Pre-existence of Diabetes Mellitus Improves Cerebral Perfusion During Middle Cerebral Artery Severe Stenosis or Chronic Occlusion

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Research Article

Keywords: collateral flow, perfusion, diabetes mellitus, cerebrovascular stenosis

Posted Date: March 2nd, 2022

DOI: <https://doi.org/10.21203/rs.3.rs-1388480/v1>

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Abstract

Background and Purpose—Collateral flow compensation followed by cerebrovascular stenosis is closely correlated to acute ischemic stroke (AIS) and chronic cerebral hypoperfusion. Many evidences indicated that diabetes mellitus (DM) probably had impact on it, but the exact extent was unclear. Aim of this study is to investigate the impact of DM on collateral flow of patients with severe stenosis or occlusion of middle cerebral artery (MCA).

Methods—We retrospectively identified patients from our registry of patients who had severe stenosis or occlusion in the MCA diagnosed by digital subtraction angiography (DSA), besides it, collateral flow compensation was also assessed by magnetic resonance perfusion (MRP). Relative parameters of perfusion (MTT, TTP, CBF, CBV) in the different areas including Am, Lm, Pm, Bm were compared between diabetic and non-diabetic patients. Based on this background, multivariable logistic regression was used to identify the independent correlation between DM and above MRP values with obvious difference, so did the correlation between them and HbA1c or fasting blood glucose (FBG) through Spearman correlation coefficient.

Results—105 patients were included in this study, with 73 patients belong to non-diabetes mellitus (NDM) group and 32 patients belong to DM group. Older age, higher fibrinogen (FIB) and fasting blood glucose (FBG), higher percent of hypertension were seen in the DM group compared to the NDM group. Higher ipsilateral/contralateral ratio of CBF and CBV in Lm area was observed in DM group in contrast with NDM group, and lower ipsilateral/contralateral ratio of MTT was observed in DM group in Am and Lm areas, so did TTP in Lm and Pm areas. Independent correlation was also maintained between DM and Lm-CBF, Lm-CBV, Lm-MTT, Lm-TTP, Am-MTT, Pm-TTP through multivariable logistic regression. Both FBG and HbA1c were correlated to part of above parameters of ipsilateral/contralateral ratio, while the impact of FBG was more prominent.

Conclusions—DM can partly improve cerebral hypoperfusion due to severe stenosis or occlusive in the MCA, which is probably originated from microvascular remodeling induced by pre-existence of DM.

1. Introduction

Atherosclerosis of middle cerebral artery (MCA) progressed to severe stenosis or occlusion, is a major cause of ischemic event in anterior circulation. Generally, annual stroke incidence in patients with symptomatic MCA stenosis and asymptomatic MCA stenosis were 12.5% and 2.8% respectively[1]. Collateral flow compensation, activated in response to chronic cerebral ischemia, is the decisive factor in the pathogenesis of ischemic cerebrovascular events. There were leptomeningeal arteries and new vessels formation (NVF) along the target MCA involved in this kind of collateral circulation compensation. Neovascularization is an innate physiologic response by which tissues respond to various stimuli including ischemia through collateral arteriogenesis and NVF from existing vessels or from endothelial progenitor cells[2].

The causes of cerebrovascular disease in diabetic patients are multifactorial, including intra/extracranial vascular diseases and microvascular pathology. Diabetes mellitus (DM) was independently related to a greater degree of intracranial atherosclerosis and a high number of involved vessels [3], also it had a major impact on the neovascularization process but responded varies between different organ systems. Metabolic abnormalities caused by DM induce microvascular changes are most closely associated with ischemic stroke.

Associations between diabetes and the collateral status have been investigate, indicating that collateralization has a significant impact on the functional outcome [4–7]. That was the reason why patients with DM tend to develop more severe events in cerebrovascular and cardiovascular diseases[8, 9]. How about the impact of DM on collateral flow

compensation in the condition of hypoperfusion? Previous studies demonstrated that reduced coronary collateralization in type 2 diabetic patients with severe coronary artery stenosis or chronic total occlusion [10], which was unknown in the patients with intracranial artery stenosis or occlusion.

Study of chronic hyperglycemia on cerebral microvascular remodeling revealed that MTT values in the nonischemic cerebral hemisphere were significantly longer in the patients with HbA1c > 6.5% compared to those with HbA1c ≤ 6.5% [11]. Also, impaired collateral flow compensation was confirmed in the Type 2 Diabetic Mice with common carotid artery occlusion (CCAO)[12]. All the evidences seemed to suggest that similar impact was played on cerebrovascular and cardiovascular, that is reduced collateralization in diabetic patients with steno-occlusive MCA.

Perfusion weighted imaging (PWI) is a well-established technique to evaluate collaterals in clinical practice, and relative parameters can be sensitive to identify the hypo-perfusion areas. In the current study, perfusion of magnetic resonance imaging (MRI) was done in all patients with severe stenosis or occlusion MCA, and final goal is to investigate the impact of diabetes on collateral flow compensation reflected by cerebral perfusion with intracranial artery stenosis or occlusion.

2. Methods

2.1 Study subjects

Data was collected from hospitalized patients of Affiliated Drum Tower Hospital of Nanjing University Medical School, from May 2018 to December 2019, and it was approved by our institutional committee (No. 2016-169-01). Strict inclusion and exclusion criteria was defined as following: (1) without acute ischemic stroke (AIS) or with AIS > 1 weeks when digital subtraction angiography (DSA) and magnetic resonance perfusion (MRP) were done; (2) severe stenosis or occlusion in the MCA was vital diagnosed by DSA, which was calculated with the formula of $[1 - (Ds/Dn)] \times 100$ (WASID, Ds is the diameter of the most stenotic portion and Dn is proximate normal vessel diameter); (3) no other significant (> 70%) stenosis in the cervical or intracranial arteries diagnosed by DSA except the target vessel; (4) patients who received mechanical thrombectomy following AIS were excluded wholly, no matter they were induced by embolism or intracranial stenosis; (5) moyamoya disease (MMD), vasculitis or arterial dissection; (6) PWI was done with parametric maps of cerebral blood volume (CBV), cerebral blood flow (CBF), mean transit time (MTT), and time to peak (TTP); (7) blood draw and measurement of hemoglobin A1c (HbA1c) and other biochemical indexes within 24 hours of admission.

2.2 Definition of DM

DM was defined as participants with history of it, or new diagnosis of it after admitting.

All the patients were detected fasting blood glucose (FBG) through venous blood at least once, fasting glucose through fingertip blood at least once, and random glucose through fingertip blood at least three times. Diagnostic criteria of DM was referred to Chinese Diabetes diagnostic guidelines. Oral glucose tolerance test (OGTT) was used when blood glucose was abnormalities but not reach the criteria of DM.

2.3 Image Processing and Interpretation

MRP was performed on a 3.0 T Magnetom Avanto Scanner (Philips, Netherlands) using a previously described protocol. Region of interest (ROI) of this study was selected referred to ASPECT study[13]. Data was generated from these ROIs including M1, M2, M3, M4, M5, M6, L(lentiform). Accorded with the territory selection of M4, M5, M6, relative territory of lentiform immediately superior to L was named as L1, and ROI of it was also generated. Then the

value of four territories named $Am=(M1 + M4)/2$ (anterior cortex of MCA), $Lm=(M2 + M5)/2$ (lateral cortex of MCA), $Pm=(M3 + M6)/2$ (posterior cortex of MCA) and $Bm=(L + L1)/2$ (basal ganglia of MCA) were calculated.

2.4 Blood collection and analysis

Venous blood was collected following overnight fasting for at least 8 hours, and analyzed by a solid-phase chemiluminescent immunometric assay on Immulite 2000 with the manufacturer's reagents as directed to detect total bilirubin (TBIL), direct bilirubin (DBIL), triglyceride (TG), total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), uric acid (UA), blood glucose (BG), C reactive protein (CRP), hemoglobin A1C(HbA1C), fibrinogen (FIB), D-dimers (D-D).

2.5 Statistical Analysis

All metric and normally distributed variables were reported as mean $\pm$ standard deviation. Categorical variables were presented as frequency (percentage). Comparison between groups were assessed by using student t test for parametric data, and Pearson Chi-Square test for categorical data. Spearman correlation coefficient was used to analyze the association of MRP values and clinical variables. Multivariate regression analyses were conducted to determine independent correlation between DM and parameters of MRP, results were reported as odds ratios (ORs) with 95% confidence intervals (CIs). A p value of < 0.05 was considered to be statistically significant. All statistical analyses were conducted using SPSS 19.0.

3. Results

3.1 Demographics and clinical characteristics

105 patients with severe stenosis or occlusion of MCA were enrolled (Fig. 1). Among them, 73 patients belong to non-diabetes mellitus (NDM) group and 32 patients belong to DM group. As shown in Table 1, no differences were found between NDM and DM groups in aspects of gender, smoking, alcohol abuse, serum bilirubin, serum lipid level and D dimer ($p > 0.05$). The average age of DM group was older than NDM group (62.3 ± 10.2 vs. 57.1 ± 10.9 , $p < 0.05$), and higher FIB was accompanied with DM individuals (3.08 ± 0.75 vs 2.66 ± 0.60 , $p < 0.05$). In addition to manifesting higher fasting blood glucose (FBG), DM group was concurrent higher rate of hypertension (87.5% vs. 67.1%, $p < 0.05$).

Table 1
Comparison of risk factors between the groups of NDM and DM

Variable	NDM (n = 73)	DM (n = 32)	P
Male (%)	63.0 (46/73)	53.1 (17/32)	0.341
Age (years)	57.1 ± 10.9	62.3 ± 10.2	0.025
Statin use (%)	19.2 (14/73)	21.9 (7/32)	0.750
Hypertension (%)	67.1 (49/73)	87.5 (28/32)	0.030
Smoking (%)	37.0 (27/73)	31.3 (10/32)	0.571
Alcohol (%)	20.6 (15/73)	28.1 (9/32)	0.395
DBIL (umol/l)	2.28 ± 1.02	2.64 ± 1.39	0.201
TBIL (umol/l)	9.68 ± 3.50	10.6 ± 4.52	0.262
FBG (mmol/l)	4.65 ± 0.63	7.02 ± 1.76	0.000
UA (umol/l)	327.7 ± 82.7	297.2 ± 95.4	0.100
TG (mmol/l)	1.56 ± 0.80	1.33 ± 0.59	0.148
TC (mmol/l)	3.63 ± 0.79	3.40 ± 0.69	0.161
HDL-C (mmol/l)	1.03 ± 0.27	0.99 ± 0.28	0.459
LDL-C (mmol/l)	1.99 ± 0.64	1.91 ± 0.72	0.561
CRP (mg/l)	4.60 ± 2.56	5.61 ± 4.71	0.259
FIB (g/l)	2.66 ± 0.60	3.08 ± 0.75	0.003
D-D (mg/l)	0.48 ± 1.08	0.38 ± 0.53	0.649
Stenosis (%)	95. 2 ± 7.9	92.9 ± 8.2	0.176

3.2 Comparison of MRP values between groups of NDM and DM

Then, we analyzed cerebral perfusion status of the two groups and compared perfusion parameters comprehensively and quantitatively. Firstly, we categorized the territory of MCA into four parts: Am, Lm, Pm and Bm. Then, cerebral perfusion parameters were compared between NDM and DM groups in the ipsilateral side, contralateral side and ipsilateral/contralateral. As shown in Table 2, compared to the contralateral side, ipsilateral side displayed declined cerebral perfusion, mainly reflected by higher MTT or TTP. However, we did not find any differences between NDM and DM groups, both in the contralateral and ipsilateral sides. It bears noting that ipsilateral/contralateral ratio of CBF (0.96 ± 0.39 in NDM group vs. 1.14 ± 0.34 in DM group, $p < 0.05$) and CBV (1.01 ± 0.42 in NDM group vs. 1.23 ± 0.42 in DM group, $p < 0.05$) in Lm area were obviously increased in DM group in contrast with NDM group (named Lm-CBF and Lm-CBV in the following text). Consistently, ipsilateral/contralateral ratio of MTT was significantly decreased in DM group in Lm ($p < 0.05$) and Am ($p < 0.05$) areas, so did TTP in Lm ($p < 0.05$) and Pm ($p < 0.05$) (named Am-MTT, Lm-MTT, Lm-TTP, Pm-TTP in the following text).

Table 2
Comparison of MRP values between groups of NDM and DM

		Contralateral of MCA			Ipsilateral of MCA			Ipsilateral/Contralateral of MCA		
		NDM(n = 73)	DM(n = 32)	P	NDM(n = 73)	DM(n = 32)	P	NDM(n = 73)	DM(n = 32)	P
CBF(mL/100g·min)	Am	13.0 ± 5.8	12.8 ± 4.6	0.892	12.5 ± 5.2	13.8 ± 5.8	0.265	1.04 ± 0.36	1.09 ± 0.36	0.505
	Lm	13.9 ± 6.2	13.4 ± 6.5	0.695	12.7 ± 6.9	14.5 ± 6.6	0.214	0.96 ± 0.39	1.14 ± 0.34	0.025
	Pm	13.1 ± 5.9	12.6 ± 5.2	0.673	12.2 ± 5.8	13.1 ± 5.2	0.455	1.00 ± 0.38	1.07 ± 0.26	0.251
	Bm	7.7 ± 3.0	8.1 ± 3.1	0.542	7.8 ± 3.9	8.4 ± 3.6	0.507	1.02 ± 0.31	1.06 ± 0.27	0.571
CBV(mL/100g)	Am	292.3 ± 102.7	300.9 ± 92.8	0.687	297.8 ± 105.8	325.9 ± 115.3	0.226	1.08 ± 0.35	1.12 ± 0.38	0.667
	Lm	314.7 ± 115.2	305.5 ± 128.5	0.717	300.5 ± 136.4	350.6 ± 129.9	0.082	1.01 ± 0.42	1.23 ± 0.42	0.015
	Pm	299.3 ± 109.6	293.3 ± 104.2	0.793	299.2 ± 128.8	321.9 ± 102.6	0.381	1.06 ± 0.39	1.13 ± 0.26	0.259
	Bm	178.2 ± 57.7	189.2 ± 64.4	0.389	188.9 ± 81.0	201.0 ± 65.8	0.459	1.08 ± 0.32	1.10 ± 0.28	0.725
MTT(s)	Am	24.4 ± 6.1	24.4 ± 4.8	0.977	25.3 ± 6.0	24.9 ± 4.9	0.774	1.04 ± 0.06	1.02 ± 0.03	0.030
	Lm	24.3 ± 6.2	24.1 ± 5.3	0.860	25.8 ± 6.0	25.0 ± 5.4	0.486	1.07 ± 0.06	1.04 ± 0.05	0.014
	Pm	24.6 ± 6.2	24.4 ± 4.9	0.882	26.0 ± 6.1	25.5 ± 4.8	0.685	1.06 ± 0.05	1.05 ± 0.05	0.184
	Bm	24.5 ± 6.2	24.5 ± 4.9	0.963	25.6 ± 6.4	25.4 ± 5.0	0.872	1.05 ± 0.10	1.04 ± 0.04	0.615
TTP(s)	Am	23.2 ± 6.1	23.6 ± 5.4	0.706	24.4 ± 6.7	24.3 ± 5.5	0.937	1.06 ± 0.12	1.03 ± 0.04	0.062
	Lm	23.1 ± 6.2	23.3 ± 4.5	0.831	25.4 ± 6.9	24.5 ± 4.9	0.475	1.11 ± 0.12	1.05 ± 0.06	0.011

		Contralateral of MCA			Ipsilateral of MCA			Ipsilateral/Contralateral of MCA		
	Pm	23.5 ± 6.9	24.4 ± 7.4	0.567	25.6 ± 6.8	24.9 ± 4.9	0.575	1.10 ± 0.13	1.04 ± 0.10	0.023
	Bm	23.6 ± 6.8	23.5 ± 5.9	0.905	25.6 ± 6.9	25.0 ± 5.8	0.670	1.09 ± 0.11	1.08 ± 0.14	0.535

3.3 Independent correlation between DM and influenced parameters of MRP

Significant difference was existed between DM and NDM groups in some ipsilateral/contralateral ratio of MRP indexes, so did the age, percent of hypertension and FIB. To abolish its role of interference, multivariate regression analyses were performed. We found, independent correlation was also maintained between DM and Lm-CBF, Lm-CBV, Lm-MTT, Lm-TTP, Am-MTT, Pm-TTP ($p < 0.05$, Table 3).

Table 3
Relative risk of DM versus MRP values

Variable	Beta estimate	Odds ratio	95% CI	P value
Lm-CBF	1.456	4.287	1.206–15.236	0.024
Lm-CBV	1.425	4.158	1.312–13.177	0.015
Lm-MTT	-16.979	0.000	0.000-0.003	0.002
Lm-TTP	-12.454	0.000	0.000-0.022	0.005
Am-MTT	-14.051	0.000	0.000-0.270	0.031
Pm-TTP	-9.647	0.000	0.000-0.138	0.014
*Multivariable logistic regression, Adjust for Age, Hypertension, FIB				

3.4 Correlation between blood glucose index and influenced parameters of MRP

FBG and HbA1C through venous blood were select as blood glucose index. Obvious correlation was existed between FBG and Lm-CBF ($R = 0.280$, $P = 0.004$), Lm-CBV ($R = 0.299$, $P = 0.002$), Lm-TTP ($R = -0.204$, $P = 0.037$), Pm-TTP ($R = -0.207$, $P = 0.034$), so did it between HbA1C and Lm-CBV ($R = 0.211$, $P = 0.049$), Lm-TTP ($R = -0.224$, $P = 0.036$) (Table 4).

Table 4
Correlation between FBG and MRP values or
HbA1C and MRP values

Variable		R	P value
FBG (n = 105)	Lm-CBF	0.280	0.004
	Lm-CBV	0.299	0.002
	Lm-MTT	-0.174	0.075
	Lm-TTP	-0.204	0.037
	Am-MTT	-0.071	0.470
	Pm-TTP	-0.207	0.034
HbA1C (n = 88)	Lm-CBF	0.203	0.058
	Lm-CBV	0.211	0.049
	Lm-MTT	-0.161	0.133
	Lm-TTP	-0.224	0.036
	Am-MTT	-0.073	0.497
	Pm-TTP	-0.085	0.433

4. Discussion

Aim of this study was to investigate the effect of DM on collateral circulation in patients with unilateral MCA severe stenosis or occlusion. Therefore, we compared MRP parameters between diabetic and non-diabetic patients. We found that diabetic patients had better collateral circulation compared with non-diabetic patients, and this kind of impact was independent correlation with DM.

Perfusion techniques provide functional and circulatory information on collateral flow[14]. Numerous studies have addressed the possibility of obtaining information on collateral circulation using MR perfusion. Some investigators have used perfusion measures like the time to maximum of the residue function (Tmax), relative cerebral blood flow (rCBF) and relative cerebral blood volume (rCBV), assuming that the severity of hypoperfusion in large artery stenosis is directly related to the abundance of collateral vessels[15– 18].

Previous studies have explored the relationship between diabetes and collateral circulation with inconsistent conclusions. Some studies have suggests there is no association between diabetes and the extent of pial collaterals in ischemic stroke patients[19]. Menon et al. analyzed patients with AIS treated with intravenous thrombolysis (IVT), mechanical thrombectomy (MT), or basic care and found no association of the blood glucose level and the collateralization [5, 7]. A small study published by Gersing et al. did not find a difference of collateral status between DM patient and NDM patient receiving MT [6]. However, Jan et al. showed that the prevalent elevated glucose levels showed a significant association with the collateral status in the diabetic subgroup [20]. Rosso C et al. shows that collateralization and infarct core did not differ between DM patient and DM patient group, whereas the penumbra was significantly smaller in DM patient than in DM patient [21, 22]. Bin et al shown that greater extent of collateral (more than one-third of the MCA distribution) was detect in DM patents with moyamoya disease. It may means that DM could promote pial collateral vessel formation in patients with chronic cerebral ischemia[23], which is consistent with

our findings. Our study shows that in patients with severe stenosis or occlusion of MCA, the ipsilateral collateral circulation of DM patients is more abundant than NDM.

Although presence of a chronic totally occluded lesion has been considered as a prerequisite for spontaneous collateral recruitment, the mechanism of collateral vessel growth is complex, and even becomes more complicated by the presence of DM in which multiple biochemical and cellular components are involved[10, 24–26]. Continuous exposure to hyperglycemia, oxidative stress and increased systemic inflammation factors might induce many changes in the vascular that might accelerate vascular stenosis [27]. The effect of diabetes on collateral supply varies among different organ systems leading to either impaired or excessive neovascularization. For example, research has shown that DM is associated with reduced coronary collateralization[28]. Excessive angiogenesis occurs in the retina while impaired angiogenesis occurs in the peripheral vasculature[19, 29–31].

The mechanism of neovascularization affected by DM in various organs remains unclear. Through, some study showed angiogenesis was deficient in diabetes groups after ischemic [32, 33]. Li et al. have confirmed that angiogenesis and arteriogenesis showed remarkable increases in the number of collaterals, the diameters of the collaterals, the number of anastomoses, and microvessel density in DM Goto-Kakizaki rats[34]. Similar to this conclusion, Mostafa et al. provide evidence that even after a short duration of relatively mild hyperglycemia, there are structural changes in the cerebral vessels still exist[35]. Some experimental results also revealed a significant rise in the level of vascular endothelial growth factor (VEGF) and nitrotyrosine[36]. Diabetic rats had augmented neovascularization. Both angiogenesis and arteriogenesis were observe, suggesting the adaptive mechanisms are capillary sprouting and remodeling of native collaterals into functional arterioles[19]. The levels of growth factors and cytokines that were regarded as important in the collateral vessels, such as the expression of VEGF, basic fibroblast growth factor, transforming growth factor, granulocyte colony-stimulating factor, and hepatocyte growth factor. It also have been proven be elevated in many studies in intracranial and extracranial artery stenosis disease patients [2, 4, 37, 38]. Angiogenesis is a complex procedure involving many positive and negative regulators. The expression of growth factors and cytokines described above might be higher in MCA stenosis patients complicated with DM than in patients without DM. Thus, more formation regarding collateral angiogenesis can be detected in MCA severe stenosis or occlusion patients with DM.

In this study, we compared the collateral supply among diabetic and nondiabetic patients through MR perfusion parameters, which is confirming that there was more frequently collateral formation of patients with severe stenosis or occlusion of MCA in the DM group. We recognize that there are several limitations have founded in this study. First, a potential weakness of our study is the small sample (especially the number of patients with DM was low). All the potential confound factors could not be controlled, and some influential factors were not taken into account. However, this also provides us with a different point of view and larger sample studies are need to further supports our research results. Second, Markers of longstanding poorly controlled diabetes such as hemoglobin A1C levels, FBG were available of these patients. Duration of diabetes and diabetic control may have varied considerably among patients and contributed of differences in MR perfusion data. Third, we studied the relationship between MR perfusion parameters and collateral circulation, and did not further follow-up and evaluate the risk of late strokes, which will be our next research direction.

5. Conclusions

The present study revealed that patients with severe stenosis or occlusion of MCA with DM had more collateral circulation assessed by MR perfusion imaging. Findings from this study may help individualize blood sugar

management in patients with macrovascular stenosis. Further clinical studies and basic research are need to explore the factors affecting formation of the collateral vessels in severe stenosis of large artery patients associated with DM.

Declarations

Acknowledgments

We are grateful to the patients who were willing to share their medical data. We thank the participants of this work for their contribution.

Authors' contributions

Jia-hui Zhang and Zheng Li: Contributions to the data collection and writing original draft. Mei-juan Zhang and Chuan-shuai Tian: Prepared figure and tables. Yun Luo: Contributions to the design of the study and review the final manuscript. All authors have read and approved the manuscript.

Funding

This work was supported by National Natural Science Foundation of China (81671140) and the Nanjing Medical Science and technique Development Foundation(QRX17002).

Availability of data and materials

All data related to this study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was performed in accordance with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Nanjing Drum Tower hospital (No.2016-169-01).Written informed consents were obtained from all participants.

Consent for publication

Not applicable.

Competing interests

The authors declare no conflicts of interest.

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Figures

Figure 1

Caption not included with this version.