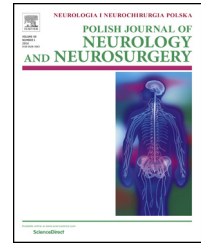


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## Original research article

# Cerebral vasomotor reactivity predicts the development of acute stroke in patients with internal carotid artery stenosis

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## ABSTRACT

**Objective:** To investigate the relationship between cerebral vasomotor reactivity (VMR) and acute stroke in patients with internal carotid artery stenosis.

**Methods:** 54 patients with internal carotid artery stenosis were enrolled. VMR was calculated by transcranial Doppler monitoring of the velocity of blood flow. 3-Dimensional dynamic contrast enhanced magnetic resonance angiography was used to detect stenosis, and diffusion weighted imaging was used to detect infarction.

**Results:** VMR value was significantly lower in patients with carotid artery stenosis than in control group ( $T = 3.112$ ,  $P = 0.002$ ), and significantly lower in patients with aortic atherosclerotic stroke than in non-infarct group ( $T = 10.930$ ,  $P = 0.000$ ). However, VMR value was significantly higher in patients with new-onset small-artery occlusion stroke than in non-infarction group ( $T = -2.538$ ,  $P = 0.013$ ). Scatter plots showed that aortic atherosclerotic stroke occurred mainly in patients with severe internal carotid artery stenosis, and VMR value in cerebral artery significantly decreased.

**Conclusion:** Decreased VMR value is an important prognostic factor for the occurrence of aortic atherosclerotic stroke, and can be used as a reference for preoperative hemodynamic evaluation in patients with internal carotid artery stenosis.

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## 1. Introduction

Carotid stenosis is a progressive narrowing of carotid artery due to the buildup of plaque (atherosclerosis) inside the artery

that reduces blood flow to the brain. Carotid artery stenosis increases the risk of atherosclerotic stroke because of plaque deposits. In recent years, more surgical interventions of internal carotid artery stenosis have been reported. Among them, internal carotid artery endarterectomy and stenting are

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the two main methods which significantly improve the prognosis of patients with internal carotid artery stenosis [1,2]. Currently, the main criteria for the selection of intervention or surgical treatment is the judgment of stenosis extent by imaging. Unfortunately, many patient with severe stenosis or even occlusion may not have clinical symptoms.

At present, the detection of cerebral blood flow can be carried out by single photon emission computed tomography (PET-CT), isotope perfusion imaging (SPECT), CT perfusion imaging (CTP), and magnetic resonance perfusion imaging (PWI), DSA angiography, and transcranial Doppler (TCD). Cerebral vasomotor reactivity (VMR) test is a method to detect the changes in cerebral blood flow velocity with changes in CO<sub>2</sub> partial pressure in vivo by TCD. VMR can reflect cerebrovascular reserve (CVR), indirectly reflect collateral circulation compensation, and provide a new evaluation criterion for the selection of surgery or intervention [3]. Currently, the relationship between VMR and the development of acute stroke in patients with internal carotid artery stenosis has been investigated but the reported data are controversial.

This study aimed to investigate the relationship between cerebral VMR and acute stroke in patients with internal carotid artery stenosis.

## 2. Subjects and methods

### 2.1. Patients

This study enrolled 54 patients hospitalized from March 2016 to November 2016, involving 107 carotid arteries (one case had no temporal window on one side). Among them, 25 cases were acute infarction, 3 cases were transient ischemic attack, 3 cases were cardiogenic cerebral embolism, 23 cases were dizziness, headache and other diseases. There were 33 males and 21 females, with an average age of  $59.50 \pm 12.66$  years. The study was approved by Institute Ethics Committee and all patients provided informed consent.

### 2.2. VMR measurement

VMR was measured using Viasys sonar Digital TCD. Two Doppler 2 MHz probes were fastened to the head over the temporal window, and the ipsilateral middle cerebral artery was chosen as the target vessel. The middle cerebral artery was further identified by compression neck test. The mean velocity ( $V_m$ ) in normocapnia ( $V_m$  Normo) and in hypercapnia ( $V_m$  Hyper) was determined and  $V_m$  change curve was drawn. VMR was calculated as follows:  $(V_m \text{ hyper} - V_m \text{ normo})/V_m \text{ normo} \times 100\%$ .

### 2.3. Detection of vascular stenosis

3-Dimensional dynamic contrast enhanced magnetic resonance angiography (3D DCE-MRA) was used to detect vascular stenosis. The stenosis rate of the blood vessel was calculated as  $(\text{the diameter of the stenotic distal normal blood vessel} - \text{the diameter of the stenosis})/\text{the diameter of the stenotic distal normal blood vessel} \times 100\%$ . For patients with multiple stenosis, the most severe stenosis part was defined as the stenosis rate of the blood vessel. According to the presence of stenosis, the patients were divided into carotid artery stenosis group and non-stenosis group, and the difference in VMR between the two groups was compared.

### 2.4. The classifications of acute infarction

All patients underwent craniocerebral MRI within three days of admission. The presence of acute infarction was determined based on the detection of high signal by carotid artery diffusion-weighted imaging (DWI). Based on clinical history, the symptoms of patients and the imaging, the patients were divided into: no cerebral infarction (NCI), large artery atherosclerosis-no artery embolism (LA-NE), large artery atherosclerosis-artery embolism (LA-E), small artery occlusion lacunar (SA), cardio embolism and other (CE). The differences in VMR among different types of acute infarct and non-infarct groups were compared.

### 2.5. Statistical analysis

All data were analyzed using SPSS Statistics 17.0 software. T-test was used to compare VMR values among different groups, and the scatter plot was drawn.  $P < 0.05$  indicated significant difference.

## 3. Results

VMR value was significantly lower in patients with carotid artery stenosis than in control group ( $T = 3.112$ ,  $P = 0.002$ ), the difference was statistically significant (Table 1). Comparison of corresponding arterial areas in different types of fresh infarcts with non-infarction showed that VMR value was significantly lower in patients with atherosclerotic stroke than in those without infarction ( $T = 10.930$ ,  $P = 0.000$ ). However, VMR value was significantly higher in patients with new-onset small artery occlusion stroke than in non-infarction group ( $T = -2.538$ ,  $P = 0.013$ ). There was no significant difference in VMR of arterial-arterial embolism group and cardiogenic cerebral embolism group, compared to non-infarction group (Table 2).

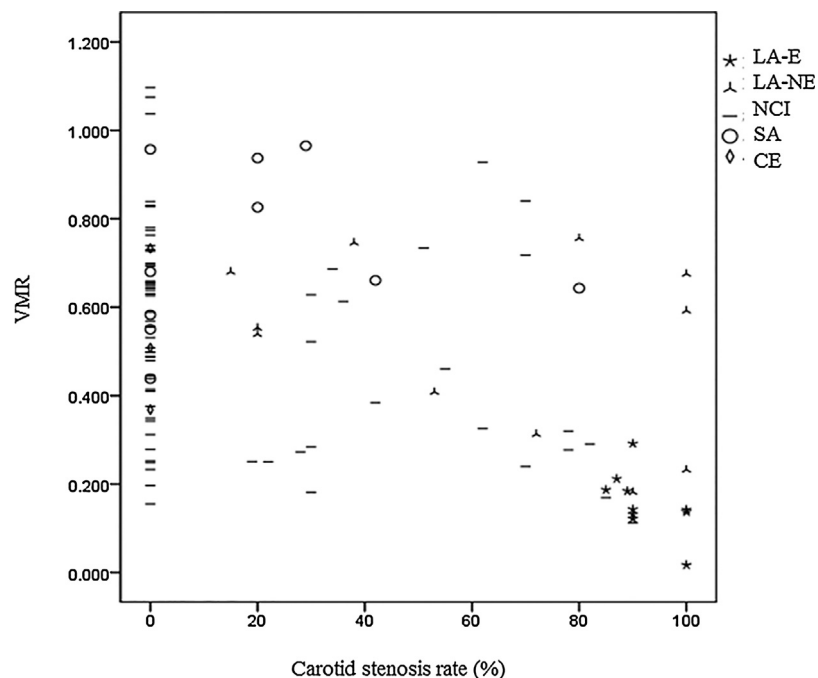
**Table 1 – Comparison of VMR in carotid artery stenosis and non-stenotic vessels.**

	N	Mean	Standard deviation	T	P
Non-carotid artery stenosis	59	0.579	0.210	3.112	0.002
Carotid artery stenosis	48	0.433	0.264		

**Table 2 – Comparison of VMR in different cerebral infarction types and non-infarct vessels.**

Infarction type	N	Mean	Standard deviation	T	P
NCI	75	0.534	0.228		
LA-NE	10	0.157	0.071	10.930	0.000
LA-E	11	0.516	0.204	0.250	0.803
SA	8	0.747	0.202	-2.538	0.013
CE	3	0.536	0.184	-0.020	0.986

No cerebral infarction (NCI), large artery atherosclerosis-no artery embolism (LA-NE), large artery atherosclerosis-artery embolism (LA-E), small artery occlusion lacunar (SA), cardio embolism and other (CE).



**Fig. 1 – The distribution of VMR in patients with internal carotid artery stenosis and different types of cerebral infarction: no cerebral infarction (NCI), large artery atherosclerosis-no artery embolism (LA-NE), large artery atherosclerosis-artery embolism (LA-E), small artery occlusion lacunar (SA), cardio embolism and other (CE).**

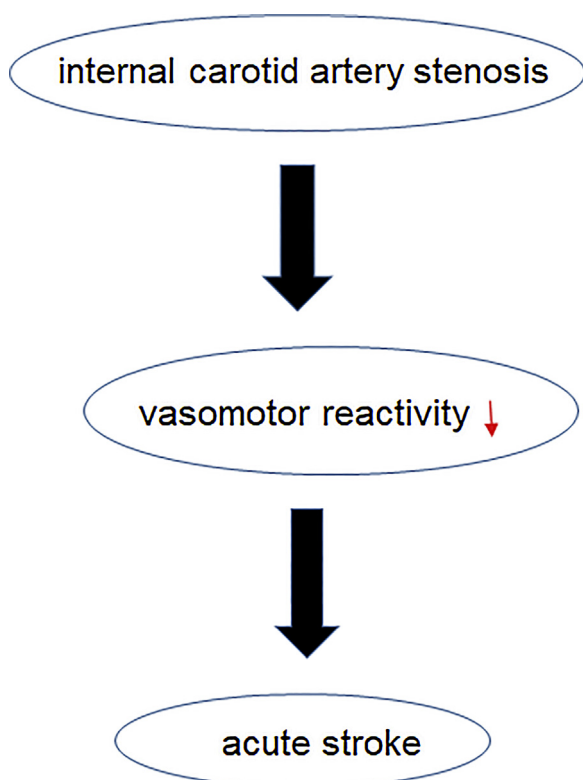
Scatter plot analysis showed that aortic atherosclerotic stroke mainly occurred in patients with severe internal carotid artery stenosis (stenosis rate >80%), while VMR value of corresponding cerebral artery was significantly lower (<0.30). Arterial thrombosis of large arterial sclerosis was distributed in the entire carotid artery stenosis area, and VMR value had no aggregation characteristics. Small artery stenosis was mainly distributed in patients with no obvious internal carotid artery stenosis or mild stenosis, and VMR value was high (>0.40). Cardiogenic cerebral embolism and other patients did not show obvious characteristics (Fig. 1).

#### 4. Discussion

Under physiological conditions, the changes in cerebral perfusion pressure are influenced by blood pressure, intracranial pressure, vascular resistance and other factors. When cerebral perfusion pressure changes, the vessels will expand or contract to maintain a constant cerebral blood

flow to ensure normal cerebral metabolism [4]. However, in pathological conditions such as carotid artery or cerebral artery stenosis, the narrow blood vessels can lead to significant decrease in distal perfusion pressure, resulting in extreme expansion of blood vessels to adapt to metabolic needs of the brain. When the extreme expansion of blood vessels cannot maintain metabolic needs, the symptoms of ischemia will occur, leading to brain necrosis and cerebral infarction.

VMR measurement employs the principle that metabolic carbon dioxide can stimulate cerebral vasodilatation to determine cerebrovascular reserve expansion. CO<sub>2</sub> inhalation test to assess VMR was safe and feasible, and the results had a good correlation with functional magnetic resonance and PET brain perfusion studies [5,6]. In patients with asymptomatic carotid stenosis, decreased VMR was often associated with impairment of cognitive function and leukoencephalopathy [7-9]. However, in patients with symptomatic carotid stenosis, decreased vascular reactivity reserve and decreased oxygen uptake were significantly



**Fig. 2 – The relationship between cerebral vasomotor reactivity, internal carotid artery stenosis and acute stroke. After internal carotid artery stenosis, cerebral vasomotor reactivity will reduce due to the presence of atherosclerotic plaque. Reduced vasomotor reactivity will increase the risk of acute atherosclerotic stroke.**

associated with stroke [10]. VMR can be improved in patients after successful carotid surgery [11].

In this study we showed that VMR value in patients with carotid artery stenosis, especially in patients with severe stenosis, was significantly lower than in control. The scatter plot showed that VMR was below 30% in new-onset acute infarction patients who also had higher carotid stenosis rate of more than 80%, consistent with the study of Puz et al. [12]. These data indicate that the compensation of blood vessels in these patients after stenosis is insufficient, leading to vascular reactivity failure. Therefore, the treatment of these patients should mainly focus on the plaques. In this study, VMR increased in patients with arterial lesions compared with patients without infarction, the reason may be related to the bias of case selection.

Internal carotid artery stenosis is a clinically common lesion of blood vessel leading to ischemic stroke, and is also the most commonly selected target vessel for surgical or interventional treatment. However, due to the difference of posterior collateral circulation compensation, preoperative multimodal hemodynamics assessment has been paid more attention [13]. VMR measurement is one of the simple and effective methods. We believe that the decline of VMR reflects the failure of the distal vessel to compensate, and thus is an important predictor of ischemic events (Fig. 2). Despite the

limitations of this study such as small sample size, our results suggest that VMR could be used as an important reference for preoperative hemodynamic assessment and screening of patients with carotid stenosis.

### Conflict of interest

None declared.

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