Autoregulation in the Posterior Circulation Is Altered by the Metabolic State of the Visual Cortex

Kazuma Nakagawa, MD; Jorge M. Serrador, PhD; Sarah L. LaRose, BA; Fatemeh Moslehi, MD; Lewis A. Lipsitz, MD; Farzaneh A. Sorond, MD, PhD

Background and Purpose—Previous studies suggest that dynamic autoregulation in the posterior cerebral artery (PCA) is less efficient compared to the middle cerebral artery (MCA). We examined the role of cerebral vasodilation caused by metabolic activation (ie, visual stimulus) on autoregulatory characteristics in the 2 vascular territories.

Methods—Blood flow velocity in the PCA and MCA and mean arterial pressure were measured continuously in 45 healthy volunteers (62±3 years) while seated with eyes open. Additional 20 subjects (60±5 years) were examined with eyes closed and open. Autoregulation was assessed using transfer function gains in both the PCA and MCA territories in the low (0.03–0.07 Hz), high (0.07–0.15 Hz), and cardiac (≈1 Hz) frequency ranges.

Results—With eyes open, gains were significantly higher in the PCA compared to the MCA in the low (PCA: 1.41±0.09 vs MCA: 1.18±0.07; \( P = 0.003 \)) and high (PCA: 2.06±0.12 vs MCA: 1.61±0.08; \( P = 0.0001 \)) frequencies. Opening eyes increased blood flow velocity and reduced cerebrovascular resistance index in the PCA but not in MCA. This vasodilation in the PCA was associated with increased gain in the low (autoregulatory) frequency, whereas MCA gain did not change (PCA: 0.89±0.14 vs 1.31±0.17, MCA: 1.24±0.16 vs 1.16±0.11; \( P = 0.02 \)).

Conclusions—Dilation of the PCA territory during visual cortex activation resulted in increased PCA transfer function gain without changing MCA gain. Thus, impaired autoregulation in the PCA reported in previous literature is likely the result of metabolic vasodilation and not an inherent difference in the autoregulatory characteristics of the posterior circulation. (Stroke. 2009;40:2062-2067.)

Key Words: cerebral autoregulation ■ cerebral blood flow ■ posterior cerebral artery

Under physiological conditions, cerebral autoregulation serves to maintain relatively constant flow to the brain in response to changes in cerebral perfusion pressure and metabolic demand. \(^1,\,^2\) Certain clinical entities such as reversible posterior leukoencephalopathy syndrome\(^3\) and eclampsia,\(^4\) conditions that predominantly affect white matter in the occipital-parietal region of the brain, suggest that the posterior circulation may be more vulnerable to changes in perfusion pressure as compared to the anterior circulation. Previous work using transcranial Doppler (TCD) ultrasound has demonstrated impaired autoregulation in the posterior cerebral artery (PCA) compared to the middle cerebral artery (MCA).\(^5\) Some have theorized that this may be caused by differences in the sympathetic innervation of the vessel walls.\(^6\) However, there is no direct evidence linking the extent of sympathetic vascular innervation and autoregulatory response of the posterior circulation. An alternative hypothesis may be that autoregulation is different in the PCA and MCA territories because they are operating under different metabolic states.

Previous work has shown that dilated vascular beds have attenuated autoregulation compared with constricted beds.\(^7\) Because neuronal activity is closely related to cerebral blood flow, a phenomenon termed neurovascular coupling, vascular beds are more dilated when they are metabolically active. This applies to the visual cortices, which in the normal awake state are constantly activated.\(^8,\,^9\) This would place the posterior circulation in a state of continuous vasodilation compared to the anterior circulation, which may explain why the posterior circulation may be more vulnerable to systemic pressure changes. However, the differences between cerebral autoregulation in the nonactivated (eyes closed) and activated (eyes open) conditions in the PCA vs MCA territories have not been previously examined.

We hypothesized that the metabolic state of the visual cortex would have a significant impact on autoregulation in the PCA territory of healthy individuals. That is, with the eyes open, autoregulation in the PCA territory would be less efficient because of vasodilation than in the MCA; however,
with the eyes closed, there would be no difference in the PCA and MCA autoregulation. We used TCD to simultaneously study dynamic cerebral autoregulation of the PCA and MCA territories in healthy volunteers using frequency domain analysis and tested the effect of visual activation on autoregulation of the posterior cerebral circulation.

Patients and Methods

Subjects

Sixty-five healthy volunteers were recruited from laboratory personnel and members of the Harvard Cooperative Program on Aging subject registry. All subjects were carefully screened with a medical history, physical examination, and ECG to exclude any acute or chronic medical conditions. Subjects were asked to refrain from alcohol or nicotine use for at least 12 hours before the study. The study was approved by the Hebrew Rehabilitation Center for Aged and Brigham and Women’s Hospital Institutional Review Boards, and followed institutional guidelines.

Experimental Protocol

Instrumentation

Subjects reported to the cardiovascular laboratory at the Hebrew Rehabilitation Center or Brigham and Women’s Hospital in the postabsorptive state, 2 hours after their last meal. Subjects were instrumented for heart rate (ECG) and beat-to-beat finger arterial pressure (Finapres; Ohmeda Monitoring Systems) as previously described.12 End-tidal CO2 was measured from nasal prongs, using a Vacumed CO2 Analyzer.

TCD ultrasonography (MultiDop X4; DWL-Transcranial Doppler Systems Inc) was used to simultaneously measure changes in the right MCA and left PCA blood flow velocity (BFV). All the studies were performed by the same TCD technician to reduce variability. The MCA and PCA signals were identified according to the criteria of Aaslid et al13 and recorded at a depth of 50 to 60 mm for the MCA and 60 to 70 mm for the PCA. A Spencer probe fixation device was used to stabilize the Doppler probe for the duration of the study. The envelope of the velocity waveform, derived from a fast-Fourier analysis of the Doppler frequency signal, was digitized at 500 Hz, displayed simultaneously with the mean arterial pressure (MAP), ECG, and end-tidal CO2 signals, and stored for later off-line analysis.

Study Protocols

Eyes Open Sitting Protocol

Blood flow velocity in the MCA and PCA, MAP, and end-tidal CO2 were simultaneously recorded for 5 minutes in 45 healthy volunteers in the eyes open sitting position.

Eyes Closed–Eyes Open Protocol

Twenty healthy volunteers initially established a steady state with eyes open after 5 minutes of rest in a supine position. The subjects then closed their eyes for 2 minutes, and the most stationary 1-minute data segment was obtained (Figure 1). The subjects were then asked to open their eyes for 2 minutes, and again the most stationary 1-minute data segment was obtained for further analysis (Figure 1). Blood flow velocity in the MCA and PCA, MAP, and end-tidal CO2 were simultaneously recorded for 1 minute each in the eyes closed and eyes open states.

Data Processing

All data were displayed and digitized with commercially available data acquisition software (Windaq; Dataq Instruments). BFV, MAP, and CO2 waveforms were resampled at 100 Hz using a custom MATLAB program. Beat-to-beat R-R interval was determined from the R wave of the ECG or from the peak blood pressure waveform. MAP and mean BFV were determined from the integrals of each waveform. A custom Matlab program was used to calculate the average mean systolic BFV and diastolic BFV from peak and minimum TCD values within each beat cycle. Flow velocities from the eyes open sitting protocol were normalized to percentage of baseline blood flow with eyes open (n=45). Flow velocities from the eyes closed–eyes open protocol were normalized to percentage of baseline blood flow with eyes closed (n=20). Individual responses were averaged across individuals to obtain mean responses for MAP and BFV to each trial. Cerebrovascular resistance index (CVR) was calculated as the ratio of MAP to mean BFV in the PCA and MCA arterial territories. Coherence, gains, and phases were calculated using the MAP and normalized BFV signal autospectra in the low (0.03–0.07 Hz), high (0.07–0.15 Hz), and cardiac (~1 Hz) frequency ranges. Detailed methods of mathematical calculations are described in our previous study.12 Gain in the low-frequency range (0.03–0.07 Hz) is considered to be autoregulatory in nature because autoregulation is a relatively slow process and can take several seconds to engage.14 Increased transfer function gains indicate greater transmission of arterial blood pressure fluctuation to cerebral blood flow, suggesting impaired autoregulation. Previous work has found decreased autoregulation during cardiovascular stress using this methodology.15 In addition, other groups have examined the phase shift between blood pressure and velocity to assess autoregulation. An angle approaching 0° can be interpreted as absence of autoregulation because flow changes are occurring at exactly the same time as pressure changes, suggesting passive modulation of flow by pressure. In contrast, ~90° is considered optimal autoregulation because changes in flow are delayed presumably because of autoregulatory mechanisms.16,17 Because gains in the cardiac frequency (ie, ~1 Hz) are occurring too rapidly to be autoregulatory, they represent passive transmission of arterial blood pressure to BFV and likely reflect the stiffness of vessels. For examination of autoregulation in the PCA and MCA territories while seated with eyes open, 5 minutes of data were analyzed. For comparison between eyes open and closed, steady-state 1-minute data sets were examined. Previous work has used similar 1-minute data sets to assess the linear dynamic relationship between MAP and BFV via fast-Fourier transform-based methodology.18–20 These short data sets are adequate to examine autoregulatory function because, according to the Nyquist-Shannon theory,
Table 1. Baseline Subject Characteristics

<table>
<thead>
<tr>
<th></th>
<th>EO Sitting</th>
<th>EC Supine</th>
<th>EO Supine</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>45</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Gender (male:female)</td>
<td>25:20</td>
<td>10:10</td>
<td></td>
</tr>
<tr>
<td>Age, yr</td>
<td>62±3</td>
<td>60±5</td>
<td></td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>129±3</td>
<td>128±6</td>
<td>125±6</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>63±2</td>
<td>64±4</td>
<td>63±4</td>
</tr>
<tr>
<td>Mean BP, mm Hg</td>
<td>84±2</td>
<td>87±4</td>
<td>85±4</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>66±2</td>
<td>65±3</td>
<td>65±3</td>
</tr>
<tr>
<td>End tidal CO₂, Torr</td>
<td>36±1</td>
<td>40±1</td>
<td>40±1</td>
</tr>
</tbody>
</table>

Baseline subject characteristics in eyes open (EO) sitting, eyes closed (EC), and EO supine position. Values are presented as means±SE. N indicates number of subjects.

only twice the desired target frequency is needed for sampling, and thus a 1-minute window is sufficient for our low-frequency range (0.03–0.07 Hz, ie, 33–14 seconds). To validate the use of 1-minute transfer function, we took 5-minute segments of data from the same subjects (n=45) and divided them into 5 1-minute segments and compared the low-frequency gains derived from each 1-minute segment to the low-frequency gains of the 5-minute segment. Gains in both the PCA and MCA were similar between 5- and 1-minute data sets (PCA: 1.41±0.63 vs 1.48±0.60; MCA: 1.17±0.49 vs 1.27±0.47, respectively) and significantly correlated. In addition, a factor analysis demonstrated a Cronbach alpha of 0.86 for the PCA and 0.78 for the MCA, indicating that all values were measuring a single construct (ie, autoregulation).

Statistical Analysis

The effects of vascular territory (PCA vs MCA) or visual activation (eyes-closed vs eyes-open) on BFV, MAP, end-tidal CO₂, cerebrovascular resistance index, and transfer function coherence, gains, and phases were assessed by using a repeated-measures 2-way ANOVA, where a 1-minute window is sufficient for our low-frequency range (cardiac: within beat). Phase shift angle in degrees. All values are considered statistically significant.

Results

Subject Characteristics

Demographic and baseline data for all the subjects studied in eyes open sitting (n=45) and eyes closed–eyes open (n=20) protocols are shown in Table 1. Subjects in the 2 groups were similar in age and hemodynamic variables.

Hemodynamics and Cerebral Autoregulation: Eyes Open, Sitting

Table 2 summarizes the cerebral hemodynamics and autoregulation in the eyes open sitting state in 45 healthy subjects. BFV was significantly lower in the PCA as compared to the MCA territory. Transfer function gains were much higher in the PCA as compared to the MCA territory in low (autoregulatory) and high-frequency ranges, but the differences were not significant in the cardiac frequency. There were no significant differences in transfer function phases between the 2 vascular territories.

Hemodynamics and Cerebral Autoregulation: Comparing Eyes Closed to Eyes Open States

The effects of visual activation on cerebral hemodynamics and autoregulation were studied during 1-minute each of eyes closed and eyes open recordings in the supine position. We selected 1-minute data sets that were in steady state without significant difference in the values across the 60 seconds (Figure 1). Despite there being no difference in mean arterial blood pressure or end-tidal CO₂ in the 2 states, PCA flow increased significantly with eyes open while cerebrovascular resistance index significantly decreased, suggesting a metabolic vasodilation unrelated to pressure or pCO₂ changes. In contrast, the MCA territory did not change (Figure 2).

Consistent with flow changes, low-frequency transfer function gains increased in the PCA with eyes open (P=0.02) but did not change in the MCA (Figure 3). Thus, as the PCA territory dilated when eyes were opened, gains increased, suggesting impaired autoregulation. In the cardiac frequency range, again only the PCA showed significant increases in transfer function gains with eyes open (P=0.012; Figure 3), whereas MCA remained unchanged. In the eyes closed conditions, the PCA gains were lower than MCA gains in low (PCA: 0.89±0.14 vs MCA: 1.24±0.16; P=0.04) and cardiac frequencies (PCA: 1.46±0.11 vs MCA: 1.74±0.10; P=0.02). In contrast, gain values were similar in the high-frequency range in both vascular beds between eyes open and closed. After eye opening, both arteries showed significant increase in the low-frequency coherence (P=0.008; Figure 3), suggesting more linear relationship between MAP and BFV, although there was no significant difference between the 2 arteries. In addition, cardiac frequency coherence was significantly lower during both eyes closed and open in the PCA (0.996±0.001) vs the MCA (0.997±0.001; P=0.021); however, this slight difference likely has little clinical relevance. Transfer function phases at all 3 frequency ranges

<table>
<thead>
<tr>
<th></th>
<th>PCA</th>
<th>MCA</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BFV, cm/sec</td>
<td>58±3</td>
<td>88±5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diastolic BFV, cm/sec</td>
<td>20±2</td>
<td>32±2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean BFV, cm/sec</td>
<td>35±2</td>
<td>55±3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CVR, mm Hg×s×cm⁻¹</td>
<td>2.74±0.20</td>
<td>1.87±0.19</td>
<td>0.002</td>
</tr>
<tr>
<td>Gain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>1.41±0.09</td>
<td>1.18±0.07</td>
<td>0.003</td>
</tr>
<tr>
<td>High</td>
<td>2.06±0.12</td>
<td>1.61±0.08</td>
<td>0.0001</td>
</tr>
<tr>
<td>Coherence</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Low</td>
<td>0.56±0.03</td>
<td>0.61±0.03</td>
<td>0.08</td>
</tr>
<tr>
<td>High</td>
<td>0.63±0.03</td>
<td>0.62±0.03</td>
<td>0.56</td>
</tr>
<tr>
<td>Cardiac</td>
<td>0.99±0.00</td>
<td>0.99±0.00</td>
<td>0.04</td>
</tr>
<tr>
<td>Phase</td>
<td></td>
<td></td>
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<tr>
<td>Low</td>
<td>−40.79±4.56</td>
<td>−45.91±4.39</td>
<td>0.08</td>
</tr>
<tr>
<td>High</td>
<td>−37.07±4.98</td>
<td>−42.75±5.40</td>
<td>0.32</td>
</tr>
<tr>
<td>Cardiac</td>
<td>−23.45±5.52</td>
<td>−24.11±4.44</td>
<td>0.90</td>
</tr>
</tbody>
</table>

Comparison of the PCA and the MCA in EO sitting position (n=45) are shown.

Transfer function coherence, gain, and phase relating fluctuations in arterial blood pressure and cerebral blood flow velocity in the low-frequency range (low: 0.03–0.07 Hz), high-frequency (high: 0.07–0.15 Hz), and cardiac-frequency range (cardiac: within beat). Phase shift angle in degrees. All values are given as mean±SE.
were not significantly different between the PCA and MCA in response to visual activation.

Discussion

Our data show that autoregulation in the PCA territory is altered by metabolic activation by eye opening in healthy older adult subjects. As we hypothesized, during eyes open, the PCA vascular bed is vasodilated and BFV is increased to meet the increased neuronal metabolic demand of the visual cortex. In this state, PCA is more vulnerable to blood pressure fluctuations as compared to the MCA territory, as reflected by the higher PCA transfer functions gains in the low-frequency (autoregulatory) range. However, when the eyes are closed and the visual cortex is in a metabolically quiescent state, the PCA autoregulation may be even more effective than the MCA, as shown by the lower gains in the low and cardiac frequency range.

Higher PCA transfer function gains have been previously reported by Haubrich et al who studied 30 older adults (mean age, 65±10 years) without cerebrovascular disease or dysautonomia and showed higher gains in the PCA compared to the MCA. However, these subjects were studied with eyes open in an illuminated room (personal communication, Haubrich). Our group has also studied autoregulation in the PCA and MCA territories in elderly healthy volunteers using a sit-to-stand protocol. In the eyes open state, transitioning from a sitting to a standing position was associated with a significantly greater decline in the PCA as compared with the MCA territory BFV. However, this response was not tested in the eyes closed state. To our knowledge, the present study is the first to assess PCA autoregulation in 2 different metabolic states of the visual cortex. Our findings are consistent with previous assessments of dynamic autoregulation in the MCA territory during hypercapnia, which showed an increase in transfer function gain and BFV, suggesting that vasodilated vascular beds have an impaired autoregulatory response.

Contrary to the current literature suggesting that autoregulation of the PCA is impaired compared to that of the MCA, our study demonstrates that transmission of the blood pressure oscillations to cerebral blood flow (low-frequency gain) in the PCA appears to be attenuated, suggesting improved autoregulation, during a quiescent eyes closed state when the vessels are less vasodilated. These findings demonstrate that the PCA autoregulation is just as effective as the MCA autoregulation when the eyes are closed.

These data highlight the importance of metabolic state on cerebral autoregulatory function. Because our study did not involve direct imaging modalities assessing cerebral metabolic rate of oxygen or cerebral perfusion, we could not show any direct evidence that eye opening resulted in regional
increase in blood flow to the visual cortex. However, previous studies using blood oxygen level-dependent MRI have shown focal increases in blood flow to the visual cortex with eye opening, suggesting that the observed changes seen in the PCA territory in this study resulted from neurovascular coupling. None of the previous studies that addressed the differences between autoregulation in the PCA and MCA territories were performed in the eyes closed state. We speculate that the constant relative vasodilation of the posterior circulation seen with awake individuals may explain why the posterior circulation has been observed to have more vulnerable autoregulation compared to the anterior circulation in clinical practice. This finding is consistent with our previous work in the MCA in which transfer function gain significantly increased as cerebrovascular resistance index decreased.

In summary, we have shown that autoregulation in the PCA territory is likely altered by neurovascular coupling and the metabolic state of the visual cortex. Whereas the transfer function gains in the PCA territory were much higher compared to the MCA territory in the eyes open state, this difference in autoregulation vanished in the eyes closed state.

**Study Limitation**

Our study only included healthy older adults without evidence of overt chronic diseases, and thus our results can be only generalized to this population. The possibility that dynamic autoregulatory property could differ in a younger population or in adults with chronic vascular diseases warrant further study. Also, our study included 2 protocols, which differed in the subject position (sitting vs supine) and the length of TCD recordings (5 minutes vs 1 minute), and thus comparisons between protocols must be examined cautiously.

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**Disclosures**

Dr Sorond is the recipient of Beeson K23 Award AG30967. Dr Lipsitz holds the Irving and Edyth S. Usen and Family Chair in Geriatric Medicine. Dr Serrador is the recipient of the SFI Walton Visiting Professorship at the National University of Ireland, Galway.

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