

Hyperintense Plaque on Intracranial Vessel Wall Magnetic Resonance Imaging as a Predictor of Artery-to-Artery Embolic Infarction

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Background and Purpose—The aim of the present study was to investigate atherosclerotic plaque characteristics in patients with artery-to-artery (A-to-A) embolic infarction by whole-brain high-resolution magnetic resonance imaging.

Methods—Seventy-four patients (mean age, 54.7±12.1 years; 59 men) with recent stroke in the territory of middle cerebral artery because of intracranial atherosclerotic disease were prospectively enrolled. Whole-brain high-resolution magnetic resonance imaging was performed in all the patients both precontrast and postcontrast administration by using a 3-dimensional T1-weighted vessel wall magnetic resonance imaging technique known as inversion-recovery prepared sampling perfection with application-optimized contrast using different flip angle evolutions. Patients were divided into A-to-A embolic infarction and non-A-to-A embolic infarction groups based on diffusion-weighted imaging findings. The characteristics of the intracranial atherosclerotic plaques were compared between groups.

Results—A total of 74 intracranial atherosclerotic plaques were analyzed (36 in A-to-A embolism group and 38 in non-A-to-A embolism group). Hyperintense plaques (HIPs) were more frequently observed in A-to-A embolism group (75.0% versus 21.1%; $P<0.001$). Eighteen of the 27 HIPs (66.7%) demonstrated hyperintense spots or areas located adjacent to the lumen versus 9 HIPs (33.3%) located within the plaque in A-to-A embolism group. Furthermore, a higher prevalence of plaque surface irregularity was also observed in A-to-A embolism group (41.7% versus 18.4%; $P=0.029$). Logistic regression analysis showed that HIP was the most powerful independent predictor of A-to-A embolic infarction ($P<0.001$), with the odds ratio of 11.2 (95% confidence interval, 3.5–36.2).

Conclusions—A-to-A embolic infarction has distinct vulnerable plaque characteristics compared with non-A-to-A embolic infarction. HIP and plaque surface irregularity may predict A-to-A embolic infarction. (*Stroke*. 2018;49:00-00. DOI: 10.1161/STROKEAHA.117.020046.)

Key Words: atherosclerosis ■ embolism ■ magnetic resonance imaging ■ stroke

Intracranial atherosclerotic disease has been considered a major cause of ischemic stroke in Asian populations.¹ The underlying mechanisms for intracranial atherosclerotic disease stroke are multifactorial and can potentially be inferred from plaque characteristics.^{2–4} For example, artery-to-artery (A-to-A) embolic infarction may be caused by shedding of vulnerable plaque debris or plaque surface thrombus.^{2,5} However, the vulnerable plaque features ultimately leading to A-to-A embolism remain unclear. Because A-to-A embolic infarction has a high risk of recurrent stroke, aggressive use

of antiplatelet agents targeting these vulnerable plaques is a commonly used treatment strategy.⁶

Routine imaging techniques are unable to depict the atherosclerotic plaque characteristics of large intracranial arteries. Recently, high-resolution magnetic resonance imaging (HRMRI) has been developed and is capable of depicting major intracranial vessel wall lesions and revealing morphological features.^{7–9} Several studies have reported that positive remodeling, intraplaque hemorrhage, and plaque enhancement were associated with unstable intracranial atherosclerotic

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disease lesions.^{10–12} Nevertheless, few studies have focused on unraveling the differences in plaque features among stroke subtypes, such as A-to-A embolism, which may help to understand the vascular pathophysiology associated with this type of ischemic stroke and predict stroke recurrence.^{13,14}

Current challenges of vessel wall imaging techniques include incomplete cerebrospinal fluid suppression, limited coverage, and spatial resolution.^{15–18} Whole-brain (WB) HRMRI was developed to further improve spatial coverage, T1 contrast weighting, and signal suppression of cerebrospinal fluid, which would lead to better delineation of total plaque burden and characteristics with higher spatial resolution and contrast of vessel wall to surrounding tissues.^{19,20} The aim of our study was to investigate the plaque characteristics in A-to-A embolic infarction using WB-HRMRI.

Methods

The data that support the findings of this study are available from the corresponding author on reasonable request.

Patients

From January 2015 to May 2017, we prospectively recruited patients who were admitted to the Department of Neurology of our hospital with the following inclusion criteria: (1) first-time acute ischemic stroke in the middle cerebral artery (MCA) territory identified by diffusion-weighted imaging (DWI) performed within 72 hours of symptom onset; and (2) any degree of stenosis on the relevant MCA or intracranial internal carotid artery, as confirmed by magnetic resonance angiography, computed tomography angiography, or digital subtraction angiography. Exclusion criteria were (1) previous history of stroke or transient ischemic attacks on the symptomatic side; (2) history of ipsilateral MCA or intracranial internal carotid artery occlusion; (3) coexistent >50% stenosis or unstable plaques of the ipsilateral extracranial carotid artery detected by ultrasound (presence of 3 of the following parameters: stenosis >70%, pure hypoechoic or hypoechoic with small hyperechoic areas, superficial irregularity, and ulceration); (4) nonatherosclerotic vasculopathy that may predispose to stroke (eg, vasculitis, Moyamoya disease, or dissection); and (5) evidence of cardioembolism (recent myocardial infarction <3 weeks, atrial fibrillation, mitral stenosis or prosthetic valve, dilated cardiomyopathy, sick sinus syndrome, acute bacterial endocarditis, patent foramen ovale, etc.).²¹ All of the enrolled patients underwent WB-HRMRI within 2 weeks of symptom onset.

Clinical information, including sex, age, vascular risk factors (hypertension, diabetes mellitus, hyperlipidemia, and current smoking), medications (statins, antiplatelet agents, anticoagulants, and r-tPA [recombinant tissue-type plasminogen activator]), and onset time of stroke were recorded for each patient. Informed consent was obtained from all participants, and all protocols were approved by the Institutional Review Board.

MRI Protocols

Routine brain MRI (T1-, T2-weighted, fluid-attenuated inversion recovery, and DWI) was initially performed for clinical evaluation of stroke patients. All patients underwent WB-HRMRI with a 3-T system (Magnetom Verio; Siemens, Erlangen, Germany), and 32-channel head coil was used. WB-HRMRI was performed in both precontrast and postcontrast administration by using a 3-dimensional T1-weighted WB vessel wall MRI technique known as inversion-recovery prepared sampling perfection with application-optimized contrast using different flip angle evolutions^{19,20} with the following parameters: repetition time=900ms; echo time=15 ms; field of view=170×170 mm²; 240 slices with slice thickness of 0.5 mm; voxel size=0.5×0.5×0.5 mm³; scan time=8 min. The MRI contrast agent, gadopentetate dimeglumine (Magnevist; Schering, Berlin, Germany), was injected through an antecubital vein (0.1 mmol/kg of body weight), and WB-HRMRI was repeated 5 minutes after injection was finished.

Routine MRI Evaluation

All DWI images were independently interpreted by 2 neurologists for the determination of infarction patterns on the Picture Archiving and Communication Systems. Discrepancies between the 2 reviewers were resolved by consensus. Patients were divided into 2 groups as follows: (1) A-to-A embolic infarction defined as ≥2 scattered hyperintense areas on DWI involved the cortical/subcortical areas or internal border-zone area of MCA territory; and (2) non-A-to-A embolic infarction defined as hyperintense areas on DWI localized in the territory of the deep perforating, including putamen, globus pallidus, internal capsule, and caudate head.²²

WB-HRMRI Image Analysis

Evaluation of WB-HRMRI studies was conducted in consensus by 2 experienced neuroradiologists (Q.Y. and F.W.) who were blinded to the clinical data of the patients using commercial software (Osirix MD; Pixmeo SARL, Switzerland). All atherosclerotic plaques on precontrast WB-HRMRI were then identified using a previously reported definition, that is, the presence of focal wall thickening.¹⁰ A culprit plaque was defined as (1) the only lesion

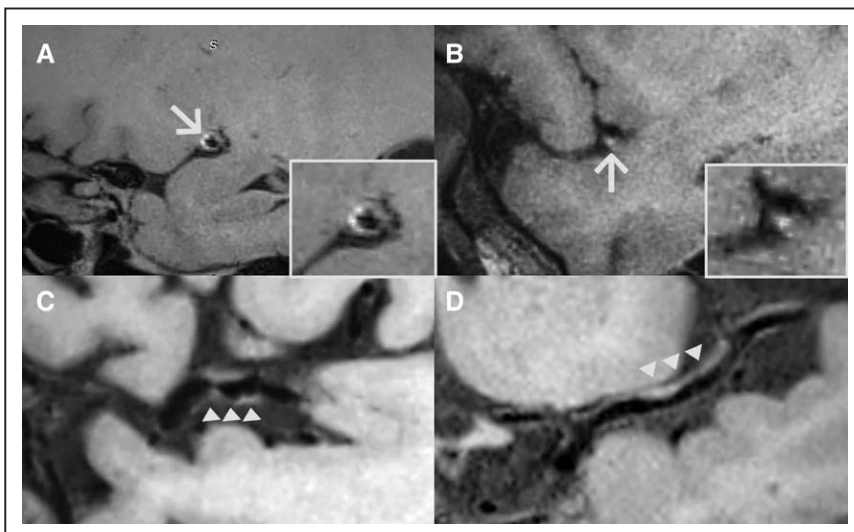


Figure 1. Different types of hyperintense plaques (HIPs) and plaque surface. High-resolution magnetic resonance imaging (HRMRI) demonstrated HIPs with hyperintense areas (arrow) located adjacent to the lumen (A)/within the plaque (B) and irregular (C)/regular (D) plaque surface (arrowhead).

Table 1. Patient Characteristics of the 2 Groups

| | A-to-A Embolism (n=36) | Non-A-to-A Embolism (n=38) | P Value |
|--|------------------------|----------------------------|---------|
| Male sex, n (%) | 28 (77.8) | 31 (81.6) | 0.684 |
| Age (mean±SD, y) | 53.1±13.9 | 56.2±10.1 | 0.261 |
| Hypertension, n (%) | 27 (75.0) | 29 (76.3) | 0.895 |
| Diabetes mellitus, n (%) | 9 (25.0) | 7 (18.4) | 0.492 |
| Hyperlipidemia, n (%) | 12 (33.3) | 18 (47.4) | 0.219 |
| Current smoking, n (%) | 17 (47.2) | 22 (57.9) | 0.358 |
| Medications, n (%) | | | |
| Statins | 0 (0.0) | 2 (5.3) | 0.494 |
| Antiplatelet agents | 3 (8.3) | 4 (10.5) | >0.999 |
| Statins and antiplatelet agents | 33 (91.7) | 29 (76.3) | 0.114 |
| r-tPA and antiplatelet agents | 0 (0.0) | 1 (2.6) | >0.999 |
| Statins, antiplatelet agents, and anticoagulants | 0 (0.0) | 2 (5.3) | 0.494 |
| Onset to WB-HRMRI time (mean±SD, d) | 8.3±4.1 | 8.3±3.7 | 0.989 |

A-to-A indicates artery-to-artery; r-tPA, recombinant tissue-type plasminogen activator; and WB-HRMRI, whole-brain high-resolution magnetic resonance imaging.

within the vascular territory of the stroke or (2) the most stenotic lesion when multiple plaques were present within the same vascular territory of the stroke.¹⁰

The sites of maximal stenosis and normal vessels (proximal to the maximal stenotic sites or the contralateral side) were, respectively, evaluated, and cross-sectional views were reconstructed for morphological and signal measurements. The location of each culprit lesion was recorded. The vessel area and lumen area were measured by manually tracing vessel and lumen boundaries. Stenosis degree was defined as $(1 - \text{lesion lumen area} / \text{reference lumen area}) \times 100\%$. The remodeling index was calculated as the ratio of the lesion vessel area to the reference vessel area. The mean signal intensity (SI) values of culprit plaques, reference vessel wall, and pituitary infundibulum were measured on precontrast and postcontrast WB-HRMRI images. Hyperintense plaque (HIP) was defined as the brightest spot of a plaque with the SI >150% of that of the reference vessel wall. The location of the hyperintense areas in A-to-A embolism group was categorized either as adjacent to the lumen (Figure 1A) or within the plaque (Figure 1B). An enhancement ratio (ER) was quantified by using the following equation: $ER = (SI_{\text{postcontrast}} - SI_{\text{precontrast}}) / SI_{\text{precontrast}} \times 100\%$. The degree of plaque enhancement was graded as follows: grade 0, ER of the culprit plaque was less than or equal to that of reference vessel wall; grade 1, ER of the culprit plaque was greater than that of the reference vessel wall, but less than that of pituitary infundibulum; and grade 2, ER of the culprit plaque was greater than or equal to that of the pituitary infundibulum.¹⁰ Either plaque surface irregularity (defined as a discontinuity of the plaque juxtalumenal surface; Figure 1C) or regularity (smooth inner wall; Figure 1D) of each culprit lesion was recorded.

Statistical Analysis

All quantitative data were expressed as means±SD, and qualitative data were summarized as count (percentage). Categorical variables were analyzed using a χ^2 test, and continuous variables were compared using *t* test or Mann-Whitney *U* test between the 2 groups. Variables were included for multivariate analysis if they were $P \leq 0.1$ in the univariate analysis. A logistic regression analysis with the

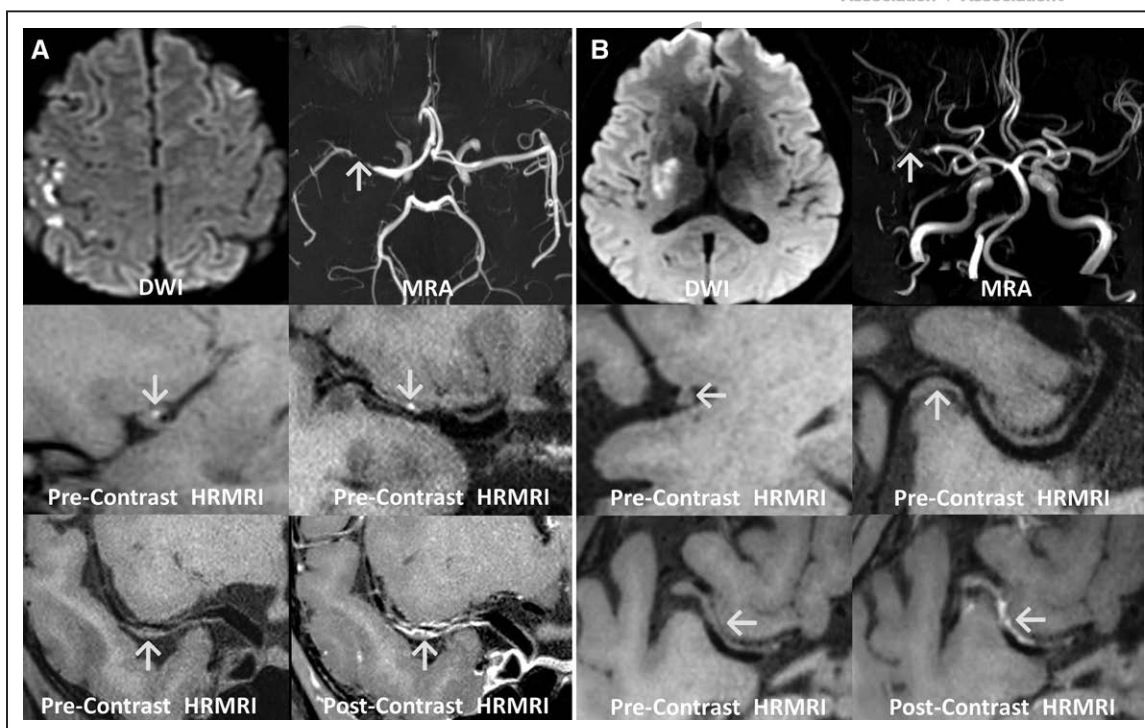


Figure 2. Examples of artery-to-artery (A-to-A) embolic (A) and non-A-to-A embolic infarction (B). **A**, Diffusion-weighted imaging (DWI) showed disseminated spotty high-signal-intensity lesions in the right cortico-subcortical area of the middle cerebral artery (MCA) territory; magnetic resonance angiography (MRA) demonstrated severe stenosis (arrow) of the right MCA; precontrast HRMRI showed a HIP (arrow) on the ventral side of MCA and irregular surface of the plaque; postcontrast HRMRI demonstrated plaque enhancement (arrow; grade 1). **B**, DWI showed a high-signal-intensity lesion in the right basal ganglia; MRA revealed severe stenosis (arrow) of the right MCA; precontrast HRMRI detected isointensity plaque (arrow) on the dorsal side of MCA and regular surface of the plaque; postcontrast HRMRI demonstrated plaque enhancement (arrow; grade 1).

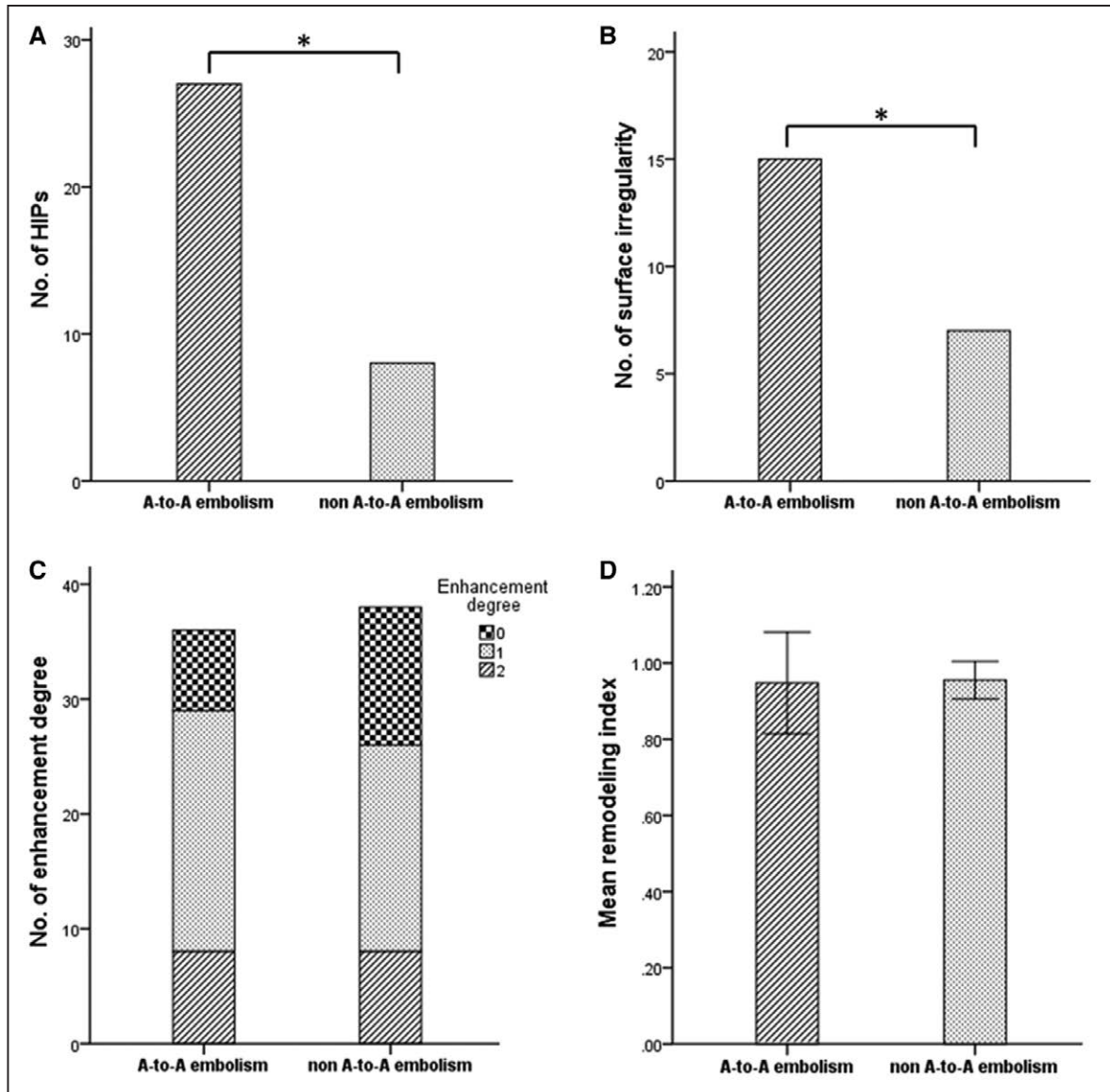


Figure 3. Comparison between 2 groups in vessel wall characteristics. Number of hyperintense plaques (HIPs; **A**), plaques with surface irregularity (**B**), plaques with various degree of enhancement (**C**), and mean remodeling index (**D**) in artery-to-artery (A-to-A) embolism and non-A-to-A embolism group.

method of enter stepwise was used to look for independent predictors of the 2 infarction patterns. A *P* value of <0.05 indicated statistical significance. All statistical analyzes were performed by using commercial software (SPSS 22.0, IBM).

Results

Patient Characteristics

Of the 74 patients, 36 (48.6%) were determined as A-to-A embolic infarction and 38 (51.4%) were non-A-to-A embolic infarction. The median time of WB-HRMRI scanning after symptom onset was 8.3 ± 4.1 days (ranging from 1 to 14 days). Patient demographics and the main clinical characteristics are presented in Table 1. No statistically significant differences were found.

Culprit Plaque Location and Degree of Stenosis

A total of 74 intracranial atherosclerotic plaques were included for the final analysis. In the A-to-A embolism group,

30 (83.3%) culprit plaques were found in MCA and 6 (16.7%) were in intracranial internal carotid artery. In non-A-to-A embolism group, 38 (100%) culprit plaques were detected in MCA. No significant difference was found in the maximal degree of stenosis between the A-to-A embolism and non-A-to-A embolism group ($51.4 \pm 24.6\%$ versus $39.5 \pm 28.6\%$; $P=0.060$).

Morphological and Textural Characteristics of Plaques

The occurrence rate of HIP was higher in the A-to-A embolism group than the non-A-to-A embolism group (75.0% versus 21.1%; $P<0.001$). In the A-to-A embolism group, 18 of the 27 HIPs (66.7%; Figure 1A) showed the hyperintense area located adjacent to the lumen versus 9 HIPs (33.3%; Figure 1B) within the plaque. A higher prevalence of plaque surface irregularity (Figure 1C) was also observed in A-to-A

embolism group (41.7% versus 18.4%; $P=0.029$). However, other vessel wall features including remodeling index (0.9 ± 0.4 versus 1.0 ± 0.1 ; $P=0.917$) and plaque enhancement (grade 1, 58.3% and grade 2, 22.2% versus grade 1, 47.4% and grade 2, 21.0%; $P=0.474$) were not significantly different between the 2 groups.

Multivariate Analysis

HIP, plaque surface irregularity, and stenosis degree were used as input variables for the logistic regression analysis. HIP and plaque surface irregularity remained significant in the multivariate analysis ($P<0.001$ and $P=0.045$, respectively), with odds ratios of 11.2 and 3.7 (95% confidence interval, 3.5–36.2 and 1.0–13.0). Details of the vessel wall features of the 2 groups were shown in Figures 2 and 3 and Table 2.

Discussion

In the current study, we found that patients with A-to-A embolism had distinct vulnerable plaque characteristics, such as HIP and plaque surface irregularity. Furthermore, 66.7% of HIPs demonstrated as hyperintense spots or areas located adjacent to the lumen versus 33.3% located within the plaque in A-to-A embolism group. Multivariate analysis showed that HIP and plaque surface irregularity were independently associated with A-to-A embolic infarction.

Previous studies have indicated that there was an association between HIP and lesion instability in coronary plaques.²³ HIP is thought to arise from intraplaque hemorrhage which is caused by the disruption of thin-walled microvessels and intraplaque vasa vasorum.²⁴ However, few studies of intracranial vessel wall imaging have reported that vulnerable plaques are associated with HIP.^{11,25} To the best of our knowledge, this is the first study using WB-HRMRI to explore the intracranial plaque characteristics in A-to-A embolism. We found the high prevalence of HIP in A-to-A

embolism patients which was thought to be the main intracranial vulnerable feature causing stroke. HIP can be used as a new imaging biomarker for the prediction of recurrent stroke, and the individualized assessment of anticoagulation therapy can be achieved.

Several studies have indicated that juxtaluminal hemorrhage/thrombus, indicating erosion or rupture, may cause further thrombotic incidents.^{26,27} A study of carotid atherosclerotic diseases with pathological confirmation has demonstrated that HRMRI can differentiate intraplaque hemorrhage from juxtaluminal hemorrhage/thrombus.²⁸ In our study, we observed more HIPs with the hyperintense areas located on the surface of the plaques in A-to-A embolism group, which is thought to be intraluminal thrombus causing embolism.

Plaque surface irregularity is another characteristic of plaques in the A-to-A embolism group observed in our study. A previous study has revealed that major surface irregularities (>2 mm) may shed emboli.²⁹ We found that patients with A-to-A embolism had a higher frequency of plaque surface irregularity and HIP. The coexistence of these vulnerable plaque pattern may be explained by the plaque ledge or plaque fragmentation which may increase the risk of the formation of surface thrombus.²⁹

Other studies^{30–32} have shown that enhancing plaques and positive remodeling are associated with symptomatic plaques. However, the mechanism of plaque enhancement remains unclear. In our study, plaque enhancement was observed in 80.5% of patients with A-to-A embolism and 68.4% of patients with non-A-to-A embolism. There was no significant difference between these groups. This may be because of the recruitment of symptomatic patients in each group.

The present study has several limitations. First, there is no pathological validation of intracranial HIP. HIP was identified on WB-MRI in 75.0% of A-to-A embolism patients in our study. The incidence was higher than that of a previous

Table 2. WB-HRMRI Characteristics of the 2 Groups

| WB-HRMRI Characteristics | Univariate | | | Multivariate | | |
|------------------------------------|-----------------|---------------------|---------|--------------|----------|---------|
| | A-to-A Embolism | Non-A-to-A Embolism | P Value | OR | 95% CI | P Value |
| No. of plaques, n (%) | 36 (48.6) | 38 (51.4) | | ... | ... | ... |
| Location | | | | ... | ... | ... |
| MCA, n (%) | 30 (83.3) | 38 (100) | | | | |
| Intracranial ICA, n (%) | 6 (16.7) | 0 (0) | | | | |
| Presence of HIP, n (%) | 27 (75.0) | 8 (21.1) | < 0.001 | 11.2 | 3.5–36.2 | < 0.001 |
| Plaque surface irregularity, n (%) | 15 (41.7) | 7 (18.4) | 0.029 | 3.7 | 1.0–13.0 | 0.045 |
| Stenosis degree (mean \pm SD, %) | 51.4 \pm 24.6 | 39.5 \pm 28.6 | 0.060 | 1.8 | 0.2–15.8 | 0.592 |
| Remodeling index (mean \pm SD) | 0.9 \pm 0.4 | 1.0 \pm 0.1 | 0.917 | ... | ... | ... |
| Enhancement | | | 0.474 | ... | ... | ... |
| Grade 0, n (%) | 7 (19.4) | 12 (31.6) | | | | |
| Grade 1, n (%) | 21 (58.3) | 18 (47.4) | | | | |
| Grade 2, n (%) | 8 (22.2) | 8 (21.0) | | | | |

A-to-A indicates artery-to-artery; CI, confidence interval; HIP, hyperintense plaque; ICA, internal carotid artery; MCA, middle cerebral artery; OR, odds ratio; and WB-HRMRI, whole-brain high-resolution magnetic resonance imaging.

study, which showed only 19.6% HIP in symptomatic MCA stenosis patients¹¹ because in our study, we recruited A-to-A embolic infarction patients, who may have more vulnerable plaques. In addition, a WB-HRMRI technique with inversion-recovery based T1-weighting-enhanced preparation instead of a simple 2-dimensional T1-weighted sequence was used, which may have a higher sensitivity in the detection of HIP. Second, we tested the practicability of WB-HRMRI in A-to-A embolism patients. Future prospective studies are still needed to explore WB-HRMRI in more stroke subtypes. Third, longitudinal studies are warranted to investigate and expound on the usage of WB-HRMRI in the prediction of stroke outcome and assessment of new therapeutic strategies.

In conclusion, A-to-A embolic infarction has distinct vulnerable plaque characteristics including HIP and irregular plaque surface compared with non-A-to-A embolic infarction. In A-to-A embolism group, 66.7% of the HIPs have hyperintense area located adjacent to the lumen which may help to better understand the relationship between plaque rupture, formation of blood clots, and embolic stroke.

Appendix

The WISP Investigators: Qi Yang (Xuanwu Hospital, Capital Medical University, Principal Investigator); Debiao Li, Zhaoyang Fan (Biomedical Imaging Research Institute, Cedars-Sinai Medical Center, University of California, Principal Investigator); Huan Yu (Liangxiang Hospital, Site Investigator); Tao Jiang (Chaoyang Hospital, Capital Medical University, Site Investigator); Bin Cui (Beijing AeroSpace Center Hospital, Site Investigator); Jiayu Sun (West China Hospital, Sichuan University, Site Investigator); Bin Sun (Fujian Medical University Union Hospital, Site Investigator); Shuang Xia (Tianjin First Center Hospital, Site Investigator); Tong Han (Tianjin First Center Hospital, Site Investigator); Jingliang Cheng (The First Affiliated Hospital of Zhengzhou University, Site Investigator).

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Disclosures

Dr Li reports receiving research support from Siemens Medical Solutions. Dr Bi is an employee of Siemens AG Healthcare. The other authors report no conflicts.

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Hyperintense Plaque on Intracranial Vessel Wall Magnetic Resonance Imaging as a Predictor of Artery-to-Artery Embolic Infarction

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