Magnetic Resonance Imaging of Plaque Morphology, Burden, and Distribution in Patients With Symptomatic Middle Cerebral Artery Stenosis

Nikki Dieleman, MSc*; Wenjie Yang, MD*; Jill M. Abrigo, MD; Winnie Chiu Wing Chu, MD, PhD; Anja G. van der Kolk, MD, PhD; Jeroen C.W. Siero, PhD; Ka Sing Wong, MD, PhD; Jeroen Hendrikse, MD, PhD; Xiang Yan Chen, MD, PhD

Background and Purpose—Intracranial atherosclerosis is a major cause of ischemic stroke worldwide. Intracranial vessel wall imaging is an upcoming field of interest to assess intracranial atherosclerosis. In this study, we investigated total intracranial plaque burden in patients with symptomatic middle cerebral artery stenosis, assessed plaque morphological features, and compared features of symptomatic and asymptomatic lesions using a 3T vessel wall sequence.

Methods—Nineteen consecutive Chinese patients with ischemic stroke and transient ischemic attack (mean age: 67 years; 7 females) with a middle cerebral artery stenosis were scanned at 3T magnetic resonance imaging; the protocol included a time-of-flight magnetic resonance angiography and the T1-weighted volumetric isotropically reconstructed turbo spin echo acquisition sequence before and after (83%) contrast administration. Chi-square tests were used to assess associations between different plaque features. Statistical significance was set at P<0.05.

Results—Vessel wall lesions were identified in 18 patients (95%), totaling 57 lesions in 494 segments (12% of segments). Lesions were located primarily in the anterior circulation (82%). Eccentric lesions were associated with a focal thickening pattern and concentric lesions with a diffuse thickening pattern (P<0.001). When differentiating between asymptomatic and symptomatic lesions, an association (P<0.05) was found between eccentricity and asymptomatic lesions, but not for enhancement or a specific thickening pattern. Symptomatic lesions did not have any specific morphological features.

Conclusions—Our results lead to a 2-fold conclusion: (1) The classification system of both thickening pattern and distribution of the lesion can be simplified by using distribution pattern only and (2) differentiation between symptomatic and asymptomatic atherosclerotic lesions was possible using intracranial vessel wall imaging. (Stroke. 2016;47:1797-1802. DOI: 10.1161/STROKEAHA.116.013007.)

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

Intracranial atherosclerotic disease is a major cause of ischemic stroke worldwide and the most common cause in the Asian population.1 Patients suffering from intracranial atherosclerosis have a high subsequent stroke risk.1 In subjects with asymptomatic middle cerebral artery (MCA) stenosis, the overall annual stroke risk is 2.8%, whereas in patients with symptomatic middle artery stenosis the risk is even 4 times high.2 For many years, lumenography-based methods were used to assess intracranial atherosclerotic disease by means of luminal narrowing, and it was thought that stenosis grade was an accurate reflection of disease burden.3 In recent years, however, a shift has taken place toward imaging the intracranial vessel wall rather than the lumen as a result of advancing knowledge on the development of atherosclerotic plaques. Nowadays, it is common knowledge that outward arterial remodeling occurs, enabling plaques to develop without luminal narrowing.4,5

From histopathologic studies, examining the carotid and coronary arteries, it is known that plaques containing a large necrotic core or intraplaque hemorrhage and of a soft composition are typically at risk for plaque rupture.5,6 Furthermore, several magnetic resonance imaging (MRI) studies have...
shown the additional value of atherosclerotic plaque characteristics, such as thin or ruptured fibrous caps, albeit in the extracranial vascular territories.²⁹ In 2014, Corban et al²⁹ showed that the combination of plaque burden, wall shear stress, and plaque phenotype (including several plaque characteristics) can predict atherosclerotic plaque progression and vulnerability in the coronary arteries. The Providing Regional Observations to Study Predictors of Events in the Coronary Tree (PROSPECT) trial demonstrated that large plaque burden is associated with more advanced plaques in the coronary arteries.¹¹ Knowledge of atherosclerotic burden and plaque characteristics/morphology of the intracranial vasculature is important because it may provide insight into vulnerability status similar to the extracranial arteries. Similar as it was for the extracranial arteries, intracranial vessel wall imaging is now an upcoming field of interest.¹²–¹⁸ However, because the intracranial arteries are much harder to assess, less is known about the total intracranial plaque burden and their morphological features. The remodeling pattern and plaque distribution within the plaque, eg, superior, inferior, dorsal, or ventral are among the few characteristics that have been assessed in MCA stenosis only.¹⁹ Several other, smaller studies have proposed specific intracranial plaque characteristics such as eccentricity and enhancement.¹⁷,²⁰,²¹ Especially, enhancement is thought to be of importance for assessment of plaque vulnerability.²² Besides morphological features of the intracranial plaques itself, understanding of the morphological plaque differences between asymptomatic and symptomatic atherosclerotic lesions may be useful for risk stratification and treatment options. Therefore, in this study, we investigated total intracranial plaque burden in patients with symptomatic middle cerebral artery stenosis, assessed morphological features of the plaque itself, and compared these features of symptomatic lesions to those of asymptomatic lesions using a 3T vessel wall sequence.

Methods

Subjects
This prospective study was approved by the Institutional Review Board of the Chinese University of Hong Kong. All subjects gave written informed consent. Between February and September 2014, consecutive Chinese patients with a symptomatic MCA stenosis, as confirmed by digital subtraction angiography (DSA), clinical workup, and conventional MRI, were included in this study. Patients were thus selected based on the presence of stenotic atherosclerotic disease. All patients had to be able to endure the MRI examination and have no contraindications for MRI. Patient characteristics including age, sex, and general vascular risk factors were collected during patient’s visit to the hospital. Some study subjects have been used in a recent technical study comparing the current sequence with 3 other vessel wall sequences for evaluating the best usable sequence (submitted data), in which summarizing baseline data (eg, average age and sex) and visualization of the vessel wall was reported.

Imaging
MRI was performed using a 3T Achieva MR system (Philips Healthcare, Cleveland, OH) with an 8-channel Sense head coil. The protocol included a transverse 3D T₁-weighted (T₁w) volumetric isotropically reconstructed turbo spin echo Acquisition (VIRTA) sequence,¹³ before and after (83% of patients) contrast administration, and a time-of-flight magnetic resonance angiography (TOF-MRA) sequence. Before acquisition of the contrast-enhanced T₁w VIRTA sequence, 0.1 mL/kg of a gadolinium-containing contrast agent (Dotarem, Gadoteric acid 0.5 mmol/mL; Guerbet, Roissy CdG Cedex, France) was administered to the patient. The following scan parameters were used for the T₁w VIRTA: field of view: 200×167×45 mm³, acquired resolution: 0.6×0.6×1.0 mm³, reconstructed resolution: 0.5×0.5×0.5 mm³ using zero filling, repetition time 1500 ms, echo time 36 ms, Sense factor 1.5 (phase-encode direction), echo spacing 4.0 ms, turbo spin echo+startup echoes 56+6, and scan duration 6:51 minutes. Anti-DRIVen Equilibrium (DRIVE) module was used for increased cerebrospinal fluid suppression. Additionally, we used a minimum flip angle of 25° in the variable flip angle refocusing pulse train for increased flow suppression (in cerebrospinal fluid and blood).²³ Scan parameters for the TOF-MRA sequence were as follows: field of view 200×200×56 mm³, acquired resolution 0.4×0.6×0.7 mm³, repetition time/echo time 23/3.5 ms, and scan duration 3:07 minutes.

Image Analysis
Images were analyzed on an offline workstation (Philips) by 1 observer (N.D., 3 years of experience); a second observer (A.K., 7 years of experience) analyzed a subset of images (n=10). The observers were blinded for clinical data. On the T₁w VIRTA images, all major arteries of the Circle of Willis and its branches were scored for presence of vessel wall lesions (both symptomatic and asymptomatic); the contralateral side or the vessel wall more proximal or distal to the lesion was used as reference. The MCA stenosis that was identified as the culprit lesion by DSA was used as the symptomatic lesion and the other lesions as asymptomatic. Next, we assessed morphological features, by scoring thickening pattern, distribution pattern, and enhancement pattern of the lesion. The thickening pattern was scored as focal or diffuse, where focal was defined as a short region or focal point lesion and diffuse as a lesion over a longer trajectory (eg, >0.5 cm). Next, the distribution of the lesion was characterized as either eccentric (<50% wall involvement) or concentric (>50% wall involvement).²⁵ Furthermore, pre- and post-contrast scans were compared to assess contrast enhancement of the vessel wall, 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. Finally, the TOF-MRA was used for confirmation of the observed vessels and to assess whether scored vessel wall lesions could be appreciated on the TOF-MRA as well. TOF-MRA lesions were defined as normal, irregular, stenotic, occluded, or irregular and occluded.

Statistical Analysis
IBM SPSS version 20.0 for Windows was used for statistical analysis. Chi-square tests were used to assess associations between different plaque morphological features, between asymptomatic and symptomatic lesions, and between symptomatic lesions and MRA findings. The Dice similarity coefficient and the intraclass correlation coefficient with 95% confidence intervals were calculated to evaluate inter-rater reproducibility.²⁴ Statistical significance was set at P<0.05.

Results

Subjects
Between February and September 2014, 19 patients (7 females; mean age: 67 years; range: 47–81 years) with a symptomatic MCA stenosis underwent 3T imaging at a median time of 592 days after symptom onset (acute/subacute patients [n=4] range: 6–72 days; chronic patients [n=15] range: 145–2740). Of these 19 patients, 2 had had a transient ischemic attack and 17 had had an ischemic stroke. No major (motion) artifacts that hampered image analysis were observed. Patient demographics and cerebrovascular risk factors are summarized in Table 1.²⁵
Table 1. Demographics of 19 Patients With Ischemic Stroke or TIA

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, mean (range), y</strong></td>
<td>67 (47–81)</td>
</tr>
<tr>
<td><strong>Sex (male)</strong></td>
<td>12 (63)</td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
<td></td>
</tr>
<tr>
<td>TIA</td>
<td>2 (11)</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>17 (89)</td>
</tr>
<tr>
<td><strong>TIA/stroke mechanism</strong></td>
<td></td>
</tr>
<tr>
<td>Large-artery atherosclerosis</td>
<td>18 (95)</td>
</tr>
<tr>
<td>Cardioembolism</td>
<td>1 (5)</td>
</tr>
<tr>
<td><strong>Cardiovascular risk factors</strong></td>
<td></td>
</tr>
<tr>
<td>Any cardiovascular risk factor</td>
<td>18 (95)</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg±SD)</td>
<td>155±30†</td>
</tr>
<tr>
<td>Hypertension</td>
<td>15 (79)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>9 (47)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>4 (21)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>6 (31)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1 (5)</td>
</tr>
</tbody>
</table>

TIA indicates transient ischemic attack.

*According to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification system.25
†Measurements available for 15 patients.

Distribution, Burden, and Characteristics

Intracranial vessel wall lesions were identified in 18 patients (95%), and multiple lesions were found in 15 patients. A strong inter-rater reliability was found: intraclass correlation coefficient, 0.71 and 95% confidence interval, 0.196 to 0.920. Inter-rater agreement on the evaluation of locations was moderate–good: Dice similarity coefficient, 0.57. A total of 57 lesions in 494 segments (12% of segments) were identified. Of these lesions, 47 (82%) were found in the anterior circulation (internal carotid artery [ICA], n=18; MCA, n=27; and anterior cerebral artery, n=2) and 10 (18%) in the posterior circulation (basilar artery, n=3 and posterior cerebral artery, n=7; Table 2 and Figure 1). Among the 57 lesions, 25 (44%) enhanced after contrast administration (Figure 2), 43 (75%) were eccentric, 14 (25%) were concentric, 42 (74%) were focal, and 15 (26%) were diffuse (Table 3). Eccentric lesions were significantly associated with a focal thickening pattern (Figure 2; Figure I in the online-only Data Supplement) and concentric lesions with a diffuse thickening pattern in plaques of the anterior circulation (P<0.001). Nineteen lesions (33%) were symptomatic (MCA lesions; 1 patient with bilateral lesions) and 38 lesions (67%) were asymptomatic. When differentiating between asymptomatic and symptomatic lesions, a significant association (P<0.05) was found between eccentricity and asymptomatic lesions (asymptomatic lesions: 32 eccentric, 84% versus symptomatic lesions: 11 eccentric, 58%) but not for enhancement or a specific thickening pattern. Symptomatic lesions did not have any specific morphological features. Furthermore, vessel wall lesions that appeared normal or irregular on MRA were more often asymptomatic, whereas lesions that appeared stenotic or occluded were symptomatic (P<0.001; Figure 2). Thirty MRA lesions were found: 26 in the anterior circulation and 4 in the posterior circulation. Besides the observed vessel wall lesions, we found, of these 30 MRA lesions, 8 additional lesions on MRA that were not visible on the vessel wall scan. Of these lesions, 6 were irregular, 1 was stenotic (Figure 3), and 1 was irregular/stenotic. Both lesions that were stenotic were also symptomatic lesions.

Discussion

In this study, we evaluated total intracranial plaque burden and plaque morphology and compared morphological features of symptomatic lesions to those of asymptomatic lesions in patients with a symptomatic MCA stenosis. We demonstrate that (1) most lesions were found in the distal ICA, intracranial bifurcation of the ICA, and in the M1 segment of the MCA, (2) besides the confirmed culprit MCA lesion, most patients had additional asymptomatic lesions, and (3) eccentric lesions were associated with focal thickening and asymptomatic lesions, whereas symptomatic lesions did not have any specific morphological features.

Similar to what has been found by other studies using lumenography-based methods, and one other vessel wall study, we observed the distal ICA, intracranial ICA bifurcation, and the M1 segment of the MCA as predilection locations for the development of atherosclerotic plaques.26–30 In a study on coronary arteries performed by Corban et al.,30 it was hypothesized that low shear stress may play a role in the predilection of plaques to develop in bifurcations. These plaques might also be at increased risk for rupture, hence higher risk for causing future ischemic events. Another explanation for the majority of lesions found in the distal ICA may be the...
fact that all of our patients had a symptomatic MCA stenosis, so our population is biased toward the anterior circulation. Nevertheless, we have also demonstrated that 18% of the lesions were not found in the anterior circulation and even more, 67% of our lesions were found to be asymptomatic and were found in areas other than the region of the culprit lesion.

Most eccentric lesions had a more focal thickening pattern. This is in line with earlier research from Swartz et al., in which the authors showed that patients suffering from atherosclerotic disease had focal, eccentric lesions compared with patients with other pathologies who had diffuse and concentric lesions. We did not observe any association between symptomatic nor with asymptomatic plaques and enhancement. Intracranial plaque enhancement has been reported inconsistently, and the exact mechanisms are not known because histopathologic validation is lacking. It could be that we have missed some lesion enhancement, because in some patients no postcontrast scan was obtained or because most patients were chronic stroke patients. On the contrary, it may be that lesion enhancement is less important for the intracranial arteries as it is for the extracranial arteries, where enhancement is a well-established feature of plaque vulnerability. For the intracranial arteries, one of the differences that may partly explain why we do not observe associations with enhancement is the abundance of vasa vasorum. In early life vasa vasorum are rare in the intracranial arteries and predominantly found in the proximal parts of the brain vessels. During aging, the vasa vasorae get more abundant, and they may also develop in patients with pathologies like vasculitis, aneurysms, and atherosclerosis. When vasa vasorum are the only causative factor for the enhancement in the intracranial vessel wall, this would imply that the entire vessel tree will enhance in older patients and patients with atherosclerosis. We do, however, not observe abundant enhancement of the intracranial vessels. This may suggest that different mechanisms are involved in the intracranial vessel wall enhancement.

Asymptomatic and symptomatic lesions were found to have a different morphological feature. The asymptomatic lesions

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**Figure 1.** A 72-year-old female patient with a left partial anterior circulation infarct. **A**, On transverse T1-weighted volumetric isotropically reconstructed turbo spin echo acquisition images, an eccentric, focal lesion was found in the P2 segment of the left posterior cerebral artery (arrow). Also, an eccentric, focal lesion (arrow in **B**) was observed in the basilar artery without causing luminal stenosis (arrow in **C**). **C**, Transverse time-of-flight magnetic resonance angiography shows an asymptomatic stenosis of the P2 segment at the same location as the vessel wall lesion (arrow).

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**Figure 2.** A 78-year-old female patient presented with an acute left transient ischemic attack. **A**, Bilateral focal vessel wall lesions were observed in the middle cerebral arteries on the transverse T1-weighted volumetric isotropically reconstructed turbo spin echo acquisition image (arrows in **A**). Sagittal image reconstructions of the (**B**) right middle cerebral artery (MCA) lesion and (**C**) left MCA lesion showing that both lesions are eccentric. **D**, Transverse time-of-flight magnetic resonance angiography shows a corresponding symptomatic left MCA stenosis and an asymptomatic irregular right MCA (arrows in **D**).
were associated with more eccentric distribution of the plaque, but symptomatic lesions were both eccentric and concentric. It may be that concentric lesions are more advanced plaques as compared with eccentric lesions, because >50% of the vessel wall (in the sagittal view) is affected in case of a concentric lesion. We also found that all DSA-proven MCA stenoses yielded a positive/outward-remodeling pattern. It might be interesting to examine whether differences exists in remodeling pattern between symptomatic and asymptomatic MCA stenoses in a group not selected based on DSA. Besides the difference between these lesions, an interesting point to mention is the differences in appearance of lesions in the Chinese population as compared with the western population. Lesions in the Chinese population appear to be thicker, more often eccentric, and less diffuse. In future research, it would be interesting to test this hypothesis directly, because risk stratification criteria may be different between different ethnicities.

There are several limitations to our study. First, our sequence has a limited field of view; some lesions may have been missed, especially in the posterior circulation and in the more distally located vessels. The number of lesions found is therefore probably an underestimation of the true plaque burden. Second, patients were selected based on the presence of an MCA stenosis, as confirmed by DSA; therefore, we only included patients with stenotic atherosclerotic disease. As a result, this may have accounted for the plaque distributions found in this study. The selection based on a symptomatic MCA stenosis also accounts for the associations found between MRA and symptomatic/atherosclerotic vessel wall lesions. In future, we should also include patients without DSA-proven stenosis or with strokes of the posterior circulation to investigate whether similar distribution patterns exist and whether correlations between MRA and vessel wall persist. Third, both acute and chronic patients were included in this study, because the patients were recruited via different ways. Therefore, the range between onset of stroke/TIA and scanning is broad. This may possibly explain the lack of association between enhancement and the MCA stenosis. However, the exact mechanisms of contrast enhancement still need to be established. Furthermore, the used sequence was added as a pilot sequence; therefore, the number of patients scanned with this sequence is relatively small. Finally, because of a lack of histology, we are not sure whether all the lesions observed are lesions that are at risk, whether they are of atherosclerotic origin, or whether they are vessel wall lesions at all. This lack of confirmation by histology is because it is rather difficult to obtain the intracranial arteries, because no intravascular interventions similar to those in the extracranial arteries are performed, such as carotid endarterectomy for the external carotid arteries. However, new research using Circle of Willis specimen shows promise in this field.

**Table 3. Plaque Characteristics of 57 Plaques in Patients With MCA Stenosis**

<table>
<thead>
<tr>
<th>Plaque Characteristic</th>
<th>Anterior Circulation*</th>
<th>Posterior Circulation*</th>
<th>Total (n=57)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enhancement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>24</td>
<td>1</td>
<td>25</td>
</tr>
<tr>
<td>No</td>
<td>16</td>
<td>5</td>
<td>21</td>
</tr>
<tr>
<td>NA</td>
<td>7</td>
<td>4</td>
<td>11</td>
</tr>
<tr>
<td>Configuration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concentric</td>
<td>12</td>
<td>2</td>
<td>14</td>
</tr>
<tr>
<td>Eccentric</td>
<td>35</td>
<td>8</td>
<td>43</td>
</tr>
<tr>
<td>Thickening</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Focal</td>
<td>33</td>
<td>9</td>
<td>42</td>
</tr>
<tr>
<td>Diffuse</td>
<td>14</td>
<td>1</td>
<td>15</td>
</tr>
<tr>
<td>MRA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>21</td>
<td>6</td>
<td>27</td>
</tr>
<tr>
<td>Irregular</td>
<td>10</td>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td>Stenosis</td>
<td>12</td>
<td>2</td>
<td>14</td>
</tr>
<tr>
<td>Occluded</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Irregular and occluded</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
</tbody>
</table>

MCA indicates middle cerebral artery; MRA, magnetic resonance angiography; and NA, no postcontrast scan available.

*Number of lesions at location.

**Conclusions**

We have demonstrated that most vessel wall lesions in patients with a symptomatic MCA stenosis are found in the distal ICA, intracranial bifurcation of the ICA, and in the M1 segment of the MCA, corresponding to similar distributions found for ischemic strokes. Moreover, intracranial atherosclerotic plaques were mainly associated with an eccentric configuration and a focal thickening pattern and concentric lesions with a diffuse thickening pattern. This may imply that the classification system of both thickening pattern and distribution of the lesion can be simplified by using distribution pattern within the lesion only. Finally, asymptomatic lesions were found to be more often eccentric, whereas symptomatic lesions did not have any specific morphological features. This may enable differentiation between symptomatic and asymptomatic atherosclerotic lesions in the future.
Disclosures

None.

References

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Figure I. A 57-year-old male patient with a left partial anterior circulation infarct caused by a left middle cerebral artery (MCA) stenosis. (A) Transverse TOF-MRA shows a symptomatic stenosis of the left MCA (arrow). Reconstructed sagittal T₁w VIRTA image shows an eccentric, focal plaque in the left MCA (arrows in B). Transverse T₁w VIRTA images before (C) and after (D) contrast administration again show the plaque in the left MCA (arrows). The plaque enhances after contrast administration (arrow in D).
背景および目的：頭蓋内アテローム性動脈硬化症は世界的に虚血性脳卒中の主要原因である。頭蓋内血管壁の画像検査は、頭蓋内アテローム性動脈硬化症の評価方法として注目されている分野である。本研究では、症候性中大脳動脈狭窄患者の頭蓋内プラーク量の調査、プラークの形態学的特徴の評価、3T血管壁画像の症候性および無症候性病変の特徴の比較を実施した。

方法：中大脳動脈狭窄による虚血性脳卒中および一過性脳虚血発作（平均年齢67歳、女性7例）の中国人患者19例で3T MRIを実施した。撮像は造影剤の投与前および投与後（83%）に、タイム・オブ・フライト法MRAおよびT1-weihted volumetric isotropically reconstructed turbo spin echo（T1強調ボリューム等方再構成ターボスピニエコー）法で実施した。χ²検定で異なるプラークの特徴の関連性を評価した。統計学的有意性はP<0.05に設定した。

結果：血管壁病変は18例（95%）に認められ、494区域に計57病変であった（全区域の12%）。病変は主に前方循環系に位置していた（82%）。偏心性病変は限局性肥厚パターンと、求心性病変はびまん性肥厚パターン（P<0.001）との関連が見られた。無症候性病変と症候性病変で区別した場合、偏心性と無症候性病変に関連（P<0.05）が認められたが、造影効果および特定の肥厚パターンについて関連は認められなかった。症候性病変には特別な形態学的特徴はなかった。

結論：本研究の結果、2つの結論に至った。1) 病変の肥厚パターンと分布からなる分類体系は、分布パターンのみで省略可能である。2) 頭蓋内血管壁画像検査により、症候性および無症候性のアテローム硬化病変の鑑別が可能である。Stroke. 2016; 47: 1797-1802. DOI: 10.1161/STROKEAHA.116.013007.
のプラクラ分布は、MCA 狭窄でのみ評価された数少ない特徴である19。そのほかにも、何件かの小規模の研究が偏心性や造影効果など特定の領域内でプラクラの特徴を提起している17,20,21。特に、プラクラの脆弱性の評価には造影効果が重要なと考えられている22。頭蓋内プラクラ自体の形態学的特徴だけでなく、無症候性および症候性アテローム硬化病変のプラクラ形状の差を理解することも、リスクの観察および治療選択肢に有用であると考えた。したがって本研究では、症候性中大脳動脈狭窄患者で頭蓋内プラクラの総量を調査した。さらに、プラクラ自体の形態学的特徴を評価し、3T 血管壁画像で症候性病変と無症候性病変の特徴を比較した。

## 方法

### 被検者

本前向き研究は Chinese University of Hong Kong 内の審査委員会に承認された。すべての被検者が同意書を提出した。2014年2月9月の間にデジタルサブトラクション血管造影 (DSA)、臨床検査、従来の MRI で確認した症候性 MCA 狭窄の中国人患者を本研究の対象とした。患者はこのように狭窄を伴うアテローム硬化病変の存在に基づいて選択された。患者はいずれも、MRI 検査に耐えられること、MRI に対する禁忌を持たないことが条件とした。患者の来院時に年齢、性別、一般的な心血管危険因子などの特徴を収集した。一部の被検者、特に有用な撮像法を評価するため最新の撮像法と3種類の血管壁撮像法を比較した新しい技術的な試験の対象となった（投稿したデータ）。ベースラインデータ（平均年齢および性別など）の要約と血管壁の画像化についてはこの中で報告した。

### 画像検査

MRI 検査は 8 チャンネル Sense ヘッドコイルの 3T Achieva MR system（Philips Healthcare, Cleveland, OH）で実施した。撮像は、造影剤投与前および投与後（全患者の 83%）に横断 3D T1-weighted volumetric isotropically reconstructed turbo spin echo（T1強調ボリューム等方再構成ターボスピンエコー）法（T1w VIRTIA）で実施し23、さらにタイム・オブ・フライテ磁気共鳴血管造影法（TOF-MRA）を使用した。造影 T1w VIRTIA の撮像前に、ガドリニウム含有造影剤 0.1 mL/kg（Dotarem、ガドテル酸 0.5 mmol/mL, Guerbet, Roissy CdG Cedex, France）を患者に投与した。T1w VIRTIA の撮像パラメータは、撮像野 200 × 167 × 45 mm3、撮像解像度 0.6 × 0.6 × 1.0 mm3、再構成解像度 0.5×0.5×0.5 mm3（zero filling 使用）、反復時間 1,500 ms、エコー時間 36 ms、Sense 係数 1.5（位相エンコード方向）、エコー間隔 4.0 ms、ターソプソンエンコーダスタートアッシュエコー 56 + 6、捕捉時間 6:51 分とした。脳脊髄液の抑制を高めるため Anti-DRIVEN Equilibrium（DRIVE）モジュールを使用した。また、変動するフリップ角度のうち 25°の最小フリップ角を用いてパルス列を再構成し、(脳脊髄液と血液の) 循環抑制を高めた24。TOF-MRA 画像の撮像パラメータは、撮像野 200×200×56 mm3、撮像解像度 0.4 × 0.6 × 0.7 mm3、反復時間/エコー時間 23/3.5 ms、撮像時間 3:07 分とした。

### 画像解析

画像はオフラインのワークステーション（Philips）で1名のオブザーバー（N.D., 経験3年）が解析した。2人目のオブザーバー（A.K., 経験7年）も一部の画像を解析した（n = 10）。オブザーバーは臨床データに対して盲検化されていた。T1w VIRTIA 画像上で、Willa 造影輪の主要動脈およびその分枝すべてを血管壁病変の有無（症候性と無症候性の両方）によりスコア化評価した。反対側または病変に対して近位または遠位にある血管壁を基準とした。DAS により責任病変を確定した MCA 狭窄は症候性病変とし、その他の病変は無症候性病変とした。次に病変の肥厚パターン、分布パターン、造影パターンをスコア化することにより形態学的特徴を評価した。肥厚パターンは限局性またはびまん性のいずれかでスコア化し、「限局性」は短い範囲の局所的、点的病変と定義し、「びまん性」は長く連なった（例、＞ 0.5 cm）病変と定義した。次に、病変の分布は偏心性（血管壁の 50%を超えない病変）または求心性（血管壁の 50%を超える病変）の特徴を分類した25。さらに、血管壁の造影効果を評価するため造影剤投与前と投与後の画像を比較し、血管壁の信号強度を血管壁近傍の脳実質の信号強度と比較した。造影剤が正しく脳に渡っていることを担保するため漏斗を使用した。最後に、観察した血管は TOF-MRA で確認し、スコア化した血管壁病変が TOF-MRA でも認識できるか否かを評価した。TOF-MRA 病変は正常、不規則、狭窄、閉塞、不規則な閉塞のいずれかに判断した。

### 統計解析

IBM SPSS version 20.0 for Windows を統計解析に使用した。さまざまなプラクラの形態学的特徴、無症候性病変と症候性病変、症候性病変と MRA 所見の関連性は、χ2 検定で評価した。Dice 類似係数およびクラストリック相関係数と 95%信頼区間に算出し、評価者間再現性の評価とした26。統計学的有意性は P < 0.05 に設定した。
【結 果】

被験者

2014年2月〜9月に、症候性MCA狭窄患者19例（女性7例、平均年齢67歳、範囲：47〜81歳）に発症後592日（中央値）[急性期/亜急性期患者（n=4）の範囲：6〜72日、慢性期患者（n=15）の範囲：145〜2,740日]の時点で3T画像検査を実施した。この19例中、2例が一過性脳虚血発作、17例が虚血性脳卒中であった。画像解析の障害となった重大な（動作）アーチファクトはなかった。患者の背景および脳血管障害の危険因子を表1に要約する。

【分布、量、特徴】

頭蓋内の血管壁病変は18例（95%）に認められ、多発病変は15例であった。クラス内相関係数0.71、95%信頼区間0.196〜0.920で、評価者間信頼性は強く、Dice類似係数は0.57で、発症部位の評価に関する評価者間一致度は中〜高であった。494区域に合計57病変が見つかった（全区域の12%）。このうち47病変（82%）は前方循環系[内頸動脈（ICA）n=18、MCA n=27、前大脳動脈n=2]、10病変（18%）は後方循環系（脳底動脈n=3および後大脳動脈n=7、表2および図1）であった。造影剤の投与後57病変中25病変（44%）に造影効果が認められ（図2）、43病変（75%）は偏心性、外側性、内側性、中央性のいずれも見られた。

【表1】虚血性脳卒中またはTIA患者19例の背景

<table>
<thead>
<tr>
<th>年齢、平均（範囲）、歳</th>
<th>合計（％）</th>
</tr>
</thead>
<tbody>
<tr>
<td>67（47〜81）</td>
<td></td>
</tr>
</tbody>
</table>

【表2】MCA狭窄患者18例のブラーク量

<table>
<thead>
<tr>
<th>場所</th>
<th>右 *</th>
<th>左 *</th>
<th>合計（n=57）</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICA</td>
<td>10</td>
<td>8</td>
<td>18</td>
</tr>
<tr>
<td>通位頸動脈域</td>
<td>6</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>M1</td>
<td>10</td>
<td>17</td>
<td>27</td>
</tr>
<tr>
<td>M1-M2分岐部</td>
<td>4</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>M2</td>
<td>9</td>
<td>13</td>
<td>22</td>
</tr>
<tr>
<td>前大脳動脈</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>A1 区域</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>A2 区域</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>脳底動脈</td>
<td>2</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>後大脳動脈</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>BA-P1分岐部</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>P1 区域</td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>P2 区域</td>
<td>22</td>
<td>32</td>
<td>57</td>
</tr>
</tbody>
</table>

* その場所にある病変の数。
症候性中大脳動脈狭窄患者におけるプラークの形態, 量, 分布のMRI画像

表3 MCA狭窄患者の57個のプラークの特徴

<table>
<thead>
<tr>
<th>プラークの特徴</th>
<th>前方循環系*</th>
<th>後方循環系*</th>
<th>合計（n=57）*</th>
</tr>
</thead>
<tbody>
<tr>
<td>造影効果</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>あり</td>
<td>24</td>
<td>1</td>
<td>25</td>
</tr>
<tr>
<td>なし</td>
<td>16</td>
<td>5</td>
<td>21</td>
</tr>
<tr>
<td>NA</td>
<td>7</td>
<td>4</td>
<td>11</td>
</tr>
<tr>
<td>形態</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>求心性</td>
<td>12</td>
<td>2</td>
<td>14</td>
</tr>
<tr>
<td>偏心性</td>
<td>35</td>
<td>8</td>
<td>43</td>
</tr>
<tr>
<td>肥厚</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>限局性</td>
<td>33</td>
<td>9</td>
<td>42</td>
</tr>
<tr>
<td>びまん性</td>
<td>14</td>
<td>1</td>
<td>15</td>
</tr>
<tr>
<td>MRA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>正常</td>
<td>21</td>
<td>6</td>
<td>27</td>
</tr>
<tr>
<td>不規則</td>
<td>10</td>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td>狭窄</td>
<td>12</td>
<td>2</td>
<td>14</td>
</tr>
<tr>
<td>閉塞</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>不規則な閉塞</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
</tbody>
</table>

MCA:中大脳動脈, MRA:磁気共鳴血管造影法, NA:造影剤投与後の画像なし。
*その箇所にあるプラークの数。

考察

本研究では、症候性MCA狭窄患者において、頭蓋内

ブラークの総量およびブラークの形態を評価し、症候性
病変と無症候性病変の形態学的特徴を比較した。その結
果、以下のことが示された。

(1) ほとんどの病変はICA
の遠位部、ICAの頭蓋内分岐部、MCA M1区域にある。
(2) ほとんどの患者に、確認された責任MCA病変以外
の無症候性病変がある。
(3) 偏心性病変は限局性肥厚パ
ターンおよび無症候性病変と関連し、症候性病変には特定の形態学的特徴がなかった。

断層撮影法を使用したその他の研究と同様の1つの血管壁研究でも見られたように、ICA遠位部、頭蓋内ICA分岐部、MCA M1区域はアテローム硬化性プラク塗効形成されやすい場所であった26-30。Corbanら10が実施した冠動脈の研究では、分岐部のずれ応力の低さがプラックの形成されやすさに関わっているとする仮説が立てられた。このようなプラックは破裂するリスクも高いため、将来に虚血性イベントを引き起こすリスクが高い。また、病変の大半はICA遠位部で発見されたが、本研究患者はすべて症候性MCA狭窄のため前方循環系に偏っていたという事実で説明がつくかもしれない。しかしながら18%の病変は前方循環系以外にあり、さらに多い67%の病変は無症候性で、責任病変の領域外にあった。

大部分の偏心性病変は限局性肥厚パターンであった。Swartzら17は初期研究でアテローム動脈硬化症を発症した患者の病変は限局性、偏心性であるのに対し、病態の異なる病変の発症および腫瘍性病変の発症においては血行障害の原因を示しており、本研究結果と一致する。症候性あるいは無症候性病変と造影効果の関連性は認められなかった。頭蓋内プラックの造影効果の報告に対する慢性骨はなく、病理組織学的に検証されていないため正確な機序は不明である22,26,31。造影剤投与後の画像が得られなかった患者がいること、またはほとんどの患者が慢性脳卒中患者であったが、造影効果を観察するための観察を示唆する。他の研究では、頭蓋内動脈の造影効果に異なる機序が関与していることを示唆すると思われる。

無症候性病変および症候性病変の形態学的特徴は異なっていた。無症候性病変はプラックが偏心性に分布していたが、症候性病変は偏心性と求心性の両方の特徴が見られた。求心性病変は血管壁の50%を超える（矢状断画像）ため、偏心性病変より進行していると思われる17。DSAで確認したMCA狭窄はすべて、ポジティブ／外周のリモデリングパターンであることも分かった。DSAに基づいて選択しなかった群で症候性および無症候性MCA狭窄のリモデリングパターンに差があるかは、興味深い研究テーマになりそうである。注意すべき興味深い点はこれらの病変の違いだけでなく、欧米人集団と中国人集団の病変の外観的な違いである21,26。中国人集団の病変は厚みがあって偏心性が多く、びまん性は少なかった。リスクの差の要因は民族によって異なるため、今後の研究でこの仮説を直接検証できれば面白そうである。

本研究にはいくつかの限界がある。第1に、画像の撮像野が限られていたため病変を見逃した可能性があり、特に後方循環系やさらに遠位の血管でそのおそれがある。したがって見つかった病変の数は実際のプラック量より少ないかもしれない。第2に、DSAで確認したMCA狭窄の存在により患者を選択したため、対象がアテローム硬化性狭窄症の患者に限られた。その結果、これで本研究で見つかったプラック分布の要因になったかもしれない。症候性MCA狭窄に基づく選択は、MRAと症候性／無症候性血管壁病変で認められた関連性の一因でもある。将来は、DSAで確認した狭窄のない患者または後方循環系脳卒中の患者を対象として、同様の分布パターンが存在するか、MRAと血管壁に同様の関連が持続するか解析しなければならない。第3に、異なる方法で患者を募集したため、本研究に急性期の偏心性の症状や患者または後方循環系脳卒中の患者を対象として、同様の分布パターンが存在するか、MRAと血管壁に同様の関連が持続するか調査しなければならない。
症候性中大脳動脈狭窄患者におけるプラークの形態,量,分布のMRI 画像

結論
症候性MCA狭窄患者の血管壁病変は,虚血性脳卒中と同様に,ほとんとICAの遠位部,ICAの頭蓋内分岐部,MCA M1区域に分布していた。また,頭蓋内のアテローム硬変性プラークは主に,偏心性構造,限局性肥厚バター,びまん性肥厚バターの形態変性と関連があった。つまり,病変の肥厚パターンと分布からなる分類体系は,病変内部の分布パターンのみで省略可能であることを意味する。最後に,無症候性病変は偏心性が多いが,症候性病変は特定の形態学的特性を持たなかった。将来,これによって症候性と無症候性のアテローム硬変病変を区別することができるかもしれない。

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情報開示
なし。

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