The Linear Behavior of the System Middle Cerebral Artery Flow Velocity and Blood Pressure in Patients With Migraine Lack of Autonomic Control?

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Background and Purpose—Migraine is considered a disorder of the autonomic nervous system. We used the frequency analysis of dynamic cerebral autoregulation to assess whether blood flow regulation disturbances can be found at the frequencies at which sympathetic and parasympathetic activity is present.

Methods—We measured simultaneously mean arterial blood pressure (BP) and the mean blood velocity (V) in the middle cerebral artery using transcranial Doppler ultrasound in 33 healthy controls (mean age ± SD: 36 ± 13 years) and in 22 patients with migraine (mean age: 39 ± 7 years). Apart from assessing spectral power density for BP and V, we calculated the transfer function parameters gain, phase, and coherence at the frequency range between 0.0 and 0.25 Hz.

Results—Compared with the controls, the spectral power density of BP and V exhibited a maximum magnitude of 10^26 in the migraine patients, whereas the maximum magnitude of BP and V in the controls was 10^23. Coherence showed no difference between patients and controls. Gain between BP and V increased in the controls at 0.01 Hz but was ≈ 0 or negative in the migraine patients over the whole frequency range (P < 0.01). The usually observed phase lead of V against BP was absent in the migraine patients in whom BP leaded V over nearly the whole frequency range (P < 0.01).

Conclusions—In terms of phase and gain, dynamic cerebral autoregulation is completely different in migraine patients compared with healthy subjects. Insofar, this can be interpreted as a lack of sympathetic and parasympathetic control of cerebral blood flow. (Stroke. 2005;36:1886-1890.)

Key Words: cerebral blood flow ■ migraine ■ ultrasonography, Doppler, transcranial

There is much evidence that migraine seems to be a state in which the cerebrovascular system shows dysfunctional behavior either during attacks or interictally. During a migraine attack, cerebral blood flow (CBF) techniques recorded CBF values as low as 23 mL/100 g per minute when aura symptoms were present.1 Transcranial Doppler (TCD) ultrasound investigations indicated that vasomotor reactivity as an index of cerebral autoregulation can be disturbed2 or is, in contrast, even better when compared with controls.3 The mechanisms of such blood flow dysfunction remain unclear. In recent years, migraine is more and more considered a vascular-mediated but not a primarily vascular-originated disorder. The success of triptans in the treatment of migraine attacks strongly indicates a common metabolic serotoninergic basis of the vascular mediated blood flow dysregulation regardless of their origin.

Migraine today is also increasingly more understood as a central nervous system disorder, eventually with a special association to the autonomic nervous system.4,5 One way to look at autonomic functions is using frequency analysis. Such a frequency-dependent approach seems reasonable because autonomic behavior is present in blood pressure (BP) and cerebral blood velocity (V) with sympathetic influence at frequencies in the range of 5 to 7 cycles per minute and parasympathetic influence at frequencies in the range of 10 to 20 cycles per minute.6–8 We hypothesize that migraine is a condition with autonomic failure; if so, autonomic failure in the regulation of CBF should be recognizable in the cerebrovascular system regulatory capabilities. Blood flow regulatory disturbances in migraineurs have been demonstrated to be similar the middle cerebral artery (MCA) and the posterior cerebral artery9 (PCA), indicating that flow regulatory failure is not present exclusively in the PCA but also in the MCA. Because of its better ability to be insonated, for our analysis, we used the blood flow in the MCA.

Materials and Methods

Normal Subjects

The group of normal subjects has been described in a previous report on transfer function estimation.10 To avoid redundancy, we reduce the report on them to the relevant points. Thus, with their written informed consent, 33 healthy subjects (18 male, 15 female, mean age ± SD, 36 ± 13 years [range 14 to 71 years]) without any cerebro-

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vascular risk factors or neurological diseases underwent simultaneous recordings of MCA blood flow V (Multi DopX4; DWL; 2 MHz probe) and of BP at the finger tip (Ohmeda 2300 Finapres) using the TCD device ability to record both signals simultaneously. The volunteers were laying in a supine position. The Doppler probes were mounted on a light metal TCD probe holder provided by the manufacturer, and both MCAs were identified according to commonly accepted criteria. Because of a poor temporal bone window at 1 side in 3 volunteers, only 1 MCA could be investigated, whereas in the remainder of 30 subjects, both MCAs could be investigated, resulting in a total of 63 insonated arteries. The subjects were comfortable with the setting over a period of 5 minutes before the recording of V and BP started for a period of 8 to 10 minutes. As a result, the transfer function parameter gain, phase shift, and coherence were unrelated to age and sex and did not show side-to-side differences, allowing us to report the result of the controls on all 63 vessels without separating into left and right or with respect to age and sex.

With the same setting, 22 patients (3 male, 19 female, mean age±SD, 39±7 years [range 23 to 52 years]) with migraine with and without aura according to the International Headache Society criteria\textsuperscript{11} were investigated. Ten patients experienced migraine without aura and 12 from migraine with aura. Other cerebrovascular risk factors were not present. All patients gave their written informed consent, and both MCAs could be insonated in each patient, resulting in 44 investigated vessels. All recordings were performed on patients without any migraine attacks within the last 24 hours and without taking any regular medication including prophylactic drugs.

Data Preparation
For all data analysis, Matlab R12 (The MathWorks Inc) was used. The TCD device collects the input data with a frequency of 50 data points per second. We reduced the amount of data by averaging 100 data points to 1 new data point every 2 seconds. The new data points were normalized to their means [eg. (x-mean)/mean], and linear trends were removed by subtracting the straight line of best fit. We used a period of 8 minutes for analysis, which was reduced to 240 data points. To compare the recordings with a standard length of observation time, the first 128 data points of each time sequence were used (corresponding to a time period of 256 seconds).

To calculate the coherence and the transfer function between BP and V, we used Welch’s averaged periodogram method by which input (BP) and output (V) signal sequences are divided into subsets of equal length (64 seconds; thus, the lowest frequency resolution is \( \approx 0.015 \text{ Hz} \)). Using Hanning windows, a data overlap of 50\% between 2 consecutive subsets was achieved. Using fast Fourier transformation, the power spectrum of BP (\( G_{bpbp}(f) \)) and of V (\( G_{vv}(f) \)) and the cross-spectrum between BP and V (\( G_{bpv}(f) \)) were calculated for each subset. The coherence function (\( \text{Coh}(f) \)) was estimated by \( \text{Coh}(f) = |\text{Gbpv}(f)|^2 / G_{vv}(f) \times G_{bpbp}(f) \).

Coherence values ranged between 0 and 1; 0 means no correlation, and 1 means perfect stability of the phase shift between input (BP) and output (V). Transferred to cerebral autoregulation, 0 means cerebral perfusion lacks any relation to BP, and 1 means V follows BP changes with a perfectly stable phase shift. Such a constant pressure-dependent perfusion is considered a total loss of cerebral autoregulation.

The complex transfer function (\( \text{TF}(f) \)) is estimated by \( \text{TF}(f) = G_{bpv}(f) / G_{bpbp}(f) \), from which the gain is calculated and the phase shift is extracted from the real and the imaginary part of \( \text{TF}(f) \).

The used software calculates \( \text{TF}(f) \) according to the linear model \( y(t) = G(f) \times u(t) \), which means that the output variable \( y(t) = (V) \) is modeled by the linear transfer function \( G \) applied to the input signal \( u(t) = (BP) \).

Statistical Analysis
The data are reported as mean value and SD. Transfer function and coherence results are plotted over the frequency range of 0 to 0.25 Hz. For simplicity of comparison, we plotted the curves of the mean values only. In the software, the frequency range contains 65 defined frequency points. For comparisons between the controls and the patient group, unpaired \( t \) test was used. We considered differences substantial when the \( t \) tests indicated significant differences over a broader frequency range with the understanding that a significant \( t \) test result at 1 or another frequency does not mean a physical finding. Thus, the reported limits of a frequency range indicate that all tests in the mentioned frequency range showed significant differences. We are aware that the testing includes multiple comparisons. To classify differences substantially, we considered the level of significance at each \( t \) test as \( P \leq 0.01 \).

Results
Mean BP was \( 88 \pm 9 \text{ mm Hg} \) in the controls, and it was \( 89 \pm 9 \text{ mm Hg} \) in the migraineurs. There were no differences between patients with and without aura regarding mean BP, mean values of blood flow velocities, and transfer function estimations and coherence. Thus, we report the results of both groups together when comparing with normal subjects.

Compared with the controls, spectral power density of the BP signal and of the V signal was significantly higher in the migraine patients (Figures 1 and 2). In migraineurs, the differences in the absolute values of spectral power density compared to Figure 2.
was an power increase from BP to V, whereas there was a small power decrease in the migraine patients. This lack of power increase is reflected in the gain function of transfer function estimation. The gain increase (Figure 3) was minimum to absent over the whole frequency range in migraine patients, whereas it was high in the frequencies >0.01 Hz in the controls. We believe this a real result because coherence function (Figure 4) was not significant different between the controls and the patients. Very surprisingly, phase shift behavior was significantly different between 0.03 and 0.22 Hz, with an absent or a mostly negative phase shift in the patients compared with the controls (Figure 5).

The large spectral power magnitude differences forced us to consider technical reasons for these differences. Therefore, we estimated the spectral power from the unfiltered original data, too, and from data that have been not smoothed or detrended. The difference remained for all analyses. Second, we collected data from 5 new control subjects. In these subjects, it turned out, the spectral power content was equal to the used control subject recordings.

**Discussion**

Our approach to look at cerebral autoregulation in migraineurs showed 2 striking results. First, the phase and gain behavior was completely different compared with the controls, and second, the spectral power magnitudes of BP and V were very much increased in the migraineurs.

One interpretation of the transfer function approach is to consider the cerebrovascular system as a high-pass filter, which delays low frequencies and lets pass through the higher beat-by-beat–depending frequencies.6,7 Phase and gain are 2 parameters to describe the filter. The findings in our controls can be interpreted in exactly that way. The V lead over BP in the controls means that slow BP changes are delayed before they enter the cerebrovascular bed. In migraineurs, the phase shift indicates that BP is always earlier in time than V, hence BP is driving V. If the filter indicates the presence or absence of cerebral autoregulation, it is evident that migraine patients lack autoregulation. An argument in favor of a real blood flow regulation failure are the findings of Nedeltchev et al.9

**Figure 2.** Power spectral density of mean arterial BP and mean blood V in migraine patients (top and bottom). Note the large difference in the absolute values of spectral power density compared to Figure 1.

**Figure 3.** Comparison of gain function between controls and migraine patients.

**Figure 4.** Comparison of coherence function between controls and migraine patients.
who investigated the flow response behavior in the MCA and PCA in migraineurs (during the attack-free interval) compared with healthy controls. After applying visual stimuli at a frequency of 0.05 Hz, the blood V in the MCA decreased after 5 stimuli in the healthy subjects, whereas it remained increased and unchanged in the migraineurs. In the PCA, blood V remained elevated in both groups as long as the stimuli were present. Thus, the behavior in the MCA of the migraineurs was characterized by a failure to habituate V to the stimulus.

One possible explanation of this failure to habituate could be the role of the autonomic mechanisms participating in the autoregulatory processes. The most impressive changes in terms of phase shift and gain in our patients were seen at frequencies believed to be influenced by such autonomic mechanisms. Zhang et al.\textsuperscript{12} induced in healthy subjects a total sympathetic and parasympathetic blockade of the cerebral vessels by trimethaphan and observed a significant decrease of phase and gain (but not coherence) in the frequency range 0.015 Hz. Our findings in the migraineurs are surprisingly congruent to these results. Insofar, our phase and gain results in the frequency range <0.015 Hz could be considered as a defective sympathetic innervation in the migraine patients. In disagreement with Zhang et al.,\textsuperscript{12} we found additional changes in the parasympathetic frequency range >0.015 Hz. However, this result is supported by a recent study on pupillary light reflex, which uncovered the presence of parasympathetic disturbances in pupil motion regulation in patients with migraine.\textsuperscript{13} Another explanation could be delineated by the concept of migraineous cortical hyperexcitability.\textsuperscript{14–17} This concept implicates that there could be a lack of cortical inhibition of neuronal activity, leading to a prolonged and widely distributed increased blood flow demand. In such a condition, an increase of blood flow inducible by physiological stimuli\textsuperscript{p} or carbon dioxide\textsuperscript{18} is less pronounced, mimicking a disturbed vasomotor reactivity and, hence, a disturbed cerebral autoregulation. In this model, the stimuli dependency of the findings of Nedeltchev et al.\textsuperscript{p} could be attributable to the lack of adequate inhibition.

A third parameter to describe cerebrovascular autoregulation as a filter is coherence, an index of how constant the correlation between V and BP over time is.\textsuperscript{19} This filter is active only at very low frequencies (<0.05 Hz), at which autoregulatory changes become more and more influenced by slow rhythmic oscillations.\textsuperscript{20,21} The lack of correlation between V and BP means a perfect state of autoregulation, whereas a high coherence indicates a close correlation between V and BP. A strong correlation over time corresponds closely to our understanding of a poor state of autoregulation: flow or its derivative over time, V, is strictly driven by BP. In terms of this filter parameter autoregulation remains intact even when the autonomic innervation of the cerebral vessels is completely blocked,\textsuperscript{12} a finding that may lead to suggestions that coherence reflects another blood flow regulation mechanism, which is less influenced by the autonomic nervous system.

The other striking difference between patients and controls is the spectral power magnitude of the BP signal in the patients. Considering that BP drives brain perfusion (which is the pathological result of our study as indicated by the phase shift results in the migraine patients), the high energy content of the BP signal has to be balanced by the autoregulatory system. Our results share a light toward the possibility that the primarily pathogenetic factor is within the BP controlling system, the failure of which allows to produce such a high energy content in the BP; and the cerebrovascular system seems not to be able to sufficiently handle such a power. It remains undetermined by our data whether an autonomic failure can be a reason to produce such a power content. Another explanation could be that low BP itself is accompanied by an increased power content, as studies with lowering the BP level by applying lower body negative pressures in healthy subjects might suggest;\textsuperscript{22} however, this condition in the healthy subjects did not change cerebral autoregulatory capabilities.

Finally, we did not find differences between migraineurs with and without aura. Whether migraine with and without aura are different entities is still under discussion. Besides the existence of aura, no significant differences in the clinical phenotypes have been described; whereas genetic twin studies as well as genetic association studies have shown a higher hereditary risk for migraine patients with aura compared with those without aura.\textsuperscript{23,24} Regarding TCD studies, resting blood flow velocities did not show differences between patients with and without aura. Differences have been found when the cerebrovascular system was stimulated by physical activity or carbon dioxide.\textsuperscript{18,25} However, these results were contradictory: although Heckmann et al.\textsuperscript{25} found a disturbed vasomotor reactivity in the MCA of patients with aura compared with those without aura, Silvetrini et al.\textsuperscript{18} described such a difference only for the basilar artery vasomotor reactivity but not for the MCA.

In conclusion, phase and gain dynamics of cerebral autoregulation seem to be completely different in migraine patients compared with healthy subjects and show some analogy to findings in healthy subjects with experimentally induced total autonomic blockade of the cerebral vessels. This might be interpreted as a lack of sympathetic and
parasympathetic control of CBF regulation. Further studies with other sympathetic or parasympathetic trigger factors in migraineurs should elucidate their autoregulatory patterns.

References
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