

Deterioration of cerebral autoregulation during orthostatic stress: insights from the frequency domain

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Zhang, Rong, Julie H. Zuckerman, and Benjamin D. Levine. Deterioration of cerebral autoregulation during orthostatic stress: insights from the frequency domain. *J. Appl. Physiol.* 85(3): 1113–1122, 1998.—To determine whether dynamic cerebral autoregulation is impaired during orthostatic stress, cerebral blood flow (CBF) velocity in the middle cerebral artery (transcranial Doppler) and mean arterial pressure (MAP; Finapres) were measured continuously in 12 healthy subjects during ramped maximal lower body negative pressure (LBNP) to presyncope. Velocity and pressure were averaged over 6-min periods of stable data at rest and during LBNP to examine steady-state cerebral hemodynamics. Beat-to-beat variability of velocity and pressure were quantified by a “variation index” (oscillatory amplitude/steady-state mean value) and by power spectral analysis. The dynamic relationship between changes in pressure and velocity was evaluated by the estimates of transfer and coherence function. The results of the study were as follows. Steady-state MAP remained relatively constant during LBNP, whereas CBF velocity decreased progressively by 6, 15, and 21% at –30, –40, and –50 mmHg LBNP, respectively ($P < 0.05$ compared with baseline). At the maximal level of LBNP (30 s before presyncope) MAP decreased by 9.4% in association with a prominent reduction in velocity by 24% ($P < 0.05$ compared with baseline). The variation index of pressure increased significantly from $3.8 \pm 0.3\%$ at baseline to $4.5 \pm 0.6\%$ at –50 mmHg LBNP in association with an increase in the variation index of velocity from 6.0 ± 0.6 to $8.4 \pm 0.7\%$ ($P < 0.05$). Consistently, the low- (0.07–0.20 Hz) and high-frequency (0.20–0.30 Hz) power of variations in pressure and velocity increased significantly at high levels of LBNP ($P < 0.05$) in association with an increase in transfer function gain (24% at –50 mmHg, $P < 0.05$). We conclude that the damping effects of autoregulation on variations in CBF velocity are diminished during orthostatic stress in association with substantial falls in steady-state CBF velocity. We suggest that these changes may contribute in part to the development of presyncope.

cerebral blood flow; blood pressure; orthostasis; Fourier analysis

ORTHOSTATIC SYNCOPE is a common problem affecting patients with autonomic dysfunction as well as normal individuals after bed rest or spaceflight (7). The specific mechanism of orthostatic syncope may not always be clear and probably is multifactorial (23). However, the final event leading to syncope must be ultimately a reduction in cerebral perfusion sufficient to cause loss of consciousness (24).

Recently, we and other investigators have shown that, even without a significant change in mean arte-

rial pressure, steady-state cerebral blood flow (CBF) velocity measured in the middle cerebral artery (MCA) by transcranial Doppler (TCD) decreases substantially during lower body negative pressure (LBNP)-induced orthostatic stress (6, 24, 37). If we assume that the changes in CBF velocity are proportional to the changes in CBF (22, 28), these findings seem to be at odds with the traditional concept of autoregulation, which would predict a relatively constant CBF within a wide range of perfusion pressure (32). Therefore, we have speculated that cerebral autoregulation becomes impaired during orthostatic stress and that it may contribute to the occurrence of orthostatic syncope (24, 37).

With the high temporal resolution of the TCD technique for noninvasive recording of CBF velocity in humans, it has been shown that cerebral autoregulation is a frequency-dependent phenomenon, with properties that may be characterized in the frequency domain by transfer-function analysis (4, 12, 36). For example, we have shown that in the frequency range of 0.07–0.30 Hz, beat-to-beat variations of CBF velocity measured in the MCA are closely related to spontaneous changes in mean arterial pressure (36). Furthermore, the dynamic relationship between these two variables can be modeled by a high-pass filter in the transmission of changes in arterial pressure to CBF velocity (4, 9, 36). On the basis of traditional concepts of cerebral autoregulation, we have speculated that effective autoregulation would attenuate spontaneous changes in CBF velocity in the face of variations in pressure, which would correspond to a relatively lower transfer function gain between these two variables. On the other hand, impairment of autoregulation would correspond to a higher gain with less-attenuated variations in velocity (36). Furthermore, a high correlation between changes in arterial pressure and CBF velocity evaluated by estimates of the coherence function would indicate an increased dependence of changes in velocity on pressure, suggesting impairment of autoregulation (12, 37).

We conducted the present study to evaluate the effects of orthostatic stress on the frequency components of cerebral autoregulation by using the method of transfer-function analysis between the spontaneous changes in arterial pressure and CBF velocity. We hypothesized that the attenuation effect of autoregulation on changes in CBF velocity would be diminished during orthostatic stress.

METHODS

Subjects

Twelve healthy subjects (5 men, 7 women) with a mean age of 32 ± 7 yr, height of 172 ± 11 cm, and weight of 70 ± 13 kg

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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.

LBNP

Progressive LBNP was used to decrease central blood volume in a graded fashion and to facilitate physiological evaluation during orthostatic stress. Subjects were placed supine in a Plexiglas LBNP box that was sealed at the level of the iliac crests. Suction was provided by a vacuum pump and was controlled with a variable autotransformer. The negative pressure of the chamber was monitored with a manometer. After at least a 30-min baseline period of quiet rest, the magnitude of the suction was increased in a stepwise fashion according to the following protocol: -15 mmHg for 13 min, -30 mmHg for 13 min, and then increasing negative pressure increments by -10 mmHg every 13 min to the point of maximal tolerance. LBNP was terminated if the subject developed signs and/or symptoms of presyncope: sudden onset of nausea, sweating, light-headedness, bradycardia, or hypotension (sustained systolic blood pressure <80 mmHg).

Instrumentation

Heart rate (HR) was monitored continuously by electrocardiogram (ECG), and arterial pressure was also measured continuously in the finger by using photoplethysmography (Finapres, Ohmeda). Intermittent arterial pressure was recorded in the arm by electrophygmomanometry (Suntech) with a microphone placed over the brachial artery and the Korotkoff sounds gated to the ECG. Spontaneous respiratory frequency was monitored by using a piezoelectric pneumograph (Protech).

CBF velocity was obtained continuously in the MCA by TCD ultrasonography. 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 (1). Breath-to-breath end-tidal CO_2 was also monitored continuously via a nasal cannula by using a mass spectrometer (model MGA 1100, Marquette Electronics).

Procedures

All experiments were performed in the morning, at least 2 h after the subjects consumed a light breakfast and >12 h after their last caffeinated or alcoholic beverage, in a quiet, environmentally controlled laboratory, with an ambient temperature of 25°C . After the subjects rested in the supine position for at least 30 min, 6-min beat-to-beat values of HR, finger arterial pressure, and CBF velocity were recorded during spontaneous respiration as baseline data for spectral- and transfer-function analysis. At the end of baseline data acquisition, -15 mmHg LBNP was applied with a 2-min period at the beginning for stabilization of cardiovascular hemodynamics. Then, 6 min of beat-to-beat arterial pressure and CBF velocity were collected for both the steady-state mean value and spectral- and transfer-function analysis. This procedure was repeated at each level of LBNP until the criteria for termination of LBNP were satisfied. The servo-reset mechanism of the Finapres instrument was turned off during the 6 min of steady-state measurements to permit an uninterrupted period of data collection. The accuracy and

reliability of this technique for recording of arterial pressure have been evaluated in numerous studies (19, 30). In our laboratory, the beat-to-beat mean values and pulsatile waveforms of arterial pressure measured in the brachial artery with an indwelling catheter are tracked well with the Finapres recordings (36). The intermittent arterial pressure measured in the arm was also monitored at each stage of LBNP.

Data Analysis

The analog arterial pressure and peak envelope of Doppler CBF velocity were sampled simultaneously at 100 Hz and digitized at 12 bits (Multi-Dop X2, DWL). Real time beat-to-beat values of mean arterial pressure and mean CBF velocity were calculated and stored for off-line analysis.

Data preprocessing. Beat-to-beat changes of mean pressure and velocity were aligned with the R-wave peaks of the ECG to construct discrete time series based on beat numbers. Then, a line was interpolated between the adjacent values of pressure or velocity to form a continuous time series for the pressure or velocity, respectively. The linearly interpolated time series were resampled at 1 Hz for time- and frequency-domain analysis. The resampling frequency was determined via the spectral analysis of spontaneous changes in pressure and velocity and was based on the Nyquist theorem (33).

Time-domain analysis. For steady-state data analysis, mean values of the time series were obtained from a 6-min average of the beat-to-beat changes in pressure and velocity. To quantify the spontaneous changes of pressure and velocity, the calculated mean values were subtracted from each of the corresponding time series to offset the time series changing around a zero value. Then, the time series were rectified and averaged to estimate mean oscillatory amplitudes of pressure and velocity. For statistical comparison, a "variation index" was defined as the mean oscillatory amplitude divided by the mean value of the steady-state data (similar to a coefficient of variation) and estimated at baseline and each level of LBNP. Comparison of the variation index of velocity to pressure allows comparison of proportional changes in velocity to proportional changes in pressure.

Frequency-domain analysis. The autospectra of changes in pressure and velocity and the cross spectrum between these two signals were calculated by the Welch method (27). The autospectrum is the result of Fourier transform of a given time series and represents the power distribution of the signal in different frequency components. The cross spectrum reflects how changes in velocity are related to changes in pressure at specific frequencies (3). The transfer function between changes in pressure and velocity was estimated as the cross spectrum divided by the autospectrum of pressure (3). In the present study, to compare dynamic properties of the cerebrovascular system under different steady-state conditions, the time series of pressure and velocity were first normalized by their steady-state mean values for transfer-function estimation (16). The transfer-function gain and phase spectrum were then derived from the real and imaginary part of the complex transfer function by standard methods (3).

The linearity of the system and reliability of the transfer-function estimation were evaluated by a coherence function (3, 26). When the coherence function approaches 1 in a specific frequency range, it suggests a linear relationship and high signal-to-noise ratio between two variables, and therefore it is a reliable estimation of the transfer function. On the other hand, coherence approximating 0 may indicate either a nonlinear relationship, severe noise in the experimental data, or simply no relation between two variables, and thus it is a poor estimation of the transfer function (3, 26).

Furthermore, to test the hypothesis that a low coherence (<0.5) between changes in pressure and velocity may indicate intrinsic nonlinearities in cerebral hemodynamics (36), correlation analysis between the estimates of coherence function and the spectral power of pressure was conducted in the present study. In a linear system, the coherence function is independent of the power of the input signal (3, 26). Conversely, nonlinear systems demonstrate significant dependent of coherence function on the power of the input signal (26).

On the basis of a previous study of coherence-function analysis (36), spectral powers of pressure and velocity were calculated in the frequency ranges of 0.02–0.07 Hz (the very-low-frequency power), 0.07–0.20 Hz (the low-frequency power), and 0.20–0.30 Hz (the high-frequency power), respectively. The mean values of transfer gain, phase, and coherence function in the above frequency ranges were also calculated for statistical analysis.

Statistical Analysis

Changes in hemodynamic variables and the spectral and the transfer-function index at each level of LBNP were compared by using one-way ANOVA with Duncan's post hoc tests for multiple comparisons. A value of $P < 0.05$ was accepted as statistically significant, and all data were represented as means \pm SE. Statistics were performed by using a personal computer-based software program (ABstat, Anderson Bell).

RESULTS

Hemodynamic Responses to LBNP

All of the subjects completed the experimental protocol through at least -40 mmHg LBNP. Five of twelve subjects ended the maximal LBNP test at the level of -50 mmHg, three at -60 mmHg, three at -70 mmHg, and one at -80 mmHg, giving a group averaged tolerance level of -60 ± 10 mmHg. Steady-state responses of systemic and cerebral hemodynamics to LBNP are presented in Table 1. As expected, systolic and pulse pressure decreased at high levels of LBNP in association with a significant increase in HR ($P < 0.05$; Table 1). In contrast to the well-maintained mean arterial pressure, CBF velocity decreased progressively by 6, 15, and 21% at -30 , -40 , and -50 mmHg LBNP, respectively ($P < 0.05$; Table 1). Compared with baseline, the averaged mean arterial pressure over 30 s immediately before the release of maximal LBNP was decreased by 9.4% from 89 ± 5 to 81 ± 6 mmHg ($P <$

0.05) in association with a further fall in the CBF velocity by 24% from 67 ± 6 to 51 ± 3 cm/s ($P < 0.05$). Representative CBF velocity and arterial pressure waveforms from one subject at rest and immediately before the onset of presyncope are shown in Fig. 1. In contrast to previous observations (24), in the present study we found that the steady-state mean value of end-tidal CO_2 also decreased by 13 and 20% at -40 and -50 mmHg LBNP, respectively ($P < 0.05$) in association with a constant respiratory rate (Table 1).

Variability Analysis

Representative beat-to-beat changes of mean arterial pressure and CBF velocity from one subject at rest and during LBNP are shown in Fig. 2. At baseline, mean arterial pressure varied around a steady-state value of 75 mmHg while mean CBF velocity varied around a steady-state value of 80 cm/s (Fig. 2). With increasing LBNP, steady-state values of pressure increased slightly, whereas steady-state values of velocity decreased progressively at high levels of LBNP (Fig. 2). In comparison with these steady-state changes in pressure and velocity, variability of pressure and velocity with a roughly 10-s rhythm (~ 0.1 Hz) increased simultaneously at -40 , -50 , and -60 mmHg LBNP (Fig. 2). For all subjects, the variation index of beat-to-beat changes in pressure increased significantly from $3.8 \pm 0.3\%$ at baseline to $4.5 \pm 0.6\%$ at -50 mmHg LBNP ($P < 0.05$; Fig. 3A). Coincident with these changes in pressure, the variation index in velocity also increased significantly from 6.0 ± 0.6 to $8.4 \pm 0.7\%$ at -50 mmHg LBNP ($P < 0.05$; Fig. 3B).

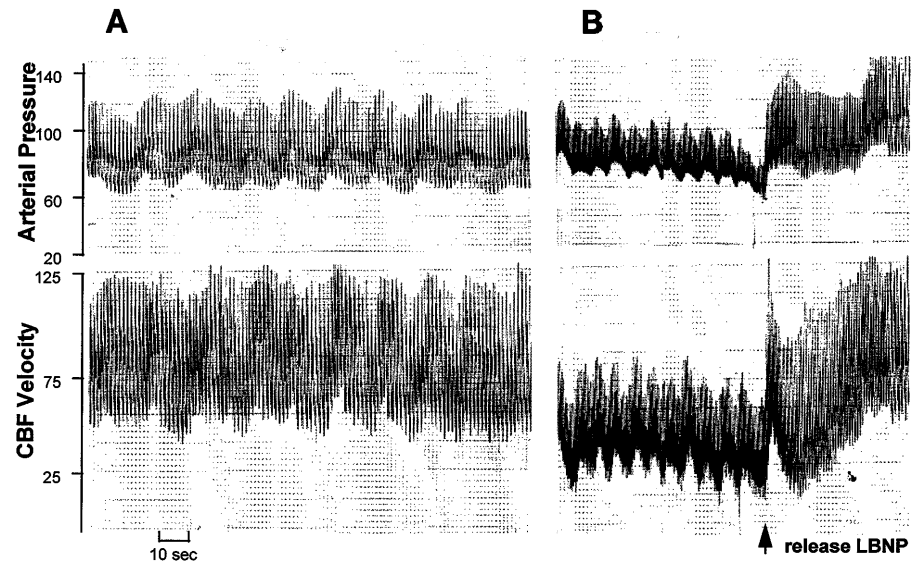
Representative frequency-domain analysis of beat-to-beat changes in pressure and velocity at baseline is shown in Fig. 4. For all subjects, there were no significant changes in the spectral power of pressure and velocity in the very-low-frequency range during LBNP. However, compared with baseline, the spectral power of arterial pressure in the low-frequency range increased significantly from 3.9 ± 0.9 at baseline to 10.5 ± 4.1 mmHg² at -50 mmHg LBNP ($P < 0.05$; Fig. 5A), and the power in the high-frequency range increased significantly from 0.2 ± 0.1 at baseline to 1.2 ± 0.8 mmHg² at -50 mmHg ($P < 0.05$) (Fig. 5B). In association with these changes in pressure, the spectral power of velocity in the low-frequency range increased significantly

Table 1. Steady-state hemodynamics during lower body negative pressure

	LBNP, mmHg				
	0	-15	-30	-40	-50
SBP, mmHg	127 \pm 6	125 \pm 6	124 \pm 5	123 \pm 5	118 \pm 5*
DBP, mmHg	72 \pm 4	73 \pm 5	75 \pm 4	77 \pm 4	77 \pm 5
PBP, mmHg	55 \pm 3	52 \pm 4	49 \pm 3	46 \pm 2*	41 \pm 2*
HR, beats/min	61 \pm 4	63 \pm 4	69 \pm 4*	78 \pm 4*	86 \pm 6*
V_{MCA} , cm/s	67 \pm 6	65 \pm 6	63 \pm 6*	57 \pm 6*	53 \pm 7*
f, breaths/min	11.6 \pm 1.0	11.3 \pm 0.9	11.4 \pm 0.8	10.7 \pm 1.0	12.2 \pm 1.5
ET _{CO₂} , mmHg	30.4 \pm 2.6	29.7 \pm 3.0	29.1 \pm 3.3	26.3 \pm 3.0*	24.4 \pm 3.6*

Values are means \pm SE. LBNP, lower body negative pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; PBP, pulse blood pressure; HR, heart rate; V_{MCA} , cerebral blood flow velocity in middle cerebral artery; f, respiratory frequency; ET_{CO₂}, end-tidal carbon dioxide. * $P < 0.05$.

Fig. 1. Tracings of arterial pressure (Finapres) and transcranial Doppler ultrasound velocity waveforms taken from middle cerebral artery in 1 subject at baseline, during maximal lower body negative pressure (-70 mmHg LBNP) immediately before onset of presyncope, and after release of LBNP. *A*: baseline. *B*: presyncope with release of LBNP. Note that fall in cerebral blood flow (CBF) velocity followed fall in arterial pressure before onset of presyncope.



from 5.1 ± 1.3 at baseline to 9.6 ± 3.8 (cm/s^2) at -50 mmHg LBNP ($P < 0.05$; Fig. 5C), and the power in the high-frequency range increased significantly from 0.5 ± 0.1 at baseline to 1.2 ± 0.3 (cm/s^2) at -50 mmHg ($P < 0.05$; Fig. 5D).

Transfer Function

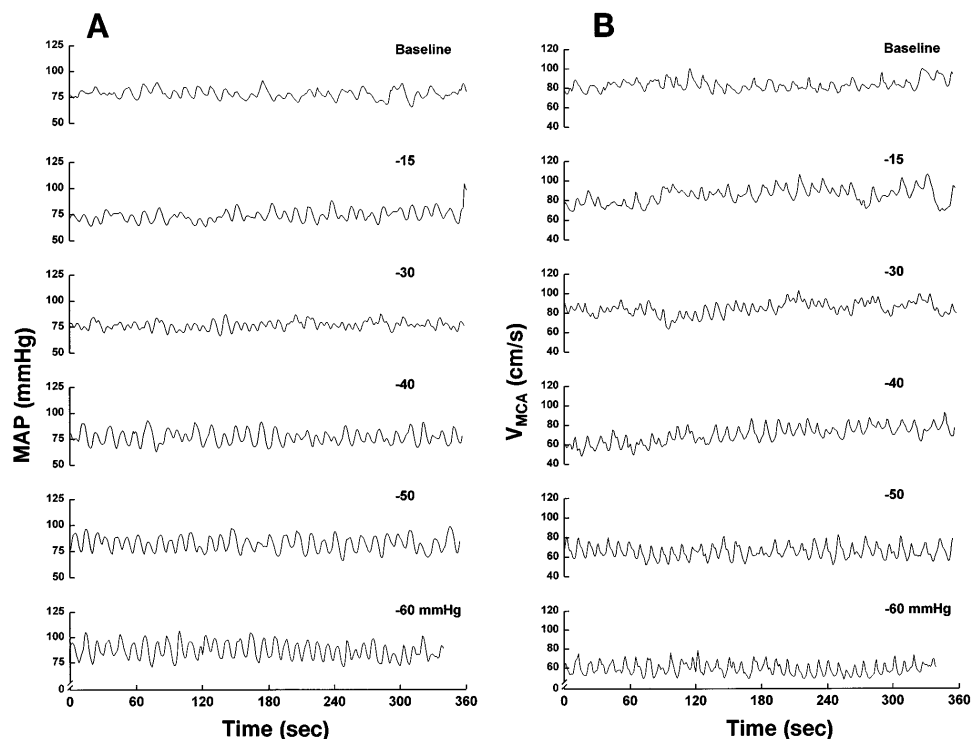
Low-frequency transfer gain increased significantly by 24% at -50 mmHg LBNP (compared with baseline, $P < 0.05$) in association with a trend toward an increase in high-frequency gain (Fig. 6, *A* and *B*). In the low-frequency range, at baseline, there was a positive phase of change in velocity to pressure ($40 \pm 12^\circ$), and this positive phase was smaller in the high-frequency

range ($16 \pm 19^\circ$) (Fig. 6D). Compared with baseline values, no significant change in the phase was observed during LBNP (Fig. 6, *C* and *D*).

Coherence Function

For all subjects, coherence function in the very-low, low-, and high-frequency range at baseline was 0.45 ± 0.24 , 0.65 ± 0.17 , and 0.65 ± 0.21 , respectively. No significant changes in coherence function were observed for the entire group during LBNP. However, in the very-low-frequency range, coherence function at baseline in eight subjects was lower than 0.5 (0.30 ± 0.12) in association with a lower spectral power of pressure, whereas in the other four subjects coherence

Fig. 2. Representative beat-to-beat variations in mean arterial pressure (MAP; *A*) and CBF velocity in the middle cerebral artery (V_{MCA} ; *B*) from 1 subject at rest and during LBNP. Note that, in contrast to the relatively constant steady-state value of pressure (~ 75 mmHg), steady-state velocity decreased from ~ 80 to ~ 60 cm/s during LBNP. Variability of pressure and velocity increased simultaneously during LBNP and synchronized at a rhythm ~ 10 s.



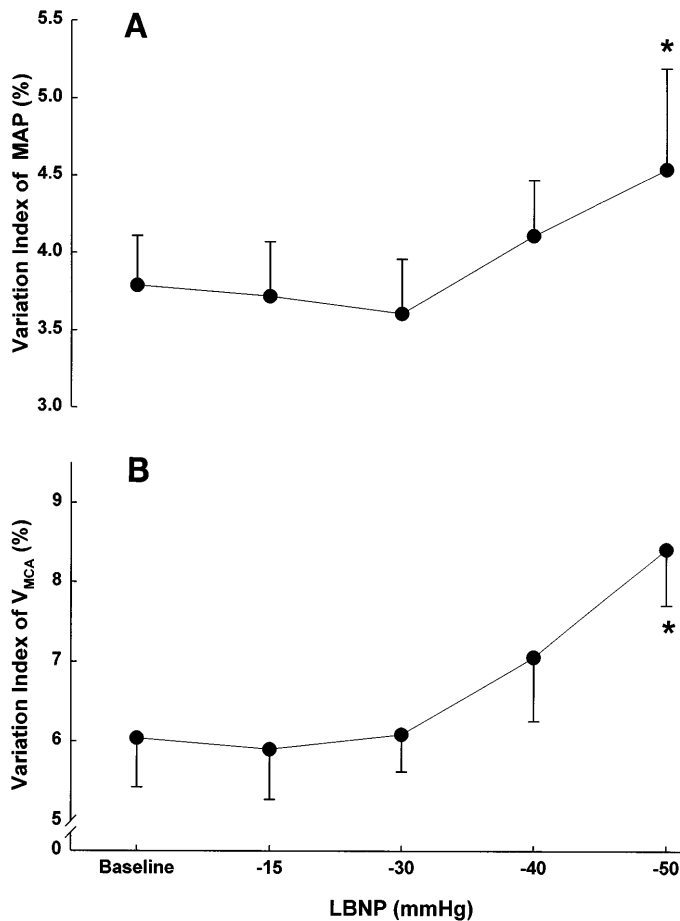


Fig. 3. Group-averaged ($n = 12$) variation indexes in MAP (A) and V_{MCA} (B) at rest and during LBNP. Values are means \pm SE. * $P < 0.05$ compared with baseline.

function was higher than 0.5 (0.74 ± 0.11) associated with a higher spectral power of pressure (Fig. 7), suggesting that estimates of coherence function may be influenced by the spectral power of pressure. This speculation was supported by the fact that in those eight subjects with a typically low coherence function at baseline, coherence increased significantly during LBNP in association with a trend toward increases in spectral power of pressure (Fig. 7), whereas in the other four subjects coherence decreased significantly during LBNP in association with significant decreases in the spectral power of pressure (Fig. 7). Further analysis showed a significant linear correlation between the estimates of coherence function and spectral power of pressure in the very-low-frequency range (Fig. 8).

DISCUSSION

The principal findings in the present study are that spontaneous variability of mean arterial pressure and CBF velocity increases significantly during LBNP in association with an augmentation of the transfer-function gain between these two variables at high levels of LBNP. These findings suggest that the attenuation effect of cerebral autoregulation on variations in CBF velocity are diminished during this form of ortho-

static stress. We speculate that this impairment of dynamic autoregulation, in association with the substantial fall in the steady-state value of CBF velocity during LBNP, may contribute to orthostatic syncope.

Methodological Considerations and Limitations

The present study of CBF in humans required a technique that is safe and noninvasive and that allows estimates of CBF on a beat-to-beat basis. To meet these requirements, we used the TCD technology to measure CBF velocity in the MCA (1). It is important to emphasize that measurements of velocity do not necessarily reflect changes in flow. Changes in flow are proportional to changes in velocity only if the diameter of the insonated MCA remains constant. Angiographic study (17) and direct visualization of the MCA during surgery (13) have suggested that, during a variety of stimuli

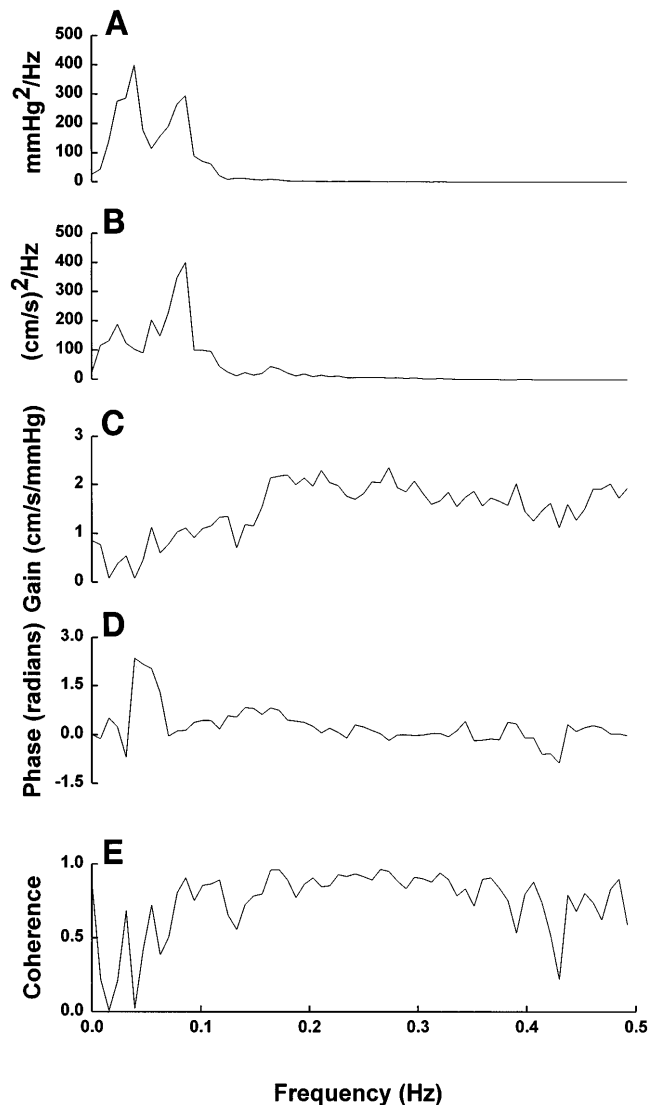
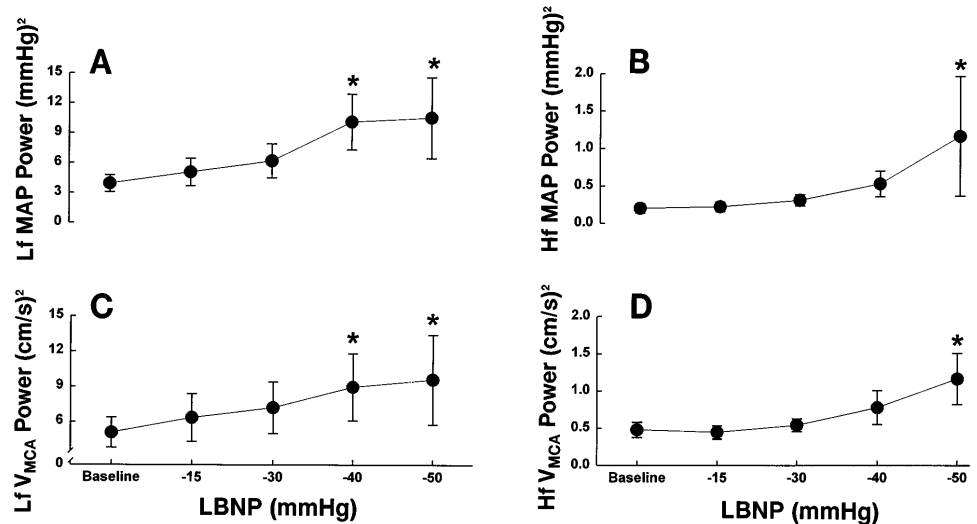


Fig. 4. Representative frequency-domain analysis of beat-to-beat changes in MAP and CBF velocity in 1 subject at rest. A: power spectral density of pressure. B: power spectral density of velocity. C: transfer-function gain between pressure and velocity. D: phase spectrum. E: coherence function.

Fig. 5. Group-averaged ($n = 12$) spectral power of arterial pressure and CBF velocity in low- (Lf) and high-frequency (Hf) range at rest and during LBNP. *A*: low-frequency spectral power of pressure; *B*: high-frequency spectral power of pressure. *C*: low-frequency spectral power of velocity. *D*: high-frequency spectral power of velocity. Values are means \pm SE. * $P < 0.05$ compared with baseline.



known to affect CBF, 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 CBF.

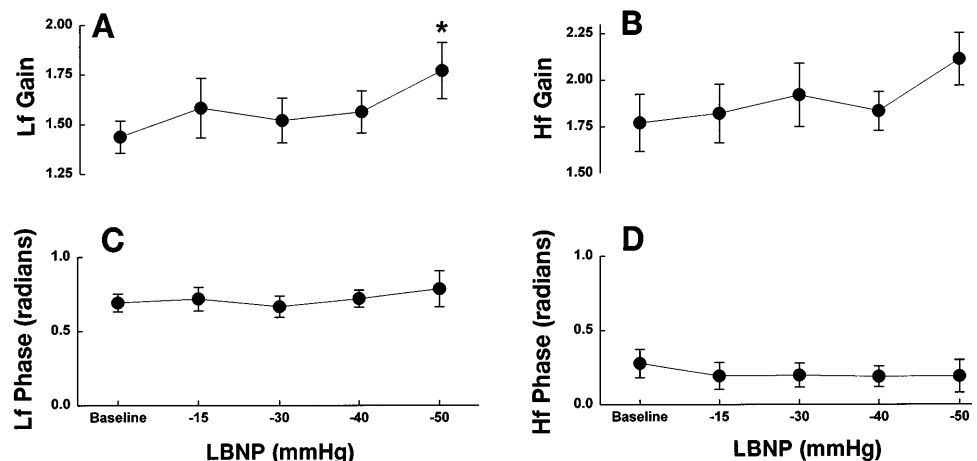
In the present study, we used transfer-function analysis to quantify dynamic cerebral autoregulation during LBNP. The validity and accuracy of this technique rely on the basic assumptions that the system being analyzed is linear and the signal-to-noise ratio of the experimental data is high. However, most physiological systems, if not all, have intrinsic nonlinearities, and experimental data have different levels of noise that are dependent on the experimental conditions. Thus, as a commonly accepted criterion, the coherence function between the input and output of a system has been estimated to assess the quality of transfer-function analysis.

In the present study, mean values of the coherence function between changes in pressure and velocity in both the low (0.07–0.20 Hz) and high-frequency range (0.20–0.30 Hz) were above 0.5 at baseline and at each

level of LBNP, suggesting that the estimation of the transfer function was acceptable. In contrast, as previously reported (36), coherence function in the very-low-frequency range was below 0.5. Therefore, transfer-function gain and phase were not calculated in the very-low-frequency range in this study. Further correlation analysis between the estimates of coherence function and the spectral power of arterial pressure supports the hypothesis that the low coherence in this very-low-frequency range represents a fundamental nonlinearity of cerebral hemodynamics. However, because we do not know the specific properties of nonlinearity in the cerebral circulation, it is difficult to assess to what degree this nonlinearity would have influences on the estimation of transfer function in the low- and high-frequency ranges by the current method (26). Nevertheless, the finding of reduced autoregulatory control over cerebral circulation, as indicated by the augmented transfer-function gain during LBNP, is consistent with the time-domain observation of increases in the variation index of CBF velocity in the present study.

Finally, as has been determined in studies of other vascular beds (8), changes in the dynamic components

Fig. 6. Group-averaged ($n = 12$) transfer-function gain and phase at rest and during LBNP. *A*: transfer gain in low-frequency range. *B*: transfer gain in high-frequency range. *C*: phase in low-frequency range. *D*: phase in high-frequency range. Values are means \pm SE. * $P < 0.05$ compared with baseline.



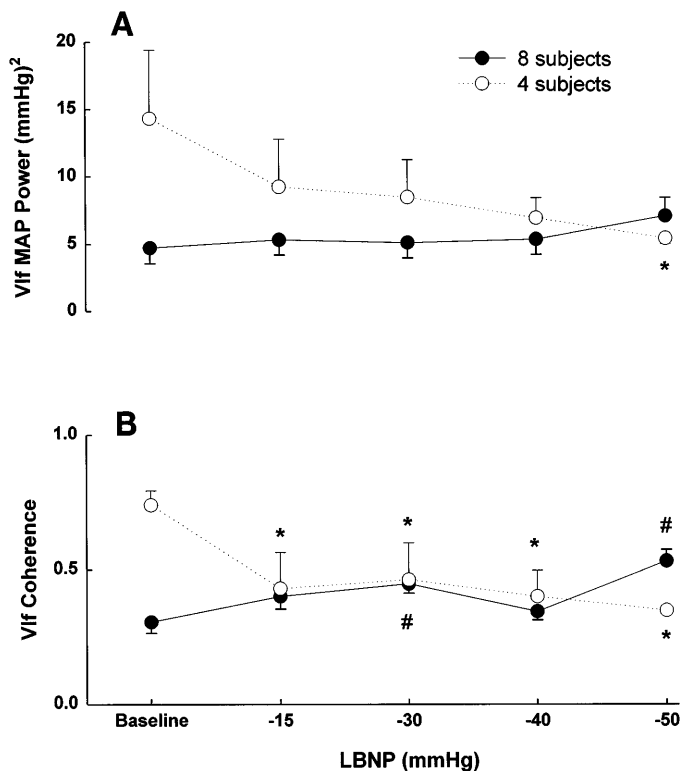


Fig. 7. Spectral power of arterial pressure (A) and coherence function (B) averaged in 1 group of subjects with baseline coherence function >0.5 ($n = 8$) and in another group of subjects with baseline coherence <0.5 ($n = 4$) in very-low-frequency (Vlf) range at rest and during LBNP. Values are means \pm SE. * $P < 0.05$ compared with baseline ($n = 4$). # $P < 0.05$ compared with baseline ($n = 8$).

of cerebral autoregulation as quantified by transfer-function analysis may not necessarily reflect changes in static cerebral autoregulation. Evaluation of dynamic autoregulation by transfer-function analysis may reveal properties of different regulatory mechanisms with different time responses to transient changes in pressure, whereas assessment of static autoregulation may reveal the regulatory capacity of the cerebrovascular bed in response to steady-state changes in pressure (32).

CBF Variability During LBNP

With the development of the TCD technique for noninvasive and continuous measurement of CBF velocity, several studies have indicated that pulsatile CBF velocity measured in the human MCA changes spontaneously over a wide frequency range (29, 34). Although it has been shown that these variations occur simultaneously with intracranial pressure B waves (29) and oscillations in arterial pressure (34), the underlying mechanisms are not clear. To our knowledge, two possible mechanisms could be formulated. 1) Changes in CBF velocity reflect changes in flow that are primarily caused by variations in arterial pressure. It has been shown that systemic arterial pressure changes spontaneously with amplitudes and frequencies similar to those observed in CBF velocity (31, 36). Therefore, if

autoregulatory changes in cerebrovascular resistance and/or intracranial pressure cannot perfectly compensate for the variations in arterial pressure, there must exist fluctuations in CBF in response to changes in arterial pressure. In fact, numerous studies have demonstrated spontaneous changes in CBF, ranging from measurements in the internal carotid artery (28) to the cerebral microcirculation (18). Thus, if the diameter of insonated MCA remains relatively constant (13, 17), changes in CBF velocity could primarily reflect the changes in CBF caused by variations in arterial pressure and/or downstream vascular resistance. 2) Alternatively, if autoregulation is so effective that the changes in vascular resistance and/or intracranial pressure would be able to compensate completely for the changes in arterial pressure, CBF would remain relatively constant. In this situation, changes in CBF velocity may reflect changes in the diameter of the insonated MCA. Because we have observed almost parallel beat-to-beat changes in velocity and pressure, a constant CBF would suggest active vasomotion in the MCA in association with the spontaneous changes in pressure, which, if true, probably reflects dynamic cerebral autoregulation in large arteries (11). Although we cannot distinguish between these two possibilities in the present study, recent studies comparing TCD measurement of CBF velocity in the MCA with the measurements of CBF by other methods suggest that changes in CBF velocity can reliably reflect changes in CBF in humans under a wide range of changes in perfusion pressure (22, 28). Therefore, it is most likely that the spontaneous changes in CBF velocity observed in the present study may reflect spontaneous changes in CBF.

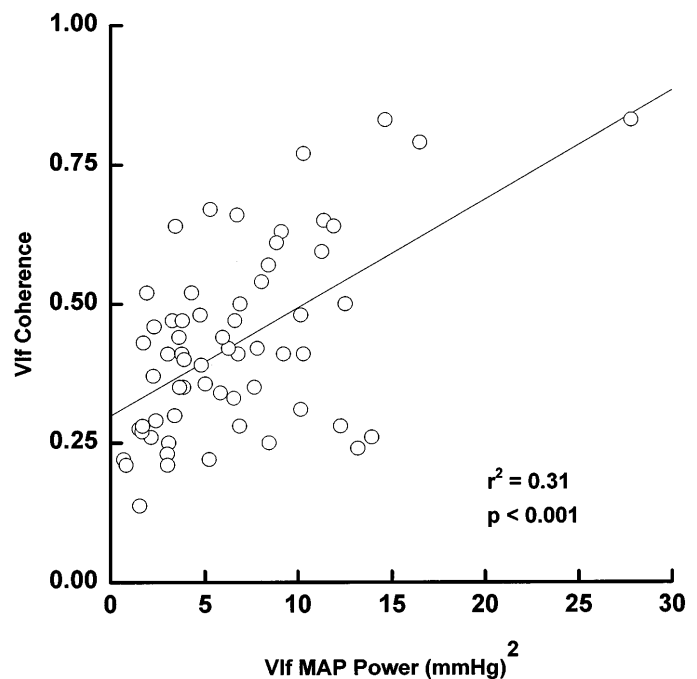


Fig. 8. Correlation analysis of estimates of coherence function with spectral power of arterial pressure in Vlf range. Data points represent estimates in each individual subject and during LBNP.

The simultaneous increases in the variability of pressure and velocity in both the time and frequency domain during LBNP observed in the present study are consistent with the hypothesis that the spontaneous changes in CBF velocity and presumably flow were primarily caused by the changes in arterial pressure. This speculation is further supported by the observations that variations in the CBF velocity seem to be entrained or synchronized with the changes in the arterial pressure at about 0.1 Hz at high levels of LBNP (Fig. 2).

We caution that the mechanisms of spontaneous changes in CBF velocity may be different at different time scales, particularly when the coherence function between the changes in arterial pressure and velocity is low in the very-low-frequency range. However, further correlation analysis showed that the estimates of coherence function were influenced by the power of arterial pressure in the very-low-frequency range, suggesting a nonlinear relationship rather than the absence of a relationship between these two variables. It should be mentioned that, although this correlation is significant, the degree of correlation is relatively low ($r^2 = 0.31$). Thus, we cannot exclude the possibility that some types of nonlinearity between changes in pressure and velocity may not be revealed by the correlation-analysis strategy and/or that some portion of the changes in velocity may not be related to changes in pressure in the very-low-frequency range.

One of the intriguing findings in the present study is that the aforementioned increases in the spontaneous changes in the CBF velocity and arterial pressure during LBNP were associated with a substantial fall in the steady-state value of CBF velocity even without any changes in the steady-state value of mean arterial pressure (6, 24). This result is consistent with the hypothesis that the autoregulatory curve may shift rightward during LBNP (24). With this curve shift, steady-state CBF velocity, and presumably flow, may decrease without any change in steady-state perfusion pressure. Furthermore, because the operational point of perfusion pressure and flow may fall into the lower limit of autoregulation in association with this curve shift, variations of flow would passively follow the changes in pressure. In this situation, increases in spontaneous changes in arterial pressure would lead to increases in spontaneous changes in velocity, as we have observed in the present study. Finally, it is also possible that the substantial decreases in the steady-state CBF velocity during LBNP may reduce shear stress-mediated nitric oxide synthase and inhibit nitric oxide-mediated modulation of vascular tone, thus leading to increases in the amplitude of spontaneous flow oscillation (10).

Cerebral Autoregulation

The specific mechanisms of the fall in steady-state CBF velocity during LBNP are not clear. We have hypothesized that the reduction in CBF velocity during LBNP was caused by cerebral vasoconstriction prob-

ably associated with an augmented sympathetic nerve activity (24). The significant increase in HR and reduction in pulse pressure observed in the present study suggest a baroreflex-mediated increase in sympathetic activity and were consistent with previous studies (6, 24, 37). However, the significant decrease in the end-tidal CO_2 at the high levels of LBNP observed in the present study raised the possibility that the reduction in CBF velocity may be related to CO_2 -mediated cerebral vasoconstriction. It is well known that CBF is sensitive to changes in arterial CO_2 content (32). Reduction in arterial CO_2 would lead to cerebral arteriolar and downstream vasoconstriction (2, 32). Although this possibility seems to be straightforward, it must be acknowledged that we measured end-tidal CO_2 , which may not always be an accurate index of arterial CO_2 (20, 35). A discrepancy between end-tidal CO_2 and arterial CO_2 may occur during the central hypovolemia of LBNP due to increased ventilation-perfusion mismatching or increased physiological dead space (20). Indeed, one invasive study has shown that the reduction in the arterial CO_2 was only ~ 2 Torr at -60 mmHg LBNP (21). However, on the basis of the data of the present study, we cannot exclude the possibility that the decrease in CBF velocity was associated with augmented sympathetic activity and/or a decrease in arterial CO_2 .

The role that cerebral hemodynamics play in orthostatic stress resulting in syncope is controversial (15, 24). The most commonly accepted hypothesis is that the fall in CBF is secondary to systemic hemodynamic collapse (5). Alternatively, some investigators recently suggested that a failure of cerebral autoregulation during orthostatic stress may compromise CBF and possibly result in a centrally mediated hemodynamic collapse (14, 15). In the present study, even though the mean CBF velocity decreased substantially at high levels of LBNP, the subjects did not report any changes in their consciousness and cognitive function before the onset of presyncope. Therefore, we speculate that, although cerebral vasoconstriction may override autoregulatory function and lead to a reduction in flow, cerebral oxygen consumption may remain relatively constant via an increase in oxygen extraction to compensate for the reduction in flow. Therefore, with well-maintained systemic pressure, the reduction in CBF induced by orthostatic stress by itself is unlikely to elicit the occurrence of presyncope. However, we and other investigators have observed that, with the onset of presyncope, CBF velocity fell passively with the rapid fall in arterial pressure, suggesting that cerebral autoregulation was impaired and may contribute in part to the occurrence of presyncope (6, 15, 24).

In the present study, we sought to evaluate the efficacy of cerebral autoregulation during orthostatic stress by using the frequency-domain analysis method. The significant increases in the transfer-function gain at high levels of LBNP suggest that the attenuation effects of cerebral autoregulation on variations in CBF velocity are diminished and are consistent with the

hypothesis of a rightward shift of the autoregulatory curve during LBNP (24). Furthermore, we speculate that, with the augmented transfer-function gain, hemodynamic instability of the systemic circulation, as indicated by the increases in the variations of arterial pressure during orthostatic stress (25), would have exaggerated rather than damped influences on the instability of cerebral hemodynamics as indicated by the increases in the variations of the CBF velocity.

In summary, the increases in the spectral power of spontaneous changes in arterial pressure and CBF velocity and the augmentation of transfer-function gain in association with the substantial fall in the steady-state value of CBF velocity indicate that dynamic cerebral autoregulation is impaired during this form of orthostatic stress and may contribute to orthostatic intolerance resulting in syncope.

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