Predicting Stenosis Aggravation in Follow-Up High-Resolution Magnetic Resonance Images of Patients with Intracranial Atherosclerosis

Hyung-Soo Lee  Jin-Man Jung  Hwa-Been Yang  Sang-Hun Lee
Department of Neurology, Korea University Ansan Hospital, Korea University College of Medicine, Ansan, Republic of Korea

Keywords
High-resolution magnetic resonance imaging · Intracranial atherosclerosis · Concentric and eccentric plaque · Plaque enhancement

Abstract
Background: High-resolution magnetic resonance imaging (HRMRI) can provide information on the histopathological characteristics of intracranial atherosclerotic lesions causing arterial stenosis; however, its clinical application in intracranial atherosclerosis lacks standardization for predicting stenosis. Therefore, this study investigated the characteristics of HRMRI that can predict progression based on comparisons of follow-up HRMRI.

Methods: We retrospectively enrolled patients who underwent HRMRI within 7 days of symptom onset to evaluate the characteristics associated with intracranial stenotic lesions. Among them, patients diagnosed with severe stenosis due to atherosclerosis and who underwent follow-up HRMRI 12–24 months after initial HRMRI were included in the final study. We analyzed distinct features, such as stenosis aggravation, the presence of initial plaque enhancement, increment of plaque enhancement, the existence of both eccentric and concentric plaques, and the presence of initial intraplaque hematoma on initial and follow-up HRMRI.

Results: Among 442 patients who underwent HRMRI for severe stenosis due to atherosclerosis, 35 underwent follow-up HRMRI 12–24 months later. Patients with stenosis aggravation showed a higher incidence of plaque enhancement (87.5% vs. 3.7%, \( p < 0.001 \)) and the presence of both concentric and eccentric plaques (75.0% vs. 11.1%; \( p = 0.001 \)). The area under the curve for the increment of plaque enhancement was 0.92 (95% confidence interval [CI] 0.78–1.00, \( p \leq 0.001 \)), while that for the presence of both concentric and eccentric plaques was 0.82 (95% CI 0.63–1.00, \( p < 0.007 \)).

Conclusions: The presence of both concentric and eccentric plaques and an increase in plaque enhancement were the strongest predictors of aggravation of intracranial artery stenosis.

Introduction
Intracranial atherosclerosis (ICAS) is a common cause of ischemic stroke and has a high rate of recurrent ischemic events and vascular mortality [1–4]. However, ICAS has received less attention because it is more difficult to access and measure than extracranial atherosclerosis [4]. Computed tomography angiography and conventional magnetic resonance angiography can measure the lumen diameter and the extent of stenosis; however, they have limitations in identifying the cause of arterial stenosis, plaque morphology, plaque composition, and the vulnerability of an atherosclerotic plaque [2, 5, 6]. High-resolution magnetic resonance imaging (HRMRI) can provide information on the histopathological characteristics of intracranial atherosclerotic lesions causing arterial stenosis; however, its clinical application in intracranial atherosclerosis lacks standardization for predicting stenosis. Therefore, this study investigated the characteristics of HRMRI that can predict progression based on comparisons of follow-up HRMRI.
information on the histopathological characteristics of intracranial atherosclerotic lesions that cause arterial stenosis [7]. However, its clinical application to ICAS has been limited by the lack of standardization for the prediction of stenosis [8]. This study identified the characteristics of HRMRI that predicted the progression of atherosclerosis and evaluated the value of HRMRI as a diagnostic method.

Methods

Patients
A prospective database (the Korea University Ansan Hospital Stroke Registry) was used to retrospectively screen consecutive patients who underwent HRMRI and were diagnosed with ischemic stroke or transient ischemic attack between January 2015 and December 2020. The patients were included in the study according to the following criteria: (1) enrollment within 7 days of symptom onset, (2) initial HRMRI within 7 days of symptom onset, and follow-up HRMRI performed 12–24 months after the initial HRMRI, and (3) severe (70–99%) stenosis that could be definitively attributed to atherosclerosis. This study was approved by the Institutional Review Board of the relevant institutions. The exclusion criteria were as follows: (1) other etiologies due to vasculitis, moyamoya disease, and cardiac embolism; (2) hypercoagulable state; and (3) radiographic findings of two or more causes and unknown causes. All patients with overt severe atherosclerotic stenosis who underwent both initial HRMRI and follow-up HRMRI at intervals of 1–2 years for 5 years were analyzed. Initial HRMRI and follow-up HRMRI of the same patient were compared and analyzed. The retrospective protocol of the current study was approved by the Institutional Review Board of Korea University Ansan Hospital (IRB No. 2020AS0072).

Imaging Protocol
All patients underwent initial and follow-up HRMRIs. HRMRI was performed using a 3-Tesla scanner with a 20-channel head coil (MAGNETOM Skyra, Siemens, Germany). Two-dimensional sequences and blood-flow suppression images were acquired using turbo spin echo with variable flip-angle refocusing radiofrequency pulses (sampling perfection with application-optimized contrast technique). Three-dimensional time-of-flight magnetic resonance angiography was performed using the following parameters: slice thickness = 0.5 mm, repetition time/echo time = 21/3.69 ms, flip angle, 18°; field of view, 230 × 186.9 mm, and matrix size, 448 × 291. Two-dimensional proton density-weighted imaging was performed using the following parameters: slice thickness = 0.39 mm, slice thickness, 2 mm; repetition time/echo time, 2,450/37 ms; field of view, 100 × 100 mm; and matrix size, 195 × 256. The number of slices was 15, and the acquisition time was 224 s. Two-dimensional 6T T1-weighted imaging was performed using the following parameters: in-plane resolution = 0.39 × 0.39 mm, slice thickness = 2 mm, repetition time/echo time = 2,450/37 ms; field of view, 100 × 100 mm; and matrix size, 195 × 256. The number of slices was 15, and the acquisition time was 222 s. Two-dimensional contrast-enhanced T1-weighted imaging after the administration of intravenous gadolinium (gadobutrol, 0.1 mmol/kg body weight) (Gadovist; Bayer Schering Pharma, Berlin, Germany) with turbo spin-echo sequences was performed using the following parameters: in-plane resolution = 0.39 × 0.39 mm, slice thickness = 2 mm, repetition time/echo time = 670/9.1 ms, field of view = 100 × 100 mm, and matrix size = 256 × 256. The number of slices was 15, and the acquisition time was 202. The total acquisition time was approximately 30 min. The scanning orientation was transversal, and the three-dimensional images were reconstructed into coronal, axial, and sagittal images.

The images were assessed independently by two stroke neurologists and one neuroradiologist blinded to the available clinical data. Discrepancies were resolved by consensus. The intracranial artery was defined as the rostral part of the intradural portion of the vertebral artery (V4) and internal carotid artery (clinoid segment). We identified atherosclerosis based on previously reported important components, including atherosclerotic plaques, lipid cores, fibrous components, intraplaque hemorrhage, and calcium [9, 10].

Data Collection and Statistical Analysis
We collected baseline demographic data and clinical information for all study participants, including age, sex, and stroke risk factors such as hypertension, diabetes mellitus, dyslipidemia, previous stroke, cardiac source, alcohol consumption, and smoking status. We analyzed distinct features such as stenosis aggravation, the presence of initial plaque enhancement, an increase in plaque enhancement, the existence of mixed (both eccentric and concentric) plaques, and the presence of initial intraplaque hematoma obtained from initial and follow-up HRMRI. The cross-sectional eccentricity index was used to evaluate the eccentricity. The cross-sectional eccentricity index was calculated as (maximum wall thickness–minimum wall thickness)/maximum wall thickness. Eccentric lesions were defined as those with a cross-sectional eccentricity index ≥0.3, whereas concentric lesions were defined as those with a cross-sectional eccentricity index of <0.3 [11]. The sample size calculation was performed using R 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

To evaluate the diagnostic efficiency of plaque features for stenosis aggravation, we evaluated the area under the curves (AUCs) via receiver operating characteristic curve analysis using R 4.0.3. Intergroup differences were evaluated using the χ 2, Student’s t, and Mann-Whitney U tests, as appropriate. McNemar’s tests were used to compare the sensitivity and specificity for the evaluation of diagnostic tests. All results were considered statistically significant at p < 0.05. All statistical analyses were performed using R 4.0.3, and IBM SPSS Statistics for Windows, version 20.0 (IBM Corp., Armonk, NY, USA).

Results

Patient Demographics

Between January 2015 and December 2020, 442 patients underwent HRMRI for ischemic stroke or transient ischemic attack. Among them, 65 underwent follow-up HRMRI at 12–24 months after the initial HRMRI. Thirty of the 65 patients were excluded for dissection (n = 16),...
vasculitis \((n = 2)\), moyamoya disease \((n = 4)\), mild atherosclerosis \((n = 7)\), or thromboembolism \((n = 1)\). Therefore, the final analysis included 35 patients (Fig. 1).

**Analysis of Outcomes**

Table 1 presents the demographic characteristics of the patients with ICAS according to stenosis aggravation. We analyzed the history of stroke risk factors including cigarette smoking, alcohol consumption, hypertension, diabetes mellitus, hyperlipidemia, and HRMRI features. There were no significant between-group differences in stroke risk factors. Among the HRMRI features, the presence of initial plaque enhancement and the presence of initial intraplaque hematoma did not differ between the groups. However, patients with stenosis aggravation showed a higher incidence of an increase in plaque enhancement (87.5% vs. 3.7%, respectively; \(p < 0.001\)) and the presence of both concentric and eccentric plaques (75.0% vs. 11.1%, respectively; \(p = 0.001\)).

To determine the accuracy of the HRMRI features for predicting stenosis aggravation, receiver operating characteristic curves were created, and AUCs were calculated.
Intracranial Atherosclerotic Stenosis Aggravation in Follow-Up HRMRI

The AUC for the increment of plaque enhancement was 0.92 (95% confidence interval [CI] 0.78–1.00, \( p \leq 0.001 \)) (Table 2). The features of increased plaque enhancement and the presence of both concentric and eccentric plaques had good diagnostic efficiency for the prediction of stenosis aggravation. In contrast, we observed no significant AUCs for the presence of initial plaque enhancement (AUC 0.53, 95% CI 0.31–0.76, \( p = 0.798 \)) and the presence of initial intraplaque hematoma (AUC 0.37, 95% CI 0.17–0.57, \( p = 0.271 \)) (Table 2).

The presence of both concentric and eccentric plaques (sensitivity 78%, CI 0.35–0.97, specificity 89%, CI 0.71–0.97) and increased plaque enhancement (sensitivity 88%, CI 0.47–1.00, specificity 96%, CI 0.81–1.00) showed high sensitivity and specificity for stenosis aggravation (Table 3). Otherwise, the presence of initial plaque enhancement (sensitivity 88%, 95% CI 0.47–1.00, specificity 19%, 95% CI 0.06–0.38) and the presence of initial intraplaque hematoma (sensitivity 0%, CI 0.00–0.37, specificity 74%, 95% CI 0.54–0.89) showed low values for either sensitivity or specificity.

Table 1. Characteristics of the study participants according to stenosis aggravation

| Variables                      | All \((N = 35)\) | Stenosis aggravation (+) \((N = 8)\) | Stenosis aggravation (−) \((N = 27)\) | \( p \) value |
|-------------------------------|-----------------|-------------------------------------|-------------------------------------|-------------|
| Age, years                    | 55.6±11.0       | 49.0±11.7                           | 57.6±10.2                           | 0.052       |
| Sex, female                   | 13 (37.1)       | 5 (62.5)                            | 8 (29.6)                            | 0.116       |
| Hypertension                  | 15 (42.9)       | 4 (50.0)                            | 11 (40.7)                           | 0.700       |
| Diabetes                      | 11 (31.4)       | 5 (62.5)                            | 6 (22.2)                            | 0.077       |
| Alcohol consumption           | 21 (60.0)       | 3 (37.5)                            | 15 (66.7)                           | 0.221       |
| Smoking                       | 21 (60.0)       | 4 (50.8)                            | 17 (63.0)                           | 0.685       |
| Hyperlipidemia                | 18 (51.4)       | 3 (37.5)                            | 15 (55.6)                           | 0.443       |
| HRMRI feature                 |                 |                                     |                                     |             |
| Presence of initial plaque enhancement | 29 (82.9) | 7 (87.5)                            | 22 (81.5)                           | 1.000       |
| Increment of plaque enhancement | 8 (22.9)    | 7 (87.5)                            | 1 (3.7)                             | <0.001      |
| Presence of mixed (both eccentric and concentric) plaques | 9 (25.7)    | 6 (75.0)                            | 3 (11.1)                            | 0.001       |
| Presence of initial intraplaque hematoma | 7 (20.0)   | 0 (0.0)                             | 7 (25.9)                            | 0.166       |

Results are expressed as \( n \) (%) or mean±standard deviation. HRMRI, high-resolution magnetic resonance imaging.

Discussion

The present study aimed to determine whether certain distinct features of initial HRMRI could play an important role in predicting the aggravation of intracranial artery stenosis. Receiver operating characteristic curve analysis showed that the presence of both concentric and eccentric plaques and an increase in plaque enhancement were the strongest predictors of aggravation of intracranial artery stenosis.
Identifying and classifying the levels of lipid cores and fibrous components in plaques is the most important measurement factor for predicting the possibility of exacerbation of vascular fragility and stenosis. However, it is difficult to distinguish these features in intracranial arteries using HRMRI because these vessels are too small. Atherosclerosis is caused by a series of endothelial dysfunction processes, infiltration of modified lipids into the intima and inflammation or remodeling of the vessel wall, therefore atherosclerotic plaque, lipid nucleus, fibrous component, hemorrhage, and calcium are the most important components in HRMRI [12, 13]. In particular, in order to distinguish the lipid core from the fibrous component, it is necessary to compare and analyze T1-weighted images and T2-weighted images. In intracranial plaques, especially in T2-weighted images, it may not be possible to characterize the intracranial plaques in detail since the resolution is limited [14, 15]. In this case, it is important to identify distinguishable and clear items that many clinicians can catch in common in the HRMRI image sequence protocol. Therefore, this study applied new measurement methods to allow easier observation of the intracranial artery, which is different from the measurement items of the extracranial artery represented by the carotid artery. Among these methods is the simultaneous identification of both concentric and eccentric plaques. Intracranial atherosclerotic plaques are generally observed as eccentric wall thickening [16]. Moreover, the progression of atherosclerotic lesions is more frequent in eccentric lesions than in concentric lesions [17, 18]. However, pathophysiological studies have described eccentric geometry as a conservation mechanism that maintains an open lumen in the presence of atherosclerosis. Hemodynamic forces acting on endothelial cells are valuable for atherosclerosis initiation, and pro-atheroplastic shear stress profiles produce different plaque phenotypes [19, 20]. Low shear stress exacerbates eccentric plaque accumulation, whereas oscillatory shear stress tends to induce small plaques with a concentric phenotype [20]. As observed in our study, the action of these multidirectional shear and oscillatory shear stresses creates both concentric and eccentric plaques. The action of various superimposed stresses may induce unstable and worsened intracranial arterial stenosis. However, the role of lesion eccentricity as a feature of plaque vulnerability has not been investigated, and the impact of lesion geometry, as defined by the type of eccentricity (transversal or longitudinal), on the degree of vulnerability is unclear. The same was true for concentric plaques. Therefore, more detailed studies are required [11].

The degree of plaque enhancement may reflect the level of inflammatory activity due to increased endothelial

### Table 2. AUC via receiver operating characteristic curve analysis for stenosis aggravation according to plaque feature identified by HRMRI

| Variables                              | AUC (95% CI)       | p value |
|----------------------------------------|--------------------|---------|
| Presence of mixed (both eccentric and concentric) plaques | 0.82 (0.63–1.00)   | 0.007   |
| Increment of plaque enhancement        | 0.92 (0.78–1.00)   | <0.001  |
| Presence of initial plaque enhancement | 0.53 (0.31–0.76)   | 0.798   |
| Presence of initial intraplaque hematoma| 0.37 (0.17–0.57)   | 0.271   |

HRMRI, high-resolution magnetic resonance imaging; AUC, area under the curve; CI, confidence interval.

### Table 3. Sensitivity and specificity of the plaque features of HRMRI for the prediction of stenosis aggravation

| Variables                              | Sensitivity (95% CI) | Specificity (95% CI) |
|----------------------------------------|----------------------|----------------------|
| Presence of mixed (both eccentric and concentric) plaques | 0.75 (0.35–0.97)     | 0.89 (0.71–0.97)     |
| Increment of plaque enhancement        | 0.88 (0.47–1.00)     | 0.96 (0.81–1.00)     |
| Presence of initial plaque enhancement | 0.88 (0.47–1.00)     | 0.19 (0.06–0.38)     |
| Presence of initial intraplaque hematoma| 0.00 (0.00–0.37)     | 0.74 (0.54–0.89)     |

HRMRI, high-resolution magnetic resonance imaging; CI, confidence interval.
permeability and neovascularity [21]. The plaque enhancement that can be observed with gadolinium contrast agents serves as a marker of inflammation and plaque instability and neovascularity [16]. Previous studies suggested that plaque enhancement was associated with inflammation, plaque instability, and downstream acute infarction; the results of the present study also showed that increased plaque enhancement is a strong predictor of worsening of intracranial arterial stenosis [22–24]. Damaged microvascular endothelium can lead to gadolinium accumulation in the perivascular space and vascular leakage, which can be detected on T1-weighted MRI sequences [22]. Therefore, the detectable enhancement on MRI may be related to endothelial dysfunction present in microvessels in diseased plaques of atherosclerotic vessels, which may be closely related to the exacerbation of vascular stenosis [25]. However, the mechanisms of plaque enhancement in vulnerable intracranial atherosclerotic plaques are complex and likely multifactorial [22], and it is possible that a leaky endothelial barrier caused by inflammation is the cause of the enhancement of gadolinium. It is also possible that the difference according to the presence or absence of vasa vasorum may also have an effect, so further studies on histopathological evaluation are needed [24].

Our study has some limitations. First, we included only a small number of patients from a single center; thus, these results cannot be generalized. Second, HRMRI has some limitations in terms of cost and availability compared to CT angiography and suffers from technical limitations such as overestimation of stenosis in post-stenotic regions of low flow. Furthermore, the disadvantage of being susceptible to motion artifacts, as with all MR sequences, can act as a limitation. Third, there is currently no universal standard protocol for HRMRI imaging that would facilitate multicenter studies. Additionally, data generated by HRMRI depend on parameters related to the sequence, environment, and MRI instrumentation, as well as patient factors, making it difficult to compare results from different centers [8]. Therefore, the development of the HRMRI ICAS research field requires the establishment of a multi-institutional network to facilitate collaboration, share protocols and data, and provide a research infrastructure to allow a fast and efficient mechanism for researching HRMRI in ICAS [8]. Finally, retrospective review of clinical registry data presented barriers to patient selection, recording, completeness of data and assessment of outcome, as well as limitations in selection bias related to follow-up scans. The findings must be further confirmed in prospective multicenter studies.

In conclusion, the presence of both concentric plaques and eccentric plaques in the initial HRMRI suggests a high possibility of future stenosis aggravation. Moreover, if the contrast enhancement of the plaque intensifies in the follow-up HRMRI compared to the previous examination, the stenosis has progressed or is likely to develop.

Statement of Ethics

Institutional review board approval was obtained from all the participants. Due to the nature of a retrospective study with anonymized data, this study was approved and the requirement for informed consent was waived by the Institutional Review Board of Korea University Ansan Hospital (IRB No. 2020AS0072).

Conflict of Interest Statement

The authors declare no conflicts of interest in relation to the current work.

Funding Sources

This study was supported by a Korea University Ansan Hospital Grant No. (K2110981).

Author Contributions

Dr. H.S. Lee contributed to the study conception and design, data analysis, acquisition of clinical and imaging data, statistical analysis, manuscript drafting, and revision. Dr. S.H. Lee contributed to the study conception and design, analysis and interpretation of the imaging and clinical data, manuscript drafting and revision, and study supervision. Dr. J.M. Jung contributed to the data analysis and manuscript revision. Dr. H.B. Yang contributed to the data statistical analysis.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

References

1. Turan TN, Maidan L, Cotsonis G, Lynn MJ, Romano JG, Levine SR, et al. Failure of antithrombotic therapy and risk of stroke in patients with symptomatic intracranial stenosis. Stroke. 2009;40:505–9.
2. Holmstedt CA, Turan TN, Chimowitz MI. Atherosclerotic intracranial arterial stenosis: risk factors, diagnosis, and treatment. Lancet Neurol. 2013;12:1106–14.
6 Skarpathiotakis M, Mandell DM, Swartz RH, Amarenco P, Bogousslavsky J, Caplan LR, Vakil P, Vranic J, Hurley MC, Bernstein RA, Chimowitz MI, Lynn MJ, Derdeyn CP, Turan, Tomlinson G, Mikulis DJ. Intracranial atherosclerotic plaque enhancement in patients with ischemic stroke. AJNR Am J Neuroradiol. 2013; 34:2252–8.

7 Ryu CW, Jahng GH, Kim EJ, Choi WS, Yang DM. High resolution wall and lumen MRI of the middle cerebral arteries at 3 tesla. Cerebrovasc Dis. 2009;27:433–42.

8 Chueh JY, van der Marel K, Gounis MJ, Le,Nan, win jai, Chan X, Yang DM. Gadolinium enhancement of intracranial atherosclerotic plaques associated with symptomatic ischemic presentations. Am J Neuroradiol. 2013;34:299–304.

11 Ratiu M, Chitu M, Benedek I, Benedek T, Kovacs I, Kat N, et al. Impact of coronary plaque geometry on plaque vulnerability and its association with the risk of future cardiovascular events in patients with chest pain undergoing coronary computed tomographic angiography—the geometry study: protocol for a prospective clinical trial. Medicine. 2018;97: e13498.

12 Oppenheim C, Naggara O, Touze E, Lacour JC, Schmitt E, Bonneville F, et al. High-resolution mri imaging of the cervical arterial wall: what the radiologist needs to know. Radiographics. 2009;29:1413–U1252.

13 Makowski MR, Botnar RM. Mr imaging of the arterial vessel wall: molecular imaging from bench to bedside. Radiology. 2013;269:34–51.

14 Choi YJ, Jung SC, Lee DH. Vessel wall imaging of the intracranial and cervical carotid arteries. J stroke. 2015;17:238–55.

15 Kamath S. Observations on the length and diameter of vessels forming the circle of willis. J Anat. 1981;133:419–23.

16 Huang J, Jiao S, Zhao X, Zhang J, Zhang C, Chen M, et al. Characteristics of patients with enhancing intracranial atherosclerosis and association between plaque enhancement and recent cerebrovascular ischemic events: a high-resolution magnetic resonance imaging study. Acta Radiol. 2019;60:1301–7.

17 Guzman RJ, Brinkley DM, Schumacher PM, Donahue RM, Beavers H, Qin X. Tibial arterial vessel wall: molecular imaging from bench to bedside. Radiology. 2013;269:34–51.