



Comparison of plaque characteristics of small and large subcortical infarctions in the middle cerebral artery territory using high-resolution magnetic resonance vessel wall imaging

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Background: The characteristics of plaque that ultimately lead to different subcortical infarctions remain unclear. We explored the differences in plaque characteristics between patients with small subcortical infarction (SSI) and large subcortical infarction (LSI) of the middle cerebral artery (MCA) using high-resolution magnetic resonance vessel wall imaging (HR-MRVWI).

Methods: The study group comprised 71 patients (mean age, 47.49±11.5 years; 55 male) with MCA territory ischemic stroke. Whole-brain HR-MRVWI was performed using a three-dimensional T1-weighted variable-flip-angle turbo spin echo (SPACE) sequence. Patients were divided into SSI and LSI groups based on routine MRI images. Plaque distribution was classified as the superior, inferior, ventral, or dorsal wall of the MCA. The number of quadrants with plaque formation, location of plaque, plaque burden (PB), arterial remodeling pattern (positive or negative), and degree of stenosis were analyzed and compared between groups.

Results: Of the 71 patients, 43 (60.6%) and 28 (39.4%) were identified as the SSI and LSI groups, respectively. The proportion of plaques involving only one quadrant was significantly higher in the SSI group, and these plaques were located in the superior or dorsal MCA vessel wall. There was no significant difference between groups in the proportion of plaques involving two or more quadrants, plaque distribution, or PB. Most plaques in both groups showed positive remodeling, and the percentage of remodeling pattern was similar. A significantly higher incidence of low-grade stenosis (<50%) was observed in the SSI group.

Conclusions: Both SSI and LSI may be associated with major intracranial artery atherosclerosis, but patients with SSI showed relatively fewer quadrants with plaque formation and a lesser degree of stenosis.

Keywords: Atherosclerotic plaque; ischemic stroke; magnetic resonance vessel wall imaging (MRVWI); subcortical infarction

Submitted Feb 20, 2020. Accepted for publication Jul 21, 2020.

doi: 10.21037/qims-20-310

View this article at: <http://dx.doi.org/10.21037/qims-20-310>

Introduction

Small subcortical infarction (SSI), which often includes 'lacunar infarction,' accounts for approximately 25% of ischemic cerebral infarctions and usually occurs in the territory of the middle cerebral artery (MCA) (1,2). It is generally believed that SSI is caused by intrinsic diseases of the penetrating arteries themselves (3,4). However, several recent studies have shown that the incidence of large artery atherosclerosis, which is important pathogenesis of large subcortical infarction (LSI), is also high in patients with SSI (5-9). This suggests that in patients with large artery atherosclerosis, the underlying mechanism of SSI may be the same as that causing LSI and could be inferred from the characteristics of the atherosclerotic plaque.

An increasing number of studies have shown that arterial wall morphology and plaque characteristics help distinguish the different mechanisms underlying stroke (10-13). The remodeling pattern (positive or negative), distribution (superior, inferior, ventral or dorsal wall), plaque burden (PB), and vulnerability of intracranial plaque may be associated with the pathogenesis and disease process of different types of infarction (6,14-16). However, the plaque characteristics that ultimately lead to SSI or LSI remain unclear.

High-resolution magnetic resonance vessel wall imaging (HR-MRVWI) has demonstrated its potential to depict large arterial vessel wall lesions and characterize arterial plaques and has proven to be reproducible (17-19). However, few studies have focused on unraveling the differences in plaque characteristics among the stroke subtypes (such as SSI and LSI), which may help determine the cause of subcortical infarction. In the present study, we explored the differences in plaque characteristics in the MCA between patients with LSI and SSI using HR-MRVWI.

Methods

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

Subjects

From October 2017 to February 2019 at one imaging center, 71 consecutive patients (mean age, 47.49±11.5 years; 55 men) with a recent ischemic event (such as one-sided numbness and weakness, etc.) were prospectively enrolled in the study and underwent HR-MRVWI examination

within 4 weeks of symptom onset. The general clinical information, including age, sex, and vascular risk factors, such as hypertension, diabetes mellitus, hyperlipidemia, smoking history, and history of transient ischemic attack or stroke, were recorded for each patient. The institutional review board approved this study of Shenzhen Institutes of Advanced Technology, Chinese Academy of Sciences (No. SIAT-IRB-180215-H0204) and written informed consent was obtained from the patient.

All the patients were enrolled according to the following inclusion criteria: (I) first-time acute ischemic stroke located subcortically to and within the unilateral MCA territory as identified by T2-weighted fluid-attenuated inversion recovery (T2W-FLAIR); (II) ipsilateral internal carotid artery not showing significant stenosis ($\geq 50\%$ stenosis), as confirmed by MR angiography, CT angiography or digital subtraction angiography; and (III) no evidence of other causes of stroke (coagulopathy, potential cardioembolic source of disease, Moya-Moya disease, dissection, etc.). Cortical strokes were excluded from this study because cortical infarct often involves more than one cerebral artery territory.

MRI protocols

MRI examinations were performed using a 3T MR system (MAGNETOM TIM Trio; Siemens Medical Solutions, Erlangen, Germany) with a 32-channel phase array head coil. Routine brain MRI (T1W- and T2W-FLAIR) was initially performed for clinical evaluation of the stroke patients. Whole-brain HR-MRVWI was subsequently performed with a three-dimensional (3D) T1-weighted variable-flip-angle turbo spin echo (SPACE) sequence with the following imaging parameters: repetition time/echo time =900/15 ms, field of view =170×170×128 mm³, number of slices =256, spatial resolution =0.53×0.53×0.53 mm³ without interpolation, sagittal orientation, generalized autocalibrating partially parallel acquisitions (GRAPPA) accelerated factor =2, turbo factor =52, bandwidth =446 Hz/pixel, and scan time 8 min 10 s.

Routine MRI assessment

The diagnosis of MCA territorial infarction was based on previous templates (20,21). The patients were divided into two groups according to the size of the lesion on the T2-FLAIR images. (I) The SSI group comprised patients with a maximal axial lesion diameter of ≤ 20 mm (22). (II) The

Table 1 General clinical, demographic data of patients with SSI and LSI

Variables	SSI (n=43)	LSI (n=28)	P value
Age (years)	47.70±11.35*	47.14±11.92*	0.844
Male	34 (79.1%)	21 (75%)	0.689
Hypertension	26 (60.5%)	15 (53.6%)	0.566
Diabetes mellitus	13 (30.2%)	6 (21.4%)	0.408
Hyperlipidemia	17 (39.5%)	14 (50.0%)	0.385
Smoking	15 (34.9%)	12 (42.9%)	0.500
History of stroke	2 (4.7%)	2 (7.1%)	0.660

*, mean ± standard deviation. LSI, large subcortical infarction; SSI, small subcortical infarction.

LSI group comprised patients with larger lesions who were not categorized as having SSIs and included large, deep perforator infarcts, border zone infarcts, and superficial perforator infarcts (21).

HR-MRVWI analysis

All the MRI images were reviewed and reconstructed using the multiplanar reconstruction tool on a workstation (Syngo Multi-Modality Workplace; Siemens Healthcare, Erlangen, Germany) by two neuroradiologists with more than 6 years' experience. A cross-sectional slice of the most stenotic part of the MCA on the ipsilateral side of the cerebral infarction was reconstructed to assess plaque distribution and PB. When there were multiple lesions, the site of maximal stenosis was analyzed. A cross-sectional slice of the ipsilateral normal vessel was reconstructed as a reference slice for calculating the remodeling pattern and degree of stenosis.

The plaque distribution on the cross-sectional image was classified as the superior, inferior, dorsal, or ventral side of the vessel well, according to a previous report (23). In the case of two or more quadrants being involved, the location and number of quadrants with plaque formation were recorded. Using commercial software (VesselMass, Leiden University Medical Center, Leiden, The Netherlands), the contours of the luminal and outer vessel wall boundaries were traced manually on a reconstructed cross-sectional plaque slice and reference slice, respectively. Lumen area (LA) and vessel area (VA) were automatically generated. The PB was calculated as $(VA - LA)/VA \times 100\%$. The remodeling index (RI) was calculated as the ratio of the VA of the plaque slice to that of the reference slice. Three remodeling patterns were defined according to the RI value:

if $RI > 1.05$, it was defined as positive; if $0.95 \leq RI \leq 1.05$, it was classified as intermediate; and negative if $RI < 0.95$ (16). The degree of stenosis was defined as $(1 - LA_{\text{lesion}}/LA_{\text{reference}}) \times 100\%$, where LA_{lesion} and $LA_{\text{reference}}$ are the LAs derived from a cross-sectional plaque slice and reference slice, respectively. The degree of stenosis was graded as low-grade if stenosis was $< 50\%$, and moderate-to-severe if stenosis was $\geq 50\%$.

Statistical analysis

All the statistical analyses were performed using SPSS software (version 25.0, IBM SPSS, Chicago, IL, USA). Fisher's test was performed to evaluate the difference in the percentage of quadrants with plaque formation, PB, remodeling pattern, and degree of stenosis between the SSI and LSI groups. The Wilcoxon signed-rank test was performed to determine the difference in PB between the two groups. A two-tailed P value ≤ 0.05 was considered to indicate a significant difference.

Results

General clinical characteristics

Of the 71 patients, 43 (60.6%) were assigned to the SSI group, and 28 (39.4%) to the LSI group. The general clinical demographics of the patients are presented in *Table 1*. No significant difference in risk factors was found between the two groups.

Plaque distribution in the MCA

For the SSI group, no eccentric or concentric wall

Table 2 Comparison of the number of quadrants with plaque formation in the SSI and LSI groups

Group	1 quadrant	2 quadrants	3 quadrants	4 quadrants
SSI (n=38)*	13 (34.2%)	17 (44.7%)	3 (7.9%)	5 (13.2%)
LSI (n=28)*	2 (7.1%)	19 (67.9%)	4 (14.3%)	3 (10.7%)
P value	0.006	0.060	0.408	0.763

*, number of plaques. LSI, large subcortical infarction; SSI, small subcortical infarction.

Table 3 Comparison of plaque distribution in the SSI and LSI groups

Group	Vessel wall location			
	Superior	Inferior	Ventral	Dorsal
SSI (n=76)*	21 (27.6%)	19 (25.0%)	22 (28.9%)	14 (18.4%)
LSI (n=64)*	18 (28.1%)	14 (21.9%)	21 (32.8%)	11 (17.2%)
P values	0.948	0.664	0.622	0.849

*, number of quadrants. LSI, large subcortical infarction; SSI, small subcortical infarction.

thickening was found in 5 of the 43 patients (11.6%). In the LSI group, all patients had eccentric or non-eccentric wall thickening of the MCA on the ipsilateral side of the cerebral infarction. A comparison of the number of quadrants with plaque formation and location of plaque distribution between the SSI group and LSI group is given in *Tables 2 and 3*, respectively. For the SSI group, the plaque in 13 patients involved only one quadrant, and the proportion was significantly higher than in the LSI group (34.2 vs. 7.1%, $P=0.006$). *Figure 1* shows representative HR-MRVWI images of two patients with SSI and LSI, respectively. The plaque in both patients involved only one quadrant.

Furthermore, the 13 plaques were more frequently located in the superior (46.2%) and dorsal (38.5%) sides of the vessel wall. The occurrence of plaques involving two or more quadrants was approximately the same in the two groups, and plaques involving two quadrants were the most common distribution pattern in both groups: 17 and 19 plaques in SSI and LSI groups, respectively (*Table 2*). The plaque distribution in four quadrants was similar between the two groups. The ventral side was a relatively commonly involved quadrant, whereas the dorsal side was a relatively rarely involved quadrant.

PB, remodeling pattern, and stenosis degree

There was no significant difference in PB between the SSI and LSI groups (0.75 ± 0.12 vs. 0.79 ± 0.10 , $P=0.162$). The

remodeling pattern and degree of stenosis between the two groups are shown in *Figure 2*. More than half of the plaques exhibited positive remodeling at a rate of 52.6% and 53.6% for the SSI and LSI groups, respectively. There was no significant difference in the percentages of positive, negative, and intermediate remodeling patterns between the two groups ($P=0.940$, 0.447 , and 0.336 , respectively). In the LSI group, more patients showed moderate-to-severe vascular stenosis ($\geq 50\%$ stenosis), whereas low-grade stenosis ($< 50\%$ stenosis) was predominant in the SSI group (*Figure 3*). A significantly higher incidence of low-grade stenosis was found in the SSI group compared with the LSI group (68.4% vs. 42.9%, $P=0.037$).

Discussion

In the present study, approximately 11.6% of the patients with SSI had no abnormality of the MCA, from which the lenticulostriate arteries are derived. Therefore, the lesions in these cases may be classical lacunar infarctions that are independent of MCA disease, such as would be caused by lipohyalinosis of the perforating arteries. In the remaining 88.4% of the patients with SSI, eccentric or non-eccentric wall thickening was present in the ipsilateral MCA. This percentage was higher (45.6–72.2%) than that reported in previous studies (5,24,25). Such a high prevalence may be due to the use of a novel HR-MRVWI and the different subjects included in the study. Advanced 3D HR-MRVWI

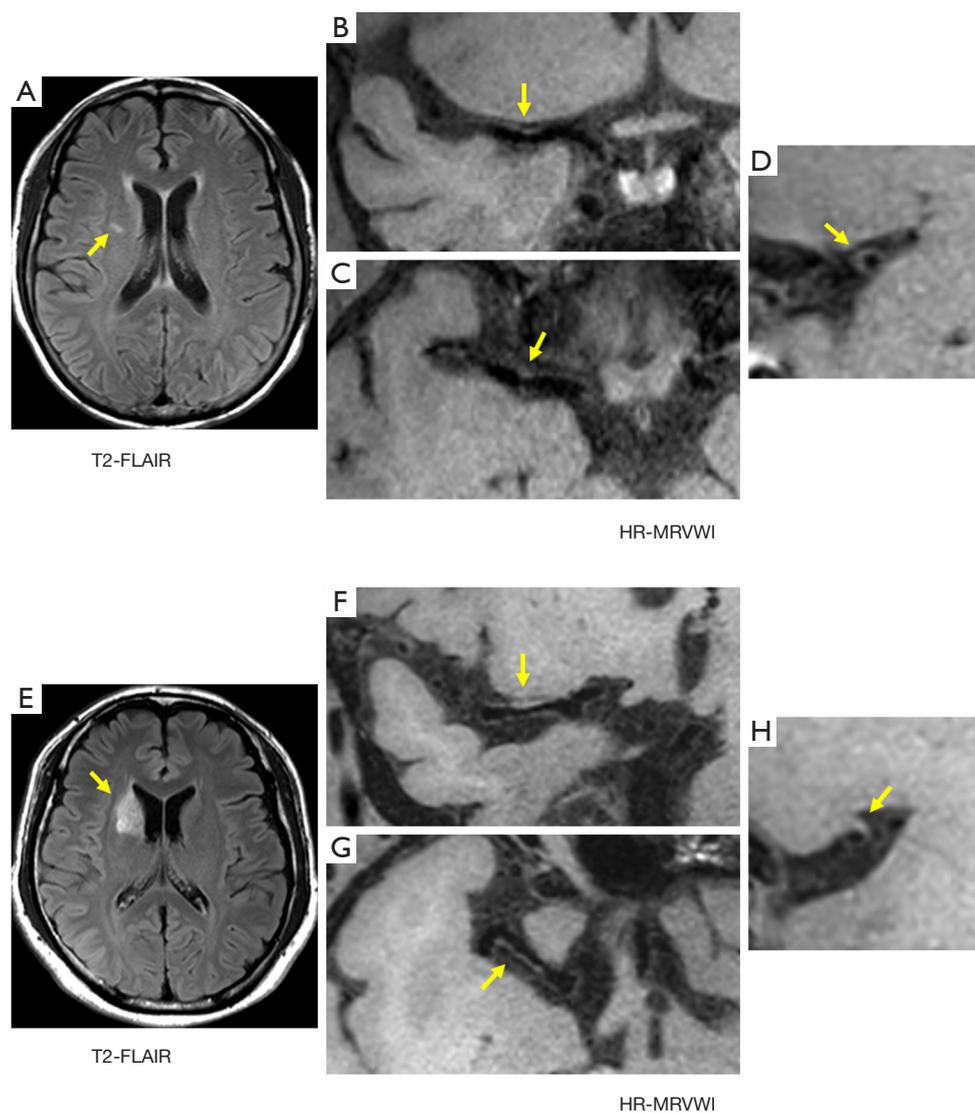


Figure 1 Representative MR images for a patient with SSI (A,B,C,D) and another with LSI (E,F,G,H). T2-FLAIR images (A,E) show a subcortical infarction of the right middle cerebral artery (MCA) territory (arrows). Plaque (arrows) was detected in the ipsilateral MCA on HR-MRVWI images (B,C,F,G) for each patient. The cross-sectional images (D,H) of the plaques (arrows) of both patients show involvement in only one quadrant, specifically ventral for SSI (D) and superior for LSI (H). FLAIR, fluid-attenuated inversion recovery; HR-MRVWI, high-resolution magnetic resonance vessel wall imaging; LSI, large subcortical infarction; SSI, small subcortical infarction.

can identify intracranial plaques that are missed on conventional angiographic imaging. Also, the patients in this study had symptomatic ischemia, and fibrohyalinosis of the arterioles is mainly associated with asymptomatic lacunes (25,26). In a previous study (6), only patients without stenosis of the MCA confirmed by MRA were included. We included patients with symptomatic subcortical ischemia confirmed by MRI, regardless of whether the MRA showed

stenosis or not. Our results suggested that atherosclerosis of the MCA may be more prevalent among patients with SSI than previously believed.

SSI caused by a focal atherosclerotic plaque of the MCA trunk may have the following possible mechanisms: (I) the origin of a perforating artery is occluded by the atherosclerotic lesions in the MCA; (II) small embolic particles from the MCA are deposited in a perforating

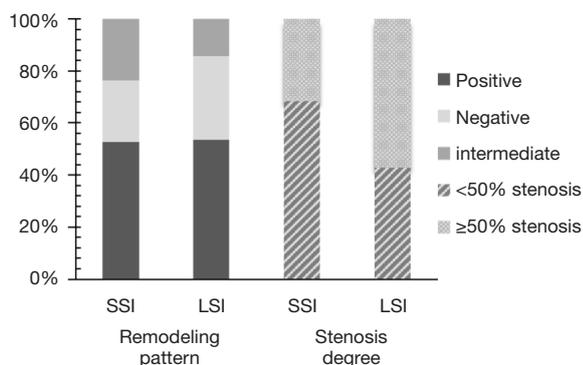


Figure 2 Frequency of positive, intermediate, and negative remodeling patterns and frequency of <50% and ≥50% stenosis. LSI, large subcortical infarction; SSI, small subcortical infarction.

artery (27). Microanatomy studies suggest that most of the penetrating branches of the MCA arise from the dorsal-superior part of the wall (28). Our study revealed that the SSI group had a higher proportion of plaque that involved only one quadrant of the wall. Also, this plaque appeared to be more frequently located in the superior (46.2%) and dorsal (38.5%) walls, thus being more likely to cause an infarct by direct occlusion of the perforating artery. The patients with LSI rarely had small-scale plaques that involved only one quadrant. Our findings suggested that SSI may be associated with MCA atherosclerosis, and plaque distribution may play an important role. Also, atherosclerotic lesions and fibrohyalinosis often coexist (4), but the walls of the perforator artery in patients with SSI could not be directly observed to confirm our hypothesis. The observation of diseased perforators depends on the further development of imaging technology.

Our results did not suggest an association of stroke type concerning involved quadrants or perforator arteries. Also, the ventral side of the vessel wall was a commonly involved quadrant in both groups. The results of other research and our studies show the same trend for the location of plaques (23). The plaque distribution in the MCA in both groups appeared to follow the same pattern as in coronary atherosclerosis, which is opposite the ostia of the penetrating arteries (29). This may be a protective mechanism. We observed that eccentric plaque involving two quadrants was most common in both groups, a finding that was consistent with a previous study showing that eccentric wall thickening is a characteristic of intracranial atherosclerotic plaque (30). However, in the current study, concentric plaques involving four quadrants were also

found in the MCA, which is consistent with findings from Dieleman *et al.*'s study (31).

Previous studies have shown that symptomatic MCA plaques have a greater wall area and prevalence of positive remodeling, compared with asymptomatic plaques (32,33). PB ≥77% on HR-MRVWI has proven to be a good predictor of the culprit and non-culprit lesions in the MCA (34). We found PB >70% in both groups, which may relate to the recruitment of symptomatic patients and the measurement of maximum PB in each group. These measured plaques on the ipsilateral side to an ischemic stroke are usually identified as culprit plaque in other studies. Similar results have been obtained in the study of the coronary artery, where PB ≥70% is a predictor of future cardiovascular events (35).

Also, PB was similar between the SSI and LSI groups, suggesting that SSI may not be a mild form of LSI in intracranial atherosclerosis. In the early stage of atherosclerosis, the vascular lumen is usually preserved by outward remodeling. Positive remodeling of the internal carotid artery can preserve the lumen, accounting for 62% of the VA at the plaque location (36). Although positive remodeling limits the hemodynamic effects of vascular stenosis, it may be associated with increased plaque vulnerability. In our study, positive remodeling of the MCA was observed in more than half of the patients in each group, but particularly in those with SSI; 68.4% of the patients showed low-grade stenosis, even when the PB was as high as 75%. Our HR-MRVWI findings were consistent with luminal changes in the internal carotid artery.

We showed that patients with low-grade stenosis accounted for the largest percentage in the SSI group. Previous reports have shown that symptomatic stenosis of the MCA is greater than 50% (37). Our results extend beyond those of previous studies. Although mild stenosis of a major intracranial artery may not be sufficient to affect the entire vascular territory, the specific location of atherosclerotic plaque may obstruct the blood flow of a perforator artery and lead to smaller infarctions. When the penetrating artery is not blocked, collateral circulation can be established, and newly generated collateral arteries can supply the territory. The territory of the MCA can then endure long-term ischemia, even if the MCA is completely occluded (38). This may be the reason why some patients with SSI showed moderate-to-severe stenosis of the MCA. However, more patients showed moderate-to-severe vascular stenosis in the LSI group. This may be due to inadequate collateral circulation and impaired cerebral

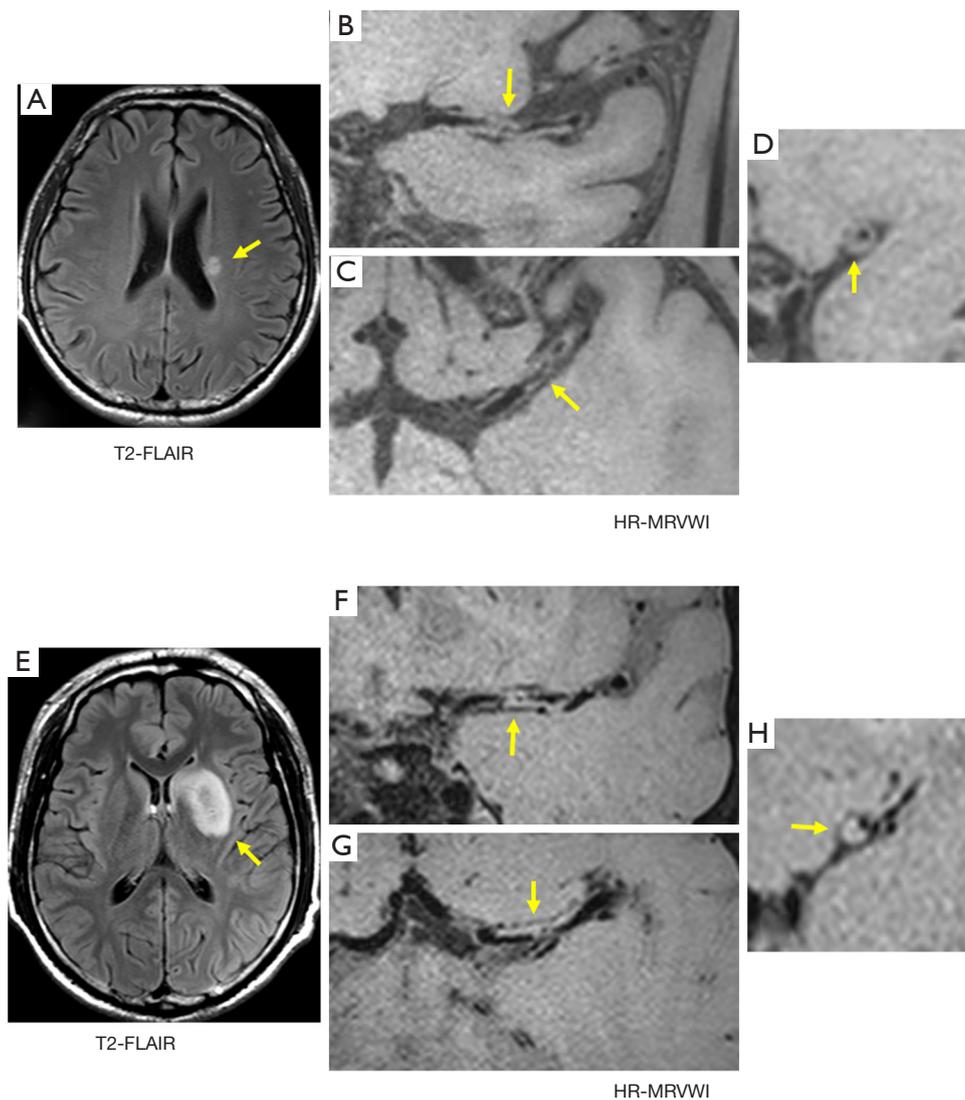


Figure 3 Representative MR images for a patient with SSI (A,B,C,D) and another with LSI (E,F,G,H), respectively. T2-FLAIR images (A,E) show a subcortical infarction of the left middle cerebral artery (MCA) territory (arrows). Plaque (arrows) was detected in the ipsilateral MCA on HR-MRVWI images (B,C,F,G) for each patient. The cross-sectional images (D,H) of the plaques (arrows) of both patients show involvement of three quadrants, but the plaque in the patient with LSI (H) caused more stenosis than in the patient with SSI (D). FLAIR, fluid-attenuated inversion recovery; HR-MRVWI, high-resolution magnetic resonance vessel wall imaging; LSI, large subcortical infarction; SSI, small subcortical infarction.

perfusion because of hypoperfusion, which leads to border zone infarction, resulting in a larger infarction. Also, the superficial cortex can sometimes remain perfused through collateral circulation, with the patient presenting only with asymptomatic radiological subcortical infarctions. The ostia of multiple penetrating arteries can be blocked by plaque, and larger infarctions of the regions of the perforator

artery can also occur, even if the lumen shows low-grade narrowing. In general, hypoperfusion due to severe stenosis may be the primary cause of infarction in patients with moderate-to-severe vascular stenosis, and the specific distribution of plaque leading to blockage of the perforating artery's orifice may be the main cause of infarction in other patients with low-grade stenosis. Therefore, the detection

of such lesions with HR-MRVWI, even in patients with mild stenosis of the MCA, is of great importance for revealing possible mechanisms of stroke in clinical practice.

This study had several limitations. First, the sample size was relatively small and was in the symptomatic cohort only. Further studies with a larger symptomatic and asymptomatic cohort are needed to determine the complementary value of plaque characteristics to confirm the association of MCA plaque features and any type of stroke in addition to LSI versus SSI. Second, the ostia of the penetrating arteries could not be visualized to prove our hypothesis, as mentioned earlier directly. And there is the possibility of including patients whose infarcts were caused by atherosclerosis of the aortic arch because we did not evaluate aortic arch angiographic images before the study. Third, in the acute stage of stroke, it would be difficult to distinguish atherosclerotic from embolic occlusion when intracranial arterial occlusion is observed. Even if the results of the cardiac assessment are within the normal range, the possibility of cardio-embolism cannot be completely ruled out. Fourth, plaque enhancement and intraplaque hemorrhage, both important features, were not analyzed because we did not have post-contrast HR-MRVWI images. Fifth, we only focused on the most stenotic area for the cross-sectional analysis. Given the roles of eccentricity and remodeling pattern, other areas of the plaque, such as greatest thickness, site of greatest remodeling, greatest eccentricity, etc. could be just as relevant. These also should be considered and evaluated in future studies. Last, because of the lack of perfusion imaging, the findings of a CBF study cannot be presented to confirm our speculation that adequate collateral circulation leads to smaller infarcts even if the patient has severe stenosis. This is warranted in subsequent research.

Conclusions

In conclusion, both SSI and LSI may be associated with major intracranial arterial atherosclerosis, but patients with SSI show relatively fewer plaque-involved quadrants and a lesser degree of stenosis.

Acknowledgments

Funding: This work was supported in part by the National Natural Science Foundation of China (81830056 and 81801691), Natural Science Foundation of Guangdong Province (2018A030313204), Guangdong Innovation

Platform of Translational Research for Cerebrovascular Diseases, and Shenzhen Basic Research Program (JCYJ20180302145700745 and JCYJ20170413161350892).

Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/qims-20-310>). The authors have no conflicts of interest to declare.

Ethical Statement: The institutional review board approved this study of Shenzhen Institutes of Advanced Technology, Chinese Academy of Sciences (No. SIAT-IRB-180215-H0204) and written informed consent was obtained from the patient for publication of this study and any accompanying images.

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Cite this article as: Zhu T, Ren L, Zhang L, Shao Y, Wan L, Li Y, Liang D, Zheng H, Liu X, Zhang N. Comparison of plaque characteristics of small and large subcortical infarctions in the middle cerebral artery territory using high-resolution magnetic resonance vessel wall imaging. *Quant Imaging Med Surg* 2021;11(1):57-66. doi: 10.21037/qims-20-310