Cerebellar and Cerebral Autoregulation in Migraine

Matthias Reinhard, MD; Joscha Schork; Arthur Allignol, MSc; Cornelius Weiller, MD; Holger Kaube, MD

Background and Purpose—Silent ischemic brain lesions frequently occur in migraine with aura and are most often located in cerebellar border zones. This may imply an impairment of cerebellar blood flow autoregulation. This study investigated the characteristics of interictal cerebellar autoregulation in migraine with and without aura.

Methods—Thirty-four patients (n=17, migraine without aura; n=17, migraine with aura) and 35 age- and sex-matched controls were studied. Triple simultaneous transcranial Doppler monitoring of one posterior inferior cerebellar artery, right posterior cerebral artery, and left middle cerebral artery was performed. Autoregulation dynamics were assessed from spontaneous blood pressure fluctuations (correlation coefficient index \( D_x \)) and from respiratory-induced 0.1-Hz blood pressure oscillations (phase and gain).

Results—Compared with controls, the autoregulatory index \( D_x \) was higher (indicating less autoregulation) in the posterior inferior cerebellar artery \((P=0.0062)\) and middle cerebral artery \((P=0.0078)\) in migraine with aura, but not in migraine without aura. Phase and gain did not significantly differ between migraine patients and controls. No significant associations of autoregulation with clinical factors were found, including frequency of migraine attacks and orthostatic intolerance.

Conclusions—This first-time analysis of cerebellar autoregulation in migraine did not show a specific cerebellar dysautoregulation in the interictal period. More static autoregulatory properties (index \( D_x \)) are, however, impaired in persons with migraine with aura both in the cerebellar and anterior circulation. The cerebellar predilection of ischemic lesions in migraine with aura might be a combination of altered autoregulation and additional factors, such as the end artery cerebellar angioarchitecture. (Stroke. 2012;43:987-993.)

Key Words: migraine ■ cerebral blood flow ■ autoregulation ■ cerebellum

Migraine is a risk factor for ischemic stroke, particularly in women with migraine with aura.1 Whereas in population-based studies, the overall infarct prevalence is not different from that of controls, a significantly higher prevalence of silent infarctions in the cerebellum among patients with migraine has been reported.2 Interestingly, these cerebellar lesions are mainly located in vascular border zones of the cerebellum, suggesting a hemodynamic cause.3 Furthermore, patients with migraine have a higher prevalence of orthostatic intolerance and syncope despite clear changes in orthostatic systemic cardiovascular regulation.4 Disturbance of cerebral autoregulation, particularly in the cerebellar circulation, might thus be present in patients with migraine with aura.5

To date, cerebellar autoregulation has not been analyzed in patients with migraine during or outside an attack. One study showed that cerebrovascular reserve capacity to inhalation of \( CO_2 \), which measures arteriolar reactivity, but not pressure autoregulation, seems to be lower in the basilar artery compared with the middle cerebral artery in persons with migraine with aura.6

Until recently, little was known about autoregulation in the human cerebellum. We have successfully applied a new monitoring method of cerebellar hemodynamics by transnuchal Doppler sonography of the posterior inferior cerebellar artery (PICA). In healthy adults without migraine, we found cerebellar autoregulation to be at least as effective as in the middle cerebral artery.7

The present study uses an advanced approach of triple simultaneous transcranial Doppler monitoring of the cerebellar, posterior, and anterior circulation. In the interictal period of persons with migraine with and without aura, we investigated whether cerebellar and cerebral autoregulation is specifically impaired in comparison with healthy controls; we also investigated how it associates with clinical factors, such as frequency of attacks or symptoms of orthostatic intolerance.

Subjects and Methods

We prospectively studied 17 patients with migraine without aura (MO), 17 patients with migraine with aura (MA), and 35 healthy
controls. Inclusion criteria for the migraine group were: diagnosis of migraine with or without aura according to criteria of the International Headache Society, absent migraine headaches or aura symptoms on the day of measurement, and absent history of previous cerebrovascular disease. Inclusion criteria for controls, who were recruited from advertisements within the medical faculty were: absent history of migraine or other chronic headaches, absent family history of migraine (parents, siblings), and absent history of cerebrovascular disease. Control selection was prospectively matched for age and sex to the simultaneously recruited patient group. The exclusion criteria for all subjects were obstructive vascular disease of brain-supplying vessels. This was ruled out in all subjects by extra- and transcranial, color-coded duplex sonography at study screening (iU22, Philips Healthcare). The study was approved by the local ethics committee, and each subject gave written informed consent to participate.

Clinical Data
A detailed migraine-related history was prospectively obtained from every subject and from additional chart review. Among factors analyzed were: type of aura, cumulative attacks per month during the last 6 months, time since last day of previous attack, and current medication (drugs for acute attacks, prophylaxis, any other). Other factors recorded were: hypertension (defined as resting blood pressure above 140/90 mm Hg or pre-existing diagnosis of hypertension and antihypertensive treatment), history of diabetes, history of stroke, current smoking, intake of oral contraceptives, history of syncope, and specific symptom score for orthostatic intolerance (SSS-OI; minimum, 0 points [asymptomatic]; maximum, 70 points). Presence of focal neurological deficits was assessed by standard clinical examination.

Furthermore, a prospective follow-up observation was performed regarding the onset, type, and duration of the next migraine attack (observation period: 90 days after completion of autoregulation study). For this purpose, patients received a form and a prepaid envelope and were instructed to fill in the form and send it back once the next migraine attack occurred. Patients received a specific headache diary to keep records of their migraine attacks and to ensure documentation of their next migraine attack. In addition, every patient was contacted by phone at the end of the follow-up period to ensure return of the form.

Measurement of Standard Hemodynamics
Arterial blood pressure at heart level was monitored continuously via finger plethysmography (Finapres, Ohmeda). End-tidal CO2 partial pressure (PETCO2) was measured by a standard capnometer (Datex). All measurements were performed with subjects in a supine position with 60° elevation of the upper body. All patients had their eyes closed throughout the measurement to avoid interference between metabolic activation and autoregulation in the posterior cerebral artery (PCA). Mean baseline hemodynamic values were calculated from a period of 120 seconds at rest. Pulsatility index (PI) of cerebral blood flow velocity (CBFV) was calculated as PI=(CBFV systole−CBFV diastole)/CBFV mean).

Assessment of Dynamic Cerebral Autoregulation
Cerebral autoregulation was calculated by 2 different methods:10,11:

1. The correlation coefficient index was calculated from 10 minutes of spontaneous fluctuations of arterial blood pressure (ABP) and CBFV: briefly, diastolic values of ABP and CBFV were averaged over 3-second periods, and from 20 consecutive 3-second
models. The association between autoregulatory ability and fre-

calculated by Spearman correlation coefficient (r). Association
did not reveal differences between pairs. Paired correlations were
assessed using Wilcoxon tests to

Departure from normality was observed; therefore, the data were
analyzed using nonparametric techniques. Differences between

Statistical Analysis

Data were checked for normality graphically using Q-Q plots.

Hemodynamics and Autoregulation in Different Vascular Territories (PICA Versus MCA and PCA)

In both patients and controls, mean CBFV was lower in the

Migraine patients had a higher score of orthostatic intolerance and more often a history of syncope; other
characteristics did not differ between patients and controls.

An illustration of the measurement situation and an example

Results

Baseline data of the patient and control group are given in
Table 1. Migraine patients had a higher score of orthostatic
intolerance and more often a history of syncope; other
characteristics did not differ between patients and controls.

An illustration of the measurement situation and an example

Hemodynamics and Autoregulation in Different Vascular Territories (PICA Versus MCA and PCA)

In both patients and controls, mean CBFV was lower in the

PICA and PCA compared with the MCA, and pulsatility was

Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Migraine Patients</th>
<th>Controls</th>
<th>Intergroup Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All (n=34)</td>
<td>MO (n=17)</td>
<td>MA (n=17)</td>
</tr>
<tr>
<td>Age, y±SD</td>
<td>28.7±7.2</td>
<td>29.1±7.6</td>
<td>28.4±7.1</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>25 (74)</td>
<td>13 (76)</td>
<td>12 (71)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>2 (6)</td>
<td>2 (12)</td>
<td>0</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hyperlipidemia, n (%)</td>
<td>3 (9)</td>
<td>2 (12)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>13 (38)</td>
<td>8 (47)</td>
<td>5 (29)</td>
</tr>
<tr>
<td>Oral contraceptive use, n (%)</td>
<td>17 (50)</td>
<td>10 (59)</td>
<td>6 (35)</td>
</tr>
<tr>
<td>History of syncope, n (%)</td>
<td>13 (38)</td>
<td>4 (24)</td>
<td>9 (53)</td>
</tr>
<tr>
<td>SSS-OI, points±SD</td>
<td>13.9±8.0</td>
<td>14.6±9.3</td>
<td>13.2±6.7</td>
</tr>
<tr>
<td>Migraine characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attacks last 6 mo, n±SD</td>
<td>9.9±10.3</td>
<td>13.5±12.8</td>
<td>6.3±6.2</td>
</tr>
<tr>
<td>Interval last attack to study, d±SD</td>
<td>32.9±39.1</td>
<td>18.5±22.4</td>
<td>47.3±47.0</td>
</tr>
<tr>
<td>Migraine prophylaxis, n (%)</td>
<td>7 (21)</td>
<td>5 (29)</td>
<td>2 (12)</td>
</tr>
<tr>
<td>Basic hemodynamics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean finger ABP, mm Hg±SD</td>
<td>77.4±9.1</td>
<td>77.8±8.2</td>
<td>77.0±10.2</td>
</tr>
<tr>
<td>Heart rate, beats/min±SD</td>
<td>66.7±6.7</td>
<td>67.2±7.2</td>
<td>66.2±6.3</td>
</tr>
<tr>
<td>Endtidal PO2, mm Hg±SD</td>
<td>33.5±5.8</td>
<td>32.9±5.9</td>
<td>34.1±5.7</td>
</tr>
</tbody>
</table>

MO indicates migraine without aura; MA, migraine with aura; SSS-OI, specific symptom score for orthostatic intolerance; ns, not significant; NA, not available.
clinical factors, including frequency of migraine attack, estimated number of lifetime attacks, smoking, use of oral contraceptives, history of syncope, β-blocker intake, or the symptom score of orthostatic intolerance, were found for any autoregulation parameter. There was also no significant association between individual autoregulatory ability and time since last attack or time to next attack for any autoregulation parameter.

Discussion
In this study, we used an advanced technique with triple simultaneous Doppler recordings of cerebellar and cerebral vessels. For the first time, we examined cerebellar autoregulation characteristics in migraine. We found no specific cerebellar autoregulatory deficit in patients with migraine. More static autoregulatory properties (index Dx) were, however, less intact in migraine with aura (MA) in the cerebellar and anterior circulation as compared with healthy controls.

Hemodynamics and Autoregulation in Migraine Patients Versus Controls
Compared with controls, the autoregulatory index Dx was significantly higher (indicating less autoregulation) in the PCA compared with the MCA and PICA in both controls and in MO patients. In MA patients, who had a higher Dx also in the PICA and MCA, this difference was smaller and not significant. In contrast, phase was slightly higher in the PCA compared with the MCA and PICA in both controls and patient groups, which indicates slightly better dynamic characteristics of autoregulation. Gain did not differ across vessels.

Relation of Autoregulation With Clinical Features in Migraine
With the present sample size, no significant associations with clinical factors, including frequency of migraine attack, lowest in the PICA, without significant differences between patients and controls (Table 2). The autoregulatory index Dx was higher (indicating less autoregulation) in the PCA compared with the MCA and PICA in both controls and in MO patients. In MA patients, who had a higher Dx also in the PICA and MCA, this difference was smaller and not significant. Phase and gain did not significantly across between MO or MA patients and controls (Table 2).

![Table 2. Cerebral Autoregulation in the MCA, PCA and PICA in Migraine vs Controls](http://stroke.ahajournals.org/)

<table>
<thead>
<tr>
<th>General hemodynamics</th>
<th>MCA, mean±SD</th>
<th>PCA, mean±SD</th>
<th>PICA, mean±SD</th>
<th>MCA vs PCA vs PICA</th>
<th>MO vs MA vs Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean CBFV (cm/s)</strong></td>
<td>57.5±7.3</td>
<td>39.0±4.9</td>
<td>38.8±5.4</td>
<td>P&lt;0.0001</td>
<td>ns</td>
</tr>
<tr>
<td>MO patients (n=17)</td>
<td>60.8±9.4</td>
<td>40±5.8</td>
<td>42.5±7.3</td>
<td>P&lt;0.0001</td>
<td>ns</td>
</tr>
<tr>
<td>MA patients (n=17)</td>
<td>60.7±8.0</td>
<td>42.2±7.0</td>
<td>41.1±4.4</td>
<td>P&lt;0.0001</td>
<td>ns</td>
</tr>
<tr>
<td>Controls (n=35)</td>
<td>60.7±8.0</td>
<td>42.2±7.0</td>
<td>41.1±4.4</td>
<td>P&lt;0.0001</td>
<td>ns</td>
</tr>
<tr>
<td><strong>Pulsatility index (n.u.)</strong></td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>MO patients (n=17)</td>
<td>0.64±0.10</td>
<td>0.56±0.11</td>
<td>0.46±0.09</td>
<td>P&lt;0.0001</td>
<td>ns</td>
</tr>
<tr>
<td>MA patients (n=17)</td>
<td>0.62±0.14</td>
<td>0.54±0.09</td>
<td>0.46±0.09</td>
<td>P&lt;0.0001</td>
<td>ns</td>
</tr>
<tr>
<td>Controls (n=35)</td>
<td>0.65±0.09</td>
<td>0.59±0.08</td>
<td>0.49±0.06</td>
<td>P&lt;0.0001</td>
<td>ns</td>
</tr>
<tr>
<td><strong>Phase (°)</strong></td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>MO patients (n=17)</td>
<td>40.4±19.5</td>
<td>50.8±23.6</td>
<td>43.4±20.1</td>
<td>P=0.0246</td>
<td>ns</td>
</tr>
<tr>
<td>MA patients (n=17)</td>
<td>32.9±20.3</td>
<td>42.0±18.4</td>
<td>36.3±16.0</td>
<td>P=0.0052</td>
<td>ns</td>
</tr>
<tr>
<td>Controls (n=35)</td>
<td>32.6±11.3</td>
<td>39.2±13.3</td>
<td>34.1±9.8</td>
<td>P=0.0005</td>
<td>ns</td>
</tr>
<tr>
<td><strong>Gain (n.u.)</strong></td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>MO patients (n=17)</td>
<td>0.83±0.21</td>
<td>0.82±0.21</td>
<td>0.81±0.24</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>MA patients (n=17)</td>
<td>0.99±0.18</td>
<td>0.91±0.25</td>
<td>1.00±0.32</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Controls (n=35)</td>
<td>0.96±0.21</td>
<td>0.88±0.19</td>
<td>0.84±0.17</td>
<td>P=0.0029</td>
<td>ns</td>
</tr>
</tbody>
</table>

MCA indicates middle cerebral artery; PCA, posterior cerebral artery; PICA, posterior inferior cerebellar artery; MO, migraine without aura; MA, migraine with aura; CBFV, cerebral blood flow velocity; n.u., normalized units; ns, not significant.

*P=0.0078 for MA vs control.
†P=0.0062 for MA vs control.
As a new finding, the correlation index Dx indicated less autoregulatory activity in the PCA both in controls and migraine patients. Others reported autoregulation during orthostatic challenge to be poorer in the PCA than in the MCA in healthy older, but not younger, persons. The index Dx does not reflect pure dynamic properties of autoregulation, such as transfer function phase and gain, but also of the response to slower ABP amplitude fluctuations or trends; it is thus a mixture of dynamic and more static properties of autoregulation. Taken together, it seems that the posterior circulation has good dynamic regulatory properties, but perhaps has less capacity for amplitude adaptations to slower blood pressure fluctuations, even in younger persons. Whether this is a result of the different intrinsic innervation of the posterior territory or other characteristics cannot be differentiated by our data.

Compared with controls, the rapid autoregulatory properties (phase and gain) were preserved in interictal migraine patients in the cerebellar, posterior, and anterior circulation. In contrast, the index Dx showed higher (ie, poorer) values in patients with migraine with aura for the PICA and MCA. Because of the already-higher Dx values in the PCA in controls, there were no differences for the PCA; however, there was also a trend toward higher Dx values in migraine patients. The observed absolute difference in Dx values does not indicate severe failure in all MA patients. Still, a considerable number of MA patients had Dx values in the MCA exceeding the cut-off of 0.24, above which significant hemodynamic impairment with a subsequent increased risk of ischemic events in carotid stenosis patients has been described.

The present findings of dysautoregulation in MA patients could represent a link to the observed increased stroke risk in this group. The observed dysautoregulation alone might, however, not be sufficient to cause ischemic strokes; however, it could be part of a cascade consisting of slow blood flow situations after migraine attacks and concurrent emboli because of coagulopathy or endothelial disorders. Because we did not observe a specific cerebellar deficit of autoregulation in MA patients, we assume that there are other factors contributing to the cerebellar predilection of border zone infarctions in migraine. One evident factor is the cerebellar angioarchitecture, which is characterized by lack of anastomoses between the cortical penetrator branches, and thus bears a specific vulnerability to hypoperfusion.

As a limitation, our results do not extend to autoregulation during a migraine attack. In the Cerebral Abnormalities in Migraine, an Epidemiological Risk Analysis (CAMERA) study, the attack frequency or number of lifetime attacks was associated with increasing frequency of deep white matter and cerebellar lesions. In our patients with interictal migraine, we could not find an association between individual autoregulation and either the time since last attack or frequency of attacks. There was also no link between individual autoregulation and the next attack during prospective follow-up. It might be speculated that autoregulation could be specifically altered during an attack because of increased autonomic dysfunction or because of cortical-spreading depressions. The effect of cortical-spreading depressions on human autoregulation is not known. Experimental data in the rat brain do not, however, suggest an impaired autoregulation after cortical spreading depression, although the vascular reactivity to CO\textsubscript{2} is impaired.

Previous Studies on Migraine and Autoregulation
To our knowledge, there are only 3 previous studies on cerebral autoregulation in migraine, all focused on the middle
cerebral artery. One study found the vasoconstrictory response during stress-induced ABP increases to being impaired in 15 MA patients.\textsuperscript{24} Using spontaneous ABP oscillations in 22 migraine patients (12 with MA), others found clearly pathological phase values in migraine patients in the MCA, both in MO and MA.\textsuperscript{25} This led to the assumption of a neurogenic disturbance of the autoregulatory mechanism because of migraine-associated autonomic dysfunction. We could not confirm these results and found phase, gain, and Dx in the MCA to be unchanged between persons with and without migraine.\textsuperscript{26} In that study, however, only 10 patients with MA were analyzed, and patients and controls were considerably older with a presumed lower disease activity.

There are a number of studies on the reactivity to carbon dioxide (CO2 reactivity) in migraine. CO2 reactivity itself is different from the complex intrinsic process of autoregulation.\textsuperscript{27} Generally in the interictal period, a broad overlap of CO2 reactivity with controls exists, and CO2 reactivity is often higher in MO and MA in the anterior and posterior circulation.\textsuperscript{27–29} During the attack, CO2 reactivity seems to be relatively unchanged, even in the basilar artery in a patient group predominantly without aura.\textsuperscript{30} Interestingly, a disturbed interictal CO2 reactivity in MA patients has been described in the basilar, but not in the middle, cerebral artery.\textsuperscript{6} Data on the neurovascular coupling (metabolic regulation) during visual stimulation protocols showed a higher flow activation in interictal migraine.\textsuperscript{31} Altogether, vasmotor function and vasoneural coupling are altered in migraine, but the underlying mechanisms are not fully understood. A possible hint could be that the pathophysiology of migraine is linked to monoaminergic brain stem nuclei involved with cerebral blood flow control.\textsuperscript{32}

### Migraine, Orthostatic Intolerance, and Cerebellar Autoregulation

Patients with migraine have a higher incidence of syncope and orthostatic intolerance despite normal results on interictal tilt-table testing.\textsuperscript{4} Therefore, we also assessed the history of syncope and a symptom score of orthostatic intolerance, both of which were also more pronounced in the migraine group.

We found, however, that individual cerebellar or cerebral autoregulation in interictal migraine patients was not associated with syncope or orthostatic intolerance. A persisting alteration in autoregulation thus is not likely to explain the orthostatic intolerance in migraine patients. This does not preclude paroxysmal disturbances in autoregulation related to migraine attacks or other disturbances.

### Limitations of the Study

Although we applied a novel triple simultaneous TCD protocol, including recording of the PICA,\textsuperscript{7} we have not been able to record additional vessels, such as the superior cerebellar artery or bilateral MCA and PCA. Focal asymmetries or changes of autoregulation thus cannot be excluded by this study. Furthermore, with the present comparatively small sample size, the lack of significant associations of specific clinical factors with autoregulation could be caused by a lack of statistical power.

### Conclusions

A specific cerebellar dysfunction of autoregulation does not exist in migraine. Certain autoregulatory properties, however, seem to be impaired in migraine with aura in cerebellar and anterior circulation. The cerebellar predilection of ischemic lesions in migraine with aura might thus be a combination of altered autoregulation and additional factors, such as the end artery cerebellar angioarchitecture. Altered autoregulation in migraine with aura could also represent a link to the observed increased stroke risk in this group of migraine patients. More research on autoregulation during or around migraine attacks is needed.

### Disclosures

None.

### References

Cerebellar and Cerebral Autoregulation in Migraine
Matthias Reinhard, Joscha Schork, Arthur Allignol, Cornelius Weiller and Holger Kaube

*Stroke*. 2012;43:987-993; originally published online February 16, 2012;
doi: 10.1161/STRK.111.644674

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2012 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/43/4/987