



## Association of atherosclerotic plaque features with collateral circulation status in elderly patients with chronic carotid stenosis

Hui-Min XU<sup>1</sup>, Ran HUO<sup>1</sup>, Rui-Jing XIN<sup>2</sup>, Dan-Dan YANG<sup>3,4</sup>, Ying LIU<sup>1</sup>, Ning LANG<sup>1</sup>, Xi-Hai ZHAO<sup>4</sup>, Tao WANG<sup>5,#</sup>, Hui-Shu YUAN<sup>1,#</sup>

<sup>1</sup>Department of Radiology, Peking University Third Hospital, Beijing, China

<sup>2</sup>Department of Radiology, Zhongda Hospital, Medical School of Southeast University, Nanjing, China

<sup>3</sup>Beijing Institute of Brain Disorders, Laboratory of Brain Disorders, Ministry of Science and Technology, Collaborative Innovation Center for Brain Disorders, Capital Medical University, Beijing, China

<sup>4</sup>Center for Biomedical Imaging Research, Department of Biomedical Engineering, Tsinghua University School of Medicine, Beijing, China

<sup>5</sup>Department of Neurosurgery, Peking University Third Hospital, Beijing, China

### Abstract

**Objective** To determine the association of carotid plaque features with collateral circulation status in elderly patients with moderate to severe carotid stenosis. **Methods** Elderly patients (> 60 years) with moderate to severe carotid stenosis were recruited and categorized into good and poor collateral circulation groups, and underwent magnetic resonance imaging and computed tomography imaging. The carotid plaque features including lipid-rich necrotic core, intraplaque hemorrhage, calcification, and fibrous cap rupture (FCR) were evaluated, and maximum wall thickness, normalized wall index (NWI), and luminal stenosis were measured. The association between these variables and collateral circulation status was analyzed. **Results** Of the 97 patients (78 males, mean age: 69.0 ± 6.1 years), 19 (19.6%) had poor collaterals. The poor collateral group had a significantly higher NWI (93.7% ± 5.0% vs. 89.0% ± 7.9%,  $P = 0.011$ ), a greater extent of stenosis (80.0% ± 11.4% vs. 75.3% ± 9.4%,  $P = 0.036$ ) and FCR (84.2% vs. 55.1%,  $P = 0.020$ ) compared with good collateral group. Carotid NWI (OR = 3.83, 95% CI: 1.36–10.82,  $P = 0.011$ ) and more FCR (OR = 6.77, 95% CI: 1.35–33.85,  $P = 0.020$ ) were associated with poor collateral circulation after adjustment for the confounding factors. The combination of NWI, FCR, systolic blood pressure, and triglycerides had the highest area- under-the-curve (AUC = 0.85) for detection of poor collaterals. **Conclusions** Carotid plaque features, specifically NWI and FCR, are independently associated with poor collateral circulation, and the combination of carotid plaque features and traditional risk factors has a stronger predictive value for poor collateral circulation than plaque features alone.

*J Geriatr Cardiol* 2020; 17: 202–209. doi:10.11909/j.issn.1671-5411.2020.04.003

**Keywords:** Atherosclerosis; Carotid stenosis; Collateral circulation; Computed tomography angiography; Magnetic resonance imaging

## 1 Introduction

Stroke, which is one of the leading causes of death worldwide, has a higher likelihood of occurring in the elderly.<sup>[1]</sup> Further, compared with younger patients, the elderly ones develop more disabilities and have poorer quality of life after stroke.<sup>[2]</sup> It has been suggested that the compensatory capability of collateral circulation declines with aging,<sup>[3,4]</sup> and this may play a role in the poor outcome of elderly

patients after stroke. Therefore, assessment of the collateral circulation status prior to stroke may be helpful for accurately predicting the clinical outcomes in elderly patients.

As the secondary collateral pathway, leptomeningeal anastomoses (LMA) are capillary networks that connect distal branches of different cerebral arteries to provide alternative routes for blood flow in patients with ischemic stroke.<sup>[5]</sup> LMA can maintain cerebral blood flow when the primary collateral flow (consisting of the circle of Willis) is insufficient and may, therefore, protect brain tissue against irreversible damage.<sup>[6,7]</sup> A number of studies have shown that better function of LMA is associated with smaller infarct volume, a lower risk of intracerebral hemorrhage after systemic thrombolysis or endovascular therapies, and eventually, better clinical outcomes.<sup>[8,9]</sup> LMA is influenced by

**#Correspondence to:** Hui-Shu YUAN & Tao WANG, Department of Radiology, Peking University Third Hospital, Beijing, China (YUAN HS) & Department of Neurosurgery, Peking University Third Hospital, Beijing, China (WANG T). E-mails: huishuy@bjmu.edu.cn (YUAN HS) & wangtao@bjmu.edu.cn (WANG T)

**Received:** January 11, 2020

**Revised:** February 20, 2020

**Accepted:** April 4, 2020

**Published online:** April 28, 2020

hemodynamic fluctuations in the upstream arteries, for example, gradual stenosis and sudden occlusion,<sup>[5]</sup> and researchers believe that patients with chronic artery stenosis, such as carotid atherosclerosis, could gradually develop better LMA than those with sudden artery occlusion.<sup>[10,11]</sup> However, the incipient development of collaterals does not guarantee their persistence in patients with carotid atherosclerosis.<sup>[7]</sup> Previous studies have suggested that several factors may affect the endurance of collateral flow, such as distal fragmentation of a thrombus and traditional vascular risk factors including age, statin use, and systolic blood pressure (SBP).<sup>[12,13]</sup> However, the relationship between the lesion characteristics of upstream arteries, especially the features of carotid plaques, and the amount of collateral flow is still unclear in patients with chronic carotid stenosis. Investigating the plaque-related factors associated with the deterioration of collateral circulation would be beneficial to develop a treatment strategy that can prevent adverse outcomes in these patients, and the present study has, therefore, undertaken this line of investigation.

For characterizing atherosclerosis in the upstream carotid arteries of LMA, vessel wall imaging with magnetic resonance (MR) is an ideal non-invasive approach, as this technique has been histologically validated and widely used in clinical settings. We hypothesized that carotid plaque features might be associated with deterioration of the LMA. Therefore, in the present study, we sought to investigate the association between carotid plaque features and collateral circulation status, and to identify the factors associated with collateral circulation in elderly patients with moderate to severe carotid stenosis.

## 2 Methods

### 2.1 Study population

This prospective study consecutively enrolled patients aged over 60 years with moderate to severe carotid artery stenosis (50%–99%) who were referred to our hospital for carotid endarterectomy. The exclusion criteria were as follows: (1) history of cardiogenic stroke and hemorrhagic stroke; (2) moderate to severe carotid artery stenosis in bilateral carotid arteries; (3) intracranial artery stenosis  $\geq 50\%$ ; (4) history of vascular intervention treatment, such as stenting, clip or coil placement for aneurysms; (5) heart failure; (6) renal dysfunction [glomerular filtration rate (GFR)  $< 60$  mL/min]; (7) allergic reaction to iodine-based contrast agents; and (8) contraindications for MR imaging. All the included patients underwent computed tomography perfusion (CTP) scan for brain and MR vessel wall imaging for

extracranial carotid arteries. The following clinical information was collected from the clinical records at baseline: age, gender, history of hypertension, hyperlipidemia, smoking, and diabetes. The study protocol was approved by the Ethics Committee of Peking University Third Hospital, Beijing, China; and all the patients provided their written informed consent before participation in this study.

### 2.2 CT imaging protocol

The brain was imaged using a 256-row wide-body detector CT scanner (Revolution CT, GE Healthcare, Waukesha, Wisconsin, USA). Routine brain non-contrast enhanced CT (NCCT) was performed before CTP to rule out intracerebral hemorrhage. After NCCT, volumetric CTP was conducted for the whole brain with the following parameters: 16-cm coverage at the z-axis; slice thickness, 0.5 mm; and tube voltage, 80 kV. Nonionic contrast agent (370 mgI/mL, Omnipaque 350, GE Healthcare, Shanghai, China) was injected intravenously using an automatic injector with a bolus of 40 mL administered at a rate of 4.5 mL/s, this was followed by the 40 mL saline flush administered at a rate of 4.5 mL/s. The CTP scan was initiated 8 s after contrast agent injection, and the following protocol was used: 10 cycles at a current of 100 mA and a 2-s time interval between two cycles, followed by seven cycles at a current of 75 mA and a 4-s time interval between two cycles. The total image acquisition time was 56 s, and the total absorbed radiation dose was 5.4 mSv.

### 2.3 MR imaging

All the patients underwent carotid MR vessel wall imaging with a 3.0T MR scanner (uMR770, UIH, Shanghai, China) with a custom-designed 8-channel carotid coil, and the following sequences were acquired: (1) 3D time-of-flight image with repeat time (TR) and echo time (TE) of 17.6 ms and 6.7 ms, respectively, flip angle of  $8^\circ$ , and slice thickness of 2 mm; (2) 2D T1-weighted image with TR and TE of 850 ms and 13.4 ms, respectively, and slice thickness of 2 mm; (3) 2D T2-weighted image with TR and TE of 2000 ms and 96.6 ms, respectively, and slice thickness of 2 mm; and (4) simultaneous non-contrast angiography and intraplaque hemorrhage (SNAP) image with TR and TE of 9.6 ms and 4.0 ms, respectively, flip angle of  $12^\circ$ , and slice thickness of 1 mm. All imaging sequences were acquired under the same field of vision (140 mm  $\times$  140 mm), spatial resolution (0.55 mm  $\times$  0.55 mm), and longitudinal coverage (32 mm). The carotid imaging was centered at the bifurcation of the index carotid artery which was defined as the artery with moderate to severe stenosis.

## 2.4 Analysis of CTP source images

The source CTP images were utilized to generate the multiphase computed tomography angiography (mCTA) images via three steps.<sup>[14,15]</sup> In Step 1, the early arterial phase (6 s before the peak arterial phase), the peak arterial phase, and the peak venous phase were selected according to the time density curve. In Step 2, the CTA images of these three phases were reconstructed into thin slices with a thickness of 0.625 mm each. In Step 3, maximum intensity projection was used to display the vessels in each phase of the mCTA images. Based on the mCTA images, the leptomeningeal collateral flow was scored on a 6-point scale by two neuroradiologists with more than three years of experience in neurovascular imaging.<sup>[14]</sup> The scores were determined based on consensus between the two neuroradiologists, and when there was a disagreement between them, another neuroradiologist with more than five years of experience determined the score. All three neuroradiologists were blinded to the clinical information and carotid artery images of the patients. Based on the scores, the patients were divided into those with good collateral circulation (if the score was 4–5) and those with poor collateral circulation (if the score was 0–3).<sup>[16,17]</sup>

## 2.5 Analysis of carotid MR image

The MR vessel wall images of index carotid arteries were reviewed by two trained radiologists with more than two years of experience in cerebrovascular imaging, with the help of a software (Vessel Explorer 2, TSImaging Healthcare, Beijing, China). The reviews were based on consensus between the two, and if there was any disagreement between them, another neuroradiologist with more than five years of experience re-evaluated the images and helped them to reach the consensus. The radiologists were blinded to the clinical information and intracranial collateral circulation status of the patients. The image quality was assessed on a 4-point scale (1 = poor, 2 = marginal, 3 = good, and 4 = excellent), and images with a score of 1 were excluded from the analysis.<sup>[18]</sup> The lumen and wall boundaries were manually outlined, and the plaque burden of the lumen area (LA), wall area (WA), total vessel area (TVA), maximum wall thickness (Max WT), and normalized wall index (NWI =  $WA/TVA \times 100\%$ ) were measured and calculated. The compositions and the surface features of carotid plaques, such as calcification (CA), intraplaque hemorrhage (IPH), lipid-rich necrotic core (LRNC), and fibrous cap rupture (FCR), were evaluated based on the published criteria.<sup>[19]</sup>

## 2.6 Statistical analysis

Continuous variables are presented as mean  $\pm$  SD, and

categorical variables are presented as percentage. Carotid plaque burden and compositional features were compared between patients with good and poor collateral circulation by the Mann-Whitney *U*-test or Pearson's chi-square test. Univariate and multivariate logistic regression analyses were used to determine the odds ratio (OR) and the corresponding 95% confidence interval (CI) of plaque features for identifying poor collateral circulation before and after adjustment for the confounding factors. Receiver operating characteristic (ROC) analysis was conducted to calculate the area-under-the-curve (AUC) of the plaque features for identifying poor collateral circulation. All statistical tests were two-sided, and *P*-value  $< 0.05$  was considered to be statistically significant. The statistical analyses were performed by using the SPSS 16.0 software (SPSS, Chicago, IL, USA).

## 3 Results

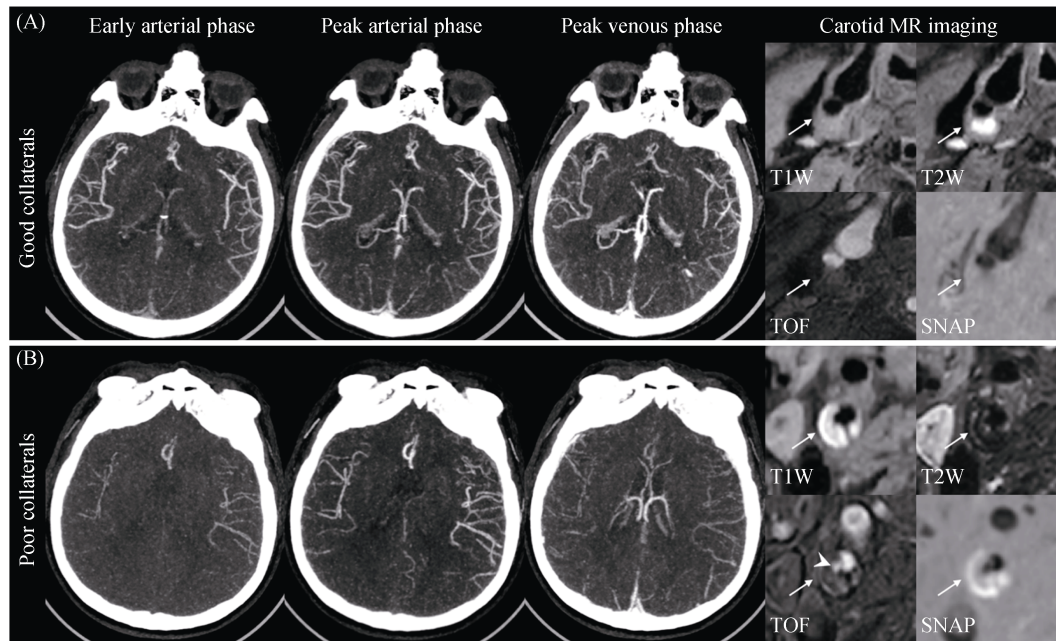
### 3.1 Comparison of carotid plaque features and collateral circulation status

This study included 97 patients, and of them, 86 (88.7%), 82 (84.5%), 65 (67.0%), and 59 (60.8%) had carotid CA, LRNC, IPH, and FCR, respectively. The mean values of NWI, Max WT, and stenosis of the index carotid arteries were  $89.9\% \pm 7.8\%$ ,  $5.7 \pm 1.5$  mm, and  $77.3\% \pm 10.3\%$ , respectively.

Compared to patients with good collateral circulation, patients with poor collateral circulation had a significantly higher NWI ( $93.7\% \pm 5.0\%$  vs.  $89.0\% \pm 7.9\%$ ;  $P = 0.011$ ), more severe stenosis ( $80.0\% \pm 11.4\%$  vs.  $75.3\% \pm 9.4\%$ ,  $P = 0.036$ ), and more extensive rupture of the fibrous cap ( $84.2\%$  vs.  $55.1\%$ ;  $P = 0.020$ ). A representative set of images showing the different plaque features in the two groups can be found in Figure 1. No significant differences were found in other plaque features between patients with poor and good collateral circulation ( $P > 0.05$  for all comparisons, as shown in Table 2).

### 3.2 Association between carotid plaque features and collateral circulation status

Univariate logistic regression analysis showed that NWI (OR = 2.96, 95% CI: 1.18–6.92,  $P = 0.021$ , increment = 10% of NWI), Max WT (OR = 1.42, 95% CI: 1.01–2.00,  $P = 0.043$ ), and FCR (OR = 4.34, 95% CI: 1.17–16.11,  $P = 0.028$ ) were significantly correlated with poor collateral circulation. After adjustment for the confounding risk factors of age, gender, SBP, and triglycerides (TG), the association of NWI (OR = 3.83, 95% CI: 1.36–10.82,  $P = 0.011$ , increment = 10% of NWI) and FCR (OR = 6.77, 95% CI: 1.35–33.85,  $P = 0.020$ ) with poor collateral circulation



**Figure 1. Images of severe right carotid stenosis patients with good and poor collateral circulation.** (A): Three-phase CTA images for a 71-year-old female patient who had good collateral circulation and an atherosclerotic plaque (arrows) in the right carotid bifurcation with an NWI of 78.6%; and (B): three-phase CTA images for a 65-year-old male patient who had poor collateral circulation, and a vulnerable atherosclerotic plaque (arrows) in the proximal right internal carotid artery with fibrous cap rupture (arrowhead) and an NWI of 93.2%. CTA: computed tomography angiography; MR: magnetic resonance; NWI: normalized wall index; SNAP: simultaneous non-contrast angiography and intraplaque hemorrhage; TOF: time of flight; T1W: T1-weighted; T2W: T2-weighted.

**Table 1. Baseline characteristics of the patients.**

Characteristic	All patients (n = 97)	Good collaterals (n = 78)	Poor collaterals (n = 19)	P-value
Age, yrs	68.4 ± 6.1	68.3 ± 6.2	69.0 ± 6.1	0.659
Male	82 (84.5%)	95 (86.4%)	23 (88.5%)	0.955
Smoking	74 (54.4%)	59 (53.6%)	15 (57.7%)	0.916
Diabetes	38 (39.2%)	41 (37.3%)	13 (50.0%)	0.415
Hypertension	53 (54.6%)	65 (59.1%)	14 (53.8%)	0.082
SBP, mmHg	135.5 ± 17.8	138.2 ± 16.9	124.5 ± 17.2	0.005
DBP, mmHg	78.2 ± 9.8	78.8 ± 9.9	75.7 ± 8.9	0.200
Hyperlipidemia	30 (30.9%)	33 (30.0%)	8 (30.8%)	0.534
HDL, mmol/L	1.1 ± 0.3	1.1 ± 0.2	1.1 ± 0.3	0.617
LDL, mmol/L	2.2 ± 0.9	2.2 ± 0.8	2.4 ± 1.0	0.206
TG, mmol/L	1.4 ± 0.9	1.3 ± 0.6	1.7 ± 0.9	0.077
TC, mmol/L	3.8 ± 1.1	3.7 ± 1.0	4.0 ± 1.6	0.564
CRP, mg/L	3.7 ± 9.2	2.6 ± 5.0	2.2 ± 0.9	0.906

Data are presented as means ± SD or n (%). CRP: C-reactive protein; DBP: diastolic blood pressure; HDL: hyper-density lipoprotein; LDL: low-density lipoprotein; SBP: systolic blood pressure; TC: total cholesterol; TG: triglycerides.

remained statistically significant, whereas the association between Max WT (OR = 1.44, 95% CI: 0.98–2.14, P = 0.067) and poor collateral circulation was considerable but not statistically significant. After further adjustment for NWI, FCR was still significantly associated with poor collateral circulation (OR = 6.48, 95% CI: 1.18–35.63, P =

0.032). Table 3 shows the detailed results for the association between carotid plaque features and collateral circulation status.

### 3.3 ROC analysis

Figure 2 summarizes the results of ROC analysis. The

**Table 2. Carotid plaque features in different collateral circulation status groups.**

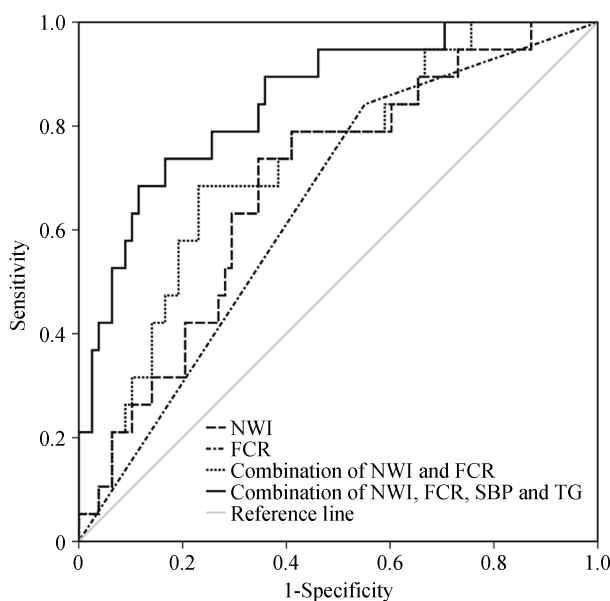
Variable	All patients (n = 97)	Good collaterals (n = 78)	Poor collaterals (n = 19)	P-value
Carotid stenosis, %				
Index side	77.3 ± 10.3	75.3 ± 9.4	80.0 ± 11.4	0.036
Contralateral side	26.8 ± 15.4	26.8 ± 14.5	32.5 ± 17.8	0.184
NWI, %	89.9 ± 7.8	89.0 ± 7.9	93.7 ± 5.0	0.011
Max WT, mm	5.7 ± 1.5	5.6 ± 1.3	6.3 ± 1.8	0.090
CA	86 (88.7%)	68 (87.2%)	18 (94.7%)	0.352
LRNC	82 (84.5%)	66 (84.6%)	16 (84.2%)	0.965
IPH	65 (67.0%)	52 (66.7%)	13 (68.4%)	0.884
FCR	59 (60.8%)	43 (55.1%)	16 (84.2%)	0.020

Data are presented as means ± SD or n (%). CA: calcification; FCR: fibrous cap rupture; IPH: intraplaque hemorrhage; LRNC: lipid-rich necrotic core; Max WT: maximum wall thickness; NWI: normalized wall index.

**Table 3. Association between carotid plaque features and collateral circulation status.**

	Poor collaterals					
	Univariate regression			Multivariate regression*		
	OR	95% CI	P-value	OR	95% CI	P-value
Index carotid stenosis <sup>#</sup>	1.60	0.96–2.68	0.074	1.69	0.95–3.02	0.075
NWI <sup>†</sup>	2.96	1.18–7.44	0.021	3.83	1.36–10.82	0.011
Max WT	1.42	1.01–2.00	0.043	1.44	0.98–2.14	0.067
FCR	4.34	1.17–16.11	0.028	6.77	1.35–33.85	0.020

\*Refer to the logistic regression was conducted before and after adjusting for the traditional risk factors, including age, gender, systolic blood pressure and triglycerides. <sup>#</sup>Refer to a reduction of 10%. <sup>†</sup>Refer to an increment of 10%. CI: confidence index; FCR: fibrous cap rupture; Max WT: maximum wall thickness; NWI: normalized wall index; OR: odds ratio.



**Figure 2. ROC curves for different variables associated with poor collateral circulation.** The ROC curves indicate that the combination of NWI, FCR, SBP, and TG had the highest AUC for detection of poor collateral circulation. AUC: area-under-the-curve; FCR: fibrous cap rupture; NWI: normalized wall index; ROC: receiver operating characteristic; SBP: systolic blood pressure; TG: triglycerides.

AUC values of NWI and FCR as indicators of poor collateral circulation were 0.69 (95% CI: 0.56–0.82) and 0.65 (95% CI: 0.52–0.77), respectively. The AUC value of NWI combined with FCR was higher at 0.73 (95% CI: 0.61–0.85). Further, when NWI was combined with FCR, SBP, and TG, the AUC reached 0.85 (95% CI: 0.76–0.95).

#### 4 Discussion

The present study used mCTA and MR vessel wall imaging to examine the association between carotid plaque features and cerebral collateral circulation status in patients aged over 60 years with unilateral moderate to severe carotid stenosis. The findings showed that NWI and FCR were independently associated with poor collateral circulation. In addition, we found that the combination of NWI, FCR, SBP, and TG was a stronger indicator of poor collateral circulation than NWI or FCR alone or the combination of NWI and FCR. Our findings indicate that carotid plaque features determined by MR vessel wall imaging, particularly NWI and FCR, might be independent indicators of poor collateral circulation in elderly patients with unilateral moderate to severe carotid stenosis.

The finding that NWI was an independent indicator of

poor collateral circulation implies that the progression of carotid plaque burden may occur in parallel with the deterioration of LMA. It has been hypothesized that deterioration of LMA might be a secondary consequence of increased resistance to blood flow caused by small-vessel disease (SVD).<sup>[20]</sup> Plaque burden is a marker of the severity of atherosclerosis, which is a multifocal disease that affects the entire vasculature.<sup>[21]</sup> Jung, *et al.*<sup>[22]</sup> found that 71.8% of patients with SVD or intracranial large-vessel disease had coexisting carotid atherosclerotic diseases, and Denisa, *et al.*<sup>[23]</sup> proved that patients with SVD had significantly larger carotid plaque burden ( $P = 0.0093$ ). This phenomenon may be due to that atherosclerosis in extracranial carotid arteries and intracranial small vessels is associated with the same risk factors, such as hypertension, hyperlipidemia, and diabetes.<sup>[24]</sup> Hence, the significant association of plaque burden with the deterioration of LMA may be explained by its association with the extent of atherosclerotic disease.

In this study, we also found that Max WT was significantly associated with poor collateral circulation before adjustment for confounding factors, but the association was weakened after adjustment for age, gender, SBP, and TG. This result indicates that Max WT is influenced by demographic factors, such as age and gender. In contrast, NWI is a normalized metric of plaque burden that is largely independent of individual differences in vessel size.<sup>[25]</sup> Thus, our results indicate that NWI, as a measure of carotid plaque burden, may be an indicator of collateral circulation status.

Our study showed that FCR was also an independent indicator of poor unilateral intracranial collateral circulation. Researchers believe that the deterioration of LMA may be caused by the falling of thrombus from the parent vessel and subsequent blockage of the distal branches of the cortical artery which provide retrograde collateral flow.<sup>[7]</sup> In fact, it is well known that FCR is the most common cause of thrombosis.<sup>[21,26]</sup> When the fibrous cap ruptured, cap collagen and the highly thrombogenic lipid core are exposed to blood and, subsequently, lead to thrombus formation.<sup>[27]</sup> Thrombus and the microemboli dropped from plaque might get washed away by blood flow over the culprit lesion, and this might result in embolization in the distal branches of the cortical artery. There is evidence of the presence of thrombus in the distal branches of the cortical artery in patients with poor collateral circulation. Qazi, *et al.*<sup>[28]</sup> found that poor collateral circulation was positively associated with the presence of a thrombus. Alves, *et al.*<sup>[29]</sup> also found that patients with poorer collateral circulation had more proximal thrombus. Thus, there is some evidence which supports our finding that FCR of carotid plaques might be a valuable indicator of the collateral circulation status.<sup>[26-29]</sup>

The present findings showed a significant association between decreased SBP and poor collateral circulation. This finding indicates that an excessive reduction in SBP during treatment may carry a risk of collateral circulation collapse in elderly patients with unilateral moderate to severe carotid stenosis. In patients with carotid stenosis, the pressure in the stenotic artery and its branches is likely to be decreased due to the obstruction of blood flow. However, non-stenotic arteries surrounding the stenotic arteries maintain a relatively higher pressure, and this causes a pressure gradient between non-stenotic arteries and stenotic arteries. This pressure gradient may promote a retrograde blood flow from the non-stenotic arteries to the stenotic arteries through LMA. The magnitude of this pressure gradient is affected by systemic blood pressure, as demonstrated by several clinical and animal studies.<sup>[5,13,30,31]</sup> For example, in monkeys, systemic blood pressure was found to strongly influence flow maintenance to deficient areas via LMA.<sup>[30]</sup> Additionally, Rusanen, *et al.*<sup>[31]</sup> showed that a moderate elevation in SBP in patients suffering from ischemic stroke was strongly associated with good collateral circulation.

The present study is one of the first to combine carotid plaque features with traditional risk factors for the diagnosis of poor intracranial collateral circulation. Our data showed that the predictive value of the combination of NWI, FCR, SBP, and TG for poor collateral circulation was stronger than that of NWI and FCR alone and even the combination of NWI and FCR. This finding was expected, because multiple factors play a role in the formation and maintenance of intracranial collateral circulation. In contrast, most previous studies focused on assessing the predictive value of a single factor for collateral circulation status. For example, Van, *et al.*<sup>[32]</sup> reported that glucose level, the presence of a proximal MCA occlusion, and an incomplete ipsilateral posterior circle of Willis are determinants of leptomeningeal collateral flow in a prospective study of acute ischemic stroke patients. However, they did not combine these factors together to predict the risk of poor collateral circulation. Thus, the combination of predictors of collateral circulation that emerged in this study is important for modification of treatment strategy and assessment of clinical outcome.

#### 4.1 Limitations

There are several limitations in our study. Firstly, the sample size of patients with poor collateral circulation was small. A study on a larger sample size should be conducted in the future to confirm these findings. Secondly, the collateral circulation status was evaluated on mCTA images extracted from the source CTP data. However, CTP is associated with high radiation exposure. In order to tackle this, in



the present study, we used 320-row CT with optimized protocols, such as lower tube voltage (80 kV) and fewer scans, in order to reduce the radiation dose to 5.4 mSv, which is much lower than the radiation dose of 9.5 mSv that is associated with conventional CTP.<sup>[33]</sup> Thirdly, the three phases of mCTA, which were extracted from the CTP source images reported by Wu, *et al.*<sup>[15]</sup>, were not exactly the same as those of the original mCTA images. We believe that the mismatched timing may not seriously affect our results, but the reliability of the mCTA protocol used in our study should be verified against that of the original mCTA protocol. Last but not least, the plaque components were not quantitatively evaluated in the present study, and the role of the size of plaque compositions in collateral circulation could not be investigated. Therefore, future studies exploring the association between the size of different plaque components and collateral circulation status are warranted.

## 4.2 Conclusions

In conclusion, carotid plaque features, particularly normalized wall index and fibrous cap rupture, are independently associated with poor intracranial collateral circulation, and the combination of these plaque features with traditional risk factors, such as SBP and TG, has a stronger predictive value for poor collateral circulation than each of these features alone. Thus, these findings shed light on the indicators of intracranial collateral circulation.

## Acknowledgments

This study was supported by the National Natural Science Foundation of China (No.81771825), Peking University Third Hospital (BYSY2015013), Beijing Municipal Science and Technology Commission (D171100003017003), and Ministry of Science and Technology of China (2017 YFC1307904). All authors had no conflicts of interest to disclose.

## References

- Roy-O'Reilly M, McCullough LD. Age and sex are critical factors in ischemic stroke pathology. *Endocrinology* 2018; 159: 3120–3131.
- Alamowitch S, Eliasziw M, Algra A, *et al.* Risk, causes, and prevention of ischaemic stroke in elderly patients with symptomatic internal-carotid-artery stenosis. *Lancet* 2001; 357: 1154–1160.
- Miller SJ, Coppinger BJ, Zhou X, *et al.* Antioxidants reverse age-related collateral growth impairment. *J Vasc Res* 2010; 47: 108–114.
- Nakae I, Fujita M, Miwa K, *et al.* Age-dependent impairment of coronary collateral development in humans. *Heart Vessels* 2000; 15: 176–180.
- Brozici M, van der Zwan A, Hillen B. Anatomy and functionality of leptomeningeal anastomoses: a review. *Stroke* 2003; 34: 2750–2762.
- Muller M, Schimrigk K. Vasomotor reactivity and pattern of collateral blood flow in severe occlusive carotid artery disease. *Stroke* 1996; 27: 296–299.
- Liebeskind DS. Collateral circulation. *Stroke* 2003; 34: 2279–2284.
- Bang OY, Saver JL, Buck BH, *et al.* Impact of collateral flow on tissue fate in acute ischaemic stroke. *J Neurol Neurosurg Psychiatry* 2008; 79: 625–629.
- Miteff F, Levi CR, Bateman GA, *et al.* The independent predictive utility of computed tomography angiographic collateral status in acute ischaemic stroke. *Brain* 2009; 132: 2231–2238.
- Berry RG. Discussion of “collateral circulation of the brain”. *Neurology* 1961; 11: 20–22.
- Fukuyama H, Akiguchi I, Kameyama M, *et al.* Krypton-81m single photon emission tomography and the collateral circulation in carotid occlusion: the role of the circle of Willis and the leptomeningeal anastomoses. *J Neurol* 1983; 230: 7–17.
- Malik N, Hou Q, Vagal A, *et al.* Demographic and clinical predictors of leptomeningeal collaterals in stroke patients. *J Stroke Cerebrovasc Dis* 2014; 23: 2018–2022.
- Wufuer A, Mijiti P, Abudusalamu R, *et al.* Blood pressure and collateral circulation in acute ischemic stroke. *Herz* 2019; 44: 455–459.
- Menon BK, d’Este CD, Qazi EM, *et al.* Multiphase CT angiography: a new tool for the imaging triage of patients with acute ischemic stroke. *Radiology* 2015; 275: 510–520.
- Wu X, Yang Y, Wen M, *et al.* Ultra-low-dose multiphase CT angiography derived from CT perfusion data in patients with middle cerebral artery stenosis. *Neuroradiology* 2020; 62: 167–174.
- García-Tornel A, Carvalho V, Boned S, *et al.* Improving the evaluation of collateral circulation by multiphase computed tomography angiography in acute stroke patients treated with endovascular reperfusion therapies. *Interv Neurol* 2016; 5: 209–217.
- Chang JY, Jeon SB, Jung C, *et al.* Postreperfusion blood pressure variability after endovascular thrombectomy affects outcomes in acute ischemic stroke patients with poor collateral circulation. *Front Neurol* 2019; 10: 346.
- Li D, Dai W, Cai Y, *et al.* Atherosclerosis in stroke-related vascular beds and stroke risk: a 3D MR vessel wall imaging study. *Ann Clin Transl Neurol* 2018; 5: 1599–1610.
- Kerwin W, Xu D, Liu F, *et al.* Magnetic resonance imaging of carotid atherosclerosis: plaque analysis. *Top Magn Reson Imaging* 2007; 18: 371–378.
- Eker OF, Rasclé L, Cho TH, *et al.* Does small vessel disease burden impact collateral circulation in ischemic stroke treated by mechanical thrombectomy? *Stroke* 2019; 50: 1582–1585.

- 21 Bentzon JF, Otsuka F, Virmani R, *et al.* Mechanisms of plaque formation and rupture. *Circ Res* 2014; 114: 1852–1866.
- 22 Jung KW, Shon YM, Yang DW, *et al.* Coexisting carotid atherosclerosis in patients with intracranial small- or large-vessel disease. *J Clin Neurol* 2012; 8: 104–108.
- 23 Berman SE, Wang X, Mitchell CC, *et al.* The relationship between carotid artery plaque stability and white matter ischemic injury. *Neuroimage Clin* 2015; 9: 216–222.
- 24 Ding X, Li C, Yu K, *et al.* Different risk factors between intracranial and extracranial atherosclerotic stenosis in Asian population: a systematic review and meta-analysis. *Int J Neurosci* 2014; 124: 834–840.
- 25 Cao Y, Sun Y, Zhou B, *et al.* Atherosclerotic plaque burden of middle cerebral artery and extracranial carotid artery characterized by MRI in patients with acute ischemic stroke in China: association and clinical relevance. *Neurol Res* 2017; 39: 344–350.
- 26 Zhou D, Li J, Liu D, *et al.* Irregular surface of carotid atherosclerotic plaque is associated with ischemic stroke: a magnetic resonance imaging study. *J Geriatr Cardiol* 2019; 16: 872–879.
- 27 Fernández-Ortiz A, Badimon JJ, Falk E, *et al.* Characterization of the relative thrombogenicity of atherosclerotic plaque components: implications for consequences of plaque rupture. *J Am Coll Cardiol* 1994; 23: 1562–1569.
- 28 Qazi EM, Sohn SI, Mishra S, *et al.* Thrombus characteristics are related to collaterals and angioarchitecture in acute stroke. *Can J Neurol Sci* 2015; 42: 381–388.
- 29 Alves HC, Treurniet KM, Dutra BG, *et al.* Associations between collateral status and thrombus characteristics and their impact in anterior circulation stroke. *Stroke* 2018; 49: 391–396.
- 30 Symon L, Ishikawa S, Meyer JS. Cerebral arterial pressure changes and development of leptomeningeal collateral circulation. *Neurology* 1963; 13: 237–250.
- 31 Rusanen H, Saarinen JT, Sillanpää N. The association of blood pressure and collateral circulation in hyperacute Ischemic stroke patients treated with intravenous thrombolysis. *Cerebrovasc Dis* 2015; 39: 130–137.
- 32 van Seeters T, Biessels GJ, Kappelle LJ, *et al.* Determinants of leptomeningeal collateral flow in stroke patients with a middle cerebral artery occlusion. *Neuroradiology* 2016; 58: 969–977.
- 33 Cohnen M, Wittsack HJ, Assadi S, *et al.* Radiation exposure of patients in comprehensive computed tomography of the head in acute stroke. *AJNR Am J Neuroradiol* 2006; 27: 1741–1745.