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Dynamic cerebral autoregulation is preserved during acute head-down tilt

William H. Cooke, Guy L. Pellegrini, and Olga A. Kovalenko
Departments of Biomedical Engineering and Biological Sciences, Michigan Technological University, Houghton, Michigan 49931

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Cooke, William H., Guy L. Pellegrini, and Olga A. Kovalenko. Dynamic cerebral autoregulation is preserved during acute head-down tilt. *J Appl Physiol* 95: 1439–1445, 2003. First published June 27, 2003; 10.1152/japplphysiol.00524.2003.—Complete ganglion blockade alters dynamic cerebral autoregulation, suggesting links between systemic autonomic traffic and regulation of cerebral blood flow velocity. We tested the hypothesis that acute head-down tilt, a physiological maneuver that decreases systemic sympathetic activity, would similarly disrupt normal dynamic cerebral autoregulation. We studied 10 healthy young subjects (5 men and 5 women; age 21 ± 0.88 yr, height 169 ± 3.1 cm, and weight 76 ± 6.1 kg). ECG, beat-by-beat arterial pressure, respiratory rate, end-tidal CO_2 concentration, and middle cerebral blood flow velocity were recorded continuously while subjects breathed to a metronome. We recorded data during 5-min periods and averaged responses from three Valsalva maneuvers with subjects in both the supine and −10° head-down tilt positions (randomized). Controlled-breathing data were analyzed in the frequency domain with power spectral analysis. The magnitude of input-output relations were determined with cross-spectral techniques. Head-down tilt significantly reduced Valsalva phase IV systolic pressure overshoot from 36 ± 4.0 (supine position) to 25 ± 4.0 mmHg (head down) ($P = 0.03$). Systolic arterial pressure spectral power at the low frequency decreased from 5.7 ± 1.6 (supine) to 4.4 ± 1.6 $mmHg^2$ (head down) ($P = 0.02$), and mean arterial pressure spectral power at the low frequency decreased from 3.3 ± 0.79 (supine) to 2.0 ± 0.38 $mmHg^2$ (head down) ($P = 0.05$). Head-down tilt did not affect cerebral blood flow velocity or the transfer function magnitude and phase angle between arterial pressure and cerebral blood flow velocity. Our results show that in healthy humans, mild physiological manipulation of autonomic activity with acute head-down tilt has no effect on the ability of the cerebral vasculature to regulate flow velocity.

transcranial Doppler; spectral analysis; transfer function

THE CEREBRAL CIRCULATION MAINTAINS relatively constant blood flow in the face of changes in pressure and other imposed demands through normal autoregulation. Determination of factors that may modulate or disrupt normal cerebral autoregulation is important for the diagnosis and treatment of patients suffering from autonomic dysfunction. Zhang and coworkers (24) recently demonstrated that the transfer function magnitude between oscillations of mean arterial pressure and mean cerebral blood flow velocity is increased by ganglion blockade, suggesting a role for autonomic neural activity in the modulation of cerebral autoregulation. Nonpharmacological, physiological modulation of autonomic neural activity may similarly provide insight into mechanisms underlying normal cerebral autoregulation.

Acute head-down tilting decreases leg volume (9) and increases central venous pressure (13). Consequent loading of baroreceptors decreases muscle sympathetic nerve activity (5, 19) and could affect regulation of cerebral blood flow velocity, although such associations have not been evaluated.

The purpose of the present study was to determine the effects of acute head-down tilt on cerebral autoregulation. We tested the hypothesis that head-down tilt, a maneuver that results in sympathetic withdrawal, would increase transfer function gain between arterial pressure and cerebral blood flow velocities and therefore reveal derangement of dynamic cerebral autoregulation.

METHODS

Subjects. We studied 10 healthy young subjects (5 men and 5 women; age 21 ± 0.88 yr, height 169 ± 3.1 cm, and weight 76 ± 6.1 kg). All subjects were nonsmokers, normotensive, and nondiabetic; had no history of autonomic dysfunction; and refrained from caffeine- and alcohol-containing beverages at least 12 h before the experiment. Female subjects were not pregnant and were not taking oral contraceptives. The study protocol was approved in advance by the Human Research Committee of Michigan Technological University. Each subject provided written, informed consent before participating.

Instrumentation. Subjects were instrumented with a three-lead ECG, a finger cuff to record beat-by-beat arterial pressure with finger photoplethysmography (model 2300, Finapres, Ohmeda, Englewood CO), a pneumobelt for respiratory excursions (uncalibrated strain-gauge pressure transducer), a mouthpiece housing a sensor for infrared measurement of end-tidal CO_2 concentrations (Gambro, Engström, Sweden), and a 2-MHz Doppler probe positioned and then fixed at a constant angle over the temporal window to record

Address for reprint requests and other correspondence: W. H. Cooke, Dept. of Biomedical Engineering, Michigan Technological University, 1400 Townsend Dr., Houghton, MI 49931 (E-mail: william.cooke@amedd.army.mil).

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cerebral blood flow velocity from the middle cerebral artery (DWL Elektronische Systeme, Sipplingen, Germany).

Protocol. Subjects rested in the supine position during instrumentation for ~10 min. After this, conditions were randomized for subjects to be studied first either in the supine or −10° head-down tilt position. Data were collected during 5 min of controlled-frequency breathing (0.25 Hz) both supine and immediately after assumption of head-down tilt via motorized tilt table (Colin Medical Instruments, San Antonio, TX). A 5-min supine recovery preceded supine measurements if subjects were first studied in the head-down position. After the initial 5-min data collection, subjects performed Valsalva maneuvers as estimates of sympathetic neural activity. We obstructed airflow through the nose with a nose clip and placed a mouthpiece connected to an analog manometer (with a leak control valve) into the subject's mouth. The manometer was positioned in front of the subject to provide visual feedback of expiratory pressure. Subjects performed three Valsalva maneuvers after a normal inspiration (40 mmHg for 15 s) separated by 1-min recovery periods.

Data acquisition and analysis. Data were sampled at 500 Hz and recorded directly to computer with commercial hardware and software (WINDAQ, Dataq Instruments, Akron, OH). Data were then imported into a commercial analysis program (WinCPRS, Absolute Aliens, Turku, Finland). R waves generated from the ECG signal were detected and marked at their occurrence in time. Diastolic and systolic pressures were subsequently marked from the Finapres and Doppler tracings. Mean cerebral blood flow velocity was calculated as a true average of each integrated waveform. However, each waveform was manually edited to correct spurious detection of maximal (systolic) and minimal (diastolic) velocities occurring as a result of noise spikes at the tops and bottoms of Doppler tracings. For this reason, mean velocity was derived as

$$V_{mean} = V_{min} + 0.4(V_{max} - V_{min})$$

where V_{max} is maximal velocity (systolic), V_{min} is minimal velocity (diastolic), and V_{mean} is middle cerebral blood flow.

Arterial pressure overshoot after release of strain from a Valsalva maneuver correlates to muscle sympathetic nerve activity, and therefore the magnitude of arterial pressure increases during phase IV of a Valsalva maneuver may be used as a general surrogate for directly measured sympathetic neural activation (3, 18). By using systolic pressures, phase IV was identified by the first pressure value that increased after release from strain and continued until the first noticeable pressure drop after overshoot. The maximum minus the minimum value represented the magnitude of arterial pressure overshoot for that maneuver. Three such analyses were averaged for statistical comparison. We used the slope method of Kautzner et al. (10) to assess cardiovagal baroreflex sensitivity during phase IV arterial pressure elevations. We calculated the magnitude of increases in R-R intervals as functions of increases in systolic pressures with linear regression analysis. We used a minimum of three consecutively increasing systolic pressure values and corresponding changes in R-R intervals, advanced by one beat (10). To be considered a valid sequence, correlation coefficients were ≥0.80. Representative R-R interval and arterial pressure responses to a Valsalva maneuver are shown in Fig. 1.

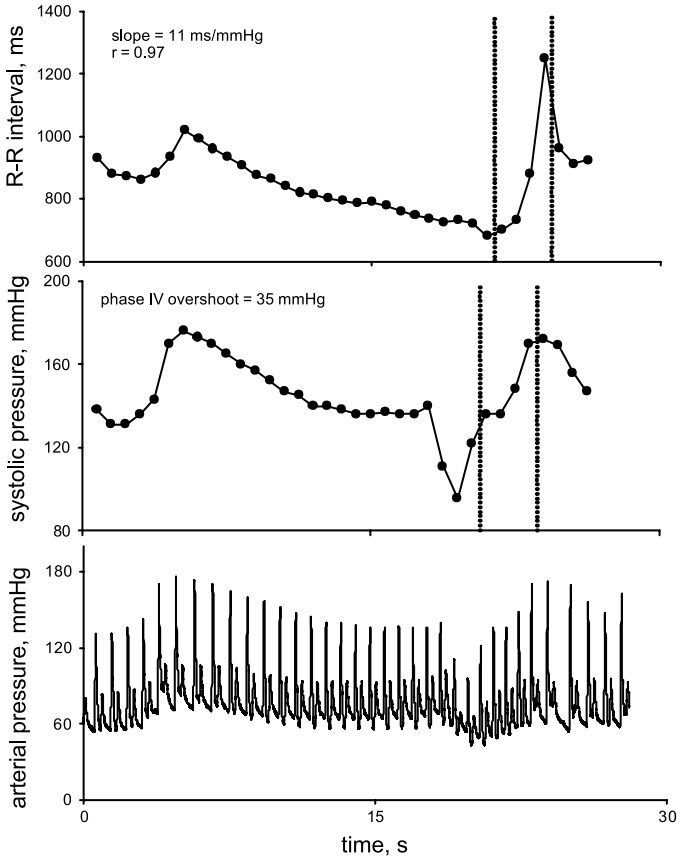

Fig. 1. Response to a Valsalva maneuver in 1 subject. Vertical lines in the systolic pressure and R-R interval window denote region of overshoot and linear regression calculation.

R-R intervals, arterial pressures, and cerebral blood flow velocities were analyzed in the frequency domain by spline interpolating the nonequidistant beat-to-beat data and resampling at 4 Hz. Data were then passed through a low-pass impulse response filter with a cutoff frequency of 0.5 Hz. Data sets comprising 64 s (256 samples) were fast Fourier transformed. Power spectral densities were calculated with the Welch algorithm for seven overlapping sections of 256 points (64 s) staggered by 128 points. Spectral power was expressed as the integrated areas in the low-frequency (0.05–0.15 Hz) and high-frequency (0.15–0.4 Hz) ranges. The squared coherence (which reflects the strength of the linear association between 2 signals at specific frequencies) was calculated by dividing the cross-spectral densities of the two signals (systolic pressure and R-R interval; mean arterial pressure and mean cerebral blood flow velocity) by the product of the individual autospectrums, and the phase angle (which represents temporal relations between input and output variables) was calculated by multiplying the arctangent by the quotient of the coincident and the quadrature cross-spectral density functions. The transfer function (which reflects the amplitude or "gain" between changes in the input and output signals) was calculated by dividing the cross-spectrum of the two signals (systolic pressure and R-R interval; mean arterial pressure and mean cerebral blood flow velocity) by the autospectrum of the input signal (4, 6, 23). Both transfer function gain and phase angle were averaged in the low- and high-frequency ranges only where the squared coherence between the two signals was at least 0.5 (20).

Statistics. All data were analyzed with commercial statistical software (SAS Institute, Cary, NC). We tested for differences in the means of our dependent variables with a one-way repeated-measures ANOVA with repeated mea-

sures on tilt angle (supine vs. −10° head down). Data are expressed as means ± SE unless otherwise specified. We accepted differences as being significant if $P \leq 0.05$.

RESULTS

Hemodynamic time series. Acute head-down tilt significantly reduced systolic pressure elevations after release from Valsalva strain. Systolic pressure overshoots were 36 ±4 mmHg in the supine position and 25 ±4 mmHg in the head-down tilt position ($P = 0.03$). Cardiovagal baroreflex sensitivity increased from 9.6 ± 1.9 to 12.6 ± 2.5 ms/mmHg, but this increase was not statistically significant ($P = 0.09$).

Figure 2 shows representative tracings of the variables we recorded from one subject during 1 min of controlled-frequency breathing in the supine position. Average values for all measured and derived variables during 5-min controlled-frequency breathing are presented in Table 1. Acute head-down tilt did not affect R-R interval or arterial pressure. Mean cerebral blood flow velocity was statistically identical between the two conditions. Controlled-frequency breathing adequately maintained constant end-tidal CO_2 concentrations.

Frequency domain analyses. Figure 3 shows representative power spectra derived from various time series. Head-down tilt had no effect on R-R interval or cerebral blood flow velocity spectral power at either the low or high frequency, but it significantly decreased systolic ($P = 0.02$) and mean ($P = 0.05$) arterial pressure oscillations at the low frequency (see Table 2). Transfer function magnitude and phase relations between systolic pressure and R-R interval, and between mean arterial pressure and mean cerebral blood flow velocity, were unaffected by head-down tilt. Figure 4 shows a representative cross-spectral analysis between mean arterial pressure and mean cerebral blood flow velocity oscillations. Transcranial Doppler data were corrupted for one subject, and so analyses of all variables that included cerebral blood flow velocities were done with $n = 9$. Group average frequency domain data are presented in Table 2.

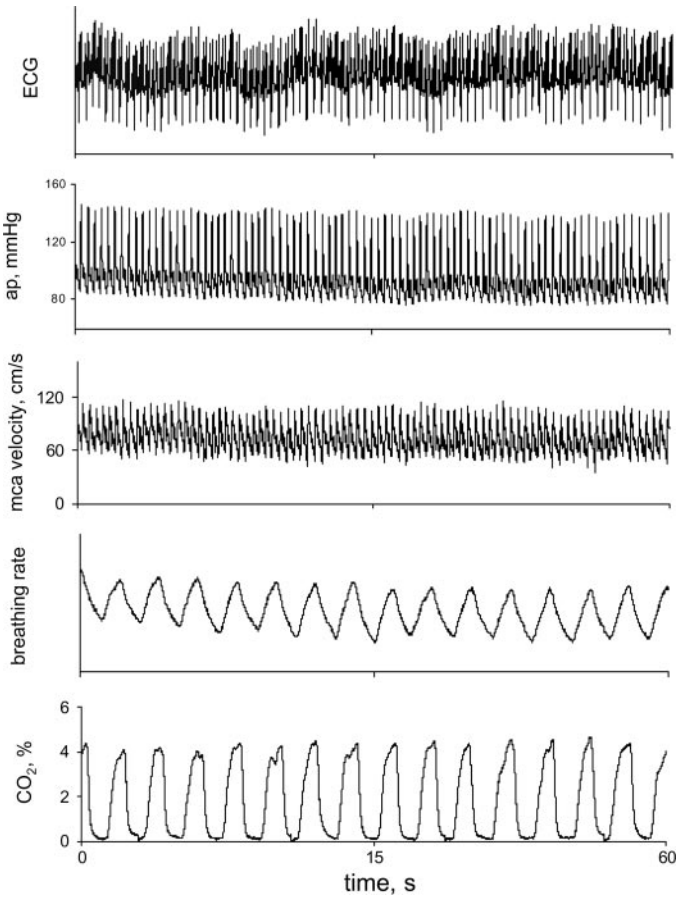

Fig. 2. Representative tracings of raw data from one subject during controlled breathing at 0.25 Hz. ap, Arterial pressure; mca, middle cerebral artery; CO_2, end-tidal CO_2 concentration.

Table 1. *Time series data during controlled-frequency breathing in the supine and 10° head-down tilt positions*

Variable	Supine	Head Down	*P* Value
RRI, ms	814 ± 31	810 ± 27	0.86
SAP, mmHg	131 ± 3.9	131 ± 4.8	0.82
DAP, mmHg	69 ± 2.5	68 ± 2.7	0.86
MAP, mmHg	90 ± 2.2	89 ± 2.7	0.86
V_{mean}, cm/s	67.2 ± 5.2	67.6 ± 5.4	0.81
CO_2, %	4.0 ± 0.1	4.2 ± 0.1	0.22

Values are means ± SE for 10 subjects. RRI, R-R interval; SAP, systolic arterial pressure; DAP, diastolic arterial pressure; MAP, mean arterial pressure; V_{mean}, mean middle cerebral artery velocity; CO_2, end-tidal carbon dioxide concentration.

DISCUSSION

We tilted subjects to a −10° head-down position to test the hypothesis that acute head-down tilt disrupts normal dynamic cerebral autoregulation. Our primary new finding is that cerebral autoregulation is preserved, whereas estimates of sympathetic neural activity are decreased. On the basis of these results, we suggest that factors other than systemic sympathetic modulation maintain cerebral autoregulation during acute head-down tilt.

Cardiovascular and hemodynamic effects of acute head-down tilt. Acute head-down tilt did not affect R-R interval or arterial pressure (Table 1). These findings were not unexpected, because our laboratory has recently documented similar results (5). Our laboratory has also shown, as others have before, that acute −10° head-down tilting significantly reduces lower leg volume and muscle sympathetic nerve activity (5, 19). Thus translocation of fluid from the lower to upper body and consequent loading of various baroreceptor populations is likely responsible for sympathetic withdrawal. In the present study, we used the Valsalva maneuver and controlled frequency breathing to noninvasively estimate autonomic changes induced by head-down tilt. The magnitude of arterial pressure overshoot after release of strain from a Valsalva maneuver correlates to the sympathetic traffic that precedes it (3, 18) (although it may not reflect baseline

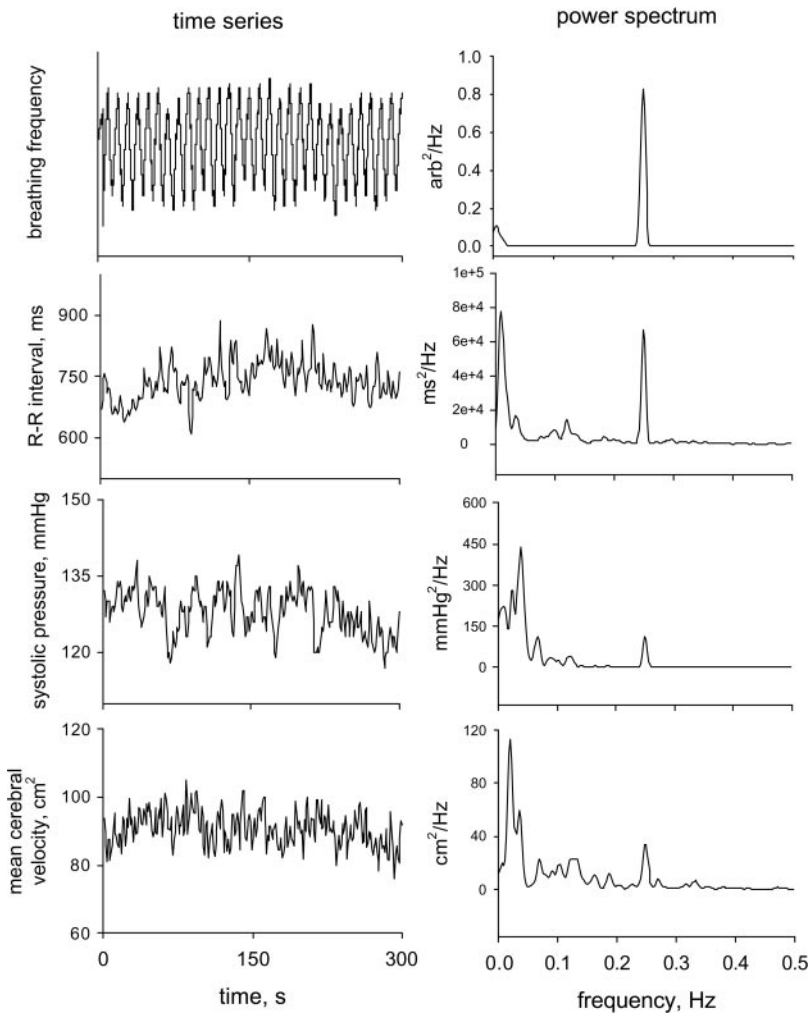

Fig. 3. Representative time series and corresponding frequency-domain analyses. arb, Arbitrary units.

sympathetic activity), and linear regression analysis between beat-by-beat increases in systolic pressure and R-R interval is used to estimate cardiovagal baroreflex gain (7, 10). In the present study, we found that head-down tilt significantly decreased systolic pressure overshoot and tended to increase cardiovagal baroreflex gain (nonsignificant). Additionally, mechanisms of arterial pressure rhythms have not been defined completely, but baroreceptor activation and inhibition of sympathetic nerve activity are clearly associated with arterial pressure oscillations at the low frequency (16, 22) [although this association is not deterministic (21)]. Our laboratory has reported previously that acute −10° head-down tilt does not affect arterial pressure oscillations at the low frequency but significantly decreases muscle sympathetic nerve activity (5). In that study, it was speculated that power spectral analysis may not be sensitive enough to detect subtle changes in autonomic activity with acute head-down tilt (5). We cannot explain why an identical head-down tilt protocol in the present study reduced low-frequency arterial pressure oscillations, but these results, in conjunction with our laboratory's earlier microneurographic data (5) and data of others (19), support the notion that acute −10° head-down tilt decreases sympathetic traffic.

We collected data as subjects breathed at a controlled rate of 0.25 Hz for two reasons. First, cerebral blood flow velocity depends importantly on arterial P_{CO_2} concentrations (8), and end-tidal CO_2 concentrations are held relatively constant during controlled breathing (Ref. 4 and Table 1). Second, integrated R-R interval spectral power at the high frequency adequately represents vagal cardiac control (1), and low-frequency oscillations of arterial pressure have been linked to sympathetic traffic through arterial baroreflexes (22). Brown et al. (2) concluded that breathing rate must be strictly controlled to accurately assess autonomic rhythms. In the present study, controlled breathing maintained end-tidal CO_2 concentrations, and so we conclude that acute −10° head-down tilting does not affect cerebral blood flow velocity. This conclusion is in agreement with Satake et al. (17), who found no change in middle cerebral blood flow velocity with −6° head-down tilt by using single-photon-emission computed tomography, and at odds with Kawai et al. (11), who documented increases of blood flow velocities with a similar −6° head-down tilt using transcra-

Table 2. *Frequency domain data during controlled-frequency breathing in the supine and 10° head-down tilt positions*

Variable	Supine	Head Down	*P* Value
RRI-HF, ms^2	709 ± 162	583 ± 92	0.32
RRI-LF, ms^2	549 ± 158	400 ± 234	0.26
SAP-HF, mmHg^2	2.6 ± 2.3	2.3 ± 2.1	0.42
SAP-LF, mmHg^2	5.7 ± 1.6	4.4 ± 1.6*	0.02
DAP-HF, mmHg^2	0.58 ± 0.13	0.61 ± 0.14	0.86
DAP-LF, mmHg^2	2.7 ± 0.62	1.9 ± 0.35	0.16
MAP-HF, mmHg^2	0.75 ± 0.16	0.67 ± 0.16	0.47
MAP-LF, mmHg^2	3.3 ± 0.79	2.0 ± 0.38*	0.05
TCD-HF, cm/s^2	2.3 ± 0.7	1.9 ± 0.7	0.20
TCD-LF, cm/s^2	2.2 ± 0.45	2.5 ± 1.9	0.52
S-RRI-TF-HF, ms/mmHg	18 ± 1.9	18 ± 6.6	0.97
S-RRI-TF-LF, ms/mmHg	9.8 ± 3.6	10.3 ± 3.2	0.72
M-TCD-TF-HF, cm/s^{-1}·mmHg^{-1}	1.6 ± 0.28	1.6 ± 0.25	0.78
M-TCD-TF-LF, cm·s^{-1}·mmHg^{-1}	1.2 ± 0.35	0.9 ± 0.4	0.39
TCD-PHASE-HF,°	10 ± 4.7	7.4 ± 6.5	0.63
TCD-PHASE-LF,°	68 ± 28	60 ± 12	0.45

Values are means ± SE for 9 for variables including cerebral blood flow velocity, and for 10 for all other variables). RRI-HF and RRI-LF, R-R interval spectral power at the high and low frequencies, respectively; SAP-, DAP-, and MAP-HF and -LF, systolic, diastolic, and mean arterial pressure spectral power at the high and low frequencies, respectively; TCD-HF and TCD-LF, transcranial Doppler mean cerebral blood flow velocity spectral power at the high and low frequencies, respectively; S-RRI-TF-HF and S-RRI-TF-LF, relationship of systolic pressure to R-R interval transfer function gain at the high and low frequencies, respectively; M-TCD-TF-HF and M-TCD-TF-LF, relationship of mean arterial pressure to mean cerebral blood flow velocity transfer function gain at the high and low frequencies, respectively; TCD-PHASE-HF and TCD-PHASE-LF, phase angle between mean arterial pressure and mean cerebral blood flow velocity at high and low frequencies, respectively. *Significantly different from corresponding supine value, $P \leq 0.05$.

nial Doppler. However, significant increases in the study by Kawai et al. were observed in the comparison of velocities in the upright vs. supine and head-down positions. Velocities were statistically identical in the comparison of supine to head-down (11).

Although loading of various baroreceptor populations should conceivably increase parasympathetic activity, we were unable to confirm such an increase. R-R intervals, R-R interval spectral power at the high frequency, and cardiovagal baroreflex sensitivity [assessed by the transfer function magnitude between systolic pressure and R-R interval (Table 2)] were unaffected by head-down tilt. This confirms some of our laboratory's earlier findings (5) and suggests that −10° head-down tilt is a mild stimulus having a greater effect on sympathetic than parasympathetic neurons.

Dynamic cerebral autoregulation. Autoregulation of any vascular bed, including the cerebral vasculature, refers to the ability of that bed to maintain constant blood flow in the face of changes in pressure. In the present study, acute head-down tilt did not affect arterial pressure, but others have shown that acute head-down tilt increases cerebral blood volume (14) and cerebral intracranial pressure (12). The cerebral circulation adjusts to such changes in pressure by constricting the vasculature through either myogenic or neurogenic factors including intrinsic oscillations from a central pacemaker (15), metabolic factors such as P_{CO_2} (8), or through influences of systemic autonomic neural activity (24). Zhang et al. (24) used ganglion blockade with trimethaphan to show dependence of cerebral autoregulation on functioning autonomic neural activity. Ganglion blockade significantly decreased arterial pressure variability but not cerebral flow velocity variability, resulting in increased transfer function gain. Complete ganglion blockade does not allow for the differentiation of parasympathetic vs. sympathetic influences, but Zhang et al. speculated that it was the blockade of sympathetic activity that modulated cerebral vascular resistance and disrupted cerebral autoregulation. In the present study, we used a physiological maneuver (head-down tilt) to decrease sympathetic neural activity to test the importance of such autonomic changes on dynamic cerebral autoregulation.

As highlighted by the data presented in Figs. 3 and 4, controlled-frequency breathing translated into oscillations of blood pressure and cerebral blood flow velocity at the breathing frequency (0.25 Hz) and effectively separated respiratory from low-frequency rhythms. As may be seen in Fig. 4 (coherence), such oscillations were significantly associated around 0.25 and 0.1 Hz. The former represents respiratory influences on the output variables, and the latter likely reflects "Mayer waves," which may be related to sympathetic responses

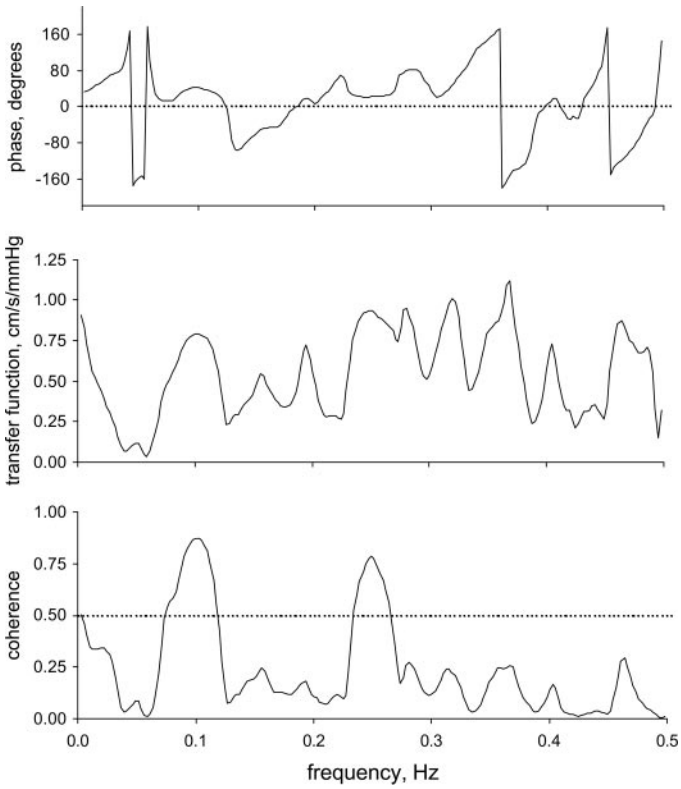

Fig. 4. Representative cross-spectral analyses showing phase relations, transfer function magnitude, and coherence between mean arterial pressure (input) and mean cerebral blood flow velocity (output).

to arterial pressure fluctuations mediated by arterial baroreflexes (22) and translated into oscillations of cerebral blood flow velocities. We found, as others have before (23), that phase angles describing temporal relations between mean arterial pressure and mean cerebral blood flow oscillations decrease from low- to high-frequency ranges. Average phase angles were 68° at low frequencies (0.05–0.15 Hz) and 10° at high frequencies (0.15–0.4). This phase lead of mean cerebral blood flow velocity to mean arterial blood pressure was not altered by acute head-down tilt, providing some evidence for unaltered cerebral autoregulation with mild systemic sympathetic neural withdrawal. Further evidence for preserved cerebral autoregulation derives from the transfer function analysis. At the low frequency, systolic and mean arterial pressure oscillations decreased with head-down tilt with no change in transfer function magnitude (Table 2). Although we cannot rule out the possibility that discrepancies between estimates of arterial pressure spectral power and transfer function gain derived from variable-frequency ranges used to quantify our values [i.e., low- and high-frequency spectral power were taken as the integrated area under the spectrum within specified frequency ranges (0.05–0.15, low; 0.15–0.4, high), whereas transfer function gains were averaged within only those frequency ranges where coherence was $\geq$0.05], low-frequency cerebral blood flow oscillations were unaffected by head-down tilt. Unchanged transfer function gain between mean arterial pressure and mean cerebral blood flow oscillations during acute head-down tilt suggests functioning dynamic cerebral autoregulation in the face of moderate sympathetic neural withdrawal.

Summary. Although evidence suggests important influences of autonomic neural modulation on dynamic cerebral autoregulation, mild physiological manipulation of autonomic activity with acute head-down tilt has no effect on the ability of the cerebral vasculature to regulate constant flow. To our knowledge, interactions between acute head-down tilt and other potential modulators of cerebral autoregulation (including myogenic, neurogenic, and metabolic factors) have not been studied. The utility of the use of acute head-down tilt as a procedure to probe mechanisms of disrupted cerebral autoregulation in patients with autonomic failure is unknown but warrants investigation.

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DISCLOSURES

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