Atherosclerosis in stroke-related vascular beds and stroke risk: A 3-D MR vessel wall imaging study

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Abstract
Objectives: To investigate the characteristics of atherosclerotic plaques in stroke-related vascular beds and their relationship with stroke using three-dimensional magnetic resonance (MR) vessel wall imaging. Methods: Fifty-two symptomatic patients (mean age: 56.3 ± 13.4 years; 38 males) were enrolled and underwent MR vessel wall imaging for stroke-related vascular beds including intracranial and extracranial carotid arteries and aortic arch and routine MR imaging for brain. The maximum wall thickness (Max WT) and luminal stenosis of each plaque were measured. The presence/absence of atherosclerotic plaque, intraplaque hemorrhage (IPH), and severe stenosis (stenosis >50%) at each vascular bed and acute ischemic lesion (AIL) were determined. The correlation between Max WT of each vascular bed and AIL was analyzed. Results: Of 52 patients, 24 (46.2%) had AILs, and 30 (57.7%), 34 (65.4%), and 11 (21.2%) had plaques in intracranial artery, extracranial carotid artery, and aortic arch, respectively. The prevalence of IPH and severe stenosis was 25% and 26.9% for intracranial arteries, 13.5% and 9.6% for extracranial carotid artery, and 3.8% and 0% for aortic arch, respectively. The prevalence of IPH and severe stenosis was 25% and 26.9% for intracranial arteries, 13.5% and 9.6% for extracranial carotid artery, and 3.8% and 0% for aortic arch, respectively. In discriminating AIL, Max WT of intracranial artery had the highest area-under-the-curve (AUC = 0.84), followed by extracranial carotid artery (AUC = 0.83) and aortic arch (AUC = 0.78) after adjusted for confounding factors. The AUC of Max WT combined three stroked-related vascular beds reached 0.87. Conclusion: Extracranial carotid arteries have the highest prevalence of plaques and intraplaque hemorrhage and severe stenosis are most frequently seen in intracranial arteries in Asian symptomatic patients. The Max WT combined three stroke-related vascular beds show stronger predictive value for AIL than each vascular bed alone.

Introduction
Atherosclerotic disease occurring in craniocervical arteries including intracranial and extracranial arteries and aortic arch is the major cause of ischemic cerebrovascular events, such as stroke and transient ischemia attack (TIA).1–3 Increasing evidences have shown that coexisting intracranial and extracranial carotid artery atherosclerosis had stronger predictive value for recurrent stroke risk.4,5 However, most of previous studies investigating relationship between atherosclerotic plaques and ischemic stroke were focused on single or two vascular beds due to the lack of comprehensive assessment tool. The characteristics of plaque distribution among these three stroke-related vascular beds in the same patient group remained unclear. Therefore, it is important to evaluate the distribution...
characteristics of atherosclerotic plaques in the entire stroke-related vascular beds for stroke prevention.

For characterizing cerebrovascular atherosclerotic diseases, angiographic approaches, such as computed tomography (CT) and magnetic resonance (MR) angiography are still widely used in clinical settings. However, luminal narrowing measured by angiography usually underestimates the disease severity due to positive remodeling effect and lacking of compositional information, particularly intraplaque hemorrhage, which is critical for the assessment of plaque vulnerability. Transesophageal echocardiography (TEE) can be utilized for detecting atherosclerotic plaques in aortic arch but this imaging technique is invasive. It is well established that MR vessel wall imaging is capable of characterizing carotid artery atherosclerosis validated by histology. Recently, investigators proposed three-dimensional (3-D) MR vessel wall imaging sequences which enable high isotropic resolution plaque imaging with large longitudinal coverage for craniocervical arteries and aortic arch. These emerging 3-D MR vessel wall imaging techniques might be appropriate imaging modalities for the identification of coexisting atherosclerotic diseases in stroke-related vascular beds.

This study sought to investigate the plaque distribution and morphological characteristics in three stroke-related vascular beds and their relationship with ischemic stroke in patients with recent symptoms using 3-D MR vessel wall imaging.

**Materials and Methods**

**Study population**

In total, 57 patients (mean age, 56.8 ± 13.8 years; range age: 23–81 years; 42 males) who had recent cerebrovascular symptoms (stroke or TIA <2 weeks) from July 2015 to December 2016 were enrolled and underwent multi-contrast MR vessel wall imaging for intracranial and extracranial carotid arteries and aortic arch. The exclusion criteria include: (1) hemorrhagic stroke; (2) cardiogenic embolism (atrial fibrillation, vascular heart disease, etc.); (3) critical conditions such as heart failure and coma; (4) claustrophobia; and (5) contraindications to MR examination. Demographic and clinical characteristics including age, gender, history of hypertension, smoke, hyperlipidemia, diabetes, and coronary heart disease were collected from clinical record. The levels of high density lipoprotein (HDL), low density lipoprotein (LDL), total cholesterol (TC), and triglyceride (TG) were also recorded. The study protocol was approved by institutional review board and written consent form was obtained from each subject.

**MR imaging**

All MR imaging was conducted on a whole body 3.0T MR scanner (Achieva TX, Philips Healthcare, Best, The Netherlands) with custom-designed 36-channel neurovascular coil (intracranial artery and extracranial carotid artery imaging) and cardiac 32-channel coil (aortic arch imaging) at Center for Biomedical Imaging Research of Tsinghua University. The entire craniocervical arteries were imaged by using multi-contrast vessel wall imaging protocol that includes three sections: (1) intracranial artery: 3D T1-VISTA and 3D SNAP sequences; (2) extracranial carotid artery: 3D MERGE and 3D SNAP sequences; (3) aortic arch: 3D PD-VISTA and 3D SNAP sequences. The detailed imaging parameters are listed in the Table 1. A routine protocol was performed to acquire the axial images of brain with the following parameters: (1) fluid attenuated inversion recovery (FLAIR), turbo spin echo (TSE), repeat time (TR)/echo time (TE) 7000/140 msec, flip angle 120°, field of view (FOV) 230 mm × 230 mm, spatial resolution 0.9 mm × 0.9 mm, and scan time 1 min52 sec; (2) T2-weighted (T2W), TSE, TR/TE 3005/90 msec, flip angle 90°, FOV 230 mm × 230 mm, spatial resolution 0.7 mm × 0.7 mm, and scan time 57 sec; and (3) diffusion weighted imaging (DWI), echo planar imaging (EPI), TR/TE 2858/94 msec, flip angle 90°, FOV 230 × 230 mm, spatial resolution 1.8 × 1.5 mm, and scan time 32 sec.

**Image analysis**

The intracranial artery, extracranial carotid artery, and aortic arch MR images were reviewed by two experienced radiologists (D. L. and Y.C.) who had >3 years of experience in vascular imaging with consensus using a custom-designed software dedicated for 3-D MR vessel wall imaging. The image quality of each axial slice reconstructed from the 3-D vessel wall imaging data perpendicular to the arterial center line was rated using 4-point scales according to the sharpness and contrast between vessel wall and the surrounding CSF/blood by eyeballing: 1, poor; 2, marginal; 3, good; and 4, excellent. The MR images with image quality ≥2 were interpreted. If the image quality is poor for a specific slice, this slice will not be analyzed. But the rest slices with acceptable image quality of this artery will be kept for analysis. If more than 1/3 of slices of one artery had poor image quality in any one imaging sequence of T1-VISTA, MERGE, and PD-VISTA, which are critical for determining presence and size of atherosclerotic plaques, the whole artery will be excluded.

The vascular bed territories were categorized as anterior circulation of intracranial arteries (A1 segment of anterior
cerebral artery, M1 segment of middle cerebral artery), posterior circulation of intracranial arteries (P1 segment of posterior cerebral artery and basilar artery), extracranial internal carotid artery, common carotid artery, and aortic arch. Since the overall image quality of cavernous sinus segment of intracranial internal carotid artery is poor due to the B1 inhomogeneity and bone structure, this arterial segment was not analyzed. The boundaries of lumen and outer wall in the entire craniofacial arteries and aortic arch on black-blood MR imaging were outlined manually by using custom-designed software of 3D CASCADE. The presence or absence of atherosclerotic plaque and IPH was determined at each vascular bed with consensus by two radiologists. The presence of atherosclerotic plaque or IPH in each vascular territory was defined if there is at least one plaque or IPH in the corresponding vascular bed. The maximum wall thickness of each vascular territory was measured no matter there is atherosclerotic plaque or not. Atherosclerotic plaque was defined as eccentric wall thickening with or without luminal stenosis seen on MR angiography. The IPH was defined as hyperintense compared to adjacent muscle (signal intensity ratio ≥1.5:1) on SNAP imaging. The luminal stenosis was measured using WASID criteria for intracranial arteries and NASCET criteria for extracranial carotid arteries on SNAP angiography. The presence or absence and the lesion volume of acute ischemic lesions (AIL) on DWI images were evaluated.

Reproducibility study

Ten subjects were randomly selected to determine the inter-observer and intra-observer reproducibility in identification of the presence of plaque and IPH at each vascular bed. The maximum wall thickness of each vascular bed was also measured for 10 subjects. A time interval of 3 months was set for testing the intra-observer reproducibility to minimize the bias of memory.

Statistical analysis

The continuous variables were described as mean value and the corresponding standard deviation (SD) and the categorical variables were presented as frequency. Clinical characteristics were compared between patients with single and multiple atherosclerotic plaques in each vascular territory using independent t test or Mann-Whitney U test when appropriate. The prevalence of atherosclerotic plaque, IPH and severe stenosis (>50% stenosis) of plaque in intracranial arteries, extracranial carotid arteries, and aortic arch was determined. Independent t test and Mann-Whitney U test were utilized to compare the maximum wall thickness, number of plaques and IPH in each vascular territory between patients with and without AIL when appropriate. Logistic regression was utilized to calculate the odds ratio (OR) and corresponding 95% confidence interval (CI) of maximum wall thickness, number of plaque and IPH in each vascular territory in discriminating presence of AIL. The ROC analysis was conducted to calculate the area-under-the-curve of the maximum wall thickness of single vascular territory and combined maximum wall thickness of all vascular territories in predicting AIL. Cohen’s kappa was analyzed to determine the inter-observer and intra-observer agreement in identification of arterial plaque, IPH, and severe stenosis of artery with plaque. The intra-class correlation coefficient (ICC) and Bland-Altman analysis were used to assess the inter-observer and intra-observer agreements in quantitatively measuring the maximum wall thickness. A P < 0.05 was considered as statistically significant. All statistical

Table 1. MR imaging protocol for stroke-related vascular beds.

| Stroke-related vascular beds | Intracranial artery | Carotid artery | Aortic arch |
|-----------------------------|---------------------|---------------|------------|
| T1-VISTA | TSE | MERGE | TSE | TSE | PD-VISTA |
| SNAP | TFE | SNAP | TFE | TFE | SNAP |
| Black-blood | DANTE | iMSDE | FSD | TSE |
| TR/TE, ms | 800/20 | 9.3/4.3 | 1000/20 | 9.4/5.3 |
| Flop angle | 90° | 6° | 90° |
| Field of view, cm² | 20 x 16 x 4 | 20 x 16 x 4 | 25 x 16 x 9 |
| In-plane resolution, mm | 0.8 x 0.8 | 0.8 x 0.8 | 1.25 x 1.25 |
| Slice thickness, mm | 0.8 | 0.8 | 1.8 |
| NEX | 1 | 1 | 1 |
| Scan time | 6 min 17 sec | 3 min 12 sec | 8 min 9 sec |

TSE, turbo spin echo; FFE, fast field echo; DANTE, delay alternating with nutation for tailored excitation; iMSDE, improved motion-sensitized driven-equilibrium; FSD, flow-sensitive dephasing; NEX, number of excitation.
analyses were performed using SPSS 16.0 (SPSS Inc. Chicago, IL, USA).

Results

Of 57 patients with recent cerebrovascular symptoms (<2 weeks) enrolled in this study, five were excluded due to poor image quality. Of the remaining 52 patients with acceptable image quality, the mean age was 56.3 ± 13.4 years, 73.1% (38/52) are males, 65.4% (34/52) had hypertension, 26.9% (14/52) had diabetes, 59.6% (28/52) had hyperlipidemia, and 53.8% (28/52) had history of smoking. The clinical characteristics of this study population and their differences between patients with single and multiple plaques in three vascular beds are summarized in Table 2. Patients with multiple atherosclerotic plaques in intracranial arteries showed significantly higher diastolic blood pressure (DBP) compared with those with single intracranial plaque (94.0 ± 18.0 mmHg vs. 79.6 ± 16.0 mmHg, \( P = 0.042 \)). There were no significant differences in all other clinical characteristics in patients with single and multiple plaques in any vascular bed (all \( P > 0.05 \)).

Characteristics of plaques in intracranial, extracranial carotid artery, and aortic arch

In this study population, the prevalence of intracranial artery, carotid artery, and aortic arch atherosclerotic plaques was 57.7% (30/52), 65.4% (34/52), and 21.2% (11/52), respectively (Fig. 1). The total number of plaques in intracranial artery, carotid artery, and aortic arch was 72, 58, and 14, respectively. The prevalence of plaque number in different vascular bed is presented in Figure 2. Co-existing intracranial and extracranial carotid artery plaques were found in 32.7% (17/52) patients, of which seven patients also had plaques in aortic arch. The prevalence of severe stenosis and IPH was 25% (13/52) and 26.9% (14/52) for intracranial arteries, 13.5% (7/52) and 9.6% (6/52) for extracranial carotid arteries, and 0% (0/52) and 3.8% (2/52) for aortic arch, respectively (Fig. 1).

Correlation between plaque characteristics and AILs

Of 52 patients, 46.2% (24/52) had cerebral AILs, 21.2% (11/52) had AILs in the territory of anterior circulation, 11.5% (6/52) had AILs in both territories of anterior and posterior circulation, and 13.5% (7/52) had AILs in posterior circulation only. The mean value of maximum wall thickness for intracranial arteries, extracranial carotid arteries and aortic arch was 1.3 ± 0.4 mm, 3.1 ± 1.2 mm, and 4.9 ± 1.5 mm, respectively. The mean value of maximum wall thickness for patients with and without atherosclerotic plaque was 1.6 ± 0.4 mm and 1.2 ± 0.3 mm for intracranial arteries, 3.9 ± 1.6 mm and 2.8 ± 0.6 mm for extracranial carotid arteries, and 6.0 ± 2.4 mm and 4.5 ± 0.8 mm for aortic arch, respectively. In discriminating presence of AIL, the OR of maximum wall thickness was 6.59 (95% CI, 1.08–40.3, \( P = 0.04 \)) for intracranial arteries and 1.81 (95% CI, 1.06–3.08, \( P = 0.03 \)) for extracranial carotid arteries, respectively. After adjusted for both stenosis and confounding factors, including age, gender, BMI, history of hypertension, smoking, diabetes, and LDL, HDL, TG, these associations remained statistically significant (all \( P < 0.05 \), Table 3). No significant correlations were found between AILs and the number of plaque and IPH in intracranial artery, extracranial carotid artery, and aortic arch (all \( P > 0.05 \), Table 3). No significant correlation was found between AILs and the maximum wall thickness of aortic arch (\( P > 0.05 \), Table 3).

ROC analysis

Table 4 summarized the results of ROC analysis for predicting AILs with stroke-related vascular atherosclerosis. In predicting AILs, the maximum wall thickness of extracranial carotid artery had the highest AUC (0.71, 95% CI, 0.57–0.93), followed by intracranial artery and aortic arch (Fig. 3A). After adjusted for confounding factors, in predicting AILs, the maximum wall thickness in intracranial artery had the highest AUC (0.84, 95% CI, 0.70–0.93), followed by extracranial carotid artery and aortic arch (Fig. 3B).

Before adjustment for confounding factors, in predicting AILs, the maximum wall thickness of combined intracranial and extracranial carotid arteries had the highest AUC (0.77; 95% CI, 0.63–0.88), followed by combined intracranial and extracranial carotid arteries and aortic arch, combined intracranial and aortic arch and combined extracranial carotid artery and aortic arch (Fig. 3C). After adjustment for confounding factors, the AUC of maximum wall thickness of combined intracranial and extracranial carotid arteries and aortic arch reached 0.87 (95% CI, 0.74–0.95), followed by combined intracranial with extracranial carotid arteries, combined intracranial and aortic arch and combined extracranial carotid artery and aortic arch (Fig. 3D). Figure 4 represents examples for patients with atherosclerotic plaques in three stroke-related vascular beds on MR vessel wall imaging and AIL.

Reproducibility

For intra-observer agreement in identification of the presence of atherosclerotic plaque, the kappa value was 1.00,
### Table 2. Clinical characteristics of study population and their difference between patients with single and multiple plaques in intra- and extracranial carotid artery and aortic arch (n = 52).

|                      | Intracranial artery | Extracranial carotid artery | Aortic arch |
|----------------------|---------------------|-----------------------------|-------------|
|                      | Intra | Extru | Aortic | P     | Intra | Extru | Aortic | P     | Intra | Extru | Aortic | P     |
| Age, years           | 56.3 ± 13.4 60.4 ± 12.3 61.4 ± 10.1 | 54.0 ± 13.0 63.4 ± 12.3 | 66.3 ± 9.4 65.5 ± 5.0 | 0.874 | 15 (83.3) 10 (75) | 0.163 | 6 (66.7) 2 (100) | 0.512 | 140.7 ± 27.1 140.0 ± 14.1 | 0.109 | 75.7 ± 8.9 70 ± 14.1 | 0.152 | 1.1 ± 0.3 1.2 ± 0.2 | 0.552 | 2.6 ± 1.1 2.8 ± 1.5 | 0.734 | 2.0 ± 1.6 1.0 ± 0.2 | 0.357 | 4.4 ± 1.2 4.7 ± 1.8 | 0.905 | 2 (22.2) 1 (50) | 0.582 |
| Gender, male         | 438 (73.1) 6 (60) 14 (70) | 15 (83.3) 10 (75) | 6 (66.7) 2 (100) | 0.442 | 150.8 ± 24.6 143.4 ± 23.7 | 0.484 | 140.7 ± 27.1 140.0 ± 14.1 | 0.109 | 75.7 ± 8.9 70 ± 14.1 | 0.152 | 1.1 ± 0.3 1.2 ± 0.2 | 0.552 | 2.6 ± 1.1 2.8 ± 1.5 | 0.734 | 2.0 ± 1.6 1.0 ± 0.2 | 0.357 | 4.4 ± 1.2 4.7 ± 1.8 | 0.905 | 2 (22.2) 1 (50) | 0.582 |
| SBP, mmHg            | 144.9 ± 33.2 139.0 ± 15.0 155.4 ± 27.8 | 150.8 ± 24.6 143.4 ± 23.7 | 140.7 ± 27.1 140.0 ± 14.1 | 0.173 | 92.8 ± 16.8 81.0 ± 16.6 | 0.422 | 75.7 ± 8.9 70 ± 14.1 | 0.152 | 1.04 ± 0.4 1.27 ± 0.4 | 0.232 | 2.2 ± 1.0 3.1 ± 1.3 | 0.230 | 1.5 ± 1.0 1.3 ± 0.7 | 0.986 | 2.0 ± 1.6 1.0 ± 0.2 | 0.357 | 3.9 ± 1.4 4.8 ± 1.5 | 0.162 | 4.4 ± 1.2 4.7 ± 1.8 | 0.905 | 2 (22.2) 1 (50) | 0.582 |
| DBP, mmHg            | 85.9 ± 22.9 79.6 ± 16.0 94.0 ± 18.0 | 92.8 ± 16.8 81.0 ± 16.6 | 75.7 ± 8.9 70 ± 14.1 | 0.042 | 1.04 ± 0.4 1.27 ± 0.4 | 0.232 | 2.2 ± 1.0 3.1 ± 1.3 | 0.230 | 1.5 ± 1.0 1.3 ± 0.7 | 0.986 | 2.0 ± 1.6 1.0 ± 0.2 | 0.357 | 3.9 ± 1.4 4.8 ± 1.5 | 0.162 | 4.4 ± 1.2 4.7 ± 1.8 | 0.905 | 2 (22.2) 1 (50) | 0.582 |
| HDL, mmol/L          | 1.1 ± 0.3 1.2 ± 0.3 1.2 ± 0.4 | 1.04 ± 0.4 1.27 ± 0.4 | 1.1 ± 0.3 1.2 ± 0.2 | 0.552 | 2.6 ± 1.1 2.8 ± 1.5 | 0.734 | 2.0 ± 1.6 1.0 ± 0.2 | 0.357 | 4.4 ± 1.2 4.7 ± 1.8 | 0.905 | 2 (22.2) 1 (50) | 0.582 |
| LDL, mmol/L          | 2.6 ± 1.4 3.1 ± 1.2 2.5 ± 1.3 | 2.2 ± 1.0 3.1 ± 1.3 | 2.6 ± 1.1 2.8 ± 1.5 | 0.734 | 1.5 ± 1.0 1.3 ± 0.7 | 0.986 | 2.0 ± 1.6 1.0 ± 0.2 | 0.357 | 4.4 ± 1.2 4.7 ± 1.8 | 0.905 | 2 (22.2) 1 (50) | 0.582 |
| TG, mmol/L           | 3.9 ± 1.6 1.4 ± 0.5 1.4 ± 1.2 | 1.5 ± 1.0 1.3 ± 0.7 | 2.0 ± 1.6 1.0 ± 0.2 | 0.357 | 3.9 ± 1.4 4.8 ± 1.5 | 0.162 | 4.4 ± 1.2 4.7 ± 1.8 | 0.905 | 2 (22.2) 1 (50) | 0.582 |
| TC, mmol/L           | 5.4 ± 3.2 4.8 ± 1.3 4.3 ± 1.6 | 3.9 ± 1.4 4.8 ± 1.5 | 4.4 ± 1.2 4.7 ± 1.8 | 0.905 | 2 (22.2) 1 (50) | 0.582 |
| Current smoker       | 28 (53.8) 1 (10) 5 (25) | 5 (27.8) 2 (12.5) | 2 (22.2) 1 (50) | 0.412 | 11 (61.1) 11 (68.75) | 0.601 | 7 (77.8) 2 (100) | 0.661 | 3 (33.3) 1 (50) | 0.624 | 5 (55.6) 2 (100) | 0.381 | 2 (22.2) 0 (0) | 0.656 |
| Hypertension         | 34 (65.4) 8 (80) 15 (75) | 11 (61.1) 11 (68.75) | 7 (77.8) 2 (100) | 0.569 | 3 (16.7) 5 (31.25) | 0.312 | 3 (33.3) 1 (50) | 0.624 | 5 (55.6) 2 (100) | 0.381 | 2 (22.2) 0 (0) | 0.656 |
| Diabetes             | 14 (26.9) 3 (30) 5 (25) | 3 (16.7) 5 (31.25) | 3 (33.3) 1 (50) | 0.547 | 9 (47.3) 12 (75) | 0.171 | 5 (55.6) 2 (100) | 0.381 | 2 (22.2) 0 (0) | 0.656 |
| Hyperlipidemia       | 28 (53.8) 5 (50) 11 (55) | 9 (47.3) 12 (75) | 5 (55.6) 2 (100) | 0.801 | 2 (1.1) 3 (18.75) | 0.442 | 2 (22.2) 0 (0) | 0.656 |
| History of CVD       | 6 (11.5) 1 (10) 3 (15) | 2 (1.1) 3 (18.75) | 2 (22.2) 0 (0) | 0.587 | 2 (1.1) 3 (18.75) | 0.442 | 2 (22.2) 0 (0) | 0.656 |

SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, High-density lipoprotein cholesterol; LDL, Low-density lipoprotein cholesterol; TG, triglycerides; TC, total cholesterol; CVD, cardiovascular disease.
Figure 1. Prevalence of plaque features in different vascular bed.

Figure 2. Prevalence of plaque number in different vascular bed.
Table 3. Correlation between stroke-related vascular plaque burden and AIL.

| Presence of AIL | Univariate regression | Multivariate regression[^1] |
|----------------|-----------------------|-----------------------------|
|                | OR  | 95% CI | P value | OR  | 95% CI | P value |
| Maximum wall thickness |     |        |         |     |        |         |
| Intracranial artery  | 6.59| 1.08–40.3 | 0.041 | 12.31| 1.23–123.8 | 0.028 |
| Extracranial carotid artery  | 1.81| 1.06–3.08 | 0.031 | 3.29 | 1.14–9.47 | 0.035 |
| Aortic arch          | 1.60| 0.95–2.69 | 0.078 | 1.55 | 0.79–3.05 | 0.202 |
| The number of plaque |     |        |         |     |        |         |
| Intracranial artery  | 1.14| 0.79–1.64 | 0.487 | 1.26 | 0.76–2.01 | 0.383 |
| Extracranial carotid artery  | 1.34| 0.79–2.28 | 0.282 | 1.08 | 0.55–2.12 | 0.821 |
| Aortic arch          | 1.14| 0.43–3.03 | 0.791 | 0.89 | 0.20–3.91 | 0.878 |
| The number of IPH    |     |        |         |     |        |         |
| Intracranial artery  | 0.39| 0.87–1.71 | 0.212 | 2.86 | 0.51–16.61 | 0.232 |
| Extracranial carotid artery  | 1.91| 0.57–6.34 | 0.301 | 0.80 | 0.15–4.21 | 0.794 |
| Aortic arch          | 1.17| 0.69–19.83 | 0.842 | 0.92 | 0.03–23.83 | 0.844 |

[^1]: Adjustments for age, gender, body mass index, smoke, hypertension, diabetes, high-density lipoprotein, low-density lipoprotein, total cholesterol, and glycerides.

Table 4. ROC analysis for predicting AIL with stroke-related vascular atherosclerosis.

| Presence of AIL | Before adjustment | After adjustment[^1] |
|----------------|-------------------|----------------------|
|                | AUC  | 95% CI | AUC  | 95% CI |
| Maximum wall thickness |     |        |     |        |
| Intracranial artery  | 0.70| 0.56–0.82 | 0.84 | 0.70–0.93 |
| Extracranial carotid artery  | 0.71| 0.57–0.83 | 0.83 | 0.70–0.92 |
| Aortic arch          | 0.62| 0.46–0.74 | 0.78 | 0.63–0.88 |
| Intra- and extracranial carotid arteries | 0.77| 0.63–0.88 | 0.85 | 0.72–0.94 |
| Intracranial artery and aortic arch | 0.74| 0.60–0.85 | 0.84 | 0.71–0.94 |
| Extracranial carotid artery and aortic arch | 0.61| 0.47–0.75 | 0.77 | 0.63–0.88 |
| Entire three vascular beds | 0.76| 0.62–0.86 | 0.87 | 0.74–0.95 |

[^1]: Adjustments for age, gender, body mass index, smoke, hypertension, diabetes, high-density lipoprotein, low-density lipoprotein, total cholesterol, and glycerides.

0.88, and 1.00 for intracranial artery, extracranial artery, and aortic arch, respectively (all P < 0.001). For the intra-observer agreement in assessment of the presence of IPH, the kappa value was 0.88 (P < 0.001). The intra-observer ICC of maximum wall thickness and stenosis was 0.97 (95% CI, 0.95–0.99) and 0.97 (95% CI, 0.95–0.98), respectively. For inter-observer agreement in identification of presence of atherosclerotic plaque, the kappa value was 0.81 (P < 0.001). The inter-observer ICC was 0.98 (95% CI, 0.96–0.99) and 0.96 (95% CI, 0.91–0.98) for measuring Max WT and stenosis, respectively.

Figure 5 represents the intra-observer (A) and inter-observer (B) agreement in quantitatively measuring the maximum wall thickness by Bland-Altman analysis.

**Discussion**

To the best of our knowledge, this is the first study to investigate the plaque distribution and characteristics in three stroke-related vascular beds including intracranial and extracranial carotid arteries and aortic arch at the same patients using 3-D MR vessel wall imaging. We found that, in this study population, atherosclerotic plaques were most prevalent in extracranial carotid artery, followed by intracranial arteries and aortic arch. Particularly, IPH and...
severe stenosis (stenosis >50%) were more frequently found in intracranial arteries. In addition, the combination of wall thickness measurement in these three vascular beds had stronger predictive value for acute ischemic lesion than each vascular bed alone. The finding of correlation between combined maximum wall thickness of the entire stroke-related vascular beds and AIL further compels the evidence that measuring plaque burden in these vascular beds is useful for determination of the risk of AIL.

In this study population, extracranial carotid arteries were found to have the highest prevalence of atherosclerotic plaques among all vascular beds. The prevalence of carotid plaques in our data (65.4%) was higher than the findings by angiography. Previous stenosis-based studies reported that, in Chinese stroke patients, the incidence of carotid atherosclerosis was ranging from 41.7% to 52%. In contrast, MR vessel wall imaging techniques may yield more lesion detection which may be underestimated by measuring luminal stenosis due to positive remodeling effect. Investigators utilized two-dimensional (2-D) MR vessel wall imaging to identify atherosclerotic plaques in symptomatic patients and

Figure 3. ROC curves of stroke-related vascular Max WT in discriminating AIL. The upper row represents the ROC curves for predicting AILs with Max WT of single vascular bed before (A) and after adjusted for confounding factors (B). The bottom row represents the ROC curves for predicting AILs with Max WT of combined multiple vascular beds before (C) and after adjusted for confounding factors (D).
found that the prevalence of carotid plaques was 66.7%. Most recently, with 2-D MR vessel wall imaging, Zhao et al.\textsuperscript{21} found that more than 60% of carotid high-risk plaques developed lower grade stenosis (stenosis $<50\%$). In carotid artery MR vessel wall imaging, traditional 2-D protocol only provides less than 40 mm of longitudinal coverage centered to the bifurcation and could not capture the plaques occurred in more distal or proximal arterial segments. In the present study, carotid artery images were acquired by 3-D vessel wall imaging techniques with large longitudinal coverage. Cai et al.\textsuperscript{22} reported that 3-D MR vessel wall imaging can detect 14.7% more carotid plaques in more distal and proximal arterial segments which were not in the coverage of

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\centering
\includegraphics[width=\textwidth]{figure4.png}
\caption{An example for high-risk plaques in right intracranial (A–B, arrows) and extracranial carotid arteries (D–E, arrows) with hyperintense IPH on SNAP images and ipsilateral AILs on DWI (C) in the same patient. Example for high-risk plaque with IPH in aortic arch of another patient (F–G, arrows).}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure5.png}
\caption{The intra-observer (A) and inter-observer (B) agreement in quantitatively measuring the maximum wall thickness by Bland-Altman analysis.}
\end{figure}
traditional 2-D imaging protocol. Using 3D vessel wall imaging sequence with large coverage will be more accurate to unveil the lesion distribution and plaque burden in extracranial arteries with relatively larger longitudinal distance compared with other cerebrovascular beds.

In the present study, we found that intracranial arteries had lower prevalence of plaques but higher prevalence of severe stenosis than extracranial carotid arteries (stenosis: 25.0% vs. 13.5%). It has been shown that atherosclerotic disease initiated approximately 20 years earlier in extracranial carotid artery than in intracranial arteries. This hypothesis may explain the differences in plaque prevalence between intracranial and extracranial carotid arteries in the same population. The prevalence of intracranial artery severe stenosis in our data is lower than that of a multicenter study by Wang et al. (intracranial artery severe stenosis: 46.6%) in which patients with acute ischemic events (<7 days) were recruited. In the present study, intracranial arteries developed more severe stenotic disease as compared with extracranial carotid arteries which may be due to the specific histological and anatomical characteristics. Luminal narrowing of arteries with atherosclerotic plaques is dependent on the capability of positive remodeling which compensates blood flow via outward enlargement of vessel wall. Histologically, carotid arteries, particularly the common carotid artery, are the elastic arteries, whereas intracranial arteries are muscular arteries. Compared to muscular arteries, elastic arteries are more likely to occur positive remodeling. In addition, the larger vessel size of extracranial carotid arteries may postpone the luminal narrowing compared to intracranial arteries.

We found that more than 20% of patients had atherosclerotic plaques in aortic arch. The prevalence of aortic arch plaques in our data is lower than previous Chinese population-based studies. Guo et al. utilized transesophageal echocardiography to study acute stroke patients and found 58.4% of them had aortic arch plaques including mild (12.4%), moderate (20.2%), and severe lesions (25.8%). Compared with MR imaging, ultrasound imaging may detect more early atherosclerotic plaques because this technique can clearly delineate the intima and media of arteries. In our study population, there were no patients having luminal stenosis in aortic arch. This might be due to the strong capability of positive remodeling in this vascular bed.

In the present study, a substantial number of atherosclerotic plaques were found to have IPH in three vascular beds. The prevalence of IPH in extracranial carotid arteries of our data (13.5%) are comparable to literature reports. A recent cross-sectional study showed that 16.6% symptomatic carotid arteries had IPH. We found the intracranial IPH in our study population was more prevalent than that in previous studies. Xu et al. reported that the intracranial artery IPH was detected in 15.8% symptomatic patients. In our study, IPH was identified by SNAP imaging which might be more sensitive than traditional T1W imaging sequences.

Our data showed that combination of wall thickness in three stroke-related vascular beds including intracranial and extracranial carotid artery and aortic arch can improve the predictive value of each vascular bed alone for ischemic stroke. To the best of our knowledge, this is one of the first studies to determine the relationship between atherosclerotic disease in three stroke-related vascular beds and ischemic stroke risk. Most of previous studies were focused on the evaluation of atherosclerosis in two vascular beds. Man et al. reported that ischemic stroke patients with concurrent stenosis in intracranial and extracranial arteries had higher risk of death and recurrent rate compared with intracranial artery only. A recent 3-D MR vessel wall imaging study showed that the combination of plaque number in intracranial and extracranial arteries had stronger predictive value for recurrent stroke compared with each vascular bed alone after adjustment for confounding factors. Our findings suggest that it is valuable to measure the maximum wall thickness at three stroke-related vascular beds in discriminating the stroke risk in clinical settings.

This study has several limitations. First, this is a cross-sectional study with small sample. Future prospective studies with larger sample size are suggested. Second, this study was focused on the identification of the presence of atherosclerotic plaque and IPH as well as the measurement of plaque burden such as maximum wall thickness with limited information on other plaque compositional features, such as calciumization and lipid-rich necrotic core. Detailed characteristics of plaque compositions in three vascular beds are warranted in future studies. Third, in the present study, the spatial resolution of 3-D MR vessel wall imaging techniques in aortic arch imaging was 1.25 × 1.25 mm². To optimize the imaging protocol for aortic arch, particularly spatial resolution, is suggested. Fourth, the MR imaging for three vascular beds was performed with two imaging sections using two different coils. This will subsequently increase the scan time during switching of coils and scan protocol. This can be avoided through designing a coil with large coverage from aortic arch to intracranial arteries and optimizing the 3-D vessel wall imaging sequences by increasing the spatial resolution and the efficacy of blood suppression in large coverage scan. Fifth, gadolinium-based contrast agent was not administered in this study. Since contrast enhancement of vessel wall in atherosclerotic disease may reflect the activity and vulnerability of plaques, it is warranted to
introduce contrast agent in future studies. Finally, the longitudinal coverage of our intracranial vessel wall imaging was near 40 mm, which cannot cover the whole V4 segment of vertebral artery for some patients. Future studies will enlarge the longitudinal coverage to include all segments of intracranial arteries.

**Conclusion**

Atherosclerotic plaques are the most prevalent in extracranial carotid artery and the intraplaque hemorrhage and severe stenosis can be most frequently seen in intracranial arteries among three stroke-related vascular beds of Asian symptomatic patients. In addition, the combination of wall thickness measurement in intracranial and extracranial carotid arteries and aortic arch is found to have strong predictive value for acute ischemic lesion than each vascular bed alone, suggesting more attention needs to be paid to plaque burden assessment of multiple vascular beds in stroke prevention.

**Acknowledgments**

None.

**Conflict of Interest**

None declared.

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