Infarct Pattern and Collateral Status in Adult Moyamoya Disease
A Multimodal Magnetic Resonance Imaging Study

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Background and Purpose—Moyamoya disease (MMD) is a unique cerebrovascular disease characterized by the progressive stenosis of large intracranial arteries and a hazy network of basal collaterals, called moyamoya vessels. Although hemodynamic studies have been applied in MMD patients, the mechanisms of stroke in MMD are still unclear. The present study evaluated the infarct pattern and collateral status using multimodal magnetic resonance imaging in MMD patients.

Methods—Adult MMD patients with acute ischemic stroke were prospectively recruited, and infarct pattern on diffusion-weighted imaging was evaluated. A collateral flow map, derived from magnetic resonance perfusion–weighted imaging data, was generated through automatic postprocessing, and collateral status was assigned into 3 grades. Transcranial Doppler monitoring was performed to detect microembolic signals in selected patients.

Results—A total of 67 hemispheres (31 patients with bilateral and 5 patients with unilateral MMD) were analyzed. Most patients (83.7%) showed embolic pattern and rarely deep (9.3%) or hemodynamic infarct pattern (7.0%) on diffusion-weighted imaging. Most cases (86%) showed good collateral status, and few patients with acute infarcts of embolic pattern showed poor collateral status (n=7). One third (31.6%) of patients who underwent transcranial Doppler monitoring showed microembolic signals.

Conclusions—In the studied population of adult MMD patients, embolic phenomenon played an important role in ischemic stroke. Therapeutic strategies against thromboembolism, as well as collateral enhancing strategies targeting improvement of hemodynamic status or increased washout of emboli, are warranted. (Stroke. 2017;48:111-116. DOI: 10.1161/STROKEAHA.116.014529.)

Key Words: cerebral infarction ■ collateral ■ diffusion-weighted imaging ■ embolism ■ Moyamoya disease

Moyamoya disease (MMD) is an uncommon cerebrovascular disease that is characterized by progressive stenosis of the terminal portion of the internal carotid artery and its main branches.1 There have been many studies on the cerebral hemodynamics in patients with MMD,2–4 and based on their findings, current guidelines recommend revascularization surgery in patients with MMD with progressive ischemic symptoms or evidence of inadequate blood flow or cerebral perfusion reserve.3

The mechanism of ischemic stroke in MMD is not well understood, and the roles of therapeutic strategies, other than surgery, are unknown.6 Given the lack of systematic evidence on antiplatelet agents and anticoagulants for stroke prevention in patients with MMD, specific stroke prevention medications cannot be recommended outside of general treatment recommendations. However, pathological data showed collapse of the artery lumen and intraluminal thrombosis in patients with MMD.7 There is also some evidence that supports thromboembolism as the cause of infarction in patients with MMD.8,9

The present study aimed to explore the mechanism of ischemic stroke in patients with MMD. Thus, we evaluated the infarct pattern and collateral status, using multimodal magnetic resonance (MR) imaging, in patients with MMD. In this study, we investigated acute infarct pattern on diffusion-weighted imaging (DWI), microembolic signals on transcranial Doppler monitoring, and collateral status using our dynamic susceptibility contrast (DSC)–enhanced, MR perfusion–based collateral map10 to estimate the role of embolic and hemodynamic mechanisms in the development of stroke in adult patients with MMD.

Patients and Methods

Patient Selection
We prospectively recruited patients >18 years of age with MMD admitted to the tertiary, university stroke center between January 2008 and

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October 2015. Patients included in this study met the following criteria: (1) diagnosed with MMD by digital subtraction angiography findings according to the Japanese MMD guideline\(^ {11}\) and its revision by the Research Committee for MMD of the Japanese Ministry of Health, Labor, and Welfare in 2015; (2) presenting with acute ischemic stroke demonstrated on DWI; (3) had magnetic resonance perfusion–weighted imaging (MRP) performed; and (4) had no prior bypass surgery, such as encephalo-duro-arterio-synangiosis, extracranial arterial bypass, or both. This study was approved by the local institutional review board.

**Evaluations**

Demographic features and vascular risk factors, including hypertension, diabetes mellitus, and dyslipidemia, were investigated. We assessed angiographic Suzuki’s grade for assessing disease severity of MMD. Both hemispheres were evaluated separately for presence of acute infarction. Suzuki’s grade, and collateral grade using MRP-derived collateral flow map. Infarct patterns were categorized into 3 groups based on the DWI patterns: (1) embolic pattern, including territorial infarcts, cortical infarcts, or mixed cortical-deep infarcts; (2) isolated subcortical pattern, defined as deep infarcts restricted to the territory of the penetrating arteries; (3) hemodynamic pattern represented with internal border-zone infarction. Cortical border-zone infarcts were categorized as embolic pattern because it was reported that internal border-zone infarcts were caused mainly by hemodynamic compromise, whereas embolic pathogenesis appeared to contribute greatly to the genesis of cortical border-zone infarcts.\(^ {15}\) In addition, we measured the long axis of the acute infarction, and some of the patients underwent transcranial Doppler monitoring.

**MRP Methods and Image Analysis**

MR imaging was performed using a 3T Philips Achieva MR scanner (Philips Medical Systems, Best, Netherlands). Identical model of the MR scanner was used for all study subjects. Typical MR imaging sequence for acute stroke assessment included DWI, DSC-MRP-based collateral map, fluid-attenuated inversion recovery, and MR angiography of the cervical and intracranial vessels (3-dimensional time-of-flight MR angiography and contrast-enhanced MR angiography, including the extracranial carotid and vertebral arteries).

DWI was performed with 2 levels of diffusion sensitization (b values of 0 and 1000 s/mm\(^2\); 5- to 7-mm slice thickness; no gap). DSC-MRP was performed using gradient-echo and echo-planar imaging techniques, after administration of intravenous gadolinium (Dotarem [gadoterate meglumine]; Guerbet, Aulnay-sous-Bois, France) with a repetition time of 1718 ms, for a total acquisition time of 90 s, with 20 to 22 slices. The contrast agent was injected with a power injector at a dose of 0.1 mmol/kg body weight, with a flow rate of 3 mL/s, into an antecubital vein, via an 18-gauge intravenous cannula, s\(^7\)s after the start of the acquisition. Other parameters for the DSC-MRP were as follows: echo time =35 ms, flip angle =40\(^\circ\), acquisition matrix =128x128, field of view =24x24 cm\(^2\), section thickness =5 mm, and intersection gap =2 mm. In total, 1000 DSC-MRP raw images, composed of 50 time points per slice, were obtained.

Perfusion delay was defined based on the perfusion parameter \(T_{\text{max}}\). \(T_{\text{max}}\) is the time to the peak of the residue function map, generated by deconvolution of the tissue concentration over the time curve, using an arterial input function from the contralateral middle cerebral artery.\(^ {11}\) The MRP postprocessing and data analysis were performed as described in our previous studies.\(^ {10,14}\) MR imaging volume measurements were performed by an investigator (J.P. Son) who was blinded to the clinical information. \(T_{\text{max}}\) volumes were stratified using a 2-s strata of \(T_{\text{max}}\) thresholds, from \(T_{\text{max}}\leq3\) s, \(3<s_{\text{max}}\leq6\) s, ..., \(\text{TM}_{22-24}\) s and \(\text{TM}_{25}\) s. Because of too small volumes, \(T_{\text{max}}\leq12-18\) s, and \(T_{\text{max}}\leq19-22\) s were merged into 4-s strata to avoid the possibility of under- or overestimation.

**Postprocessing Techniques to Generate an MRP-Derived Collateral Flow Map**

Collateral flow maps were generated based on source data derived from DSC-MRP, as previously described.\(^ {10}\) Collateral flow maps were automatically generated using in-house software, Fast Analysis System for Collaterals, developed using MATLAB (MathWorks, Natick, MA). All steps were typically completed within 5 minutes. There was a good correlation between the MRP-based and the digital subtraction angiography–based collateral grades.\(^ {10}\) Criteria for collateral flow map–based grades were chosen based on the American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology grading system\(^ {13}\) with a classification of grade 0 (no visible collaterals), grade 1 (slow collaterals, visible only during the late phase, toward the part of the occluded middle cerebral artery territory with a persistence of some of the defect), grade 2 (rapid collaterals, visible during the mid to late phase, toward the part of the occluded middle cerebral artery territory with a persistent defect portion), grade 3 (slow, but complete, collateral flow to the ischemic bed), and grade 4 (complete and rapid collateral flow to the entire vascular bed in the occluded middle cerebral artery territory). Six axial slices of the collateral flow maps were used to assess the leptomeningeal collateral grade. The striatocapsular region was not assessed owing to limitations of digital subtraction angiography–based collateral grading in this region. For statistical analysis, hemispheres were divided into 3 groups according to the MRP-derived collateral grade: poor (digital subtraction angiography grade 0–2), intermediate (grade 3), and excellent (grade 4). Collateral flow images were reviewed independently by 2 investigators (D.Y. Kim and J.P. Son) aware of the symptomatic side and occlusion site. When the ratings between the 2 raters were inconsistent, a decision was made by consensus.

**Statistical Analysis**

Numeric data are presented as mean±SD, and categorical data are presented as percentage. \(T\) tests, Fisher’s exact tests, Mann–Whitney tests, and Kruskal–Wallis tests were used to compare binary and continuous variables between groups. Statistical analyses were performed using SPSS version 18.0 (SPSS Inc, Chicago, IL). All calculated \(P\) values were 2-tailed, and statistical significance was defined as \(P<0.05\).

**Results**

During the study period, a total of 268 patients, who met the diagnostic criteria of MMD, were identified, and 62 patients were confirmed to have acute ischemic stroke based on DWI. Among them, patients with no MRP (\(n=22\)), lost imaging data (\(n=2\)), concomitant brain tumor (\(n=1\)), and iatrogenic infarction during angiography (\(n=1\)) were excluded.
excluded. A total of 36 patients were finally enrolled, and total of 67 hemispheres, including 5 cases of unilateral MMD, were analyzed (Figure 1). One of the patients had recurrent ischemic stroke with interval period of 23 months, so each stroke event was included in the analysis. The mean age at diagnosis was 45.1±11.8 years. There was a slight predominance of female patients in our sample (female: male ratio = 1.77), and two patients had a family history of MMD.

Among 43 hemispheres with acute infarcts, 36 (83.7%) showed embolic pattern, 4 (9.3%) showed isolated subcortical pattern, and only 3 (7.0%) showed hemodynamic pattern on DWI. Representative images are shown in Figure 2. There was no significant difference in sex, age at diagnosis, family history, and vascular risk factors depending on the DWI pattern. All the patients with stenosis (without occlusion) showed embolic pattern; however, embolic pattern was also observed in cases of total occlusion. Transcranial Doppler monitoring

![Collateral Flow Map](image)

**Figure 2.** Representative images of infarct pattern and corresponding collateral flow map and $T_{\text{max}}$ based on magnetic resonance perfusion-weighted imaging. **A1.** Embolic pattern with poor collaterals (slow collaterals to the periphery of the ischemic site with persistence of some of the defect). **A2.** Embolic pattern with poor collaterals (rapid collaterals to the periphery of the ischemic site, but only to a portion of the ischemic territory with persistence of some of the defect). **B1.** Embolic pattern with intermediate collateral grade (slow but complete blood flow of the ischemic bed by the late venous phase). **B2.** Hemodynamic pattern with intermediate collateral grade. **C.** Isolated subcortical pattern with excellent collaterals (complete and rapid collateral blood flow to the vascular bed in the entire ischemic territory by retrograde perfusion). Region of decreased collateral flow is marked with arrowhead. DWI indicates diffusion-weighted images.
was performed in 19 patients, and out of those, 6 patients (31.6%) showed positive embolic signals.

Collateral status was examined on large intracranial arteries in 50 hemispheres with occlusion, on either symptomatic (DWI+) or asymptomatic (contralateral) side. If there was stenosis, rather than occlusion, collateral grade assessment using MRP could not be applied because collateral flow is developed by retrograde flow when there is no antegrade flow. Most cases (86%) showed relatively good collaterals and complete retrograde perfusion to the vascular bed in the entire ischemic territory, such as intermediate (slow retrograde perfusion by the late venous phase) or excellent (rapid retrograde perfusion) collateral grades. Only 7 hemispheres had poor collaterals; 5 hemispheres (10%) showed rapid collaterals to the periphery of the ischemic site, but only to a portion of the ischemic territory, with persistence of some of the defect; and 2 hemispheres (4%) showed slow collaterals to the periphery of the ischemic site, with persistence of some of the defect. Collateral grade was significantly different depending on the infarct pattern (P=0.016; Figure 3). Poor collateral grade was observed only in the embolic group, but about three fourths of that group showed intermediate or good collaterals. Poor collaterals were not observed in the nonembolic group or contralateral (DWI−) hemispheres. Excellent collateral grade was observed in more than two thirds of DWI+ hemispheres, in half of those of nonembolic pattern, and a third of those of embolic pattern.

There was a trend of a larger size of infarction coinciding with a poorer collateral grade: the infarct size on DWI was 45 mm (interquartile range, 38–60 mm) for poor, 32 mm (15–55 mm) for intermediate, and 18 mm (6–37 mm) for excellent collateral grades (P=0.054). Although all the patients showed some degree of $T_{\text{max}}$ perfusion delay, perfusion in the ischemic site was observed at a later time point ($T_{\text{max}}>16$ s) in most patients, except in those with poor collaterals (Figure 2A1 and 2A2).

**Discussion**

The main findings of this study were the following: (1) most of the diffusion restriction patterns (83.7%) were of embolic type, and hemodynamic pattern was rarely observed in the acute symptomatic patients with MMD; (2) microembolic signals could be observed in approximately a third of patients (31.6%) in transcranial Doppler monitoring; and (3) most hemispheres (86%) showed good collateral status, and few patients with acute infarcts of embolic pattern showed poor collateral status. Contrary to previous line of thought, our results suggest that ischemic stroke is more likely to be because of thromboembolism than to collateral failure. Although there have been studies of impaired vascular reserve in patients with MMD, studies evaluating the degree of collateral status in MMD are relatively limited. To the best of our knowledge, this is the first study to address the stroke mechanisms and collateral status, using multimodal imaging techniques, in a relatively large cohort of patients with MMD.

Most ischemic cerebrovascular events in patients with MMD were attributed to reduced blood flow caused by obstruction of major intracranial arteries. Data from our present study emphasize embolic phenomenon as the predominant mechanism of brain infarction in MMD. Embolism from intraluminal thrombosis may be involved in the development of ischemic stroke in MMD. Yamashita et al evaluated histopathologic changes of moyamoya vessels in 22 patients with MMD and showed intraluminal thrombosis in the stenotic segment and microaneurysm formation or attenuation of vessel thickness. Our transcranial Doppler results are in line with previous case reports, suggesting that microembolism is associated with disease progression and development of brain infarction in patients with MMD.

Our present collateral map results showed that collateral circulation was well developed in MMD, except in some patients with acute symptomatic MMD. This may be, in part, because MMD has a chronic course allowing enough time for collaterals to develop. In addition, MMD may be a disease outcome of enhanced angiogenesis. Direct or indirect surgery is the main strategy for treatment in patients with MMD for improving regional cerebral hemodynamics. Bypass surgery improves cerebral perfusion and also helps washout thromboemboli in patients with MMD. Caplan et al described that hypoperfusion and embolism often coexist in the mechanism of infarction,
and the interrelationship involves 2 factors: decreased perfusion limiting blood flow to regions rendered ischemic by emboli and decreased blood flow impeding washout of the emboli.23,24 Our results showed that embolic infarcts occurred exclusively in patients with poor collaterals, suggesting the role of established strategies (eg, bypass surgery) for enhancing collaterals in MMD. Beside surgical approaches, further studies on the role of antiplatelet agents in MMD are needed. The use of dual antiplatelet agents was reported to reduce microembolism in atherosclerotic, occlusive, cerebrovascular diseases.25,26 In addition, cilostazol was reported to have pleiotropic effects, such as inhibition of smooth muscle cell proliferation27 and activation of endothelial progenitor cells for angiogenesis.28 However, no clinical trials have been conducted to evaluate the role of antiplatelet agents in MMD patients.

Our study has several limitations. First, MMD is a rare disease, and this study contains a small number of patients. In addition, this is a single-center study conducted in a university hospital, and so the sample could be affected by selection bias. In regard to the MRP-derived collateral grade, because it was initially developed for evaluation of collateral status in acute infarction of middle cerebral arteries, the implications of the MRP-derived collateral grade in the chronic stage of MMD were not validated. Finally, data on vascular reserve were not analyzed in this study because studies of vascular reserve, such as Diamox single-photon emission computed tomography, were performed at the chronic stage of stroke, while the collateral status was examined at the acute phase of stroke.

In conclusion, embolic mechanism plays an important role in ischemic stroke of patients with MMD, and good collateral status in patients with MMD might be associated with washout of emboli. Taking into account the contribution of these 2 mechanisms, therapeutic strategies against thromboembolism, as well as collateral-enhancing strategies targeting improvement of hemodynamic status or increased washout of emboli, might be an important treatment option for preventing thromboembolic stroke in MMD.

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Disclosures

None.

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