The risk of ischemic events increased in patients with asymptomatic carotid stenosis with decreased cerebrovascular reserve

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ABSTRACT

Identifying high-risk patients with asymptomatic carotid stenosis (ACS) is necessary regardless of whether intensive medical therapy or aggressive treatment is applied. In order to assess the relationship between cerebrovascular reserve (CVR) measured by perfusion CT with inhalation of CO_2 and the risk of ischemic events in ACS, this long-term follow-up study was conducted. Forty-five patients with ACS who underwent the examination of CVR measured by perfusion CT with inhalation of CO_2 were collected and followed-up for at least 5 years. The primary end point was the occurrence of ipsilateral cerebral ischemic events. HRs and their 95% CI were calculated by Kaplan-Meier survival analysis and Cox regression models. The mean follow-up time was 68.7±10.7 months (40.0–84.0 months). 13 (28.9%) ipsilateral ischemic events were observed. The annual risk of ipsilateral ischemic events was 4.8%. Kaplan-Meier survival analysis and univariate Cox regression analysis indicated that patients with less CVR experienced more ischemic events (p=0.006 and p=0.013, respectively), which was confirmed by multiple Cox regression analysis (p=0.012). CVR measured by perfusion CT may potentially be the factor which can predict the risk of ipsilateral ischemic events in patients with ACS. Multidisciplinary management is necessary for these high-risk patients.

Significance of the study

What is already known about this subject?

- Carotid stenosis is a recognized risk factor for the development of ischemic cerebrovascular disease.
- Identifying high-risk patients with asymptomatic carotid stenosis (ACS) is necessary.
- There are less data about the association between cerebrovascular reserve (CVR) and ACS.

What are the new findings?

- Patients with less CVR experienced more ischemic events.
- CVR may potentially be the factor predicting the risk of ipsilateral ischemic events in patients with ACS.
- Multidisciplinary management is necessary for these high-risk patients.

How might these results change the focus of research or clinical practice?

- Although CVR cannot yet be used to selected patients with ACS for aggressive treatment, multidisciplinary management is still necessary for high-risk patients.

INTRODUCTION

Ischemic cerebrovascular disease, characterized by high morbidity and mortality, has increasingly endangered human health and inflicted great financial burden on the society. Carotid stenosis is a recognized risk factor for the development of ischemic cerebrovascular disease. However, the rate of ischemic stroke in patients with symptomatic carotid stenosis is only approximately 20%.[1] Since carotid artery atherosclerosis can progress quietly during an asymptomatic phase, asymptomatic carotid stenosis (ACS) is a silent harbinger of fatal stroke as the first clinical manifestation. Identification of carotid stenosis in an asymptomatic population can significantly prevent the occurrence of cerebrovascular diseases. Although the annual risk of stroke in patients with ACS is only 1%–3%,[2] ACS affects approximately 7%–12% of elderly people which is a huge number and it will be increasing with age.[3] The goal of ACS treatment is to reduce the risk of ischemic events and related deaths. Encouragingly, the overall annual risk of stroke in patients with ACS has dramatically decreased to 0.5% over past decades due to the improvement of intensive medical therapy and the changes of lifestyles.[4]

To develop individualized treatment plans and minimize the risk of ischemic events, the screening and identification of high-risk patients with ACS is extremely important in clinical practice. Several previous studies have identified possible predictors of stroke including the degrees of stenosis, the sizes, location and characteristics of carotid plaques. Since changes in cerebral hemodynamics underlie a broad spectrum of ischemic cerebrovascular disorders, more and more studies have proved

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that intracranial hemodynamics played an essential role in predicting stroke.[5] Cerebrovascular reserve (CVR), defined as the increase in cerebral blood flow in response to a vasodilatory stimulus, is known to reflect the capacity of the brain to maintain adequate blood flow by compensatory vasoconstricition or vasodilatation in the face of decreased perfusion due to arterial stenosis. Liu and Zhou[6] suggested that CVR might be a more accurate predictor of stroke than degree of internal or middle carotid artery stenosis.

Although CVR has been identified as a predictor of ischemic stroke in patients with carotid occlusion,[7] the relationship between CVR and asymptomatic stenosis is still not fully understood.[8] Moreover, there are several shortages in previous CVR-related studies. On one hand, the time of follow-up is not long enough which seriously reduces the credibility of studies. On the other hand, transcranial Doppler sonography (TCD) has been used to measure cerebral blood flow in most studies. Although TCD is non-radioactive and inexpensive compared with CT, positron emission tomography (PET) and MRI, TCD cannot provide sufficient information about brain tissues and it is unable to be used in some patients without acoustic windows.[9] Therefore, in the present study, the long-term follow-up prospective study was conducted for investigating the relationship between CVR measured by perfusion CT with inhalation of CO_2 and the risk of ischemic events in patients with ACS.

MATERIALS AND METHODS

Patients, inclusion criteria and exclusion criteria

Between April 2007 and January 2010, 45 patients wit ACS from LinYi People's Hospital were enrolled in this study and followed-up for at least 5 years until January 2015. The inclusion criteria were the following: (1) age from 30 to 80 years; (2) the stenotic degree of ipsilateral internal carotid artery (ICA) ≥70%; (3) no history of stroke, transient ischemic attack (TIA), dementia or depression; (4) functional disability (modified Rankin Scale score 0 or 1). The exclusion criteria were as follows: (1) intracranial stenosis; (2) contralateral internal carotid artery stenosis ≥50%; (3) inability to tolerate carbon dioxide (CO_2) inhalation; (4) functional disability (modified Rankin Scale ≥2); (5) serious systemic diseases and neuropsychiatric diseases, such as cancer, respiratory disease, cardiovascular disease and history of stroke.

Based on the standard guideline, the diagnosis of stroke was established by combination between clinical manifestations (Face Arm Speech Test) and brain imaging examinations, including Doppler ultrasound, CT, MRI, digital subtraction angiography, MR angiography and CT angiography .[10]

The subjects were informed of the methods and purposes of this study and signed a consent form. This study was approved by the ethics committee of the LinYi People's Hospital.

Estimation of carotid artery stenosis

Carotid artery stenosis was diagnosed with color Doppler ultrasound according to the standardized criteria in outpatient or physical examination center.[11] Doppler evaluation was performed on a high-resolution duplex ultrasound system, Advance Technical Laboratories HDI 3000 duplex, using a probe at scanner frequency of 7–10 MHz. Evaluation of carotid arteries was performed in longitudinal and transverse planes with anterior, lateral and posterior approaches with the subjects in supine position. The carotid artery disease was detected and classified according to the established criteria, in which plaque characteristics (homogenous, heterogeneous and calcific) were noted, and the degree of stenosis was calculated. The ultrasonography examination was performed by a qualified radiologist, experienced in neurosonology and the findings were confirmed by the stroke neurologist.

Follow-up and therapy

All the subjects were followed-up for at least 5 years until January 2015. The primary end point was the occurrence of ipsilateral cerebral ischemic events, including strokes, TIA or sudden death. During the follow-up, subjects with significant stenosis were prescribed aspirin 150 mg/day.

Measurement of cerebrovascular reserve

CVR was measured using 16-detector row dynamic CT with the inhalation of a mixed gas consisting of 5% CO_2 and 95% oxygen (O_2). The subjects wore a face mask that was connected to gas bag with a one-way valve, which was connected to a humidification bottle and then to a 2 L steel 10 kPa CO_2/O_2 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: one through the basal ganglia and one through the corona radiata. Non-ionic 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 middle cerebral artery 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[12]:

$$\mathrm{CVR} = \frac{(\mathrm{CBF}_{\mathrm{stimulated}} \ \mathrm{CBF}_{\mathrm{rest}})}{\mathrm{CBF}_{\mathrm{rest}} \ 100\%}$$

Statistical analysis

All data were analyzed by means of SPSS V.18.0 (IBM Software, Armonk, New York, USA) and were shown as the mean±SD. Independent-sample t-tests or Pearson's χ^2 tests were applied to compare the categorical variables. HR and 95% CI were calculated by Kaplan-Meier survival analysis and Cox regression models. Statistical significance was defined as $p<0.05$.

RESULTS

As shown in table 1, of the 45 patients enrolled, 29 (64.4%) were men and 16 (35.6%) were women. The mean age of the cohort was 60.7±10.5 years. On assessment of vascular risk factors, 28 subjects (62.2%) were hypertensive, 22 patients (48.9%) had dyslipidemia, 25 subjects (55.6%) had diabetes, 2 patients (4.4%) had atrial fibrillation, 11 subjects

Table 1 Baseline characteristics of the study population

Characteristic	Total (n=45)	Ipsilateral ischemic events		p Value
		Yes (n=13)	No (n=32)	
Mean age, years	60.7±10.5	60.1±8.8	61.0±11.3	0.787
Sex, M/F	29/16	8/5	21/11	0.795
Overweight, n *(%)	26 (57.7)	8 (61.5)	16 (50)	0.482
Hypertension, n (%)	28 (62.2)	7 (53.8)	17 (53.1)	0.965
Dyslipidemia, n (%)	22 (48.9)	8 (61.5)	21 (65.6)	0.795
Diabetes, n (%)	25 (55.6)	7 (53.8)	16 (50)	0.815
Atrial fibrillation, n (%)	2 (4.4)	9 (69.2)	14 (43.8)	0.121
Coronary artery disease, n (%)	11 (24.4)	9 (69.2)	8 (25)	0.006
Ever smoker, n (%)	20 (44.4)	8 (61.5)	15 (46.9)	0.372
Warfarin, n (%)	1 (2.2)	9 (69.2)	17 (53.1)	0.321
Statins, n (%)	29 (64.4)	8 (61.5)	17 (53.1)	0.607
Aspirin, n (%)	30 (66.7)	7 (53.8)	15 (46.9)	0.672
Beta-blockers, n (%)	21 (46.7)	10 (76.9)	14 (43.8)	0.043
Degree of carotid stenosis, n (%)				0.043
70%–89%	22 (48.9)	3 (23.1)	18 (56.3)	
90%–99%	23 (51.1)	10 (76.9)	14 (43.8)	
Mean CVR, %	29.5±27.3	10.1±22.6	37.5±25.2	0.001
CVR category				0.019
CVR≥10%, n (%)	32 (71.1)	6 (46.2)	26 (81.3)	
CVR<10%, n (%)	13 (28.9)	7 (53.8)	6 (18.7)	

Values are expressed as number (percentage) or mean±SD. The percentage was a calculation of the number of occurrence events divided by total number.
CVR, cerebrovascular reserve.

(24.4%) had coronary artery disease, 20 subjects (44.4%) were ever smoker and 30 patients (66.7%) were prescribed aspirin. There were no significant differences between patients with and without ipsilateral ischemic events in terms of age, gender, frequency of overweight, hypertension, dyslipidemia, diabetes mellitus, smoking status, the frequencies of atrial fibrillation, the use of warfarin, statins and aspirin (p>0.05). The degree of carotid stenosis in 22 patients (48.9%) was 70%–89% and 23 (51.1%) patients reached 90%–99%. Mean CVR was 29.5%±27.3% and the mean CVR of patients without ipsilateral ischemic events (37.5±25.2) was significantly higher than that of patients with ipsilateral ischemic events (10.1±22.6) (p=0.001). The number of patients with CVR ≥10% (32, 71.1%) was significantly higher than that of patients with CVR <10%.

The mean follow-up of the 45 patients was 68.7±10.7 months ranging from 40.0 to 84.0 months. Neither deaths nor contralateral ischemic events occurred. Thirteen cases (13.3%) of ipsilateral ischemic events were observed during the follow-up, including nine TIAs (20%) and four stroke (8.9%). Among them, the degree of carotid stenosis in seven patients with TIA and two patients with stroke was 70%–89%; 90%–99% carotid stenosis was found in two patients with TIA and two patients with stroke. CVR ≥10% was observed in six patients with TIA and one patient with stroke. Moreover, three patients with TIA and three patients with stroke exhibited CVR <10%. The annual risk of ipsilateral ischemic events was 4.8% in this study.

To determine which variables might be predictors of ipsilateral ischemic events, risk factors were entered into a Cox regression analysis (table 2). Univariate Cox regression analysis indicated that more ischemic events were observed in patients with the history of coronary artery disease (p=0.026), higher degree of carotid stenosis (p=0.037) and less CVR (p=0.013). Subsequently, the factors with p<0.05 in univariate analysis were chosen for further multivariate analysis. The result of multiple analysis proved that patients with history of coronary artery disease (p=0.034) and less CVR (p=0.012) would suffer from more ischemic events. The degree of carotid failed to be the available predictor of ipsilateral ischemic events (p>0.05). As shown in figure 1, Kaplan-Meier survival analysis further confirmed that patients with less CVR experienced more ischemic events (p=0.006).

DISCUSSION

Increasing evidences suggested that impaired CVR was strongly associated with occurrence of ischemic events which was helpful to identify patients with ACS with greater risk for ischemic events.[13 14] In consideration of radiation hazard and cost considerations, few prospective studies had investigated the relationship between CVR and ischemic events by using CT or MRI perfusion techniques. In this long-term follow-up prospective study, the CVR was measured by perfusion CT with inhalation of CO_2. We suggested that impaired CVR was strongly associated with ischemic events, indicating that CVR was a potential predictor for assessing the risk of ipsilateral ischemic events in patients with ACS.

There are mainly two methods for measuring CVR. One method is TCD, which measures flow velocities of distal damage area before and after vasodilatory stimulus. The other approach is the cerebral blood flow measurement based on flow sensitive imaging techniques, including CT perfusion, MR perfusion and PET. Comparing with CT,

Table 2 HRs of ipsilateral ischemic events estimated by Cox regression analysis for each factor considered

	Univariate analysis			Multivariate analysis		
Factor	**HR**	**95% CI**	**p Value**	**HR**	**95% CI**	**p Value**
Age, ≥60/<60 years	1.153	0.374 to 3.549	0.805	4.206	1.307 to 16.413	0.041
Sex, male/female	1.002	0.326 to 3.079	0.997	13.681	1.064 to 29.523	0.047
Overweight, yes/no	1.623	0.529 to 4.983	0.397	0.083	0.003 to 2.277	0.141
Hypertension, yes/no	1.060	0.356 to 3.159	0.917	13.621	0.657 to 82.207	0.091
Dyslipidemia, yes/no	0.728	0.231 to 2.299	0.589	1.709	0.303 to 2.905	0.028
Diabetes, yes/no	0.933	0.311 to 2.799	0.901	1.388	0.078 to 24.735	0.823
Atrial fibrillation, yes/no	1.981	0.609 to 6.445	0.256	9.624	0.268 to 45.812	0.215
Coronary artery disease, yes/no	3.813	1.170 to 12.431	0.026	2.449	0.979 to 24.427	0.034
Ever smoker, yes/no	1.217	0.386 to 3.844	0.737	1.679	0.867 to 7.649	0.023
Warfarin, yes/no	1.389	0.417 to 4.628	0.592	0.316	0.000 to 0.830	0.018
Statins, yes/no	1.278	0.417 to 3.918	0.667	0.089	0.058 to 1.913	0.062
Aspirin, yes/no	0.968	0.312 to 3.004	0.955	0.254	0.007 to 9.537	0.459
Beta-blockers, yes/no	2.293	0.618 to 8.506	0.215	0.473	0.000 to 0.916	0.022
Degree of carotid stenosis, 90%–99%/70%–89%	3.992	1.087 to 14.662	0.037	2.089	0.080 to 54.780	0.658
CVR, <10%/≥10%	4.311	1.365 to 13.620	0.013	3.767	0.369 to 4.910	0.012

CVR, cerebrovascular reserve.

PET and MRI, TCD is a non-radioactive, non-invasive, inexpensive method with procedures. However, many researches indicated that TCD could not provide sufficient information of brain tissue and failed to be used in patients without acoustic windows. Perfusion CT is a more convenient and widely used clinical examination due to good consistency of cerebral blood flow measurement.[15] Therefore, we choose to apply perfusion CT to measure cerebral blood flow in this study. However, there are still several limitations of perfusion CT including radiation hazard and high financial cost.

The inhalation of mixed CO_2 gases is widely used in clinical research and it is quick, easy and repeatable.[16] Totaro *et al* compared CO_2 inhalation, breath holding and hyperventilation, the results revealed that CO_2 inhalation exhibited reliable short-term and long-term response indices and good repeatability.[17] Recently, Donahue *et al* also reported that carbogen-induced (5% CO_2 in O_2) CVR measurements were more safe and effective than those methods by utilizing 5% CO_2 in air.[18]

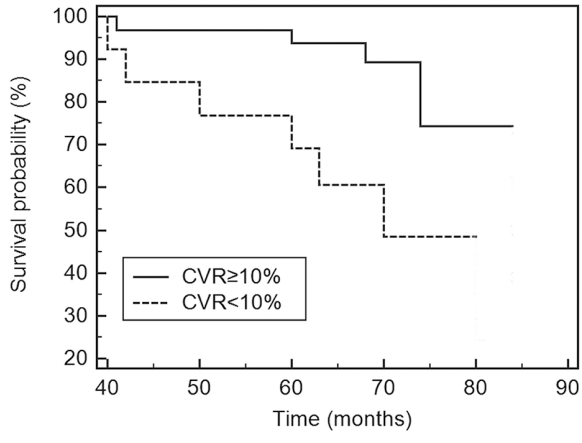

Figure 1 Kaplan-Meier curves for event-free survival of patients with asymptomatic carotid stenosis. CVR, cerebrovascular reserve.

Conventional risk factors, such as dyslipidemia and diabetes mellitus, may play an important role in the progression of atherosclerosis. In the present study, more than 50% of the patients with ACS were receiving statins and aspirin at baseline, and all of the patients received aspirin during the follow-up. These medical therapies may have affected the associations between the conventional risk factors and the ipsilateral ischemic events.

In this study, the annual risk of ipsilateral stroke or TIA was 4.8%, which was less than the global annual risk of 5.7% but higher than some recent studies.[10 19] These differences in the findings might reflect a limitation of our study which was a lack of integrated management during the follow-up. We only concerned about the exhibited signs or symptoms of ischemic events after taking aspirin instead of other risk factors. Moreover, the lack of efficient comorbidities managements, such as hypertension and diabetes mellitus, had occurred in the follow-up of this study. Additionally, our patients generally performed less physical exercise due to the cold weather in northern China. Therefore, we believed that if we strengthened the multidisciplinary management, the risk of cerebrovascular ischemic events would significantly decrease. In the future, we will perform a prospective study regarding this area.

This study has some shortcomings. First, the number of patients included in this study was small. Second, as previously mentioned, due to China's current imperfect medical structure, the integrated multidisciplinary management of the patients was poor.

CONCLUSIONS

The results of the present study indicate that CVR is a potential predictor for assessing the risk of ipsilateral ischemic events in patients with ACS. Although CVR cannot be used to selected patients with ACS for aggressive treatment,

multidisciplinary management is still necessary for high-risk patients. Additional studies are needed to assess inclusive and convenient approaches to identify these patients.

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Competing interests None declared.

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