Characterization of Cortical Microvascularization in Adult Moyamoya Disease

Marcus Czabanka, MD; Pablo Peña-Tapia, MD; Gerrit A. Schubert, MD; Johannes Woitzik, MD; Peter Vajkoczy, MD; Peter Schmiedek, MD

Background and Purpose—Increased cortical microvascularization has been proposed to be a Moyamoya disease (MMD)–specific characteristic. It was the aim of our study to characterize the anatomic pattern and microhemodynamics of cortical microvascularization in MMD.

Methods—Intraoperative indocyanine green videoangiography was performed in 16 adult MMD patients, 15 patients with atherosclerotic cerebrovascular disease (ACVD), and 10 control patients. Cortical microvascularization and microvascular hemodynamics were categorized and analyzed according to anatomic and functional indocyanine green angiographic aspects. Anatomic analysis included microvascular density, microvascular diameter, and microvascular surface per analyzed area. Microhemodynamic analysis included microvascular transit time, arterial microvascular transit time, and venous microvascular transit time.

Results—Microvascular density and diameter were significantly increased in MMD patients (1.8 ± 0.2 mm/mm² and 0.24 ± 0.03 mm, respectively) compared with those in ACVD patients (1.5 ± 0.2 mm/mm² and 0.20 ± 0.02 mm, respectively) and controls (1.5 ± 0.1 mm/mm² and 0.19 ± 0.03 mm, respectively). This resulted in significantly increased microvascular surface per analyzed area in MMD (67 ± 13%) vs ACVD patients (47 ± 7%) and controls (45 ± 6%). Anatomic changes were paralleled by significantly increased microvascular and arterial microvascular transit times in MMD patients (11.55 ± 3.50 and 6.79 ± 2.96 seconds, respectively) compared with those in ACVD patients (8.13 ± 1.78 and 4.34 ± 1.30 seconds, respectively) and controls (8.04 ± 2.16 and 4.50 ± 1.87 seconds, respectively).

Conclusion—Cortical microvascularization in MMD is characterized by significantly increased microvascular density and microvascular diameter, leading to increased microvascular surface. These anatomic alterations are accompanied by prolonged microvascular hemodynamics. These observations might represent an MMD-specific compensation mechanism for impaired cerebral blood flow. (Stroke. 2008;39:1703-1709.)

Key Words: Moyamoya disease ■ cortical vascularization ■ indocyanine green videoangiography ■ cerebral blood flow ■ compensation mechanism

Moyamoya disease (MMD) is a rare and unique cerebrovascular disease. It is characterized by progressive occlusion of the basal arteries of the circle of Willis in association with a network of fine “moyamoya vessels” at the base of the brain.1 Furthermore, there are several additional mechanisms in MMD, like transdural and extracranial-intracranial collateral formation, dilation of peripheral cerebral arteries, or the development of leptomeningeal anastomoses, that compensate for the reduced cerebral blood flow (CBF).2 Despite those compensating mechanisms, MMD patients have chronic cerebral ischemia with cerebrovascular hemodynamic insufficiency. Therefore, surgical revascularization represents an effective treatment option for this disease.

Cortical vascularization plays an important role in regulating cerebral perfusion and blood flow.3 Many reports suggest increased cortical microvascularization in MMD as a compensating mechanism for chronically impaired CBF.2,4 However, cortical microvascularization has not been thoroughly analyzed in MMD so far, and consequently, there is little knowledge about cortical microvascularization and microhemodynamics in this form of cerebrovascular disease. With the introduction of intraoperative indocyanine green (ICG) videoangiography, visualization and investigation of cortical vascularization have become possible.5,6 With this technique, it was the aim of our study to characterize the anatomic and microhemodynamic aspects of cortical microvascularization.

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in MMD. As a reference, we analyzed cortical microvascularization and microhemodynamics in patients with atherosclerotic cerebrovascular disease (ACVD) with coexisting hemodynamic compromise and in control patients with physiologic cortical angioarchitecture and microhemodynamics.

Subjects and Methods

Patient Population and Surgical Procedures

Between March 2006 and February 2007, a total of 41 patients were included in our study. Of these, 16 patients were diagnosed with MMD according to diagnostic criteria. MMD patients received combined cerebral revascularization by standard extracranial-intracranial bypass surgery in combination with encephalomyosynangiosis. Fifteen patients with ACVD and hemodynamic compromise were included in our study. All ACVD patients received standard extracranial arterial bypass surgery.

As a control group, 10 patients with physiologic cortical angioarchitecture and microhemodynamics were analyzed. Nine of these patients underwent surgery for an unruptured intracranial aneurysm, and 1 patient underwent surgery via a transtentorial approach for an intracranial aneurysm. All surgeries were performed with use of the Pentero OPMI surgical microscope (Carl Zeiss AG, Jena, Germany) with an integrated ICG videoangiography system.

Preoperatively, MMD and ACVD patients underwent conventional catheter digital subtraction angiography and morphological imaging by magnetic resonance imaging. Functional regional cerebral blood flow (rCBF) measurements were made at rest and after the administration of acetazolamide (15 mg/kg body weight) by stable xenon computed tomography (Xe-CT; DDP Inc, Houston, Tex). Cerebrovascular reserve capacity (CVRC) was calculated as described elsewhere in detail. To obtain CBF values for the region analyzed by ICG videoangiography, regions of interest (ROIs) on the Xe-CT images were located in the vascular territory under investigation (eg, vascular territory of the middle cerebral artery).

ICG Videoangiography

In all patients, ICG videoangiography was performed according to the surgical indications. Placement of a millimeter-scale grid on the cerebral surface before intraoperative ICG videoangiography guaranteed dimensional accuracy during postoperative analysis. During application of the fluorescent marker, blood pressure monitoring was recorded and evaluated to exclude hemodynamic alterations that could interfere with cerebral perfusion during ICG injection.

Cortical Vascularization

For analysis of cortical vascularization, we categorized arterial and venous macrovascularization as well as cortical microvascularization according to the functional ICG angiographic aspects. The early filling arteries (A1) and their direct branches (A2) and the last draining veins (V1) and their direct branches (V2) were referred to as cortical macrovascularization. All vessels that appeared between A2 and V2 vessels were regarded as cortical microvascularization (Figure 1).

Microvascularization was quantified postoperatively by a computer-assisted analysis system (CAPIMAGE, Zeintl Software Engineering, Heidelberg, Germany). For quantification of cortical microvascularization, we analyzed 3 suitable ROIs per cerebral cortex. ROIs were characterized as an area of 25 to 100 mm² without A1, A2, V1, or V2 vessels within that area. According to a previously described procedure, quantification of microvascular density (MD) was performed by measuring the length of all microvessels per analyzed ROI (Figure 1). Furthermore, microvascular diameter (D) was analyzed, and microvascular surface area (MVS) per analyzed ROI was calculated from the following formula:

\[ MVS = \pi \times D^2 / 2 \times MD. \]

Microhemodynamic Analysis of Cortical Microvascularization

Microhemodynamic analysis was performed postoperatively with IC-CALC 1.1 software (Pulsion Medical Systems). For analysis of cortical microhemodynamics, we analyzed fluorescence intensity in 3 distinct compartments in a time-dependent manner: ie, the arterial compartment (A2 vessels), capillary compartment (brain parenchyma), and venous compartment (V2 vessels). Figure 1A demonstrates the different compartments during ICG videoangiography. By comparing the time points of peak fluorescence intensity in the arterial (A2 vessels) and venous (V2 vessels) compartments, we...
were able to measure the time required for the fluorescent dye to pass the cortical microvasculature. This time was defined as microvascular transit time (MVTT). Furthermore, we analyzed the time difference of peak fluorescence intensity between the arterial (A2 vessels) and capillary compartments. This time was defined as arterial microvascular transit time (AMVTT). According to this procedure, venous microvascular transit time (VMVTT) was defined as the time difference between the capillary and venous (V2 vessels) compartments. Figure 1B demonstrates microhemodynamic definitions and illustrates the analysis procedure.

Statistical Analysis
For comparisons between 3 groups, 1-way ANOVA and subsequent comparison with Fisher’s least significant difference test were used. Student’s t test was applied for comparisons of CBF values between MMD and ACVD patients. Differences were considered statistically significant for P<0.05. All values are given as mean±SD.

Results

Patient Population
The mean age of the MMD patient group was 41±12 years. In the ACVD patient group, the mean age was 57±10 years, and the mean age of control patients was 53±9 years. There was a significant difference in mean age between the MMD patients and the ACVD and control patients. No difference was observed between ACVD patients and controls. Detailed descriptions of the patient groups are illustrated in Table.

rCBF Assessed by Xe-CT
We analyzed rCBF in 13 MMD patients. Measurement of CBF could not be performed in 3 patients due to intolerance of the procedure: nausea and vomiting in 2 cases and asthma bronchiale in 1 patient. Therefore, a total of 13 CBF measurements were included in our study. Mean basal CBF was 52±20 mL/100 g per min, and mean stimulated CBF was 55±22 mL/100 g per min. CVRC was 7±25%.

In the ACVD patient group, we included 14 CBF measurements, as 1 patient did not tolerate the Xe-CT due to nausea and vomiting. Mean basal CBF was 49±10 mL/100 g per min, and mean stimulated CBF was 53±18 mL/100 g per min. CVRC was 6±26%. There was no significant difference in rCBF and CVRC values between both patient groups. Table summarizes CBF values of the ACVD and MMD patients.

Intraoperative Blood Pressure Monitoring
Mean systolic blood pressure during ICG videoangiography in MMD patients was 134±16 mm Hg, and mean diastolic blood pressure was 69±10 mm Hg (Table). In ACVD patients, mean systolic blood pressure was 129±11 mm Hg, whereas mean diastolic blood pressure was 66±8 mm Hg (Table). Mean systolic blood pressure in control patients was 129±8 mm Hg, and mean diastolic blood pressure was 69±6 mm Hg (Table). There was no statistical difference in systolic and diastolic blood pressures between all groups.

Cortical Microvascularization
Cortical MD of MMD patients was 1.8±0.2 mm/mm². In ACVD patients, cortical MD was 1.5±0.2 mm/mm², and control patients showed an MD of 1.5±0.1 mm/mm². There was a statistically significant difference between MMD patients and the 2 other groups. We found no difference between ACVD patients and controls. Furthermore, D in MMD patients was 0.24±0.03 mm. In ACVD patients, D was 0.20±0.02 mm, and in controls, 0.19±0.03 mm. There was a statistically significant difference in D between MMD patients versus ACVD and patients controls.

MVS was found to be 67±13% in MMD patients compared with 47±7% in ACVD and 45±6% in control groups. There was a statistically significant difference in MVS between MMD patients and the other 2 groups. We found no significant differences in MD, D, and MVS between ACVD patients and control patients. Figure 2A comprises intraoperative images of cortical microvascularization and the corresponding ICG videoangiogram; Figure 2B is a graphical illustration of our results for MD, D, and MVS.

Cortical Microhemodynamics
Functional analysis revealed an AMVTT for MMD patients of 11±3 seconds. MVTT in ACVD patients was 8±2 seconds, and in controls, it was 8±2 seconds. Statistical analysis revealed a significantly increased MVTT in MMD patients compared with the 2 other patient groups. There was no statistically significant difference between ACVD patients and controls.

In terms of AMVTT, functional analysis revealed an AMVTT for MMD patients of 4±3 seconds. ACVD patients displayed an AMVTT of 4±1 seconds, and in control patients, AMVTT was 4±2 seconds. There was a statistically significant difference in AMVTT between MMD patients versus ACVD patients and controls. We found no difference in AMVTT between ACVD patients and controls. MVTT in MMD patients was 5±2 seconds. In ACVD patients MVTT was 4±2 seconds, and in control patients it was 3±2 seconds. We found no significant differences in VMVTT between all patient groups. Figure 3 demonstrates the graphical results of microhemodynamic analysis.

Discussion
In our study, we observed significant increases in MD, D, MVS, and AMVTT in adult MMD patients compared with ACVD patients and controls. Adult MMD patients are additionally characterized by significantly prolonged AMVTT compared with that in ACVD patients and controls. In terms of VMVTT, we found no differences between our patient groups. Therefore, we have demonstrated an MMD-specific structural increase in cortical microvessels and significantly prolonged cortical microhemodynamics in MMD. These observations might represent an MMD-specific compensation mechanism for the reduced CBF and oxygen supply.

The brain uses a number of compensating mechanisms to adapt to chronic ischemia, like collateral blood flow from the other hemisphere via the circle of Willis, a reduction in cerebral metabolism, maximal dilatation of basal cerebral arteries, and the development of leptomeningeal and extracranial anastomoses. However, these mechanisms vary on an individual basis and often do not completely restore CBF. Patients with chronically decreased CVRC are at particular risk for ischemic stroke. In our study, MMD as well as ACVD patients displayed typical features of hemodynamic cerebral ischemia with impaired CVRC.
Extracranial-intracranial bypass surgery has been shown to restore CVRC and thus, represents an efficient treatment option for patients with such reductions.11 Especially in MMD, surgical revascularization represents a very effective treatment option for restoring CBF and for preventing cerebral ischemia. In MMD, cortical microvascularization is of special interest, as Takeuchi et al4 described surgically exposed cortical surfaces that appeared reddish intraoperatively due to multiple leptomeningeal anastomoses and dilated pial arteries. Our surgical experience in the treatment of MMD confirms this observation.2

Intraoperative ICG videoangiography allows excellent visualization of cortical vascularization and has already been applied successfully to study cortical perfusion after decom-

### Table. Summary of Patient Groups Included in our Study

<table>
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<tr>
<th>Case</th>
<th>Age, y</th>
<th>Sex</th>
<th>CBF, Basal/Stimulated, mL/100 g per min</th>
<th>CVRC, %</th>
<th>Blood Pressure, mm Hg</th>
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<td>Bypass</td>
</tr>
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M indicates male; F, female; NP, not performed; COPD, chronic obstructive pulmonary disease; N&V, nausea and vomiting; Bypass, standard extracranial arterial bypass; EMS, encephalomyosynangiosis; R, right; L, left; ICA, internal carotid artery; and MCA, middle cerebral artery. A negative CVRC value indicates steal phenomenon during acetazolamide stimulation.
pressive craniectomy for malignant stroke. Using this technique, we observed a 20% increase in MD paralleled by significantly increased D and MVS in MMD patients, whereas ACVD patients with a comparable ischemic deficit displayed values comparable to those of controls. MMD has significant neoangiogenic potential, which might explain our observation of increased MD, D, and MVS. However, until now, no molecular mechanism has been identified, and it remains unclear whether MMD-associated neovascularization is a result of a distinct disease-related molecular pathway or an adaptive mechanism to cope with impaired cerebral hemodynamics.

Cerebral hemodynamics in MMD differs substantially from hemodynamics in ACVD. First of all, MMD is defined by bilateral steno-occlusive lesions of the basal cerebral arteries. ACVD does not refer to bilateral steno-occlusive lesions but it includes unilateral steno-occlusive lesions. In MMD, the posterior circulation may also be affected; therefore, compensation for low CBF by cross-flow through the circle of Willis might be more limited in certain MMD patients.

In atherosclerosis, leptomeningeal arteries and ophthalmic collaterals play a major role in compensating for low CBF. In MMD, collateralization via the ophthalmic artery is not possible, as the definition of MMD includes supraophthalmic steno-occlusive lesions of basal cerebral arteries. However, leptomeningeal anastomoses are also observed in MMD patients and are regarded as significant contributors to the collateral blood supply. We evaluated the vascular territory of the middle cerebral artery in all cases except for one. Leptomeningeal anastomoses are defined as arteries between 2 major cerebral arteries that supply 2 different cortical territories. Therefore, cortical microvascularization according to our definition does not refer to leptomeningeal anastomoses. However, we expect similar effects, as observed in our study, on the level of leptomeningeal anastomoses.

In contrast to ACVD patients, compensation for low CBF in MMD is achieved by a unique MMD-specific neoangiogenenic process. Neovascularization in the form of moyamoya vessels at the base of the brain has been demonstrated to lead to significantly increased CBF and cerebrovascular CO2 reactivity in the basal ganglia of MMD compared with ACVD patients. Because cortical vasculization plays an important role in regulating CBF, increased MD, D, and MVS might exert significant effects on cerebral microhemodynamics and thus, contribute to the compensation for hemodynamic impairment. Increased MD, D, and MVS might consequently compensate for the impaired CBF either by increasing collateral blood flow or by reducing microvascular...
resistance. As mentioned earlier, MMD is characterized by multiple stenotic lesions of the circle of Willis\textsuperscript{30,21}; therefore, increasing collateral blood flow might represent a rather inefficient mechanism.\textsuperscript{7} In this scenario, decreasing microvascular resistance might be the more efficient mechanism for compensating for impaired CBF.

To investigate cerebral microhemodynamics, we measured MVTT, AMVTT, and VMVTT. According to our definitions, MVTT indirectly represents microvascular blood flow velocity, as the time from maximum fluorescence intensity in A2 to V2 vessels represents the time required for peak blood flow to pass the cortical microvascularization. This parameter was significantly increased in MMD patients compared with ACVD and control groups. Our results are supported by results from Taki et al.,\textsuperscript{22} who demonstrated prolonged cerebral circulation time in MMD patients.

Cortical arterial microvascularization plays an important role in regulating cerebral perfusion, as more than half of the total cerebral vascular resistance is located in the extraparenchymal vessel segments.\textsuperscript{3} An increase in arteriolar resistance vessels leads to an increase in microvascular cross-sectional area and thus, decreased peripheral microvascular resistance. Therefore, conductance of the microvascular segment in the organ vasculature is increased, resulting in decreased blood flow velocity. By measuring AMVTT and VMVTT, we were able to localize the vascular compartment responsible for the reduction in MVTT. According to our results, MVTT was lost in the arterial compartment in MMD patients. The observation of increased AMVTT in combination with increased MD, D, and MVS suggests decreased peripheral microvascular resistance as the mechanism of choice. In support of this hypothesis, Okada et al.,\textsuperscript{23,24} were able to demonstrate diminished vascular resistance between cortical arteries of the middle cerebral artery territory and the corresponding veins in MMD patients.

Moreover, there is experimental evidence that an increase in cortical arterial microvascularization represents a suitable mechanism for the compensation of reduced CBF. Schneider et al.,\textsuperscript{25} demonstrated an increase in the number of extraparenchymal and intraparenchymal arterioles in response to application of granulocyte-macrophage colony stimulating factor in a rat model of cerebrovascular occlusive disease. The authors showed that increasing the number of pial arterial resistance vessels led to decreased total peripheral resistance and a concomitant restoration of CVRC.\textsuperscript{25}

Therefore, we propose a potentially new compensation mechanism in MMD: ie, increased MD, D, and MVS at the level of cerebral microvascularization, potentially resulting in decreased peripheral vascular resistance. Further studies will be needed to investigate and characterize the clinical significance of this potential new compensation mechanism in MMD.

**Summary**

Intraoperative ICG videoangiography was used to investigate and characterize cortical microvascularization and microhemodynamics in MMD compared with ACVD patients and in subjects with normal cerebral microvascularization. On an anatomic level, we demonstrated increases in MD, D, and MVS in MMD patients compared with the other 2 groups. In terms of microhemodynamic characteristics, we demonstrated increases in MVTT and AMVTT in MMD patients compared with ACVD patients and controls. Our observations might represent an MMD-specific compensation mechanism for reduced CBF, either by increasing collateral blood flow or by reducing peripheral vascular resistance.

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**Disclosures**

None.

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Characterization of Cortical Microvascularization in Adult Moyamoya Disease
Marcus Czabanka, Pablo Peña-Tapia, Gerrit A. Schubert, Johannes Woitzik, Peter Vajkoczy and Peter Schmiedek

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