

# Plaque features and vascular geometry in basilar artery atherosclerosis

Li Zhou, MD, Yufeng Yan, MD, Heng Du, MD, Xiaoxing Ni, MD, Guodong Wang, MD, Qiaoshu Wang, MD, PhD\*

## Abstract

Hemodynamic changes occurring at the segments of arterial bifurcations, up and down stream of stenotic vessels appear to play a critical role in the development of atherosclerosis. Therefore, we hypothesized that basilar artery (BA) geometry may be related to the distribution of atherosclerotic plaque.

In this retrospective cross-sectional study, all patients hospitalized with ischemic stroke and intracranial atherosclerotic disease were sifted from March 2017 to October 2017. Sixty-seven patients with intracranial atherosclerotic disease (39 with and 28 without BA atherosclerosis) were analyzed. Magnetic resonance imaging, magnetic resonance angiography, and high-resolution black-blood MRI were performed within 7 days after symptoms onset. BA tortuosity, plaque location, and plaque enhancement were assessed. Plaque burden and vascular remodeling were measured.

Of the 39 patients with BA atherosclerosis, plaques preferred to be formed at the inner arc than the outer arc (27/39, 69% vs 12/39, 31%) in the tortuous BA. In addition, patients with BA plaque had a greater vascular tortuosity compared with those without plaque ( $113.1 \pm 10.2$  vs  $107 \pm 4.6$ ;  $P = .034$ ). Finally, patients with apparent BA plaque had greater plaque enhancement (14/21, 67% vs 5/18, 28%;  $P = .017$ ) and plaque burden ( $0.76 \pm 0.15$  vs  $0.70 \pm 0.09$ ;  $P = .036$ ) compared with those with minimal plaque.

Plaque may be more likely to form at the inner arc of tortuous BA with atherosclerotic disease, and increased BA tortuosity is associated with its likelihood to form plaque.

**Abbreviations:** BA = basilar artery, HR-BBMRI = high-resolution black-blood magnetic resonance imaging, ICAD = intracranial atherosclerotic disease, MRA = magnetic resonance angiography, MRI = magnetic resonance imaging, LA = lumen area, OWA = outer wall area, RR = remodeling ratio.

**Keywords:** basilar artery, intracranial atherosclerosis, ischemic stroke, magnetic resonance imaging, plaque, vascular geometry

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LZ and YY contributed equally to this work.

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The study was approved by the Institutional Review Board of Shanghai General Hospital.

No animals were used for studies that are base of this research. All the humans used were in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2013 (<http://ethics.iit.edu/ecodes/node/3931>).

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Department of Neurology, Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China.

\* Correspondence: Qiaoshu Wang, Department of Neurology, Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, 650 New Songjiang Road, Shanghai 201620, China (e-mail: [qwang624@139.com](mailto:qwang624@139.com)).

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## 1. Introduction

Intracranial atherosclerotic disease (ICAD) is an important cause of ischemic stroke, especially in East Asian, Hispanic, and African American population with high risk of stroke.<sup>[1–7]</sup> Risk factors, such as: smoking, hypertension, hyperlipidemia, may cause ICAD via promoting the inflammation and atherosclerotic lesions of vascular endothelial cells.<sup>[8,9]</sup> Besides, local hemodynamic forces are thought to play a vital role in the formation and progression of atherosclerosis. It has been demonstrated that mechanical forces variation caused by vascular geometry mediated the pathophysiological process of atherosclerosis by regulating signaling pathways of vascular endothelial cells.<sup>[10,11]</sup> A previous study reported that vascular tortuosity is positively related to the level of middle cerebral artery atherosclerosis.<sup>[12]</sup> Furthermore, several studies indicated that vascular geometry is associated with plaque locations.<sup>[12,13]</sup>

Magnetic resonance angiography (MRA) and computed tomography angiography are used to identify the stenotic degree of atherosclerotic vessels in most institutions. However, subclinical atherosclerotic plaque may appear in vessel wall before evident luminal stenosis being detected.<sup>[14]</sup> Therefore, even if the arterial lumen is not narrowed, plaques may exist in the vessel wall and result in the occurrence of ischemic events.<sup>[13,14]</sup> At present, high-resolution black-blood magnetic resonance imaging (HR-BBMRI) has been demonstrated to be a non-invasive and reliable tool to assess vessel wall characteristics and plaque features including locations, plaque burden, and plaque vulnerability.<sup>[14,15]</sup> Compared with conventional techniques used

for intracranial vessel assessment, HR-BBMRI can offer a direct visualization of the vessel wall and plaque morphological features. In addition, HR-BBMRI had been recommended for clinical practice by American Society of Neuroradiology in 2017 to differentiate among causes of intracranial arterial narrowing and assess atherosclerotic plaque activity.<sup>[16,17]</sup>

In this study, we hypothesize that the geometry of basilar artery (BA) in patients with intracranial atherosclerosis may be related to plaque formation and distribution. Therefore, we investigated the relationship between basilar artery geometry and plaque locations and features by using MRA and HR-BBMRI.

## 2. Materials and methods

### 2.1. Patients

We reviewed our computerized stroke database of patients consecutively admitted to our center from March 2017 through October 2017 in Shanghai General Hospital with the approval of the Institutional Review Board of Shanghai General Hospital. Informed consent was waived to allow inclusion of deidentified data of patients. Patients were included in the analysis if

- they underwent diffusion weighted MRI, MRA, and HR-BBMRI within 7 days after symptoms onset and
- they were diagnosed as ischemic stroke with intracranial large artery atherosclerotic disease including anterior or posterior circulation.

Patients were excluded from the study with the following conditions

- extracranial carotid and vertebral artery disease
- nonatherosclerotic intracranial vascular diseases such as vasculitis, moyamoya disease, dissection, reversible cerebral vasoconstriction syndrome
- bad MR imaging quality or complete artery occlusion. Eventually, 67 patients were included for imaging analysis.

### 2.2. Imaging analysis

MRI scans were performed with a 3.0T MRI Acheiva scanner (VISTA; Philips Healthcare, Best, the Netherlands). A standard protocol was applied to acquire high-resolution intracranial vessel wall imaging that included 3D HR-BBMRI imaging (3D T1-VISTA TSE) and 3D time-of-flight (TOF) MRA sequences. The 3D TOF MRA was acquired in a transverse plane by using the following parameters: repetition time 20 ms; echo time 3.5 ms; flip angle 18°; field of view  $170 \times 170 \times 61 \text{ mm}^3$ ; acquired resolution  $0.6 \times 0.84 \times 1.60 \text{ mm}^3$ ; reconstructed resolution  $0.35 \times 0.35 \times 0.80 \text{ mm}^3$ ; and scan time 1.5 minutes. The 3D HR-BBMRI imaging sequence was performed with the following parameters: field of view  $200 \times 167 \times 45 \text{ mm}^3$ ; acquired resolution  $0.6 \times 0.6 \times 1.0 \text{ mm}^3$ ; reconstructed resolution  $0.5 \times 0.5 \times 0.5 \text{ mm}^3$ ; repetition time/echo time 1500 ms/36 ms; turbo-spin-echo factor 56 echos; echo spacing 4.0 ms; sense factor 1.5 (right-left direction); scan time 6.51 minutes.

Atherosclerotic plaque on magnetic resonance images was defined as eccentric wall thickening identified on both the reconstructed precontrast and the reconstructed postcontrast HR-BBMRI. We divided patients with plaques into “minimal plaque” that the basilar artery wall was narrowing with crescentic thickening of less than 50% stenosis and “apparent

plaque” that a typical lesion with a crescentic thickening of more than 50% stenosis could be identified (Fig. 1).<sup>[14]</sup> Two experienced neurologists (LZ and HD) analyzed the HR-BBMRI images using Vesselmass software (Leiden University Medical Center, The Netherlands) and independently measured lumen area (LA), outer wall area (OWA), wall area ( $\text{WA} = \text{OWA} - \text{LA}$ ), plaque burden ( $\text{WA}/\text{OWA} \times 100\%$ ) (Fig. 1). The distal and proximal normal OWAs were measured. The reference OWA ( $\text{OWA}_{\text{reference}}$ ) was defined as the mean of normal OWAs. The arterial remodeling ratio (RR) was calculated as  $\text{OWA}/\text{OWA}_{\text{reference}}$ .  $\text{RR} \geq 1.05$  was defined as positive remodeling,  $0.95 < \text{RR} < 1.05$  as intermediate remodeling, and  $\text{RR} \leq 0.95$  as negative remodeling.<sup>[15,18]</sup> According to previous study, we measured basilar artery vascular tortuosity with the following steps

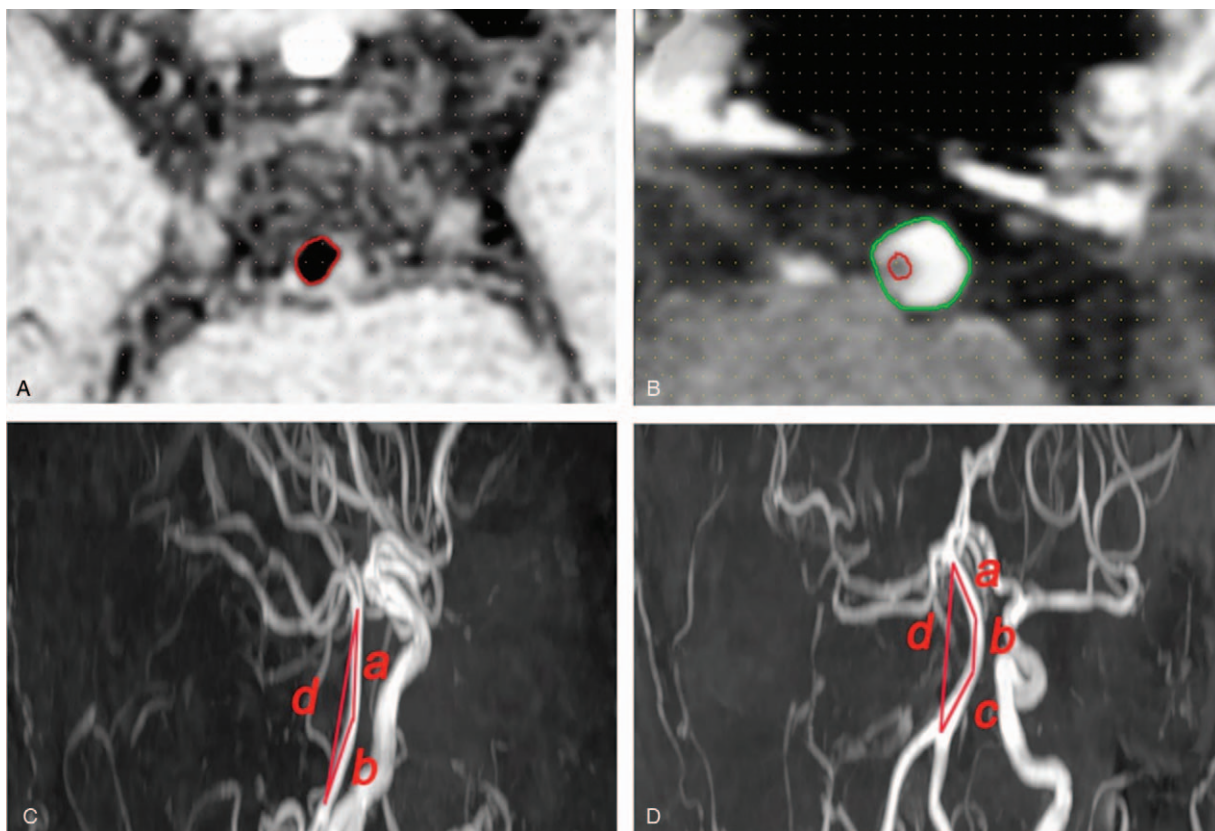
- selecting obviously maximum angle of BA by visual inspection of MRA;
- measuring the minimal length (ML) between the two ends and the actual length ( $\text{AL} = a + b$  or  $a + b + c$ ) of main trunk of the BA;
- vascular tortuosity is measured as  $\text{ML}/\text{AL}$  (Fig. 1).<sup>[12]</sup> To explore the plaque distribution in tortuous BA, we studied the vertical and transverse plane of 3D HR-BBMRI to observe the relationship of the configuration of tortuous BA and plaque location, and the vessel wall was divided into “inner arc” and “outer arc” according to the direction of BA with greatest tortuosity (Fig. 2). Furthermore, in vertical view, the direction of BA tortuosity was classified into “ventral”, “dorsal”, “left”, and “right”. In transverse area we divided the vessel area into 2 halves as “outer” area and “inner” area (Fig. 3). If the plaque was observed in both areas, the area with larger plaque (>50%) was chosen. The vulnerability of plaques was assessed according to with or without contrast enhancement on HR-BBMRI images.<sup>[19]</sup>

### 2.3. Statistical analysis

All data were analyzed using SPSS 20.0 (IBM SPSS statistics 20, Chicago). First, baseline characteristics and BA geometry were compared between patients with and without plaque. Chi-Squared test, Fisher test, and Mann-Whitney test were used. Variables with potential association with plaque ( $P < .10$ ) from univariate analysis were used for multivariate analysis, and  $P < .05$  was regarded as statistically significant. Then we compared plaque burden and plaque stability between minimal plaque and apparent plaque with Mann-Whitney test. Linear regression analysis was used to compare the relationship between plaque burden and vascular tortuosity. Intra-class correlation coefficients (ICC) was used to evaluate the inter-observer reliability.

## 3. Results

A total of 67 patients were included in the analysis, including 39 patients with and 28 patients without BA plaque. The mean age was  $60.7 \pm 10.9$  and 44 patients were men (65.7%). There was no difference in sex, current smoker, diabetes, hypertension, and hyperlipidemia between patients with and without BA plaque (Table 1). There were significant differences between patients with and without BA plaque in age ( $64 \pm 10$  vs  $56 \pm 11$ ,  $P = .016$ ) and plaque tortuosity ( $113.1 \pm 10.2$  vs  $107 \pm 4.6$ ;  $P = .034$ ). In the univariate, age and vascular tortuosity were associated with BA



**Figure 1.** Measurement of basilar artery plaque, plaque burden, and vascular tortuosity. High-resolution black-blood magnetic resonance imaging showed minimal plaque (A) and apparent plaque (B) of basilar artery. Red circle shows LA, green circle shows outer wall area, plaque burden =  $(OWA - LA) / OWA \times 100\%$  (B). Vascular tortuosity =  $(a + b) / d$  (C) or  $(a + b + c) / d$  (D). LA = lumen area, OWA = outer wall area.

plaque (Table 2) in consistent with multivariate analysis (age, OR, 0.927, 95% CI, 0.872–0.984,  $P = .013$ ; vascular tortuosity, OR, 0.901, 95% CI 0.814–0.997,  $P = .043$ ).

Among the 39 patients with BA plaques, there were 22 patients who had plaques in other intracranial arteries. In the 28 patients without BA plaques, the distribution of plaques is anterior cerebral artery ( $n = 2$ ), middle cerebral artery ( $n = 21$ ), posterior cerebral artery ( $n = 3$ ), and the intracranial segment of the internal carotid artery ( $n = 5$ ) and vertebral artery ( $n = 2$ ). Among the 39 patients with BA plaque, there were 18 patients with minimal plaque and 21 patients with apparent plaque. The inter-observer reliability of the BA tortuosity, plaque location, plaque burden, and vascular remodeling was very good (ICC = 0.90, 0.98, 0.92, 0.95).

### 3.1. BA plaque location

In terms of plaque location, BA plaques were more likely resided at the inner arc than the outer arc (27/39, 69% vs 12/39, 31%). There was no significant difference in selected risk factors between patients with inner arc and outer arc plaques. The direction of BA tortuosity was classified as ventral in 26 (66.7%), dorsal in 1 (2.6%), left in 5 (12.8%), right in 7 (17.9%).

### 3.2. BA plaque burden, vascular remodeling, and plaque enhancement

BA vascular tortuosity was not significantly associated with plaque burden (correlation coefficient, 0.076;  $P = .646$ ). LA,

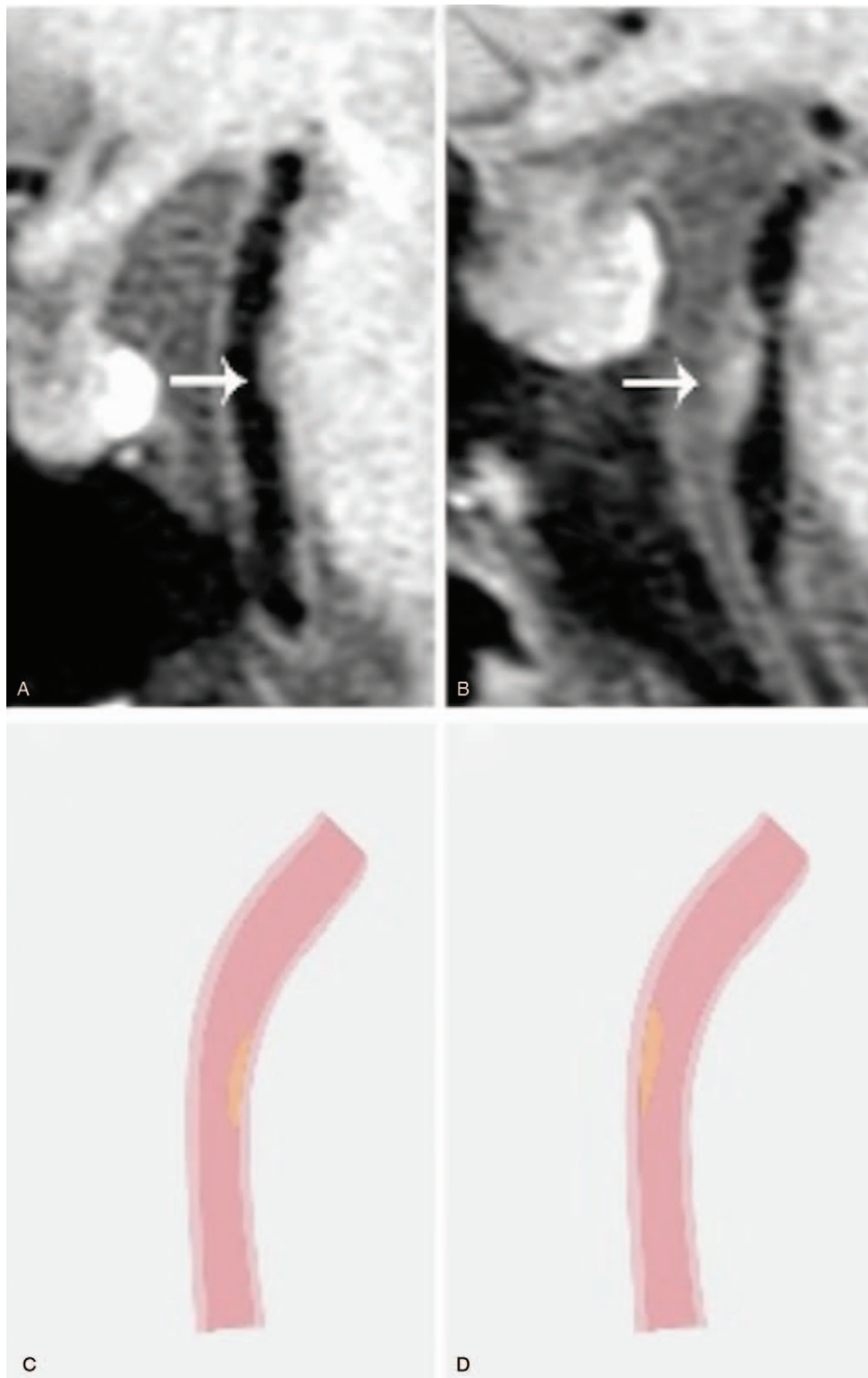
OWA, and wall area were not significantly different between the 2 groups (Table 3). The vascular remodeling of BA with plaque is positive (19/39, 49%), negative (13/39, 33%), and intermediate (7/39, 18%). Apparent plaques had greater plaque enhancement (14/21, 67% vs 5/18, 28%;  $P = .017$ ) and plaque burden ( $0.76 \pm 0.15$  vs.  $0.70 \pm 0.09$ ;  $P = .036$ ) in comparison with minimal plaques.

## 4. Discussion

Our study indicated that BA plaques were more likely to form at inner arc of tortuous vessel, and were associated with greater vascular tortuosity compared with BA without plaque. In addition, BA with plaque was prone to develop positive remodeling, and apparent plaque had greater plaque burden and enhancement compared with minimal plaque.

In this study we selected patients with ischemic stroke and intracranial atherosclerotic disease with similar baseline characteristics, which aimed to identify the risk factors related to basilar artery plaque. Consistent with the study of middle cerebral artery,<sup>[12]</sup> we proved that greater vascular tortuosity was associated with plaque formation in BA. Blood flow is laminar and wall shear stress is high in straight parts of arterial tree; in branches and tortuous arteries, blood flow is disturbed with irregular distribution of low wall shear stress. Disturbed blood flow occurs in arterial segments with geometric irregularities (e.g., curvatures, branches, bifurcations), or upstream and downstream of stenosis, which may cause local atherosclerosis via promoting low-density lipoprotein cholesterol synthesis,

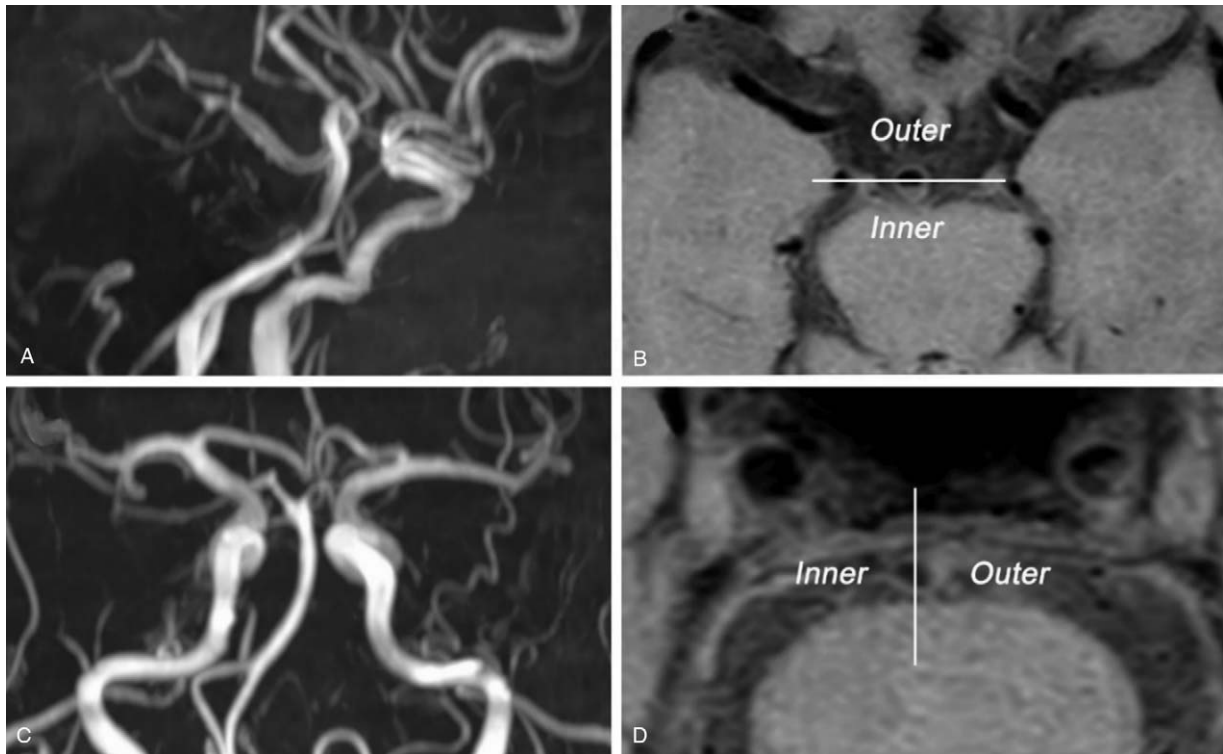




**Figure 2.** Basilar artery plaque location according to the direction of tortuous basilar artery. High-resolution black-blood magnetic resonance imaging showed the plaques located at “Inner arc” (A, C) and “Outer arc” (B, D).

oxidative stress, inflammation etc.<sup>[11,20,21]</sup> The area of laminar blood flow can resist the development of early atherosclerosis.<sup>[21,22]</sup> Our analysis indicated that disturbed flow caused by tortuous basilar artery might promote the atherosclerotic plaque formation. Hademenos et al reported that greater vascular

tortuosity with small radius of curvature easily initiate a lesion due to abnormal shear stress.<sup>[20]</sup> Currently, although the relevant molecular mechanism is unclear, several fundamental studies explored the effect of hemodynamics on endothelial cells via specific signal pathways.<sup>[23–26]</sup>



**Figure 3.** Measurement of plaque location using time of flight and high-resolution black-blood magnetic resonance imaging. According to different tortuous direction (A=ventral, C=right), the vessel area with plaque was divided into outer and inner area (B, D).

In addition, we, for the first time, explored the mechanism of plaques formation and found that most of the plaques were located at the inner arc of tortuous basilar artery. It is recognized that the localization of atherosclerosis is inclined to occur at the areas of low shear stress and turbulence. Outer wall of curved vessel had greater shear stress than the inner wall, and the latter is easier to cause deposition of atherosclerotic particles.<sup>[20]</sup> Furthermore, Chatzizisis et al reported that atherosclerotic lesions were prone to form at the outer wall of bifurcations and the inner wall of curvatures.<sup>[11]</sup> A mice study showed that the

disturbed blood flow in the inner curvature of aortic arch promoted atherosclerosis via Yes-associated protein signaling pathway.<sup>[26]</sup>

At present, cerebral vascular remodeling has been gradually acknowledged due to the development of HR-MRI.<sup>[15,18]</sup> The formation and progression of atherosclerosis may cause increased plaque burden with positive or negative vascular remodeling.<sup>[11,27]</sup> In a study of intracranial artery remodeling, Qiao et al identified that intracranial arteries plaque burden developed prior to the occurrence of vessel stenosis, especially in

**Table 1**  
**Baseline characteristics of patients with and without basilar artery plaque.**

Baseline characteristics	With plaque (n=39)	Without plaque (n=28)	P
Age	64 ± 10	56 ± 11	.016
Male	26 (67%)	18 (64%)	1.000
Current smoker	18 (46%)	13 (46%)	1.000
Diabetes	15 (39%)	7 (25%)	.298
Hypertension	28 (72%)	15 (54%)	.196
Hyperlipidemia	17 (44%)	15 (54%)	.465
Vascular geometry of BA			
Proximal diameter (mm)	12.7 ± 3.1	13.08 ± 4.8	.725
Distal diameter (mm)	11.3 ± 4.1	10.3 ± 3.3	0.256
length of BA (mm)	27.5 ± 5.8	24.5 ± 6.3	0.103
Minimal distance of BA (mm)	24.2 ± 4.2	22.9 ± 4.6	0.522
Vascular tortuosity	113.1 ± 10.2	107 ± 4.6	0.034

Values are presented as mean ± standard deviation or number (%).  
BA = basilar artery.

**Table 2**  
**Univariate analysis of factors associated with basilar artery plaque formation.**

	OR	P
Age	0.915 (0.862–0.971)	.003
Male	0.900 (0.324–2.496)	.840
Current Smoker	1.011 (0.382–2.677)	.982
Diabetes	0.533 (1.183–1.557)	.250
Hypertension	0.453 (0.164–1.256)	.128
Hyperlipidemia	1.493 (0.563–3.962)	.421
Proximal diameter	1.024 (0.904–1.161)	.707
Distal diameter	0.931 (0.816–1.063)	.290
Length of BA	0.920 (0.843–1.004)	.063
Minimal distance of BA	0.941 (0.848–1.045)	.256
Vascular tortuosity	0.893 (0.816–0.976)	.013

Data were presented as odds ratios (95% confidence interval). Factors with potential associated with plaque formation (P < .1) from univariate analysis (age, vascular tortuosity) were used for multivariate analysis.

BA=basilar artery, OR = odds ratio.

**Table 3****Vascular characteristics of basilar artery with minimal and apparent plaque.**

	Minimal plaque (18)	Apparent plaque (21)	P
Lumen area	0.06±0.03	0.06±0.06	.266
Outer wall area	0.20±0.06	0.20±0.12	.863
Wall area	0.14±0.04	0.14±0.07	.863
Plaque burden	0.70±0.09	0.76±0.15	.036
Plaque enhancement	5 (28%)	14 (67%)	.017

Values are presented as mean±standard deviation or number (%).

posterior circulation arteries.<sup>[15]</sup> Consistent with previous studies, our study showed that atherosclerosis in posterior circulation was more likely to occur positive remodeling. Although the mechanism is not clear, there are several possibilities. First, the blood flow velocity of BA is lower compared to anterior circulation, which may cause low shear stress on endothelial cells and mediate vessel remodeling and atherogenesis.<sup>[11,28]</sup> Second, genetic factors may affect the modulation of the arterial wall remodeling.<sup>[29]</sup> Third, there is sparse sympathetic innervation in posterior circulation, compared to anterior circulation, which indicates poor cerebral autoregulation and could lead to tortuous basilar artery and plaque development.<sup>[30,31]</sup> Furthermore, it is believed that the intracranial arterial dolichoectasia has a predilection for basilar artery.<sup>[32]</sup>

Several studies indicated that greater plaque burden was related to plaque vulnerability.<sup>[15,19]</sup> Consistently, our study proved that apparent plaque of BA had greater plaque burden and enhancement than minimal plaque. In our study, the basilar artery vascular tortuosity was not significantly related to plaque burden, which indicates that vessel tortuosity is associated with plaque formation other than plaque development.<sup>[33]</sup> We suspect that tortuous artery may promote atherosclerosis, and the development of plaque is decided by systemic factors such as diabetes, hypertension, infection, etc.

There are several strengths to our study, including accurate identification of BA geometry and plaques with 3D HR-BBMRI, exploration of the mechanism of disturbed flow induced BA atherosclerosis, and strict inclusion criteria of patients with intracranial atherosclerosis. The main limitation of our study was the retrospective nature with relatively small sample size, and the HR-BBMRI images lack histologic validation.

## 5. Conclusion

Our study indicates that in atherosclerotic basilar artery, plaque tends to form at inner wall of curved vessels. BA with plaque is more likely to have greater vascular tortuosity compared with that without plaque.

## Author contributions

**Conceptualization:** Li Zhou, Yufeng Yan.

**Funding acquisition:** Qiaoshu Wang.

**Investigation:** Li Zhou, Yufeng Yan, Xiaoxing Ni.

**Methodology:** Li Zhou, Heng Du, Guodong Wang.

**Data curation:** Li Zhou, Yufeng Yan.

**Supervision:** Guodong Wang, Qiaoshu Wang.

**Writing – original draft:** Li Zhou, Yufeng Yan.

**Writing – review & editing:** Qiaoshu Wang.

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