

# Different risk factors in identical features of intracranial atherosclerosis plaques in the posterior and anterior circulation in high-resolution MRI

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## Abstract

**Background:** We constructed a high-volume registry to identify whether risk factors of intracranial atherosclerotic plaque (ICAP) features differ in the posterior and anterior circulation in patients with symptomatic intracranial atherosclerotic stenosis (ICAS) investigated by high-resolution magnetic resonance imaging (HRMRI).

**Methods:** The registry was constructed for patients with symptomatic ICAS who underwent HRMRI for culprit plaques. ICAP-vulnerable features included positive remodelling, diffuse distribution, intraplaque haemorrhage and strong enhancement.

**Results:** We analysed risk factors for the same ICAP features between the posterior and anterior circulation in data of 97 patients in the posterior circulation and 105 patients in the anterior circulation ICAPs. In patients with diffuse distribution, the probability of being female were lower [odds ratio (OR):0.08; 95% confidence interval (CI):0.02–0.34;  $p=0.001$ ] and having diabetes mellitus was higher (OR: 7.75; 95% CI:1.75–34.39;  $p=0.007$ ) in posterior circulation patients. In patients with strong enhancement, the probability of having diabetes was higher in posterior circulation patients (OR:6.71; 95% CI:1.37–32.81;  $p=0.019$ ).

**Conclusions:** Our results demonstrate more risk factors in the posterior than in the anterior circulation in patients with the same ICAP-vulnerable features, highlighting the need for stratification of risk factors in symptomatic ICAPs.

**Trial Registration:** URL: <http://www.clinicaltrials.gov>. Unique identifier: NCT02705599.

**Keywords:** risk factors, intracranial atherosclerosis plaque, high resolution MRI, location

Received: 22 September 2019; revised manuscript accepted: 15 January 2020.

## Introduction

Intracranial atherosclerotic stenosis (ICAS) is a major cause of ischemic stroke, and is highly prevalent in East Asia.<sup>1,2</sup> Epidemiological reports have identified gender, age, hypertension, diabetes mellitus, smoking and dyslipidaemia as risk factors for intracranial atherosclerotic disease.<sup>3–5</sup> Differences in risk factors (including age, gender, hypertension and diabetes mellitus) have been identified between the posterior and anterior circulation in ICAS.<sup>6,7</sup>

The Stenting *versus* Aggressive Medical Therapy for Intracranial Arterial Stenosis (SAMMPRIS)<sup>8</sup> and Warfarin–Aspirin for Symptomatic Intracranial Disease (WASID)<sup>9</sup> trials reported that modifying risk factors reduced stroke recurrence in patients with ICAS. However, despite aggressive medical treatment, around 15% of severe ICAS patients still experience recurrent stroke.<sup>10</sup> In addition, differences in recurrent stroke have been identified between patients with posterior and anterior circulation ICAS.<sup>11</sup>

*Ther Adv Neurol Disord*

2020, Vol. 13: 1–8

DOI: 10.1177/  
1756286420909991

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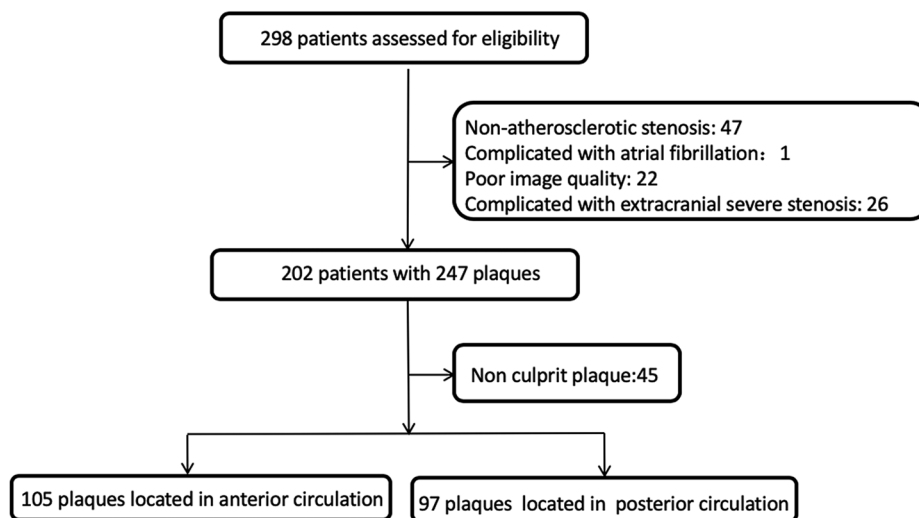
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**Figure 1.** Flow chart of study.

However, it remains unclear whether the incidence of risk factors and intracranial atherosclerotic plaque (ICAP)-vulnerable features in the posterior circulation are comparable to those in the anterior circulation. Identifying ICAP-vulnerable features, and understanding differences in risk factors and plaque features between the posterior and anterior circulation, may, therefore, have utility for risk stratification for recurrent stroke.

High-resolution magnetic resonance imaging (HRMRI) can subtract the signal from blood flow in the vessel lumen and allow direct visualization of ICAP *in vivo*.<sup>12,13</sup> In previous studies, ICAP features based on HRMRI including positive remodelling,<sup>14</sup> diffuse distribution,<sup>15</sup> intraplaque haemorrhage and strong enhancement have been identified as markers for future stroke risk.<sup>16,17</sup> We therefore designed a prospective and observational registry focusing on patients with symptomatic ICAS who underwent HRMRI to evaluate differences in risk factors of ICAP-vulnerable features between the posterior and anterior circulation.

## Methods

This was a observational study conducted at two high-volume stroke centres. All study protocols were approved by the ethics committees of Beijing Tiantan hospital and Chinese PLA General Hospital. Written informed consent was obtained from the patients or their legal guardians, and all research was performed in accordance with the relevant guidelines and regulations.

## Enrolment of patients

Patients admitted with suspected symptomatic intracranial arterial disease between September 2014 and January 2017 were enrolled. Patients received one or more types of examination to determine the cause of ischemic events, including transient ischemic attack or ischemic stroke, using carotid duplex ultrasound, transcranial Doppler, echocardiography, electrocardiography, computer tomography (CT), CT angiography (CTA), magnetic resonance imaging (MRI), magnetic resonance angiography (MRA) and (or) digital subtraction angiography (DSA). If these examinations indicated that ischemic events were considered to be due to ICAS, patients were referred to the MRI centre for scanning of the culprit lesions by HRMRI. Patients were enrolled in this study according to the following criteria: (1) ischemic events in the target regions of intracranial anterior or posterior circulation within 90 days of presentation, (2) lack of coexistent ipsilateral extracranial carotid artery or vertebral artery stenosis of  $\geq 50\%$ , (3) no potential sources of cardioaortic embolism based on the modified Trial of ORG 10 172 in Acute Stroke Treatment (TOAST) classification,<sup>18</sup> (4) age  $\geq 18$  years and (5) one or more atherosclerotic risk factors. The study flow chart is shown in Figure 1.

Patients with the following conditions were excluded: (1) nonatherosclerotic vasculopathy, such as vasculitis and arterial dissection, diagnosis through comprehensive laboratory work (such as erythrocyte sedimentation rate or C-reactive protein elevation,

antinuclear antibody or antiphospholipid antibody positivity), vascular imaging or clinical evaluation; or (2) contraindication to MR examination or medical instability precluding MR examination.

#### *Definitions of risk factors*

Hypertension was defined as systolic blood pressure of  $\geq 140$  mmHg, diastolic blood pressure  $\geq 90$  mmHg or current antihypertensive drug use. Hypercholesterolemia was defined as a total cholesterol level  $\geq 6.22$  mmol/l, low-density lipoprotein cholesterol level  $\geq 4.14$  mmol/l or current use of cholesterol-lowering medication. Patients who used antidiabetic medications (insulin or oral hypoglycaemics) were considered to have diabetes mellitus. Patients who smoked in the past or currently were considered to have a history of smoking cigarettes. Obesity was defined as a body mass index greater than 30 kg/m<sup>2</sup>.

#### *HRMRI acquisition*

All HRMRI studies were performed using a 3T GE DISCOVERY MR 750 (GE Healthcare, Waukesha, WI, USA) or a 3T Siemens Trio MR scanner (Siemens Healthcare, Ehrlangen, Germany). The multiple pulse sequences included three-dimensional time of flight MR angiography (3D TOF MRA), 3D T1-weighted imaging, proton attenuation weighted imaging, magnetization-prepared rapid acquisition with gradient-echo sequence (MPRAGE), and contrast enhanced T1-weighted imaging. Details of the sequence parameters are presented in the supplemental eTable 1 online. Images were reconstructed using the Reformat tool in the AW 4.5 workstation (GE Healthcare) or the D multiple planer reconstruction tool in the Siemens workstation.

#### *Imaging analysis and measurements*

All HRMR images were analysed by two neuroradiologists (L.X. and L.J.H.). All readers were blinded to the patients' clinical data. An image-quality rating (1 = poor, 2 = adequate and 3 = good) was given to each image by the two neuroradiologists. Patients with poor-quality images due to severe motion artefacts or low signal-to-noise ratio were excluded. In the initial group of 10 patients evaluated using both scanners, these images were also reviewed by two neuroradiologists (S.B.B. and S.M.) for the inter-observer and intra-observer variability of the two scanners. The

present study did not display intra- and inter-observer variabilities with the same or different scanners in light of previous research showing that these variabilities are small.<sup>19</sup>

Remodelling index was calculated as the ratio of the vessel area at the maximal lumen narrowing site to that at the reference site. The reference site was selected based on the WASID method.<sup>20</sup> A remodelling index  $\geq 1.05$  was defined as positive remodelling, 0.95–1.05 as intermediate remodelling,  $\leq 0.95$  as negative remodelling (eFigure S1 in the online-only Data Supplement).<sup>21</sup>

Distribution patterns were identified at the narrowest slices. Plaque distribution was recorded as one of four quadrants of the vessel wall on cross-sectional images (eFigure 2 in the online-only Data Supplement). Plaques that were distributed across at least three quadrants of the lumen perimeter were defined as diffuse, and those across at least two were defined as nondiffuse. Intraplaque haemorrhage was defined as a signal intensity of  $>150\%$  of that of the adjacent grey matter on all pulse sequences (eFigure 3 in the online-only Data Supplement).<sup>22</sup>

Contrast enhancement was performed on black blood T1WI (three-dimensional T1 CUBE and T1 SPACE) 5 min after Gadolinium administration (0.1 mmol/kg gadopentetate dimeglumine, Magnevist; Bayer Schering Pharma, Berlin, Germany) using the same parameters as with the precontrast black blood T1WI.<sup>23</sup> The enhancement was classified into one of three grades: nonenhancement, moderate enhancement or strong enhancement. Moderate enhancement was defined as less than that of the pituitary infundibulum. Strong enhancement was equal to or stronger than that of the pituitary infundibulum (eFigure 4 in the online-only Data Supplement).<sup>19</sup>

In this study, positive remodelling, diffuse distribution, intraplaque haemorrhage and strong enhancement were recognized as ICAP-vulnerable features as previous studies have showed their close relationships with future ischemic events.<sup>14–17</sup>

Image reconstruction was performed at the workstation. MR images were subsequently processed using freely available software ImageJ (Rasband, National Institute of Mental Health, Bethesda, USA).<sup>24</sup>

### ICAP location

The culprit plaques located in the intracranial internal carotid artery, middle cerebral artery, intracranial vertebral artery or basilar artery were recorded. Culprit plaques in the intracranial internal carotid and middle cerebral arteries were categorized as anterior circulation ICAPs, while those in the intracranial vertebral and basilar arteries were categorized as posterior circulation ICAPs. Culprit plaques were determined by two experienced neurologists through clinical symptoms and vascular imaging including DWI and MRA, CTA or DSA.

### Statistical analysis

Continuous variables are presented as mean  $\pm$  standard deviation (SD) and categorical variables as percentages. The differences in risk factors of patients with the same ICAP features between posterior and anterior circulation were analysed. Chi-square tests were used to analyse the differences in risk factors and ICAP-vulnerable features between posterior and anterior circulation. Chi-square tests and multiple variable logistic regression analysis were used to evaluate differences in risk factors of patients with same ICAP-vulnerable features between posterior and anterior circulation. All statistical tests were two-sided, and  $p < 0.05$  was considered statistically significant.

## Results

### General subject characteristics

A study flow chart is presented in Figure 1. In total, 202 patients were enrolled, 247 plaques were found and 202 culprit plaques were available for analysis (Table 1). We analysed data from 97 patients with posterior circulation plaques and 105 patients with anterior circulation plaques. The mean age of the patients was  $52.96 \pm 11.71$  years (range: 26–82) and the median age was 54 years. Of the subjects, 158 (78.2%) were male, 23 (11.5%) were obese, 135 (66.8%) had hypertension, 65 (32.2%) had diabetes mellitus, 96 (47.5%) had hyperlipidaemia and 124 (61.4%) were cigarette smokers. The mean low-density lipoprotein cholesterol (LDL-C) level was  $2.10 \pm 0.78$  mmol/l and the mean body mass index was  $26.14 \pm 3.21$  kg/m<sup>2</sup>.

**Table 1.** General subject characteristics.

Variable	Patients (n=202)
Risk factors	
Age, years <sup>a</sup>	53.77 (45–62)
Male	158 (78.2)
Obesity	23 (11.5)
Hypertension	135 (66.8)
Diabetes mellitus	65 (32.2)
Hyperlipidemia	96 (47.5)
Smoking	124 (61.4)
LDL-C, mmol <sup>a</sup>	1.96 (1.51–2.65)
Body mass index, kg/m <sup>2</sup> <sup>a</sup>	25.92 (23.75–27.90)
Clinical events	
TIA	38 (18.8)
Cerebral infarction	164 (81.2)
Plaque location	
Anterior circulation	105 (52.0)
Posterior circulation	97 (48.0)

<sup>a</sup>Data are presented as median (interquartile range). LDL-C, low-density lipoprotein cholesterol; TIA, transient ischaemic attack.

### Differences in risk factors between posterior and anterior circulation

In patients with posterior circulation ICAP, there were higher incidences of age  $\geq 54$  years (61.9% versus 34.3%,  $p = 0.001$ ), hypertension (79.4% versus 55.2%,  $p = 0.001$ ) and diabetes mellitus (42.3% versus 22.9%,  $p = 0.003$ ) in patients with posterior circulation ICAP compared with patients with anterior circulation ICAP except females (28.57% versus 14.43%,  $p = 0.002$ ) (Table 2).

### Differences in ICAP-vulnerable features between posterior and anterior circulation

There were no differences in ICAP-vulnerable features between posterior and anterior circulation, including positive remodelling (31.9% versus 39.2%,  $p = 0.511$ ), intraplaque haemorrhage (19.6% versus 18.1%,  $p = 0.786$ ) and strong

**Table 2.** The association risk factors with location of intracranial atherosclerosis plaques, using multiple logistic regression model.

Variable	Anterior (n = 105)	Posterior (n = 97)	OR (95%CI)	p
Female	30 (28.57)	14 (14.43)	0.21 (0.08–0.56)	0.002
Age, ≥54 years	36 (34.29)	60 (61.86)	3.66 (1.87–7.14)	0.001
Obese	10 (9.52) <sup>a</sup>	13 (13.40)	1.89 (0.70–5.12)	0.209
Hypertension	58(55.24)	77 (79.38)	2.26 (1.08–4.71)	0.029
Diabetes	24 (22.86)	41 (42.27)	2.77 (1.34–5.72)	0.006
Hyperlipidemia	53 (50.48)	43 (44.33)	0.57 (0.30–1.10)	0.093
Smoking	63 (60.00)	61 (62.89)	0.92 (0.43–1.97)	0.832

<sup>a</sup>Data are presented from 103 patients.  
OR, odds ratio.

enhancement (37.9% versus 54.0%,  $p=0.094$ ) between posterior and anterior circulation, respectively. However, diffuse distribution was significantly different between posterior and anterior circulation (73.6% versus 31.6%, respectively,  $p=0.001$ ).

#### *Differences in risk factors in patients with the same ICAP-vulnerable features between posterior and anterior circulation*

Multivariate logistic regression analysis showed that, in patients with diffuse distribution, there were higher odds of diabetes [odds ratio (OR): 7.75; 95% confidence interval (CI): 1.75–34.39;  $p=0.07$ ] in the posterior than the anterior circulation, and higher odds of being female (OR: 0.08; 95% CI: 0.02–0.34;  $p=0.001$ ) in the anterior than in the posterior circulation. In patients with strong enhancement, the odds of diabetes (OR: 6.71; 95% CI: 1.37–38.81;  $p=0.019$ ) were higher in the posterior than in the anterior circulation (Table 3).

## Discussion

In this study, we found that risk factors were different between the posterior circulation and the anterior circulation in patients with the same ICAP-vulnerable features.

In patients with diffuse distribution, we found that there were higher odds of having diabetes mellitus and lower odds of being female in the posterior than in the anterior circulation. Use of HRMRI enables clear visualization of plaque

distribution.<sup>25,26</sup> Changes in plaque distribution from focal to diffuse indicate increasing plaque progression. Our data indicated that female patients may be more susceptible to diffuse plaque distribution in the anterior circulation, and that this may be related to metabolic factors secondary to diabetes mellitus.

The patients with strong enhancement of plaques had higher odds of diabetes in the posterior circulation than in the anterior circulation. Plaque enhancement on HRMRI is a marker of plaque vulnerability and progression is strongly associated with stroke.<sup>27</sup> Plaque enhancement is also associated with endothelial dysfunction and neovascularization of the artery wall.<sup>17</sup> Several studies have found that arterial wall enhancement is closely related to age and the degree of intracranial artery stenosis.<sup>28,29</sup> Our data indicated that strong enhancement in the posterior circulation may be more related to metabolic factors caused by dyslipidaemia.

In patients with positive remodelling and intra-plaque haemorrhage, risk factors did not differ between the posterior and the anterior circulation. Artery remodelling is a compensatory response to stenosis that may involve haemodynamic changes and inflammatory mechanisms.<sup>28</sup> A previous study showed that there is a strong correlation between positive remodelling and ischemic events.<sup>14</sup> Positive remodelling in the coronary artery is associated with several risk factors including hypertension, diabetes and dyslipidaemia.<sup>30</sup> The lack of difference in risk factors in

**Table 3.** The association of related variables with position of intracranial atherosclerosis plaques, using multiple logistic regression model by each characteristics of plaques.

Variable	Diffuse distribution (n = 98)	
	OR (95%CI)	p
Female	0.08 (0.02–0.34)	0.001
Age, ≥54 years	2.47 (0.85–7.21)	0.098
Obese	2.67 (0.49–14.65)	0.259
Hypertension	1.34 (0.41–4.46)	0.628
Diabetes	7.75 (1.75–34.39)	0.007
Intraplaque haemorrhage (n = 38)		
OR (95%CI)		
p		
Female	0.48 (0.08–3.00)	0.436
Age, ≥54 years	0.97 (0.17–5.46)	0.969
Obese	0.39 (0.02–8.49)	0.550
Hypertension	8.03 (0.71–90.98)	0.093
Diabetes	3.16 (0.6–16.57)	0.174
Positive remodelling (n = 67)		
OR (95%CI)		
p		
Female	0.3 (0.07–1.27)	0.103
Age, ≥54 years	2.04 (0.63–6.65)	0.236
Obese	1.64 (0.17–15.77)	0.667
Hypertension	2.59 (0.71–9.4)	0.149
Diabetes	1.62 (0.5–5.23)	0.421
Strong enhancement (n = 49)		
OR (95%CI)		
p		
Female	0.25 (0.05–1.34)	0.106
Age, ≥54 years	2.85 (0.66–12.42)	0.162
Obese	4.86 (0.71–33.37)	0.107
Hypertension	1.67 (0.33–8.5)	0.538
Diabetes	6.71 (1.37–32.81)	0.019
OR, odds ratio.		

patients with positive remodelling between the posterior and the anterior circulation may be due to the small sample size and should be studied further in the future.

Although there were no risk factor differences between the posterior and anterior circulation in patients with intraplaque haemorrhage, there were higher odds of hypertension in the posterior than in the anterior circulation ( $p=0.093$ ). The small sample may be the major reason that the tendency did not reach significance. Intraplaque haemorrhage is a well-recognized marker of plaque destabilization and is also associated strongly with plaque progression, thin or ruptured fibrous caps, active inflammation within plaques and ischemic events.<sup>31</sup> Intraplaque haemorrhage may arise because the plaque cannot obtain sufficient nutrients from the vasa vasorum during progression, causing extravasation of red blood cells.<sup>32</sup> A study focusing on basilar artery plaques found that intraplaque haemorrhage was closely related to the degree of stenosis.<sup>16</sup>

This study showed that there were higher incidences in older, hypertensive and diabetes mellitus patients with posterior circulation ICAPs compared with patients with anterior circulation ICAPs. These findings were similar to those reported in previous studies showing that age and diabetes mellitus were significantly related to basilar artery plaques, while being male and hypertensive were associated with intracranial vertebral plaques.<sup>29</sup> A previous study found that hypertension and diabetes mellitus were related to posterior circulation disease.<sup>7</sup> The results of subgroup analysis from the WASID trial showed that basilar stenosis was associated with age and hyperlipidaemia, that intracranial vertebral artery stenosis was associated with coronary artery disease and that intracranial carotid artery stenosis was associated with diabetes mellitus and middle cerebral artery stenosis in females.<sup>6</sup>

In addition, our study showed no significant differences in ICAP features, including positive remodelling, intraplaque haemorrhage and strong enhancement between the posterior and anterior circulation; however, diffuse distribution showed a significant difference between the two groups. Larger ICAPs with diffuse distribution appeared to be a specific feature of posterior circulation lesions over those in the anterior circulation (74.3% in posterior, 31.8% in anterior circulation), which is consistent with the results of a previous study.<sup>33</sup>

There are several limitations of the current study. First, all enrolled patients are Chinese, and therefore the results may not be applicable to other ethnicities. Second, the sample size was relatively small. Third, ICAP features based on HRMRI may not reflect the true intracranial plaque features *in vivo* because of its limitations in terms of resolution. In patients with the same ICAP-vulnerable features, there are more risk factors in the posterior circulation than in the anterior circulation, suggesting that stratification may be required for risk factor management in patients with symptomatic intracranial ICAP. These findings should be confirmed or refuted with future studies.

### Acknowledgements

Authors Ziqi Xu, Mingyao Li, Benyan Luo and Ning Ma contributed equally to the manuscript. We thank Jingyi Liu from the Neurology Department of Beijing Tiantan Hospital for polishing the article.


### Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the National Natural Science Foundation of China (Contract grant numbers: 81671126 and 81730048 to X.L., 81471390 to N.M., 81371290 to Z.R.M., and 81361120402 to B.B.S and M.S.), Beijing High-level Personnel Funds (Contract grant number: 2013-2-19 to Z.R.M.), and National Key R&D Program of China (Contract grant number: 2016YFC0100100 to X.L.), Medical and Health Science and Technology of Zhejiang Province (Contract grant number: 2015KYA080 to Z.Q.X).

### Conflict of interest statement

The authors declare that there is no conflict of interest.

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### Supplemental material

Supplemental material for this article is available online.

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