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Collateral Flow in Magnetic Resonance Angiography: Prognostic Value for Vertebrobasilar Stenosis With Stroke Recurrence

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Department of Radiology, Chinese PLA General Hospital, 28 Fuxing Road, Beijing 100853, China Tel +86-18601226301 Fax +86-01066936620 E-mail louxin@301hospital.com.cn **Background and Purpose** Intracranial vertebrobasilar atherosclerotic stenosis (IVBAS) is a major cause of posterior circulation stroke. Some patients suffer from stroke recurrence despite receiving medical treatment. This study aimed to determine the prognostic value of a new score for the posterior communicating artery and the P1 segment of the posterior cerebral artery (PCoA-P1) for predicting stroke recurrence in IVBAS.

Methods We retrospectively enrolled patients with severe IVBAS (70%–99%). According to the number of stroke recurrences, patients were divided into no-recurrence, single-recurrence, and multiple-recurrences groups. We developed a new 5-point grading scale, with the PCoA-P1 score ranging from 0 to 4 based on magnetic resonance angiography, in which primary collaterals were dichotomized into good (2–4 points) and poor (0 or 1 point). Stroke recurrences after the index stroke were recorded. Patients who did not experience stroke recurrence were compared with those who experienced single or multiple stroke recurrences.

Results From January 2012 to December 2019, 176 patients were enrolled, of which 116 (65.9%) had no stroke recurrence, 35 (19.9%) had a single stroke recurrence, and 25 (14.2%) had multiple stroke recurrences. Patients with single stroke recurrence (odds ratio [OR]= 4.134, 95% confidence interval [CI]=1.822–9.380, *p*=0.001) and multiple stroke recurrences (OR=6.894, 95% CI=2.489–19.092, *p*<0.001) were more likely to have poor primary collaterals than those with no stroke recurrence.

Conclusions The new PCoA-P1 score appears to provide improve predictions of stroke recurrence in patients with IVBAS.

Keywords posterior cerebral artery; ischemic stroke; magnetic resonance angiography; collateral circulation.

INTRODUCTION

Approximately 35% of posterior circulation ischemic strokes are caused by intracranial vertebrobasilar atherosclerotic stenosis (IVBAS).¹ Despite receiving medical treatment, the rate of stroke recurrence in patients with IVBAS ranges from 24.6% to 38.7%.²⁻⁴ This makes it necessary to identify high-risk patients, especially those with multiple stroke recurrences, for whom aggressive medical therapy or elective intervention might fundamentally improve their management.

Many factors have been reported to be associated with stroke recurrence in patients with IVBAS, including a chief complaint of dysphagia, repeated transient ischemic attacks within 3 months before the stroke, \geq 70% stenosis in the responsible artery, multisector infarcts, and not being on antithrombotic treatment at discharge.⁵ However, these factors are insufficient

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for accurately predicting stroke recurrence. Collateral circulation dramatically alters the subsequent stroke risk in intracranial atherosclerosis.⁶ Patients with impaired collateral flow in the anterior circulation have a particularly high risk of stroke recurrence even when they receive medical treatment.⁷ Few studies have investigated the association between stroke recurrence and collateral circulation in patients with IVBAS, and there is no practicable scoring system for evaluating the primary collaterals.

Given the understudied nature of the above-mentioned association, we examined the relationship between stroke recurrence and collateral circulation in patients with IVBAS using a newly designed score for the posterior communicating artery (PCoA) and the P1 segment of the posterior cerebral artery (P1). The aim of our study was to determine the prognostic value of this new magnetic resonance angiography (MRA)-based grading system focusing on the primary collateral pathways.

METHODS

Study population

This study was approved by the Institutional Review Board of Beijing Tiantan Hospital, Capital Medical University. We used prospectively curated clinical and radiological databases to retrospectively identify consecutive ischemic stroke patients with intracranial atherosclerosis stenosis from 2012 to 2019. Eligible patients had experienced posterior circulation ischemic stroke due to severe IVBAS (70%-99%). Newly developed ischemic stroke was diagnosed by diffusion-weighted imaging (DWI) within 7 days after symptom onset. The degree of stenosis was measured according to the Warfarin-Aspirin for Symptomatic Intracranial Disease (WASID) trial.8 Patients with Moyamoya disease, vasculitis, dissection, atrial fibrillation, or extracranial tandem lesions were excluded. Patients diagnosed with transient ischemic attack and those for whom radiological images were unavailable were also excluded.

Clinical information assessment

Demographic and clinical information was collected, including sex, age, risk factors, and National Institutes of Health Stroke Scale (NIHSS) score at enrollment, as was whether any antithrombotic agents were taken before or after the index stroke. Stroke recurrence was defined as relapse or aggravation on the basis of the previous symptom, extension of a previous infarction, or new infarction in the territory of vertebrobasilar artery. According to the number of stroke recurrences, patients were divided into the no-recurrence, single-recurrence, and multiple-recurrences groups. The time interval from the index stroke to enrollment was also recorded. Hypertension was defined as a history of hypertension or taking any hypotensive drug. Diabetes mellitus was defined as a history of diabetes mellitus, taking any hypoglycemic agent, or glycosylated hemoglobin \geq 7%. Hyperlipidemia was defined as a history of hyperlipidemia, or receiving lipid-lowering treatment. Coronary artery disease was defined as a history of myocardial infarction or angina pectoris. Smoking was defined as current or previous smoking.^{9,10}

Magnetic resonance imaging analysis

Imaging sequences were performed, including T1-weighted imaging, T2-weighted imaging, DWI, and three-dimensional time-of-flight (3D-TOF) MRA. The stroke mechanisms, lesion location, PCoA-P1 score, and vertebral artery (VA) anatomic patterns were evaluated. All images were interpreted by two of the authors (a neurosurgeon and a neurologist) on a consensus basis. To reduce bias, each author first independently reviewed all the data, and then they conferred to reach an agreement. If they did not reach agreement, a third author was consulted to decide the results. The evaluated parameters are described in detail below.

Based on the infarcts seen on DWI distributed in the distal territories of the culprit artery, stroke mechanisms were divided into artery-to-artery (A-A) embolism, hypoperfusion, perforator, and mixed mechanism:¹¹ 1) A-A embolism, multiple infarcts located in the cerebellum and/or cortex; 2) hypoperfusion, infarcts located in a border zone; 3) perforator, single or multiple infarcts located in the brainstem; 4) mixed mechanism, coexistence of two or more of the above mechanisms.

Lesion location was divided into the intracranial VA and basilar artery (BA) based on MRA imaging.

The PCoA-P1 score was determined as follows from 3D-TOF MRA observations as depicted in Fig. 1: 1) 0 points: absence of a bilateral anterior-to-posterior circulation connection; 2) 1 point: presence of a unilateral PCoA-to-P1 connection, but with PCoA or P1 hypoplasia; 3) 2 points: presence of a unilateral normal PCoA-to-P1 connection or a bilateral PCoAto-P1 connection, but with either PCoA or P1 hypoplasia; 4) 3 points: presence of a bilateral PCoA-to-P1 connection, but with one side normal combined with contralateral PCoA or P1 hypoplasia; 5) 4 points: presence of bilateral connections between a normal PCoA and P1. Primary collaterals was dichotomized into good (2–4 points) and poor (0 or 1 point).

VA anatomic patterns were divided into unilateral VA (contralateral VA absent), bilateral VA (the two VAs of equal size), and dominant VA (one VA dominant and hypoplasia in the contralateral VA). Hypoplasia was defined as in a previous study.¹²

Yan L et al.



Fig. 1. Schematics for explaining the score for the posterior communicating artery (PCoA) and the P1 segment of the posterior cerebral artery (P1) as determined from three-dimensional time-of-flight magnetic resonance angiography: 0 points, absence of a bilateral anterior-to-posterior circulation connection; 1 point, presence of a unilateral PCoA-to-P1 connection, but with PCoA or P1 hypoplasia; 2 points, presence of a unilateral PCoA-to-P1 connection, but with either PCoA or P1 hypoplasia; 3 points, presence of a bilateral PCoA-to-P1 connection, but with either PCoA or P1 hypoplasia; 3 points, presence of a bilateral PCoA-to-P1 connection, but with one side normal combined with contralateral PCoA or P1 hypoplasia; and 4 points, presence of bilateral connections between a normal PCoA and P1.

Statistical analysis

We performed statistical analysis using SPSS software (version 20.0, IBM Corp., Armonk, NY, USA). Categorical data are expressed as frequencies and percentages. Normally distributed continuous data are expressed as mean±standarddeviation values, while nonnormally distributed continuous data are expressed as median and interquartile range (IQR) values. The characteristics of patients with no recurrence, single recurrence, and multiple recurrences were compared. The χ^2 test was used for comparisons of categorical variables. ANOVA was used for comparisons of continuous variables conforming to a normal distribution, while the other continuous variables were compared using the Kruskal-Wallis test. Multivariable analysis was performed while adjusting for sex and age. A probability value of p<0.05 was considered to indicate a statistically significant difference.

RESULTS

We rescreened 1,960 patients with symptomatic intracranial atherosclerotic stenosis, and 176 patients who met the inclusion criteria were finally enrolled (Fig. 2). These patients comprised 116 (65.9%) with no recurrence, 35 (19.9%) with a single recurrence, and 25 (14.2%) with multiple recurrences. The patients were aged 58.9 ± 9.6 years, and most of them were male (81.8%). Hypertension was present in 145 (82.4%)



Fig. 2. Flowchart of study enrollment. DWI, diffusion-weighted imaging; MRA, magnetic resonance angiography; TIA, transient ischemic attack; 3D-TOF, three-dimensional time-of-flight.

patients, diabetes mellitus in 77 (43.8%), hyperlipidemia in 47 (26.7%), smoking in 106 (60.2%), and coronary heart disease in 22 (12.5%). The median NIHSS score at enrollment was 0.5 (IQR=0–2). Thirty-three (18.8%) and 169 (96.0%) patients were taking antithrombotic agents before and after the index stroke, respectively. The median time interval from the index stroke to enrollment was 35.9 days (IQR=25.4–63.1 days). A-A embolism was found in 99 (56.3%) patients, followed by perforator in 40 (22.7%) and mixed mechanism in 37 (21.0%), while hypoperfusion was not found. The lesion was located in the BA for 83 (47.2%) patients and in the intracranial VA for 93 (52.8%) patients. The baseline patient features are listed in Table 1.

PCoA-P1 score

The 176 patients comprised 38 (21.6%), 43 (24.4%), 76 (43.2%), 15 (8.5%), and 4 (2.3%) with PCoA-P1 scores of 0, 1, 2, 3, and 4 points, respectively, and hence 95 and 81 patients were classified as having good and poor primary collaterals, respec-

Table 1. Comparison of characteristics in the no-recurrence, single-recurrence, and multiple-recurrences groups

Mariable	No recurrence	o recurrence Single recurrence		
variable	(<i>n</i> =116)	(n=35)	(n=25)	р
Sex, male	95 (81.9)	29 (82.9)	20 (80.0)	0.960
Age (yr)	59.7±9.5	56.7±10.0	58.6±9.2	0.255
Hypertension	96 (82.8)	27 (77.1)	22 (88.0)	0.544
Diabetes mellitus	53 (45.7)	13 (37.1)	11 (44.0)	0.671
Hyperlipidemia	31 (26.7)	7 (20.0)	9 (36.0)	0.385
Coronary artery disease	15 (12.9)	5 (14.3)	2 (8.0)	0.726
Smoking	68 (58.6)	21 (60.0)	17 (68.0)	0.685
NIHSS score at enrollment	0.0 (0.0-1.0)	2.0 (1.0-3.0)	1.0 (0.0–3.0)	<0.001
Taking any antithrombotic agents before the index stroke	20 (17.2)	6 (17.1)	7 (28.0)	0.441
Taking any antithrombotic agents after the index stroke	112 (96.6)	34 (97.1)	23 (92.0)	0.594
Time interval from index stroke to enrollment (day)	35.7 (23.7-61.2)	40.7 (27.0-67.0)	31.6 (25.7-63.2)	0.586
Index stroke mechanism				0.990
Artery-to-artery embolism	64 (55.2)	21 (60.0)	14 (56.0)	
Perforator	27 (23.3)	7 (20.0)	6 (24.0)	
Mixed	25 (21.6)	7 (20.0)	5 (20.0)	
Hypoperfusion	0 (0)	0 (0)	0 (0)	
Lesion location				0.078
ВА	48 (41.4)	19 (54.3)	16 (64.0)	
VA	68 (58.6)	16 (45.7)	9 (36.0)	
PCoA-P1 score				< 0.001
2-4	77 (66.4)	12 (34.3)	6 (24.0)	
0 or 1	39 (33.6)	23 (65.7)	19 (76.0)	
VA anatomic pattern				0.562
Unilateral	27 (23.3)	9 (25.7)	7 (28.0)	
Hypoplasia	50 (43.1)	18 (51.4)	8 (32.0)	
Bilateral	39 (33.6)	8 (22.9)	10 (40.0)	

Data are mean \pm standard deviation, n (%), or median (interquartile range) values.

BA, basilar artery; NIHSS, National Institutes of Health Stroke Scale; PCoA, posterior communicating artery; P1, P1 segment of the posterior cerebral artery; VA, vertebral artery.

tively (Figs. 3 and 4). Two patients with normal PCoA and P1 connections received 0 points because of the presence of retrograde blood flow from the posterior to the anterior circulation due to occlusion of the internal carotid artery.

Comparison of no recurrence, single recurrence, and multiple recurrences

There was no significant difference among the three groups in sex, age, the taking of any antithrombotic agents before and after the index stroke, time intervals from the index stroke to enrollment, lesion location, or VA anatomic patterns. Patients with no recurrence had a lower NIHSS score (median=0.0, IQR=0.0–1.0, p<0.001). There was an increasing trend in the prevalence of BA involvement from the no-recurrence group to the single-recurrence and multiple-recurrences groups (41.4%, 54.3%, and 64.0%, respectively), and also in poor primary collaterals (33.6%, 65.7%, and 76.0%, respectively).

Multivariable analysis adjusting for sex and age revealed that patients with multiple stroke recurrences were more likely to have BA involvement (odds ratio [OR]=2.851, 95% confidence interval [CI]=1.105-7.358, p=0.030). The prevalence of poor primary collaterals was higher in both single recurrence (OR=4.134, 95% CI=1.822-9.380, p=0.001) and multiple recurrences (OR=6.894, 95% CI=2.489-19.092, p<0.001) (Table 2).

DISCUSSION

We have proposed an MRA-based primary collateral score called the PCoA-P1 score for quantifying the collateral status of patients with IVBAS. Patients with poor primary collaterals (0 or 1 point) were more likely to have multiple stroke recurrences. The goal is for the PCoA-P1 score to serve as a prognostic tool for screening high-risk patients who may benefit from aggressive medical therapy or endovascular treatment.

The collateral status was an independent predictor of stroke recurrence in patients with intracranial atherosclerotic stenosis.⁶ A distal flow status of symptomatic vertebrobasilar ath-







Fig. 4. A female adult presented with dizziness with a 1-day history. DWI demonstrated infarcts distributed in the left occipital lobe (A). The index stroke mechanism was classified as artery-to-artery embolism. She had a history of hyperlipidemia, hypertension, and diabetes mellitus. 3D-TOF MRA showed that the PCoA-to-P1 connection was present on the right side while the PCoA was hypoplastic, and there was no connection on the left side (arrows) (B-D). The PCoA-P1 score was 1 point. The patient experienced two strokes during the 35-day period following the initial onset. DWI, diffusion-weighted imaging; MRA, magnetic resonance angiography; PCoA, posterior communicating artery; P1, P1 segment of the posterior cerebral artery; 3D-TOF, three-dimensional time-of-flight.

Variable		Single recurrence		Multiple recurrences	
	No recurrence	Adjusted OR (95% CI)	р	Adjusted OR (95% CI)	р
Sex, male	Reference	1.054 (0.358–3.101)	0.924	0.997 (0.306–3.242)	0.996
Age, years	Reference	0.964 (0.924-1.006)	0.095	0.984 (0.936-1.034)	0.521
Lesion located in BA	Reference	1.823 (0.816-4.070)	0.143	2.851 (1.105–7.358)	0.030
PCoA-P1 score=0 or 1	Reference	4.134 (1.822-9.380)	0.001	6.894 (2.489–19.092)	< 0.001

Table 2. Results from multivariable analysis of characteristics associated with stroke recurrence

BA, basilar artery; CI, confidence interval; OR, odds ratio; PCoA-P1, posterior communicating artery and the P1 segment of the posterior cerebral artery.

erosclerotic stenosis was associated with a higher risk of subsequent stroke.¹³ Furthermore, it was difficult to define the hemodynamics in patients with posterior circulation ischemic stroke due to IVBAS, because of the challenge in determining the presence of border-zone infarction. However, hemodynamics factors may play a role in stroke occurrence by coexisting with other stroke mechanisms.¹⁴ The PCoA is the most important primary collateral between the anterior and posterior circulations, and so it was selected for predicting stroke recurrence in the present study. The results showed that the new PCoA-P1 score may be both practical and effective in evaluating the collateral status in patients with IVBAS, since poor primary collaterals were more common among the patients in this study with single stroke recurrence and multiple stroke recurrences than in those without recurrence.

Several scoring systems have been proposed for evaluating the collateral status of the posterior circulation. For example, the Basilar Artery on Computed Tomography Angiography¹⁵ and Posterior Circulation Collateral Score¹⁶ scoring systems are based on computed tomography angiography. However, these scoring systems focus on patients with acute BA occlusion rather than IVBAS. Scoring systems for BA stenosis have been proposed, but they have been used to predict functional outcomes rather than stroke recurrence,^{17,18} and there has been no scoring system for predicting stroke recurrence in patients with IVBAS.

The PCoA-to-P1 channel is the primary collateral circulation for patients with IVBAS and is more important than other collateral routes, including the anterior spinal arteries and leptomeningeal and dura arteriolar anastomoses with cortical vessels. The proposed scoring system considers not only the existence of a PCoA-to-P1 connection but also the sizes of the PCoA and P1. This study found that smaller PCoA and P1 were associated with lower PCoA-P1 scores in patients with IVBAS, indicating a higher risk of multiple stroke recurrences. One advantage of the new scoring system is that MRA is a routine, noninvasive examination; however, its predictive value needs to be confirmed by prospective studies in the future.

This study found that more lesions were located in the intracranial VA than in the BA in patients with posterior circulation ischemic stroke due to IVBAS (52.8% vs. 47.2%). A similar result was observed in the New England Medical Center Posterior Circulation Registry.¹⁹ However, patients with multiple stroke recurrences were more likely to demonstrate BA involvement in the present study (OR=2.851, 95% CI 1.105–7.358, p=0.030). To our knowledge, this is the first report of an association between multiple recurrences and BA involvement.

This study found that atherosclerotic risk factors were not related to stroke recurrence, which is consistent with several previous reports.⁵ The stroke mechanism was not associated with stroke recurrence in patients with IVBAS. A previous study found that the mixed mechanism of A-A embolism plus hypoperfusion was associated with stroke recurrence in patients with intracranial atherosclerotic stenosis.²⁰ The difference in the study populations—patients with \geq 70% IVBAS in the present study vs. patients with intracranial atherosclerotic stenosis—may explain the difference.

This study found no difference between taking antithrombotic agents before or after the index stroke, or in the time intervals from index stroke to enrollment among the three groups. The WASID study also suggested that taking antithrombotic agents at the time of the qualifying event was not associated with stroke recurrence.²¹ Furthermore, the present study found that the NIHSS score was higher in patients with stroke recurrence. These high-risk patients with multiple stroke recurrences who were refractory to medical management may benefit from endovascular treatment.

The present study did not include patients with total occlusion. Posterior circulation ischemic strokes are more commonly caused by stenotic lesions than by total occlusion. In a Taiwan Stroke Registry study, 3.8% cases of ischemic stroke or transient ischemic attack were due to vertebrobasilar total occlusion. Furthermore, the severity was greater in patients with symptomatic total occlusion than in those with a stenotic lesion. Compared with patients with 0%–49% vertebrobasilar artery stenosis, the risks of recurrent stroke (hazard ratio [HR]=1.94, 95% CI=1.03–3.64) and death (HR=2.10, 95% CI=1.46–3.04) were significantly higher among patients with vertebrobasilar artery occlusion. No difference in the rate of recurrent ischemic stroke or death was observed between patients with 50%–99% and 0%–49% stenosis of the verte-brobasilar artery.²²

This study had some limitations. First, 3D-TOF MRA might not reveal the actual blood flow in certain circumstances. Second, the study had a single-center, retrospective design, and so enrollment elective bias was probably present. Third, there may have been bias in the timing of stroke recurrence and the occurrence of stroke events. Therefore, the conclusions drawn from this study need to be confirmed in future prospective studies.

In conclusion, this study developed a new MRA-based scoring system for evaluating the primary collaterals in IVBAS. The new PCoA-P1 score may be useful for predicting stroke recurrence. These patients may benefit from early identification and aggressive treatment.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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