Dynamic Autoregulation Testing in Patients With Middle Cerebral Artery Stenosis

C. Haubrich, MD; W. Kruska; R.R. Diehl, PhD; W. Möller-Hartmann, MD; C. Klötzschi, MD

Background and Purpose—Cross-spectral analysis (CSA) of spontaneous oscillations in cerebral blood flow velocity (CBFV) and arterial blood pressure is considered a sensitive and convenient method for dynamic autoregulation testing. So far, it has been unclear whether CSA can be used to assess stenoses of the intracranial arteries.

Methods—This study for the first time applies CSA to 26 patients with low-, moderate-, and high-degree M1 stenoses and 14 normal control subjects. Using CSA, we studied spontaneous oscillations (M waves, 3 to 9 cpm; B waves, 0.5 to 3 cpm) in continuous recordings of transcranial Doppler of the middle cerebral artery and simultaneously recorded beat-to-beat blood pressure.

Results—A gradual decrease in pulsatility indexes confirmed the increasing hemodynamic relevance of the stenoses. Compared with control subjects, M-wave phase shifts between CBFV and blood pressure were gradually reduced with increasing degree of M1 stenosis (control subjects, 44.6±21.1°; high-degree stenosis, 16.7±19.5°). The phase relation between B waves in blood pressure and CBFV was shifted to positive values (low-degree stenosis, −9.7±108.4°; high-degree stenosis, 50.9±43.8°).

Conclusions—Because B- and M-wave phase shifts seem to characterize the degree of autonomy of CBFV modulation, this study suggests that with increasing degree of M1 stenosis, the arteriolar function is impaired. It shows that CSA is of indicative use for the assessment of intracranial artery stenosis. (Stroke. 2003;34:1881-1885.)

Key Words: autoregulation ■ middle cerebral artery ■ pulsatile flow ■ spectrum analysis ■ ultrasonography, Doppler, transcranial

Transcranial Doppler (TCD) has been shown to be an appropriate tool for the evaluation of cerebral autoregulation. Concerning autoregulatory measures such as acetazolamide vasoreactivity, the validity of TCD is comparable to other methods like the single photon emission technique. Although for many years the evaluation of cerebral autoregulation was performed at various steady-state levels of blood pressure, in the late 1980s, Aaslid and coworkers developed a dynamic autoregulation test that promoted the use of TCD for autoregulation tests. During stepwise deflation of leg cuffs, cerebral blood flow velocity (CBFV) was measured in response to rapid drops in mean arterial blood pressure (ABP). Newell et al.5 using the same paradigm, demonstrated that time courses in CBFV expressed as percentage deviations from the baseline were nearly identical to responses in cerebral blood flow measured directly within the internal carotid artery. TCD therefore is a good evaluation tool to test dynamic cerebral autoregulation. The rapid CBFV responses described above were also demonstrated under the Valsalva maneuver by Tiecks et al and under deep breathing at a rate of 6 breaths per minute by Diehl et al.7 By analyzing the phase relation between blood pressure changes and CBFV responses, Blaber et al,8 Diehl et al,9 Kuo et al,10 and Zhang et al11 demonstrated that even spontaneous blood pressure oscillations are followed by modulations in CBFV of the same frequency.

According to findings of Diehl et al,7,9 Mayer waves (M waves), spontaneous oscillations of CBFV in the range of 3 to 9 cpm in particular, carry information on cerebral autoregulation. Cross-correlation studies by Diehl et al,9,12 have suggested that these M waves are transmitted from ABP to CBFV following a high-pass filter model. The autoregulatory capacity is reflected by the positive phase relation between M waves of ABP (input function) and CBFV (output function). Confirming the assumption that M waves of ABP are regulated by peripheral autonomic nerve activity, Fernandez de Molina and Perl13 demonstrated that systemic ABP modulations are correlated with synchronous discharges of sympathetic neurons.13 Oscillations of slower frequency, B waves (0.5 to 3 cpm), which can also be detected in cerebral circulation, normally have no significant phase relation to ABP modulations of the same frequency.12 Microelectrode studies within the locus ceruleus and nuclei raphe by Meada et al14 provided evidence that B waves are generated by a
serotoninergic and monoaminergic brain stem generator. Their role is not yet understood. In contrast, the phase angle shift (\( \phi \)) between M waves in ABP and CBFV can be viewed as a surrogate measure for the filter function of cerebral autoregulation. According to Diehl and Berlit,\textsuperscript{12} phase angle shifts of \( \phi = 57.5 \pm 16.3^\circ \) can be considered normal reference values for M-wave phase shifts.\textsuperscript{12} Autoregulatory deficits such as those in carotid artery disease can be detected by significantly reduced phase angle shifts between M waves in ABP and CBFV.\textsuperscript{7,15,16} As demonstrated by Hu et al,\textsuperscript{15} this phase shift decline is positively correlated with a reduction in CO\(_2\) vasomotor reactivity.\textsuperscript{15} Reinhard et al\textsuperscript{16} found a good correlation between oscillation of 6 cpm and 2 different autoregulation indexes calculated from the Valsalva maneuver (Valsalva time index and autoregulation slope index) in patients with severe carotid stenosis and carotid occlusion.\textsuperscript{16}

Systematic studies on autoregulatory effects of an intracranial artery stenosis have not been published yet. According to recently presented data, the degree and progression of stenosis of the middle cerebral artery (MCA) have to be considered highly predictive for the occurrence of ischemic stroke.\textsuperscript{17} Using cross-spectral analysis (CSA) of spontaneous oscillations in CBFV and ABP, we examined whether the M-wave phase shift is dependent on the degree of M1 stenosis and whether B-wave characteristics are changed by intracranial artery disease.

### Subjects and Methods

#### Subjects

All 22 patients (13 male, 9 female; age, 61.7 ± 10.5 years [mean ± SD]) included in this study were found to have a stenosis of the M1 segment of the MCA detected by TCD. Bilateral M1 stenoses were found in 6 patients. Sides were counted separately. Degree of stenosis was classified according to the scheme of Sliwka et al.\textsuperscript{18} Peak flow velocities of >140 to 180 cm/s indicated a low degree of stenosis (group 1; n = 9); velocities to 220 cm/s, a moderate degree of stenosis (group 2; n = 9); and velocities >220 cm/s, high-grade M1 stenosis (group 3; n = 10). Six of 10 patients with high-grade M1 stenoses were examined by cerebral angiography, which confirmed the diagnosis. TCD of the MCA revealed an anterior cross flow in 4 patients with high-grade MCA stenosis and 1 patient with moderate-degree MCA stenosis. Patients with hemodynamically relevant ipsilateral carotid stenosis of >70% were not included in the study. Five of the 22 patients had further intracranial stenoses of low and moderate degree. Fourteen healthy adults (8 male, 6 female; age, 55 ± 12 years) served as control subjects. All subjects gave informed consent. Two and 5 days before the study, 2 patients had suffered acute small territorial ischemias ipsilateral to a moderate-degree M1 stenosis. A total of 9 ischemic strokes had occurred 1 to 11 years before our study: 6 lacunar and 1 small territorial infarction ipsilateral to a high-grade MCA stenosis, 1 lacunar ischemia within basal ganglia ipsilateral to a stenosis of moderate degree, and 1 lacunar ischemia ipsilateral to a low-grade stenosis. At the time of inclusion in our study, 11 of 22 patients with M1 stenosis had already been followed up for 4 months to 11 years by repeated TCD examinations. Vascular risk factors were noted in 18 of 22 patients: 15 patients had arterial hypertension, 8 had hypercholesterinemia, 4 had diabetes mellitus, and 5 had a history of smoking.

#### TCD Method

All Doppler measurements were continuously and simultaneously monitored by a Multidop X4 TCD machine (DWL, Sipplingen). The

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### Data Analysis

As a measure for the vascular resistance, we calculated the pulsatility index (PI) according to Gosling defined by the difference between systolic and diastolic extremes of CBFV divided by the mean CBFV. Each of these values was taken as mean over a 5-minute period in subjects in the supine position. In a second step, these curves were analyzed for spontaneous oscillations. Using fast Fourier transformation, we detected spontaneous oscillations in every ABP and CBFV data file. The sampling rate was 56 Hz. Coefficients of variation (CoV, as a percentage of mean values) were calculated as measures for B- and M-wave amplitudes. A sweep length of at least 3 minutes was required. This resulted in a minimal frequency resolution of 0.3 cycles per minute. By means of CSA and established mathematical equations,\textsuperscript{7} coherences and average phase angle shifts were calculated for CBFV and ABP oscillations in the frequency ranges of 0.5 to 3 cpm (B waves) and 3 to 9 cpm (M waves). The correlation between oscillations of ABP and CBFV is described as coherence and varies between 0 (variable phase difference) and 1 (constant phase difference). Phase lag between ABP and CBFV is defined by the phase angle shift, varying between 0° and 360°. Gain was computed as the ratio between CoV of CBFV and ABP. Phase shifts and gains between oscillations of ABP and CBFV were calculated only if the coherence was ≥0.4 because this algorithm provides the highest reliability to quantify the cross spectra.\textsuperscript{9,12} According to the high-pass filter model of cerebral autoregulation,\textsuperscript{7} autoregulatory capacity is reflected by the positive phase relation between oscillations of ABP (input function) and CBFV (output function). Therefore, the significantly reduced M-wave phase shift serves as a surrogate measure for the diminished autoregulatory capacity.

Analyses of TCD and ABP recordings were performed offline. Recordings were coded to ensure that data analysis was done without knowledge of the degree of M1 stenosis. All values are given as mean ± SD. Student’s \( t \) test was used to compare CoV, coherences, phase angle shifts, gains, and PI values between different degrees of
M1 stenosis and normal control subjects. Pearson’s correlation coefficients were calculated to provide quantitative measures for the dependence between autoregulatory parameters such as between PI values and the degree of M1 stenosis. For comparison of phase shift variance of B-waves between patients and control subjects, we used the variance analysis according to Bartlett. For each statistical test, \( P < 0.05 \) was defined as statistically significant. To evaluate the variance of B-waves between patients and control subjects, we used values and the degree of M1 stenosis. For comparison of phase shift dependence between autoregulatory parameters such as between PI and B-waves phase shifts (D). PIs and M-wave phase shifts are decreased with increasing degree of MCA stenosis. B-wave phase shifts turn to positive values with higher grades of stenosis and gradually reduced PI values.

Results

Each of the finally included 26 data files recorded ipsilaterally to the M1 stenoses of low \( (n=8) \), moderate \( (n=10) \), and high \( (n=8) \) degree depicts the time courses of ABP and CBFV in subjects in the supine position. An example is given in Figure 1, which shows B and M waves during a 6-minute period in a patient with high-grade stenosis of the right MCA. Two files had to be eliminated because of poor signal quality. One of the eliminated files was taken from a low-degree M1 stenosis and the other from a patient with moderate-degree M1 stenosis that was symptomatic with acute territorial stroke 5 days before the study. Twenty-six data files were taken from control subjects; 12 were examined bilaterally. The remaining 2 subjects had a suitable temporal bone window unilaterally.

Patients and control subjects significantly differed according to peak flow velocities within the M1 segment of the MCA. Peak flow velocities in patients with low-degree M1 stenoses were 159.4±11.3 cm/s compared with 196.6±13.8 cm/s in M1 stenosis of moderate degree and 297.4±49.7 cm/s in M1 stenosis of high degree. With increasing peak flow velocities at the stenosis, PI values were gradually reduced; the PI was moderately and inversely correlated with the degree of M1 stenosis \( (r=-0.44; \) see Figure 2C). In patients with high-grade M1 stenosis, the PI was significantly lower \( (PI=0.8±0.1, \ P<0.05) \) than in control subjects \( (PI=1.0±0.1; \) see the Table).

Also listed in the Table are CoV, coherences, and gains of M and B waves obtained by CSA. None of these parameters significantly differed between patients and control subjects.

By means of CSA, phase angle shifts of M waves (3 to 9 cpm) and B waves (0.5 to 3 cpm) were calculated. Prerequisite for the calculation of phase shifts is a coherence of ≥0.4 between ABP and CBFV for both types of oscillations. In control subjects, this requirement was fulfilled for 82.3% B-wave and M-wave data files (24 of 26). In patients, all M- and B-wave data files fulfilled this criteria. Analysis of M-waves showed a gradual decrease in phase shift angles between CBFV and ABP with increasing peak flow velocities of the MCA and a moderate and inverse correlation \( (r=-0.43, \ P<0.05) \) between both parameters in subjects in the supine position (Figure 2A). Minimal phase shift of 2°

<table>
<thead>
<tr>
<th></th>
<th>Control ((n=24))</th>
<th>Low ((n=8))</th>
<th>Moderate ((n=10))</th>
<th>High ((n=10))</th>
</tr>
</thead>
<tbody>
<tr>
<td>PI</td>
<td>1.0±0.1</td>
<td>1.0±0.2</td>
<td>1.0±0.2</td>
<td>0.8±0.1*</td>
</tr>
<tr>
<td>M waves</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CoV</td>
<td>3.3±1.5</td>
<td>2.4±0.7</td>
<td>2.6±1.2</td>
<td>3.0±1.7</td>
</tr>
<tr>
<td>COH</td>
<td>0.66±0.19</td>
<td>0.71±0.11</td>
<td>0.69±0.16</td>
<td>0.63±0.19</td>
</tr>
<tr>
<td>( \phi ), °</td>
<td>44.6±21.1</td>
<td>43.5±34.4</td>
<td>24.0±25.5*</td>
<td>16.7±19.5*</td>
</tr>
<tr>
<td>Gain</td>
<td>1.6±0.7</td>
<td>1.3±0.4</td>
<td>1.5±0.8</td>
<td>1.3±0.8</td>
</tr>
<tr>
<td>B waves</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CoV</td>
<td>4.7±2.7</td>
<td>4.3±1.1</td>
<td>3.8±1.5</td>
<td>3.9±1.4</td>
</tr>
<tr>
<td>COH</td>
<td>0.67±0.17</td>
<td>0.55±0.18</td>
<td>0.58±0.12</td>
<td>0.48±0.13</td>
</tr>
<tr>
<td>( \phi ), °</td>
<td>24.2±70.8</td>
<td>-9.7±108.4</td>
<td>48.9±61.6</td>
<td>50.9±43.8</td>
</tr>
<tr>
<td>Gain</td>
<td>1.5±0.8</td>
<td>1.7±0.8</td>
<td>1.7±1.3</td>
<td>1.6±0.9</td>
</tr>
</tbody>
</table>

COH indicates coherence between spontaneous oscillations in CBFV and ABP. Values are given for patients with coherence ≥0.4 as mean±SD.

*\( P<0.05 \), Student’s t test.
was determined in a patient with a peak flow velocity of 340 cm/s. In this case, M waves in ABP were almost passively followed by M waves in CBFV. Compared with control subjects (\(d=44.6 \pm 21.1\)) patients with high- and moderate-degree M1 stenosis showed significantly lower M-wave phase shifts (the Table). In patients with moderate- and high-grade M1 stenosis, the detection of a significantly decreased M-wave phase shift (cutoff threshold, \(d<30\)) reached sensitivities of 70% and 44%, respectively, and a specificity of 90% for stenoses of both degrees of stenosis.

With increasing peak flow velocities in the MCA, B waves showed a trend toward positive phase shift angles between ABP and CBFV (Figure 2B) and a decrease in SD (the Table). Whereas in low-degree M1 stenosis positive B-wave phase shifts were found in only 4 of 8 patients, analysis of moderate- and high-degree stenosis revealed positive phase shift values in 6 of 8 and 9 of 10 patients, respectively. Ipsilateral to low-degree M1 stenoses, B-wave phase shifts were distributed between \(-118.1°\) and \(98.7°\). In high-degree M1 stenosis, phase shifts varied between \(7.1°\) and \(93.8°\); in patients with M1 stenosis of moderate degree, phase shifts were between \(-12.7°\) and \(110.5°\). Both groups presented variances that, accordingly to Bartlett’s test, were significantly lower than in control subjects and subjects with low-degree M1 stenosis (\(P<0.05\)).

The patient with acute cerebral ischemia (2 days before the study) showed M-wave (\(\phi=37.7°\)) and B-wave (\(\phi=73.9°\)) phase shifts similar to those of all other patients with M1 stenosis of moderate degree.

When plotted against each other, the linear regression coefficients for PI values and M-wave phase shifts were not significant in the patient group (\(r=0.17\), \(P>0.05\)). This coefficient was higher and significantly different from zero (\(r=-0.45\), \(P<0.05\)) if B-wave phase shifts and PI values were compared (Figure 2D).

**Discussion**

It has been demonstrated in numerous studies that the analysis of spontaneous oscillations in CBFV and ABP has great potential in the evaluation of cerebral autoregulation.\(^7,8,10,11,15,16\) This technique allows us to identify impaired cerebral autoregulation quickly and easily, which was shown already for patients with carotid artery disease or autonomic failure. The dynamic relationship between CBFV and ABP can be modeled by a high-pass filter in the transmission of changes in arterial pressure to CBFV.\(^7,8,11\)

As suggested by Diehl et al,\(^7\) M waves as measured in this study are transmitted from ABP to CBFV following a high-pass filter model. The filter function is described by the phase shift between ABP and CBFV. In our study, M waves showed a gradual decrease in phase shift angles with increasing peak flow velocities in the MCA, indicating that cerebral autoregulation also is gradually altered with increasing degree of stenosis. Both parameters, M-wave phase shifts and MCA peak flow velocities, were significantly and inversely correlated. Patients with high and moderate degrees of M1 stenosis in particular were found to have a significant deficit of the filter function of cerebral autoregulation. Because this filter function can be attributed to the intracranial resistance vessels, our results point to an arteriolar dysfunction in these patient groups. Supporting this hypothesis, Hu et al\(^{15}\) showed that the phase shift decrease in the frequency range of 0.04 to 0.15 Hz is correlated with diminished vasomotor reactivity. Unlike vasomotor reactivity, analysis of ABP and CBFV cross spectra is a dynamic testing method that enables monitoring of cerebral autoregulation. In contrast to the application of extrinsic dilators (CO\(_2\) and acetazolamide) by means of dynamic autoregulation testing methods, the intrinsic flexibility of cerebral circulation can be measured.\(^{16}\) As a further advantage, compared with other autoregulation testing methods, CSA of spontaneous oscillation in ABP and CBFV does not require special maneuvers such as leg cuff deflation, the Valsalva maneuver, or deep breathing and thus needs less cooperation from patients. It has much less discomfort and risk for patients suffering from acute cerebrovascular diseases.

In contrast to M waves, which seem to follow a high-pass filter model of cerebral autoregulation, typically no significant relation can be seen between B waves in CBFV and ABP.\(^{12}\) This observation is supported by the model of an independent serotoninergic and monoaminergic B-wave generator within the brain stem by Meada et al.\(^{14}\) They showed that B waves occur simultaneously with neuronal discharges of the locus ceruleus. As measured in healthy control subjects, B-wave phase shifts are evenly scattered between \(-180°\) and \(180°\).\(^{12}\) Accordingly, control subjects and patients with low-grade M1 stenosis showed a large SD in phase shift angles between ABP and CBFV that was \(>2\)-fold of the mean. With increasing degree of stenosis, the B-wave phase relation was shifted to positive values and showed a significantly lower SD. Following the hypothesis that B waves in cerebral circulation are normally generated autonomously, the shift to a closer phase relation and positive phase shift values in moderate- and high-degree stenosis would suggest a gradual loss of autonomy. With respect to the model of Meada et al,\(^{14}\) these data would suggest that the arteriolar responsiveness to serotoninergic and monoaminergic stimuli can be impaired with increasing degree of M1 stenosis.

Distally to a hemodynamically relevant arterial stenosis, the velocity waveforms are usually damped, and the PI is decreased.\(^{20}\) Thus, the gradually decreased PI values pointed to an increasing hemodynamic relevance of the MCA stenoses included in this study that was correlated with elevated peak flow velocities. However, we could not find a significant correlation between PI values and M-wave phase shifts. Similar results were reported by Ley-Pozo et al.\(^{20}\) They observed that in patients with carotid stenosis of different degrees, the relationship between PI and vasomotor reactivity was not strong enough to predict the degree of vasomotor deficits by exclusively measuring the PI. Richards et al\(^{21}\) showed that according to various physiological conditions, PI changes do not differ significantly between autoregulating and nonautoregulating animals.\(^{21}\) Although there is no final explanation, data suggest that PI and M-wave phase shifts are related to different hemodynamic aspects of occlusive vascular disease. Whereas PI seems to be determined by static conditions as the hemodynamic relevance of stenosis, M-wave phase shifts are reflecting a more sensitive dynamic
component: the filter function of cerebral resistance vessels modulating CBFV oscillations. This difference between the 2 parameters may be the reason why significantly reduced PI values could be found only in high-grade M1 stenosis, whereas M-phase wave shifts were significantly decreased in moderate- and high-degree M1 stenosis. In contrast, B-wave phase shifts were moderately and inversely correlated with PIs determined ipsilaterally to the M1 stenosis. As animal experiments have proved and mathematical models have explained, a decrease in PI values within intracranial arteries is accompanied by a reduction in cerebral perfusion pressure, which usually is caused by a generalized relaxation of arterial smooth muscles and arteriolar vasodilatation. Applied to patients with occlusive MCA disease, this vasodilating effect could have impaired the arteriolar responsiveness to vasomotor stimuli and could be a reason for the loss of B-wave autonomy observed in this study. Accordingly, we hypothesize that B-wave autonomy, similar to cerebral perfusion pressure, depends directly on the integrity of arteriolar function.

Given that the subgroups of low-, moderate-, and high-degree stenosis were small, the conclusions drawn from this study are preliminary. Nevertheless, the present study shows for the first time that dynamic autoregulation testing can be used to distinguish intracranial artery stenoses of different degrees. Results indicate a gradual loss of autonomy in the regulation of CBFV with increasing degree of M1 stenosis. CSA of spontaneous oscillations in the range of M and B waves points to a disturbed filter function of cerebral autoregulation and an impaired response to monoaminergic and serotoninergic vasomotor stimuli. Both findings suggest a dysfunction of the intracranial small vessels with increasing degree of M1 stenosis.

References
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