t test. Cohen’s k values were calculated to quantify the level of agreement between the two observers who evaluated the 3D-TOF-MRA MIP images for the presence of HIS in plaques. A k value ≥ 0.75 was considered to indicate a high level of agreement, and 0.4 < k < 0.75 indicated moderate agreement [22]. Values of p < 0.05 were considered to indicate a statistically significant difference. All statistical analyses were performed using StatView 5.0 software (SAS Institute Inc., Cary, N.C., USA).

**Results**

After review of 8,838 carotid arteries from 4,419 consecutive carotid MRAs, 8,754 carotid arteries were excluded because of carotid artery stenosis from < 50%. Twenty-two carotid arteries were excluded because of carotid artery stenosis from ≥ 70% or occluded. The remaining 62 carotid arteries with moderate carotid artery stenosis were included into this study. Of the 62 carotid...
arteries scanned, one was excluded during image review due to insufficient image quality. Among the remaining 61 carotid arteries from 61 patients available for analysis, 51 were men with an age range of 65–87 (mean 79). HIS in carotid plaques on 3D-TOF-MRA MIP images was present in 27 (44%) of 61 patients (HIS-positive group) and absent in 34 patients (HIS-negative group). Cardiovascular risk factors were not significantly different between the HIS-positive and HIS-negative groups (table 1). The assessment of HIS in plaques was highly reproducible between the two observers, as indicated by a Cohen’s κ value of 0.89. The median time between onset of prior ipsilateral ischemic stroke and carotid MRI was 2 days (interquartile range 0–4 days). Prior ipsilateral ischemic stroke occurred more frequently in the HIS-positive group than in the HIS-negative group (67 vs. 9%, p < 0.001; fig. 2). Furthermore, there were more smokers in the ischemic stroke-positive group than in
the ischemic stroke-negative group (62 vs. 25%, p = 0.005; table 2). In multivariate logistic regression analysis, the presence of HIS in carotid plaque (OR 23.4, 95% CI 4.62–118.3, p < 0.001) and smoking (OR 5.44, 95% CI 1.20–24.6, p = 0.028) were independent determinants of prior ischemic strokes after adjustment for age (table 3).

### Discussion

This study demonstrated that prior ischemic strokes were more frequent in the HIS-positive plaque patients than in the HIS-negative plaque patients and in patients who had a history of smoking. Multivariate regression analysis showed that HIS in carotid plaques on 3D-TOF-MRA MIP images was one of the independent determinants of prior ischemic strokes in patients with moderate carotid artery stenosis.

Recently, some researchers reported that carotid IPH was detected in 36–48% of patients with moderate carotid artery stenosis using 3-dimensional T1-weighted fat-suppressed spoiled gradient-echo sequence or T1-weighted turbo-field echo MRI [23, 24]. In this study, HIS in carotid plaques on 3D-TOF-MRA was present in 44% of patients and the rate of the presence of carotid IPH was similar with their results.

Several investigators have reported an association between the presence of carotid IPH and cerebral ischemic events [25–29]. Hosseini et al. [28] performed meta-analysis and showed a strong association between the presence of carotid IPH and recurrent cerebral ischemic events in symptomatic carotid artery stenosis (OR 12.2, 95% CI 5.5–27.1, p < 0.001), thereby suggesting that IPH is a promising predictor of future cerebrovascular events in patients with carotid artery stenosis. However, these studies mainly focused on patients with high-grade stenosis (>70%), and required specialized multi-contrast sequences or devices such as high-resolution surface coils that were difficult to use routinely in the clinical setting. This study demonstrated that patients with moderate carotid artery stenosis in the HIS-positive group were almost 23 times more likely to have suffered ischemic strokes compared with patients in the HIS-negative group. The results of our study are in agreement with previous findings in patients with high-grade stenosis (>70%), and required specialized multi-contrast sequences or devices such as high-resolution surface coils that were difficult to use routinely in the clinical setting. Moreover, this method enables us to acquire not only carotid IPH information but also luminal information at the same time [18]. Those are the advantages of 3D-TOF-MRA MIP image screening for carotid IPH. In addition, this study stratified patients with moderate carotid artery stenosis who did not have an indication for medical treatment, whereas previous studies exclusively focused on patients who had an indication for medical treatment. This study suggests the possibility for the detection of subclinical carotid plaques that were prone to cause strokes in the future.

In this study, prior ischemic strokes were more frequent in patients who had a history of smoking. Recently, McNally et al. [30] reported that optimal discrimination of carotid-source stroke was obtained in patients who had a history of smoking. Smoking may cause active inflammation unaccounted for by IPH. Smokers have been reported to have increased carotid plaque neovascularity and permeability [31, 32]. It is also reported that smoking

| Table 2. Characteristics between patients with and without a prior ischemic stroke |
|---------------------------------|-----------------|-----------------|-----------------|
| Prior ischemic stroke positive (n = 21) | Prior ischemic stroke negative (n = 40) | p value |
| Age, years | 79±5 | 79±6 | 0.67 |
| Male, n (%) | 20 (95) | 31 (78) | 0.16 |
| HIS-positive, n (%) | 18 (86) | 9 (23) | <0.001 |
| Degree of stenosis, % | 58±6 | 57±6 | 0.67 |
| Hypertension, n (%) | 20 (95) | 36 (90) | 0.83 |
| Diabetes mellitus type 2, n (%) | 6 (29) | 10 (25) | 0.76 |
| Hyperlipidemia, n (%) | 8 (38) | 9 (23) | 0.19 |
| Ischemic heart disease, n (%) | 2 (10) | 8 (20) | 0.49 |
| Statin use, n (%) | 8 (38) | 9 (23) | 0.19 |
| Smoking, n (%) | 13 (62) | 10 (25) | 0.005 |
| Body mass index, kg/m² | 22.3±3.2 | 21.9±2.9 | 0.68 |

Laboratory parameters are shown as the mean ± SD.

| Table 3. Multivariate logistic regression analysis to identify the independent determinant of prior ischemic stroke in patients with moderate carotid artery stenosis |
|---------------------------------|-----------------|-----------------|-----------------|
| OR | 95% CI | p value |
| HIS-positive | 23.4 | 4.62–118.3 | <0.001 |
| Smoking | 5.44 | 1.20–24.6 | 0.028 |
activates a proembolic component of carotid plaque [33]. Evidence suggests that smoking results in platelet activation and thrombogenesis in atherosclerotic plaques [30, 34]. Our data support a role of smoking in thromboembolic strokes from carotid artery stenosis.

This study had several limitations. First, the occurrence of stroke is affected by many factors such as the degree of stenosis, blood coagulability, atherosclerotic risk factors, and dehydration and chronic kidney disease [35]. However, these factors could not be included in the analysis due to the limited number of patients. This is one of the major limitations of this study. Moreover, this study was performed in a retrospective manner. Therefore, a prospective follow-up study with a large number of subjects will be required in the future to establish the causality of IPH and embolic stroke. Second, images were acquired on a 1.5 T MR scanner, which is widely used in the clinical hospitals. However, if it targets anatomical detail within plaques such as HIS in the plaque for the analysis, it may be preferable to use higher field strength magnet such as 3 T MR scanner. Further study using 3 T MR scanner or more higher field strength magnet is needed to determine whether these study findings can be generalized to the clinical setting. Third, we focused on the presence of HIS in the plaque on 3D-TOF-MRA, but the volume of HIS in the plaque might be another important predictor of ischemic stroke because this correlates with the volume of IPH. The relationship between the volume of HIS in plaque and cerebral ischemic stroke should also be elucidated in future analyses.

**Conclusion**

We demonstrated that HIS in carotid plaques on 3D-TOF-MRA MIP images was one of the independent determinants of prior ischemic stroke in patients with moderate carotid artery stenosis. 3D-TOF-MRA MIP images allow for rapid determination not only of the degree of stenosis and other anatomical findings but also of the presence of carotid IPH as HIS in carotid plaque using rotational views. HIS in carotid plaques on 3D-TOF-MRA MIP images can potentially provide a reliable risk stratification of patients with moderate carotid artery stenosis.

**Disclosure Statement**

The authors have no conflicts of interest to declare.

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**References**


