




The role of hypertension and diabetes mellitus on the etiology of middle cerebral artery disease

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Abstract

Background: Ischemic stroke (IS) caused by middle cerebral artery (MCA) disease is the most common type of IS caused by intracranial artery disease in the Chinese population. Hypertension and diabetes mellitus are the common risk factors of cerebral small vessel disease and large artery atherosclerosis (LAA). However, little is known about whether hypertension and diabetes mellitus had different correlations with the small artery occlusion (SAO) and LAA etiology of MCA disease. Therefore, our aim was to identify the predictors of the etiology of MCA disease.

Methods: We consecutively enrolled 967 patients with noncardiogenic IS in unilateral MCA territory. Vascular risk factors and the clinical–radiologic features of IS were analyzed. The etiology of IS were classified as SAO or LAA according to the Stop Stroke Study Trial of Org 10172 in Acute Stroke Treatment classification criteria. Multivariable logistic regression was used to identify the differences in the predictors between SAO and LAA etiology of MCA disease.

Results: Multivariable logistic regression identified male and hypertension as the predictors of the SAO etiology of MCA disease, however diabetes mellitus, repeated transient ischemic attack before the stroke, gaze palsy, aphasia, headache at admission, and disability at discharge as the predictors of the LAA etiology of MCA disease.

Conclusion: Hypertension and diabetes mellitus are related with the different etiology of MCA disease.

KEYWORDS

ischemic stroke, middle cerebral artery disease, risk factors

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1 | INTRODUCTION

Middle cerebral artery (MCA) is the most common location of intracranial artery disease in the Chinese population (Pu et al., 2013), so ischemic stroke (IS) caused by MCA disease is also the most common type of IS caused by intracranial artery disease. At present, little is known about the differences in the predictors between small artery occlusion (SAO) and large artery atherosclerosis (LAA) subtype of IS caused by MCA disease. Hypertension and diabetes mellitus are the common risk factors of cerebral small vessel disease and LAA. However, little is known about whether hypertension and diabetes mellitus had different correlation with the SAO and LAA etiological subtype of MCA disease. Therefore, the purpose of this study was to identify whether hypertension and diabetes mellitus had different correlation with the SAO and LAA etiological subtype of MCA disease.

2 | SUBJECTS AND METHODS

2.1 | Subjects

Chinese IntraCranial AtheroSclerosis Study (CICAS) is a prospective, multicenter, hospital-based study. From October 2007 to June 2009, 2864 patients with noncardioembolic IS or transient ischemic attack (TIA) in 22 Chinese general hospitals were enrolled.

Patients enrolled had the onset of symptoms within 7 days and were between 18 and 80 years old. Patients were excluded if they were clinically unstable, required close monitoring, unable to comply with magnetic resonance imaging (MRI). We excluded patients with cardioembolic risk factors (atrial fibrillation, atrial flutter, valvular heart disease, bioprosthetic or mechanical heart valve replacement, myocardial infarct within the past month, sick sinus syndrome, dilated cardiomyopathy, endocarditis, etc.) or other causes of IS as well as undetermined causes. Patients who were diagnosed as TIA, patients without available MR images identifying new cerebral infarct or responsible artery of acute infarcts, patients with IS involving posterior circulation or unilateral internal carotid artery territory or unilateral anterior cerebral artery territory or bilateral anterior circulation, patients with IS involving both anterior and posterior circulation, and patients who underwent angioplasty or stent implantation of intracranial or extracranial artery were also excluded. Finally, 967 patients with noncardiogenic IS in unilateral MCA territory were enrolled (Figure 1). The study protocol was approved by the ethics committee of Beijing Tiantan Hospital, and all participants or their legal proxies signed written informed consent for involvement of the research.

Clinical information including hypertension, diabetes mellitus, hyperlipidemia, history of coronary heart disease (CHD), smoking history, and heavy drinking history were defined according to the methods in previous paper (Pu et al., 2013). Primary symptoms and signs at admission, National Institutes of Health stroke scale score at admission and discharge, modified Rankin Scale (mRS) at discharge were also recorded. Disability was defined as mRS ≥ 2 .

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

2.2 | MRI analysis

All patients underwent MRI including three-dimensional time-of-flight MR angiography (MRA), axial T2-weighted, T1-weighted imaging, fluid-attenuated inversion recovery sequences, and diffusion weighted imaging (DWI).

MCA was confirmed as the responsible artery when acute infarcts located in unilateral MCA territory, or acute borderzone infarcts were caused by $\geq 50\%$ degree of stenosis or occlusion in the M1 segment of ipsilateral MCA, and there was no stenosis in the ipsilateral carotid artery. The degree of intracranial artery on MRA was calculated using the published method for the Warfarin–Aspirin Symptomatic Intracranial Disease Study (Samuels et al., 2000). The degree of extracranial artery stenosis was estimated by ultrasonography according to the published diagnostic criteria (Grant et al., 2003) or according to the North American Symptomatic Carotid Endarterectomy Trial criteria by contrast-enhanced magnetic resonance angiography (CEMRA) (Fox, 1993).

The topographical distribution of acute infarcts (including single or multiple acute infarcts, borderzone infarcts, small cortical infarct, territorial infarct, and single perforating artery infarct) and etiological subtypes of IS were evaluated (Figure 2) (Zhang et al., 2019). Multiple acute cerebral infarcts were defined as ≥ 2 separate lesions that were hyperintense on DWI. Single perforating artery infarct was defined as a single infarct in the lenticulostriate artery territory. Borderzone infarcts were defined as the infarcts located at the junction of two (or three) artery territories with arterial collateral circulation. Borderzone infarcts were classified as internal borderzone infarcts and cortical borderzone infarcts. Internal borderzone infarcts were defined as rosary-like pattern of infarcts arranged in a linear fashion parallel to the lateral ventricle and located in the centrum semiovale or corona radiata. Cortical borderzone infarcts are distinguished as anterior cortical borderzone infarcts and posterior cortical borderzone infarcts. Small cortical infarct was defined as the cortical infarct with a maximum diameter of < 2 cm, excluding cortical borderzone infarct. Territorial infarct was defined as a large ischemic lesion with a maximum diameter of ≥ 2 cm involving the cerebral cortical and subcortical structure in one or more major cerebral artery territories. The etiological subtypes of IS were classified according to the Stop Stroke Study Trial of Org 10172 in Acute Stroke Treatment classification criteria. The stroke mechanism of LAA subtype of IS was determined as parent artery occluding penetrating artery if there was a single acute infarct located in the penetrating artery territory accompanied by any degree of stenosis in the parent artery; artery-to-artery embolism, when single or multiple small cortical infarcts, borderzone infarcts, or territory infarcts were caused by the stenosis of MCA; and multiple mechanisms, when two above mechanisms were present simultaneously (S. Gao et al., 2011).

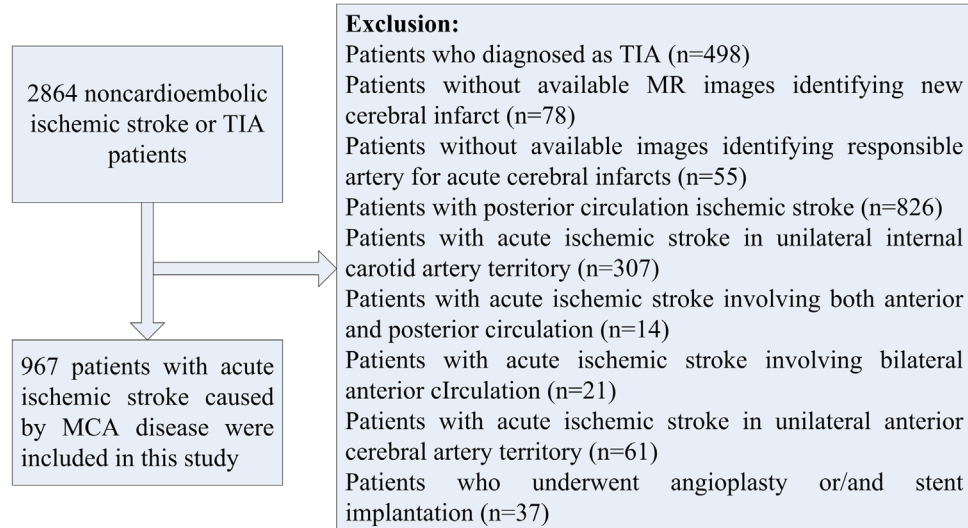


FIGURE 1 Flow chart of patient enrollment

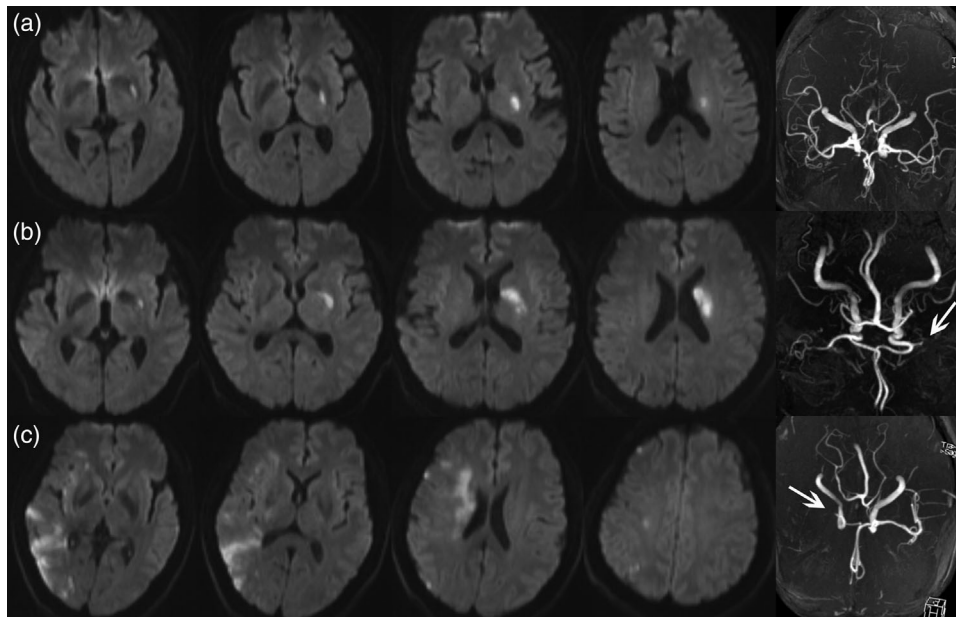


FIGURE 2 Topographical distribution of acute ischemic stroke caused by middle cerebral artery (MCA) disease. (a) Single perforating artery infarct in the left lentulostriate artery territory, without the stenosis of left MCA. Small artery occlusion was the most probable etiology. (b) Single perforating artery infarct with occlusion of left MCA. Large artery atherosclerosis (LAA) and parent artery occluding penetrating artery were considered as the etiology and stroke mechanism, respectively. (c) Multiple acute infarcts (including internal borderzone infarcts, cortical borderzone infarcts, and small cortical infarct) in the right MCA territory, with the occlusion of right MCA. LAA and artery–artery embolism were considered as the etiology and stroke mechanism, respectively

Two radiologists blinded to the clinical details read all MRI scans. Consensus was reached by them if they had disagreement on interpretations.

2.3 | Statistics

Mann–Whitney *U* test was used for comparison of continuous variables with non-normal distribution, χ^2 test was used for comparison

of categorical variables. Multivariable logistic regression was used to identify the predictors of the SAO versus LAA etiology of MCA disease. All parameters that were significant on univariate analysis with $p < .05$ or likely to have pathophysiological influence were included in the multivariable regression analysis. All probability values were two-tailed; $p < .05$ was considered statistically significant. All analyses were performed by using SAS Version 9.1 (SAS Institute, Cary, NC).

TABLE 1 Demographic features and vascular risk factors of 967 acute ischemic stroke caused by SAO or LAA etiology of middle cerebral artery disease

| Variables | Total (n = 967) | SAO (n = 405) | LAA (n = 562) | p |
|--|--------------------|------------------|------------------|------|
| Demographics | | | | |
| Age, median (IQR), years | 61 [52,71] | 61 [52,71] | 61 [52,71] | .935 |
| Age ≥65 years | 405 (41.9) | 161 (39.8) | 244 (43.4) | .255 |
| Male | 656 (67.8) | 292 (72.1) | 364 (64.8) | .016 |
| Vascular risk factors | | | | |
| Smoking | 392 (40.5) | 169 (41.7) | 223 (39.7) | .522 |
| Heavy drinking | 50 (5.2) | 24 (5.9) | 26 (4.6) | .368 |
| Hypertension | 748 (77.4) | 325 (80.2) | 423 (75.3) | .068 |
| Left SBP at admission (IQR), mmHg | 150 [135,168] | 150 [139,170] | 146 [130,162] | .028 |
| Right SBP at admission (IQR), mmHg | 150 [135,169] | 150 [135,170] | 150 [132,161] | .023 |
| Left DBP at admission (IQR), mmHg | 90 [80,97] | 90 [80,100] | 86 [80,95] | .008 |
| Right DBP at admission (IQR), mmHg | 90 [80,98] | 90 [80,100] | 89 [80,95] | .056 |
| Diabetes mellitus | 307 (31.7) | 112 (27.7) | 195 (34.7) | .020 |
| Diabetes mellitus without hypertension | 39 (12.7) | 13 (11.6) | 26 (13.3) | .662 |
| Hyperlipidemia | 735 (76.0) | 312 (77.0) | 423 (75.3) | .525 |
| Coronary heart disease | 59 (6.1) | 26 (6.4) | 33 (5.9) | .725 |
| History of ischemic stroke | 222 (23.0) | 79 (19.5) | 143 (25.4) | .030 |

Note: Data are n (%) unless otherwise indicate.

DBP, diastolic blood pressure; IQR, interquartile range; LAA, large artery atherosclerosis; SAO, small-artery occlusion; SBP, systolic blood pressure.

3 | RESULTS

3.1 | General patient characteristics

We analyzed 967 patients with noncardiogenic IS caused by MCA disease. A total of 405 patients (41.9%) and 562 patients (58.1%) were diagnosed as the SAO and LAA subtype of IS, respectively. As for vascular risk factors, 748 patients (77.4%) had hypertension and 307 (31.7%) had diabetes mellitus. Among 307 patients with diabetes mellitus, 268 patients had hypertension, while 39 patients did not (Table 1). Admission symptoms and signs, and imaging features of IS are presented in Table 2.

3.2 | Predictors of the SAO versus LAA etiology of MCA disease

Univariate analysis demonstrated that compared to the SAO group, the LAA group more often had diabetes mellitus and a history of IS. Regarding the clinical manifestations, the LAA group more commonly had decreased alertness, gaze palsy, aphasia, neglect, and headache, while less commonly had limb ataxia at admission. However, the SAO group more often were male and more frequently had a higher systolic blood pressure (SBP) at admission. There were no significant differences in the prevalence of hypertension between the SAO and the LAA group among these patients with diabetes mellitus.

Multivariable logistic regression identified male (OR, 1.382; 95% CI, 1.027 to 1.858; $p = .032$) and hypertension (OR, 1.690; 95% CI, 1.207 to 2.368; $p = .002$) as the predictors of the SAO etiology of MCA disease, however, diabetes mellitus (OR, 0.697; 95% CI, 0.514 to 0.944; $p = .020$), repeated TIA before the stroke (OR, 0.464; 95% CI, 0.250 to 0.861; $p = .015$), gaze palsy (OR, 0.358; 95% CI, 0.140 to 0.915; $p = .032$), aphasia (OR, 0.331; 95% CI, 0.232 to 0.471; $p < .0001$), headache at admission (OR, 0.562; 95% CI, 0.338 to 0.934; $p = .026$), and disability at discharge (OR, 0.583; 95% CI, 0.422 to 0.806; $p = .001$) as the predictors of the LAA etiology of MCA disease (Table 3).

4 | DISCUSSION

The proportion of ischemic cerebrovascular disease caused by intracranial atherosclerosis in the Chinese population is much higher than in the Western White population (Pu et al., 2013; White et al., 2005). Our previous study also found IS in the MCA territory is far more common than IS in the internal carotid artery territory (Zhang et al., 2019).

MCA is the most common location of intracranial artery disease in the Chinese population (Pu et al., 2013); therefore, IS caused by MCA disease is also the most common type of IS caused by intracranial artery disease. In this study, we demonstrated the SAO subtype of MCA disease more frequently had a higher systolic blood pressure at admission, while the LAA subtype of MCA disease more frequently had diabetes

TABLE 2 Clinical and imaging features of 967 patients with acute ischemic stroke caused by middle cerebral artery disease

| Variables | Total (n = 967) | SAO (n = 405) | LAA (n = 562) | p |
|--|--------------------|------------------|------------------|--------|
| Admission symptoms and signs | | | | |
| Decreased alertness | 44 (4.6) | 5 (1.2) | 39 (6.9) | <.0001 |
| Gaze palsy | 51 (5.3) | 6 (1.5) | 45 (8.0) | <.0001 |
| Facial palsy | 687 (71.0) | 281 (69.4) | 406 (72.2) | .333 |
| Unilateral limb weakness | 581 (60.1) | 241 (59.5) | 340 (60.5) | .756 |
| Limb ataxia | 76 (7.9) | 40 (9.9) | 36 (6.4) | .048 |
| Sensory loss | 303 (31.3) | 123 (30.4) | 180 (32.0) | .583 |
| Aphasia | 275 (28.4) | 58 (14.3) | 217 (38.6) | <.0001 |
| Dysarthria | 454 (46.9) | 199 (49.1) | 255 (45.4) | .247 |
| Neglect | 14 (1.4) | 1 (.2) | 13 (2.3) | .008 |
| Dysphagia | 64 (6.6) | 24 (5.9) | 40 (7.1) | .462 |
| Headache | 43 (4.4) | 10 (2.5) | 33 (5.9) | .011 |
| Prestroke mRS, median (IQR) | 0 [0,0] | 0 [0,0] | 0 [0,0] | .111 |
| Admission NIHSS, median (IQR) | 4 [2,8] | 3 [2,6] | 5 [2,9] | <.0001 |
| Admission NIHSS \leq 3 | 403 (41.7) | 205 (50.6) | 198 (35.2) | <.0001 |
| Discharge NIHSS, median (IQR) | 2 [1,5] | 2 [1,3] | 3 [1,6] | <.0001 |
| Discharge mRS, median (IQR) | 1 [1,3] | 1 [1,2] | 2 [1,3] | <.0001 |
| Discharge mRS \geq 2 | 469 (48.5) | 154 (38.0) | 315 (56.0) | <.0001 |
| Repeated TIA before the stroke | 52 (5.4) | 18 (4.4) | 34 (6.0) | .275 |
| Imaging features | | | | |
| Multiple acute infarcts | 386 (39.9) | 5 (1.2) | 381 (67.8) | <.0001 |
| Single perforating artery infarct | 572 (59.2) | 400 (98.8) | 172 (30.6) | <.0001 |
| Borderzone infarcts | 358 (37.0) | 0 (0) | 358 (63.7) | <.0001 |
| Internal borderzone infarcts | 319 (33.0) | 0 (0) | 319 (56.8) | <.0001 |
| Anterior cortical borderzone infarcts | 188 (19.4) | 0 (0) | 188 (33.5) | <.0001 |
| Posterior cortical borderzone infarcts | 215 (22.2) | 0 (0) | 215 (38.3) | <.0001 |
| Territorial infarcts | 159 (16.4) | 0 (0) | 159 (28.3) | <.0001 |
| Small cortical infarct | 286 (29.6) | 0 (0) | 286 (50.9) | <.0001 |
| Stenosis of MCA M1 segment \geq 70% | 470 (48.6) | 0 (0) | 470 (83.6) | <.0001 |

Note: Data are n (%) unless otherwise indicate.

IQR, interquartile range; LAA, large artery atherosclerosis; MCA, middle cerebral artery; mRS, the Modified Rankin Scale; NIHSS, National Institutes of Health stroke scale; SAO, small-artery occlusion; TIA, transient ischemic attack.

mellitus. Hypertension was the predictor of the SAO etiology of MCA disease; however, diabetes mellitus was the predictor of the LAA etiology of MCA disease. These findings suggest that hypertension has a stronger correlation with SAO instead of LAA, while diabetes mellitus has a closer correlation with LAA instead of SAO. Therefore, hypertension and diabetes mellitus are associated with different etiology of MCA disease.

Previous studies found hypertension was the risk factor of both silent brain infarction (SBI) and symptomatic lacunar infarction (sLAC), while diabetes mellitus was only the risk factor of sLAC (Kim et al., 2011). We found the LAA group more frequently had serious clinical manifestations than the SAO group. Therefore, more sLAC patients might be the LAA subtype in the above study; however, more SBI

patients might be the SAO subtype. The SAO subtype of IS belongs to the category of cerebral small vessel disease. Hypertension is the most important risk factor for cerebral small vessel disease (Filomena et al., 2015). But compared with hypertension, the correlation between diabetes mellitus and cerebral small vessel disease is not very definite (Vermeer et al., 2007). In our CICAS study, 33.8% (967/2864) IS were caused by MCA disease. Among them, the SAO group accounted for 41.9%, and 77.4% patients with MCA disease had hypertension. These percentages are all very high. Our study found the SAO group more frequently had a higher systolic blood pressure at admission than the LAA group. Therefore, we speculated the higher prevalence and lower control rate of hypertension may be responsible for the higher prevalence of MCA disease in the Chinese populations (Danaei et al., 2011; Wang

TABLE 3 Multivariable logistic regression for the predictors of the SAO versus LAA etiology of MCA disease

| Variables | OR (95% CI) | p |
|--------------------------------|---------------------|--------|
| Age ≥ 65 years | 0.921 (0.686–1.236) | .584 |
| Male | 1.382 (1.027–1.858) | .032 |
| Smoking | 0.867 (0.622–1.208) | .399 |
| Drinking | 1.194 (0.637–2.237) | .580 |
| Hypertension | 1.690 (1.207–2.368) | .002 |
| Diabetes mellitus | 0.697 (0.514–0.944) | .020 |
| Hyperlipidemia | 1.198 (0.872–1.646) | .265 |
| Coronary heart disease | 1.093 (0.615–1.944) | .761 |
| History of ischemic stroke | 0.769 (.545–1.084) | .134 |
| Repeated TIA before the stroke | 0.464 (0.250–0.861) | .015 |
| Admission NIHSS ≤ 3 | 1.072 (0.767–1.500) | .683 |
| Discharge mRS ≥ 2 | 0.583 (0.422–0.806) | .001 |
| Decreased alertness | 0.516 (0.182–1.461) | .213 |
| Gaze palsy | 0.358 (0.140–0.915) | .032 |
| Limb Ataxia | 1.525 (0.922–2.521) | .100 |
| Aphasia | 0.331 (0.232–0.471) | <.0001 |
| Neglect | 0.178 (0.021–1.475) | .110 |
| Headache | 0.562 (0.338–0.934) | .026 |

CI, confidence interval; LAA, large artery atherosclerosis; MCA, middle cerebral artery; mRS, the Modified Rankin Scale; NIHSS, National Institutes of Health stroke scale; OR, odds ratio; SAO, small-artery occlusion; TIA, transient ischemic attack.

et al., 2018; White et al., 2005), especially for the higher prevalence of the SAO subtype of MCA disease, in spite of the variations in genetic susceptibility may also be a possible cause (Saposnik et al., 2003; White et al., 2005). Therefore, improving the control rate of hypertension may reduce the incidence of MCA disease in the Chinese population.

The SAO and LAA subtype of MCA disease accounted for 41.9% and 58.1% in our study, respectively. Our study also found that single perforating artery infarct was the most common infarction pattern caused by MCA disease, and the most common etiology of single perforating artery infarct was SAO, followed by LAA. We found 98.8% (400/405) patients in the SAO group had single perforating artery infarct, and only five patients (1.2%) had multiple and simultaneous perforating artery infarcts in ipsilateral lenticulostriate artery territory. Previous researches reported that patients with acute simultaneous multiple lacunar infarcts (MLI) had a higher recurrence risk and a higher proportion of disability compared to acute single lacunar infarct (SLI). Hypertension was found to be more prevalent, and admission SBP and diastolic blood pressure were found to be higher in MLI patients (Ohara et al., 2005; Spolveri et al., 1998). Therefore, MLI may be a more severe entity of small artery disease compared to SLI (Lee et al., 2012). Fibrinoid necrosis or hyalinosis caused by hypertension was thought to be the underlying vasculopathy of MLI (Ohara et al., 2005). Simultaneous bilateral hypertensive putamen or thalamus hemorrhage was also reported, and simultaneous rupture of microaneurysms in the perforating arteries by the sharply increased blood pressure was believed to be the probable etiology of symmetric hemorrhages simultaneously (Kono & Terada, 2014). Arteriosclerosis is strongly associated with

hypertension, its main pathological features include fibrinoid necrosis, hyalinosis, microatheroma, and microaneurysms and can result in ischemic consequences (i.e., leukoaraiosis and lacunar lesions) and hemorrhagic lesions of the brain parenchyma (i.e., microbleeds and large hematoma in basal ganglia) (Pantoni, 2010). Since the sharp increase of blood pressure can lead to the simultaneous rupture of microaneurysms in bilateral lenticulostriate arteries and the secondary cerebral hemorrhage in bilateral basal ganglia, and then it can also lead to the simultaneous fibrinoid necrosis or hyalinosis of multiple lenticulostriate arteries and the secondary acute MLI. Therefore, hypertension was believed to be the main reason for multiple and simultaneous lenticulostriate artery infarcts in the SAO group of our study.

Diabetes mellitus was reported to be related to the severity and progression of white matter hyperintensities (Gouw et al., 2008; Lucatelli et al., 2016). However, many large-scale observational studies did not find the significant correlation between diabetes mellitus and the incidence of SBI (Gouw et al., 2008; Vermeer et al., 2002). Therefore, whether diabetes mellitus was a risk factor of SBI or the SAO subtype of IS remains unclear (Vermeer et al., 2007). However, diabetes mellitus was an important risk factor of intracranial arteriosclerosis. Intracranial stenosis was approximately 3.13 times more frequently observed in the diabetic population than in the non-diabetic population (Mendes et al., 1999). Compared to non-diabetic patients with recent lacunar stroke, diabetic patients with recent lacunar stroke more frequently had intracranial stenosis $\geq 50\%$ (Palacio et al., 2014). High-resolution magnetic resonance imaging also demonstrated that patients with the SAO subtype of IS had a higher prevalence of hypertension compared

with the patients with LAA subtype of IS (80% versus 29%; $p < .001$); however, patients with the LAA subtype of IS had a higher prevalence of diabetes mellitus compared with the patients with the SAO subtype of IS (40% versus 15%; $p = .054$) (T. Gao et al., 2014). In diabetic patients, insulin deficiency often causes glucose to convert into a large amount of fat, which results in hyperlipidemia and LAA. However, the main pathological features of SAO or arteriosclerosis are fibrinoid necrosis and hyalinosis, which are most often caused by hypertension. Therefore, hypertension is the most widely accepted risk factor for SBI or SAO subtype of IS. Consequently, it is not hard to understand why diabetes mellitus has a closer correlation with LAA instead of SAO, while hypertension has a stronger correlation with SAO instead of LAA.

Our study had some limitations. First, this is a hospital-based study, and patients who were clinically unstable, unable to comply with MRI were excluded, and these may possibly result in a selection bias. Second, high-resolution MR was not performed; therefore, some patients in the SAO group may have a MCA plaque in the high-resolution MR, although there are no abnormalities in the MRA at all. This is another limitation of our study.

5 | CONCLUSIONS

Hypertension and diabetes mellitus are related with different etiology of middle cerebral artery disease.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

PEER REVIEW

The peer review history for this article is available at <https://publons.com/publon/10.1002/brb3.2521>

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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