

Changes in Linear Dynamics of Cerebrovascular System After Severe Traumatic Brain Injury

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Background and Purpose—We sought to describe the dynamic changes in the cerebrovascular system after traumatic brain injury by transfer function estimation and coherence.

Methods—In 42 healthy volunteers (mean±SD age, 37±17 years; range, 17 to 65 years), spontaneous fluctuations of middle cerebral artery blood flow velocity and of finger blood pressure (BP) were simultaneously recorded over a period of 10 minutes under normocapnic and hypocapnic conditions to generate normative spectra of coherence, phase shift, and gain over the frequency range of 0 to 0.25 Hz. Similar recordings were performed in 24 patients with severe traumatic brain injury (Glasgow Coma Scale score ≤8; mean±SD age, 50±20 years) serially on days 1, 3, 5, and 8 after trauma. Cranial perfusion pressure was kept at >70 mm Hg. Each blood flow velocity/BP recording was related to the presence or absence of middle cerebral artery territory brain parenchyma lesions on cranial CT performed within a close time frame.

Results—In controls, hypocapnia decreased coherence (0.0 to 0.20 Hz), increased phase shift (0.0 to 0.17 Hz), and decreased gain in the frequency range of 0.0 to 0.11 Hz but increased gain at frequencies of 0.20 to 0.25 Hz ($P<0.01$ for all frequency ranges reported). In patients with traumatic brain injury, 102 investigations were possible. Compared with controls, coherence was increased in the frequency range <0.03 Hz and between 0.13 and 0.25 Hz in both normocapnia and hypocapnia, irrespective of the CT findings. Gain was unchanged in normocapnia and in the absence of a CT lesion. Gain was decreased in hypocapnia at frequencies >0.12 Hz irrespective of the presence/absence of a CT lesion. Phase shift decreased rapidly between 0.06 and 0.13 Hz under hypocapnic conditions and under normocapnic conditions in the presence of a CT lesion ($P<0.01$).

Conclusions—Use of spontaneous fluctuations of blood flow velocity and BP to assess the cerebrovascular system dynamically requires consideration of the $Paco_2$ level. In different conditions, including severe traumatic brain injury, the cerebrovascular system behaves linearly only in parts of the investigated frequency range. (*Stroke*. 2003;34:1197-1202.)

Key Words: cerebral circulation ■ head injury ■ transfer ■ ultrasonography, Doppler, transcranial

Cerebral autoregulation (CA) is the ability of the cerebrovascular system to provide a constant cerebral blood flow (CBF) supply to the brain in the presence of spontaneous blood pressure (BP) changes between 50 and 150 mm Hg (mean arterial BP). With the use of transcranial Doppler ultrasound (TCD), the integrity of CA is usually assessed by 2-point static measuring methods by which CBF velocity is measured at rest and after a challenge induced by either BP changes, CO_2 , or acetazolamide application as stressor.¹⁻³ In recent years, the fast time resolution of TCD had made possible the development of dynamic methods for this purpose. These dynamic methods analyze the relationship between CBF velocity changes and BP changes by using either differential equations empirically^{4,5} or transfer function analysis.⁶⁻⁹ The underlying hypothesis is to accurately model

mathematically the intact system and to consider deviations as an impairment of the system involved in CA. Tiecks et al⁵ modeled CBF velocity changes as a second-order linear differential equation describing response to a rapid BP drop and classifying the state of CA according to the time required by CBF velocity to return to its level before the decline in BP. Using transfer function analysis, other groups consider CA a frequency-dependent filter system influencing the relationship between corresponding frequencies in BP as input and CBF velocity as output.^{6-8,10,11} The filter characteristics and hence the behavior of the filtering system are described by phase shift, gain, and coherence. Phase shift is a correlate of the time delay between CBF velocity and BP; the time delay is low at high frequencies, indicating that BP changes are transmitted to CBF velocity; the time delay is high at low

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frequencies, indicating that BP changes are delayed before they affect CBF velocity. The energy (gain) transmitted from BP to CBF velocity is increased by the system at high frequencies but is clearly decreased by the system at low frequencies. Coherence describes the constancy over time of the phase relationship between CBF velocity and BP. A low coherence, as found in the low-frequency range, indicates low phase shift stability; a high coherence, as found at higher frequencies, indicates a very stable relationship. In the frequency-dependent model, any loss of these filter characteristics, such as lack of time delay at low frequencies, lack of gain increase at higher frequencies, or high coherence at low frequencies, can then be interpreted as a loss of CA.

A correlation exists between the dynamic CA assessment methods and the static methods,^{5-7,12,13} prompting suggestions that the dynamic approach to assess CA may be clinically useful.^{6,8,14-16} However, clinical experience with the dynamic CA assessment methods is limited. The static CA assessment methods provide convincing between-method comparisons. Such comparisons between different dynamic models suggest that the dynamic approach to CA is poorly understood and provides only fair between-model reproducibility.⁸ Such a result may lead to doubts regarding whether the dynamic approaches are truly able to test CA or may suggest that the different models investigate different aspects of the system.⁸ The aim of our study was to characterize the changes in cerebrovascular system behavior after severe traumatic brain injury (TBI) with the understanding that, if the observed changes are in agreement with similar observations in other diseases, such a model-dependent reproducibility would strengthen the assumption that the dynamic approach can reflect the behavior of the system that controls CA.

Subjects and Methods

Normal Subjects

With their written informed consent, 42 healthy subjects (23 male, 19 female; mean±SD age, 37±17 years; age range, 14 to 71 years) without any cerebrovascular risk factors or neurological diseases underwent simultaneous recordings of middle cerebral artery (MCA) CBF velocity (Multi DopX4, DWL; 2-MHz probe) and of BP at the finger tip (Ohmeda 2300 Finapres) with the use of TCD. End-tidal PaCO₂ was measured with Enhancer 3000sx equipment (Diversified Diagnostic Products Inc). The volunteers were lying in the supine position. The Doppler probes were mounted on a light metal transcranial Doppler probe holder provided by the manufacturer, and both MCAs were identified according to commonly accepted criteria. Because of a poor temporal bone window on 1 side in 3 volunteers, only 1 MCA was investigated in these subjects, while in the other subjects both MCAs were investigated, resulting in a total of 81 insonated arteries under normocapnic conditions. When the subjects signaled that they were comfortable with the setting, the recording of CBF velocity and BP began. During the 10-minute recording period, end-tidal PaCO₂ values were collected every 20 seconds and summarized as a mean over the whole time period. After 10 minutes the recording was stopped, and the volunteers were asked to breathe in a forced manner. When forced breathing had induced a steady state of fallen end-tidal PaCO₂ that could be maintained comfortably by the volunteers, they were asked to maintain the intensity of forced breathing, and the recording of CBF velocity and BP was started again for 10 minutes. The end-tidal PaCO₂ values were again collected every 20 seconds and are reported as the mean value. Nine subjects refused to hyperventilate in the setting, allowing

a direct comparison between normocapnic and hypocapnic conditions in 63 arteries. Because hypoventilation is usually not used in the treatment of acute severe TBI, we did not investigate hypercapnia.

TBI Patients

All procedures involved in the investigation of the TBI patients were approved by the local ethics committee. We included 24 patients (19 male, 5 female; mean±SD age, 50±20 years) with severe TBI (Glasgow Coma Scale score ≤8)¹⁷ whom we intended to investigate repeatedly on days 1, 3, 5, and 8 after trauma using the same TCD device and the same probe holder and by feeding the arterial line signal into the TCD device. All patients had received a Spiegelberg III system to be used as an external ventricular drainage device and to measure intracranial pressure (ICP). With the ICP known, cerebral perfusion pressure as the difference between mean arterial BP and ICP was maintained at >70 mm Hg with the use of catecholamines and/or mannitol when necessary; other vasoactive substances such as glyceryl trinitrate or nimodipine were not used. All patients received regular cranial CT scan follow-ups within a close time frame with the TCD studies. At the time of investigation, the actual ICP was noted, and the actual PaCO₂ was measured by blood gas analysis. TCD recordings were possible on 44 MCAs; the remainder were excluded for reasons such as lack of a temporal bone window or TCD probe movements due to patient movement. The recording time ranged between 6 and 10 minutes. Although CT scanning is only a fair method to assess the total traumatic lesion extent, it can provide first insights into the relationship between brain lesion size and CA disturbances. To compare the CA assessment results with the morphological CT findings, we classified the brain parenchyma of each MCA territory in terms of whether or not a traumatic brain lesion was present. A traumatic subarachnoid hemorrhage (SAH) was present in 32 of 102 possible comparisons. In each SAH-positive CT scan, the parenchyma in the MCA territory under consideration showed a traumatic lesion, leading us to relate the SAH to the injured parenchyma in each case.

Data Preparation

For all data analyses, 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. A 6-minute recording time was reduced to approximately 200 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 CBF velocity, we used Welch's averaged periodogram method, by which input (BP) and output (CBF velocity) signal sequences are divided into subsets of equal length (64 seconds; thus, the lowest frequency resolution is approximately 0.015 Hz). With the use of Hanning windows, a data overlap of 50% between 2 consecutive subsets was achieved. With the use of fast Fourier transformation, the power spectrum of BP [G_{bp}(f)] and of CBF velocity [G_{cv}(f)] and the cross-spectrum between BP and CBF velocity [G_{bvp}(f)] were calculated for each subset. The coherence function [Coh(f)] was estimated as follows:

$$\text{Coh}(f) = |G_{bvp}(f)|^2 / G_{bp}(f) \times G_{cv}(f)$$

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

CA. The complex transfer function [TF(f)] is estimated as follows:

$$TF(f) = G_{bpv}(f) / G_{bpbp}(f)$$

from which the gain is calculated and the phase shift is extracted from the real and the imaginary part of TF(f). The software we used calculates TF(f) according to the linear model

$$y(t) = G(f) \times u(t)$$

in which 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 \pm SD values. 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 we used, the frequency range contains 65 defined frequency points. At each frequency point, linear regression analysis was used to test for age and sex dependency for both normal subjects and TBI patients. To compare the effect of the P_{aCO_2} changes within the controls, we used the paired t test. For comparisons between controls and the different patient groups, we used the unpaired t test. We considered differences to be substantial when the t tests indicated significant differences over a broader frequency range with the understanding that a significant t test result at one 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 as substantial, we considered the level of significance for each t test as $P \leq 0.01$.

Results

Normal Subjects

Under normocapnia, end-tidal P_{aCO_2} was 34 ± 3 mm Hg and mean arterial BP was 88 ± 9 mm Hg. Under hypercapnia, P_{aCO_2} was lowered to 21 ± 3 mm Hg, while mean arterial BP remained constant (89 ± 9 mm Hg). Neither coherence, gain, nor phase shift showed a dependence on age or sex. Hypocapnia substantially changed all 3 parameters: coherence (Figure 1A) was reduced in the frequency range between 0.0 and 0.20 Hz; gain (Figure 1B) decreased between 0.0 and 0.11 Hz but increased from 0.20 to 0.25 Hz; and phase shift (Figure 1C) was increased between 0.0 and 0.17 Hz ($P < 0.001$ over each frequency range).

TBI Patients

Of the 24 patients, 5 were investigated once, 6 twice, 5 three times, and 8 four times. The trauma data were analyzed in terms of 3 considerations: first, we analyzed whether the patients were normocapnic or hypocapnic; second, recordings were summarized regarding whether or not a CT lesion was present, irrespective of the day of the recording; and third, the recordings were summarized at each day of recording, irrespective of the CT findings. The 102 possible comparisons were recorded on day 1 ($n=29$), day 3 ($n=29$), day 5 ($n=25$), and day 8 ($n=19$). To classify normocapnia and hypocapnia, we used a threshold of P_{aCO_2} of 36 mm Hg (hypocapnia, < 36.0 mm Hg). According to the actual P_{aCO_2} , 56 examinations were performed under normocapnic conditions and 46 under hypocapnic conditions. A traumatic SAH was present in 17 investigations under normocapnic conditions and in 15 investigations under hypocapnic conditions. Mean MCA flow velocity was 89 ± 15 cm in the absence of SAH and 92 ± 14

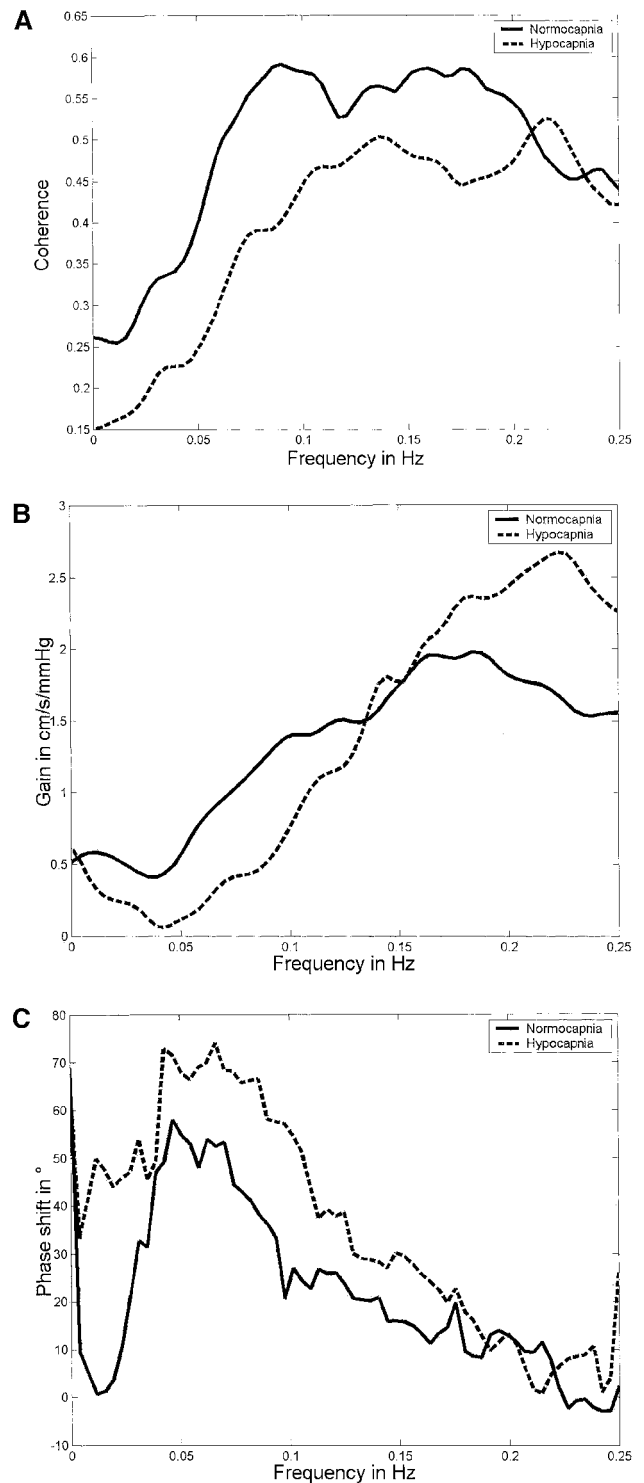


Figure 1. Changes of coherence (A), gain (B), and phase shift (C) during hypocapnia compared with normocapnia. Curves represent mean values. Over a broad range of frequencies, coherence is significantly reduced and phase shift is increased. Gain is significantly reduced at < 0.11 Hz but increased at > 0.20 Hz.

cm in the presence of SAH. In each group (those without and those with an SAH) there was 1 investigation during which a slight vasospasm according to Doppler criteria (mean flow velocity > 120 cm/s) was present. In every instance cranial perfusion pressure was ≥ 70 mm Hg, and the maximum

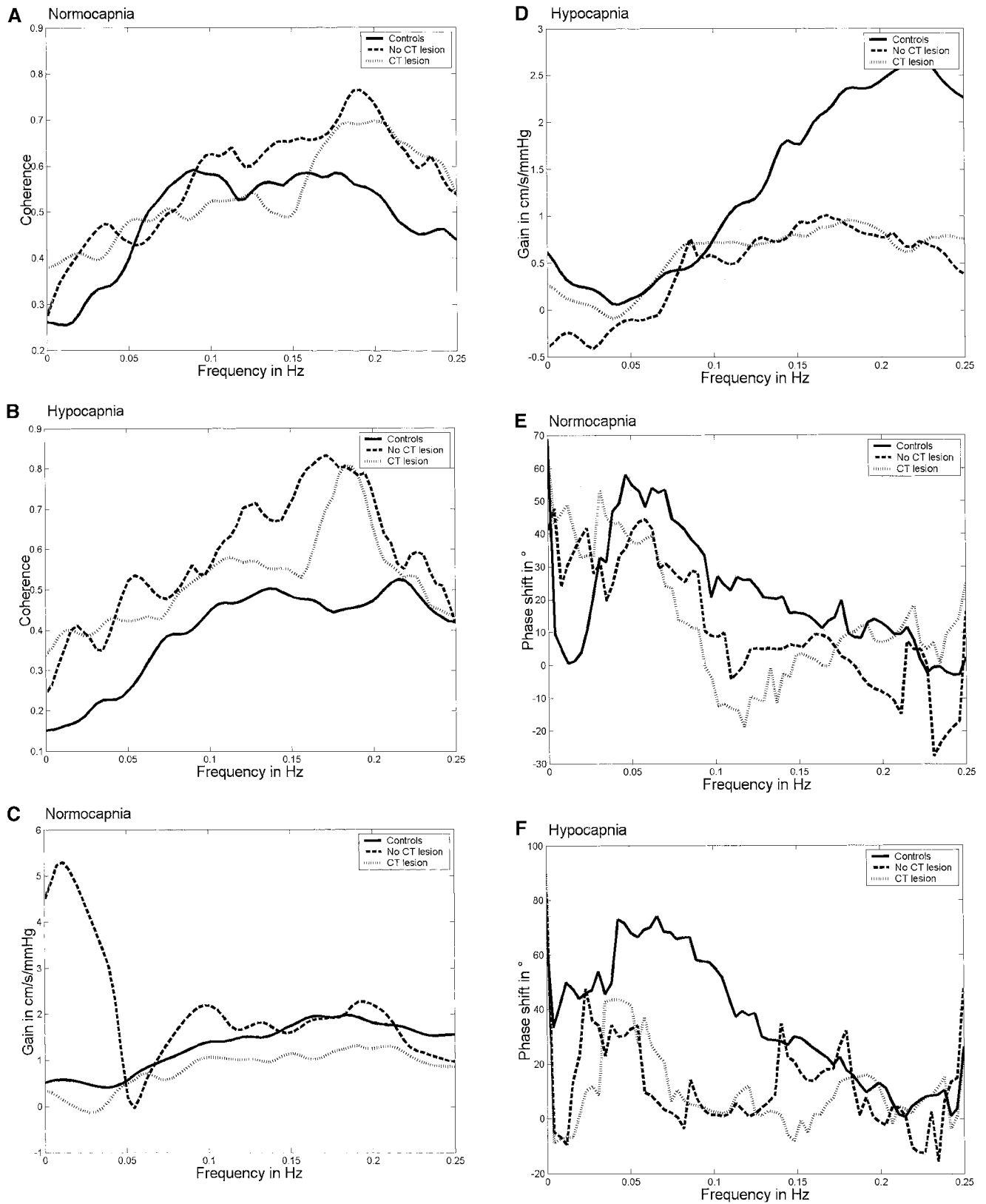


Figure 2. Trauma-induced changes of coherence, gain, and phase shift compared with controls. Findings in the trauma patients are subdivided according to cranial CT results. For details of differences, see text. A, Coherence changes under normocapnic conditions. B, Coherence changes under hypocapnic conditions. C, Gain changes under normocapnic conditions. D, Gain changes under hypocapnic conditions. E, Phase shift changes under normocapnic conditions. F, Phase shift changes under hypocapnic conditions.

recorded ICP was 30 mm Hg. None of the CA assessment results showed a correlation with age, mean arterial BP, ICP, cranial perfusion pressure, or patient outcome 1 month after trauma. Despite the fact that the TBI patients were older than the controls, we used the findings of the normal subjects as reference for comparison with the TBI patients because we and other investigators⁶ did not find the investigated linear parameter to be age dependent.

Controls Versus Presence of CT Lesions, Irrespective of Day of Recording

Figure 2 summarizes the substantial changes of coherence, phase shift, and gain compared with controls with respect to normocapnia or hypocapnia.

In normocapnia (56 examinations, 35 with and 21 without a CT lesion; catecholamines were used in 21 recordings), coherence was increased in the frequency range <0.03 Hz and between 0.18 and 0.25 Hz, irrespective of the presence of a CT lesion. Under hypocapnic conditions (46 examinations, 30 with and 16 without a CT lesion; catecholamines were used in 19 recordings), coherence was increased between 0.0 and 0.13 Hz and between 0.17 and 0.21 Hz when a lesion was not present; when a lesion was present, coherence was increased between 0.0 and 0.07 Hz and again between 0.11 and 0.20 Hz.

In hypocapnia (with and without a CT lesion) and in normocapnia with a CT lesion, gain was reduced between 0.12 and 0.25 Hz. When a CT lesion was absent and the patient was in a normocapnic state, gain was remarkably increased in the frequency range <0.05 Hz, while the gain in the faster frequency range did not differ from that of controls.

Phase shift was not different from that of controls over the whole frequency range when a CT lesion was not present under normocapnic conditions. When a CT lesion was present, phase shift showed a rapid decline toward zero in the frequency range between 0.05 and 0.16 and no difference in the slower (<0.05 Hz) and the faster frequencies. In hypocapnia, phase shift was substantially decreased at <0.03 Hz and in the range between 0.06 and 0.13 Hz, irrespective of the presence or absence of a CT lesion.

Controls Versus Day of Recording, Irrespective of Presence of CT Lesions

The 102 examinations were distributed with respect to day and state of ventilation as follows: on day 1, 12 MCAs in normocapnia and 17 in hypocapnia; on day 3, 14 in normocapnia and 15 in hypocapnia; on day 5, 16 in normocapnia and 9 in hypocapnia; and on day 8, 14 in normocapnia and 5 in hypocapnia.

Compared with controls, coherence was substantially increased over most of the frequencies under normocapnic and hypocapnic conditions on day 1 (normocapnia, 0 to 0.25 Hz; hypocapnia, 0.0 to 0.07 Hz and 0.13 to 0.21 Hz). On days 3 to 8, coherence was increased at <0.03 Hz in normocapnia and at <0.05 Hz in hypocapnia and showed a second substantially increased peak occurring around 0.20 Hz, with limits ranging between 0.13 and 0.25 Hz. Gain was neither increased nor decreased on days 1, 5, and 8 under normocapnic conditions. Only on day 3 did gain show a substantial

peak of increase between 0.0 and 0.07 Hz, which corresponded to the gain peak of those patients without a CT lesion in normocapnia shown in Figure 2C. In hypocapnia, gain was substantially decreased between 0.13 and 0.25 Hz on days 1 to 5. On day 8 there was no difference between patients and controls. In both normocapnia and hypocapnia, phase shift decreased substantially between 0.05 and 0.17 Hz on all days except day 3 in normocapnia, on which phase shift was not different from that of controls. The phase shift decline was of the same shape as shown in Figure 2E and 2F.

Discussion

The cerebrovascular system regulates CBF or its first derivative CBF velocity from the input power BP. We used the frequency-dependent filter model to describe changes in the linear behavior of this system. The major findings in the normal subjects may be described as follows: (1) a hypocapnia-induced linear behavior of coherence and phase shift changes over a wide frequency range; this agrees with previously reported similar linearity induced by hypercapnia^{6,7,13,18}; and (2) a hypocapnia-induced S-shaped and hence nonlinear behavior of gain as an index of the manner in which the system regulates the transmission of energy. To our knowledge, such behavior has not been described previously. Zhang et al⁷ described, for hypercapnia, an increase of gain in the frequency range between 0 and approximately 0.15 Hz, an unchanged gain between 0.15 and 0.23 Hz, and an increased gain at >0.23 Hz, showing also a frequency range in which gain does not change. From the work of Panerai et al,¹⁹ it can also be assumed that the cerebrovascular system can buffer sudden BP changes without changing its linearity and its linear stability. However, such a buffering behavior argues for nonlinear mechanisms within the system. The major finding in the TBI patients was the phase shift decrease between 0.05/0.06 Hz and 0.15 Hz. Similar phase shift decreases in this frequency range have been reported for patients with severe carotid artery disease,¹⁴ arteriovenous malformations,⁶ and spontaneous SAH.²⁰ In addition, the phase shift decreases in this frequency range have been shown to correlate significantly with impaired CO₂ reactivity.^{6,14} One third of our investigations were performed in the presence of a traumatic SAH. We cannot definitely rule out that the similar phase shift behavior in our TBI patients and in those with a spontaneous SAH²⁰ is due to SAH-mediated mechanisms, but among them vasospasm did not play a role in our patients.

The changes in coherence and gain agree only in part with the results found in TBI and in other diseases.^{11,14,15,21} It is still undetermined whether systemic vasoconstrictors affect the behavior of the cerebral circulation.²² As stated above, phase shift decreases comparable to our results were reported in patients with severe carotid artery disease¹⁴ or arteriovenous malformations⁶ in which no vasoconstrictors were applied at the time of the TCD examination. This seems to support the theory that vasoconstrictors do not affect CA substantially. Regarding coherence, a possible explanation may be that the phase shift changes between 0.06 and 0.16 Hz were too inhomogeneous to produce more consistent coherence values. Thus, the question is whether the trauma induces phase shift changes, which interrupt the assumed linearity for coherence found in the controls. Other possible explanations

for incongruent results include input power problems¹⁸; an inhomogeneous population in which patients without CA disturbances are included with those with loss of CA and the number of investigations for statistical analysis is low; or a loss of linear stability of the system, a condition assumed to be observed by Panerai et al,²³ who demonstrated that the system behaved completely differently in TBI patients with ICP >20 mm Hg compared with TBI patients with ICP <20 mm Hg. Finally, the impressive phase shift changes must be reconsidered when other mathematical models emerge. Evidence is growing that parameters of resistance and of storage capacity may have to be included into the models or may be better targets to be controlled for than CBF velocity.^{24–26}

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