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. Patients suffering from intracranial atherosclerosis have a high subsequent stroke risk. 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. 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. 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.

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. 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.\textsuperscript{9} In 2014, Corban et al\textsuperscript{10} 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 coronaries.\textsuperscript{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.\textsuperscript{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.\textsuperscript{19} Several other, smaller studies have proposed specific intracranial plaque characteristics such as eccentricity and enhancement.\textsuperscript{17,20,21} Especially, enhancement is thought to be of importance for assessment of plaque vulnerability.\textsuperscript{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), and a time-of-flight magnetic resonance angiography (TOF-MRA) sequence. Before acquisition of the contrast-enhanced T\textsubscript{1w} 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 T\textsubscript{1w} VIRTA: field of view: 200×167×45 mm\textsuperscript{3}, acquired resolution: 0.6×0.6×1.0 mm\textsuperscript{3}, reconstructed resolution: 0.5×0.5×0.5 mm\textsuperscript{3} 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-DIRVEn 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).\textsuperscript{23} Scan parameters for the TOF-MRA sequence were as follows: field of view 200×200×56 mm\textsuperscript{3}, acquired resolution 0.4×0.6×0.7 mm\textsuperscript{3}, 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 T\textsubscript{1w} 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).\textsuperscript{22} 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.\textsuperscript{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.\textsuperscript{25}
Intracranial Symptomatic Plaque Morphology

Table 1. Demographics of 19 Patients With Ischemic Stroke or TIA

| Total (%) | Location | Right* | Left* | Total (n=57)* |
|-----------|----------|--------|-------|--------------|
| Age, mean (range), y | 67 (47–81) | 12 (63) | | | |
| Sex (male) | 2 (11) | | | | |
| TIA | 17 (89) | | | | |
| Ischemic stroke | 18 (95) | | | | |
| Cardioembolism | 1 (5) | | | | |
| Cardiovascular risk factors | | | | | |
| Any cardiovascular risk factor | 18 (95) | | | | |
| Systolic blood pressure (mm Hg±SD) | 155±30† | | | | |
| Hypertension | 15 (79) | | | | |
| Hyperlipidemia | 9 (47) | | | | |
| Diabetes mellitus | 6 (31) | | | | |
| Current smoker | 4 (21) | | | | |
| Atrial fibrillation | 1 (5) | | | | |

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 14 (25%) were diffuse (posterior cerebral artery, n=3; and posterior circulation, n=11). 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 2). 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 symptomatic 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

Table 2. Plaque Burden in 18 Patients With MCA Stenosis

| Location | Right* | Left* | Total (n=57)* |
|----------|--------|-------|--------------|
| Distal carotid segment | 6 | 3 | 9 |
| Bifurcation A1-M1-ICA | 4 | 5 | 9 |
| MCA | 10 | 17 | 27 |
| M1 segment | 9 | 13 | 22 |
| Bifurcation M1-M2 | 0 | 2 | 2 |
| M2 segment | 1 | 2 | 3 |
| Anterior cerebral artery | 0 | 2 | 2 |
| A1 segment | 0 | 1 | 1 |
| A2 segment | 0 | 1 | 1 |
| Basilar artery | 3 | 2 | 5 |
| Posterior cerebral artery | 2 | 5 | 7 |
| Bifurcation BA-P1 | 2 | 2 | 4 |
| P1 segment | 0 | 0 | 0 |
| P2 segment | 0 | 3 | 3 |
| Total number of lesions | 22 | 32 | 57 |

BA-P1 indicates bifurcation of the basilar artery-P1 segment; ICA, internal carotid artery; and MCA, middle cerebral artery.

*Number of lesions at location.
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 vasora get more abundant, and they may also develop in patients with pathologies like vasculitis, aneurysms, and atherosclerosis. When vasa vasora 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
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/asymptomatic 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**

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

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

*Number of lesions at location.

**Figure 3.** A 64-year-old male patient presented with a left partial anterior circulation infarct caused by a left middle cerebral artery (MCA) stenosis. **A,** Transverse time-of-flight magnetic resonance angiography shows a small stenosis in the left MCA (white arrow). **B,** On the transverse T1-weighted volumetric isotropically reconstructed turbo spin echo acquisition image, no corresponding vessel wall lesion was found (black arrow).

**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.
Sources of Funding

The work described in this article was supported by Lui Che Woo Foundation and grants from the Research Grants Council of the Hong Kong Special Administrative Region, China (SEG CUHK02). J.H. is supported by the Netherlands Organization for Scientific Research (NWO) under grant no. 91712322 and the European Research Council under grant agreements no. 637024.

Disclosures

None.

References

1. Arenillas JF. Intracranial atherosclerosis: current concepts. Stroke. 2011;42(suppl 1):S20–S23. doi: 10.1161/STROKEAHA.110.957278.

2. Kern R, Steinke W, Daffertshofer M, Prager R, Henrici M. Stroke recurrences in patients with symptomatic vs asymptomatic middle cerebral artery disease. Neurology. 2005;65:859–864. doi: 10.1212/01.wnl.0000175983.76110.59.

3. Lehrke S, Egenlauf B, Steen H, Lossnitzer D, Korosoglou G, Merten C, et al. Prediction of coronary artery disease by a systemic atherosclerosis score index derived from whole-body MR angiography. J Cardiovasc Magn Reson. 2009;11:36. doi: 10.1186/1532-429X-11-36.

4. Glagov S, Weisenberg E, Zarins CK, Stankunavicius R, Koletis GJ. Compensatory enlargement of human atherosclerotic coronary arteries. N Engl J Med. 1987;316:1371–1375. doi: 10.1056/NEJM198705283162204.

5. Kiehl S, Williet J. The natural course of atherosclerosis. Part II: vascular remodeling. Brueneck Study Group. Arterioscler Thromb Vasc Biol. 1999;19:1491–1498.

6. Cari S, Farb A, Pearce WH, Virmani R, Yao JS. Atherosclerotic plaque rupture in symptomatic carotid artery stenosis. J Vasc Surg. 1996;23:755–765, discussion 765.

7. Arroyo LH, Lee RT. Mechanisms of plaque rupture: mechanical and bio- logical interactions. Cardiovasc Res. 1999;41:369–375.

8. Falk E. Why do plaques rupture? Circulation. 1992;86(suppl 6):III30–III42.

9. Takaya N, Yuan C, Chu B, Saam T, Underhilt H, Cai J, et al. Association between carotid plaque characteristics and subsequent ischemic cerebrovascular events: a prospective assessment with MRI-initial results. Stroke. 2006;37:818–823. doi: 10.1161/01.STR.0000204638.91099.91.

10. Corban MT, Estebanri P, Suo J, McDaniel MC, Timmins LH, Rassoul-Arzrumy E, et al. Combination of plaque burden, wall shear stress, and plaque phenotype has incremental value for prediction of coronary atherosclerotic plaque progression and vulnerability. Atherosclerosis. 2014;232:271–276. doi: 10.1016/j.atherosclerosis.2013.11.049.

11. Stone GW, Maehara A, Lansky AJ, de Bruyne B, Cristea E, Mintz GS, et al; PROSPECT Investigators. A prospective natural-history study of coronary atherosclerosis. N Engl J Med. 2011;364:226–235. doi: 10.1056/NEJMoa1002558.

12. van der Kolk AG, Zwanenburg JJ, Brundel M, Biessels GJ, Visser F, Luijten PR, et al. Intracranial vessel wall imaging at 7.0-T MRI. AJNR Am J Neuroradiol. 2011;32:2259–2264. doi: 10.3174/ajnr.A3631.

13. Corbetta N, Vos P, van der Kolk AG, van Veluw SJ, Frings CJ, Harteveld AA, Luijten PR, et al. Patterns of intracranial vessel wall changes in relation to ischemic infarcts. Neurology. 2014;83:1316–1320. doi: 10.1212/ WNL.0000000000000868.

14. Qiao Y, Zeiler SR, Mirbagheri S, Leigh R, Urrutia V, Wityk R, et al. Intracranial plaque enhancement in patients with cerebrovascular events on high-spatial-resolution MR images. Radiology. 2014;271:534–542. doi: 10.1148/radiol.13122812.

15. Busse RF, Brau AC, Vu A, Michelich CR, Bayram E, Kijowski R, et al. Effects of refocusing flip angle modulation and view ordering in 3D fast spin echo. Magn Reson Med. 2008;60:640–649. doi: 10.1002/mrm.21680.

16. Kuijf HJ, van Veluw SJ, Viergever MA, Vincken KL, Biessels GJ. How to assess the reliability of cerebral microbleed rating? Front Aging Neurosci. 2013;5:57. doi: 10.3389/fnagi.2013.00057.

17. Adams HP Jr, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke. 1993;24:35–41.

18. Kolk AG Van Der, Zwanenburg JMJ, Brundel M, Biessels GJ, Visser F. Distribution and natural course of intracranial vessel wall lesions in patients with ischemic stroke or TIA at 7.0 tesla MRI. Eur Radiol 2015; 25:1692–700.

19. Chimowitz MI, Kokkinos J, Strong J, Brown MB, Levine SR, Silliman S, et al. The Warfarin-Aspirin Symptomatic Intracranial Disease Study. Neurology. 1995;45:1488–1493.

20. Mazighi M, Tanasescu R, Ducrocq X, Vicaut E, Bracard S, Houdart E, et al. Prospective study of symptomatic atherothrombotic intracranial stenoses: the GESICA study. Neurology. 2006;66:1187–1191. doi: 10.1212/01.wnl.0000208404.94585.b2.

21. Turan TN, Makki AA, Tsappidis S, Cotsonis G, Lynn MJ, Clotf HJ, et al; WASID Investigators. Risk factors associated with severity and location of intracranial arterial stenosis. Stroke. 2010;41:1636–1640. doi: 10.1161/STROKEAHA.110.584672.

22. Wang Y, Pu Y, Liu L, Wang Y, Zou X, Pan Y et al. Geographic and sex difference in the distribution of intracranial atherosclerosis in China. Stroke. 2013;44:2109–2114.

23. Skarpnatioktsis M, Mandell DM, Swartz RH, Tomilinson G, Mikulis DJ. Intracranial atherosclerotic plaque enhancement in patients with ischemic stroke. AJNR Am J Neuroradiol. 2013;34:299–304. doi: 10.3174/ ajnr.A3209.

24. Sluimer JC, Koldogid FD, Bijens AP, Maxfield K, Pacheco E, Kutsy B, et al. Thin-walled microvessels in human coronary atherosclerotic plaques show incomplete endothelial junctions relevance of compromised structural integrity for intraplaque microvascular leakage. J Am Coll Cardiol. 2009;53:1517–1527. doi: 10.1016/j.jacc.2008.12.056.

25. Qiao Y, Etesami M, Astor BC, Zeiler SR, Trout HH 3rd, Wasserman BA. Carotid plaque neo-vascularization and hemorrhage detected by MR imaging are associated with recent cerebrovascular ischemic events. AJNR Am J Neuroradiol. 2012;33:755–760. doi: 10.3174/ajnr.A2863.

26. Portanova A, Hakakian N, Mikulis DJ, Virmani R, Abdalla WM, Wasserman BA. Intracranial vasa vasorum: insights and implications for imaging. Radiology. 2013;267:667–679. doi: 10.1148/radiol.13122310.

27. Ritzi K, Denswil NP, Stamm OC, Van Lieshout JJ, Daemen MJ. Cause and mechanisms of intracranial atherosclerosis. Circulation. 2014;130:1407–1414. doi: 10.1161/CIRCULATIONAHA.114.011147.

28. van der Kolk AG, Zwanenburg JJ, Daemen MJ, Vink A, Splitter WG, Daemen MJ, et al. Imaging the intracranial atherosclerotic vessel wall using 7T MRI: initial comparison with histopathology. AJNR Am J Neuroradiol. 2015;36:694–701. doi: 10.3174/ajnr.A4178.

29. Majidi S, Sein J, Watanabe M, Hassan AE, Van de Moortele PF, Suris MF, et al. Intracranial-derived atherosclerosis assessment: in an vitro comparison between virtual histology by intravascular ultrasonography, 7T MRI, and histopathologic findings. AJNR Am J Neuroradiol. 2013;34:2259–2264. doi: 10.3174/ajnr.A3631.

30. Bogousslavsky J, Van Melle G, Regli F. The Lausanne Stroke Registry: analysis of 1,000 consecutive patients with first stroke. Stroke. 1988;19:1083–1092.
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*Stroke*. 2016;47:1797-1802; originally published online June 14, 2016; doi: 10.1161/STROKEAHA.116.013007

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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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 VRTA image shows an eccentric, focal plaque in the left MCA (arrows in B). Transverse T₁w VRTA 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).
日本語版

Vol. 11, No. 4

Stroke 日本語版 Vol. 11, No. 4

Full Article

磁気共鳴断層像検査によるアテローム性動脈硬化症の形態、量、分布のMRI画像

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

Nikki Dieleman, MSc1; Wenjie Yang, MD2; Jill M. Abrigo, MD3; Winnie Chiu Wing Chu, MD, PhD3; Anja G. van der Kolk, MD, PhD1; Jeroen C.W. Siero, PhD1; Ka Sing Wong, MD, PhD3; Jeroen Hendrikse, MD, PhD1; Xiang Yan Chen, MD, PhD2

1Department of Radiology, University Medical Center Utrecht, The Netherlands; and 2Department of Medicine and 3Department of Imaging and Interventional Radiology, Chinese University of Hong Kong, Shatin, Hong Kong SAR, China

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最大の原因である。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つつある分野である。本研究では、症候性中大脳動脈狭帯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 MRI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：中大脳動脈狭帯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、男性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強調ボリューム等方再構成ターボスピネークロエーフ法で実施した。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性動脈硬化症の鑑別が可能である。

Stroke. 2016; 47: 1797-1802. DOI: 10.1161/STROKEAHA.116.013007.
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

のブラーク分布は、MCA狭帯でのみ評価された数少ない特徴である。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の特定の頭蓋内ブラークの特徴を提起した。特に、ブラークの脆弱性の評価には造影効果が重要と考えられている。頭蓋内ブラーク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ブラーク形状の差を理解することも、リスクの判定および治療選択肢に有用であろう。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ブラークの総量を調査した。さらに、ブラーク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

被験者

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。すべての被験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狭帯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帯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。患者はあるいはMRI検査に耐えられること、MRIに対する禁忌を持つことなどが条件とされた。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。一部の被験者は、最も有用な撮像法を評価するため最新の撮像法とその他の3種類の血管壁撮像法を比較した新しい技術的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も報告した。

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。撮影は、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 VIRTA）で実施し、さらにタイム・オブ・フライト磁気共鳴血管造影法（TOF-MRA）を使用した。造影T1w VIRTA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 VIRTA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）、エコーパルス間隔4.0 ms、ターボスピンエコー+スタートアップエコー56+6、撮像時間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編成し、(脳脊髄液と血液の）循環抑制を高めた。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

画像はオン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7年）が解析した。2人目のオブザーバー（A.K., 経験7年）は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ついて盲検化されていた。T1w VIRTA画像上で、Willis動脈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（症候性及び無症候性の病変）によりスコア化評価した。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。DSAにより責任病変を確定したMCA狭帯は症候性病変とし、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。肥厚パターンは局所性またはびまん性のいずれかでスコア化し、「局所性」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）の特徴で分類した。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に漏斗を使用した。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。さまざまなブラークの形態学的特徴、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内相関係数と95％信頼区間を算出し、評価者間再現性の評価とされた。統計学的有意性はP<0.05に設定した。
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。⑤

表1 虚血性脳卒中またはTIA患者19例の背景

| 年齢（平均（範囲））, 歳 | 合計（%） |
|-------------------------|-----------|
| 性別（男性） | 12（63） |
| 診断 | 2（11） |
| TIA | 17（89） |
| 虚血性脳卒中 | 18（95） |
| 大血管のアテローム性動脈硬化 | 1（5） |
| 心塞栓 | 0 |
| 何らかの心血管危険因子 | 18（95） |

収縮期血圧（mm Hg）±SD: 155 ± 30 †
高血圧: 15（79）
高脂血症: 9（47）
糖尿病: 4（21）
喫煙: 6（31）
心房細動: 1（5）

| 検査 | 右* | 左* | 合計（n = 57）* |
|-------------------|-----|-----|----------------|
| ICA | 10 | 8 | 18 |
| MCA | 10 | 17 | 27 |
| A1-M1-ICA分岐部 | 4 | 5 | 9 |
| M1-M2分岐部 | 0 | 2 | 2 |
| M2分岐部 | 1 | 2 | 3 |
| 前大脳動脈 | 0 | 2 | 2 |
| A1分岐部 | 0 | 1 | 1 |
| A2分岐部 | 0 | 1 | 1 |
| 脳底動脈 | … | … | 3 |
| 後大脳動脈 | 2 | 5 | 7 |
| BA-P1分岐部 | 2 | 2 | 4 |
| P1分岐部 | 0 | 0 | 0 |
| P2分岐部 | 0 | 3 | 3 |
| 病変合計数 | 22 | 32 | 57 |

†15例の測定値が得られた。

Table 1: Background of ischemic stroke or TIA patients

Table 2: Plaque volume of MCA stenosis patients

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かった。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（全区域の12％）が観察された。このような投与後57病変中55病変（44％）に造影効果が認められ（図2）、43病変（75％）は偏心性、

図1

左側前方循環部分梗塞の72歳女性患者。A. T1-weighted volumetric isotropically reconstructed turbo spin echo横断像で、左後大脳動脈のP2区域に偏心性限局性病変が見つかった（矢印）。脳底動脈にも内腔狭窄のない（C矢印）偏心性限局性病変（B矢印）が見つかった。C. ダム・オブ・ライブMRA横断像には、血管壁病変と同じ場所にP2区域の無症候性狭帯が見える（矢印）。
症候性中大脳動脈狭窄患者におけるブラークの形態, 量, 分布の MRI 画像

表 3

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

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。
* その場所にある病変の数。

考察

本研究では、症候性 MCA 狭窄患者において、頭蓋内

图 2

左側の急性一過性脳虚血発作で来院した 78 歳女性患者。A. T1-weighted volumetric isotropically reconstructed turbo spin echo 横断像で、中大脳動脈の頭端性血管壁病変が両側に見つかった（A 矢印）。B. 右中大脳動脈（MCA）病変および（C）を MCA 病変の矢状断再構成画像から両側病変を示す因子であることが分かる。D. タイム・オブ・フライト MRA 横断像には、上記病変に一致する症候性の左 MCA 狭窄および無症候性の不規則な右 MCA 閉塞（D 矢印）が見られる。

14 病変（25%）は求心性であった。42 病変（74%）は限局性。15 病変（26%）はびまん性であった（表 3）。偏心性病変は限局性肥厚パターンと有意に関連し（図 2 およびオンラインデータ補遺図 1），求心性病変は前方循環系ブラークのびまん性肥厚パターンと有意に関連した（P < 0.001）。19 病変（33%）は症候性（MCA 病変，両側 1 例）, 38 病変（67%）が無症候性であった。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有意な関連（P < 0.05）が認められた（無症候性病変：偏心性 32，84% vs. 症候性病変：偏心性 11，58%）。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。症候性病変に特定の形態学的特徴はなかった。MRA で正常または不規則に見えた血管壁病変は無症候性が多く，狭苔または閉塞しているように見えた病変は症候性であった（P < 0.001，図 2）。MRA では 30 の病変が見つかり，26 病変は前方循環系，4 病変は後方循環系であった。観察した血管壁病変のほかに，30 の MRA 病変のうち 8 病変は血管壁画像で見えない病変であった。このうち 6 病変は不規則，1 病変は狭苔（図 3），1 病変は不規則/狭苔であった。狭苔していた 2 病変も症候性病変であった。

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もう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領域はアテローム硬化性プラーカが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、分岐部のずり応力の低さがプラーカの形成されやすさに関わっていると仮説が立てられた。このようなプラーカは破裂するリスクも高いため、将来的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、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、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性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、病態の異なる患者の病変はびまん性、求心性であることを示しており、本研究ではこれらの結果を確認した。

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ーカ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考えられる。DSAで確認したMCA狭窄はすべて、ピジティブ／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どうか、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はなく、欧米人集団と中国人集団の病変の外観的違いである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。リスクの層別基準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いであろう。

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漏れ、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。したがって見つかなかった病変の数は実際のプラーカ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。この結果、これが本研究で見つかったプラーカ分布の要因になったかもしれない。無症候性MCA狭窄に基づく選択は、MRAおよび症候性/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選択として、同様の分布パターンが存在するか、MRAと血管壁に同様の相関が持続するかも調査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、本研究には急性期と慢性期の2患者が含まれていた。そのため、脳卒中／TIAの発症からの間隔の範囲が異なる。造影効果とMCA狭窄に関連が見られなかった理由の一部は、これで説明される。しかしコントラスト増強の正確な機序について
は、なお確立する必要がある。また、使用した撮像法は試験的方法として追加したものであり、この方法で撮像した患者数は比較的少なかった。最後に、組織検査をしなかったため観察した病変すべてがリスクのある病変なのか、アテローム硬化に由来するものなのか、完全に血管壁病変なのかは定かでない。頭蓋外の動脈内膜切除術のような頭蓋外動脈病および脳の脳内病変検査は実施されていないので頭蓋内動脈の入手はかなり困難であり、そのため組織検査による確認は行わなかった。この分野ではWillis動脈輪の標本を使用した新しい研究が有望である。

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、ほとんどの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化性ブロックは主に、偏心性構造、限局性肥厚パターン、びまん性肥厚パターンの軽心性病変と関連があった。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解析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徴を持たなかった。将来、これによって症候性と無症候性のアテローム硬化病変を区別することができるかもしれない。

研究費財源
本論で述べた研究はLui Che Woo Foundationおよび香港特別行政区のResearch Grants Council(SEG-CUHK02)の助成を受けた。J.H.はNetherlands Organization for Scientific Research(NWO)の助成金no.91712322およびEuropean Research Councilの助成契約no.637024による支援を受けていた。

情報開示
なし。

References
1. Arenillas JF. Intracranial atherosclerosis: current concepts. Stroke. 2011;42(suppl 1):S20–S23. doi:10.1161/STROKEAHA.110.597278.
2. Kern R, Steinke W, Daughtersherfer M, Prager R, Hemmerci M. Stroke recurrences in patients with symptomatic vs asymptomatic middle cerebral artery disease. Neurology. 2005;65:859–864. doi:10.1212/01.wnl.0000175983.76101.59.
3. Lehrke S, Eigenlaub B, Steen H, Lossnitzer D, Korosoglou G, Mertens C, et al. Prediction of coronary artery disease by a systemic atherosclerosis score index derived from whole-body MR angiography. J Cardiovasc Magn Reson. 2009;11:36. doi:10.1186/1532-429X-11-36.
4. Glagow S, Weisenberg E, Zarins CK, Stankunavicius R, Koletis GI. Compensatory enlargement of human atherosclerotic coronary arteries. N Engl J Med. 1987;316:1371–1375. doi:10.1056/NEJM198705283162204.
5. Kiechl S, Willeit J. The natural course of atherosclerosis. Part II: vascular remodeling. Bruneck Study Group. Arterioscler Thromb Vasc Biol. 1999;19:1491–1498.
6. Carr S, Farb A, Pearce WH, Virmani R, Yao JS. Atherosclerotic plaque rupture in symptomatic carotid artery stenosis. J Vasc Surg. 1996;23:755–765. discussion 765.
7. Arroyo LH, Lee RT. Mechanisms of plaque rupture: mechanical and bio-logic interactions. Cardiovasc Res. 1999;41:369–375.
8. Falk E. Why do plaques rupture? Circulation. 1992;86(suppl 6):III-30–III42.
9. Takaya N, Yuan C, Chiu B, Saam T, Underhill H, Cai J, et al. Association between carotid plaque characteristics and subsequent ischemic cerebrovascular events: a prospective assessment with MRI-initial results. Stroke. 2006;37:818–823. doi:10.1161/01.STR.000020638.91099.91.
10. Corban MT, Eshtehardi P, Suo J, McDaniel MC, Timmins LH, Rassoul Azzarum E, et al. Combination of plaque burden, wall shear stress, and plaque phenotype has incremental value for prediction of coronary atherosclerotic plaque progression and vulnerability. Atherosclerosis. 2014;232:271–276. doi:10.1016/j.atherosclerosis.2013.11.049.
11. Stone GW, Maruha A, Lansky AJ, de Bruyne B, Cristea E, Mintz GS, et al. PROSPECT Investigators. A prospective natural-history study of coronary atherosclerosis. N Engl J Med. 2011;364:226–235. doi:10.1056/NEJMoai1002358.
12. van der Kolk AG, Zwanenburg JJ, Brundel M, Biessels GJ, Visser F, J.H. van der Kolk, A.L., Zwanenburg, J.J., Brundel, M., Biessels, G.J., Visser, F. (1996). Intracranial vessel wall imaging using high-resolution 3-tesla magnetic resonance imaging: initial comparison with histopathology. AJNR Am J Neuroradiol. 2011;32:22–30. doi:10.3174/ajnr.a22592.
13. Xu WH, Li ML, Gao S, Ni J, Zhou LX, Yao M, et al. In vivo high-resolution MR imaging of symptomatic and asymptomatic middle cerebral artery atherosclerotic stenosis. Stroke. 2010;41:212:507–511. doi:10.1161/j. jstroke.2010.06.035.
14. Chung GH, Kwak HS, Hwang SB, Jin GY. High resolution MRI imaging in patients with symptomatic middle cerebral artery stenosis. Eur J Radiol. 2012;81:4069–4074. doi:10.1016/j.ejrad.2012.07.001.
15. Swartz RH, Bhutta SS, Farb RI, Agid R, Willinsky RA, Terbrugge KG, et al. Intracranial arterial wall imaging using high-resolution 3-tesa contrast-enhanced MRI. Neurology. 2009;72:627–634. doi:10.1212/ WNL.0b013e3181e73933.
16. Dieelenman N, van der Kolk AG, Zwanenburg JJ, Harteveld AA, Biessels GJ, Luijten PR, et al. Imaging intracranial vessel wall pathology with magnetic resonance imaging: current prospects and future directions. Circulation. 2014;130:192–201. doi:10.1161/CIRCULATIONAHA.113.069619.
17. Zhu XJ, Du B, Lou X, Hui FK, Ma L, Zheng BW, et al. In vivo high-reso- lution MR imaging of symptomatic and asymptomatic middle cerebral artery atherosclerotic stenosis. Atherosclerosis. 2010;212:507–511. doi:10.1016/j. atherosclerosis.2010.06.035.
18. Dieelenman N, van der Kolk AG, van Veluw SJ, Frijns CJ, Harteveld AA, Luijten PR, et al. Patterns of intracranial vessel wall changes in relation to ischemic infarcts. Neurology. 2014;83:1316–1320. doi:10.1212/WNL.0000000000000868.
19. Qiao Y, Zeiler SR, Mirbagheri S, Leigh R, Urrutia V, Wityk R, et al. Intracranial plaque enhancement in patients with cerebrovascular events on high-spatial-resolution MR images. Radiology. 2014;271:534–542. doi:10.1148/radiol.13112812.
20. Busse RF, Brau AC, Vu A, Micheli CR, Bayram E, Kijowski R, et al. Effects of refocusing flip angle modulation and view ordering in 3D fast spin echo. Magn Reson Med. 2008;60:640–649. doi:10.1002/mrm.21680.
21. Kuijf HJ, van Veluw SJ, Viergever MA, Vincken KL, Biessels GJ. How to assess the reliability of cerebral microbleed rating? Front Aging Neurosci. 2013;5:57. doi:10.3389/fnagi.2013.00057.
22. Adams HP Jr, Bendixen BH, Kappelle LJ, Bütler I, Love BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke. 1993;24:35–41.
23. Kolk AG Van Der, Zwanenburg JJM, Brundel M, Biessels GJ, Visser F. Distribution and natural course of intracranial vessel wall lesions in
patients with ischemic stroke or TIA at 7.0 tesla MRI. *Eur Radiol* 2015; 25:1692–700.

27. Chimowitz MI, Kokkinos I, Strong J, Brown MB, Levine SR, Silliman S, et al. The Warfarin-Aspirin Symptomatic Intracranial Disease Study. *Neurology*. 1995;45:1488–1493.

28. Mazighi M, Tanasescu R, Ducrocq X, Vicaut E, Bracard S, Houdart E, et al. Prospective study of symptomatic atherothrombotic intracranial stenoses: the GESICA study. *Neurology*. 2006;66:1187–1191. doi: 10.1212/01.wnl.0000208404.94585.h2.

29. Turan TN, Makki AA, Tsuupridi S, Cotonnis G, Lynn MJ, Cloft HJ, et al; WASID Investigators. Risk factors associated with severity and location of intracranial arterial stenosis. *Stroke*. 2010;41:1636–1640. doi: 10.1161/STROKEAHA.110.584672.

30. Wang Y, Pu Y, Liu L, Wang Y, Zou X, Pan Y et al. Geographic and sex difference in the distribution of intracranial atherosclerosis in China. *Stroke*. 2013;44:2109–2114.

31. Skarpathiotakis M, Mandell DM, Swartz RH, Tomlinson G, Mikulis DJ. Intracranial atherosclerotic plaque enhancement in patients with ischemic stroke. *AJNR Am J Neuroradiol*. 2013;34:299–304. doi: 10.3174/ajnr.A3209.

32. Shimri JC, Kolodgie FD, Bijnens AP, Maxfield K, Pacheco E, Kutys B, et al. Thin-walled microvessels in human coronary atherosclerotic plaques show incomplete endothelial junctions relevance of compromised structural integrity for intraplaque microvascular leakage. *J Am Coll Cardiol*. 2009;53:1517–1527. doi: 10.1016/j.jacc.2008.12.056.

33. Qiao Y, Etesami M, Astor BC, Zeiler SR, Trout HH 3rd, Wasserman BA. Carotid plaque neovascularization and hemorrhage detected by MR imaging are associated with recent cerebrovascular ischemic events. *AJNR Am J Neuroradiol*. 2012;33:755–760. doi: 10.3174/ajnr.A2863.

34. Portanova A, Hakakian N, Mikulis DJ, Virmani R, Abdalla WM, Wasserman BA. Intracranial vasa vasorum: insights and implications for imaging. *Radiology*. 2013;267:667–679. doi: 10.1148/radiol.13112310.

35. Ritz K, Denswil NP, Stam OC, van Lieshout JJ, Daemen MJ. Cause and mechanisms of intracranial atherosclerosis. *Circulation*. 2014;130:1407–1414. doi: 10.1161/CIRCULATIONAHA.114.011147.

36. van der Kolk AG, Zwanenburg JJ, Denswil NP, Vink A, Spliet WG, Daemen MJ, et al. Imaging the intracranial atherosclerotic vessel wall using 7T MRI: initial comparison with histopathology. *AJNR Am J Neuroradiol*. 2015;36:694–701. doi: 10.3174/ajnr.A4178.

37. Majidi S, Sein I, Watanabe M, Hassan AE, Van de Moortele PF, Suri MF, et al. Intracranial-derived atherosclerosis assessment: an in vitro comparison between virtual histology by intravascular ultrasonography, 7T MRI, and histopathologic findings. *AJNR Am J Neuroradiol*. 2013;34:2259–2264. doi: 10.3174/ajnr.A3631.

38. Bogousslavsky J, Van Melle G, Regli F. The Lансanne Stroke Registry: analysis of 1,000 consecutive patients with first stroke. *Stroke*. 1988;19:1083–1092.