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Effect of Mid-Basilar Artery Angle and Plaque Characteristics on Pontine Infarction in Patients with Basilar Artery Plaque

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Aims: The basilar artery (BA) geometry and plaque characteristics may play an important role in the development of atherosclerosis. This study was performed to explore the relationship between the mid-BA angle and plaque characteristics and its effect on pontine infarction using high-resolution magnetic resonance imaging and three-dimensional time-of-flight magnetic resonance angiography.

Methods: In total, 77 patients with BA plaques were included in this study. According to the presence of acute pontine infarction on diffusion-weighted imaging, the patients were divided into a pontine infarction group and pontine non-infarction group. The mid-BA angle, plaque burden, stenosis ratio, positive remodeling, and intraplaque hemorrhage were evaluated to investigate their effects on stroke.

Results: The pontine infarction group had a greater plaque burden, stenosis ratio, positive remodeling, and mid-BA angle than the pontine non-infarction group. The correlation between the plaque burden and mid-BA angle was the highest ($r=0.441$, $P<0.001$). Multivariate logistic regression analysis showed that the plaque burden (odds ratio, 1.164; 95% confidence interval, 1.093–1.241; $P<0.001$) was an independent risk factor for pontine infarction.

Conclusion: The mid-BA angle may increase the incidence of pontine infarction by increasing the plaque burden.

Key words: Mid-basilar artery angle, High-resolution magnetic resonance imaging, Plaque burden, Pontine infarction

Introduction

Pontine infarction accounts for approximately 7% of ischemic strokes and is the most common type of posterior circulation stroke[1]. Long-term follow-up has revealed that some patients with pontine infarction have a poor prognosis[2, 3]. The mechanisms of stroke differ between anterior and posterior circulation atherosclerosis; the latter is closely associated with local branch occlusion[4]. The basilar artery (BA) and its branches are the main blood vessels of the posterior intracranial circulation, and BA atherosclerotic plaque formation is a common and important cause of pontine infarction[5]. Many studies have confirmed the feasibility of using high-resolution magnetic resonance imaging (HRMRI) to evaluate intracranial arterial atherosclerosis plaques[6, 7]. However, previous studies mainly focused on the relationship between the plaque

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location, plaque enhancement, arterial remodeling, intraplaque hemorrhage (IPH), and stroke events[8-11], ignoring the relationship between vascular geometry and the occurrence of dangerous plaques.

Biomechanical forces influence the initiation and progression of atherosclerosis, and vascular geometric characteristics influence local hemodynamic forces and play an important role in the development of atherosclerotic plaques[12, 13]. The posterior circulation has a greater degree of geometric variation than the anterior circulation[14]. A unique feature of the BA is that it displays angulation in its course because of its anatomic relationships with surrounding structures[15]. Recent studies have used BA vascular geometrical risk factors to explain the presence and location of plaques[16]. For example, high tortuosity was associated with atherosclerotic plaques in the middle cerebral artery[17], BA[18], and superficial femoral artery[19]. BA plaques were frequently distributed in the lateral walls in symptomatic patients[18]. Asymptomatic BA plaques were demonstrated in 9.5% of individuals who underwent HRMRI during a routine health check-up[16]. Furthermore, the influence of the BA curvature on the presence and location of plaques has been found to be helpful in explaining the mechanism of infarct occurrence[17-19], but the effects of the presence and location of plaques on the occurrence of infarcts have not yet been studied. In the present study, we used HRMRI and three-dimensional time-of-flight magnetic resonance angiography (3D-TOF-MRA) to investigate (a) plaque characteristics that serve as risk factors for pontine infarction in patients with BA plaques, (b) the correlation of the mid-BA angle and BA plaque characteristics, and (c) the association between the mid-BA angle and pontine infarction.

Materials and Methods

Study Population

This retrospective analysis involved 399 patients who underwent HRMRI in the China-Japan Friendship Hospital from November 2015 to June 2021 for neurological symptoms or signs, such as headache, dizziness, giddiness, vertigo, or stroke. Patients were included if they (1) had undergone an HRMRI examination within 2 weeks of symptom onset, (2) had a BA plaque, and (3) had two or more risk factors for atherosclerosis (e.g., hypertension, diabetes, obesity).

The exclusion criteria were (1) non-atherosclerotic vasculopathy that may predispose to stroke (e.g., dissection, Moyamoya disease, or vasculitis), (2) poor imaging quality, (3) coexistent unilateral or bilateral vertebral artery stenosis or luminal irregularity of >50% on MRA or HRMRI, (4) subclavian steal syndrome detected by Doppler ultrasound, and (5) evidence of embolic sources from the heart (atrial fibrillation or valvular heart disease).

In total, 77 patients with BA plaques were included in this study. According to the presence of acute pontine infarction on diffusion-weighted imaging, the 77 patients were divided into 2 groups: the pontine infarction group (n=30) and the pontine non-infarction group (n=47). The patients' demographic and clinical information, including age, sex, body mass index, history of hyperlipidemia, hypertension, diabetes mellitus, homocysteine concentration, smoking status, and alcohol drinking, was collected from the medical records. The study protocol was reviewed and approved by the Institutional Review Board, and the requirement for written informed consent was waived because of the retrospective nature of the study.

HRMRI Protocol

All HRMRI examinations were performed using a 3-Tesla MRI scanner (Ingenia; Philips Healthcare, Best, The Netherlands) with a 15-channel phased-array head coil. The images were acquired in a traversal plane to cover the major intracranial arteries identified on TOF-MRA. The image scanning parameters were as follows: repetition time/echo time=800 ms/21 ms, field of view=180×180×105 mm^3, matrix=300×300×350, and number of excitations=2. The acquisition voxel volume was 0.5×0.6×0.5 mm^3, and the reconstruction voxel volume was 0.5×0.5×0.5 mm^3. The short axial cross sections were constructed automatically with a 0.5-mm slice thickness.

Measurement of BA Plaque Characteristics

The images were independently analyzed on a digital picture archiving and communication system workstation by two experienced radiologists (5 and 15 years of experience, respectively) using visual inspection. An atherosclerotic plaque on MRI was defined as eccentric wall thickening with or without luminal stenosis on both the reconstructed precontrast image and the reconstructed postcontrast image[20]. A plaque was recorded when it was (a) the only plaque in the BA or (b) the same-level plaque as the pontine infarction (when there was a pontine infarction) or the most stenotic lesion (when there was no pontine infarction) when multiple plaques were present in the BA. Differences between the two observers were resolved by consensus.

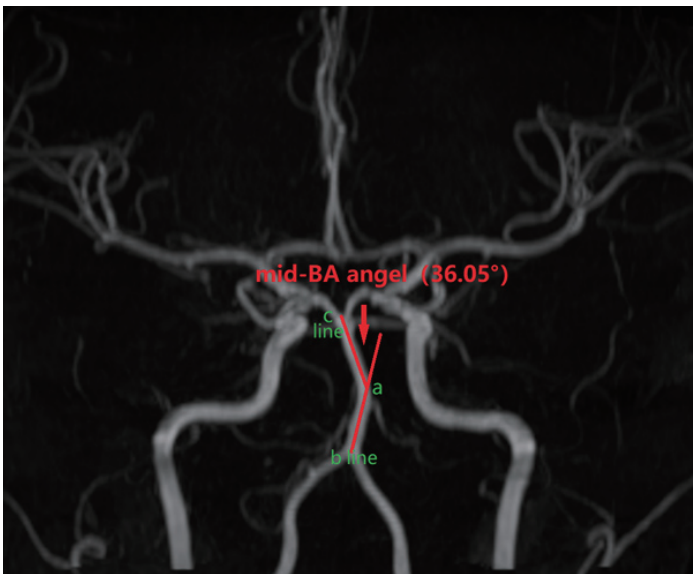

Fig. 1. Illustration of measurement of mid-BA angle

a, the most curved point of the BA; b line, imaginary line connecting point a to the vertebrobasilar junction; c line, imaginary line connecting point a to the top of the BA; mid-BA angle. the acute angle between lines b and c.

The sites of the plaque and reference vessels (the normal layer adjacent to the plaque or the least diseased layer) were respectively evaluated according to the method established in the WASID trial[21], and measurements were made perpendicular to the long axis of the vessel. When the measured plane was inclined to the long axis of the vessel, multiplanar reformation reconstruction was performed in the post-processing workstation to adjust and ensure that the measured plane was perpendicular to the lumen. The vessel area (VA) and lumen area (LA) were measured by manually tracing the vessel and lumen boundaries. The wall area (WA) was calculated as VA – LA, and the plaque burden was calculated as [(WA plaque – WA reference) / VA plaque] × 100%. The degree of stenosis was defined as (1 – LA plaque / LA reference) × 100%. The remodeling index was defined as VA plaque / VA reference. A remodeling index of ≥ 1.05 was defined as positive remodeling, 0.95 to 1.05 as intermediate remodeling, and ≤ 0.95 as negative remodeling[10].

Measurement of Mid-BA Angle

The mid-BA angle was measured in the anteroposterior view of 3D-TOF-MRA. Imaginary lines were drawn from the most curved point of the BA (a point) to the vertebrobasilar junction (b line) **(Fig. 1)** and the top of the BA (c line) **(Fig. 1)** in the anteroposterior view. The acute angle between these two lines was considered the mid-BA angle.

The above parameters were measured once by each radiologist, and the average was taken as the result. Two months later, the plaque parameters of any 10 patients were measured again by the 2 radiologists.

Statistical Analysis

Statistical analyses were performed using SPSS 25.0 (IBM Corp., Armonk, NY, USA). Quantitative variables are described as mean ± standard deviation and qualitative variables as frequency and percentage. The *t*-test was used to compare quantitative variables, and the chi-square test or continuity correction was used for qualitative variables. Covariates with a univariate *P*-value of <0.05 were subsequently enrolled in the multivariate logistic regression analysis using a forward selection algorithm. Pearson correlation analysis and partial correlation analysis were used to evaluate the relationship between the mid-BA angle and plaque characteristics. *P*-values of <0.05 were considered to indicate statistical significance.

Intraobserver and interobserver consistency was evaluated by the intraclass correlation coefficient (ICC). An ICC of <0.40 indicated poor consistency, an ICC of 0.40 to ≤ 0.75 indicated moderate consistency, and an ICC of >0.75 indicated good consistency.

Results

The demographic and clinical characteristics of the study population are summarized in **Table 1**. In

Table 1. Demographic and clinical characteristics of the study population (n=77)

	Mean ± SD or n (%)
Age(yr)	60.49 ± 10.76
Male sex	55
Hyperlipidemia	63
Hypertension	65
Diabetes	36
Homocysteine	16
Smoking	34
Alcohol drinking	26
Obesity	9

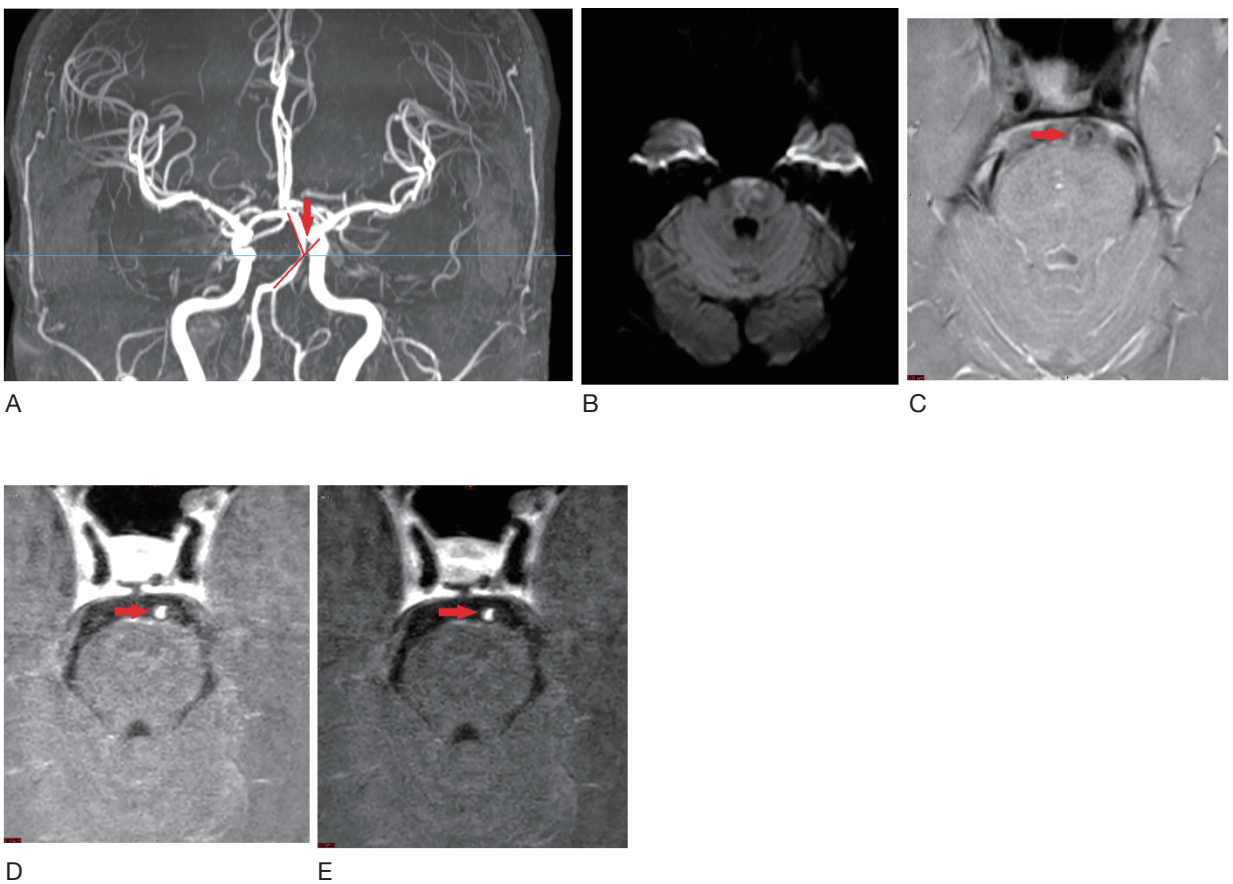

Fig. 2. A 54-year-old man with BA plaque and pontine infarction

A, 3D-TOF-MRA shows a large mid-BA angle (arrow, 66.14°). B, Diffusion-weighted imaging shows diffusion restriction in the pons at the same level of the plaque. C, D, and E show PDWI, T1WI, and CE-T1WI, respectively, indicating an eccentric plaque in the BA (arrows) and intraplaque hemorrhage.

total, 77 patients with BA plaques were included in this study. The BA was straight in 27 patients (27/77, 35.06%) and curved to varying degrees in the remaining 50 (50/77, 64.94%). The BA plaque was located at the most curved point in 47 patients (47/50, 94.00%) and was located at the proximal site of the curve in 3 patients (3/50, 6.00%). Of all 77 patients, 30 patients (mean age, 59.00 ± 8.14 years) had a pontine infarction and 47 patients (mean age, 61.45 ± 12.13 years) had no pontine infarction (**Figs. 2, 3**). Among the 30 patients with a pontine infarction, the infarcts and plaques were located at the

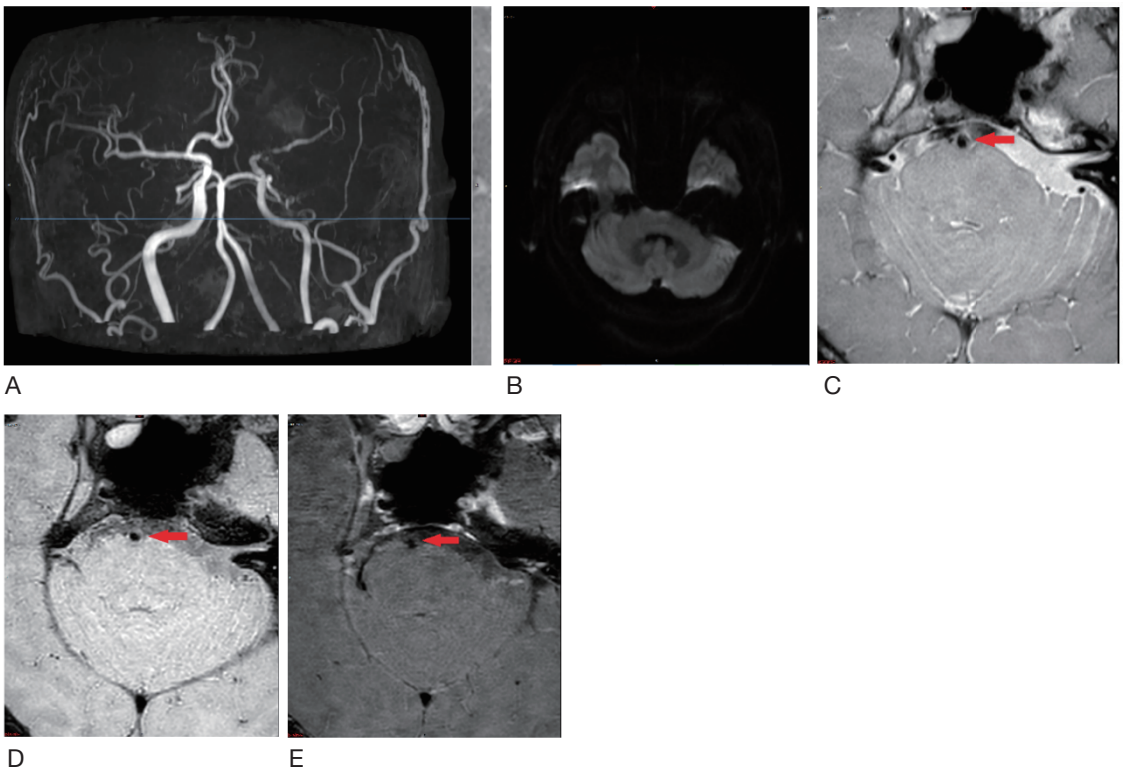

Fig. 3. A 60-year-old man with BA plaque without pontine infarction

A, 3D-TOF-MRA shows that the BA is straight. B, Diffusion-weighted imaging shows no diffusion restriction in the pons. C, D, and E show PDWI, T1WI, and CE-T1WI, respectively, indicating an eccentric plaque in the BA (arrows).

Table 2. Differences in clinical risk factors, BA plaque characteristics, and mid-BA angle between the two groups

	Mean ± SD or *n* (%)		*P*-value
	pontine infarction group (*n* = 30)	pontine non-infarction group (*n* = 47)	
Age(yr)	59.00 ± 8.14	61.45 ± 12.13	0.334
Male sex	24	31	0.183
Hyperlipidemia	25	38	0.783
Hypertension	26	39	0.663
Diabetes	15	21	0.648
Homocysteine	6	10	0.893
Smoking	16	18	0.195
Alcohol drinking	11	15	0.667
Obesity	4	5	0.72
Positive remodeling	25	16	<0.001
IPH	4	3	0.301
Plaque burden	38.06 ± 13.50	12.73 ± 10.27	<0.001
Stenosis ratio	38.63 ± 22.85	24.17 ± 18.18	0.003
Mid-BA angle	36.78 ± 21.90	20.70 ± 21.92	0.002

same level in 28 patients (28/30, 93.33%), proximal to the plaque in 1 patient (1/30, 3.33%), and distal to the plaque in 1 patient (1/30, 3.33%). There were no significant differences between the two groups in age, sex, hyperlipidemia, hypertension, diabetes mellitus, homocysteine concentration, smoking status, alcohol drinking, or obesity (all $P>0.05$), and the results of the comparison of clinical risk factors between the two groups are shown in **Table 2**.

Table 3. Correlation analysis of mid-BA angle and BA plaque characteristics

		unadjusted		adjusted	
Dependent variable	Independent variable	Correlation r	*P*-Value	Partial correlation	*P*-Value
Mid-BA angle	Remodeling index	0.308	0.006	0.295	0.015
	Plaque burden	0.441	<0.001	0.420	<0.001
	Stenosis ratio	0.371	0.001	0.389	0.001

The partial correlation coefficients were adjusted for age, sex, hyperlipidemia, hypertension, diabetes, homocysteine concentration, smoking, alcohol drinking, and obesity.

Table 4. Results of logistic regression analyses of effects of BA plaque characteristics and mid-BA angle on pontine infarction

	Univariate logistic regression		Multivariate logistic regression	
	OR (95%CI)	*p* value	OR (95%CI)	*p* value
Age (yr)	0.979 (0.937, 1.022)	0.332	–	–
Plaque burden	1.164 (1.093, 1.241)	<0.001	1.164 (1.093, 1.241)	<0.001
Stenosis ratio (%)	1.035 (1.010, 1.060)	0.005	–	–
Positive remodeling	9.687 (3.117, 30.109)	<0.001	–	–
IPH	2.256 (0.468, 10.884)	0.311	–	–

Table 5. Interobserver and intraobserver reproducibility of measurement of BA plaque and VBA geometry characteristics

	ICC(95%CI)	
	Inter-observer	Intra-observer
VA_{plaque}	0.884	0.888
LA_{plaque}	0.900	0.915
$VA_{reference}$	0.898	0.949
$LA_{reference}$	0.784	0.843
Mid-BA angle	0.970	0.983

Comparison of BA Plaque Characteristics and Mid-BA Angle between the Two Groups

The pontine infarction group had a greater plaque burden than the pontine non-infarction group (38.06% ± 13.50% vs. 12.73% ± 10.27%, respectively; $P<0.001$). The stenosis ratio of the plaques in the pontine infarction group was higher than that in the pontine non-infarction group (38.63% ± 22.85% vs. 24.17% ± 18.18%, respectively; $P=0.003$). Positive remodeling was observed in 25 patients (25/30, 83.33%) in the pontine infarction group and 16 patients (16/47, 34.04%) in the pontine non-infarction group ($P<0.001$). Compared with patients without pontine infarction, those with pontine infarction had a larger mid-BA angle (36.78° ± 21.90° vs. 20.70° ± 21.92°, $P=0.002$). There was no significant difference in IPH between the two groups ($P=0.301$) **(Table 2)**.

Correlation of Mid-BA Angle and BA Plaque Characteristics

A positive relationship was observed between the mid-BA angle and remodeling index (r=0.308, $P=0.006$), plaque burden (r=0.441, $P<0.001$), and stenosis ratio (r=0.371, $P=0.001$). After adjusting for age, sex, hyperlipidemia, hypertension, diabetes, homocysteine concentration, smoking, alcohol drinking, and obesity, the partial correlation coefficient of the plaque burden was still the highest (r=0.420, $P<0.001$) **(Table 3)**.

Effects of BA Plaque Characteristics on Pontine Infarction

Table 4 shows the results of the logistic regression analysis of the effects of the BA plaque characteristics on pontine infarction. After adjustment for confounders, the plaque burden (odds ratio, 1.164; 95% confidence interval, 1.093–1.241; $P<$

0.001) was an independent risk factor for pontine infarction.

Reproducibility

Excellent interobserver (ICC, 0.784–0.970) and intraobserver (ICC, 0.843–0.983) agreement was found in the measurements of the vessel area, lumen area, and mid-BA angle **(Table 5)**.

Discussion

This study mainly investigated the effect of the mid-BA angle and plaque characteristics on pontine infarction in patients with BA plaques. We found that the plaque burden was an independent risk factor for pontine infarction and that the correlation between the mid-BA angle and plaque burden was the highest. Our results provide further compelling evidence that geometrical characteristics may play a role in high-risk atherosclerotic plaque progression and support the hypothesis that the mid-BA angle may play an important role in pontine infarction development and progression by influencing the plaque burden.

This study demonstrated that the plaque burden was an independent risk factor for pontine infarction in patients with BA plaques, which is consistent with previous studies. The intracranial atherosclerotic stenosis plaque burden maybe a predictor of major clinical events in patients with ischemic stroke during the long term[22-24]. One study showed that the risk of a clinical vascular outcome increased according to the intracranial atherosclerotic stenosis burden[25], and other studies have suggested that progression of the plaque burden was independently associated with recurrent ischemic cerebrovascular events[26]. A larger plaque burden has a larger contact area with blood vessels, where there are many small perforator openings in the lateral wall of the BA. In our study, 28 of the 30 patients with infarction had plaques at the same level as the infarct, which were thought to induce blockage of small branch openings. In addition, a large plaque burden may indicate that the intraplaque composition is more complex and susceptible to the shear force of blood flow, making it more likely to become a vulnerable plaque and cause infarction. Only 1 of the 30 patients with infarction had plaques located proximal to the infarct; in this patient, the larger plaque burden resulted in hypoperfusion of the BA area and caused the pontine infarction.

In our study, there was a higher rate of stenosis and positive remodeling in the pontine infarction group than in the non-infarction group, but we did not find that positive remodeling or the stenosis ratio were risk factors for stroke. Qiao *et al.*[27] suggested that culprit plaques were associated with positive remodeling compared with non-culprit and indeterminate plaques in patients with >50% stenosis, but the correlation became non-significant after adjusting for the plaque burden. This is consistent with our results. In addition, we found no difference in the stenosis ratio between the two groups. Although the stenosis ratio has been reported as a risk factor for ischemic stroke[28], further studies demonstrated that using luminal stenosis to assess disease severity was limited[29, 30]. Increasing evidence shows that vessel wall features provide additional value over the degree of stenosis alone[31-33]. According to the calculation method of the stenosis rate and positive remodeling, the stenosis rate only focuses on LA and positive remodeling only focuses on VA; however, the plaque burden combines both and is focused more on the area of the WA. We suggest that the plaque burden more accurately reflects the vascular condition than any other indices. The plaque burden uniquely accounts for both the magnitude of narrowing in incorporating the minimal lumen area while also providing information regarding vessel remodeling[26]. It might serve as a more precise marker for stroke risk than stenosis and remodeling.

There was no significant difference in IPH between the two groups. Previous studies have shown that the presence of carotid IPH is one of the features of vulnerable plaques[34] and is a strong predictor of cerebrovascular ischemic events[35]. However, some researchers have found that IPH was also observed in asymptomatic carotid atherosclerotic plaques and plaques without stenosis[36, 37]. In addition, a study suggested that plaques proximal to the BA are more prone to IPH[38]. A small number of plaques showed IPH in our study, and no difference was found between the two groups. The significance of the signal intensity of the plaque in our study cannot be concluded based on the present data.

Most previous studies mainly focused on the relationship between the tortuosity of the BA and the plaque presence, location, and mean wall thickness[14, 16, 18, 38], or they only focused on differentiating plaque characteristics on HRMRI between symptomatic and asymptomatic patients[39]. However, very few studies have established the relationship between different mid-BA angle and plaque characteristics and pontine infarction when the BA has plaques. In our study, 94% of the plaques in the curved BA were located at the most curved point, and the mid-BA angle in the pontine infarction group was greater than that in the non-infarction group. Additionally, the correlation between the mid-BA angle and plaque burden was the

highest among the plaque characteristics, and a positive correlation was present; the plaque burden was an independent risk factor for pontine infarction. This may indicate that a larger mid-BA angle is more conducive to the formation of a larger plaque burden and that the probability of pontine infarction is higher when the BA has plaques. We believe that the mechanism underlying the relationship of the mid-BA angle and plaque characteristics is comprehensive, but the role of wall shear stress (WSS) should be emphasized. As an important hemodynamic parameter, WSS is the parallel frictional force exerted by blood flow on the endoluminal surface of the arterial wall[40]. Changes in the luminal geometry affect WSS[41], which is low at the inner curvature of the vessel wall[42, 43]. The potential for *in vivo* WSS calculations was first demonstrated using a combination of coronary angiography and intravascular ultrasound to reconstruct the luminal geometry, and the researchers observed significant increases in plaque thickness associated with the regions of low WSS[41]. Previous studies also showed that the arterial segments with low WSS at baseline had greater subsequent plaque progression[44]. Our study extends these results in intracranial BAs, which means that an increase of the mid-BA angle may lead to a decrease of the WSS, further leading to an increase in the plaque burden and an increase in the incidence of pontine infarction.

In summary, the identification of mid-BA angle helps to identify and improve stroke risk stratification, and this result also suggests to clinicians that the greater mid-BA angle is, the greater the probability of plaque burden is, and the risk of pons infarction is also greatly increased, and early intervention or larger doses of drugs may help to improve the survival rate of patients.

Our study has several notable limitations. First, the sample size was small, and only a single center was included. Because of the insufficient sample size, the mid-BA angle could not be further stratified to explore the significance of different mid-BA angles on the plaque burden. This requires further analysis in our next study. Second, this was a retrospective study; a comprehensive prospective study with follow-up is needed to ascertain the relationship between the plaque burden and mid-BA angle and to assess both as predictors of future events. Finally, a strong correlation was not found between the mid-BA angle and the plaque burden, which may mean that in addition to the index of the mid-BA angle, other unknown factors influence the plaque burden. These factors require further exploration in future studies.

Conclusions

We have shown that a greater mid-BA angle is associated with a higher plaque burden and a greatly increased risk of pontine infarction. The mid-BA angle may contribute to a larger plaque burden, leading to pontine infarction. These indicators can provide insight into the risk of future events for patients with BA plaques, enabling the identification of individuals who harbor an occult burden of vulnerable features and who might benefit from preventive therapeutic interventions.

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Conflict of Interest

The authors declare no conflicts of interests.

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