

# Spontaneous fluctuations in cerebral blood flow: insights from extended-duration recordings in humans

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**Zhang, Rong, Julie H. Zuckerman, and Benjamin D. Levine.** Spontaneous fluctuations in cerebral blood flow: insights from extended-duration recordings in humans. *Am J Physiol Heart Circ Physiol* 278: H1848–H1855, 2000.—To determine the dependence of cerebral blood flow (CBF) on arterial pressure over prolonged time periods, we measured beat-to-beat changes in mean CBF velocity in the middle cerebral artery (transcranial Doppler) and mean arterial pressure (Finapres) continuously for 2 h in six healthy subjects (5 men and 1 woman, 18–40 yr old) during supine rest. Fluctuations in velocity and pressure were quantified by the range [(peak – trough)/mean] and coefficients of variation (SD/mean) in the time domain and by spectral analysis in the frequency domain. Mean velocity and pressure over the 2-h recordings were  $60 \pm 7$  cm/s and  $83 \pm 8$  mmHg, associated with ranges of  $77 \pm 8$  and  $89 \pm 10\%$  and coefficients of variation of  $9.3 \pm 2.2$  and  $7.9 \pm 2.3\%$ , respectively. Spectral power of the velocity and pressure was predominantly distributed in the frequency range of 0.00014–0.1 Hz and increased inversely with frequency, indicating characteristics of an inverse power law ( $1/f^\alpha$ ). However, linear regression on a log-log scale revealed that the slope of spectral power of pressure and velocity was steeper in the high-frequency (0.02–0.5 Hz) than in the low-frequency range (0.002–0.02 Hz), suggesting different regulatory mechanisms in these two frequency ranges. Furthermore, the spectral slope of pressure was significantly steeper than that of velocity in the low-frequency range, consistent with the low transfer function gain and low coherence estimated at these frequencies. We conclude that 1) long-term fluctuations in CBF velocity are prominent and similar to those observed in arterial pressure, 2) spectral power of CBF velocity reveals characteristics of  $1/f^\alpha$ , and 3) cerebral attenuation of oscillations in CBF velocity in response to changes in pressure may be more effective at low than that at high frequencies, emphasizing the frequency dependence of cerebral autoregulation.

blood pressure; spectral analysis; Doppler

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REGULATION OF CEREBRAL BLOOD flow (CBF) is a dynamic process requiring short- and long-term adjustments to match substrate delivery with metabolic demand. Continuous measurements of CBF with high temporal resolution, such as the transcranial Doppler (TCD) technique, have revealed prominent beat-to-beat fluctuations, similar to those observed in heart rate and

arterial pressure (13, 36, 42). Although the specific mechanisms underlying this phenomenon are not clear, data from several studies suggest that different frequency components in the fluctuations in CBF velocity may have different mechanisms (7, 11, 31, 42). For example, short-term ( $>0.20$  Hz) fluctuations in CBF velocity closely match those observed in arterial pressure and likely reflect mechanical/biophysical properties of the cerebrovascular bed in response to changes in arterial pressure (42). In contrast, at lower frequencies ( $<0.20$  Hz), changes in velocity are more independent of changes in arterial pressure and, therefore, may reflect dynamic properties of cerebral autoregulation (11, 42).

At very low frequencies ( $<0.07$  Hz), traditional methods to quantify the variability of biological signals, including linear systems and spectral analysis, are likely to be unrevealing or, frankly, inappropriate (20, 41, 42). Moreover, although the presence of such low-frequency fluctuations in CBF velocity have been identified by us (42, 44) and others (7, 17, 34), the precision with which this variability can be measured has been hampered by the relatively short duration of most reported observations. Fluctuations in CBF at even larger time scales are entirely unknown.

In contrast to such low fluctuations in CBF, it has been well known that arterial pressure fluctuates spontaneously over a wide range of time scales from seconds to hours, and the amplitude of these fluctuations becomes larger at low frequencies, obeying an inverse power law ( $1/f^\alpha$ ) (22, 32, 39). We speculated that large fluctuations in arterial pressure at low frequencies may impose substantial pressure gradients across the cerebrovascular bed. If these fluctuations in pressure are not fully compensated for by changes in cerebrovascular resistance, there should be detectable fluctuations in CBF at these very low frequencies. Furthermore, we hypothesized that dynamic changes in CBF in response to changes in arterial pressure would be attenuated more effectively at low than at high frequencies and, therefore, may result in spectral distributions in CBF velocity different from those in arterial pressure. We tested these hypotheses by recording CBF velocity in the middle cerebral artery (MCA) simultaneously with arterial pressure over an extended duration (2 h) in normal humans.

## METHODS

*Subjects.* Six healthy subjects (5 men and 1 woman,  $29 \pm 8$  yr old,  $76 \pm 15$  kg body wt,  $177 \pm 7$  cm height) participated in

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the study. All were nonsmokers and were free of known cardiovascular, pulmonary, and cerebrovascular disease. 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 the Presbyterian Hospital of Dallas.

*Instrumentation and procedure.* Heart rate was monitored by electrocardiogram. Arterial pressure was measured in the finger by photoplethysmography (Finapres, Ohmeda). For the 2-h data collection in the present study, to avoid the possibility that prolonged duration of recordings from one finger may influence the accuracy of the measurements (15), arterial pressure was measured alternately from the middle finger of each hand for 20 min at a time by using two Finapres devices (15). The measurements in one finger started 5 min before the recording in the contralateral finger was stopped. After 5 min of stabilization, the servo-reset mechanism of the Finapres was turned off, allowing 15 min of uninterrupted data collection (29). The consecutive and overlapping data segments collected from both fingers were linked by off-line processing to construct a continuous time series for arterial pressure.

In the present study, consistent with the reports of other investigators (29), no significant zero drifts in the pressure measurements were observed when the Finapres servo-reset mechanism was turned off during the 15-min data collections. Furthermore, the relative consistency of beat-to-beat changes in pressure from the two fingers was confirmed by performing linear regression between the beat-to-beat values of mean pressure from the simultaneous recording periods [regression slope =  $1.006 \pm 0.06$ , correlation coefficient ( $r^2$ ) = 0.94]. However, an absolute difference of  $2 \pm 4$  mmHg was observed between the two finger measurements. The accuracy of the finger arterial pressure was confirmed with intermittent cuff pressure measurements at the brachial artery by electrophygmomanometry (Suntech). These comparisons were conducted at the beginning of the data collection period during establishment of hemodynamic steady state and every 20 min during the intermittent breaks of the pressure recordings in one finger. Consistent with the finger pressure recordings, no significant drift in the cuff pressure was observed during the 2-h data collection period.

CBF velocity was measured continuously in the MCA by TCD ultrasonography. A 2-MHz Doppler probe (Multiflow, DWL Elektronische Systeme) was placed over the temporal window and fixed at a constant angle and position with an adjustable head gear to obtain optimal signals according to standard techniques (2). The acoustic power of the ultrasound transducer was adjusted as low as reasonably achievable while adequate signal quality was maintained. The power was constant during the 2-h data recordings ranging from 50 to 60 mW/cm<sup>2</sup>. These power levels provided a calculated thermal cranial index <1 at all times, which is below the safety limits recommended by the American Institute for Ultrasound in Medicine and Biology (3). During the data collections, end-tidal PCO<sub>2</sub> was also monitored continuously via nasal cannula with a mass spectrometer (model MGA 1100, Marquette Electronics).

All experiments were conducted between 10 AM and 4 PM,  $\geq 2$  h after a meal and  $>24$  h after the last caffeinated beverage or alcohol, in a quiet, environmentally controlled laboratory with an ambient temperature of 25°C. After  $\geq 30$  min of supine rest, arterial pressure, heart rate, and CBF velocity were recorded continuously for 2 h during spontaneous breathing with the subjects remaining quiet and awake.

*Data analysis.* The analog arterial pressure and spectral envelope of Doppler CBF velocity were sampled simultaneously at 100 Hz and digitized at 12 bits (Multi-Dop X2,

DWL Elektronische Systeme). Beat-to-beat values of mean arterial pressure and velocity were obtained by waveform integration of pressure and velocity from each cardiac cycle. The beat-to-beat values of mean pressure and velocity were then aligned with each corresponding pulse interval and interpolated linearly between the adjacent values to construct a continuous time series, which was then resampled at 1 Hz for spectral analysis (42).

To quantify the variability of pressure and velocity, time domain measures of mean, range [(peak – trough)/mean], and the coefficient of variation (SD/mean) over the 2 h of data collection were calculated for each subject and then averaged to obtain group mean values. For spectral analysis, the mean value of the entire 2 h of data collection was subtracted from each beat of the time series to remove the direct-current component. Two methods were used for spectral estimation. First, to obtain maximal spectral resolution, periodograms for the entire 2-h data set were obtained with a spectral resolution of  $\sim 0.00014$  Hz (21). However, the statistical instability of such a periodogram with high variance may not be appropriate for further quantitative analysis (21). Therefore, the Welch method was employed to reduce the spectral variance at the expense of spectral resolution (40). Considering a trade-off between sufficient spectral resolution and reduction of variance, the 2-h data sets were subdivided into multiple segments of 512 s with 50% overlap and weighted with a Hanning window for spectral estimation. This process resulted in 27 data segments for the spectral average and a reduction in the spectral variance by  $\sim 27$  times of the periodogram estimates, as well as an ultimate spectral resolution of  $\sim 0.002$  Hz (40).

Finally, to quantify the relationship between the changes in pressure and velocity, the transfer and coherence functions were estimated by using the Welch method (8, 40). The transfer function,  $H(f)$ , was defined as

$$H(f) = S_{pv}(f)/S_{pp}(f)$$

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

$$|H(f)| = [H_R^2(f) + H_I^2(f)]^{1/2}$$

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

$|H(f)|$  reflects coupling intensity, and phase reflects the time relationship between the two signals. The magnitude-squared coherence (MSC) function was defined as

$$MSC(f) = |S_{pv}(f)|^2/[S_{pp}(f)S_{vv}(f)]$$

where  $S_{vv}(f)$  is the autospectrum of CBF velocity. A coherence function approximating 1 at a given frequency suggests a linear correlation between the two signals, whereas coherence approaching 0 may indicate a nonlinear relationship or a low signal-to-noise ratio in the estimates (8).

*Statistical analysis.* Power spectra of pressure and velocity were plotted in log-log scales to reveal characteristics of  $1/f^\alpha$  (4). Discrete linear ranges of the spectra were identified by visual inspection. This analysis was feasible especially with the Welch spectra associated with substantial reductions in variances. Linear ranges of the spectra of the periodogram and the Welch estimates were then fitted by linear equations to determine the spectral slope index of  $\alpha$ . Residuals from the regressions were tested for randomness by using the Durbin-Watson test (24, 34). Because significant autocorrelations in

the residuals were found using ordinary least-square curve-fitting procedures, regressions were further conducted by using a generalized least-square (GLS) algorithm with the correlated residuals being modeled by a first-order autoregressive process (24). With the GLS algorithm, the randomness of regression residuals was also confirmed by the Durbin-Watson test. The estimated slope indexes of pressure and velocity with the GLS algorithm were compared using the paired *t*-test. Values are means  $\pm$  SE.  $P \leq 0.05$  was considered statistically significant. Because similar results of the regressions were obtained from the periodogram and from the Welch method, the results presented here are only those estimated from the Welch method. Statistics were performed using PC-based software (SAS Institute, Cary, NC).

## RESULTS

**Time domain analysis.** Group-averaged mean arterial pressure, CBF velocity, and end-tidal  $PCO_2$  over the 2-h recordings were  $83 \pm 3$  mmHg,  $60 \pm 3$  cm/s, and  $36 \pm 1$  mmHg, respectively. Beat-to-beat arterial pressure and CBF velocity revealed prominent variations around these mean values with different time scales (Figs. 1 and 2). Moreover, fluctuations with small amplitudes at short time scales appeared nested within the fluctuations, with large amplitudes at longer time scales (Figs. 1 and 2). The group-averaged coefficients of variation in arterial pressure and velocity were  $7.9 \pm 1.0$  and  $9.3 \pm 0.9\%$  and the ranges were  $77 \pm 8$  and  $89 \pm 10\%$ , respectively.

**Spectral analysis.** The periodogram of beat-to-beat changes in pressure and velocity showed a broad distribution from 0.00014 to 0.5 Hz, with the power predominantly located below 0.1 Hz (Fig. 3). The ratio of spectral power in the frequency range of 0.00014–0.1 Hz to the total spectral power was  $97 \pm 1\%$  for the pressure and  $93 \pm 1\%$  for the velocity. When plotted on

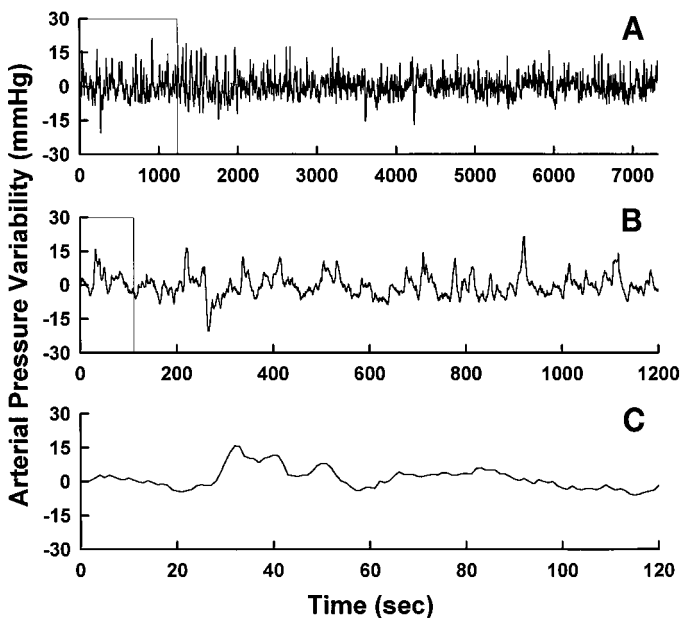


Fig. 1. Representative beat-to-beat changes in arterial pressure. *A*: 2 h of recordings. *B* and *C*: zoomed periods of 20- and 2-min recordings, respectively, within rectangular boxes. Mean value of pressure normalized for plot of beat-to-beat changes is 76 mmHg in this subject.

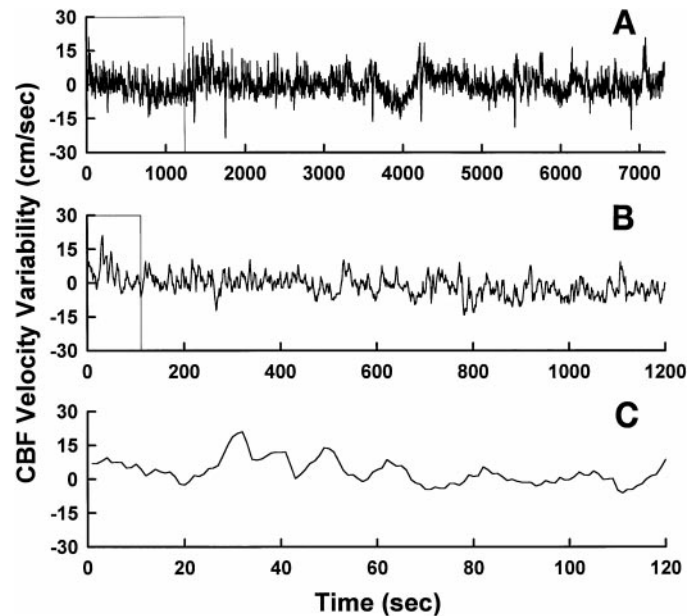


Fig. 2. Simultaneous recordings of beat-to-beat changes in mean cerebral blood flow (CBF) velocity from subject in Fig. 1. *A*: 2 h of recordings. *B* and *C*: zoomed periods of 20- and 2-min recordings, respectively, within rectangular boxes. Mean value of CBF velocity normalized for plot of beat-to-beat changes is 67 cm/s in this subject.

a log-log scale, spectral power of pressure and velocity increased inversely with frequency, demonstrating characteristics of an inverse power law (Figs. 4 and 5). However, the rate of increase appeared to be higher in the high- than in the low-frequency range (Figs. 4 and 5). The deflection points of spectral slopes were identified in the Welch spectra with substantial reduction of variance compared with the periodograms (Figs. 4 and 5). Two frequency ranges were identified: one in the 0.02- to 0.5-Hz range, with high rates of increases in spectral power, and one in the 0.002- to 0.02-Hz range, with low rates of increases in the spectral power (Figs. 4 and 5). These characteristics were observed in all

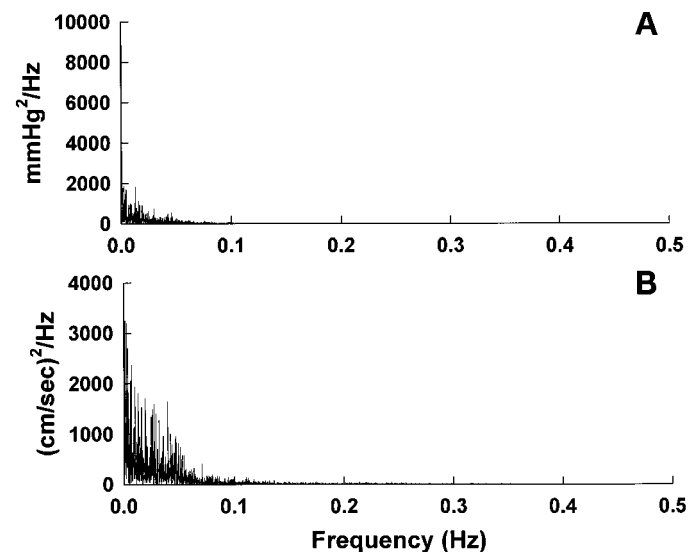


Fig. 3. Linear scale representations of power spectral density of beat-to-beat changes in arterial pressure (*A*) and mean CBF velocity (*B*).

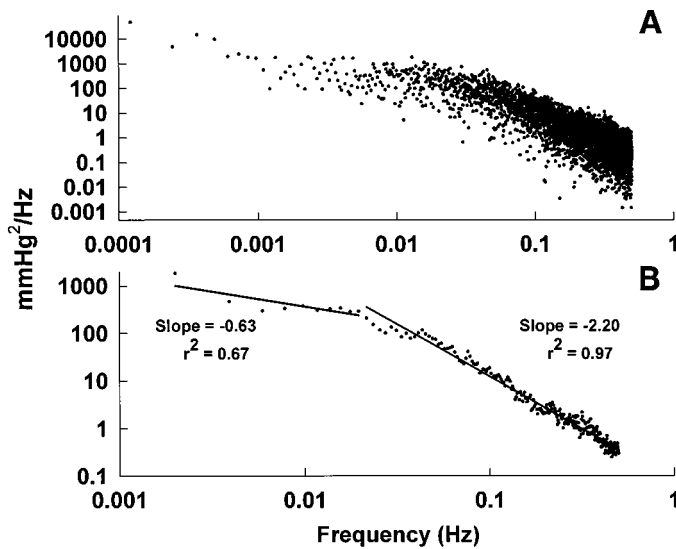


Fig. 4. Log-log scale representations of power spectral density of beat-to-beat changes in arterial pressure. *A*: estimate from periodogram. *B*: estimate from Welch method. Spectral variance in periodogram decreased substantially by using Welch method, and dual range distribution of  $1/f^{\alpha}$  relationship is clearly shown with reduction of variance.

subjects in the present study. Therefore, linear regression was performed separately in each of these two frequency ranges with use of the Welch estimates.

In the low-frequency range of 0.002–0.02 Hz, the group-averaged  $r^2$  values for the pressure and velocity were  $0.69 \pm 0.07$  ( $P < 0.01$ ) and  $0.40 \pm 0.14$  ( $P = 0.3$ ), respectively. The group-averaged slope indexes ( $\alpha$ ) were  $-1.08 \pm 0.19$  for the pressure and  $-0.34 \pm 0.09$  for the velocity ( $P < 0.05$ , pressure vs. velocity). In the high-frequency range of 0.02–0.5 Hz, the  $r^2$  values for the pressure and velocity were  $0.98 \pm 0.01$  ( $P < 0.001$ ) and

$0.98 \pm 0.01$  ( $P < 0.001$ ), respectively. The  $\alpha$  values were  $-2.31 \pm 0.11$  for the pressure and  $-2.31 \pm 0.08$  for the velocity ( $P = 0.97$ , pressure vs. velocity). Both of these  $\alpha$  values of pressure and velocity were greater in the high- than in the low-frequency range ( $P < 0.001$ ).

The Durbin-Watson  $d$  statistics were  $1.39 \pm 0.07$  and  $1.99 \pm 0.07$  for the pressure and  $1.46 \pm 0.07$  and  $2.06 \pm 0.05$  for the velocity in the low- and high-frequency ranges, respectively, associated with no significant autocorrelations of the regression residuals.

**Transfer and coherence function.** Group-averaged transfer function gain revealed high-pass filter properties up to 0.3 Hz associated with a gradual decrease in phase (Fig. 6). The coherence function was high in the frequency range of 0.10–0.30 Hz, suggesting linear associations between the changes in pressure and velocity and, therefore, reliable transfer function estimates (Fig. 6). The low coherence above 0.30 Hz was likely due to the absence of substantial variability in pressure or velocity at these frequencies and, consequently, a low signal-to-noise ratio. In contrast, the low coherence at the low frequencies  $< 0.10$  Hz may suggest a fundamentally nonlinear relationship between the two variables, inasmuch as spectral power in pressure and velocity was high at these frequencies (Fig. 6).

**DISCUSSION**

In the present study we observed long-term fluctuations in CBF velocity in the MCA that occurred simultaneously with those in arterial pressure. Specifically, spectral power of arterial pressure and CBF velocity was predominantly distributed in the frequency range of 0.00014–0.1 Hz. The presence of these high-amplitude, low-frequency fluctuations in the CBF velocity associated with the variations in arterial pressure appears contrary to what might be predicted from the

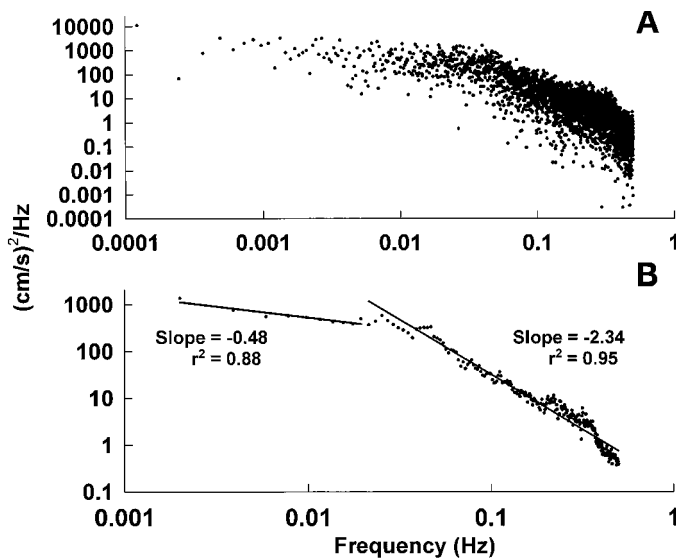


Fig. 5. Log-log scale representations of power spectral density of beat-to-beat changes in mean CBF velocity. *A*: estimate from periodogram. *B*: estimate from Welch method. Spectral variance in periodogram decreased substantially by using Welch method, and dual range distribution of  $1/f^{\alpha}$  relationship is clearly shown with reduction of variance.

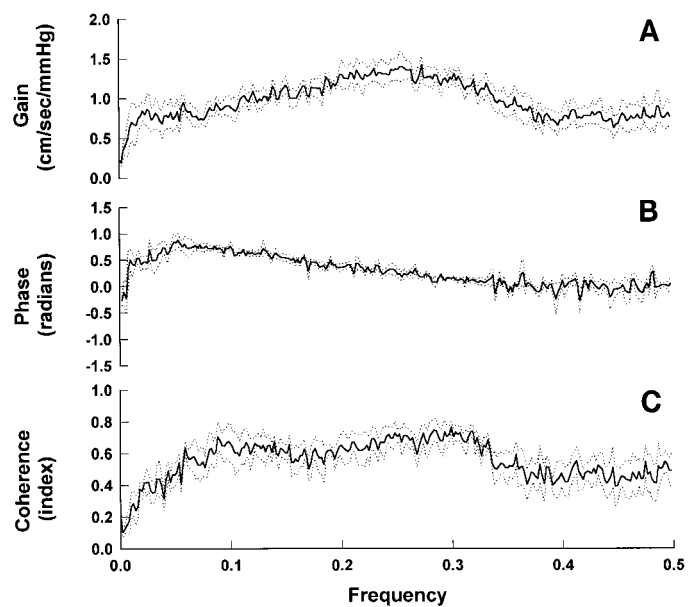


Fig. 6. Group-averaged transfer function gain (*A*), phase (*B*), and coherence function (*C*) between changes in arterial pressure and CBF velocity. Solid line, averaged estimates; dotted lines, SE.

traditional concept of autoregulation, which would anticipate a relatively constant flow in response to changes in pressure (33). Furthermore, we found that, when plotted on log-log scales, spectral power of arterial pressure and CBF velocity revealed characteristics of an inverse power law. However, the spectral slope of velocity was significantly lower than that of pressure in the low-frequency range of 0.002–0.2 Hz, associated with low transfer function gain and low coherence. These data are consistent with our hypothesis that dynamic cerebral autoregulation is more effective at low than at high frequencies.

*Methodological considerations and limitations.* In the present study we used high temporal resolution TCD ultrasound to measure beat-to-beat changes in CBF velocity in the MCA. The accuracy and reliability of this technique for measurement of relative changes in CBF have been well documented by many studies (1, 18, 25). In the present study, on the basis of the data from angiographic studies (14) and direct visualization of the MCA during surgery (12), we assumed that diameter of the MCA remained relatively constant in these normal subjects. Thus beat-to-beat changes in the CBF velocity should reflect primarily beat-to-beat changes in CBF in the MCA (19, 42).

We also measured beat-to-beat changes in arterial pressure continuously for 2 h using finger plethysmography. Two limitations should be considered with use of this technique in the present study. First, arterial pressure measured by finger plethysmography may not be exactly the same as that obtained from intra-arterial pressure recordings (15). However, accumulated evidence, including our own experience, indicates that, under a variety of physiological and pathological conditions, beat-to-beat changes in pressure, rather than the absolute values, can be measured accurately by using this noninvasive method (15, 29, 42). Second, it has been reported that recording of pressure in one finger for >30 min may cause numbness and pain in the finger and affect the accuracy and reliability of the measurements (15). To avoid this possibility, pressure was measured alternately from two fingers in the present study. Although we found  $2 \pm 4$  mmHg differences in the mean pressure between the two fingers, linear regression of beat-to-beat changes from the simultaneous recordings showed a slope of identity, indicating that the relative changes in the mean arterial pressure were virtually the same at the two fingers.

One question we have considered is whether spontaneous fluctuations in mean arterial pressure would reflect spontaneous changes in cerebral perfusion pressure (CPP). By definition, CPP is mean arterial pressure minus intracranial pressure (ICP). Thus, without measurement of ICP, it is difficult to calculate the actual changes in CPP. Furthermore, it has been shown that ICP also fluctuates spontaneously in the frequency range of 0.008–0.03 Hz with different amplitudes depending on the steady-state value of ICP (26, 36). Thus, if changes in ICP were completely in phase with changes in mean arterial pressure, variations in CPP could be less than changes in arterial pressure. How-

ever, data have shown that low-frequency fluctuations in arterial pressure precede changes in ICP by several seconds, suggesting that fluctuations in ICP are a secondary effect of changes in arterial pressure (36). In the present study we assumed that fluctuations in ICP were small in normal subjects (26); therefore, spontaneous changes in arterial pressure were assumed to reflect changes in CPP.

In the present study, using an ordinary least-squares algorithm, we found that regression residuals of the spectra of pressure and velocity were not random. To improve the statistical efficacy of the regression, a GLS algorithm was employed, with the correlated residuals being modeled by a first-order autoregressive process (24). With this algorithm, optimal estimates of spectral slopes were obtained, as evidenced by the Durbin-Watson tests (24). However, within the scope of the data of the present study, it is unknown whether the correlated residuals modeled by the autoregressive process are intrinsic properties of the physiological process or simply reflect nonrandom measurement noise imposed on the inverse power law distributions observed in pressure and velocity.

*Blood pressure variability.* Spontaneous variations in arterial pressure have been recognized for >100 years since Ludwig first observed this phenomenon in 1847 (27). However, only recently has it been realized that these fluctuations in pressure may reveal important information about the regulation of cardiovascular function (32). For short-term data recordings of several minutes, power spectral analysis has shown that blood pressure variability mainly consists of three components: one at a high-frequency range around respiratory frequencies, one in a middle-frequency range of  $\sim 0.1$  Hz, and one in a low-frequency range below 0.05 Hz (32). Although the underlying mechanisms for generating these rhythmic fluctuations are not always clear, studies have shown that the 0.1-Hz component is likely controlled by baroreflex function and is associated with changes in peripheral sympathetic nerve activity (30). For long-term ambulatory pressure recordings of 24 h, it has been shown that the spectral power of fluctuations in pressure increases inversely with frequency, obeying an inverse power law ( $1/f^\alpha$ ) (28, 32). Such low-frequency oscillations in pressure have significant clinical implications and have been shown to predict end-organ damage in patients with hypertension (10).

However, it is not clear whether the inverse power law spectral distribution measured over 24 h is an intrinsic property of cardiovascular function or simply reflects the response of arterial pressure to daily activities associated with these ambulatory recordings (28, 32). In the present study we found that spectral power increased inversely with frequency similar to that observed in 24-h recordings, despite the recordings being obtained entirely in the quiet resting state (28). However, in contrast to the spectral distribution of the 24-h recordings, which could be fitted with a  $1/f^\alpha$  model with one constant  $\alpha$  (28, 32), the power spectra obtained in the present study showed two range distributions

with different rates of increases in the spectral power. Fitting these spectral distributions with two  $1/f^\alpha$  models, we found that  $\alpha$  was significantly lower in the frequency range below 0.02 Hz than above 0.02 Hz. One possibility for the discrepancy between spectral distributions of 24-h recordings and the present study may be that the changes in pressure with very large time scales, such as circadian rhythms, could not be detected by the 2-h time window used in the present study and, therefore, could not contribute to the increases in the spectral power in the low-frequency range. However, the fact that the deflection point of the two range distributions was 0.02 Hz and the low-frequency range identified robustly by using the Welch method was 0.002–0.02 Hz suggests that this characteristic of spectral distribution occurred entirely within the time scale of <10 min. Therefore, variations in pressure with larger time scales, e.g., circadian rhythms, should have limited influence on the spectral power in the frequency ranges identified in the present study. These data thus suggest that physical activity may contribute importantly to the spectral distribution of 24-h recordings in the frequency ranges that overlap those in the present study (28, 32).

However, it is important to emphasize that the data reported in the present study are primarily descriptive, and thus the specific mechanisms underlying the two spectral range distributions are not known. Interestingly, in infants and in conscious dogs under resting conditions, power spectra of spontaneous changes in arterial pressure also have shown a bimodal, dual range distribution similar to that observed in the present study (34, 39). Moreover, it has been shown that baroreceptor denervation markedly increased the slope of the high-frequency component of the  $1/f^\alpha$  relationship, suggesting that the baroreflex is primarily responsible for buffering variations in pressure in this frequency range (>0.03 Hz). However, other autonomic influences also appear to play a role in the low-frequency component of the  $1/f^\alpha$  relationship (<0.03 Hz), although the exact mechanisms or pathways involved are ill defined (39). These data suggest that fluctuations in pressure in the two frequency ranges of the  $1/f^\alpha$  relationship may be modulated independently by different mechanisms. In addition, as mentioned above, spectral analysis of short-term recordings of arterial pressure indicates that, even within the high-frequency range of 0.02–0.5 Hz, fluctuations in pressure around 0.1 Hz may have mechanisms different from the respiratory modulations at 0.2–0.3 Hz. However, owing to the relatively low power of these spectral components in the long-term recordings, distinct spectral peaks similar to those observed in short-term recordings could not be demonstrated in the present study.

*CBF velocity variability.* Recently, spontaneous fluctuations in CBF velocity in the MCA have been reported using the TCD technique (13, 36, 42). Although the physiological significance and specific mechanisms responsible for this phenomenon are still not clear, studies have shown similar fluctuations in brain tissue

metabolic substrates,  $PO_2$ , and red blood cell velocity in the capillary vascular beds in animals (6, 37) and in the signal intensity of magnetic resonance imaging in humans that likely reflect changes in brain oxygenation and blood volume (5). These findings suggest the possibility that changes in the velocity in the MCA may transfer downstream to cerebrovascular beds and influence brain perfusion or, conversely, may be mediated by metabolic regulation of cerebrovascular resistance.

In a previous study, with short-term recordings of several minutes, we found spectral distributions in the CBF velocity similar to those in arterial pressure, suggesting that short-term fluctuations in CBF velocity are closely related to changes in arterial pressure (42). The present study extends these previous observations by using extended-duration recordings to demonstrate spontaneous fluctuations in CBF velocity at multiple time scales from a frequency of 0.00014 to 0.5 Hz, with spectral power predominantly located at <0.1 Hz.

Furthermore, we found an inverse power law spectral distribution in the CBF velocity similar to that observed in arterial pressure. In a complex system such as control of CBF in response to changes in perfusion pressure, it is not surprising that nonlinear regulatory mechanisms may result in a system output with an inverse power law spectral distribution (4). Nonlinearity in the cerebral circulation has also been reported using other methods (35, 38, 41). For example, by systematically aggregating data using the relative dispersion method, it has been shown that spontaneous variations in CBF velocity demonstrate characteristics of temporal fractals (35, 41). Nonlinear characteristics in the velocity waveforms also have been shown by using the phase reconstruction method and by the estimation of Lyapunov exponents (38). However, we caution that an inverse power law spectral distribution does not necessarily guarantee the presence of nonlinear mechanisms underlying an observed time series (4). Furthermore, the similar time and frequency domain characteristics in the changes in pressure and velocity suggest that any nonlinearity apparent in the signal of CBF velocity may originate from the systemic circulation.

In the present study we found that although no significant differences in the spectral slopes were found between the pressure and velocity in the high-frequency range, the slope of pressure was significantly higher than that of velocity in the low-frequency range. These findings, in association with the low transfer function gain estimated at the low frequencies, suggest that cerebral attenuation of fluctuations in CBF velocity in response to changes in pressure is more effective in the low- than in the high-frequency range.

Two cautions, however, should be highlighted. First, although the estimates of spectral slopes in pressure and velocity were virtually the same in the high-frequency range, owing to the limited number of subjects in the present study, we cannot exclude a possibility of type II error. That is, a true difference may exist between the spectral slopes of pressure and velocity. However, on the basis of the estimates of spectral slopes

and the associated standard errors, such a difference, if any, should be <14% of the group-averaged estimates with a statistical power >80%. Second, although the estimated spectral slopes of velocity in the low-frequency range were negative in all the subjects, suggesting increases in the spectral power with decreases in frequency, the group-averaged estimates were not significantly different from zero. However, this limitation should have few confounding effects on the spectral slope comparisons in the present study.

**Cerebral autoregulation.** In the present study the dynamic relationship between changes in pressure and velocity was further quantified by transfer function and coherence function analysis. Transfer function gain and coherence function are low at frequencies <0.1 Hz compared with those at high frequencies. Extended-duration recordings were used to obtain these data, and therefore, with improved spectral resolution and enhanced statistical stability in the estimates, these data are consistent with our previous findings (42). First, the ability of the cerebral vascular bed to attenuate oscillations in arterial pressure and minimize changes in CBF appears to be more effective in the low- than in the high-frequency range. Second, the low coherence function reveals that nonlinear regulatory mechanisms may play an important role in the cerebral circulation at the low frequencies <0.10 Hz (43).

We also have considered that if variations in CBF velocity and, presumably, flow are induced by changes in arterial pressure, especially at low frequencies with large amplitudes, how can these data be reconciled with the traditional concept of cerebral autoregulation, which implies that CBF should remain relatively constant, despite slow variations in pressure (33)? One explanation may be that the amplitudes of the observed spontaneous changes in pressure and velocity were too small to be detected effectively by autoregulatory mechanisms. However, 77% changes in pressure and 89% changes in velocity, associated with large amounts of spectral power in the low-frequency ranges, observed in the present study argue against this possibility. In contrast, we speculate that the well-known steady-state pressure-flow relationship may be defined only when variations in pressure and flow are averaged out over large time scales. In real-life situations, however, CBF must vary constantly in response to dynamic changes in arterial pressure. Different autoregulatory mechanisms of the cerebrovascular bed may attenuate the effects of variations in pressure on flow at different time scales with different time constants (42). For example, a metabolically driven stimulus may be more effective in attenuating changes in pressure at low frequencies, whereas endothelium-dependent nitric oxide-mediated regulation with a short time constant may be more effective at higher frequencies (9). Although dynamic regulation of cerebrovascular resistance activated by these mechanisms may attenuate oscillations in flow in response to changes in pressure (42), data observed in the present study suggest that this process is not as efficient as would be expected from the traditional concept of cerebral autoregulation.

**Clinical implications.** With the extensive application of the TCD technique in clinical diagnosis of cerebrovascular diseases and in physiological studies of cerebral hemodynamics, it is essential to understand the time scale properties of spontaneous changes in CBF velocity, because measurements obtained with short time segments of seconds to minutes may not necessarily reflect CBF velocity over more prolonged periods or at different times (16, 23). Thus comparisons between measures of CBF velocity with different lengths of time segments must be made with great caution. However, quantifying the variability of CBF velocity by using spectral analysis and evaluation of the dynamic relationship between spontaneous changes in arterial pressure and CBF velocity by use of the transfer and coherence function technique may be useful in the assessment of cerebral autoregulation in clinical and physiological studies.

In summary, with use of extended-duration recordings of arterial pressure and CBF velocity, this study documents long-term fluctuations in CBF velocity that occurred mainly in the frequency range of 0.00014–0.1 Hz and simultaneously with those observed in arterial pressure. Furthermore, the spectrum of CBF velocity reveals characteristics of an inverse power law with a dual range distribution similar to those observed in arterial pressure. These data, combined with the estimates of transfer and coherence function, suggest that regulation of CBF in response to dynamic changes in pressure may have different regulatory mechanisms in different frequency ranges.

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