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Original Article

Hyperglycemia indicates poor cerebral collaterals in patients underwent acute ischemic stroke

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Abstract: Collateral circulation plays a key role in stroke and cardiovascular diseases. Hyperglycemia is known to aggravate cerebral ischemia. However, whether hyperglycemia directly contributes to collateral circulation after acute ischemic stroke is unknown. We sought to investigate the relationship between collaterals and fasting glucose levels in acute ischemic stroke patients. 45 patients (mean age, 61.9±11.4 years; 29 males) underwent acute ischemic stroke were enrolled from September 2014 to August 2015. M1 segment of middle cerebral artery (MCA) ± intracranial internal carotid artery (ICA) occlusions were measured using Digital Subtraction Angiography (DSA). Two neurologic clinical specialists evaluated the DSA images and graded the cerebral collaterals using Collateral Flow Grading System (Grade 0-4). Poor collaterals (Grade 0-2) were observed in 32/45 (71.1%) patients. Univariate analysis identified that patients with poor collaterals at baseline had higher fasting glucose levels at admission (P=0.025). At multivariate analysis, fasting glucose at admission did not achieve independent predictor status for poor cerebral collaterals (P=0.120). This study of 45 patients shows that hyperglycemia indicate higher risk of poor cerebral collaterals in patients underwent acute ischemic stroke, but hyperglycemia is not an independent predictor of poor cerebral collaterals in these patients.

Keywords: Cerebral collaterals, hyperglycemia, acute ischemic stroke, fasting glucose.

Introduction

Stroke is the leading cause of mortality and acquired disability worldwide. Ischemic stroke accounts for ~87% of cases annually, whereas the remaining cases are hemorrhagic. Most patients who experience an acute cerebral ischemic attack receive proper clinical intervention due to the extremely short critical window. In cases of severe impairment after ischemic stroke, difficult decisions regarding the stroke treatment must be made within days of hospitalization [1]. An urgent need in clinical practice is to conduct an accurate establishment of collateral circulation, in order to start the initiation of therapy as early as possible. An accurate establishment is also helpful in maintaining cerebral circulation and improves stroke prognosis. Recent studies have indicated that rapid and complete collateral circulation can reduce infarct volume, and decrease the risk of recurrent stroke and hemorrhagic transformation [2-4].

Imaging studies suggested that collateral complexity at baseline exhibits individual variability, and patients with fewer collateral vessels have worse outcomes after stroke [5-9]. In spite of that, how collateral circulation regulates clinical outcomes after stroke remains unclear [9]. Age, acute hyperglycemia, statin use, sex, hypertension, systolic blood pressure (BP) at admission, and admission National Institutes of Health Stroke Scale (NIHSS) scores are all reported as determinants of native collaterals. In this study, we aim to analyze whether there is an association between hyperglycemia and collateral circulation in a cohort of patients presenting with M1 segment of middle cerebral artery (MCA) ± intracranial internal carotid artery (ICA) occlusions.

Materials and methods

Study population

This study was a retrospective analysis of patients with a diagnosis of ischemic stroke sec-

Table 1. Baseline characteristics of patients

Variables	(mean ± SD, or %)
Age	61.9±11.4
Gender (male, %)	64.4
Hypertension (%)	51.1
Diabetes (%)	20.0
Heart diseases (%)	24.4
Smoking history (%)	42.2
Cerebral vascular diseases (%)	26.7
Atrial fibrillation (%)	20.0
Admission NIHSS (median, IQR)	13, 11
Systolic blood pressure (mmHg)	141.9±26.0
Admission fasting glucose (mmol/L)	6.6±2.3
BNP (pg/ml)	250.7±428.0
CRP (mmol/L)	6.7±4.9
Uric acid (mmol/L)	272.5±94.0
Cholesterol (mmol/L)	4.1±1.3
LDL (mmol/L)	2.5±1.1
MCA occlusion (%)	42.2
Poor collaterals (%)	71.1

BNP Brain natriuretic peptide; CRP C reactive protein; LDL low density lipoprotein; MCA Middle cerebral artery.

ondary to M1 segment MCA ± ICA occlusion. They were enrolled in the neurology ICU of TianTan Hospital from September 2014 to August 2015. Patients with acute ischemic stroke were consecutively entered. The analysis was restricted to patients who had digital subtraction angiography (DSA) within 24 hours of symptom onset. Patients in the study met the following criteria: (1) an ischemic stroke proven by initial diffusion weighted imaging (DWI) or head computerized tomography (CT) scan; (2) admission within 24 hours from symptom onset; and (3) an admission score on the National Institutes of Health Stroke Scale (NIHSS) between 5 and 25; and (4) have a DSA within 24 hours of symptom onset and have M1 segment MCA ± ICA occlusion confirmed by DSA. Symptom onset was defined as the last time the patient was seen in normal health conditions. The exclusion criteria were life-threatening conditions that limited follow-up visits, or absence of DSA within 24 hours of symptom onset. This study was approved by the local institutional review board.

Data collection

Clinical data (age, gender, stroke risk factors, admission National Institutes of Health Stroke Scale [NIHSS] score, systolic pressure, admission fast glucose, brain natriuretic peptide, C-reactive protein, uric acid, cholesterol and low density lipoprotein) were collected for each patient through the departmental database and retrospective chart review.

Collateral assessment on angiography

Two neurologic clinical specialists evaluated the bilateral internal carotid and vertebral artery angiograms (anterior/posterior and lateral views) blindly. Angiograms were graded according to the Higashida collateral scale from the PROACT-II trial on a scale from 0 to 4:0) no collaterals visible to the ischemic site; 1) slow collaterals to the periphery of the ischemic site with persistence of some of the defect; 2) rapid collaterals to the periphery of ischemic site with persistence of some of the defect and to only a portion of the ischemic territory; 3) collaterals with slow but complete angiographic blood flow of the ischemic bed by the late venous phase and 4) complete and rapid collateral blood flow to the vascular bed in the entire ischemic territory by retrograde perfusion [10].

Statistical analysis

Patients were divided into two groups (poor, Grade 0-2; good, Grade 3-4) according to their collateral circulation. Patient characteristics were compared across these two groups using a Mann-Whitney U test for continuous variables and a chi-squared test for categorical variables. Multiple regression analysis was performed to identify independent variables that predicted collateral circulation. Logistic regression models tested the associations among the predictors (eg, age, uric acid, diabetes, hypertension and admission fasting blood glucose) and poor cerebral collaterals. Statistical analysis was carried out using Statistical Package for the Social Sciences (SPSS version 17.0) software for Windows (SPSS, Chicago, IL, USA). Continuous variables are expressed as mean ± standard deviation in the text and tables. Values of $P < 0.05$ were considered statistically significant.

Results

Patient characteristics

A total of 45 patients with M1 segment MCA ± ICA occlusion were enrolled in this study. All patients had undergone DSA within 24 hours of

Table 2. Clinical characteristics and outcomes in the poor and good collaterals

Variables	Poor collateral (32)	Good collateral (13)	*P* value
Age	62.97±10.15	59.23±14.01	0.394
Gender (male, %)	21, 65.6	8, 61.5	1.000
Hypertension (%)	17, 53.1	6, 46.2	0.672
Diabetes (%)	7, 21.9	2, 15.4	1.000
Heart diseases (%)	8, 25.0	3, 23.1	0.695
Smoking (%)	14, 43.8	5, 38.5	0.645
Cerebral vascular diseases (%)	8, 25.0	4, 30.8	0.721
Atrial fibrillation (%)	6, 18.8	3, 23.1	0.704
Admission NIHSS (median, IQR)	13, 9.25	10, 12	0.111
Systolic blood pressure (mmHg)	142.47±23.56	140.46±32.25	0.841
Admission fasting glucose (mmol/L)	6.97±2.56	5.72±1.06	0.025*
BNP (pg/ml)	311.27±495.08	114.32±155.41	0.070
CRP (mmol/L)	6.91±5.22	6.14±4.32	0.627
Uric acid (mmol/L)	279.42±105.00	256.12±60.83	0.363
Cholesterol (mmol/L)	4.22±1.67	3.83±1.46	0.409
LDL (mmol/L) SD	2.55±1.03	2.35±1.19	0.614

*The *P* value was less than 0.05, which was statistically significant.

Table 3. Multiple regression analysis of factors related to infarct volume

Characteristics	95% CI	OR	b	*P* value
Age	0.925-1.047	0.984	-0.016	0.611
Uric acid	0.987-1.005	0.996	-0.004	0.351
Diabetes	0.087-5.160	0.669	-0.402	0.700
Hypertension	0.280-4.886	1.170	0.157	0.803
Fasting glucose	0.383-1.117	0.654	-0.425	0.120

symptom onset. **Table 1** shows baseline characteristics of the patients. Subjects average age was 61.9 (±11.4) years. 29 patients (64.4%) were males. 23 patients (51.1%) had hypertension, 9 patients (20.0%) had diabetes and 11 patients (24.4%) had heart diseases. The median (IQR) NIHSS at admission was 11.0 and the mean systolic pressure was 141.9 (±26.0) mmHg. The mean admission fasting blood glucose was 6.6 (±2.3) mmol/l, and the mean uric acid was 272.5 (±94.0) mmol/l. Overall, collaterals were considered to be poor (the Higashida collateral scale 0-2) in 32 patients (71.1%) and 19 patients (42.2%) had MCA occlusion.

Association of hyperglycemia with cerebral collateral circulation in univariate analyses

Table 2 shows a comparison between good and poor collateral circulation. In summary, no significant difference was observed between patients with poor and good collaterals in conditional risk factors such as age, gender, stroke risk factors, admission NIHSS score and clinical experimental data such as systolic pressure, BNP, C-reactive protein, uric acid, cholesterol and low-density lipoprotein. In contrast to that, patients with poor collaterals have significant higher fasting blood glucose at admission (P=0.025).

Correlation between Hyperglycemia and cerebral collateral circulation

A multivariate analysis included age, uric acid, diabetes, hypertension and fasting glucose in the logistic regression model to predict poor cerebral collaterals was performed. Surprisingly, none of the associations between poor cerebral collaterals and fasting glucose (P=0.120), or the other studied variables remained significant (**Table 3**).

Discussion

In the present study, we aim to explore whether hyperglycemia and cerebral collateral patterns are correlated in patients underwent acute ischemic stroke. The result of our cohort study showed that there is an association between fasting glucose andcerebral collaterals. In contrast, fasting glucose is not an independent predictor of poor cerebral collaterals events in these patients.

Collateral circulation plays a critical role in sustaining tissue perfusion following a proximal arterial occlusion and, thereby, has a great influence on tissue and clinical outcomes after ischemic stroke. Therefore, it is important to identify clinical features in the adequacy of leptomeningeal collateral circulation to obtain a better grasp of variability in cerebral hemodynamics, especially during the initial hours of stroke. Although some published studies failed to identify key variables, it is believed that certain baseline characteristics, such as age, gen-

der and heart diseases, might have an impact on the extent of leptomeningeal collaterals in stroke patients. For example, aging was reported to cause rarefaction and insufficiency of the collateral circulation in multiple tissues, resulting in more severe ischemic tissue injury [11-14].

In this prospective study we showed the association between hyperglycemia and poor collaterals (**Table 2**), despite that this relationship lost significance in multivariate analysis. To our best knowledge, other studies also agreed with our hypothesis that better collaterals were associated with lower glucose and lower blood pressure [15]. Hyperglycemia was previously reported as a predictive factor of worse prognosis of cardiovascular events with a significant increase in mortality [16, 17]. In addition to that, collateral flow definitely contributes to stroke outcomes and mortality in animal models [18, 19]. It is also notable that our data indicated hyperglycemia is not an independent predictor of poor collaterals in the overall cohort of patients, which is supported by a previous finding that hyperglycemia induced infarct expansion is independent of collateral circulation status [20].

The impact of glucose metabolism on the cerebral vasculature, as measured by angiography, has not been well described. Weihrauch et al. reported that in dogs with hyperglycemia or repeated ischemia, the activity of myocardial fluid matrix metalloproteinase (MMP-9) was upregulated and the level of angiostatin, an angiogenesis inhibitor protein, was increased [6]. It is believed that, in dogs with high blood sugar, collateral circulation grade is lowered due to the increase of angiostatin, which leads to the inhibition of angiogenesis [21]. In another experimental study on rabbit diabetes, it was observed that high blood sugar could reduce the number of vascular branches and the diameter of blood vessels [22]. Although the molecular mechanisms involved in collateral vessel growth are not fully understood yet, collateral vessel growth was reported to determine the ischemic stroke severity and functional prognosis [23]. The other molecular factors and pathways associated with cerebral collateral include vascular endothelial growth factor (VEGF) and beta fibroblast growth factor (bFGF), endothelium dependent vasodilation, and reactive oxygen species (ROS) [24-29]. Taken together, all clinical research and the biological studies suggest a complicated correlation between hyperglycemia cerebral collateral at the molecular, pre-clinical, and clinical levels.

In conclusion, admission hyperglycemiais associated with cerebral collaterals, but does not act as an independent predictor for poor cerebral collaterals inpatients with ICA or MCA occlusion. Certain limitations of our study merit consideration. First, the present study is limited by its retrospective design. Blood glucose levels were measured at a single time point, which does not allow stress hyperglycemia to be considered. Second, many factors influence cerebral collateral circulation, and the present study only considers one factor. Further study will identify other pathogenic factors. Additionally, the ideal study design to further examine the relationship between hyperglycemia and cerebral collaterals is a prospective cohort study with larger sample size is required to test our hypothesis rigorously.

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Disclosure of conflict of interest

None.

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