Non-moyamoya vessel network formation along steno-occlusive middle cerebral artery

Yu-Yuan Xu, MD
Ming-Li Li, MD
Shan Gao, MD
Bo Hou, MD
Zhao-Yong Sun, MD
Hai-Long Zhou, MD
Feng Feng, MD
Wei-Hai Xu, MD

Correspondence to
Dr. Wei-Hai Xu:
xuwh@pumch.cn

ABSTRACT

Objective: In this study, we sought to examine the prevalence and clinical relevance of deep tiny flow voids (DTFV) in patients with steno-occlusive middle cerebral artery (MCA) disease on high-resolution MRI (HRMRI).

Methods: We retrospectively reviewed the HRMRI and clinical data of 477 patients with MCA steno-occlusive disease. The presence and distribution of DTFV, defined as 3 or more flow voids along the affected MCA on at least 2 consecutive T2-weighted image slices on HRMRI, were observed. The relationships among DTFV, the degree of stenosis (mild <50%, moderate 50%–70%, severe 70%–99%, and occlusion), and infarctions were analyzed. To clarify the difference between DTFV and moyamoya collaterals, we compared the HRMRI findings of the patients with DTFV and 102 patients with moyamoya disease.

Results: The prevalence of DTFV was 1.4% in mild stenosis, 12.8% in moderate stenosis, 40.6% in severe stenosis, and 50.7% in MCA occlusions. Of the 112 patients with DTFV, 57 (50.9%) had all 4 quadrants (superior, inferior, dorsal, and ventral sides) of the MCA involved. DTFV were more common in asymptomatic patients than in symptomatic patients with severe stenosis (49.3% vs 30.9%, $p = 0.025$) and occlusions (68.0% vs 41.7%, $p = 0.033$). Obvious flow voids in the basal ganglia region were observed in 58 patients (56.9%) with moyamoya disease but in none of the patients with DTFV ($p < 0.001$).

Conclusions: DTFV are common in patients with severe steno-occlusive MCA disease, especially in asymptomatic patients. We hypothesize that DTFV originate from new vessel network formation in response to chronic cerebral ischemia. *Neurology*® 2016;86:1957–1963

GLOSSARY

CI = confidence interval; **DTFV** = deep tiny flow voids; **HRMRI** = high-resolution MRI; **MCA** = middle cerebral artery; **MRA** = magnetic resonance angiography.

Intracranial atherosclerosis is an important etiology of stroke worldwide. It accounts for approximately 30% to 60% of ischemic strokes in patients with Asian ancestry.^{1–4} Clinically, intracranial atherosclerosis can cause a major stroke, a minor stroke, or even be asymptomatic.^{5,6} The underlying pathophysiologies are not fully understood. Multiple factors may be involved, including the degree of intracranial stenosis, plaque features, and the collaterals.⁷

In the past decade, the technique of high-resolution MRI (HRMRI) has been developed.^{8–11} Using HRMRI, the properties of intracranial atherosclerosis, such as remodeling types, plaque components, and plaque distribution, can be assessed in vivo.^{9,11,12} Intracranial collaterals can be identified on HRMRI as well. In 2014, a novel finding of “deep tiny flow voids” (DTFV), defined as 3 or more flow voids along the middle cerebral artery (MCA) on HRMRI, was reported.¹³ DTFV were commonly observed along MCA occlusions but never seen along normal MCAs, supporting that they are pathologic collaterals. The aim of the present study was to further examine the prevalence and clinical relevance of DTFV in patients with stenotic or occlusive MCA disease.

From the Departments of Neurology (Y.-Y.X., S.G., W.-H.X.) and Radiology (M.-L.L., B.H., Z.-Y.S., H.-L.Z., F.F.), Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing, China.

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METHODS Patients. We retrospectively reviewed our institutional, prospectively collected HRMRI database (from January 2007 to March 2015).^{8,9,12–14} All patients had undergone routine MRI and magnetic resonance angiography (MRA) examinations for a clinical diagnosis. Patients with symptomatic MCA stenotic disease were recruited if there was an ischemic stroke in the distribution of the affected MCA within 3 months of stroke onset.^{11,13} Patients with asymptomatic MCA stenotic disease were included if there was no history of cerebrovascular events or if an ischemic event occurred in a vascular territory outside the affected MCA.⁹ Patients with moyamoya disease were enrolled if they had bilateral stenosis and/or occlusion of the intracranial internal carotid artery and its proximal branches, with development of a collateral network.¹⁵

Patients were excluded if they had any of the following characteristics: (1) coexistent with >50% ipsilateral internal carotid artery stenosis; (2) evidence of cardioembolism, including atrial fibrillation or recent myocardial infarction within 3 months; (3) evidence of vasculitis or arterial dissection, diagnosed by comprehensive laboratory work, vascular imaging, and clinical evaluation; and (4) poor image quality caused by motion artifact.

Standard protocol approvals, registrations, and patient consents. The ethics committee of the Peking Union Medical College Hospital approved this study. All patients or their relatives signed a written consent to participate.

High-resolution MRI. All patients were imaged using a 3-tesla (T) magnetic resonance scanner (Signa VH/I, GE Medical Systems, from January 2007 to June 2013; GE Discovery MR750, from

June 2013 to March 2015) and a standard 8-channel head coil. The protocol included conventional T2-weighted imaging, diffusion-weighted imaging, 3-dimensional time-of-flight MRA, and high-resolution T1- and T2-weighted imaging of the MCA. The detailed HRMRI protocol was described elsewhere.^{8,13} Briefly, the cross-section imaging was obtained with a display resolution of $0.25 \times 0.25 \times 2$ mm, and perpendicular to the M1 segment of the MCA.

Image analysis. Image analysis was performed using a standard workstation (ADW 4.5; GE Medical Systems). Two experienced readers blinded to the clinical details reviewed the cross-sectional image slices of the bilateral MCA on HRMRI. Differences between the 2 observers were solved by consensus. The presence of DTFV, defined as 3 or more flow voids along the affected MCA on at least 2 consecutive T2-weighted image slices on HRMRI, was recorded¹³ (figure 1). Penetrating arteries regularly arise from the dorsal and superior sides of the MCA.^{16,17} To clarify the relationship between DTFV and penetrating arteries, we separated the MCA into 4 quadrants in each cross-section—superior, inferior, dorsal, and ventral sides (figure 2)—and observed the distribution of DTFV. We also compared the HRMRI findings of the patients with DTFV and the patients with moyamoya disease to clarify the difference between the 2 types of collaterals.

All cross-sectional image slices of a stenotic MCA on T2-weighted HRMRI were analyzed for artery wall abnormalities. Plaques were identified if there was markedly eccentric wall thickening, while the thinnest part of the wall was estimated to be less than 50% of the thickest point by visual inspection on T2-weighted

Figure 1 DTFV in patients with a stenotic or occlusive MCA in high-resolution MRI

(A–E) In a patient with a moderate MCA stenosis (arrowhead, B), no DTFV are revealed (empty arrowheads, C–E). (F–J) In a patient with severe MCA stenosis (arrowhead, G), DTFV (short arrows, H and I) along the affected MCA (empty arrowheads, H and I) are seen, as compared with the reference segment (empty arrowhead, J). (K–O) In a patient with right MCA occlusion, DTFV (short arrows, M and N) can be seen around the occluded MCA (empty arrowheads, M and N), as compared with the left MCA for reference (empty arrowhead, O). DTFV = deep tiny flow voids; MCA = middle cerebral artery.

(A) Magnetic resonance angiography shows a stenosis at the M1 segment of the right MCA. (B, C) The luminal area of the sites can be measured manually (demonstrated by the magnified images). The plaque (arrow, B) at the maximal lumen narrowing site and the reference site (arrow, C) are shown. (D) Four quadrants (superior, inferior, dorsal, and ventral) are separated to assess the distribution of deep tiny flow voids along the MCA. MCA = middle cerebral artery.

images.⁹ Quantitative measurements were performed on the T2-weighted HRMRIs. The window width and level were adjusted to optimize the conspicuity of the vessel contour. The contour of the outer wall and lumen at the maximal narrowing site and reference site were traced manually. The vessel area and luminal area were measured. The reference sites were defined as the nearest plaque-free or minimally diseased segments proximal or distal to the maximal lumen narrowing sites (figure 2). When the vessel lesions involved the entire M1 segments, the plaque-free counterpart from the contralateral M1 segment was used as the reference site. The degree of stenosis on HRMRI was then calculated as follows: $(1 - \text{luminal area at the maximal lumen narrowing site} / \text{reference luminal area}) \times 100\%$.⁹ The degree of MCA stenosis was graded as mild ($<50\%$), moderate ($50\% - 69\%$), severe stenosis ($70\% - 99\%$, with apparently patent poststenotic segment), and occlusion.¹⁸ To assess interobserver variability and intraobserver variability, 2 readers independently remeasured the luminal area of the initial 10 consecutive patients 2 months later. The intraobserver and interobserver reproducibility of measurements of the luminal area were 0.913 (95% confidence interval [CI], 0.778–0.968) and 0.886 (95% CI, 0.715–0.957).

Statistical analysis. The intraclass correlation coefficient was used to find the intraobserver and interobserver reproducibility for measurements of the luminal area. Continuous variables were described as mean $\pm$ SD in normally distributed data. The continuous variables between the 2 groups were compared by the

independent samples *t* test. Categorical variables were compared by the χ^2 test or Fisher exact test. Binary logistic regression modeling was performed, using an enter algorithm, to study the relationship between predictive variables (cerebral infarction, degree of stenosis, and demographic variables including age, sex, hypertension, hyperlipidemia, and diabetes) and the dependent variable (presence of DTFV). A value of $p < 0.05$ was used to indicate statistical significance.

RESULTS In the HRMRI database, 235 patients with symptomatic and 272 patients with asymptomatic MCA steno-occlusive disease, as well as 102 patients with moyamoya disease, were considered for inclusion. Thirty patients (4.9%), including 17 stroke patients, were excluded because of poor image quality. Finally, the data of 218 symptomatic patients, 259 asymptomatic patients, and all patients with moyamoya disease were analyzed. Table 1 summarizes the demographic data, showing no difference between symptomatic and asymptomatic patient groups. Of the 102 patients with moyamoya disease (mean age 28.0 ± 12.3 years, 39 males), 3 patients (2.9%) presented with intracranial hemorrhage, 7 (6.9%) with TIAs, 20 (19.6%) with acute ischemic strokes, and 44 (43.1%)

Table 1 Demographic, clinical, and HRMRI data of steno-occlusive MCA disease and moyamoya disease

	Symptomatic MCA steno-occlusive disease (n = 218)	Asymptomatic MCA steno-occlusive disease (n = 259)	Moyamoya disease (n = 102)	p Value
Age, y	53.7 ± 16.1	55.7 ± 15.0	28.0 ± 12.3	<0.001
Male	152 (69.7)	165 (63.7)	39 (38.2)	<0.001
Hypertension	149 (68.3)	159 (61.4)	10 (9.8)	<0.001
Hyperlipidemia	110 (50.5)	123 (47.4)	4 (3.9)	<0.001
Diabetes	41 (18.8)	56 (21.6)	1 (1.0)	<0.001
Smokers	80 (36.7)	74 (28.6)	13 (12.7)	<0.001
Clinical manifestations				
Asymptomatic	0	259 (100)	25 (24.5)	
Migraine	0	0	3 (2.9)	
Intracranial hemorrhage	0	0	3 (2.9)	
TIA's	0	0	7 (6.9)	
Acute ischemic events	218 (100)	0	20 (19.6)	
Ischemic stroke history	0	0	44 (43.1)	
HRMRI characteristics				
Eccentric plaques	218 (100)	259 (100)	0	<0.001
Deep tiny flow voids	44 (20.2)	68 (26.3)	102 (100)	<0.001
Flow voids in the basilar ganglia region	0	0	58 (56.9)	<0.001

Abbreviations: HRMRI = high-resolution MRI; MCA = middle cerebral artery.
Data are mean ± SD or n (%).

with a history of ischemic stroke but without recent clinical ischemic events. The patients with moyamoya disease had a much lower prevalence of hypertension ($p < 0.001$), hyperlipidemia ($p < 0.001$), diabetes ($p < 0.001$), and smoking ($p < 0.001$) (table 1). On HRMRI, eccentric plaques were identified in 100% in the symptomatic and asymptomatic patient groups with steno-occlusive MCA disease but in none of the patients with moyamoya disease ($p < 0.001$).

The prevalence of DTFV was 1.4% in mild stenosis, 12.8% in moderate stenosis, 40.6% in severe stenosis, and 50.7% in MCA occlusions. The grade of stenosis and the number of patients with DTFV are presented in table 2. DTFV were more common in asymptomatic

patients than in symptomatic patients with severe stenosis (49.3% vs 30.9%, $p = 0.025$) and occlusions (68.0% vs 41.7%, $p = 0.033$). A binary logistic regression model was constructed to include cerebral infarction, degree of stenosis, and demographic variables including age, sex, hypertension, hyperlipidemia, and diabetes. The degree of stenosis (odds ratio, 3.297; 95% CI, 2.496–4.356; $p < 0.001$) and cerebral infarction (odds ratio, 0.340; 95% CI, 0.203–0.569; $p < 0.001$) were independent predictors for DTFV. Of the 112 patients with DTFV, 57 patients (50.9%) had all 4 quadrants (superior, inferior, dorsal, and ventral sides) and 23 patients (20.5%) had 3 quadrants of the MCA involved.

Table 2 Prevalence of DTFV in patient subgroups with steno-occlusive MCA disease

	Symptomatic MCA steno-occlusive disease		Asymptomatic MCA steno-occlusive disease		p Value
	No.	n/DTFV (%)	No.	n/DTFV (%)	
Occlusion	48	20 (41.7)	25	17 (68.0)	0.033
Severe stenosis	68	21 (30.9)	75	37 (49.3)	0.025
Moderate stenosis	46	3 (6.5)	71	12 (16.9)	0.101
Mild stenosis	56	0 (0)	88	2 (2.3)	0.521
Total	218	44 (20.2)	259	68 (26.3)	0.119

Abbreviations: DTFV = deep tiny flow voids; MCA = middle cerebral artery.

In the 102 patients with moyamoya disease, multiple flow voids within the sylvian fissure were observed that were consistent with the definition of DTFV. However, there were additional flow voids distributed outside the sylvian fissure, particularly in the basal ganglia region (figure 3). Obvious flow voids in the basal ganglia region were found in 58 patients with moyamoya disease (56.9%) but in none of the patients with DTFV ($p < 0.001$).

DISCUSSION In our study, DTFV were mainly observed along $>70\%$ stenotic or occlusive MCAs and were relatively uncommon along mild and moderate stenosis. The distribution of DTFV was not confined to the dorsal and superior sides of the MCA where the penetrating arteries arise.¹⁶ Flow voids within the basal ganglia region, indicating moyamoya collaterals, were not found in patients with DTFV.¹⁵ Taken together, our results suggested that DTFV are associated with severe steno-occlusive MCA disease and distinct from well-known penetrating arteries or moyamoya collaterals.

The pathophysiology of DTFV is intriguing. It is known that brain collaterals are classified into primary pathways (e.g., the circle of Willis), secondary pathways (e.g., pial branches from intracranial arteries), and new arteries through the processes of angiogenesis and arteriogenesis.¹⁹ The anatomical features of DTFV suggest that they are more likely to originate from the formation of new vessels. Unfortunately, there has been no angiography study that systematically investigated the collaterals along MCAs to provide supportive evidence. However, using ultra-high field 7T MRI, numerous microvessels invisible by conventional MRA (1.5T or 3T) have been revealed around steno-occlusive MCAs.^{20,21} These microvessels are comparable with the findings of DTFV on HRMRI. A similar phenomenon was also reported in coronary atherosclerosis,^{22,23} which is supposed to be triggered by chronic hypoxia/ischemia.^{22–26} Multiple cytokines in response to ischemia, such as vascular endothelial growth factor and basic fibroblast growth factor, are involved in this process.^{27–29} The key role of hypoxia/ischemia may also account for the difference between DTFV and moyamoya collaterals. A single MCA steno-occlusive lesion causes less severe hypoxia/ischemia in the deep basilar ganglia area than occlusions of the bilateral internal carotid artery and its proximal branches. Therefore, DTFV do not occur in basilar ganglia regions such as moyamoya collaterals.

The findings of DTFV are clinically meaningful and should be investigated in future studies. First, DTFV were more common in asymptomatic patients than in symptomatic patients with advanced MCA steno-occlusive disease. It is necessary to know the type of patients who develop DTFV and those who do not, and the underlying mechanisms. Potentially, this could help to identify subgroups of patients with steno-occlusive

Figure 3 Distribution of multiple flow voids in moyamoya disease

(A–E) In a patient with moyamoya disease, bilateral internal carotid artery occlusions are shown (arrowheads, A). Multiple dispersed flow voids (arrows, B–E) are seen around the circle of Willis, in the right sylvian fissure, and in the basal ganglia regions.

disease that would benefit more from aggressive medical therapy or interventional procedures. Second, it is unknown whether DTFV are micro feeding arteries of cerebral hemispheres. If so, the changes of DTFV should be closely monitored in patients undergoing interventional procedures when refractory to medical therapy, because angioplasty and stenting implantation may distort and obstruct these vessels. Third, it is important to make a differential diagnosis since the imaging findings of DTFV can occur in both steno-occlusive atherosclerotic MCA disease and moyamoya disease. Our results suggested the coexistence of eccentric plaques, atherosclerotic risk factors, and the DTFV without basal ganglia region involvement favors the diagnosis of steno-occlusive atherosclerotic MCA disease.

Our current study has several limitations. First, the retrospective design made it impossible to study the development process of DTFV. For example, it is unknown whether DTFV can develop after an ischemic event. Second, the luminal area may be overestimated in some cases resulting from lower in-plane and through-

plane spatial resolution. Third, the flow voids detected on MRI in the basal ganglia region are a specific but not the only image sign for moyamoya disease. In recent studies, the abnormal vessels around the terminal portions of the internal carotid arteries on MRI have been proposed as another important marker in diagnosing moyamoya disease,³⁰ which was not investigated in our study. Finally, digital subtraction angiography is the gold standard for studying vascular pathology to date. Regarding DTFV, HRMRI cannot provide physiologic information such as direction of blood flow and territory supplied. Thus, comparative studies using superselective angiography as well as microanatomical evaluations are warranted to characterize these collateral vessels.³¹

AUTHOR CONTRIBUTIONS

Drs. Ming-Li Li and Wei-Hai Xu were responsible for designing the study and revising the manuscript. Dr. Yu-Yuan Xu was responsible for analyzing the data and drafting the manuscript. Drs. Bo Hou, Zhao-Yong Sun, and Hai-Long Zhou were responsible for data collection. Drs. Feng Feng and Shan Gao were responsible for the study supervision and coordination.

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DISCLOSURE

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Comment: Implications of non-moyamoya vessel formation in MCA steno-occlusive disease

Xu et al.¹ should be commended for their study that assesses the importance of middle cerebral artery (MCA) “deep tiny flow voids” (DTFV) on high-resolution MRI in patients with steno-occlusive disease. The incidence of DTFV increased with the degree of MCA stenosis and was more common in asymptomatic patients. Obvious flow voids in the basal ganglia region were observed in 57% of patients with moyamoya disease but no patients with DTFV.

This is an important study that provides further evidence that DTFV are a response to chronic ischemia and provide protection from infarction.² DTFV thus may influence patient diagnosis, risk stratification, and treatment.

In select cases, it is difficult to differentiate steno-occlusive atherosclerotic and moyamoya disease. The present study suggests that DTFV occur with severe steno-occlusive disease and remain distinct from penetrating moyamoya collaterals. Correlation studies of DTFV on MRI and cerebral angiography may help differentiate these phenomena in patients with characteristics of both diseases.

From the current study, it appears that DTFV are associated with asymptomatic status. Because of the retrospective nature, it remains unknown whether DTFV form as a result of chronic ischemia or whether progressive occlusion of DTFV contributes to symptomatic status. Further analysis is indicated to assess whether DTFV provide independent prediction of outcome (stroke and functional status) after controlling for patient and disease characteristics.

Prospective studies are necessary to determine how DTFV might be used to tailor patient management. It remains unknown whether DTFV are micro feeding arteries of cerebral hemispheres. If so, changes in DTFV should be closely monitored in patients undergoing interventional procedures, because angioplasty and stenting may lead to thrombosis. A greater understanding of the mechanisms underlying DTFV formation and which patients form DTFV might help identify subgroups of patients with steno-occlusive disease who would benefit more from aggressive medical therapy or interventional procedures.

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Robert M. Starke, MD, MSc

From the Department of Neurological Surgery, University of Virginia, Charlottesville.

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