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# Associations between Morphological Characteristics of Intracranial Arteries and Atherosclerosis Risk Factors in Subjects with Less Than 50% Intracranial Arterial Stenosis

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## Original Article

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**Purpose:** To assess associations between morphological characteristics of intracranial arteries in time-of-flight MR angiography (TOF-MRA) and atherosclerotic risk factors.
**Materials and Methods:** From January 2014 to October 2015, a total of 129 patients (65 men and 64 women) without intracranial arterial stenosis > 50% were included in this study. All MRIs were performed using a 3T machine with 3D TOF-MRA sequences. We evaluated irregularity, tortuosity, and dilatation of intracranial arteries in maximal intensity projection (MIP) of TOF-MRA. Subjects' risk factors for atherosclerosis including history of hypertension and diabetes were collected by reviewing their medical records. Associations between morphological characteristics and each known atherosclerosis risk factor were examined using univariate regression analysis. Multivariate regression models were built to determine combined association between those risk factors and morphologic changes of intracranial arteries.
**Results:** In multivariate analysis, hypertension (coefficient [95% CI]: 0.162 [0.036, 0.289], P = 0.012) and absence of diabetes (coefficient [95% CI]: -0.159 [-0.296, -0.023], P = 0.022) were associated with large diameter of intracranial arteries. Males (coefficient [95% CI]: 0.11 [-0.006, 0.23], P = 0.062) and higher age (coefficient [95% CI]: 0.003 [-0.001, 0.008], P = 0.138) had marginal association with increased diameter. Tortuosity was associated with old age (OR: 1.04 [1.02, 1.07], P < 0.001). Irregular contour of intracranial arteries was significantly associated with old age (OR: 1.05 [1.02, 1.09], P = 0.004), presence of diabetes (OR: 2.88 [1.36, 6.15], P = 0.0058), and previous ischemic stroke (OR: 3.91 [1.41, 11.16], P = 0.0092).
**Conclusion:** Morphological characteristics (irregularity, tortuosity, dilatation) of intracranial arteries seen in TOF-MRA might be associated with atherosclerotic risk factors in subjects with no or mild stenosis.

**Keywords:** Time-of-flight MR angiography; Morphologic characteristics; Atherosclerosis; Hypertension

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## INTRODUCTION

Time-of-flight MR angiography (TOF-MRA) is a widely used MR imaging technique for assessing cerebral arterial diseases such as aneurysmal dilatation and intracranial atherosclerosis (1-5). Because atherosclerotic plaques protrude into lumen, the resultant luminal stenosis is an important finding of atherosclerotic change of intracranial arteries on TOF-MRA (5, 6). However, not all atherosclerotic changes will result in luminal stenosis. Atherosclerotic changes without arterial steno-occlusive lesions such as positive remodeling have been reported (3, 5). In addition to atherosclerotic plaques and associated stenosis, gross morphologic changes of vasculatures such as tortuosity and dolichoectasia have been suggested as imaging findings of atherosclerotic changes and age-related changes of intracranial arteries (7-10). Especially, tortuosity of intracranial arteries might be associated with risk factors of atherosclerosis including ageing (7, 9, 11, 12). These results suggest that morphological characteristics of non-stenotic intracranial arteries might be imaging surrogates of atherosclerotic changes. White matter hyperintensity (WMH) has been suggested as an imaging marker of atherosclerosis changes and ageing (13, 14). A previous study has suggested the association between WMH and intracranial arterial tortuosity (7). Other reports have suggested association between WMH and intracranial arterial atherosclerosis (13, 15, 16), although such association remains controversial.

In recent experience, we observed that contour irregularity coincided with morphological changes such as stenosis and tortuosity in patients with old age or atherosclerotic diseases. This contour irregularity might be associated with early atherosclerotic changes due to subtle plaques and wall thickenings (5, 17). We hypothesized that such irregularity might be another imaging phenotype of atherosclerotic changes, especially for those with mild atherosclerosis. In this study, we explored the value of morphological characteristics of intracranial arteries found on TOF-MRA as imaging phenotypes of atherosclerosis. We also evaluated the association between luminal irregularity and atherosclerotic changes. Because irregularity might be associated with subtle atherosclerotic changes, we studied subjects without stenotic intracranial arteries which suggested advanced atherosclerosis (18, 19). The purpose of this study was to investigate whether irregularity of intracranial arteries was associated with atherosclerosis risk factors as well as dilatation and tortuosity in patients without significant (> 50% in WASID criteria) stenotic intracranial arterial lesion using TOF-MRA at 3T.

## MATERIALS AND METHODS

### Study Population and Clinical Data Collections

From 2014 January to 2015 October, we identified patients using radiology database according to the following criteria: 1) those with brain MR imaging including TOF-MRA at 3T, 2) no acute ischemic stroke at MR imaging, 3) no stenosis of intracranial arteries more than 50% on WASID criteria in TOF-MRA. Excluded criteria were: 1) missing MRI data (n = 0), 2) underlying malignancy (n = 492), 3) anatomical variations in intracranial arteries (n = 524), or 4) missing information on atherosclerosis risk factors and relevant medical history (n = 1584). As described in the introduction, we excluded patients with significant intracranial arterial stenosis (> 40% WASID criteria). Thus, patients with large atherosclerosis burden and those with focal diseases were excluded. In addition, morphological assessment of intracranial arteries using TOF-MRA might be limited for such patients due to different hemodynamics and flow-related enhancement in stenotic and peri-stenotic segments (20).

A total of 129 patients (65 men and 64 women) were included in this study (Fig. 1). This retrospective study was approved by our Institutional Review Board. Requirement for informed consent was waived due to its retrospective nature. From medical records, we investigated known risk factors of atherosclerotic changes, including hypertension,

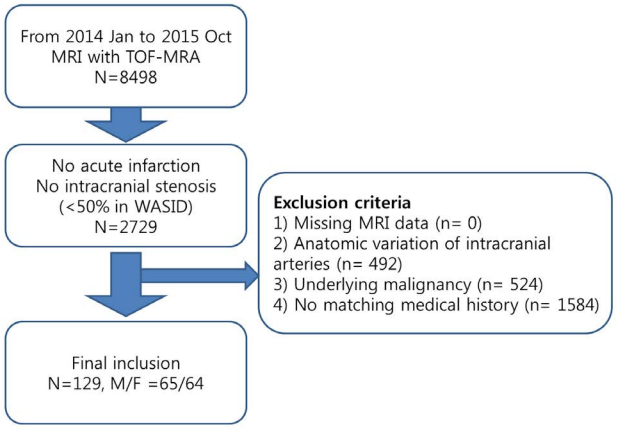


Fig. 1. Patient selection flow chart. After systematic review of radiologic database, we included 129 subjects in this study.

diabetes, smoking history, previous ischemic stroke, and previous coronary heart disease. Hypertension was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or currently taking antihypertensive drugs. Patients taking anti-diabetic medications (insulin or oral hypoglycemic) were considered as having diabetes mellitus. Previous ischemic stroke was defined as a history of hospital admission for management of acute ischemic stroke. History of coronary heart disease was defined as previous angina pectoris, myocardial infarction, or coronary artery bypass.

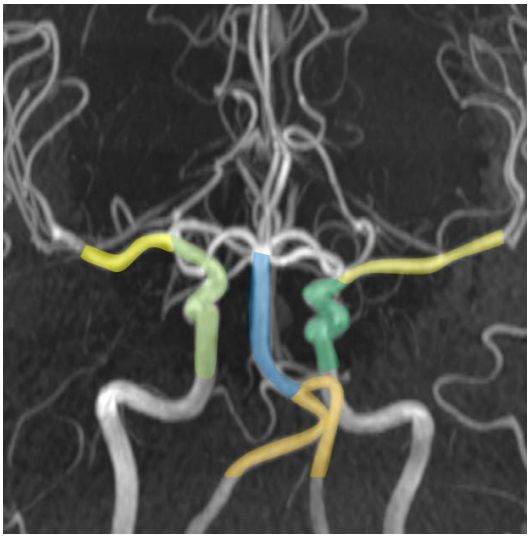

Fig. 2. A scheme showing seven segments of assessed intracranial arteries. Blue = basilar arteries; Green = distal internal carotid arteries; Orange = V4 segments of vertebral arteries; Yellow = M1 segments of middle cerebral arteries

### MRI Acquisition

MR images were acquired using a 3T machine (MAGNETOM Verio, Siemens Healthineers, Erlangen, Germany) equipped with a 12-channel neurovascular coil. All patients had 3D TOF-MRA and axial T2-weighted images (T2WI). Other images such as diffusion-weighted images, T1-weighted images (T1WI), fluid-attenuation inversion recovery images, and contrast-enhanced T1WI were performed based on clinical circumstances. 3D TOF-MRA was achieved with 6 slabs, each with 40 axial slices of 0.5 mm in thickness without interslice gaps using the following parameters: repetition time/echo time/flip angle = 22 ms/3.6 ms /18°, frequency/phase encoding matrix = 384 × 331, NEX = 1, and bandwidth = 186 Hz/pixel. A voxel at size of 0.4 × 0.4 × 0.5 mm was acquired after interpolation. GRAPPA parameters were set to an acceleration factor of 2 in phase encoding direction with 24 reference k-space lines for calibration. A saturation band of 40 mm in thickness was applied for venous saturation. Acquisition time was 7 min 28 sec.

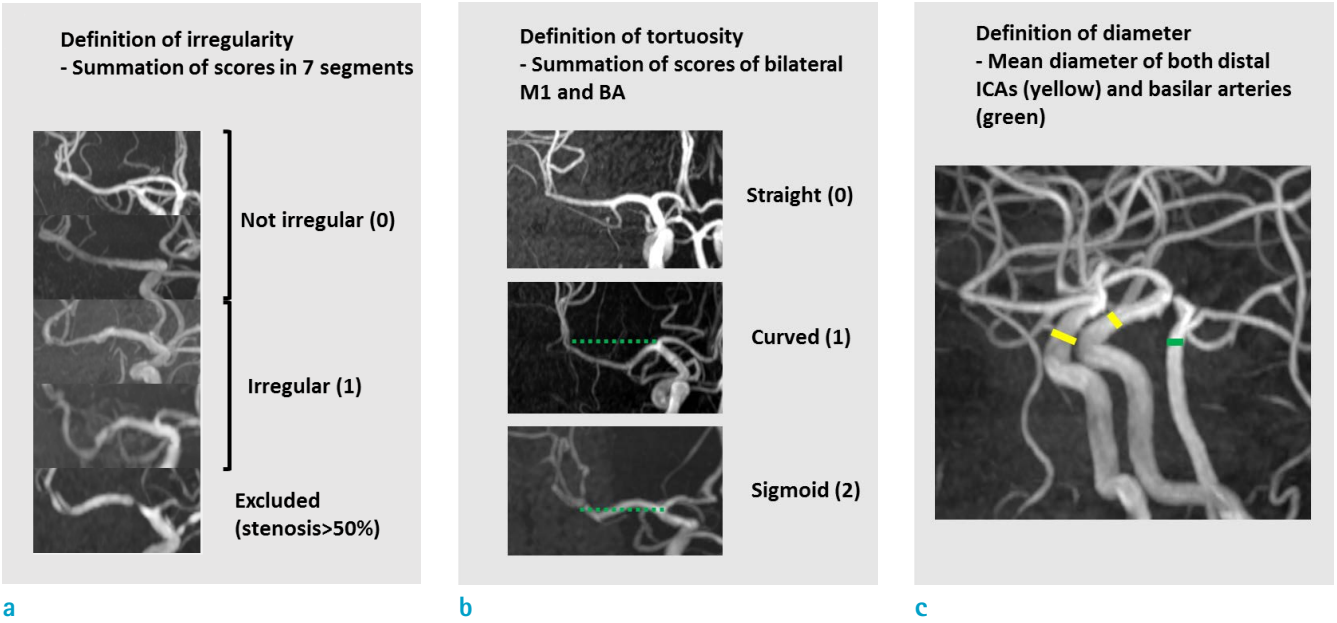


Fig. 3. Three schemes used to assess morphological features of intracranial arteries. Each panel explains criteria for irregularity (a), tortuosity (b), and diameter (c).

### Evaluation of Morphological Characteristics of Intracranial Arteries

Horizontal and vertical rotation maximal intensity projection (MIP) images of brain TOF-MRA were evaluated to assess morphological characteristics of intracranial arteries. Three morphologic characteristics (irregularity, tortuosity, and dilatation) were analyzed. For each analysis, we selected seven representative segments of intracranial arteries (Fig. 2): terminal segment of both distal internal carotid arteries (ICA), M1 segments of both middle cerebral arteries (MCA), and V4 segments of both vertebral arteries (VA) and basilar artery (BA). Presence of irregularity was assessed visually using a 4-point scale (none-suspicious-probable-definite). Segment with probable or definite irregular segments were considered as irregular while others were considered as 'not irregular' (Fig. 3a). If hypoplastic V4 segment of VA was found, it was considered as 'not irregular.' Total number of irregular segment was used as an 8-point scale irregular score. Tortuosity was analyzed in M1 segments of both MCA and BA (Fig. 3b). Tortuosity of distal ICAs or V4 segments of VA was not assessed due to natural curvature. The shape of the vessel was classified as straight (0 point), curved (1 point), or sigmoid (2 points) (9). The sum of three segment scales was used for a 7-point scale tortuosity score. For assessment of intracranial arterial dilatation, maximal diameter of BA and both distal ICA terminal segments were measured (Fig. 3c). Four segments, those with smaller calibers (M1 segment of MCA and V4 segments of VA) were not measured.

### Evaluation of White Matter Hyperintensity

Two radiologists assessed MR images for imaging surrogates of small vessel disease under consensus. White matter lesion was assessed on axial T2WI using modified Fazekas's scale: 0 = absent, 1 = punctate foci, 2 = beginning confluence, and 3 = large confluent area (21).

### Statistical Analysis

We performed two steps of statistical analysis. First, we examined the association between imaging characteristics and each known atherosclerosis risk factor using univariate regression analysis. For mean diameter of intracranial arteries, we used linear regression model. Because irregularity score and tortuosity score were ordinal responses, a cumulative logit model based on multinomial distribution with proportional odds assumption was used (22). Second, we built multivariate regression models to determine combined association between those risk factors and morphological changes of cerebral arteries. To build multivariate regression models, variables with significance level of 0.20 in univariate analysis were used for multivariable analysis. Final model selection was done using backward elimination based on comparison of Akaike information criterion (AIC). Multicollinearity was checked by calculating inflation factor of each variable included in the model. A variable inflation factor of 2.5 was considered multicollinearity that could influence the estimated power. All analyses were performed with R statistical packages version 3.2.2 (R Foundation, Vienna, Austria; www.R-project.org).

## RESULTS

### Patients Characteristics

Patient characteristics are summarized in Table 1. There

**Table 1. Patients Characteristics (n = 129)**

| Variables | | |
|---|---|---|
| Sex | Male | 65 (50.4%) |
| | Female | 64 (49.6%) |
| Age | | 66.4 ± 13.2 |
| Hypertension | None | 50 (38.8%) |
| | Present | 79 (61.2%) |
| Diabetes | None | 94 (72.9%) |
| | Present | 35 (27.1%) |
| Dyslipidemia | None | 92 (71.3%) |
| | Present | 37 (28.7%) |
| Previous ischemic stroke | None | 112 (86.8%) |
| | Present | 17 (13.2%) |
| History of ischemic heart disease | None | 113 (87.6%) |
| | Present | 16 (12.4%) |
| Deep white matter grading (Fazeka's scale) | 0 | 72 (55.8%) |
| | 1 | 37 (28.7%) |
| | 2 | 12 (9.3%) |
| | 3 | 8 (6.2%) |
| Irregularity score | | 1.2 ± 1.8 [0, 0-2] |
| Tortuosity score | | 2.3 ± 1.3 [2, 1-3] |
| Mean diameter | | 2.8 ± 0.4 [2.74, 2.52-2.93] |

Numbers in parenthesis is percentage. Numbers in bracket are median and interquartile range.

was 64 (49.6%) women and 65 (50.4%) men. Their mean age was 66.4 ± 13.2 years. More than half (79/129, 61.2%) of these patients had hypertension while about one fourth (35/129, 27.1%) of these patients had diabetes. Thirty-seven (28.7%) patients had dyslipidemia. Seventeen (13.2%) patients had previous history of stroke or TIA. History of prior ischemic heart disease was present in 16 (12.4%) patients. Mean and standard deviation of irregularity score was 1.2 ± 1.8. Tortuosity score was 2.3 ± 1.3. Mean diameter of intracranial arteries was 2.8 ± 0.4 mm. White matter was grade 0 in 68 (56.2%) patients, grade 1 in 33 (27.3%) patients, grade 2 in 12 (9.9%) patients, and grade 3 in 8 (6.6%) patients.

### Univariate Analysis

In univariate analysis (Table 2), vessel diameter had significant positive association with hypertension (coefficient [95% confidence interval (CI)]: 0.158 [0.034, 0.282], P = 0.012). High tortuosity score or tortuous intracranial artery was significantly associated with old age (odd ratio (OR) [95% CI]: 1.04 [1.01, 1.07], P < 0.001) and hypertension (OR [95% CI]: 2.05 [1.09, 3.92], P = 0.028). High irregularity score was associated with ageing (OR: 1.06 [1.03, 1.10], P < 0.001), hypertension (OR: 2.77 [1.34, 6.03], P = 0.008), diabetes (OR: 3.35 [1.62, 6.99], P = 0.0017), and history of previous ischemic stroke or TIA (OR: 4.85 [1.74, 13.80], P = 0.0026). WMH, a surrogate of small vessel disease of the brain, was not significantly associated with morphological characteristics of intracranial arteries.

### Multivariate Analysis

In multivariate analysis (Table 3), hypertension (coefficient

**Table 2.** Univariate Analysis Results

| | Diameter | | Tortuosity score | | Irregularity score | |
|---|---|---|---|---|---|---|
| | Coefficient (95% CI) | P-value | Odd ratio (95% CI) | P-value | Odd ratio (95% CI) | P-value |
| Sex | 0.08 (-0.04~0.20) | 0.188 | 0.65 (0.35, 1.21) | 0.174 | 0.98 (0.50, 1.93) | 0.96 |
| Age | 0.004 (0~0.008) | 0.097 | 1.04 (1.01, 1.07) | 0.0006 | 1.06 (1.03, 1.10) | 0.00012 |
| Hypertension | 0.158 (0.034~0.282) | 0.012 | 2.05 (1.09, 3.92) | 0.0277 | 2.77 (1.34, 6.03) | 0.008 |
| Diabetes | -0.098 (-0.236~0.04) | 0.159 | 1.13 (0.56, 2.30) | 0.730 | 3.35 (1.62, 6.99) | 0.0017 |
| Dyslipidemia | 0.027 (-0.111~0.165) | 0.7 | 0.56 (0.28, 1.14) | 0.114 | 1.00 (0.46, 2.12) | 0.99 |
| Previous ischemic stroke | -0.053 (-0.236~0.131) | 0.566 | 1.51 (0.60, 3.85) | 0.380 | 4.85 (1.74, 13.80) | 0.0026 |
| Ischemic heart disease | 0.129 (-0.055~0.313) | 0.17 | 0.56 (0.22, 1.46) | 0.233 | 1.95 (0.69, 5.33) | 0.196 |
| WMH | | | | | | |
| Grade 1 | 0.121 (-0.019~0.261) | 0.09 | 1.72 (0.85-3.45) | 0.138 | 1.39 (0.64-3.05) | 0.413 |
| Grade 2 | 0.122 (-0.094~0.338) | 0.261 | 1.22 (0.41-3.66) | 0.719 | 1.72 (0.55-5.35) | 0.359 |
| Grade 3 | 0.264 (0.006~0.522) | 0.043 | 1.75 (0.52-5.90) | 0.367 | 2.64 (0.71-9.81) | 0.148 |

CI = confidence interval; WMH = white matter hyperintensity
Linear regression was done for mean diameter. Ordinal logistic regression was done for tortuosity and irregularity score.

**Table 3.** Multivariate Analysis Results

| | Diameter | | Tortuosity | | Irregularity | |
|---|---|---|---|---|---|---|
| | Coefficient (95% CI) | P-value | Odd ratio (95% CI) | P-value | Odd ratio (95% CI) | P-value |
| Sex | 0.11 (-0.006, 0.23) | 0.062 | NA | | NA | |
| Age | 0.003 (-0.001, 0.008) | 0.138 | 1.04 (1.02, 1.07) | 0.0005 | 1.05 (1.02, 1.09) | 0.004 |
| Hypertension | 0.162 (0.036, 0.289) | 0.012 | NA | | 1.97 (0.89, 4.54) | 0.10 |
| Diabetes | -0.159 (-0.296, -0.023) | 0.022 | NA | | 2.88 (1.36, 6.15) | 0.0058 |
| Previous ischemic stroke | NA | | NA | | 3.91 (1.41, 11.16) | 0.0092 |

CI = confidence interval; NA = non-applicable.
Linear regression was done for mean diameter. Ordinal logistic regression was done for tortuosity and irregularity score.

[95% CI]: 0.162 [0.036, 0.289], P = 0.012) and absence of diabetes (coefficient: -0.159 [-0.296, -0.023], P = 0.022) were associated with large diameter of intracranial arteries. Males (coefficient: 0.11 [-0.006, 0.23], P = 0.062) and higher age (coefficient 0.003 [-0.001, 0.008], P = 0.138) showed marginal association with increased diameter. Tortuosity was associated with old age (OR: 1.04 [1.02, 1.07], P < 0.001). Irregular contour of intracranial arteries was significantly associated with old age (OR: 1.05 [1.02, 1.09], P = 0.004), presence of diabetes (OR: 2.88 [1.36, 6.15], p = 0.0058), and previous ischemic stroke (OR: 3.91 [1.41, 11.16], P = 0.0092). Multicollinearity between variables was not observed in final models.

## DISCUSSION

In this study, we found that morphological characteristics of intracranial arteries were associated with aging and risk factors of atherosclerosis. Irregularity of intracranial arteries not clearly presented in previous studies was associated with ageing, diabetes, and previous ischemic stroke. Tortuous intracranial arteries showed significant association with aging while increased luminal diameter was associated with the presence of hypertension. However, WMH as a surrogate marker of small vessel disease of the brain was not significantly associated with morphological changes of intracranial arteries.

The irregularity of intracranial arterial lumen was associated with old age, diabetes, and previous ischemic stroke. We observed irregular contour in patients with atherosclerosis risk factors (i.e., diabetes and hypertension) and in patients with end-organ disease of atherosclerosis (i.e., acute ischemic stroke). Our results suggest that irregular intracranial arterial contour might be an imaging phenotype of atherosclerosis. There are some evidences of ubiquitous atherosclerotic plaques in both ageing and diseased arteries (23, 24). Although some plaques might induce significant or visible degree of luminal stenosis, others are too small to induce stenosis or form positive remodeling without luminal narrowing (3-5). Subtle protrusion by small atherosclerotic plaque might result in loss of smooth continuity of vascular luminal contour. Different calibers might also induce some differences in the profile of laminar flow. This might be another explanation for the irregular contour of atherosclerotic arteries on TOF-MRA. Previous studies have reported that focal atherosclerotic plaque is presented as focal irregularity in TOF-MRA (25). This supports our hypothesis.

Among morphologic characteristics of arterial systems, tortuosity has been investigated the most (7, 9, 11, 12). Aging and high blood pressure are known to be associated with tortuous intracranial arteries (9, 26, 27). Current explanation for arterial tortuosity is based on long standing hemodynamic stress such as hypertension. An animal experiment has shown that high flow can lead to formation of tortuous head and neck arteries (10). Another *in vitro* study on extracted dog arteries has shown that increasing blood pressure can lead to increased tortuosity (28). A study that measured tortuosity quantitatively and used large participants also showed an association between tortuosity and hypertension (12). Our result is concordant with these findings, suggesting that hypertension and aging are significantly associated with increased tortuosity.

We observed increasing diameter of intracranial arteries in hypertension patients but decreased diameter in diabetes patients. Diabetes is one well-known systemic disease involving vasculatures. It also involves intracranial arteries (23). While luminal narrowing or negative remodeling is focused on the evaluation of TOF-MRA, luminal dilatation especially subtle changes might be neglected. Dolichoectasia is a descriptive term for the mixture of morphologic changes of intracranial arteries - tortuous and dilated arteries (8). Multiple pathophysiological processes might contribute to the development of arterial ectasia such as hypertension associated with atherosclerosis (8). However, histological studies support that degeneration of the internal elastic lamina and thinning of the media secondary to smooth muscle atrophy as well as prolonged systemic hypertension are the basis of this pathology (29). Our study also supports this hypothesis since vessel diameter is increased with hypertension. Hypertension plays a major role in atherosclerosis by causing and accelerating endothelial injury. Findings of arterial ectasia and atherosclerotic plaque could be ubiquitous, thereby causing irregular vessel contour (30).

WMH is one of the most well-known imaging surrogates of small vessel disease (14, 31). Recent studies have suggested association between WMH and intracranial arterial atherosclerosis (15), although this remains controversial. In addition, the association of WMH and atherosclerotic change has been suggested (32). To validate our hypothesis, we investigated surrogate markers of small vessel disease such as WMH. WMH did not show significant association with morphologic changes of intracranial arteries. Different pathophysiologic background might

constitute no or weak association between small and large vessels of intracranial arteries.

Our study had several limitations. First, we did not confirm pathological changes with irregular contours of intracranial arteries. Like many previous MR-based studies of cerebral arteries, our results were based on associated results of similar earlier studies. While it is nearly impossible to directly compare vessel wall pathology and findings of MR, making evaluation of cerebral artery morphology and properties is subjective to a certain extent. A recent study has suggested that vessel wall imaging might be used for imaging intracranial atherosclerotic changes (3). However, subjects included in that study did not have vessel wall imaging due to clinical circumstances. Future study might be needed to compare irregular contour and vessel wall imaging findings. TOF-MRA is insensitive to slow flow or in-plane flow due to in-plane saturation which occurs when a blood vessel travels in the same plane as the imaging slice, thereby saturating the aortic blood. This is also caused by post-stenotic turbulence distal to a stenosis that can accelerate phase dispersion. Therefore, it is difficult to apply TOF-MRA to regions with complex vessel geometries as it might lead to overestimation for the severity of stenosis or false diagnoses of vascular occlusion (20). Last but not least, the small number of studied population and its retrospective nature should be considered when interpreting our results, including potential selection bias.

In conclusion, morphological characteristic (irregularity, tortuosity, dilatation) of intracranial arteries seen in TOF-MRA might be associated with atherosclerotic risk factors in subjects with no or mild stenosis. Dilatation is associated with hypertension and diabetes. Tortousity is associated with older age. Irregularity is associated with older age, diabetes, and previous history of ischemic stroke.

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