Dynamic Autoregulation Testing in the Posterior Cerebral Artery

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Background and Purpose—Dynamic autoregulation has been studied predominantly in the middle cerebral artery (MCA). Because certain clinical conditions, ie, presyncopal symptoms or hypertensive encephalopathy, suggest a higher vulnerability of autoregulation within posterior parts of the brain, we investigated whether the cerebral blood flow velocity (CBFV) is modulated differently within the posterior cerebral artery (PCA).

Methods—Spontaneous oscillations of CBFV and arterial blood pressure (ABP) in the frequency range of 0.5 to 20 cycles per minute were studied in 30 volunteers (supine and tilted positions). Analysis was based on the “high-pass filter model,” which predicts a specific frequency-dependent phase and amplitude relationship between oscillations in CBFV to ABP. These parameters, characterized as phase shift angles and transfer function gains, were calculated from simultaneously recorded beat-to-beat blood pressure and transcranial Doppler signals of the PCA and MCA by means of cross-spectrum analysis.

Results—In the MCA and PCA, phase shift angles were decreased, and gains were elevated with increasing oscillation frequency. The PCA gain values in supine and tilted positions were significantly higher than in the MCA.

Conclusions—The phase and amplitude relationship between CBFV and ABP showed a frequency dependence in the PCA similar to that in the MCA. The study therefore suggests that the high-pass filter model of dynamic cerebral autoregulation can be applied to the PCA. In this model the generally higher gain values in the PCA indicate a lower damping of ABP oscillations, which are transmitted to the posterior part of cerebral circulation. (Stroke. 2004;35:848-852.)

Key Words: spectrum analysis ▪ autoregulation ▪ middle cerebral artery ▪ posterior cerebral artery ▪ ultrasonography, Doppler, transcranial

Dynamic autoregulation testing offers a noninvasive technique to study structure and efficiency of intracerebral hemodynamic regulation on a beat-to-beat basis. In the late 1980s, Aaslid and coworkers developed the first dynamic autoregulation test that promoted the use of transcranial Doppler ultrasonography as an autoregulation testing tool. It is now widely accepted that the cerebral blood flow velocity (CBFV) as measured by Doppler sonography is, under most conditions, proportional to the blood flow through the insonated vessel. Testing methods such as leg cuff deflation or Valsalva maneuver were applied to measure CBFV alterations in response to rapid changes in the mean arterial blood pressure. Blaber et al (1997), Diehl et al (1995), Kuo et al (1998), and Zhang et al (1998) reported that even spontaneous blood pressure oscillations are followed by modulations of CBFV of the same frequency.

By analysis of oscillations in 3 different frequency ranges between 0.5 and 20 cycles per minute (cpm), dynamic autoregulation testing may provide complex information on the intrinsic flexibility of cerebral circulation. Slow spontaneous oscillations of 0.5 to 3 cpm (B waves) are probably generated by monoaminergic or serotonergic nuclei within the brain stem. They are mediated by metabolic, myogenic, and endothelium-derived processes and are compensated by cerebral resistance vessels that act as low-pass filters in biological systems. Fast oscillations of 9 to 20 cpm termed respiratory waves (R waves) are generated by thoracic pressure changes. R waves and the sympathetically generated Mayer (M) waves of 3 to 9 cpm are transmitted from arterial blood pressure (ABP) to CBFV in a high-pass filter model, described in Subjects and Methods. The relation between these waves can be determined by cross-spectrum analysis. This method has also been applied for the detection of autoregulatory deficits in patients with extracranial or intracranial artery diseases.

To date, dynamic cerebral autoregulation has been studied almost exclusively in the middle cerebral artery (MCA). Only rare and contradictory information is available on autoregulation in the posterior part of the cerebral circulation. These studies show a lower cerebrovascular reserve capacity and a...
lower tolerance to hypotonia in the vertebrobasilar circulation. Recently, 2 studies on vasomotor reactivity in the basilar artery and dynamic autoregulation in the posterior cerebral artery (PCA) suggested a similar sufficiency of autoregulation in the anterior and posterior parts of the cerebral circulation. However, certain clinical conditions, ie, presyncopal symptoms or hypertensive encephalopathy, point to a higher vulnerability of cerebral autoregulation within posterior parts of the brain. We sought to investigate whether the CBFV is modulated differently within the PCA. Using cross-spectrum analysis, we compared spontaneous flow velocity modulations in the PCA and MCA.

Subjects and Methods

Subjects
Thirty adults (20 male, 10 female; mean±SD age, 65±10 years) were included in the study. All volunteers gave their informed consent to the application of transcranial Doppler monitoring and passive tilt as well as to the scientific use of the data. Inclusion criterion was normal extracranial and intracranial vascular status, including normal flow in the P1 and the P2 segments of the PCA on the basis of Doppler and duplex sonography results. Exclusion criteria were acute stroke, history of dysautonomia, or orthostatic dysregulation.

Transcranial Doppler Method
All Doppler measurements were continuously monitored by a Multidop X4 apparatus (DWL). The 2-MHz probes were fixed bilaterally over the temporal bone windows with the use of a headband (Marc 600, Spencer Technologies). Transcranial Doppler envelope curves were registered simultaneously in the M1 segment of the left MCA at a depth of 53 mm as well as in the P2 segment of the right PCA at a depth of 65 mm and stored on a hard disk together with the ABP. The location was verified by testing the vaso neural coupling, eg, the selective increase of CBFV in the PCA of at least 20% in the presence of a light stimulus. After a resting period of 15 minutes with the subject in the supine position, the recording was started. Measurements were taken 5 minutes before (supine position) and 6 minutes after tilting to an 80° head-up position.

ABP Measurement
Continuous beat-to-beat blood pressure (mm Hg) and pulse rate (beats per minute [bpm]) were registered tonometrically by piezo electric sensors placed at the wrist over the radial artery (CBM 7000, Colin Medical Instruments). During the study protocol, ABP was verified oscillometrically with a blood pressure cuff. Before measurements were taken, the tonometric sensor was calibrated for systolic and diastolic pressure.

Passive Tilt
The study was performed on a tilt table, which enabled a motor-driven change from a supine to an 80° upright position within 15 seconds. A securing belt was fastened over the thorax. For blood pressure measurements, the arm was fixed on a board in 80° abduction with the wrist at heart level.

Data Analysis
Data analysis was based on the high-pass filter model of cerebral autoregulation. According to this model, the autoregulatory filter effect is reflected by the positive phase relation between oscillations of ABP (input function) and CBFV (output function). B waves (0.5 to 3 cpm) are largely excluded, while ABP oscillations in the range of 3 to 20 cpm are transmitted completely to the output function. The high-pass filter model predicts a frequency-dependent relationship between the phases as well as between the amplitudes of ABP and CBFV. Parameters characterizing these relationships are the phase shift angle and the transfer function gain. With increasing oscillation frequency the phase shift angles are decreased, whereas the gains are elevated.

With the use of the fast Fourier transformation, spontaneous oscillations were detected in every ABP and CBFV data file. The sampling rate was 56 Hz, and the sweep length was at least 3 minutes. This resulted in a minimal frequency resolution of 0.3 cpm. Coefficients of variation indicate amplitudes of oscillations, given as percentage of the temporal mean value calculated between the lower and upper limits within a particular frequency range. These amplitude measures were calculated for spontaneous oscillations of CBFV as well as of ABP. By means of cross-spectrum analysis and established mathematics, coherence values and average phase shift angles between CBFV and ABP oscillations were calculated in the frequency ranges of 0.5 to 3 cpm (B waves), 3 to 9 cpm (M waves), and 9 to 20 cpm (R 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 oscillations of ABP and CBFV is defined by the phase shift angle varying between −180° and 180°. The gain was computed as ratio between coefficients of variation of CBFV and ABP. Phase shift angles 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.

The pulsatility index according to Gosling was calculated as a measure for vascular resistance, which is defined by the difference between systolic and diastolic extremes of CBFV divided by the CBFV mean. Analyses of Doppler and ABP recordings were performed offline. All values are given as mean±SD. The Student t test for paired samples was used for the comparison of coefficients of variation, coherence values, phase shift angles, gains, and pulsatility index values between the MCA and the PCA. For each statistical test, P<0.05 was taken as significant.

Results
Thirty data files depicting time courses of ABP and CBFV during 5 minutes of supine position and 6 minutes of head-up position were recorded simultaneously at the left MCA and the right PCA. An example is given in Figure 1. Four files depicting the time period of standing had to be eliminated because of a poor signal quality. Peak flow velocity measured in the supine position was 88.2±13.9 and 59.9±16.5 cm/s in the MCA and the PCA, respectively. When probands focused...
a bright lamp, flow velocities within the PCA were increased by 29.7±9.5% and by only 8.9±9.3% within the MCA. Both vascular territories did not differ according to the pulsatility index, which for the supine position was 0.9±0.2 (PCA and MCA).

By means of cross-spectrum analysis, phase shift angles and transfer function gains of R waves, M waves, and B waves were calculated. Examples for B and M waves are shown in Figure 1. The prerequisite for this calculation is a coherence of ≥0.4 between oscillations of ABP and CBFV. In the MCA and PCA, the majority of probands fulfilled these coherence criteria in the supine position and during passive tilt. In the supine position, the proportion of data files showing a significant coherence according to cross-spectrum analysis was 100% for M waves and R waves and 97% for B waves in the MCA. Proportions were slightly lower in the PCA (R waves, 97%; M waves, 93%; B waves, 83%). During passive tilt, proportions of significantly coherent data files for M and R waves were approximately the same and were only slightly lower for B waves (MCA, 85%; PCA, 77%).

Analysis of phase shift angles showed similar values for each oscillation frequency (Table 1). No firm phase relation could be determined between B waves. Phase shift angles in both vascular territories were widely scattered in the PCA (from -48.9° to 93.9°) and in the MCA (from -19.6° to 98.2°). With increasing oscillation frequency, phase angles showed a shift toward positive and smaller values. When the MCA and the PCA were compared for all frequency ranges, phase shift angles did not significantly differ between both parts of the cerebral circulation.

Analysis of the transfer function between amplitudes of ABP and CBFV oscillations revealed significant differences between MCA and PCA territories (Table 1). At any oscillation frequency, transfer function gains in the PCA were significantly higher than in the MCA (P<0.05). The fact that coefficients of variation, the amplitude measures of spontaneous oscillations, were also higher in the PCA supports the observation of generally higher transfer function gains in the PCA (Figure 2). The amplitude difference between CBFV oscillations in the PCA and MCA was significant for all frequency ranges (P<0.05). Similar to the MCA, in the PCA gain values rose with increasing oscillation frequency.

During passive tilt, the changes measured for systolic blood pressure levels (7.4±14.7 mm Hg), pulse rate (7.9±7.4 bpm), and MCA peak flow velocities (6.0±6.8 cm/s) were in accordance with the literature within physiological limits. Changes of peak flow velocities did not differ significantly from the MCA. None of the subjects complained about dizziness in the tilted position or fainted.

Passive tilt led to an increase of the coefficients of variation in the frequency ranges of M waves from 3.69±1.20% to 4.89±2.15% (P<0.05) in the PCA and from 2.59±1.14% to 3.61±2.41% (P<0.05) in the MCA. In addition, R waves significantly increased during orthostasis from 2.92±1.39° to 4.19±1.82° in the PCA as well as from 2.26±1.40° to 3.50±2.01° in the MCA. Coefficients of variation of B waves were comparatively stable (3.62±1.41% versus 3.57±1.53% for MCA and 5.43±1.91% versus 5.67±1.95% for PCA).

In the tilted position, transfer function gains for all frequency ranges again were significantly higher in the PCA than in the MCA (Table 2). This difference can be attributed to significantly larger values of coefficients of variation in the PCA.

| TABLE 1. Cross-Spectrum Analysis of the MCA and PCA (Supine) |
|-----------------|-----------------|-----------------|-----------------|-----------------|
|                | Coherence       | Phase Shift     | Variation       | Gain             |
| R waves         |                 |                 |                 |                 |
| MCA             | 0.78±0.15       | 10.7±11.5       | 2.26±1.40       | 1.90±0.43       |
| PCA             | 0.66±0.18       | 12.5±12.9       | 2.92±1.39*      | 2.72±1.13*      |
| M waves         |                 |                 |                 |                 |
| MCA             | 0.63±0.17       | 44.9±13.9       | 2.59±1.14       | 1.80±0.65       |
| PCA             | 0.58±0.13       | 39.4±23.8       | 3.69±1.20*      | 2.54±0.73*      |
| B waves         |                 |                 |                 |                 |
| MCA             | 0.48±0.09       | 39.3±58.9       | 3.62±1.41       | 1.59±0.72       |
| PCA             | 0.47±0.07       | 22.5±71.4       | 5.43±1.91*      | 2.34±0.82*      |

Variation indicates coefficient of variation given as a percentage; phase shift, phase shift angle in degrees. All values are given as mean ± SD. *P<0.05 according to Student’s t test.

| TABLE 2. Cross-Spectrum Analysis of the MCA and PCA (Head-Up) |
|-----------------|-----------------|-----------------|-----------------|-----------------|
|                | Coherence       | Phase Shift     | Variation       | Gain             |
| R waves         |                 |                 |                 |                 |
| MCA             | 0.83±0.17       | 13.9±12.6       | 3.50±2.01       | 2.53±0.83       |
| PCA             | 0.73±0.18       | 9.7±11.9        | 4.19±1.82*      | 3.24±1.13*      |
| M waves         |                 |                 |                 |                 |
| MCA             | 0.70±0.20       | 40.6±24.9       | 3.61±2.41       | 1.97±0.64       |
| PCA             | 0.63±0.18       | 36.2±28.8       | 4.89±2.15*      | 3.01±1.65*      |
| B waves         |                 |                 |                 |                 |
| MCA             | 0.53±0.16       | 48.2±56.5       | 3.57±1.53       | 1.53±0.70       |
| PCA             | 0.46±0.08       | 17.9±65.4       | 5.67±1.95*      | 2.38±1.08*      |

Variation indicates coefficient of variation given as a percentage; phase shift, phase shift angle in degrees. All values are given as mean ± SD. *P<0.05 according to Student’s t test.
PCA, as shown in Table 2, but not to a decrease in blood pressure variability under orthostasis. When we compared blood pressure variability in supine versus tilted positions, coefficients of variation in ABP were $1.32 \pm 0.98\%$ versus $1.58 \pm 1.00\%$ for R waves, $1.60 \pm 0.79\%$ versus $2.01 \pm 1.23\%$ for M waves, and $2.60 \pm 1.15\%$ versus $2.47 \pm 0.95\%$ for B waves. No significant difference could be seen between phase angles shifts in supine and tilted positions (MCA and PCA).

**Discussion**

Similar to the MCA, spontaneous oscillations of the PCA showed a decrease of phase shift angles and an elevation of transfer function gains with increasing oscillation frequency. These specific characteristics in the transmission of spontaneous ABP modulations to CBFV are key features of the high-pass filter model postulated by Diehl et al\textsuperscript{12} (1998) and Zhang et al\textsuperscript{9} (1998), which therefore can also be applied to the PCA.

According to this model, the phase shift angles between oscillations of CBFV and ABP in the frequency range of 3 to 20 cpm can be considered surrogate measures for the time delay of the autoregulatory response.\textsuperscript{9} The phase shift angles in our study suggest that this latency of cerebral autoregulation in the PCA territory can be considered as sufficient as in the MCA. As a further similarity of both vascular territories, the pattern of the phase shifts between the blood pressure and flow velocity oscillations was much less linear in the low-frequency B-wave range.\textsuperscript{21}

Concerning oscillations of all frequency ranges, transfer function gains in the PCA were significantly higher compared with the MCA. The transfer function gain quantifies the damping effect of cerebral autoregulation on changes in ABP and marks the efficiency of the autoregulatory response.\textsuperscript{9} Significantly higher transfer function gains indicate that in the PCA territory greater variations of ABP were permitted to pass through as variations in CBFV than in the MCA territory. This observation basically correlates to an impaired filter function of cerebral autoregulation. However, higher transfer function gains in the posterior cerebral circulation cannot be compared easily with an impaired filter function of cerebral autoregulation. In this case, the latency of the autoregulatory response would be altered before the autoregulatory efficiency was diminished.\textsuperscript{5} Furthermore, in the case of impaired cerebral autoregulation, the frequency-dependent nature of transfer function gains is changed.\textsuperscript{6} The different proportions of transfer function gains in the PCA and MCA rather seem to be related to intrinsic features of these vascular territories.

Even if a reduction of changes in cerebral blood flow is achieved by autoregulation, transfer function gains are almost always $>1.0\textsuperscript{23}$ because the vascular resistance is much higher for the static relation between ABP and CBFV than for oscillatory waves. Moreover, vascular resistance decreases with higher frequencies of the input signal. This observation gave rise to the concept of frequency-dependent dynamic input impedances. This concept elucidates why the relative change of oscillation amplitudes in CBFV may be higher than those of oscillations in blood pressure. It explains why transfer function gains increase with the frequency of ABP oscillations.\textsuperscript{12} The static component of the input impedance probably influences oscillations of all frequency ranges to the same extent. This component depends on several factors, for instance, resistance and compliance, which determine the resonance properties of the vascular bed.\textsuperscript{22} Thus, the generally higher gain values in the PCA compared with the MCA suggest different resonance properties for both parts of the cerebral circulation. In support of this hypothesis, the histological studies of Edvinsson et al\textsuperscript{23} (1976) have shown regional differences concerning the density of $\beta$-adrenergic, cholinergic, and serotoninergic innervation of the intracerebral vessels, which may have different influences on the cerebrovascular resistance in the anterior and posterior parts of the cerebral circulation. In addition, pharmacological studies have suggested regional differences in the sensitivity to vasoactive substances, eg, noradrenaline.\textsuperscript{24}

Similar to the supine position, transfer function gains of spontaneous oscillations were significantly larger in the PCA territory during passive tilt. Thus far, increased gain values during orthostatic stress were described only in patients with autonomic failure.\textsuperscript{6,21} Because blood pressure, heart rate, and clinical condition in our study gave no indication for dysautonomia, the higher transfer function gains under orthostasis point rather to a lower input impedance. This observation suggests a diminished attenuation of spontaneous oscillations in the PCA comparable to the supine position.

The transfer function gains in this study imply that in the PCA greater variations of ABP are permitted to pass through the autoregulatory filter. This might indicate a generally higher tolerance for lower perfusion pressures.\textsuperscript{6} During orthostatic stress, however, a diminished attenuation effect of cerebral autoregulation, if associated with a substantial fall of the steady state value of cerebral blood flow, may play a role in the pathogenesis of an orthostatic syncope.\textsuperscript{21} Moreover, the lower attenuation effect in the posterior part of the cerebral circulation may contribute to the fact that most clinical symptoms related to such a sudden decrease of cerebral blood flow are generated in the vertebrobasilar territory. This may explain why symptoms such as dizziness, nausea, and disturbed consciousness, which are related to the vertebrobasilar circulation, are predominant symptoms during syncope.\textsuperscript{17} On the other hand, the lower attenuation effect may possibly account for a higher vulnerability of the posterior cerebral circulation to a sudden rise in ABP. This hypothesis requires further research of hypertensive responses in the PCA.

In the PCA, phase shift angles and transfer function gains between oscillations of ABP and CBFV showed the same frequency dependence as in the MCA. This high-pass filter property of dynamic autoregulation is described in the PCA for the first time. The significantly higher transfer function gains in the supine position and under orthostatic stress indicate that damping effects of cerebral autoregulation in the PCA are lower than in the MCA territory. Our results therefore suggest that the high-pass filter model of dynamic cerebral autoregulation initially described for the MCA can
be applied to the PCA as well, but with a lower input impedance.

References
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