Perfusion Characteristics of Moyamoya Disease
An Anatomically and Clinically Oriented Analysis and Comparison

Gerrit Alexander Schubert, MD; Marcus Czabanka, MD; Marcel Seiz, MD; Peter Horn, MD; Peter Vajkoczy, MD; Claudius Thomé, MD

Background and Purpose—Moyamoya disease (MMD) is characterized by unique angiographic features of collateralization. However, a detailed quantification as well as comparative analysis with cerebrovascular atherosclerotic disease (CAD) and healthy controls have not been performed to date.

Methods—We reviewed 67 patients with MMD undergoing Xenon-enhanced computed tomography, as well as 108 patients with CAD and 5 controls. In addition to cortical, central, and infratentorial regions of interest, particular emphasis was put on regions that are typically involved in MMD (pericallosal territory, basal ganglia). Cerebral blood flow (CBF), cerebrovascular reserve capacity (CVRC), and hemodynamic stress distribution were calculated.

Results—MMD is characterized by a significant, ubiquitous decrease in CVRC and a cortical but not pericallosal decrease in CBF when compared with controls. Baseline perfusion is maintained within the basal ganglia, and hemodynamic stress distribution confirmed a relative preservation of central regions of interest in MMD, indicative for its characteristic proximal collateralization pattern. In MMD and CAD, cortical and central CBF decreased significantly with age, whereas CVRC and hemodynamic stress distribution are relatively unaffected by age. No difference in CVRC of comparable regions of interest was seen between MMD and CAD, but stress distribution was significantly higher in MMD, illustrating the functionality of the characteristic rete mirabilis.

Conclusions—Our data provide quantitative support for a territory-specific perfusion pattern that is unique for MMD, including central preservation of CBF compared with patients with CAD. This correlates well with its characteristic feature of proximal collateralization. CVRC and hemodynamic stress distribution seem to be more robust parameters than CBF alone for assessment of disease severity. (Stroke. 2014;45:101-106.)

Key Words: computed tomography ■ Moyamoya disease ■ perfusion ■ Xenon
coining the phrase moyamoya (Japanese for puff of smoke),9 and the Fisher anastomosis, a collateral from the posterior to the anterior circulation running along the corpus callosum (Figure 1C).

Although frequently assumed to be characteristic as well as diagnostic or even pathognomonic, the functionality of these collaterals lack a more detailed description, such as a circumscribed quantification. Although our group recently summarized perfusion data on patients with CAD,10 an anatomic analysis of CBF and CVRC in distinct cortical and central representations of MMD has not been performed to date. The influence of age as well as disease severity on perfusion characteristics are also unclear. Although this information at present may seem of potential academic interest only, a detailed description using a simplified classification system for regions of interest (ROIs) may also facilitate comparison with other chronic or even acute pathologies with vessel stenosis or occlusion.

This analysis aims to discern and quantify the characteristic compensatory mechanisms of MMD by means of XeCT compared with CAD with particular emphasis on anatomic landmarks, as well as age and disease severity.

Materials and Methods

We retrospectively analyzed 67 adult patients with documented MMD seen at our neurosurgical department (Universitätsmedizin Mannheim, University of Heidelberg, Heidelberg, Germany) from 2005 to 2008 for further workup. All patients underwent cerebral angiography, MRI, and XeCT investigation at our institution, and detailed neurological history and physical examination were obtained. The diagnosis of MMD was made on the basis of classical angiographic findings consistent with the characteristic rete mirabilis (possibly, but not mandatory: extracranial/intracranial or pericallosal anastomosis) in conjunction with stenosis or occlusion of either terminal internal carotid artery or proximal anterior cerebral artery or MCA. Patients with previous hemorrhage or evidence of stenotic lesions within the posterior circulation were excluded. Five patients undergoing preoperative workup for elective aneurysm clipping and potential revascularization served as controls, and 108 patients with cerebral atherosclerotic disease and their corresponding XeCT scans were included for comparison.

XeCT scanning (DDP Inc; Houston, TX), described elsewhere in greater detail,11 included acquisition of 6 continuous axial slices (300 mA, 80 kV, 5 mm collimation thickness). Briefly, 2 baseline scans were followed by 6 successive scans during the 4.5-minute wash-in period of a standardized gas mixture (50% oxygen, 28% xenon gas) to determine baseline CBF. To ensure patient safety, Xenon saturation curves as well as clinical monitoring and measurement of end-tidal CO2 were observed. To calculate stimulated CBF, we performed a second scanning sequence 15 minutes after administration of azetazolamide (15 mg/kg body weight; Goldshield Pharmaceuticals Ltd; Croydon, United Kingdom). Specialized, dedicated software (XeCT System, Diversified Diagnostic Products Inc; Houston, TX) was used for off-line analysis (Figure 2A).

For this investigation, we selected an average of 25 to 30 representative ROIs in each of the 180 patients within the following vascular territories: MCA, adjacent cortical watershed (anterior and posterior to MCA territory), basal ganglia (including striatum and globus pallidus), pons and the pericallosal territory of cortical, mixed gray–white matter (Figure 2B), as well as the cerebellar cortex. ROIs within areas of demarcated, territorial infarction were excluded from analysis. To reliably determine regional CBF and to minimize a sampling error with adequate signal-to-noise ratio, each ROI contained ≥300 pixels.12 We collected several ROIs per specific territory on corresponding slices that were later averaged to minimize the inherent variation error. CBF was corrected for variance in CO2 and current hematocrit. CVRC was defined as the percentage of change in CBF between baseline and stimulated scans.

Figure 2. A characteristic cerebral blood flow (CBF) examination in a patient with Moyamoya disease is shown (A). Although baseline measurements approach normal values, a distinct decrease is seen after stimulation (blue color), indicating a loss of vasomotor reserve capacity, also seen in the summation image (cerebrovascular reserve capacity [CVRC]). Classically, a bihemispheric loss of CVRC within the anterior circulation is observed, as seen in this scan in which the territory of the anterior cerebral artery, middle cerebral artery (MCA), and the adjacent watershed areas are most severely affected. We then selected representative regions of interest (B) for the supracallosal territory (left), the basal ganglia (middle), and the MCA territory (right), as well as for the adjacent watershed regions (interrupted lines).
We used an ROI classification system that was described previously in the evaluation of patients with CAD. Taking into account the relative severity of disease, this simplified stratification aims to provide for a more representative comparison of territories between different disease entities. Within this system, each ROI is assigned 1 of 3 levels of significance: class I without evidence of proximal stenosis or occlusion (not applicable in the anterior circulation in MMD); class II with angiographic evidence of proximal stenosis or occlusion, but without clinical symptoms; and class III with angiographic evidence of symptomatic proximal stenosis or occlusion.

To detect relative changes in cortical perfusion when compared with central areas of interest, we analyzed the hemodynamic stress distribution (hdSD), which is defined as the calculated ratio of mean CBF in central versus cortical ROIs.

**Statistics**

CBF data are presented as mean±SD. A territorial ROI was averaged over all acquired ROIs of all slices within the specific territory. Student t test, Pearson correlation, linear regression analysis, ANOVA with Bonferroni correction, and ANCOVA were used as applicable (Numbers, Apple Inc, Cupertino, CA; GraphPad Prism, GraphPad Software, Inc, La Jolla, CA). Statistical significance was set at P<0.05, P<0.01, and P<0.001, respectively.

**Results**

Of 180 patients undergoing cerebral angiography and XeCT imaging, a total of 67 had clinical and morphological findings consistent with MMD (control: n=5; CAD: n=108). Mean age of patients with MMD was 39±11 years, which was comparable to patients within the control group (43±17 years; P=0.43) but significantly younger than patients with CAD (57±12 years; P<0.001).

All ROIs within the pons and the cerebellar cortex were assigned class I significance attributable to the documented angiographic absence of proximal stenosis. Supratentorial ROIs were assigned class I to III significance as dictated by the classification system.

**Perfusion Alterations With MMD Compared With a Control Group**

In MMD, baseline CBF and CVRC of cortical ROIs were significantly lower when compared with the control group (Table 1). Stimulated hdSD increased significantly with MMD, and a trend toward higher hdSD in baseline scans was observed. In the pericallosal territory and the basal ganglia, CBF was not decreased. CVRC was diminished in both regions, but the difference only reached statistical significance in the basal ganglia.

Only baseline CBF was able to depict a significant difference between class II and III ROIs (P<0.05; data not shown); neither did the number of ROIs with cortical steal phenomenon (CVRC<0%) nor did the significant decrease in CVRC (<30%) differ significantly between groups (P=0.33 and P=0.59, respectively; data not shown).

**Perfusion Alterations With MMD Compared With CAD**

In patients with MMD, baseline CBF decreases significantly with age in all supratentorial ROIs as well as within the pons (Table 2; P<0.001) but remains stable within the cerebellar cortex. Equivalent results were obtained for patients with CAD (P<0.001), with the exception of the pons, in which CBF did not decrease with age. Effect of age on perfusion was comparable for MMD and CAD according to linear regression comparison, with the exception of the pons (P<0.001). No influence of age was seen on baseline and stimulated hdSD in MMD and CAD.

Although CBF in the pons and the cerebellum was comparable in both groups, supratentorial CBF was significantly higher in patients with MMD than in patients with CAD (P<0.001). Adjusting for age, only a trend toward higher CBF in patients with MMD was seen (P=0.06). Stress distribution was significantly higher in patients with MMD, and comparative linear regression analysis showed a clearly significant difference for the slopes in baseline hdSD versus CVRC but not stimulated hdSD versus CVRC (P<0.001; data not shown).

CVRC remained stable over time in both MMD and CAD in every ROI investigated, with no significant difference in between the 2 groups.

<p>| Table 1. Patients With MMD Compared With Control Group With Respect to CBF, CVRC, and hdSD |
|-----------------------------------------------|----------------|----------------|----------------|----------------|</p>
<table>
<thead>
<tr>
<th><strong>Anatomic Localization</strong></th>
<th><strong>Parameter</strong></th>
<th><strong>Control</strong></th>
<th><strong>Class II</strong></th>
<th><strong>Class III</strong></th>
<th><strong>Control vs MMD</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>MCA+adjacent border zones</td>
<td>BasCBF, mL/100 g×min</td>
<td>64.2±15.6</td>
<td>55.4±22.8</td>
<td>49.3±17.2</td>
<td>P&lt;0.01</td>
</tr>
<tr>
<td>CVRC, %</td>
<td>54.8±38.4</td>
<td>26.8±64.0</td>
<td>27.5±64.2</td>
<td>P&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>hdSD&lt;sub&gt;bas&lt;/sub&gt;,</td>
<td>1.14±0.22</td>
<td>1.46±0.98</td>
<td>1.48±0.84</td>
<td>P&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>hdSD&lt;sub&gt;stim&lt;/sub&gt;,</td>
<td>1.06±0.15</td>
<td>1.59±0.89</td>
<td>1.52±0.70</td>
<td>P&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Pericallosal territory</td>
<td>BasCBF, mL/100 g×min</td>
<td>64.2±12.8</td>
<td>51.8±16.1</td>
<td>55.9±18.7</td>
<td>Ns</td>
</tr>
<tr>
<td>CVRC, %</td>
<td>47.3±22.5</td>
<td>27.2±62.6</td>
<td>22.6±46.4</td>
<td>Ns</td>
<td></td>
</tr>
<tr>
<td>Basal ganglia</td>
<td>BasCBF, mL/100 g×min</td>
<td>68.8±17.2</td>
<td>65.8±16.4</td>
<td>61.4±14.8</td>
<td>Ns</td>
</tr>
<tr>
<td>CVRC, %</td>
<td>40.7±23.3</td>
<td>23.9±24.5</td>
<td>21.6±29.4</td>
<td>P&lt;0.05</td>
<td></td>
</tr>
</tbody>
</table>

CBF was generally lower in patients with MMD when compared with a control group, although the difference did not reach statistical significance in the pericallosal territory and the basal ganglia. Reserve capacity (CVRC) was significantly reduced in all but the pericallosal territory. A significant increase of stress distribution (hdSD) was seen for stimulated scans, with a trend toward increase in baseline scans.

BasCBF indicates baseline CBF; CBF, cerebral blood flow; CVRC, cerebrovascular reserve capacity; hdSD, hemodynamic stress distribution; hdSD<sub>bas</sub>, baseline hdSD; hdSD<sub>stim</sub>, stimulated hdSD; MCA, middle cerebral artery; MMD, Moyamoya disease; and Ns, not significant.
Stroke January 2014

Table 2. ROIs Analyzed According to Their Anatomic Location With Respect to CBF, CVRC, and Influence of Age

<table>
<thead>
<tr>
<th>Anatomic Localization (Class)</th>
<th>MMD</th>
<th>CAD</th>
<th>t Test</th>
<th>Linear Regression Comparison</th>
<th>MMD</th>
<th>CAD</th>
<th>t Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCA, cortical watershed (II+III)</td>
<td>CBF, mL/100 g×min</td>
<td>52.6±20.6</td>
<td>46.8±17.7</td>
<td>&lt;0.001</td>
<td>CVRC, %</td>
<td>28.2±64.0</td>
<td>27.4±52.6</td>
</tr>
<tr>
<td>Influence of age</td>
<td>↓↓↓</td>
<td>↓↓↓</td>
<td>Ns</td>
<td>Influence of age</td>
<td>Ns</td>
<td>Ns</td>
<td>Ns</td>
</tr>
<tr>
<td>BG/Thal (II+III)</td>
<td>CBF, mL/100 g×min</td>
<td>63.7±15.7</td>
<td>53.1±2.7</td>
<td>&lt;0.001</td>
<td>CVRC, %</td>
<td>22.7±27.0</td>
<td>19.5±38.4</td>
</tr>
<tr>
<td>Influence of age</td>
<td>↓↓↓</td>
<td>↓↓↓</td>
<td>Ns</td>
<td>Influence of age</td>
<td>Ns</td>
<td>Ns</td>
<td>Ns</td>
</tr>
<tr>
<td>Pericallosal (II+III)</td>
<td>CBF, mL/100 g×min</td>
<td>53.8±17.5</td>
<td>47.1±12.2</td>
<td>&lt;0.01</td>
<td>CVRC, %</td>
<td>25.1±55.4</td>
<td>30.6±31.4</td>
</tr>
<tr>
<td>Influence of age</td>
<td>↓↓↓</td>
<td>Ns</td>
<td>Ns</td>
<td>Influence of age</td>
<td>Ns</td>
<td>Ns</td>
<td>Ns</td>
</tr>
<tr>
<td>Pons (I)</td>
<td>CBF, mL/100 g×min</td>
<td>62.3±14.3</td>
<td>58.1±12.6</td>
<td>Ns</td>
<td>CVRC, %</td>
<td>46.1±41.0</td>
<td>40.2±40.0</td>
</tr>
<tr>
<td>Influence of age</td>
<td>↓↓↓</td>
<td>Ns</td>
<td>P=0.001</td>
<td>Influence of age</td>
<td>Ns</td>
<td>Ns</td>
<td>Ns</td>
</tr>
<tr>
<td>Cerebellar cortex (I)</td>
<td>CBF, mL/100 g×min</td>
<td>65.8±19.5</td>
<td>62.1±16.5</td>
<td>Ns</td>
<td>CVRC, %</td>
<td>44.9±42.9</td>
<td>39.4±33.1</td>
</tr>
<tr>
<td>Influence of age</td>
<td>Ns</td>
<td>Ns</td>
<td>Influence of age</td>
<td>Ns</td>
<td>Ns</td>
<td>Ns</td>
<td></td>
</tr>
<tr>
<td>MCA, cortical watershed+BG/Thal (II+III)</td>
<td>hdSDbas</td>
<td>1.47±0.92</td>
<td>1.30±0.53</td>
<td>&lt;0.01</td>
<td>hdSDstim</td>
<td>1.56±0.81</td>
<td>1.30±0.57</td>
</tr>
<tr>
<td>Influence of age</td>
<td>Ns</td>
<td>Ns</td>
<td>Influence of age</td>
<td>Ns</td>
<td>Ns</td>
<td>Ns</td>
<td></td>
</tr>
</tbody>
</table>

To illustrate the influence of age on perfusion, ROIs were analyzed according to their anatomic location with respect to CBF (mL/100 g×min), CVRC (%), and the influence of age (as determined by Pearson correlation classification: ↓↓↓ =P<0.001). Differences between groups were calculated by t-test, and approximation of differences in age contribution by comparison of linear regression slopes. Correlation analysis showed significant decrease of basal CBF with age in MMD and CAD for all supratentorial ROIs and also for the pons in MMD; supratentorial CBF was generally lower in patients with CAD. CVRC was comparable in MMD and CAD and was stable over time. Basal and stimulated hdSD were significantly lower in CAD (P<0.01 and P<0.001, respectively) but stable over time. Linear regression analysis estimated comparable slopes for age effect on CBF in MMD and CAD, but for the pons, where aging in MMD leads to a significantly more pronounced decrease in CBF (but not CVRC).

BG indicates basal ganglia; CAD, cerebrovascular atherosclerotic disease; CBF, cerebral blood flow; CVRC, cerebrovascular reserve capacity; hdSD, hemodynamic stress distribution; hdSDbas, baseline hdSD; hdSDstim, stimulated hdSD; MCA, middle cerebral artery; MMD, Moyamoya disease; Ns, not significant; ROI, region of interest; and Thal, thalamus.

Discussion

CBF and CVRC are established parameters in the functional workup of patients with cerebrovascular steno-occlusive disease, such as MMD and CAD, and have been used frequently to assess the efficacy of revascularization procedures. Despite its unique angiographic features and an abundance of descriptive publications on MMD, an anatomically driven analysis of MMD perfusion characteristics quantifying these compensatory patterns, has not been performed to date. Observations on differences in CBF of pediatric and adult patients are available, although it has been postulated previously that juvenile and adult MMD may constitute distinctly different disease entities, and the effect of age on respective clinical findings in adults remains unclear. Apart from the frequent observation of posterior dominance in CBF, likely attributable to the absence of compromise in the posterior circulation, CBF distribution in general has been found to yield heterogeneous results, even if investigated in descriptive case reports. This is generally thought to be based on a supposed heterogeneity of MMD subtypes and difference in severity of disease burden. In our cohort, we aimed to minimize these variations by only including adult patients with ischemic but not hemorrhagic presentation and without evidence of compromise within the posterior circulation.

Few comparative studies exist to date investigating differences in cerebral hemodynamics as measured in MMD and CAD, which, in part, also feature significant differences in age of the 2 groups. The authors are not aware of a more detailed anatomic differentiation of MMD or a comparative analysis with other disease entities. Given the larger number of patients and a more homogenous stratification of ROIs for comparison, we hope that our study may be able to provide additional information in terms of MMD perfusion characteristics and overall differences to CAD.

Perfusion Alterations With MMD Compared With a Control Group

First, we compared patients with MMD with a control group of comparable age, and we found a highly significant decrease of CBF in the cortex, and baseline CBF also detected a significant difference between class II and III ROIs. However, supratentorial CBF, in general, was found to be significantly influenced by age alone. Stress distribution, on the contrary, as the ratio of central and cortical CBF, was not influenced by age but was found to be consistently higher in MMD, indicative of...
a characteristic central CBF preservation. This finding is in line with the observation that absolute CBF within the basal ganglia, unlike cortical CBF, does not decrease significantly with disease progression, whereas CVRC is significantly compromised. This is also reflected in the development of hdSD in MMD versus CAD. Not only is the hdSD significantly higher than in control patients, but it is also significantly higher in patients with MMD than in patients with CAD of comparable disease burden (class II+III ROIs).

We believe that CBF maintenance and CVRC exhaustion observed on XeCT represent a quantitative correlate to the angiographic hallmark of MMD, namely the proximal collateralization pattern (rete mirabilis), which gave the disease its name. Recently, the pericallosal anastomosis has been postulated as also being indicative of MMD (M. Czabanka et al, unpublished data, 2013), and our data may provide further support to this frequent observation: the pericallosal territory features a comparable perfusion pattern, with maintenance of CBF and a nearly 50% reduction of CVRC; although this did not reach statistical significance.

Perfusion Alterations With MMD Compared With CAD

We used a previously described classification system, which, although possibly considered arbitrary and overly simplistic, may facilitate the comparison of equally compromised vascular territories of different pathologies. Based on this classification system, we were able to identify and exclude all supratentorial class I ROIs in CAD from further analysis because MMD by definition can only yield class II and III ROIs for comparison.

We compared affected ROIs (class II+III) of patients with MMD and CAD, and we observed that CBF was consistently higher in patients with MMD in all supratentorial ROIs, a finding in accordance with other observations. At the same time, patients with MMD were found to be significantly younger. A correlation of aging and a concomitant decrease in CBF has been postulated previously, and we were able to confirm a highly significant decrease of CBF with age for both MMD and CAD. Comparative linear regression analysis provided evidence that both disease entities are affected comparably by age, and after an ANCOVA adjusted for age, only a trend toward higher CBF values in MMD was found. Therefore, we do believe that higher CBF values generally observed in patients with MMD, to a large extent, represent an epiphemomenon attributable to the fact that patients with MMD are significantly younger.

As mentioned previously, CBF is known to decrease with age in the healthy population. Previously documented parallel decrease of both CBF and cerebral blood volume in healthy volunteers with age led to the assumption that CVRC as the ratio of CBF and CBF is likely unaffected by aging alone. With our patient cohort, we were able to affirm this hypothesis because CVRC did not change significantly with age in neither MMD nor CAD for any of the territories investigated. Furthermore, reserve capacity of MMD and CAD was diminished comparably in all ROIs. Relative stability to age and significant reduction in pathological territories seem to make CVRC a more robust parameter than CBF alone for quantitative assessment of disease burden.

An unexpected observation was the fact that the pons in MMD, unlike in CAD and the control group (data not shown), features a significant decrease in blood flow with age. Although the statistical results seem robust, we do not yet have an explanatory hypothesis for why this region may be more sensitive to aging in MMD in particular.

Limitations

We are critically aware of the small size of our control group in this analysis. This is because of the infrequent necessity of blood flow imaging in patients with presumably normal perfusion (in our case, patients having to undergo aneurysm clipping), possibly requiring additional revascularization. To obtain a larger control group, one will have to resort to other imaging methods with significantly less radiation exposure, an approach that would have made a meaningful comparison with our MMD and CAD cohort even more difficult.

Although angiographically almost identical, it has been postulated that Asian patients with MMD may portray a different subtype of the disease than white patients do, and therefore, the results of our analysis of predominantly European patients can only be extrapolated cautiously.

We used a classification system to be able to exclude presumably healthy ROIs in patients with CAD, hopefully allowing for a more homogenous match of ROIs for comparison (MMD versus control, MMD versus CAD). We did see a gradual decrease of perfusion and reserve capacity in most instances with progression of disease (class II to class III), which was most evident in baseline cortical CBF, but the quantitative differences were too subtle to reach statistical significance. It must be postulated that a more detailed subclassification of pathological ROIs may not contribute significantly to our understanding of the disease.

Conclusions

Our data provide quantitative support for a territory-specific perfusion pattern that is unique for MMD, including a relative central preservation of CBF compared with healthy controls and patients with CAD. This correlates well with previously described angiographic features of proximal collateralization. CBF, but not CVRC, is influenced by age in both MMD and CAD. CVRC and hdSD seem to be a more robust parameter than CBF alone for disease assessment in MMD and CAD.

Acknowledgments

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Disclosures

None.

References

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