Cerebrovascular Reserve may be a More Accurate Predictor of Stroke than Degree of ICA or MCA Stenosis

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
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Background: It is currently unclear whether the degree of stenosis or the cerebrovascular reserve (CVR) is a better predictor of ischemic stroke.

Material/Methods: In this study, CVR was measured by perfusion computed tomography with inhalation of 5% CO_2 in 37 symptomatic patients with internal carotid artery (ICA) or middle cerebral artery (MCA) stenosis or occlusion. Patients were divided into groups according to the degree of stenosis: ≥70% stenosis (stenosis group 1) or <70% stenosis (stenosis group 2); and according to CVR: ≥10% CVR (CVR group 1) or <10% CVR (CVR group 2). All patients were given medical treatment.

Results: During a mean follow-up period of 56.9 months (range 24–73 months), recurrent ipsilateral ischemic stroke occurred in 7 patients. Ischemic stroke occurred in 0 of 19 patients in CVR group 1 (annual risk 0%), 7 of 18 patients in CVR group 2 (annual risk 7.7%), 3 of 18 patients in stenosis group 1 (annual risk 3.3%), and 4 of 19 patients in stenosis group 2 (annual risk 4.7%). Comparisons using Pearson's chi-square test showed a significant difference in the rate of ischemic stroke between CVR group 1 and CVR group 2 (odds ratio 1.700; 95% confidence interval 1.142–2.530; P=0.003), but no significant difference between stenosis group 1 and stenosis group 2 (P=0.691).

Conclusions: Cerebrovascular reserve may be a more accurate predictor of stroke than degree of ICA or MCA stenosis.

MeSH Keywords: **Carbon Dioxide • Prognosis • Stroke**

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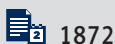
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Background

In ischemic stroke patients with >70% stenosis of the internal carotid artery (ICA) or middle cerebral artery (MCA), the risk of recurrent stroke is high, and stent placement is considered to decrease the risk of further ischemic events. However, there is limited evidence to support this guideline [1]. Cerebrovascular reserve (CVR), defined as the increase in CBF in response to a vasodilatory stimulus, is known to reflect the capacity of the brain to maintain adequate blood flow in the face of decreased perfusion due to arterial stenosis. CVR has been identified as a predictor of ischemic stroke [2], but it is currently unclear whether the degree of stenosis or the CVR is a better predictor of ischemic stroke.

CVR can be measured by perfusion computed tomography (CT) with inhalation of CO_2 [3]. The aim of this study was to measure CVR by perfusion CT with inhalation of CO_2, and to determine whether CVR is a better predictor of stroke than the degree of stenosis of the ICA or MCA.

Material and Methods

Patients

This study analyzed 37 patients who were treated at Capital Medical University Affiliated Beijing Chaoyang Hospital between March 2006 and July 2009. The inclusion criteria were: age 25–80 years; ICA or MCA stenosis or occlusion; cerebral angiography performed; and medical treatment only without stent placement, endarterectomy, or bypass surgery. Patients were excluded if they had evidence of infarction in the territory of a stenosed or occluded ICA or MCA.

The patients were 27 men and 10 women with a mean age of 58.0±11.9 years (range 25–76 years). All patients were initially treated for ipsilateral ischemic events, including transient ischemic attacks in 21 patients and minor completed ischemic strokes in 16 patients. All 37 patients underwent cerebral angiography, which showed ICA occlusion in 7 patients, MCA occlusion in 3 patients, and 30–95% stenosis of the ICA or MCA in the remaining patients. CT and fluid-attenuated inversion-recovery magnetic resonance imaging (MRI) showed no evidence of infarction in the territories of the stenosed or occluded arteries. The study protocol was approved by our institute's committee on human research and written informed consent was obtained from every participant.

Patients were divided into groups according to the degree of stenosis: 70–99% stenosis or occlusion (stenosis 1) or 30–69% stenosis (stenosis 2); and according to CVR: ≥10% CVR (CVR 1) or <10% CVR (CVR 2).

Measurement of cerebrovascular reserve

Cerebrovascular reserve was measured using 16-detector row dynamic CT with inhalation of 5% CO_2 and 95% O_2 (carbogen). Patients wore a face mask that was connected to a gas bag with a one-way valve, which was connected to a humidification bottle and then to a 2-L steel 10-kPa carbogen bottle. The gas flow varied from 4 to 10 L/min to ensure that the patient was able to breathe comfortably. The face mask and head of the patient were fixed to the scan bed to avoid movement of the head. Dynamic CT was first performed at rest. Inhalation of carbogen started 20 min later, followed by a second dynamic CT scan.

Two axial slices (thickness 10 mm) were selected: 1 through the basal ganglia and 1 through the corona radiata. Nonionic contrast agent (40 mL) was administered at a constant rate of 6 mL/s via an antecubital vein using a power injector. For each of the MCA territory sections studied, an experienced neuroradiologist manually marked regions of interest on the cerebral blood flow (CBF) map over the parietal cortical gray matter of the expected territory of the MCA bilaterally. The mean CBF values in each region of interest were averaged. CVR was calculated according to the formula:

$$CVR = (CBF_{stimulated} - CBF_{rest}) / CBF_{rest} \times 100\%.$$

Follow-up

All patients received medical treatment and were followed up at the outpatient clinic or by telephone. Aspirin was prescribed throughout the follow-up period. The mean follow-up period was 56.9 months (range 24–73 months). The primary endpoint was recurrence of stroke.

Statistical analysis

The clinical background characteristics were compared between groups using the independent samples t test or Pearson's chi-square test. The rate of ischemic stroke was compared between groups using Pearson's chi-square test. A value of $P < 0.05$ was considered statistically significant.

Results

Patient groups

Eighteen of the 37 patients had ≥70% stenosis (stenosis group 1) and 19 had <70% stenosis (stenosis group 2). Nineteen patients had ≥10% CVR (CVR group 1) and 18 had <10% CVR (CVR group 2) (Table 1).

Table 1. Clinical characteristics of patients.

	Stenosis 1	Stenosis 2	CVR 1	CVR 2
Patients, n	18	19	19	18
Age, y	61.1±7.1	55.2±14.8	58.1±10.4	58.0±13.7
Sex, n				
Male	13	14	16	11
Female	5	5	3	7
Diagnosis, n				
TIA	11	10	13	8
Minor stroke	7	9	6	10
Risk factors, n				
Coronary heart disease	2	2	2	2
Diabetes mellitus	2	6	4	4
Hypercholesterolemia	16	14	15	15
Smoking	8	6	9	5
rCBF mL, 100 g^{-1}, min^{-1}				
Rest	90.1±30.7	98.0±42.0	80.0±27.5	100.3±44.0
Challenged	91.1±30.8	94.9±32.5	99.0±32.7	86.8±29.3
rCVR,%	16.5±3.7	2.6±1.2	26.5±8.9	−8.7±3.3
Mean follow-up, mo	60.3±13.6	53.7±16.7	53.6±16.2	60.4±14.2
Future ipsilateral stroke, n	3	4	0	7
Annual risk of ipsilateral stroke,%/y	3.3	4.7	0	7.7
P value		0.691		0.003
OR value		None		1.700 (95% CI 1.142~2.530)

Stenosis 1: 70–99% stenosis or occlusion; Stenosis 2: <70% stenosis; CVR 1: ≥10% cerebrovascular reserve; CVR 2: <10% cerebrovascular reserve.

Background characteristics

Comparisons of the clinical background characteristics between groups using the independent samples *t* test or Pearson's chi-square test did not show any significant differences between groups divided according to the degree of stenosis or the CVR (all *P*>0.05; Table 1).

Recurrence of stroke during the follow-up period

During an average follow-up period of 56.9 months (range 24–73 months), ischemic stroke occurred in 7 of the 37 patients. The recurrent stroke was on the ipsilateral side in all cases. Ischemic stroke occurred in 0 of 19 patients in CVR group 1 (annual risk 0%), 7 of 18 patients in CVR group 2 (annual risk 7.7%), 3 of 18 patients in stenosis group 1 (annual risk 3.3%), and 4 of 19 patients in stenosis group 2 (annual risk 4.7%).

Comparisons using Pearson's chi-square test showed a significant difference in the rate of ischemic stroke between CVR group 1 and CVR group 2 [odds ratio (OR) 1.700; 95% confidence interval 1.142–2.530; *P*=0.003]. There was no significant difference in the rate of ischemic stroke between stenosis group 1 and stenosis group 2 (*P*=0.691; Table 1).

Two patients died during the follow-up period. One was a 52-year-old male with <70% stenosis (ICA 50% stenosis) and <10% CVR (-5%) who died of acute myocardial infarction after

Table 2. Prognosis in medically treated symptomatic patients with ICA or MCA stenosis or occlusion.

Investigator	Date	N	Modality	Vasodilator	Subjects	Follow-up, mo	Annual rate of ipsilateral stroke, %	
							Impired CVR	Normal CVR
Kleiser et al. [8]	1992	85*	TCD	CO2	ICO	38	17	0
Hasegawa et al. [12]	1992	49	SPECT (IMP)	ACZ	ICO, ICS, MCO, MCS	18.5	0	0
Yonas et al. [9[	1993	68	Xenon CT	ACZ	ICS,ICO	24	18	2.2
Webster et al. [10]	1995	95	Xenon CT	ACZ	ICO	19.6	11.3	0
Yokota et al. [13]	1998	105	SPECT (IMP)	ACZ	ICO, ICS, MCO, MCS	32.5	3.6	3.5
Vernieri et al. [11]	1999	65**	TCD	CO2	ICO	24	15.3	1.7
Kuroda et al. [1[	2001	77	SPECT (xenon)	ACZ	ICO, MCO	43	21.8 (Type 3)	0.5–2.4 (Type 1, 2, and 4)
Present study		37	Perfusion CT	CO2	ICS, ICO, MCS, MCO	56.9	7.7	0

* Including 46 asymptomatic patients; ** including 23 asymptomatic patients.

69 months, and the other was a 69-year-old male with <70% stenosis (ICA 40% stenosis and tandem MCA stenosis 50%) and ≥10% CVR (20%) who died of heart failure after 24 months.

Discussion

Patients with ≥70% symptomatic stenosis of the ICA or MCA are considered to have a high risk of ischemic stroke [4–6], and are often treated by arterial stenting. However, it has been reported that not all patients with ≥70% stenosis have an increased risk of stroke. Scott et al. [7] reported that patients with 90–99% stenosis have a relatively low risk of stroke. Domenico et al. [8] reported a similar phenomenon in patients with symptomatic ICA stenosis of 95–99%. It seems that the risk of stroke risk does not always increase as the degree of stenosis increases, but the reason for this is unknown.

There is increasing evidence suggesting that CVR may be an independent predictor of stroke in symptomatic patients with large cerebral artery stenosis or occlusion [2,9–12], although some studies have reported conflicting results [13,14] (Table 2). A meta-analysis found that impairment of CVR was strongly associated with an increased risk of ischemic events in patients with carotid artery stenosis or occlusion (OR 3.86) [15]. Another meta-analysis found that impairment of CVR was

associated with an increased risk of stroke in asymptomatic patients (OR 6.14) [16].

The results of this study show that impairment of CVR was associated with an increased risk of stroke (OR 1.70), and that stenosis of ≥70% was not associated with a higher risk of stroke than stenosis of <70%. The reasons for this are not clear. A follow-up research reported that 20% future strokes are not related to ICA stenosis in patients with ICA stenosis of ≥70% [17]. There are 2 main mechanisms causing stroke: embolism and low perfusion. Embolism formation is associated with vulnerable atherosclerotic plaque, which is not necessarily associated with the degree of stenosis. Detachment of the embolism may result in dilation of the arteriole, which affects CVR. In a stenosed artery, the degree of stenosis affects flow, but reduced flow may also result in formation of collateral circulation. The degree of stenosis is not necessarily well correlated with perfusion, such as in a patient with severe stenosis of the ICA but abundant collateral circulation in the temporal lobe. However, the collateral circulation may affect CVR.

When measuring CVR, there are 2 methods of inducing cerebral vasodilation: inhalation of CO_2 or injection of acetazolamide. The increase in CBF after inhalation of CO_2 may result from vasodilatation secondary to extracellular and intracellular acidification of vascular smooth muscle cells, or from

neurogenic mechanisms via stimulation of the vasomotor center of the brain stem [18]. Acetazolamide selectively inhibits carbonic anhydrase in erythrocytes, glial cells, capillary endothelium, and the choroid plexus; and induces extracellular acidosis of vascular smooth muscle cells, resulting in vasodilation [19]. Although there may be differences in the mechanisms underlying these 2 methods [20], they are both widely used in clinical practice [2,9–14], and long-term CVR follow-up studies using these methods have reported similar results (Table 2) [2,9–12].

Why did we choose 10% as a cut-off point to divide CVR groups? To the best of our knowledge, no prospective studies assessing CVR impairment and stroke risk have been performed with perfusion CT. A study using single-photon emission CT and acetazolamide to measure CVR, and adopting 11% as a cut-off point to divide CVR groups, reported a positive result [21]; therefore, we tried 10% as a cut-off point to divide CVR groups and obtained satisfactory results.

This study included 10 patients with ICA or MCA occlusion, of which 1 patient (CVR −5%) had a recurrent stroke. The other 9 patients (CVR 49%, 19%, 12%, 4%, −5%, −19%, 34%, 92%, and 11%) did not develop TIA or recurrence of stroke during the follow-up period. This may be because the development of collateral circulation prevented stroke recurrence.

Two of the 37 patients in this study died of heart disease. One was a 52-year-old male with 50% ICA stenosis and −5% CVR who died of acute myocardial infarction (AMI) 69 months later. This man did not have heart disease or diabetes mellitus history, but did have hypertension, lipid metabolism disturbance, and smoking history, as well as ICA-unstable atherosclerosis plaque (2.6-mm thick). A large and unstable coronary artery plaque rupture may have caused AMI and death. The other patient was a 69-year-old male with ICA 40% stenosis, tandem MCA stenosis 50% and 20% CVR, who died of heart failure 24 month later. This man did not have heart disease or smoking history, but had hypertension, lipid metabolism disturbance, and diabetes mellitus history, as well as ICA unstable atherosclerosis plaque (3.6-mm thick). Hypertension and diabetes mellitus may have damaged heart function and caused his death.

This study has some limitations. Firstly, the CBF recorded in this study was 91.7±37.5 mL/100 g/min, which is higher than previously reported values. The CBF in the parietal cortex was previously reported be 72.0±8.5 mL/100 g/min in healthy individuals. This difference may be because the measured CBF is higher on perfusion CT than on positron emission tomography [22]. Secondly, this was a single-center study with a small sample, and multiple large-sample studies are needed to confirm this result.

Conclusions

Cerebrovascular reserve may be a more accurate predictor of stroke than degree of ICA or MCA stenosis. In clinical practice, when screening patients for stent placement to prevent future stroke, CVR should be considered because it may be more important than ICA or MCA stenosis degree.

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