https://doi.org/10.1016/j.jstrokecerebrovasdis.2021.105724

Association of plaque features with infarct patterns in patients with acutely symptomatic middle cerebral artery atherosclerotic disease

Shuang Li[a*], Xiaoyan Song[a*], Qimin Hu[a], Jinglong Zhao[b], Heng Du[a], Yufeng Yan[a], Guodong Wang[a], Xiangyan Chen[c], Qiaoshu Wang[a]

[a] Department of Neurology, Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, 650 New Songjiang Road, Shanghai, 201620, China.

[b] Department of Radiology, Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, 650 New Songjiang Road, Shanghai, 201620, China.

[c] Department of Health Technology and Informatics, The Hong Kong Polytechnic University, Hung Hom, Kowloon, Hong Kong Special Administrative Region of the People's Republic of China

*Dr. Shuang Li and Dr. Xiaoyan Song contributed equally to this work.

Short title: MCA Plaque Features and Infarct Patterns

Corresponding author:

Xiangyan Chen, MD，PhD；

Department of Health Technology and Informatics, The Hong Kong Polytechnic University

Hung Hom, Kowloon, Hong Kong Special Administrative Region of the People's Republic of China.

Telephone: 852-34008891;

Fax number: 852-23624365;

Email: fiona.chen@polyu.edu.hk.

Qiaoshu Wang, MD, PhD;

Department of Neurology, Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine

650 New Songjiang Road, Shanghai, 201620, China. Phone: 86-13816983808; Fax：86-2163240090;

E-mail: qwang624@139.com.

Key words: cerebral infarction; middle cerebral artery occlusion; plaque; magnetic resonance imaging; atherosclerosis

Table：3

Figure：4

Word Count: 3485

Abstract

Background and Purpose Understanding the stroke mechanism of middle cerebral artery (MCA) atherosclerosis is important for stroke triage and future trial design. The aim of this study was to characterize intrinsic MCA plaque and acute cerebral infarct in vivo by using high-resolution black-blood (BB) and diffusion-weighted magnetic resonance (MR) imaging and to investigate the relationship between plaque features and infarct patterns.

Methods A single-center retrospective study was conducted at a tertiary referral center between March 2017 and August 2019. Patients consecutively admitted for acute ischemic stroke with MCA stenosis underwent diffusion-weighted and BB MR imaging. Plaque features and infarct patterns were assessed. The association between plaque features and infarct patterns (binary variable: single/multiple) was evaluated using a multivariate logistic regression model.

Results Of 49 patients with MCA atherosclerotic stenosis, diffusion-weighted MR

imaging showed that 28 patients (57%) had multiple acute cerebral infarcts and 21 patients had single acute cerebral infarcts. In contrast to single infarct, multiple infarcts were associated with greater plaque burden (81.9±7.24 versus 71.3±13.7; *P*=0.012). A multivariate logistic regression model adjusted for 7 potential confounders confirmed a statistically significant positive association between plaque burden and multiple acute infarcts (adjusted R^2 =0.432, *P*< 0.001). The rate of plaque surface irregularity was significantly greater in patients with multiple infarcts than those with single infarct (71% versus 43%, *P*=0.044). For single acute penetrating artery infarct, patients with infarct size > 2cm had greater plaque burden compared with patients with infarct size < 2cm (75.3±13.4 versus 63.4±10.9; *P*=0.016).

Conclusions Increased plaque burden , plaque surface irregularity in patients with MCA stenosis is associated with its likelihood to have caused an artery-to-artery embolism that produces multiple cerebral infarcts, especially along the border zone region, and increased plaque burden may promote subcortical single infarct size by occluding penetrating arteries. Our results provide important insight into stroke mechanism of MCA atherosclerosis.

Introduction

Intracranial atherosclerotic disease (ICAD) is one of the most common causes of ischemic stroke worldwide, however, the mechanism of cerebral infarction in partially

occluded cerebral arteries remain not well known.[1; 2] Possible mechanisms for cerebral infarction caused by ICAD include artery-to-artery embolism, perforating artery occlusion, in situ thrombosis, hemodynamic compromise, or a combination of these factors. Advances in neuroimaging such as diffusion-weighted magnetic resonance imaging (DWI) and transcranial Doppler ultrasound (TCD) microembolic detection or positron emission tomography were used to identify the mechanism of stroke in patients with ICAD.[3; 4] Among them, DWI is the most sensitive diagnostic modality in detecting small cerebral infarcts, and is able to differentiate acute ischemic lesions from old ones.[5] Several studies used DWI to explore the mechanism of ischemic stroke with middle cerebral artery (MCA) atherosclerosis, but those studies were limited to the analysis of lesions distribution and stenosis degree.[6; 7; 8]

The visualization of intracranial atherosclerotic plaques in vivo was not possible until the development of high-resolution magnetic resonance imaging (HRMRI). Characterization of intracranial atherosclerotic plaque using HRMRI is already well established.[9; 10; 11] HRMRI can provide valuable pathophysiology information of atherosclerotic plaques and intracranial luminal thrombosis. In this study, using the latest techniques of HRMRI along with DWI, we explored the mechanism of how MCA plaques produce acute cerebral infarction.

Methods

Study design and participants

We retrospective sifted consecutive patients with acute ischemic stroke and middle cerebral artery atherosclerotic disease from our prospectively collected stroke center database at the Shanghai General Hospital of the Shanghai Jiao Tong University between March 2017 and August 2019 with the approval of The Institutional Review Board. Informed consent was waived to allow inclusion of deidentified data of patients.

Etiologic origin of the stroke was determined according to the medical records of the patients using the Causative Classification System for Ischemic Stroke and its electronic implementation available online (https://ccs.mgh.harvard.edu/main.php). For patients with a ischemic stroke diagnosed by clinical features and head CT, magnetic resonance imaging were done within 7 days of onset of symptoms including DWI, fluid attenuated inversion recovery (FLAIR) and magnetic resonance angiography (MRA) examination. When DWI showed infarct in MCA territory and MRA indicated stenosis of MCA, HRMRI was performed, 2-3 days afterward. Patients were included in this study if they had (1) a DWI confirmed acute ischemic stroke within the territory of MCA; (2) ≥50% diameter reduction in the MCA based on the findings of preceding MRA according to the Warfarin–Aspirin Symptomatic Intracranial Disease (WASID) study criteria[12] (Figure 1) for intracranial stenoses or plaque with <50% diameter reduction that is seated at the site of the origin of the penetrating artery of MCA supplying the region of an acute infarct (Figure 2); (3) HRMRI confirmed eccentric atherosclerotic plaque in the relevant MCA. We excluded patients who had (1) infarcts in multiple vessel territories beyond unilateral MCA; (2) stroke subtypes other than large artery atherosclerosis (cardio-emboli scoures, lacunar infarction, other causes); (3) extracranial cervical artery stenosis of more than 50% ipsilateral to the stenotic MCA or <50% diameter reduction with plaque ulceration or thrombosis according to NASCET criteria;[13] (4) contraindications to gadolinium-containing contrast agents.

Magnetic resonance imaging

MRI scans were performed on a 3.0T MRI Acheiva scanner (Philips Healthcare, Best, the Netherlands). Conventional MRI protocol included T1- and T2-weighted, FLAIR, axial trace DWI with 2 b-values (0 and 1,000 s/mm), apparent diffusion coefficient, time-of-flight (TOF) intracranial MRA. The MRI parameters for DWI were a slice thickness of 5 mm (no gap between slices) with a matrix size of 128 × 128 mm, 24–30 axial slices, and a field-of-view of 240 mm. DWI (EPI spin echo) parameters were a

repetition time (TR) of 4,528 ms, an echo time (TE) of 103 ms. Other imaging parameters were as follows: T1 (TR 420 ms; TE 8.8 ms), and T2 (TR 4,500 ms; TE 95 ms), FLAIR (TR 9,000 ms; TE 84 ms). The 3D TOF MR angiograms were acquired by using the following parameters: TR 23 ms; TE 3.5 ms; flip angle, 25°; field of view, 160 × 160 mm; acquired resolution, 0.55 × 0.55 × 1.1 mm; and reconstructed resolution, 0.55 × 0.55 × 0.55 mm.

The 3D high-resolution black-blood (BB) MRI sequence was performed using a volumetric isotropic turbo spin-echo acquisition (VISTA; Philips Healthcare, Best, the Netherlands) in a coronal plane (40-mm-thick slab) optimized for flow suppression and intracranial vessel wall delineation. BBMRI sequence parameters were as follows: field of view, 200×167×45 mm; acquired resolution, 0.6×0.6×1.0 mm; reconstructed resolution, 0.5×0.5×0.5 mm; TR/TE, 1500ms/36ms; turbo-spin-echo factor, 56 echoes; echo spacing, 4.0 ms; sense factor, 1.5 (right–left direction); scan time of 6.51 minutes. Before acquisition of the contrast-enhanced T1w VIRTA sequence, a gadolinium-containing contrast agent (Dotarem, Gadoteric acid 0.5 mmol/mL; Guerbet, Roissy CdG Cedex, France) was injected intravenously (0.1 mmol per kilogram of body weight), and BBMRI was repeated 5 minutes after contrast material administration.

Image analysis

Acute infarcts were diagnosed when these lesions were shown to be hyperintense on the DWI and hypointense on the apparent diffusion coefficient map. To evaluate the distribution of acute infarcts, the DWI data was reviewed and categorized as lesion patterns as border zone infarct (BI), cortical infarct (CI) and perforating artery infarct (PAI) on the basis of published templates.[3; 4; 14] BIs were defined as anterior border zone infarcts when the infarcts occurred between anterior and middle cerebral artery territories, posterior border zone infarcts between posterior and middle cerebral artery territories and internal border zone infarcts between the deep and superficial perforators of the MCA. CI was defined as an infarct occurring in the vascular territories supplied by the superior or inferior branches of the MCA. PAI include striatocapsular infarcts or

perforating vessel infarcts of the MCA with plaque in the parent artery at the site of the origin of the perforating artery identified by BBMRI. Multiple infarcts in this study referred to more than 1 noncontiguous lesion occurring in the vascular territories described above.

We reconstructed BBMR and TOF MRA images in both short and long axes relative to the flow direction at the site of apparent wall thickening identified on the coronal source BBMRI, and analyzed the BBMRI using Vesselmass software (Leiden University Medical Center, The Netherlands). Diameter-based luminal stenosis was also measured according to WASID study criteria based on the TOF MRA.[12] Atherosclerotic plaque was defined as focal vessel wall eccentric wall thickening (<50% wall involvement) identified on the reconstructed BBMRI. Because of the small size of intracranial artery, we mainly focused on plaques in M1 segments of the middle cerebral artery. The culprit plaque was identified based on the clinical presentation of the patient and clinical judgment of the neurologist. A plaque was considered a culprit plaque when it was the only lesion within the MCA territory of the index stroke or the most stenotic lesion when multiple plaques were identified within the same symptomatic MCA.[15] All cross-sections were classified based on the quadrants that the culprit plaques located at (the superior, inferior, dorsal or ventral side of MCA).[16]

The volume of culprit plaque noted on BBMRI was calculated using the semiautomatic method. For calculating the cross-sectional area of the vessel, a region of interest was manually drawn along the lumen and outer wall contours of the vessel at the plane with the most stenotic segment as previously described.[17] The reference outer wall area ($OWA_{reference}$) was defined as the mean of normal outer wall areas. The distal and proximal normal outer wall areas were measured. The cross section that contained the thinnest wall was chosen as the reference site. We measured lumen area (LA), outer wall area (OWA), wall area (WA=OWA-LA) and plaque burden (WA/OWA×100%) of culprit plaque. The arterial remodeling ratio (RR) was calculated as OWA / $OWA_{reference}$. RR≥1.05 was defined as positive remodeling, 0.95＜RR＜1.05

as intermediate remodeling, and RR≤0.95 as negative remodeling.[17] Plaque surface irregularity was defined as a discontinuity of the plaque surface margin or disruption of the plaque inner wall (Figure 1).[18] Intraplaque hemorrhage was identified by high signal on T1-weighted fat-suppressed images (HST1) of BBMRI within the culprit plaque, and the intensity of HST1 was >150% of the signal of adjacent muscles (Figure 3).[19; 20] HST1 within the cross-section of MCA lumen was defined as luminal thrombosis (Figure 4).[21] In addition, contrast enhancement of the vessel wall was evaluated by comparison of pre- and post- contrast scans, where the signal intensity of the vessel wall was compared with the signal intensity of brain parenchyma next to the wall. The infundibulum was used to assure normal cerebral distribution of contrast agent.[15]

DWI lesions were analyzed independently by one investigator (Q.W.) without knowledge of clinical data and atherosclerotic lesions. One neurologist and one neuroradiologist (S.L., and J.Z.) independently reviewed each detected plaque blinded to DWI patterns. Cases in which readers disagreed were reviewed together and resolved by consensus.

Statistical analysis

Categorical variables were presented as frequencies, and continuous variables were presented as means ± standard deviations or the median and the range. Comparison of continuous variables was performed by a 2-sample Student's t tests or Mann–Whitney test for normally or abnormally distributed data. The chi-square or Fisher's exact test was used for categorical statistical analysis. For the prediction of multiple infarcts on DWI, multivariate logistic analysis was conducted. The following covariates were included: plaque burden, plaque surface irregularity, remodeling ratio, positive remodeling, negative remodeling, plaque enhancement, and MCA stenosis degree. Variables with *p*-values less than 0.20 from univariate analysis were considered candidate predictors and entered into a backward selection algorithm to identify a set

of independent predictors. We also performed forward and stepwise procedures to guarantee the elimination of a false positive. Receiver operating characteristic (ROC) curve was plotted for further analysis of the predictors. A value of two-tailed $P<0.05$ was considered indicative of a significant difference. Inter-rater reproducibility for plaque measurements was estimated using intraclass correlation coefficient. Interreader agreement for plaque surface irregularity, plaque enhancement, HST1 and culprit plaque were estimated based on all detected lesions by using κ coefficients before reader consensus to settle disagreements. Reliability less than 0.4 were characterized as poor, 0.4 to 0.75 as fair to good, and greater than 0.75 as excellent. All data were analyzed using SPSS 20.0 (IBM SPSS statistics 20, Chicago, USA).

Results

Between March 2017, and August 2019, we identified 49 consecutive acute stroke patients with acute infarcts on DWI within the MCA territories who had relevant MCA stenosis detected by MRA and BBMRI. There were 33 (67%) men, and the median age was 59 years (mean±SD, 59±12 years; range, 33-82 years). Baseline characteristics included hypertension in 37 patients (76%), diabetes mellitus in 16 (33%), and smoking in 25 (51%). The median interval between symptom onset and BBMRI was 7 days (interquartile range, 4 days to 8 days) and median National Institutes of Health Stroke Scale (NIHSS) was 4 (range, 0-19). Tissue plasminogen activator (t-PA) were given in six patients (12%), and MCA stenting was performed in 1 patient. On MRA, 17 patients had severe stenosis (> 75% diameter reduction), and 20 had moderate stenosis (50 - 75% diameter reduction). The remaining 12 patients had plaque in the parent MCA obstructing a penetrating artery causing an acute infarct with <50% diameter reduction of MCA.

All 3 types of infarcts (BI, CI, and PAI) were detected. BIs were present in 25 of 28 patients with multiple acute infarcts (89%), and no isolated BI was found. CIs were found in 15 of 28 patients with multiple acute infarcts (53%), and an isolated CI was

detected in 1 patient. PAIs were found in 29 patients, and single PAI was found in 20 of 21 patients with single acute infarct (95%).

Table 1 and 2 summarized the infarct types in relation to the plaque burden of 49 culprit plaques. Compared with single acute infarct, multiple acute infarcts were associated with greater plaque burden (multiple versus single: 81.9±7.24 versus 71.3±13.7; *P*=0.012). Patients with single PAI tended to have relatively small plaque burden (70.6±0.14). Plaque burden showed significant difference when grouped patients with single PAI by infarct size (<2cm versus >2cm: 63.4±10.9 versus 75.3±13.4; *P*=0.016). The RR of atherosclerotic MCA in patients with multiple infarcts was similar to that in those with single infarct (multiple versus single: 0.92±0.30 versus 0.99±0.27; *P*=0.46, Table 2). When the positive remodeling and negative remodeling between multiple and single infarct patterns were analyzed, no significant relationships were found (positive remodeling, multiple versus single: 10/28 (36%) versus 6/21 (29%), *P*=0.60; negative remodeling, multiple versus single: 17/28 (61%) versus 12/21 (57%), *P*=0.80). The rate of plaque surface irregularity was significantly greater in patients with multiple infarcts than that in those with single infarct (multiple versus single: 71% versus 43%, *P*=0.044, Table 2). Among the 49 culprit plaques identified in patients with acute MCA territory stroke, 40 plaques (40/49, 82%) enhanced including 25 (25/28, 89%) in multiple infarcts pattern and 15 (15/21, 71%) in single infarct pattern (Table 2). Intraplaque HST1 was found in 5 of 28 (18%) patients with multiple infarcts and in 2 of 21 (10%) patients with single infarct (Table 2). All intraplaque HST1 were observed in MCA over 50% stenosis. Luminal HST1 was present in 2 of 28 (7%) multiple infarcts patients and 1 of 21 (5%) single infarct patients. All luminal HST1 were detected in MCA over 75% stenosis. Besides, we found that culprit plaques were more likely to situate at the superior side of MCA with no difference between single and multiple infarcts group (multiple versus single: 41% versus 43%, Table 2).

Furthermore, we used multivariate logistic regression to identify independent predictors of multiple infarcts on DWI including risk factors, treatment and plaque

features. A backward selection algorithm indicated that plaque burden (odd ratio, 30.6; 95% confidence interval [CI], 21.3-73.9; *P* = 0.004), positive remodeling (odd ratio, 6.6; 95% CI, 2.3-18.4; *P* = 0.015) were positively associated with multiple infarcts pattern, and RR (odd ratio, 0.0015; 95% CI, 0.00-0.30; *P* = 0.016) were negatively associated with single infarct. After using forward and stepwise procedures, plaque burden was found to be the only variable independently associated with multiple infarcts (adjusted R^2=0.432, *P*<0.001). The result of ROC curve analysis showed that plaque burden presented an acceptable performance in determining multiple infarcts pattern (area under curve, AUC: 0.71).

Inter-reader reliability (intraclass correlation coefficient) estimates for the LA, OWA, RR were 0.83, 0.91, and 0.86, respectively. Inter-reader agreement for determining plaque surface irregularity (weighted κ = 0.82; 95% CI, 0.70-0.95), plaque enhancement (weighted κ = 0.83; 95% CI: 0.74-0.91), and culprit plaque (weighted κ = 0.90; 95% CI: 0.77-0.95) was excellent.

Discussion

We reported our findings on using a combination of HRMRI and DWI in exploring the pathophysiology of cerebral infarcts in acute stroke patients with MCA atherosclerotic disease. We observed that infarct patterns in response to plaque formation, that plaque burden was positively associated with multiple infarcts, that multiple infarcts occurred when plaque surface is irregular, and that increased plaque burden was found more frequently in patients with single PAI of > 2cm than in those with that of < 2cm.

For patients with acute coronary syndrome, vulnerable atherosclerotic plaques had greater plaque area compared with stable plaques.[22] MCA unstable atherosclerosis may share some common vascular biological features with coronary and carotid atherosclerosis such as large lipid core, intraplaque inflammation, and thin fibrous cap.[23; 24] Unstable lipid-rich plaques and ulcerations in MCA predispose to deposition of white and red thrombi and thrombosis. Furthermore, the loosely attached

thrombi can propagate and embolize distally as well as occlude the orifices of the penetrating lenticulostriate arteries. Caplan et al reported that intrinsic MCA atherosclerotic plaque may cause symptoms by: (1) being the intra-arterial source of emboli mostly to pial branches on the convexal surface; (2) decreased perfusion causing borderzone infarction both involving deep and superficial borderzone regions; and (3) by plaques and thrombi blocking flow through deep lenticulostriate branches causing deep gray and white matter infarcts.[25; 26] Conventional techniques, such as CTA, MRA and DSA, reveal abnormalities of the vessel lumen, but they can fail to characterize the atherosclerotic disease that resides within the vessel wall. HRMRI is able to visualize the vessel wall directly, and is used to assess atherosclerotic plaque activity on a clinical basis at many institutions. In consistent with past reports,[3; 8; 27] we found that border zone infarcts caused by artery-to-artery embolism were the most common pattern (25/28, 89%) of multiple infarcts, and patients with multiple infarcts had greater plaque burden and higher rate of plaque surface irregularity within the atherosclerotic MCAs comparing with those with single infarct. Increased plaque burden may promote the formation of platelet-fibrin and erythrocyte-fibrin thrombi engrafted upon irregular plaques, causing hypoperfusion and artery-to-artery embolism. Hypoperfusion and embolism are intertwined and complementary mechanisms, being considered to cause infarction in patients with MCA atherosclerosis due to markedly decreasing the clearance and washout of the embolic particles. Our results were similar to previous studies that culprit plaques were more likely to locate at the superior side of MCA,[16; 28; 29; 30] indicating that the location of plaques may be related to the occurrence of infarction, especially at the site close to the orifices of perforating arteries.

Besides plaque burden and surface irregularity, HRMRI has the potential to distinguish between atherosclerotic plaques in symptomatic and asymptomatic MCA stenosis by other imaging features such as vessel wall remodeling, intraplaque hemorrhage, plaque enhancement and luminal thrombus.[10; 11; 18; 31] As demonstrated previously in coronary and middle cerebral arteries, positive remodeling

was found to result in vessel enlargement and was strongly associated with acute symptoms,[18; 32] though some studies found no significant difference.[33; 34] In our series, MCA remodeling ratio was similar to previous study,[17] and no difference was identified between single and multiple infarcts patterns. Prior studies found intraplaque HST1 (thought to indicate intraplaque hemorrhage) was associated with symptomatic MCA plaques.[19; 35] Similar with past report, we observed HST1 in 14% patients with symptomatic MCAs.[19] In our study, HST1 was more likely to be present in patients with multiple infarcts than in those with single infarct. It is possible that patients with single infarct had relatively small plaque burden, which is less likely to be discerned on HR-MRI by visual inspection. Previous studies reported inconsistent results of relationship between plaque enhancement and acute stroke. Several studies found that contrast enhancement of intracranial atherosclerotic plaques were associated with acute ischemic events.[15; 36] Another study failed to distinguish plaque enhancement of patients with acute ischemic stroke from that of patients with stroke any time in the preceding 3 months.[37] We found no difference in enhancement when comparing patients with multiple infarcts versus those with single infarct, indicating that plaque enhancement has no influence on lesion patterns. There are several studies using HRMRI to explore intracranial luminal clot. Xu et al analyzed the relationship between luminal HST1 (thought to indicate luminal thrombus) and infarct patterns in patients with MCA occlusions, and found the presence of HST1 was similar in those with and without border zone infarcts.[10] In this study, we investigated luminal thrombus in stenostic MCAs and identified HST1 in 14% patients with severe stenosis (>75%)，and HST1 tended to present in stenostic MCAs with multiple infarcts.

For patients with atherosclerotic MCAs, deep infarction within the basal ganglia and internal capsule is usually explained by plaques within mainstem MCAs leading to occlusion of lenticulostriate branches.[38; 39] Kim et al defined four types of single subcortical infarction, including (a) obliteration of perforators by focal parent artery disease, (b) parental artery disease with diffuse wall involvement, (c) atherosclerotic

proximal small artery disease and (d) lipohyalinotic distal small artery disease, and (a) and (b) can be identified by HRMRI.[38] In our series, using imaging techniques of DWI and HRMRI, we found most of single infarcts (20/21, 95%) were deep infarction caused by penetrating artery occlusion. Furthermore, we demonstrated that patients with single infarct had less plaque burden than those with multiple infarcts, and plaque burden in patients with infarct size of > 2cm was greater than that in those with infarct size of < 2cm, indicating a positive association of plaque burden with number and size of acute infarcts.

There are several limitations to this study. First, MRI has a limited field of view, especially in the more distally located segment of MCA, which may in turn limit resolution and lead to underestimating the true plaque burden. Second, culprit lesions were identified based on the severity of stenosis, raising the possibility that some symptomatic plaques were missed, especially those with positive remodeling in which the cross-sectional area of the lumen is relatively preserved. Third, our BBMRI images of MCA stenosis lack histologic validation because it is inaccessible to obtain the intracranial arteries, although there is no reason to suspect that image interpretation would differ from prior intracranial atherosclerosis biopsy studies and carotid artery techniques.

Conclusions

We have shown that plaque burden and plaque surface irregularity are important mechanisms of cerebral infarcts in patients with atherosclerotic MCA disease. Increased plaque burden, in conjunction with surface irregularity, may result in border zone and cortical infarcts, possibly because of unstable plaques and hemodynamic comprise in ischemic brain area. Furthermore, increased plaque burden inclined to form relatively large lesion in patients with single infarct caused by penetrating artery

occlusion. Those features may serve as markers of MCA infarction patterns and provide target preventive therapeutic interventions based on different mechanisms.

Conflict of Interests Statement

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Author Contribution

Conceptualization: X.Z., Q.W.; Statistical analysis: Q.W., X.S.; Image analysis: S.L., J.Z., Q.W.; Drafting of the manuscript: S.Y., Q.W.; Acquisition of the data: H.D., Y.Y.; Critical revision for the important intellectual content: Q.H., G.W.; Supervision: X.C., Q.W.;

Funding

This study is supported by grant from the Clinical Research Plan of SHDC (16CR2046B), grant from the National Natural Science Foundation of China (81371304), grant from Shanghai Pujiang Program (15PJD031).

Acknowledgement

None.

Statement of Ethics

All subjects have given their written informed consent and that the study protocol was approved by the Institutional Review Board of Shanghai General Hospital.

References

[1] L.R. Caplan, P.B. Gorelick, and D.B. Hier, Race, sex and occlusive cerebrovascular disease: a review. Stroke 17 (1986) 648-55.

[2] K.S. Wong, H. Li, Y.L. Chan, A. Ahuja, W.W. Lam, A. Wong, and R. Kay, Use of

transcranial Doppler ultrasound to predict outcome in patients with intracranial large-artery occlusive disease. Stroke 31 (2000) 2641-7.

[3] K.S. Wong, S. Gao, Y.L. Chan, T. Hansberg, W.W. Lam, D.W. Droste, R. Kay, and E.B. Ringelstein, Mechanisms of acute cerebral infarctions in patients with middle cerebral artery stenosis: a diffusion-weighted imaging and microemboli monitoring study. Annals of neurology 52 (2002) 74-81.

[4] D.K. Lee, J.S. Kim, S.U. Kwon, S.H. Yoo, and D.W. Kang, Lesion patterns and stroke mechanism in atherosclerotic middle cerebral artery disease: early diffusion-weighted imaging study. Stroke 36 (2005) 2583-8.

[5] S. Warach, J. Gaa, B. Siewert, P. Wielopolski, and R.R. Edelman, Acute human stroke studied by whole brain echo planar diffusion-weighted magnetic resonance imaging. Ann Neurol 37 (1995) 231-41.

[6] O.Y. Bang, J.H. Heo, J.Y. Kim, J.H. Park, and K. Huh, Middle cerebral artery stenosis is a major clinical determinant in striatocapsular small, deep infarction. Arch Neurol 59 (2002) 259-63.

[7] P.H. Lee, S.H. Oh, O.Y. Bang, I.S. Joo, and K. Huh, Isolated middle cerebral artery disease: clinical and neuroradiological features depending on the pathogenesis. J Neurol Neurosurg Psychiatry 75 (2004) 727-32.

[8] P.H. Lee, S.H. Oh, O.Y. Bang, S.Y. Joo, I.S. Joo, and K. Huh, Infarct patterns in atherosclerotic middle cerebral artery versus internal carotid artery disease. Neurology 62 (2004) 1291-6.

[9] R.H. Swartz, S.S. Bhuta, R.I. Farb, R. Agid, R.A. Willinsky, K.G. Terbrugge, J. Butany, B.A. Wasserman, D.M. Johnstone, F.L. Silver, and D.J. Mikulis, Intracranial arterial wall imaging using high-resolution 3-tesla contrast-enhanced MRI. Neurology 72 (2009) 627-34.

[10] W. Xu, High-resolution MRI of intracranial large artery diseases: how to use it in clinical practice? Stroke Vasc Neurol 4 (2019) 102-104.

[11] D.M. Mandell, M. Mossa-Basha, Y. Qiao, C.P. Hess, F. Hui, C. Matouk, M.H. Johnson, M.J. Daemen, A. Vossough, M. Edjlali, D. Saloner, S.A. Ansari, B.A. Wasserman, D.J. Mikulis, and N. Vessel Wall Imaging Study Group of the American Society of, Intracranial Vessel Wall MRI: Principles and Expert Consensus Recommendations of the American Society of Neuroradiology. AJNR Am J Neuroradiol 38 (2017) 218-229.

[12] M.I. Chimowitz, M.J. Lynn, H. Howlett-Smith, B.J. Stern, V.S. Hertzberg, M.R. Frankel, S.R. Levine, S. Chaturvedi, S.E. Kasner, C.G. Benesch, C.A. Sila, T.G.

Jovin, J.G. Romano, and I. Warfarin-Aspirin Symptomatic Intracranial Disease Trial, Comparison of warfarin and aspirin for symptomatic intracranial arterial stenosis. N Engl J Med 352 (2005) 1305-16.

[13] C. North American Symptomatic Carotid Endarterectomy Trial, H.J.M. Barnett, D.W. Taylor, R.B. Haynes, D.L. Sackett, S.J. Peerless, G.G. Ferguson, A.J. Fox, R.N. Rankin, V.C. Hachinski, D.O. Wiebers, and M. Eliasziw, Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. N Engl J Med 325 (1991) 445-53.

[14] H. Damasio, A computed tomographic guide to the identification of cerebral vascular territories. Arch Neurol 40 (1983) 138-42.

[15] Y. Qiao, S.R. Zeiler, S. Mirbagheri, R. Leigh, V. Urrutia, R. Wityk, and B.A. Wasserman, Intracranial plaque enhancement in patients with cerebrovascular events on high-spatial-resolution MR images. Radiology 271 (2014) 534-42.

[16] D.L. Zhao, G. Deng, B. Xie, S. Ju, M. Yang, X.H. Chen, and G.J. Teng, High-resolution MRI of the vessel wall in patients with symptomatic atherosclerotic stenosis of the middle cerebral artery. Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia 22 (2015) 700-4.

[17] Y. Qiao, Z. Anwar, J. Intrapiromkul, L. Liu, S.R. Zeiler, R. Leigh, Y. Zhang, E. Guallar, and B.A. Wasserman, Patterns and Implications of Intracranial Arterial Remodeling in Stroke Patients. Stroke 47 (2016) 434-40.

[18] G.H. Chung, H.S. Kwak, S.B. Hwang, and G.Y. Jin, High resolution MR imaging in patients with symptomatic middle cerebral artery stenosis. Eur J Radiol 81 (2012) 4069-74.

[19] W.H. Xu, M.L. Li, S. Gao, J. Ni, M. Yao, L.X. Zhou, B. Peng, F. Feng, Z.Y. Jin, and L.Y. Cui, Middle cerebral artery intraplaque hemorrhage: prevalence and clinical relevance. Ann Neurol 71 (2012) 195-8.

[20] X.Y. Chen, K.S. Wong, W.W. Lam, and H.K. Ng, High signal on T1 sequence of magnetic resonance imaging confirmed to be intraplaque haemorrhage by histology in middle cerebral artery. Int J Stroke 9 (2014) E19.

[21] W.H. Xu, M.L. Li, J.W. Niu, F. Feng, Z.Y. Jin, and S. Gao, Luminal thrombosis in middle cerebral artery occlusions: a high-resolution MRI study. Ann Transl Med 2 (2014) 75.

[22] M. Yamagishi, M. Terashima, K. Awano, M. Kijima, S. Nakatani, S. Daikoku, K. Ito, Y. Yasumura, and K. Miyatake, Morphology of vulnerable coronary plaque: insights from follow-up of patients examined by intravascular ultrasound before

504 an acute coronary syndrome. Journal of the American College of Cardiology 35
505 (2000) 106-11.

506 [23] G.A. Rodriguez-Granillo, P.W. Serruys, H.M. Garcia-Garcia, J. Aoki, M.
507 Valgimigli, C.A. van Mieghem, E. McFadden, P.P. de Jaegere, and P. de Feyter,
508 Coronary artery remodelling is related to plaque composition. Heart 92 (2006)
509 388-91.

510 [24] X.Y. Chen, K.S. Wong, W.W. Lam, H.L. Zhao, and H.K. Ng, Middle cerebral artery
511 atherosclerosis: histological comparison between plaques associated with and
512 not associated with infarct in a postmortem study. Cerebrovascular diseases
513 (Basel, Switzerland) 25 (2008) 74-80.

514 [25] L. Caplan, V. Babikian, C. Helgason, D.B. Hier, D. DeWitt, D. Patel, and R. Stein,
515 Occlusive disease of the middle cerebral artery. Neurology 35 (1985) 975-82.

516 [26] L.R. Caplan, Intracranial large artery occlusive disease. Curr Neurol Neurosci Rep
517 8 (2008) 177-81.

518 [27] F. Wu, H. Song, Q. Ma, J. Xiao, T. Jiang, X. Huang, X. Bi, X. Guo, D. Li, Q. Yang,
519 X. Ji, and Z. Fan, Hyperintense Plaque on Intracranial Vessel Wall Magnetic
520 Resonance Imaging as a Predictor of Artery-to-Artery Embolic Infarction.
521 Stroke 49 (2018) 905-911.

522 [28] W.H. Xu, M.L. Li, S. Gao, J. Ni, L.X. Zhou, M. Yao, B. Peng, F. Feng, Z.Y. Jin,
523 and L.Y. Cui, Plaque distribution of stenotic middle cerebral artery and its
524 clinical relevance. Stroke 42 (2011) 2957-9.

525 [29] S. Jiang, Y. Yan, T. Yang, Q. Zhu, C. Wang, X. Bai, Z. Hao, S. Zhang, Q. Yang, Z.
526 Fan, J. Sun, and B. Wu, Plaque Distribution Correlates With Morphology of
527 Lenticulostriate Arteries in Single Subcortical Infarctions. Stroke 51 (2020)
528 2801-2809.

529 [30] S.S. Lu, S. Ge, C.Q. Su, J. Xie, H.B. Shi, and X.N. Hong, Plaque Distribution and
530 Characteristics in Low-Grade Middle Cerebral Artery Stenosis and Its Clinical
531 Relevance: A 3-Dimensional High-Resolution Magnetic Resonance Imaging
532 Study. Journal of stroke and cerebrovascular diseases : the official journal of
533 National Stroke Association 27 (2018) 2243-2249.

534 [31] A. de Havenon, M. Mossa-Basha, L. Shah, S.E. Kim, M. Park, D. Parker, and J.S.
535 McNally, High-resolution vessel wall MRI for the evaluation of intracranial
536 atherosclerotic disease. Neuroradiology 59 (2017) 1193-1202.

537 [32] S. Glagov, E. Weisenberg, C.K. Zarins, R. Stankunavicius, and G.J. Kolettis,
538 Compensatory enlargement of human atherosclerotic coronary arteries. N Engl

J Med 316 (1987) 1371-5.

[33] W.W. Lam, K.S. Wong, N.M. So, T.K. Yeung, and S. Gao, Plaque volume measurement by magnetic resonance imaging as an index of remodeling of middle cerebral artery: correlation with transcranial color Doppler and magnetic resonance angiography. Cerebrovasc Dis 17 (2004) 166-9.

[34] J. Gutierrez, J. Goldman, L.S. Honig, M.S. Elkind, S. Morgello, and R.S. Marshall, Determinants of cerebrovascular remodeling: do large brain arteries accommodate stenosis? Atherosclerosis 235 (2014) 371-9.

[35] W.Q. Yang, B. Huang, X.T. Liu, H.J. Liu, P.J. Li, and W.Z. Zhu, Reproducibility of high-resolution MRI for the middle cerebral artery plaque at 3T. Eur J Radiol 83 (2014) e49-55.

[36] M. Skarpathiotakis, D.M. Mandell, R.H. Swartz, G. Tomlinson, and D.J. Mikulis, Intracranial atherosclerotic plaque enhancement in patients with ischemic stroke. AJNR Am J Neuroradiol 34 (2013) 299-304.

[37] X. Lou, N. Ma, L. Ma, and W.J. Jiang, Contrast-enhanced 3T high-resolution MR imaging in symptomatic atherosclerotic basilar artery stenosis. AJNR Am J Neuroradiol 34 (2013) 513-7.

[38] J.S. Kim, and Y. Yoon, Single subcortical infarction associated with parental arterial disease: important yet neglected sub-type of atherothrombotic stroke. Int J Stroke 8 (2013) 197-203.

[39] Y. Yoon, D.H. Lee, D.W. Kang, S.U. Kwon, and J.S. Kim, Single subcortical infarction and atherosclerotic plaques in the middle cerebral artery: high-resolution magnetic resonance imaging findings. Stroke 44 (2013) 2462-7.

Figure Legends

Figure 1 High resolution MRI of symptomatic middle cerebral artery plaque with multiple infarcts.

(A) MR angiography shows a severe stenosis in the right middle cerebral artery (arrow). (B) Diffusion-weighted MR imaging demonstrates multiple chainlike small infarcts along the internal border zone and cortical regions. (C) 3D BB MR images (right: coronal acquisition) show wall thickening at the corresponding location and irregularity of plaque surface (arrow), reconstructions perpendicular to flow direction through the wall thickening show an eccentric atherosclerotic plaque (arrow).

Figure 2 High resolution MRI of symptomatic middle cerebral artery plaque with single infarct.

(A) TOF maximum intensity projection MR angiogram of the right middle cerebral artery shows a mild stenosis in the M1 segment (arrow). (B) Diffusion-weighted MR imaging demonstrates a small infarct (< 20mm) in the basal ganglion region. (C) 3D BB MR images (right: coronal acquisition) show wall thickening at the corresponding location (arrow), reconstructions perpendicular to flow direction through the wall thickening show an eccentric atherosclerotic plaque (arrow).

Figure 3 High resolution MRI of intraplaque hemorrhage in symptomatic middle cerebral artery stenosis.

(A) TOF maximum intensity projection MR angiogram of the right middle cerebral artery shows a severe stenosis in the M1 segment (arrow). (B) Diffusion-weighted MR imaging shows an acute infarct in the right corona radiata. (C) 3D BB MR images (right: coronal acquisition) show wall thickening at the corresponding location (arrow), sagittal views of 3D BB MR imaging shows intraplaque hemorrhage (arrow).

Figure 4 High resolution MRI of luminal thrombosis in symptomatic middle cerebral artery stenosis

(A) TOF maximum intensity projection MR angiogram of the right middle cerebral artery shows a severe stenosis in the M1 segment (arrow). (B) Diffusion-weighted MR imaging demonstrates multiple chainlike small infarcts along the internal border zone. (C) 3D BB MR images (right: coronal acquisition) suggests luminal thrombosis within MCA (arrow), sagittal views of 3D BB MR imaging shows an stenotic vessel lumen with clots (arrow).

609 **Table 1 Infarct patterns and plaque burden**

	Multiple Infarcts		Single Infarct	
Infarct Type	n	Plaque Burden, %	n	Plaque Burden, %
PAI	9	79.6±7.57	20	70.6±0.14
PAI	1	63.7	20	70.6±0.14
BI+PAI	3	83.9±3.73	0	0
BI+CI+PAI	5	80.3±5.49	0	0
Non-PAI	19	83.0±7.02	1	86.1
BI	9	84.3±5.78	0	0
BI+CI	8	82.0±8.43	0	0
CI	2	81.4±9.67	1	86.1
Total	28	81.9±7.24	21	71.3±13.7[a]

610 [a]Multiple vs single (P = 0.012, Mann-Whitney test)

611 PAI, penetrating artery infarct; CI, cortical infarct; BI, border zone infarct.

612

613

614

615

616

617

618

619

620

621

622

623

624

625 **Table 2 Association between infarct patterns and plaque imaging features**

Infarct Type	n	Remodeling Ratio(RR)	Plaque Surface Irregularity	Plaque Enhancement	Intraplaque HST1	Luminal HST1	Plaque Location			
							V	S	D	I
Single	21	0.99±0.27	9 (43%)	15 (71%)	2 (10%)	1 (5%)	5 (24%)	8 (38%)	5 (24%)	3 (14%)
PAI (> 2 cm)	12	1.00±0.28	5	10	1	1	3	4	3	2
PAI (< 2 cm)	8	0.99±0.31	3	4	1	0	2	4	1	1
CI	1	0.90	1	1	0	0	0	0	1	0
Multiple	28	0.92±0.30[a]	20 (71%)[b]	25 (89%)[c]	5 (18%)[d]	2 (7%)	8 (29%)	12 (43%)	4 (14%)	4 (14%)
BI	9	0.90±0.29	7	9	2	0	0	4	3	2
BI+CI	8	0.93±0.31	5	8	2	1	6	1	0	1
CI	2	0.70±0.06	1	1	0	0	1	1	0	0
PAI	1	0.93	0	0	0	0	1	0	0	0
BI+PAI	3	1.17±0.40	3	2	1	0	0	2	0	1
BI+CI+PAI	5	0.91±0.36	4	5	0	1	0	4	1	0

Total	49	0.95±0.29	29 (59%)	40 (82%)	7 (14%)	3 (6%)	13 (27%)	20 (41%)	9 (18%)	7 (14%)

[a]Multiple vs single (P = 0.46, Unpaired t test)

[b]Multiple vs single (P = 0.044, Chi-square)

[c]Multiple vs single (P = 0.15, Fisher's exact test)

[d]Multiple vs single (P = 0.68, Fisher's exact test)

PAI, penetrating artery infarct; CI, cortical infarct; BI, border zone infarct; T1-weighted fat-suppressed images (HST1); V, ventral; S, superior; D, dorsal; I, inferior.