Critical Analysis of Cerebrovascular Autoregulation During Repeated Head-Up Tilt

Richard L. Hughson, PhD; Michael R. Edwards, MSc; Deborah D. O’Leary, MSc; J. Kevin Shoemaker, PhD

Background and Purpose—Cerebrovascular autoregulation has been described with a phase lead of cerebral blood flow preceding changes in cerebral perfusion pressure (CPP), but there has been less focus on the effect of CPP on cerebral vascular resistance. We investigated these relations during spontaneous fluctuations (control) and repeated head-up tilt.

Methods—Eight healthy adults were studied in supine rest and repeated tilt with 10-second supine, 10 seconds at 45° head-up tilt for a total of 12 cycles. Cerebral blood flow was estimated from mean flow velocity (MFV) by transcranial Doppler ultrasound, CPP was estimated from corrected finger pressure (CPPf), and cerebrovascular resistance index (CVRi) was calculated in the supine position from CPPf/MFV. Gain and phase relations were assessed by cross-spectral analysis.

Results—In the supine position, MFV preceded CPPf, but changes in CVRi followed CPPf. Gain and phase relations for CPPf as input and MFV as output were similar in supine and repeated tilt experiments. Thus, changes in cerebrovascular resistance must have had a similar pattern in the supine and tilt experiments.

Conclusions—Cerebrovascular autoregulation is achieved by changes in resistance in response to modulations in perfusion pressure whether spontaneous or induced by repeated tilt. The phase lead of MFV before CPPf is a mathematical and physiological consequence of the relation the input variable (CPPf) and the manipulated variable (cerebrovascular resistance) that should not be taken as an indication of independent control of cerebral blood flow. (Stroke. 2001;32:2403-2408.)

Key Words: autoregulation • cerebral blood flow • ultrasonography, Doppler transcranial
and MFV during repeated tilt that induced large, rapid variations in CPPF. We hypothesized that the changes in CPPF are followed by changes in CVRi that function to restore MFV toward normal levels. We show that the apparent phase lead of MFV before CPPF is a mathematical consequence of the normal lag of CVRi after changes in CPPF.

Subjects and Methods

Eight healthy young subjects (6 men and 2 women, 25±5.9 years of age, mean±SD) volunteered for this study after receiving complete verbal and written details. The Office of Research Ethics at the University of Waterloo approved the research protocol.

Subjects were allowed to rest quietly in the supine position after instrumentation had been completed. Data were collected in the supine position before being alternately tilted to 45° for 10 seconds and returned to the supine position for 10 seconds for a total of 12 cycles in 4 minutes. Tilting was accomplished on a manually operated tilt table in <2 seconds.

MFV was determined by Doppler ultrasound (Transpect TCD, Medasonics) from the right middle cerebral artery (MCA) through the temporal window. Arterial blood pressure was estimated continuously by a servo-controlled photoplethysmograph (Finapres, Ohmeda) placed on the middle finger of the right hand. The finger cuff pressure is widely used as an estimate of arterial pressure, although absolute values sometimes differ.11 Given this limitation, we chose to refer to gravity-corrected finger arterial pressure as CPPF to provide an estimate of CPP. Heart rate was recorded by ECG. End-tidal PCO2 was monitored from a nasal cannula with an infrared CO2 analyzer (Pilot, Colin). Average values of end-tidal PCO2 were obtained in the supine and tilted positions.

The finger cuff of the blood pressure monitor was positioned to rest comfortably on the subject’s chest and then held in position by a sling connected to the tilt table. To correct blood pressure from this device to heart level and also to brain level, 2 pressure transducers (Transtar, Furon) were connected to amplifier circuits (Pilot, Colin). Both of these transducers were placed on the lateral midline to coincide with the aortic valve so that when subjects were tilted there was no change in the reference point with respect to the heart. One water-filled catheter tip was placed at the level of the finger cuff to correct finger pressure to arterial pressure; the other catheter tip was positioned at the cerebral Doppler probe so that arterial pressure could be adjusted to CPPF. The transducers were calibrated against a column of water, and values were converted to millimeters of mercury.

Data Analysis and Statistics

Data were recorded on digital format tape (TEAC), then transferred for analysis by a computer-based system to yield a data set sampled at 100 Hz. MFV was determined from the outer envelope of the fast Fourier transformed cerebral Doppler signal. Beat-by-beat values were obtained for mean arterial pressure (MAP) and CPPF by averaging the corrected pressure waveforms over each cardiac cycle. CVRi was calculated as CPPF/MFV without reference to intracranial pressure, as discussed later. Autospectra of MFV, CPPF, and CVRi were calculated within 3 distinct frequency regions (very low frequency [VLF] from 0 to 0.07 Hz, low frequency [LF] from 0.07 to 0.2 Hz, and high frequency [HF] from 0.2 to 0.3 Hz) to correspond to those used previously by Zhang et al.9 Cross-spectral power, transfer function gain, phase, and coherence were determined within the same frequency regions for the relations between CPPF→CVRi and CPPF→MFV. Gain and phase relations were obtained only from those regions of the spectra where coherence was ≥0.5. This critical value is commonly used because it represents a value well above that required (0.32) to indicate a squared coherence that was significantly different from zero (P<0.01).

Data are expressed as mean±SD. The observed responses during baseline and tilt periods for autospectral power as well as gain and phase relations of the cross-spectra were compared by 1-way, repeated-measures ANOVA.

Results

A sample of the continuous data record is shown in Figure 1. This figure reveals the spontaneous variation in CPPF, MFV, and CVRi that occurred in the baseline collection and during tilt. The magnitude of these variations and the increase with repeated tilt can be appreciated from the spectral power (Table 1). To provide a visual analysis of the spontaneous phase relation, a solid vertical line has been added to Figure 1 at the peak of the CPPF oscillation that occurred just before the first tilt. With reference to this line, it is clear that the peak of the oscillation in MFV preceded the peak in CPPF and that the peak change in CVRi followed. That this was the common observation is confirmed from the cross-spectral analysis for

![Image](http://stroke.ahajournals.org/)

**Figure 1.** MFV, CPPF, and CPPF/MFV (in baseline, CPPF/MFV is equivalent to CVR index as defined in text) are shown in the final 30 seconds of baseline and during first three 45° tilts for one subject. Data were obtained with 100-point moving average to smooth within-beat variations. From solid vertical line near end of baseline period, one can appreciate phase relations with CVR after CPPF and MFV apparently “leading” CPPF. Vertical dotted lines indicate onset of tilt up.

| TABLE 1. Autospectral Power During Baseline and Repeated Tilt Periods |
|------------------------|------------------------|
| MFV, cm/s²              | Baseline | Repeated Tilt |
| VLF                    | 1.25±0.82  | 5.09±4.8  |
| LF                     | 0.76±0.28  | 2.19±1.33* |
| HF                     | 0.12±0.03  | 0.4±0.2*  |
| CPPF, mm Hg²           | 2.73±2.15  | 58.4±32.0* |
| VLF                    | 1.51±1.24  | 16.9±8.4* |
| HF                     | 0.12±0.08  | 1.7±0.8*  |
| CPPF/MFV† (mm Hg · cm-² · s)² | 0.0011±0.0009  | 0.016±0.013* |
| VLF                    | 0.0005±0.0003  | 0.0044±0.0034* |
| HF                     | 0.0007±0.00012  | 0.0004±0.0006 |

Values are mean±SD for 8 subjects. VLF, LF, HF frequency regions as described in Materials and Methods. 
*Significantly different from baseline, P<0.05. †For baseline, CPPF/MFV is equivalent to CVRi as defined in text.
TABLE 2. Transfer Function Gain and Phase Relations During Baseline and Repeated Tilt Protocols

<table>
<thead>
<tr>
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<th>Baseline</th>
<th>Repeated Tilt</th>
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<tbody>
<tr>
<td>CPPF→MFV</td>
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<tr>
<td>Gain, cm·s·mm Hg⁻¹</td>
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<td>VLF</td>
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<tr>
<td>HF</td>
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<td>0.93±0.31</td>
<td>0.52±0.17*</td>
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<td>Phase, degrees</td>
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<tr>
<td>VLF</td>
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<tr>
<td>HF</td>
<td>8</td>
<td>8.2±62.8</td>
<td>−9.1±1.2</td>
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<tr>
<td>CPPF→(CPPF/MVF)†</td>
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<tr>
<td>Gain, units/mm Hg</td>
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<td>0.019±0.005</td>
<td>0.016±0.003</td>
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<tr>
<td>LF</td>
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<td>0.014±0.003</td>
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<tr>
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<td>0.012±0.005</td>
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<td>Phase, degrees</td>
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<tr>
<td>HF</td>
<td>6</td>
<td>−53.1±26.9</td>
<td>−13.3±13.7</td>
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</table>

Values are mean±SD. Number of subjects (n) was determined by coherence ≥0.5 in baseline. When there was not sufficient coherence in baseline, only those same subjects were included under repeated tilt.

*Significantly different from baseline by repeated-measures ANOVA, P<0.05.
†For baseline, CPPF/MVF is equivalent to CVRi as defined in text, (units=mm Hg·cm⁻¹·s⁻¹).

Discussion
These data support our hypothesis that a cyclic change in CPP, whether spontaneous or induced by rapid tilt, would be followed by an appropriate change in cerebrovascular resistance in an attempt to maintain MFV near the desired set point value. Further, the supine baseline data clearly show how the interaction between CPP and CVRi result in an apparent phase lead of MFV before CPP. As previously suggested by Aaslid and colleagues on the basis of their leg cuff deflation experiments, CPP and CVRi are the appropriate variables to investigate to understand the control of CBF. We have shown that the apparent phase “lead” of MFV to CPP is merely a mathematical consequence of the relation between the physiological response of CVRi to CPP. This latter observation is in stark contrast to the speculation of some researchers that the phase lead of MFV to CPP indicates autonomic control over cerebral blood vessels that precedes and then establishes the vascular tone in the rest of the body.

Methodological Considerations
We used transcranial Doppler ultrasound to continuously monitor changes in CBF. This technique has been widely used under the assumption that the cross-sectional area of the middle cerebral artery does not change. Recent measurements of the MCA during application of lower body negative pressure in both hypocapnia and hypercapnia confirmed that this vessel is quite stable across a marked range of CBF.

Vascular resistance is defined as the ratio of the pressure drop to flow across the vascular bed. The three components, pressure drop, flow, and resistance, are not and cannot be independent variables. In the case of cerebrovascular resistance, calculation is complicated by the difficulty in directly determining the pressure drop due to unknown values of intracranial pressure and venous pressure. We have used the ratio CPPF/MVF as an estimate of CVRi during supine studies. This estimate will provide a reliable indicator of changes in cerebrovascular resistance as long as venous pressure does not change appreciably and as long as the components (CPPF and MFV) are measured without error. The stable Doppler probe will minimize any random error in measurement of MFV, and the Finapres, although often...
subject to systematic error, is not subject to random error. Thus, CVRi will reflect changes in CVR in the supine position.

During the repeated tilt experiments, we reported the CPP/MFV as a reflection of changes in CVR. Under the tilt protocol, intracranial and venous pressure almost certainly varied, invalidating the ratio CPP/MFV as an index of CVR across body positions. CPP/MFV responded in the manner that we anticipated during the up and down tilts. It is interesting that the magnitude and phase relations for CPP/MFV during repeated tilt were similar to those of CVR across supine baseline. This suggests to us that the CPP/MFV provided a useful indicator of changes in cerebrovascular dynamics. In our population of healthy young volunteers it was impossible to obtain direct measurements of intracranial pressure in an attempt to improve our understanding of cerebrovascular resistance. It is not clear how much intracranial pressure changes with head-up tilt, especially with our repeated tilt protocol, and recent direct measurements suggest that intracranial pressure might change independent of changes in cerebrovascular tone.

Alternative methods to interpret changes in CVR such as estimation of critical closing pressure (CCP) or resistance area product derived with respect to CCP (RAPc) have been used, although questions remain about this approach. CCP is obtained by extrapolation to the pressure axis of the linear regression between CPP and MFV over individual cardiac cycles. RAPc is the inverse of the slope of the linear regression. For the subject shown in Figure 1, estimated CCP was 12.9 mm Hg in supine and −6.1 mm Hg during tilt. The corresponding RAPc values were 0.95 and 0.84 mm Hg · s⁻¹ · cm⁻¹. These alternative indirect indexes are consistent with our data suggesting lower vascular resistance during the tilt.

Baseline Cerebrovascular Dynamics
Spectral analysis of the modulations in CPP and MFV yielded transfer gain and phase relations between these variables that were similar to those reported in previous investigations. We selected our frequency ranges to permit direct comparison to the results for spontaneous fluctuations in CPP reported by Zhang et al. In the VLF region of the spectrum (0.0 to 0.07 Hz), the low coherence between CPP and MFV suggests that autoregulation is effective in this region. At relatively higher frequencies, greater coherence indicated a link between changes in MFV and CPP. CPP suggests that autoregulation is effective in this region. At relatively higher frequencies, greater coherence indicated a link between changes in MFV and CPP. CPP suggests that autoregulation is effective in this region.

We used repeated tilting in this study to accomplish reproducible oscillations in CPP with a frequency similar to that investigated by repeated squatting exercise. As with this previous study, we were limited by lack of information about the true pressure gradient across the cerebrovascular bed as intracranial pressure changes with tilt and probably with squatting. However, we found that the gain and phase relations for CPP−→MFV were similar during the repeated tilting and the baseline measurements. This finding was important because it allowed us to use repeated tilt to explore cerebrovascular control under known conditions. Our finding from phase analysis that MFV preceded CPP was consistent with the phase relation between CPP and CVR. The consequence of this sequence of events was that cross-spectral analysis suggested that changes in MFV preceded CPP, but in reality it was only the mid-point of the peak change in MFV that occurred before the mid-point of the change in CPP.
with the results from the squatting exercise. By comparing responses for CVRi during baseline with the CPP/MFV during repeated tilt, we found that there, too, the gain and phase relations were similar during baseline and repeated tilt protocols. Visual analysis of Figure 1 indicates how the repeated tilt protocol has been able to provide valuable insight because it can be appreciated that changes in CPP, whether spontaneous or induced by repeated tilt, caused a change in the indicators of cerebrovascular resistance, which then in turn modified MFV.

**Interaction With PCO2**

With the repeated tilting, there was a consistent decrease in end-tidal $Pco_2$ in the upright position. This decrease in $Pco_2$ is a common finding that might be a consequence of maintained alveolar ventilation with reduced CO2 return to the lungs as venous return decreases with tilt. It is well established that reductions in arterial $Pco_2$ will cause an increase in CVR. Thus, regulation of CBF on going to the head-up position is the sum of the complex interactions of altered pressure gradient, dilatation to counter the reduction in CPP, and constriction resulting from lower arterial $Pco_2$. Indeed, Figure 1 shows the clear reduction in MFV in the upright position compared with the supine baseline or the supine position between tilts. This suggests that in addition to changes in CPP, the change in arterial $Pco_2$ did play an important role in establishing CBF.

**Interpreting Cerebrovascular Dynamics**

In a recent article, Cencetti et al concluded that the phase lead of MFV before CPP was an indication of neural control of the cerebrovascular system. They based their conclusion on spectral analysis of various signals from the cardiovascular system that showed oscillations in MFV preceding all of these other variables. We present an argument to demonstrate that the response of MFV is simply a consequence of the changes in perfusion pressure and the attempts of vascular resistance to regulate MFV close to the desired set point.

From the baseline period in Figure 1, we can appreciate that relative to the peak change in CPP, MFV does appear to lead CPP, whereas CVRi follows CPP. To explore this relation, a new figure has been constructed (Figure 2). The first assumption in this figure was that normally measured MFV and CPP, could be represented by sine waves. The exact function applied for this simulation does not influence the argument, as can be appreciated with respect to the phase relations shown by the solid vertical line in Figure 1. Second, we selected a frequency of 0.1 Hz as an example of the LF range. Third, to align the sine waves, we used our own calculated phase relation of MFV ahead of CPP by 42° which is equal to 1.17 seconds. Finally, we calculated CVR to satisfy the relation CVR = CPP/MFV. (In this model, we can use CVR rather than CVRi because intracranial pressure can be taken as constant.) To clearly illustrate a point, we have arbitrarily selected the mean amplitude to be 2, with a range of ±1 for each of MFV and CPP. Selection of these values emphasizes the nonlinearity in the calculation of CVR, but this nonlinearity occurs even when realistic values are introduced for the mean and variance of the MFV and CPP signals.

Given the above conditions for the measured variables MFV and CPP, it is apparent that CVR must lag behind CPP. Indeed, this is the only way in which a negative feedback control system could operate. Cerebrovascular autoregulation is normally considered to be a feedback system and thus our results should not be surprising, even though they are contrary to the recent opinion of Cencetti et al. The novel outcome of the analysis is the nonlinearity introduced into the control of CVR. Specifically, it appears that when MFV and CPP are assumed to bear a linear relation, CVR responds more slowly to an increase in CPP than it does to a decrease (Figure 2). If these assumptions prove to be true, the nonlinear response of CVR might be a very valuable physiological response to prevent fainting, because it would allow for rapid adjustments in CBF on moving from a supine to an upright posture. Panerai et al recently suggested application of a nonlinear model to fit MFV and CPP. Further research is required to determine where nonlinear models might improve our interpretation of the results.

**Conclusions**

The repeated tilt model demonstrated that the cerebrovascular system behaved as a closed-loop negative feedback system. The primary regulated variable, CBF, was kept within a relatively narrow range by rapid adaptations of the manipulated variable, CVR, in response to changes in CPP. The important concept advanced by this study was that research should focus on the control of CVR in response to changes in CPP. Unlike previous research that indicated the importance of the “phase lead” of MFV before CPP, we showed that this phase lead is simply a consequence of the interaction of the mechanisms responsible for control of CBF. The “phase lead” is a mathematical consequence of the phase lag of CVR. The response of CVR occurring with spontaneous fluctuations in...
CPP, repeated tilt, or leg cuff deflation is a better indication of the efficiency of cerebrovascular autoregulation.

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