

Transfer function analysis of dynamic cerebral autoregulation in humans

RONG ZHANG, JULIE H. ZUCKERMAN, COLE A. GILLER, AND BENJAMIN D. LEVINE

Institute for Exercise and Environmental Medicine, Presbyterian Hospital of Dallas, Dallas 75231; and The University of Texas Southwestern Medical Center at Dallas, Dallas, Texas 75235

Zhang, Rong, Julie H. Zuckerman, Cole A. Giller, and Benjamin D. Levine. Transfer function analysis of dynamic cerebral autoregulation in humans. *Am. J. Physiol.* 274 (*Heart Circ. Physiol.* 43): H233–H241, 1998.—To test the hypothesis that spontaneous changes in cerebral blood flow are primarily induced by changes in arterial pressure and that cerebral autoregulation is a frequency-dependent phenomenon, we measured mean arterial pressure in the finger and mean blood flow velocity in the middle cerebral artery (\dot{V}_{MCA}) during supine rest and acute hypotension induced by thigh cuff deflation in 10 healthy subjects. Transfer function gain, phase, and coherence function between changes in arterial pressure and \dot{V}_{MCA} were estimated using the Welch method. The impulse response function, calculated as the inverse Fourier transform of this transfer function, enabled the calculation of transient changes in \dot{V}_{MCA} during acute hypotension, which was compared with the directly measured change in \dot{V}_{MCA} during thigh cuff deflation. Beat-to-beat changes in \dot{V}_{MCA} occurred simultaneously with changes in arterial pressure, and the autospectrum of \dot{V}_{MCA} showed characteristics similar to arterial pressure. Transfer gain increased substantially with increasing frequency from 0.07 to 0.20 Hz in association with a gradual decrease in phase. The coherence function was >0.5 in the frequency range of 0.07–0.30 Hz and <0.5 at <0.07 Hz. Furthermore, the predicted change in \dot{V}_{MCA} was similar to the measured \dot{V}_{MCA} during thigh cuff deflation. These data suggest that spontaneous changes in \dot{V}_{MCA} that occur at the frequency range of 0.07–0.30 Hz are related strongly to changes in arterial pressure and, furthermore, that short-term regulation of cerebral blood flow in response to changes in arterial pressure can be modeled by a transfer function with the quality of a high-pass filter in the frequency range of 0.07–0.30 Hz.

cerebral blood flow; arterial pressure; Doppler; Fourier analysis

UNDER PHYSIOLOGICAL conditions, steady-state cerebral blood flow is maintained relatively constant over a wide range of perfusion pressure. This phenomenon, known as cerebral autoregulation, has been well documented in animals and humans (17, 31). However, with the development of technology allowing measurements with high temporal resolution, such as transcranial Doppler ultrasonography (TCD) and laser Doppler flowmetry, it has been recognized that there are prominent variations of cerebral blood flow around these steady-state values (7, 10, 16, 20, 26). Such variations may reflect flow regulation in the face of cyclical perturbation of perfusion pressure or, alternatively, may represent an intrinsic variation of cerebral blood flow via cerebral vasomotion (12, 20) or central control mechanisms (26, 34).

It is well known that arterial pressure also varies spontaneously over a wide range of time scales (25, 28,

30). We hypothesized that because cerebral autoregulation is sensitive to changes in tissue perfusion and would respond to the changes in arterial pressure within several seconds (2, 11, 31), the variation in cerebral blood flow due to changes in arterial pressure would be effectively damped in the low-frequency range of changes in pressure. However, in a relatively high-frequency range, autoregulation may be less effective, and changes in arterial pressure may transfer simply to changes in cerebral blood flow. In the present study we took advantage of the technique of transfer function analysis to examine the relationship between spontaneous changes in arterial pressure and cerebral blood flow velocity and to test the hypothesis that cerebral autoregulation is a frequency-dependent phenomenon.

METHODS

Subjects. Ten healthy subjects (4 men, 6 women) with a mean age of 33 ± 7 yr, height of 171 ± 12 cm, and weight of 69 ± 14 kg voluntarily participated in the study. All were nonsmokers and were free of known cardiovascular, pulmonary, and cerebrovascular disorders. Each subject was informed of the experimental procedures and signed a written consent form approved by the Institutional Review Boards of The University of Texas Southwestern Medical Center and Presbyterian Hospital of Dallas.

Procedures and measurements. All experiments were performed in the morning, at least 2 h after a light breakfast and >12 h after the last caffeinated beverage or alcohol, in a quiet, environmentally controlled laboratory with an ambient temperature of 22°C . After at least 30 min of supine rest, 6-min segments of arterial pressure and cerebral blood flow velocity data were recorded during spontaneous uncontrolled respiration for spectral and transfer function analysis. Immediately after this steady-state data collection, two thigh pressure cuffs were inflated to at least 30 mmHg higher than each subject's systolic pressure for 3 min to produce temporary ischemia in the lower extremities. The cuffs were then deflated rapidly to induce a transient change in arterial pressure and cerebral blood flow velocity. It has been demonstrated that the transient changes in velocity provoked by this protocol may indicate dynamic cerebral autoregulation in humans (1, 2, 32).

To test the hypothesis that hypercapnia may impair dynamic cerebral autoregulation, a gas mixture of 5% CO_2 and 21% O_2 balanced with N_2 was given to three subjects during a repeated steady-state data collection on a separate occasion. End-tidal CO_2 was monitored using a mass spectrometer (model MGA 1100, Marquette Electronics).

Arterial pressure was measured in the finger by photoplethysmography (Finapres, Ohmeda). The servo-reset mechanism of the Finapres was turned off to permit uninterrupted data collection during steady-state and thigh cuff deflations. Intermittent blood pressure was also measured in the arm by electrospigmomanometry (Suntech) with a microphone placed over the brachial artery and the Korotkoff sounds

gated to the electrocardiogram. Spontaneous respiratory frequency was monitored using a piezoelectric pneumograph (Protech). Cerebral blood flow velocity was obtained in the middle cerebral artery (MCA) by transcranial Doppler ultrasonography. This technique allows noninvasive and repeatable estimates of changes in cerebral blood flow on a beat-to-beat basis. A 2-MHz Doppler probe (DWL Elektronische Systeme) was placed over the temporal window and fixed at a constant angle and position with an adjustable headgear to obtain optimal signals from the MCA according to standard techniques (3).

Data analysis. The relationship between changes in arterial pressure and cerebral blood flow velocity was evaluated using the method of transfer function analysis. The transfer function $H(f)$ between the two signals was calculated as

$$H(f) = S_{xy}(f)/S_{xx}(f)$$

where $S_{xx}(f)$ is the autospectrum of changes in arterial pressure and $S_{xy}(f)$ is the cross-spectrum between the two signals. The transfer function magnitude $|H(f)|$ and phase spectrum $|\Phi(f)|$ were derived from the real part $H_R(f)$ and the imaginary part $H_I(f)$ of the complex transfer function as

$$|H(f)| = \sqrt{[H_R(f)]^2 + [H_I(f)]^2}$$

$$\Phi(f) = \arctan [H_I(f)/H_R(f)]$$

The transfer magnitude (gain) and phase reflect the relative amplitude and time relationship between the changes in arterial pressure and cerebral blood flow velocity over a specified frequency range. The linearity of the cerebrovascular system modeled by $H(f)$ and the reliability of $H(f)$ estimation were evaluated by a magnitude-squared coherence (MSC) function, which is defined as

$$MSC(f) = |S_{xy}(f)|^2 / [S_{xx}(f)S_{yy}(f)]$$

where $S_{yy}(f)$ is the autospectrum of changes in cerebral blood flow velocity. MSC approaching unity in a specific frequency range suggests a linear relationship between two signals in this frequency range, whereas MSC approximating zero may indicate a nonlinear relationship, severe extraneous noise in the signals, or simply no relationship between signals (13, 24).

The analog finger blood pressure and peak envelope of sequential frequency spectrums of the Doppler frequency shift signal of cerebral blood flow velocity were sampled simultaneously at 100 Hz and digitized at 12 bits (Multi-Dop X2, DWL). Real time beat-to-beat mean values of pressure and velocity were calculated as waveform integration of the sampled pressure and velocity signal within each cardiac cycle divided by the corresponding pulse interval and stored for off-line analysis. For steady-state data analysis, beat-to-beat changes in mean pressure and velocity were aligned with the time of R wave peaks of the electrocardiogram and linearly interpolated, then resampled at 1 Hz to convert the unequally spaced beat-to-beat time series to a uniformly spaced time series for spectral and transfer function analysis. The resampling frequency was determined via the spectral analysis of pressure and velocity signals and based on the Nyquist theorem. In this study, estimation of spectral and transfer function was based on the Welch algorithm (6). The time series were first detrended with third-order polynomial fitting and then subdivided into 128-point segments with 50% overlap for spectral estimation. This process resulted in five segments of data for the segment periodogram average and a spectral resolution of ~ 0.0078 Hz. In the present study the data segmentation is based on a trade-off between a reduction

in spectral variance and keeping a sufficient spectral resolution. However, the random error of estimation of transfer and coherence function associated with five segments may be high when the coherence function is < 0.5 (6). Fast Fourier transforms were implemented with each Hanning-windowed segment and averaged to calculate the autospectrum, cross-spectrum, coherence, and transfer functions.

For transient data analysis, changes in mean arterial pressure during the thigh cuff deflation were convolved with the impulse response function, which is derived as an inverse Fourier transform of the transfer function estimated under steady-state conditions, to predict the change in cerebral blood flow velocity when the cerebrovascular system was driven by a transient change in mean arterial pressure. The predicted changes in velocity were then compared with the measured change in velocity by evaluation of the mean value and standard deviation of residuals between each data point of the two signals 10 s before and 20 s after the thigh cuff deflation. The null hypothesis supposes that the mean value of residuals is zero. We speculated that if spontaneous changes in cerebral blood flow velocity are caused by changes in arterial pressure and the dynamic relationship between the two variables can be modeled by the transfer function, then the change in velocity predicted by the impulse response function should precisely match the measured changes in velocity during the acute hypotensive stimulus. Data analysis was performed with commercially available software (DADiSP, DSP Development, Cambridge, MA).

RESULTS

Time series and autospectra. Average values for the entire group for arterial pressure (finger), heart rate, and mean cerebral blood flow velocity, as well as respiratory frequency, are presented in Table 1. Figure 1 shows representative time series (A and B) and autospectra (C and D) of beat-to-beat changes in mean arterial pressure and cerebral blood flow velocity from one subject and group-averaged autospectra (E and F). Similar to the spontaneous changes in arterial pressure, velocity showed a $7 \pm 3\%$ beat-to-beat change around the mean value (coefficient of variation, SD/mean) and demonstrated a complex pattern of variation of cerebral blood flow velocity with prominent low-frequency components (Fig. 1). The autospectra of pressure and velocity demonstrated similar characteristics with a very low-frequency component (< 0.07 Hz), a low-frequency component (~ 0.10 Hz), and a high-frequency component (~ 0.20 Hz) that was linked with each individual's respiratory frequency (Fig. 1, C and D). The high-frequency peak in the group-averaged spectra was blurred as a result of the average processing of individual spectra with different respiratory frequencies.

Table 1. Group-averaged hemodynamic variables

SBP, mmHg	DBP, mmHg	MBP, mmHg	HR, beats/min	f, breaths/min	\dot{V}_{MCA} , cm/s
123 \pm 6	70 \pm 5	87 \pm 5	63 \pm 4	12 \pm 1	71 \pm 6

Values are means \pm SE; $n = 10$. SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean arterial pressure; HR, heart rate; f, respiratory frequency; \dot{V}_{MCA} , mean cerebral blood flow velocity measured in middle cerebral artery.

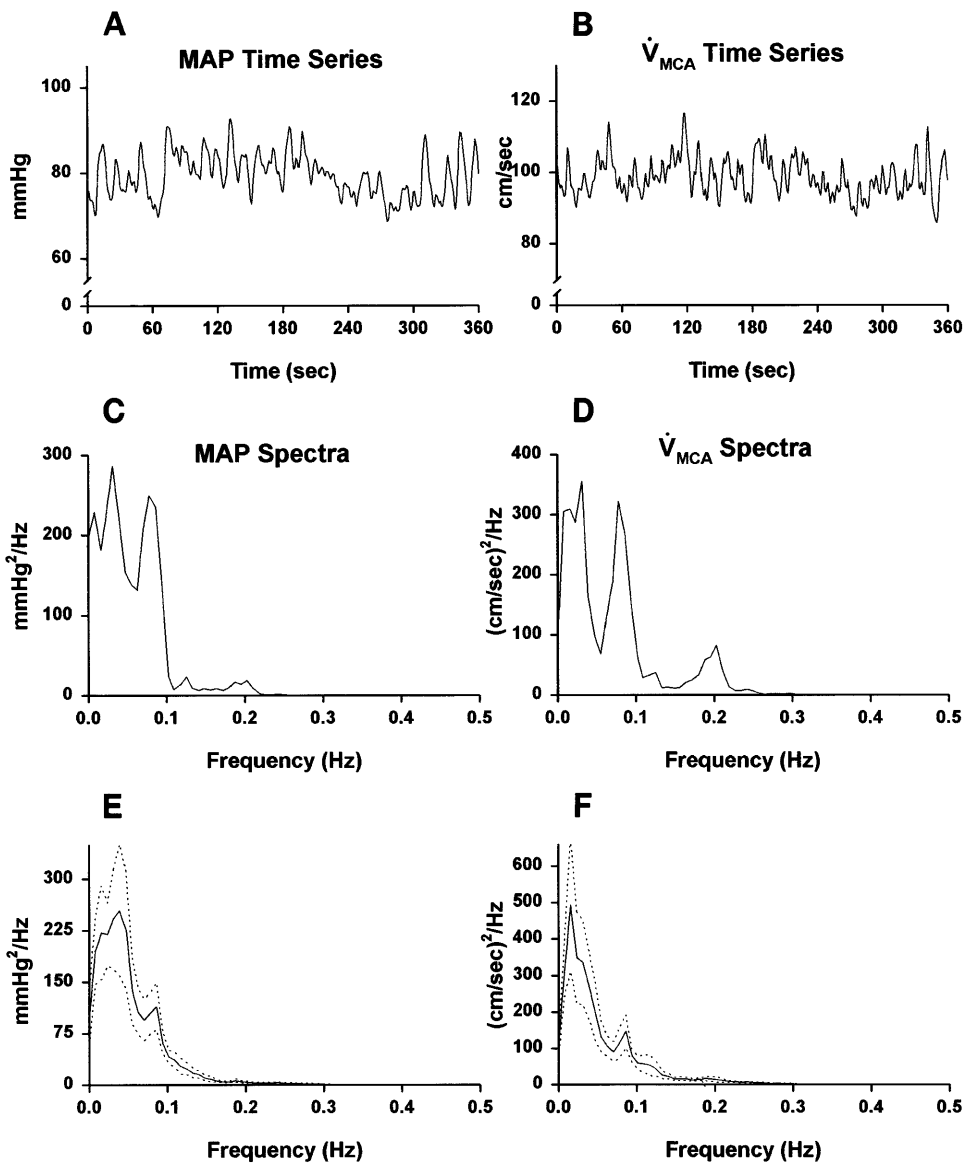


Fig. 1. Representative time series (A and B) and autospectra (C and D) of beat-to-beat changes in mean arterial pressure (MAP) and mean cerebral (middle cerebral artery) blood flow velocity (\dot{V}_{MCA}) for 1 subject and group-averaged autospectra (E and F) for all subjects. Solid lines, averaged estimates; dotted lines, SE.

Transfer function. Estimates of transfer gain, phase, and coherence function are shown in Fig. 2. In the frequency range of 0.07–0.30 Hz the coherence was >0.5 (measured from the group-averaged coherence estimation, Fig. 2C), suggesting that, in this frequency range, changes in velocity are linearly related to the changes in pressure. In contrast, in the very low-frequency range (<0.07 Hz) the coherence was <0.5 , suggesting 1) a nonlinear relationship between changes in velocity and pressure, 2) the presence of a low signal-to-noise ratio, or 3) no relationship between the two signals (Fig. 2C). Transfer gain showed a substantial increase with increasing frequency in the frequency range of 0.07–0.20 Hz, reflecting properties of a high-pass filter seen in the relationship between pressure and velocity (Fig. 2A). Furthermore, the phase fell gradually with increasing frequency from $48 \pm 12^\circ$ at 0.07 Hz to $-2 \pm 11^\circ$ at 0.30 Hz, indicating that, in the low-frequency range, changes in velocity lead changes in pressure. However, in the high-frequency range,

changes in velocity are almost in phase or indicate a $\sim 360^\circ$ delay with changes in pressure (Fig. 2B).

During 5% CO_2 inhalation, end-tidal CO_2 increased from 33 ± 3 to 38 ± 2 mmHg in association with an increase in mean velocity from 69 ± 13 to 84 ± 18 cm/s (averaged from steady-state data) and no change in mean arterial pressure. Transfer gain and coherence increased and phase decreased in the frequency range of 0.07–0.20 Hz compared with baseline, suggesting an impairment of dynamic cerebral autoregulation during hypercapnia (Fig. 3).

Impulse response function. Figure 4 shows the impulse response function derived from the transfer function in one subject (A) and group-averaged results (B). The impulse response function represents the response of cerebral blood flow velocity to a very brief positive unit change in arterial pressure. The impulse response function showed an immediate positive deflection in velocity with a group-averaged peak value of $0.90 \pm 0.12 \text{ cm} \cdot \text{s}^{-1} \cdot \text{mmHg}^{-1}$ (Fig. 4B). This was followed by a

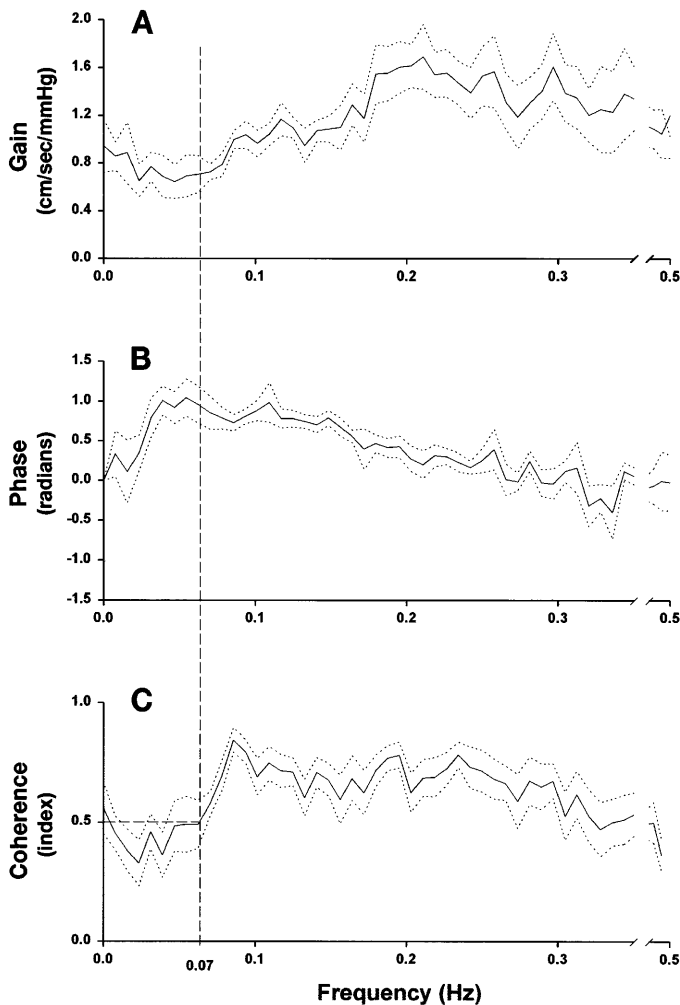


Fig. 2. Group-averaged transfer function gain (A), phase (B), and coherence function (C) between changes in mean arterial pressure and mean cerebral blood flow velocity for all subjects. Solid lines, averaged estimates; dotted lines, SE.

transient decrease to $-0.39 \pm 0.06 \text{ cm} \cdot \text{s}^{-1} \cdot \text{mmHg}^{-1}$ below the baseline and a gradual increase with a small overshoot of $0.05 \pm 0.02 \text{ cm} \cdot \text{s}^{-1} \cdot \text{mmHg}^{-1}$ above baseline (Fig. 4B) within ~ 5 s. These data show that dynamic cerebral autoregulation as evaluated by the change in cerebral blood flow velocity to a unit impulse stimulation in mean arterial pressure is completed within ~ 5 s and suggest that the response of cerebral blood flow velocity is sensitive to transient changes in arterial pressure (Fig. 4).

Prediction of cerebral blood flow velocity. The transient changes in arterial pressure and cerebral blood flow velocity during thigh cuff deflation and the predicted change in velocity are presented in Fig. 5. The group-averaged plots were obtained by aligning the change in arterial pressure at the time of cuff deflation. The maximum drop in arterial pressure and in velocity during the cuff deflation were $12 \pm 2 \text{ mmHg}$ and $11 \pm 2 \text{ cm/s}$, respectively (Fig. 5B). The difference (mean \pm SD of residuals) between the predicted and measured changes in cerebral blood flow velocity is $0.22 \pm 1.45 \text{ cm/s}$ ($P = 0.40$ compared with 0; Fig. 5B). Interestingly,

the predicted changes in velocity matched very well the measured changes in velocity during thigh cuff deflation (Fig. 5), suggesting that the relationship between the transient changes in arterial pressure and velocity can be modeled by the transfer function estimated from the steady-state changes in arterial pressure and cerebral blood flow velocity.

DISCUSSION

There are three primary findings in the present study. 1) We observed similar time domain characteristics and spectral distribution of beat-to-beat changes in arterial pressure and cerebral blood flow velocity in humans. 2) Transfer function analysis indicated that the response of cerebral blood flow velocity to the change in arterial pressure could be modeled by a high-pass filter in the frequency range of 0.07–0.30 Hz. 3) The predicted cerebral blood flow velocity, calculated as a convolution of the changes in arterial pressure with the impulse response function, well matched the

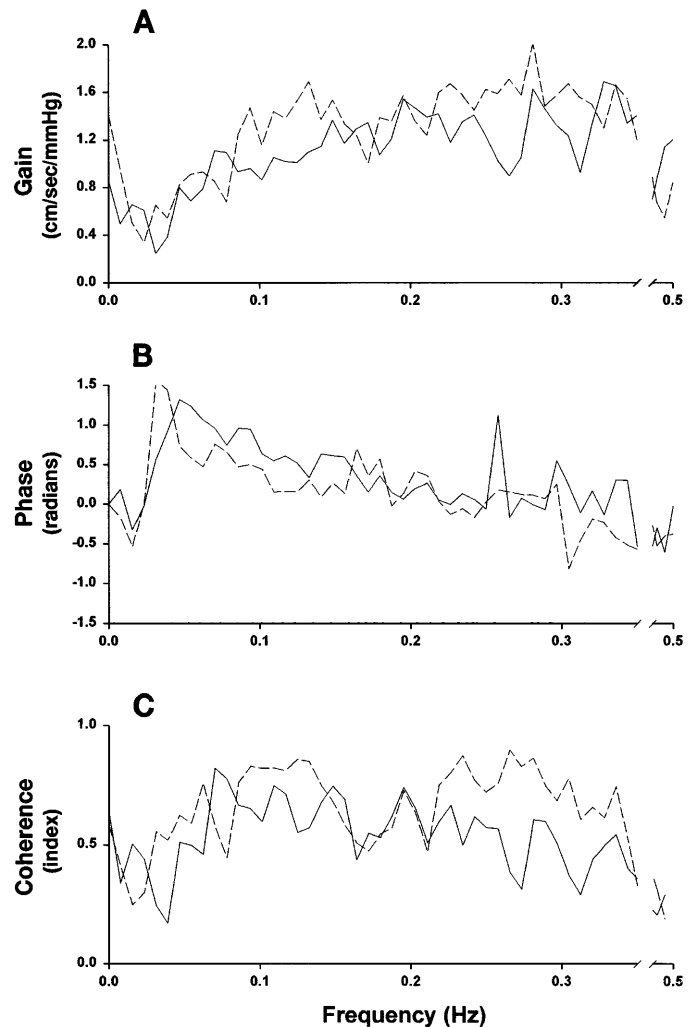


Fig. 3. Group-averaged transfer function gain (A), phase (B), and coherence function (C) between changes in mean arterial pressure and mean cerebral blood flow velocity for 3 subjects during 5% CO_2 inhalation. Solid lines, baseline estimates; dashed lines, estimates during 5% CO_2 inhalation.

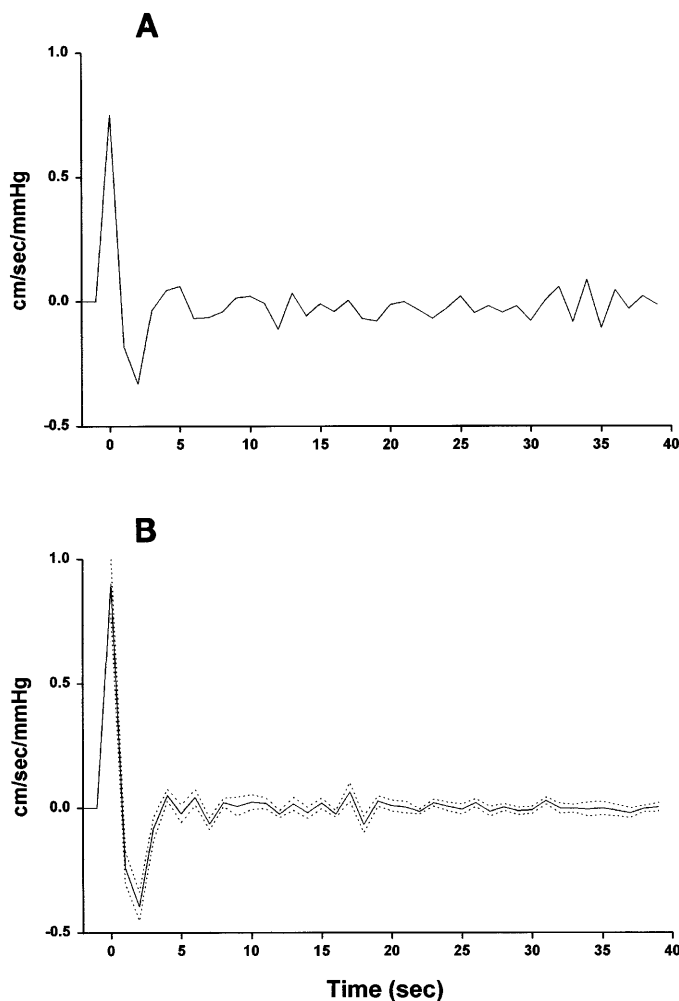


Fig. 4. Impulse response function estimated as inverse Fourier transform of transfer function for 1 subject (A) and group-averaged for all subjects (B). Solid line, averaged estimate; dotted lines, SE.

transient change in the velocity measured directly during the thigh cuff deflation. These findings suggest a strong, possibly deterministic, relationship between the spontaneous changes in arterial pressure and cerebral blood flow velocity >0.07 Hz and are consistent with a frequency dependence of dynamic cerebral autoregulation.

Methodological considerations. Traditionally, the relationship between cerebral blood flow and perfusion pressure has been measured by comparing a stable change in flow with a stable change in pressure (31). This static method has been valuable, but animal and human studies suggest that cerebral blood flow regulation is a dynamic process with substantial temporal heterogeneity (4, 13). Dynamic cerebral blood flow regulation in humans has not been systematically studied because of the limited technology for high temporal resolution and continuous measurement of cerebral blood flow noninvasively.

Although TCD methods permit the temporal resolution necessary to study these changes, it is important to emphasize that velocity is not necessarily equal to flow. Changes in flow are proportional to changes in mean

velocity only if the diameter of the MCA remains constant. Angiographic studies (9, 19) and direct visualization of the MCA during surgery (14) have suggested that, during a variety of stimuli known to affect cerebral blood flow, the diameter of the MCA changes minimally ($<3.0\%$). However, small changes in diameter are difficult to measure and may produce large changes in velocity. The assumption made in this study is that changes in diameter of the MCA are minimal; therefore, beat-to-beat changes in mean velocity may represent predominantly beat-to-beat changes in cerebral blood flow (23). An alternative possibility is that cerebral blood flow was maintained relatively constant, with active changes in the diameter of large cerebral arteries and compensatory changes in resistance in downstream small vessels. In this context, the dynamic relationship between changes in pressure and velocity may represent autoregulation of large cerebral arteries in response to spontaneous changes in pressure. Although theoretically we cannot exclude this possibility, recent studies of cerebral autoregulation in humans support the notion that beat-to-beat changes in mean MCA velocity may represent beat-to-beat changes in cerebral blood flow (1, 2, 32).

We used the method of photoplethysmography to measure arterial pressure in the finger. This technique

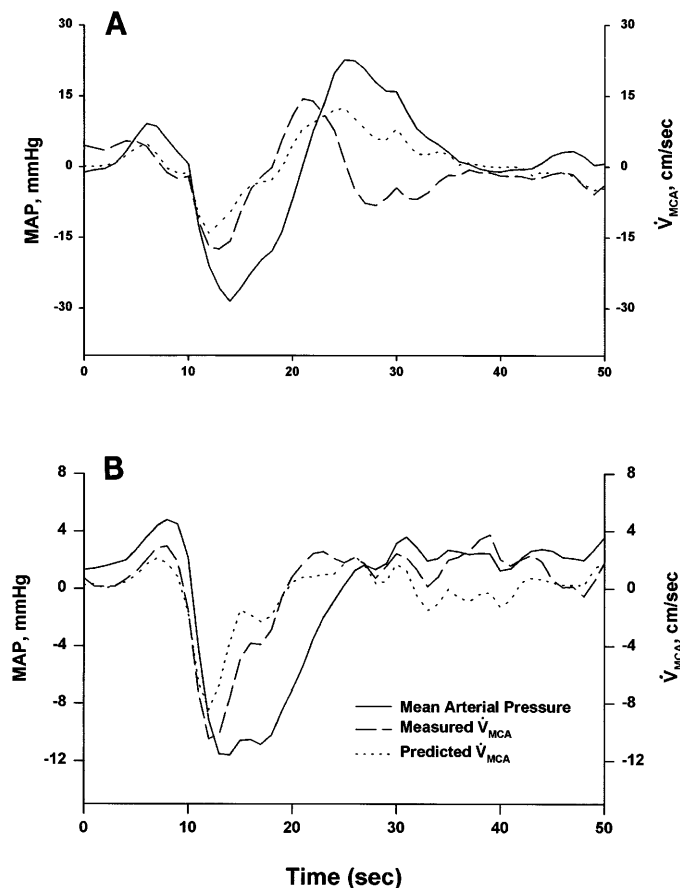


Fig. 5. Comparison of predicted change in mean cerebral blood flow velocity during thigh cuff deflation with direct measured change in mean cerebral blood flow velocity for 1 subject (A) and group-averaged for all subjects (B).

has been used extensively for continuous measurements of systemic arterial pressure, and its reliability has been demonstrated by numerous studies in the time and frequency domain (21, 22, 28). The mean and oscillatory components of the arterial pressure are tracked well using this method (Fig. 6). If it is considered that the arterial pressure wave moves at a velocity of $\sim 5\text{--}8$ m/s in large vessels (27), the time delay between the finger arterial pressure and cerebral arterial pressure should be small and negligible. Furthermore, although waveforms of arterial pressure differ in different vascular beds because of reflected waves and pulsatility of pressure waveforms increases in peripheral arteries, mean arterial pressure is likely to be proportional or identical in arteries of similar size (27). Therefore, despite the fact that the pressure waveform in the finger may be different from the pressure waveform in the MCA (but similar to that in the brachial artery; Fig. 6), the assumption was made that the changes in mean arterial pressure in the finger are proportional to changes in mean arterial pressure in the MCA. We also assumed that intracranial pressure is low and that fluctuation of intracranial pressure is relatively small and secondary to variations in cerebral blood flow in healthy subjects (26). Changes in mean finger arterial pressure should therefore represent closely the changes in mean cerebral perfusion pressure.

Beat-to-beat variability of cerebral blood flow velocity. Spontaneous changes in cerebral blood flow and velocity have been reported by several investigators (7, 16, 26). However, the underlying mechanism is not clear. Possible explanations include cerebral vasomotion (12, 20) and oscillations of central control mechanisms (26, 34). Vasomotion has been described mainly in the cerebral microcirculation, and it has been proposed that vasomotion may affect local microvascular pres-

sure and blood flow (20). Hence, changes in global cerebral blood flow caused by vasomotion occur only if there is a synchrony of small vessel vasomotion or vasomotion in basal cerebral arteries (12, 20).

The central mechanism hypothesis argues that spontaneous changes in cerebral blood flow may be caused by a neural pacemaker in the brain stem that alters activity of vasomotor neurons and changes cerebral blood flow in a rhythmic pattern (26). Alternatively, a central feedback loop may exist for the regulation of cerebral blood flow with intrinsic oscillation (34). In the present study we observed similar characteristics of spontaneous changes in arterial pressure and cerebral blood flow velocity in the time and frequency domain with high coherence in the frequency range of 0.07–0.30 Hz. Furthermore, the transient changes in cerebral blood flow velocity during thigh cuff deflation could be predicted well by the convolution of changes in arterial pressure, with the impulse response function estimated from spontaneous changes in arterial pressure and cerebral blood flow velocity during quiet tidal breathing. If changes in the diameter of the MCA are minimal, changes in velocity should parallel changes in flow. Therefore, contrary to the hypotheses of vasomotion and central mechanisms, our data argue for a primary importance of dependence of flow variability on pressure variability within this specific frequency range. However, the time domain and frequency domain properties of spontaneous changes in cerebral blood flow and arterial pressure may be different at different time scales with different mechanisms. Particularly in the low-frequency range <0.07 Hz, influences of cerebral vasomotion or central oscillations on changes in cerebral blood flow cannot be excluded.

Transfer function analysis. The estimation of the transfer function between the arterial pressure and cerebral blood flow velocity indicates that dynamic

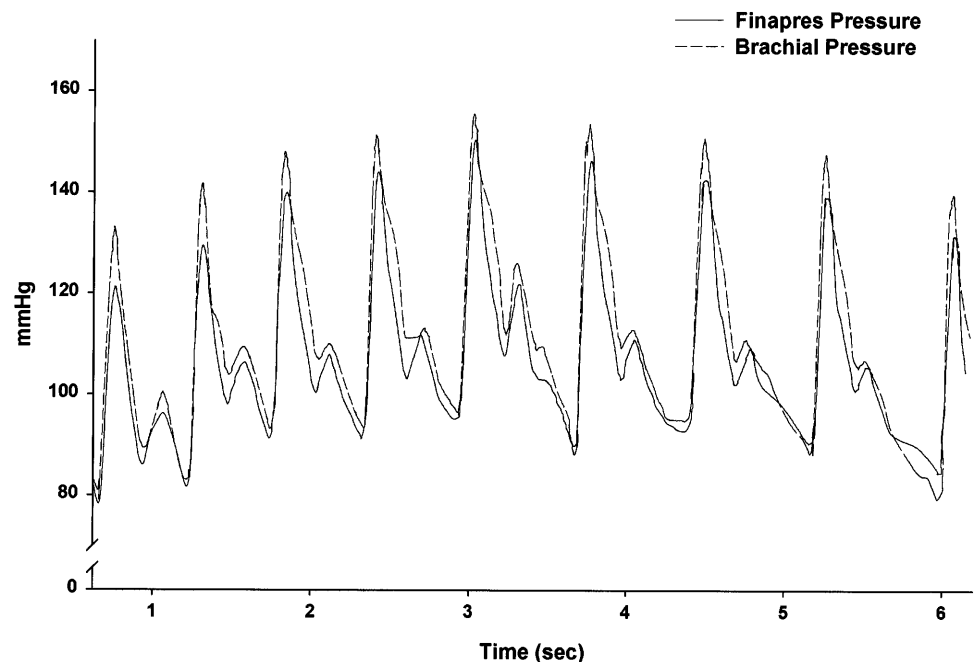


Fig. 6. Simultaneous recordings of intra-arterial pressure in brachial artery (dashed line) and finger arterial pressure (solid line) in 1 subject. A catheter (3-Fr) was placed percutaneously in brachial artery of nondominant arm. Probe of Finapres was placed in finger distal to arterial catheter in same hand.

cerebral autoregulation is a frequency-dependent phenomenon (13). Examination of the components of the transfer function suggests that three frequency ranges may be identified that appear to have different characteristics: 1) a low-frequency component (<0.07 Hz) with a low coherence, 2) a high-frequency component (>0.20 Hz) with a high coherence, relatively large gain, and minimal phase lead, and 3) an intermediate-frequency component (0.07–0.20 Hz) characterized by increasing coherence, increasing gain, and decreasing phase.

The concept of linearity deserves comment here. Two signals such as velocity and pressure are linearly related if their relationship can be described by a linear differential equation with constant coefficients. A consequence of linearity is that variations of a particular frequency in the input signal (pressure) are transformed to signals of the same frequency in the output signal (velocity). The degree to which the frequency is transmitted is the gain of the system at that frequency. We speculate that, for a linear function relating changes in velocity to pressure, a damping effect of autoregulation on changes in pressure may be quantified by the transfer gain, allowing autoregulation to be considered at each particular frequency.

A common test of linearity is the coherence function, which is close to 1.0 when the system is linear. However, a low coherence (<0.5) may be produced by a number of different processes: 1) extraneous noise is present in the measurements; 2) the system relating output to input is nonlinear; 3) the output is due to more than one input; or 4) there is no relationship between input and output (13, 24).

In the low-frequency range in the present study, coherence between the changes in pressure and velocity is <0.5 , suggesting that the condition of linearity relating changes in velocity to pressure and, thus, the fundamental assumption for the estimation of linear transfer function gain and phase may be violated in this frequency range (24). However, analysis of coherence, without calculation of gain by itself, may be useful for evaluating cerebral autoregulation, and this speculation is based on the following considerations. First, if we assume a "white" property of measurement noise in the pressure and velocity signals (i.e., Finapres blood pressure and TCD velocity) within the time scales of several minutes and note that coherence is high in the high-frequency range, the signal-to-noise ratio should be sufficiently high in our experimental system. Thus the observed low coherence in the low-frequency range is unlikely to be a result of measurement noise. Second, if it is assumed that measurement noise is acceptably low, we speculate that perfect autoregulation would be manifested by a coherence of zero between the changes in pressure and velocity. That is, the fluctuations in the velocity would be nonexistent, despite fluctuations in the arterial pressure. The simplest explanation for the low coherence observed in the present study is that it is produced by inherently nonlinear properties of autoregulation (24). Alternatively, a complex linear feedback regulatory system may exist that controls changes

in arterial pressure externally and thereby causes a low coherence between changes in pressure and velocity. Although the present data cannot distinguish between these two possibilities, the low coherence observed at frequencies <0.07 Hz indicates effective cerebral autoregulation regardless of the specific model. The mechanisms mediating autoregulation in the low-frequency range have been a subject of much debate and may include metabolic, myogenic, and endothelium-derived processes (31). Although all could be effective at these time scales, we speculate that the low-frequency oscillations are most consistent with metabolically derived flow regulation.

In the high-frequency range, pressure and velocity vary in parallel (high coherence) with less of a damping effect on changes in pressure (high gain) and small phase lead, suggesting that autoregulation is ineffective in this frequency range. Thus the relationship between perfusion pressure and flow velocity is likely determined predominantly by the impedance properties of the cerebral vascular system, i.e., vascular resistance, compliance, and inertia of the blood column (15).

It is in the intermediate-frequency range that interpretation of our findings becomes most complex. Over the frequency range of 0.07–0.20 Hz the capacity of autoregulation appears to deteriorate as coherence and transfer gain increase. The system was acting to "filter out" slow variations and allowing pressure to drive velocity only at high frequencies. It is likely that, with increasing frequency, biophysical properties become more significant and autoregulatory processes, including metabolic, myogenic, and endothelial control, become less able to stabilize cerebral blood flow in the face of changing perfusion pressure. Although the response time of each of these processes has not been measured precisely, we speculate that myogenic and endothelial mechanisms may play more important roles in cerebral autoregulation within this frequency range (31). Furthermore, the increase in transfer gain associated with the approximate linear decline in the phase lead within this frequency range suggests that the changes in velocity may be related to the rate of changes in pressure; i.e., the dynamic relationship between changes in pressure and velocity may have properties similar to a positive differentiator with a time delay that transfers the changing rate of an input signal (changes in pressure) to an output signal (changes in velocity).

The significance of transfer function gain and phase for dynamic autoregulation is supported by the increase in gain and decrease in phase during 5% CO_2 inhalation in the present study and by several other reported observations. First, in a cycling maneuver of 10 s of squatting and 10 s of standing (5), which results in large, cyclical swings in arterial pressure, the phase lead of cerebral blood flow velocity to arterial pressure with normal breathing is $46 \pm 14^\circ$, which is nearly identical to the estimated phase lead of $48 \pm 12^\circ$ at 0.07 Hz in the present study. Moreover, in that same study the authors observed a significant reduction in phase lead with hypercapnia, which causes vasodilation and diminished autoregulatory reserve, and a significant

increase in phase lead with hypocapnia, which induces vasoconstriction and augmented autoregulatory reserve (5). Second, with modeling of autoregulation as a high-pass filter, a positive phase lead of changes in cerebral blood flow velocity to changes in arterial pressure was also reported in healthy subjects during a deep breathing maneuver, and reduction of phase lead was demonstrated in patients with compromised cerebral autoregulation (8). Finally, transfer gain increases in patients with subarachnoid hemorrhage compared with normal subjects, suggesting an impairment of cerebral autoregulation (13). Although the exact interpretation of phase lead of velocity to pressure and changes in transfer gain and phase during hypercapnia and hypocapnia, as well as under different pathophysiological conditions, cannot be determined from the present and aforementioned studies, it is possible that these changes may be related to an alteration of feedback control of cerebrovascular impedance via metabolic or flow-dependent mechanisms.

Other vascular beds may demonstrate similar properties of dynamic autoregulation. For example, with a broad-band forcing of arterial pressure as input and renal blood flow as output, the transfer function gain between changes in arterial pressure and renal blood flow also shows properties of a high-pass filter with a phase lead of flow to pressure (18). Interestingly, the transfer gain, phase, and coherence function show frequency distributions similar to those of the present study (18), despite the fact that the underlying mechanisms may be different between renal and cerebral autoregulation. Impairment of renal autoregulation has been associated with an increased transfer gain and reduced phase (33).

Therefore, the high-pass filter nature of transfer gain and the phase decrease with increasing frequency observed in the present study may indicate that the damping effects of cerebral autoregulation on changes in arterial pressure are more effective in the low- than in the high-frequency range. Furthermore, these results suggest that the dynamic regulation of cerebral blood flow may have different mechanisms in different frequency ranges.

Impulse response function analysis. The impulse response function represents the output of a linear system to a positive unit stimulation with a very short duration. Time domain properties of a linear system can be analyzed by estimation of the impulse response function. Several mechanisms of flow control are suggested by the shape of the impulse response function. The expected initial rise in velocity is followed by a decrease below baseline and then small oscillations until a steady state is reached. Although we suspect that this phenomenon is explained by the fact that autoregulatory feedback dilation may act in these time intervals (1), we cannot rule out the possibility that the oscillations are due to passive storage properties (i.e., compliance and blood inertia) of the cerebrovascular bed (15). However, the agreement between measured and predicted velocity response to the thigh cuff provo-

cation was striking and confirms the action of autoregulation as a high-pass filter for frequencies >0.07 Hz.

The impulse response function of cerebrovascular resistance index to cerebral blood flow velocity has also been characterized in neonates, which showed a gradual increase followed by a gradual decrease of resistance index within ~ 10 s (29). Although the time course of the impulse response function between resistance index and velocity may be different from that of the impulse response function between velocity and pressure defined in the present study, the longer time interval in neonates suggests that the time constant of dynamic cerebral autoregulation in neonates may be different from that in adults.

In conclusion, the results from this study suggest a close relationship between the spontaneous fluctuations of arterial pressure and cerebral blood flow velocity within the frequency range of 0.07–0.30 Hz. Quantification of this relationship by transfer function analysis indicates that cerebral autoregulation is more effective for low- than for high-frequency changes in arterial pressure. We speculate that the frequency-dependent phenomenon of cerebral autoregulation may be related to different mechanisms of cerebrovascular responses to different rates of change in perfusion pressure.

This study was supported by National Aeronautics and Space Administration Specialized Center for Research and Training Grant NAGW-3582 and National Heart, Lung, and Blood Institute Grants HL-53206-01 and AO-93-OLMSA-01.

Address for reprint requests: B. D. Levine, Institute for Exercise and Environmental Medicine, Presbyterian Hospital of Dallas, 7232 Greenville Ave., Dallas, TX 75231.

Received 3 January 1997; accepted in final form 5 September 1997.

REFERENCES

1. Aaslid, R., K. Lindegaard, W. Sorteberg, and H. Nornes. Cerebral autoregulation dynamics in humans. *Stroke* 20: 45–52, 1989.
2. Aaslid, R., D. W. Newell, R. Stooss, W. Sorteberg, and K. Lindegaard. Assessment of cerebral autoregulation dynamics from simultaneous arterial and venous transcranial Doppler recordings in humans. *Stroke* 22: 1148–1154, 1991.
3. American Academy of Neurology. Therapeutics and Technology Assessment Subcommittee. Assessment: transcranial Doppler ultrasound. *Neurology* 40: 680–681, 1990.
4. Baumbach, G. L., and D. D. Heistad. Regional, segmental, and temporal heterogeneity of cerebral vascular autoregulation. *Ann. Biomed. Eng.* 13: 303–310, 1985.
5. Birch, A. A., M. J. Dirnhuber, R. Hartley-Davies, F. Iannotti, and G. Neil-Dwyer. Assessment of autoregulation by means of periodic changes in blood pressure. *Stroke* 26: 834–837, 1995.
6. Carter, G. C., C. H. Knapp, and A. H. Nuttall. Estimation of the magnitude-squared coherence function via overlapped fast Fourier transform processing. *IEEE Trans. Audio Electroacoust.* AU-21: 337–344, 1973.
7. Daffertshofer, M., and M. Hennerici. Cerebrovascular regulation and vasoneuronal coupling. *J. Clin. Ultrasound* 23: 125–138, 1995.
8. Diehl, R. R., D. Linden, D. Lucke, and P. Berlit. Phase relationship between cerebral blood flow velocity and blood pressure. A clinical test of autoregulation. *Stroke* 26: 1801–1804, 1995.
9. DuBoulay, G., L. Symon, R. H. Ackerman, D. Dorsch, B. E. Kendall, and S. H. Shah. The reactivity of the spastic arteries. *Neuroradiology* 5: 37–39, 1973.
10. Fasano, V. A., R. Urciuoli, P. Bolognese, and M. Mostert. Intraoperative use of laser Doppler in the study of cerebral

- microvascular circulation. *Acta Neurochir. (Wien)* 95: 40–48, 1988.
11. **Florence, G., and J. Seylaz.** Rapid autoregulation of cerebral blood flow: a laser-Doppler flowmetry study. *J. Cereb. Blood Flow Metab.* 12: 674–680, 1992.
 12. **Fujii, K., D. D. Heistad, and F. M. Faraci.** Vasomotion of basilar arteries in vivo. *Am. J. Physiol.* 258 (*Heart Circ. Physiol.* 27): H1829–H1834, 1990.
 13. **Giller, C. A.** The frequency-dependent behavior of cerebral autoregulation. *Neurosurgery* 27: 362–368, 1990.
 14. **Giller, C. A., G. Bowman, H. Dyer, and L. Mootz.** Cerebral arterial diameters during changes in blood pressure and carbon dioxide during craniotomy. *Neurosurgery* 32: 737–741, 1993.
 15. **Giller, C. A., B. Ratcliff, B. Berger, and A. Giller.** An impedance index in normal subjects and in subarachnoid hemorrhage. *Ultrasound Med. Biol.* 22: 373–382, 1996.
 16. **Giller, C. A., A. Roseland, and M. Lam.** Periodic variations in transcranial Doppler mean velocities. *J. Neuroimaging* 3: 160–162, 1993.
 17. **Heistad, D. D., and H. A. Kontos.** Cerebral circulation. In: *Handbook of Physiology. The Cardiovascular System. Peripheral Circulation and Organ Blood Flow.* Bethesda, MD: Am. Physiol. Soc., 1983, sect. 2, vol. III, pt. 1, chapt. 5, p. 137–182.
 18. **Holstein-Rathlou, N. H., A. J. Wagner, and D. J. Marsh.** Tubuloglomerular feedback dynamics and renal blood flow autoregulation in rats. *Am. J. Physiol.* 260 (*Renal Fluid Electrolyte Physiol.* 29): F53–F68, 1991.
 19. **Huber, P., and J. Handa.** Effect of contrast material, hypercapnia, hyperventilation, hypertonic glucose and papaverine on the diameter of the cerebral arteries. *Invest. Radiol.* 2: 17–32, 1967.
 20. **Hudetz, A. G., R. J. Roman, and D. R. Harder.** Spontaneous flow oscillations in the cerebral cortex during acute changes in mean arterial pressure. *J. Cereb. Blood Flow Metab.* 12: 491–499, 1992.
 21. **Imholz, B. P., J. J. Settels, A. H. van der Meiraker, K. H. Wesseling, and W. Wieling.** Non-invasive continuous finger blood pressure measurement during orthostatic stress compared to intra-arterial pressure. *Cardiovasc. Res.* 24: 214–221, 1990.
 22. **Imholz, B. P., G. A. van Montfrans, J. J. Settels, G. M. van der Hoeven, J. M. Karemaker, and W. Wieling.** Continuous non-invasive blood pressure monitoring: reliability of Finapres device during the Valsalva maneuver. *Cardiovasc. Res.* 22: 390–397, 1988.
 23. **Levine, B. D., C. A. Giller, L. D. Lane, J. C. Buckley, and C. G. Blomqvist.** Cerebral versus systemic hemodynamics during graded orthostatic stress in humans. *Circulation* 90: 298–306, 1994.
 24. **Marmarelis, V. Z.** Coherence and apparent transfer function measurements for nonlinear physiological systems. *Ann. Biomed. Eng.* 16: 143–157, 1988.
 25. **Marsh, D. J., J. L. Osborn, and A. W. J. Cowley.** 1/f fluctuations in arterial pressure and regulation of renal blood flow in dogs. *Am. J. Physiol.* 258 (*Renal Fluid Electrolyte Physiol.* 27): F1394–F400, 1990.
 26. **Newell, D. W., R. Aaslid, R. Stooss, and H. J. Reulen.** The relationship of blood flow velocity fluctuations to intracranial pressure B waves. *J. Neurosurg.* 76: 415–421, 1992.
 27. **Nichols, W. W., and M. F. O'Rourke.** *McDonald's Blood Flow in Arteries: Theoretical, Experimental and Clinical Principles.* Philadelphia, PA: Lea & Febiger, 1990, p. 77–250.
 28. **Omboni, S., G. Parati, A. Frattola, E. Mutti, M. Di Rienzo, P. Catiglioni, and G. Mancia.** Spectral and sequence analysis of finger blood pressure variability: comparison with analysis of intra-arterial recordings. *Hypertension* 22: 26–33, 1993.
 29. **Panerai, R. B., A. W. R. Kelsall, J. M. Rennie, and D. H. Evans.** Analysis of cerebral blood flow autoregulation in neonates. *IEEE Trans. Biomed. Eng.* 43: 779–788, 1996.
 30. **Parati, G., J. P. Saul, M. Di Rienzo, and G. Mancia.** Spectral analysis of blood pressure and heart rate variability in evaluating cardiovascular regulation: a critical appraisal. *Hypertension* 25: 1276–1286, 1995.
 31. **Paulson, O. B., S. Strandgaard, and L. Edvinsson.** Cerebral autoregulation. *Cerebrovasc. Brain Metab. Rev.* 2: 161–192, 1990.
 32. **Tiecks, F. P., A. M. Lam, R. Aaslid, and D. W. Newell.** Comparison of static and dynamic cerebral autoregulation measurements. *Stroke* 26: 1014–1019, 1995.
 33. **Wittmann, U., B. Nafz, H. Ehmke, H. R. Kirchheim, and P. B. Persson.** Frequency domain of renal autoregulation in the conscious dog. *Am. J. Physiol.* 269 (*Renal Fluid Electrolyte Physiol.* 38): F317–F322, 1995.
 34. **Zernikow, B., E. Michel, J. Steck, R. M. Schmitt, and G. Jorch.** Cerebral autoregulation of preterm neonates—a nonlinear control system? *Arch. Dis. Child.* 70: F166–F173, 1994.