Regional Cerebral Autoregulation During Orthostatic Stress: Age-Related Differences

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Background. We used transcranial Doppler ultrasonography to examine the cerebral blood flow response to orthostatic stress in the middle and posterior cerebral circulations and to determine the effects of healthy aging on regional cerebral blood flow regulation.

Methods. Continuous simultaneous middle (MCA) and posterior (PCA) cerebral artery blood flow velocities (BFV) and mean arterial pressure (MAP) were measured in response to standing from a sitting position in 13 younger (30 ± 7 years) and 13 older (73 ± 4 years) healthy participants.

Results. The older participants had a significantly larger decline in MAP (−31% ± 3 in the older and −21% ± 2 in the younger) and a smaller increase in heart rate (HR) (15 bpm ± 1 in the older, 24 bpm ± 2 in the younger) during the posture change. Despite a larger decline in MAP, the older participants had a decline very similar to that of the younger participants in BFVs in both vascular territories. This was associated with a significantly larger vasodilatory response in the MCA and PCA vascular territories of the older participants. There were no regional differences of the cerebrovascular resistance and BFV responses to orthostasis in the younger participants. However, in the older participants, there was a significantly larger BFV decline and a smaller vasodilatory response in the PCA as compared to the MCA territory.

Conclusions. Healthy aging is associated with preserved cerebrovascular adaptation to orthostatic hypotension. However, in older persons, the PCA territory blood flow may be more vulnerable to reduced perfusion during orthostatic stress.

Cerebral autoregulation serves to maintain constant blood flow to the brain over a wide range of cerebral perfusion pressures. Syncope, which is often associated with upright posture, can be provoked by any condition that threatens cerebral blood flow (CBF). Upright posture challenges cerebral autoregulation by reducing arterial pressure, cardiac output, and cerebral perfusion pressure. Although syncope is thought to be due to a global decrease in CBF, the initial prodromal symptoms are often referable to the posterior cerebral circulation. Most patients initially describe nausea, sweating, dizziness, blurred vision, and tingling of the ears, with progression to yawning, hyperventilation, and pupillary dilation before losing consciousness. However, it is not known whether there is a disproportionate reduction in posterior CBF during conditions that provoke syncope. Transcranial Doppler (TCD) ultrasonography is a noninvasive tool frequently used to measure CBF velocity, which can be used to measure instantaneous changes in CBF in response to a variety of stimuli. Given the high prevalence of orthostatic hypotension in elderly people (1), we aimed to determine if healthy aging altered regional CBF regulation during orthostatic stress.

We used TCD to simultaneously study CBF regulation in two vascular territories, the middle (MCA) and posterior cerebral arteries (PCA), in response to step changes in systemic blood pressure in healthy younger and older volunteers. Numerous methods have been used to estimate cerebral autoregulation. These include the thigh cuff test, valsalva maneuver, lower body negative pressure, antihypertensive medication administration, and most recently, the sit-to-stand protocol (2–6). We chose the sit-to-stand protocol (4), a similar but more physiological stimulus than the thigh cuff test, because it is much better tolerated by elderly participants and simulates a common activity of daily living (ADL) that potentially threatens cerebral perfusions.

Methods

Participants

Seventeen healthy younger persons and 13 healthy older persons volunteered to participate in the study. Participants were recruited from among laboratory personnel and members of the Harvard Cooperative Program on Aging registry. All participants were carefully screened with a medical history, physical examination, and electrocardiogram (ECG) to exclude any persons with acute or chronic medical conditions. Participants were asked to refrain from alcohol or nicotine for at least 12 hours. Files for four younger participants were excluded from analysis due to poor TCD signal quality. Exclusion criteria were as follows: change in mean arterial pressure (ΔMAP) <10 mmHg, a prolonged MAP drop lasting >5 seconds after standing, or an unstable state of MAP or blood flow velocity (BFV). The study was approved by the Hebrew Rehabilitation Center for Aged institutional review board, and followed institutional guidelines.


Table 1. Participant Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Young</th>
<th>Old</th>
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<tbody>
<tr>
<td>N</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>Male:Female ratio</td>
<td>6:7</td>
<td>9:4</td>
</tr>
<tr>
<td>Age, y</td>
<td>30 (7)</td>
<td>73 (4)</td>
</tr>
<tr>
<td>Mean arterial pressure, mmHg</td>
<td>88 (17)</td>
<td>85 (12)</td>
</tr>
<tr>
<td>Baseline heart rate, bpm</td>
<td>70 (12)</td>
<td>63 (4)</td>
</tr>
<tr>
<td>MCA baseline CBFV, cm/s</td>
<td>70 (14)</td>
<td>50 (17)*</td>
</tr>
<tr>
<td>PCA baseline CBFV, cm/s</td>
<td>40 (14)</td>
<td>36 (14)</td>
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Note: All values are mean (standard deviation).

*Significant difference between two groups (p < .05).

MCA = middle cerebral artery; PCA = posterior cerebral artery; CBFV = cerebral blood flow velocity.

Experimental Protocol

Instrumentation.—Participants reported to the cardiovascular laboratory in the postabsorptive state, ≥ 2 hours after their last meal. Instrumentation for HR (ECG) and beat-to-beat arterial pressure monitoring (MAP, Finapres; Ohmeda Monitoring Systems, Englewood, CO) were as previously described (4). End-tidal CO₂ was measured using a Vacuumed CO₂ Analyzer (Ventura, CA).

TCD ultrasonography (MultiDop X4; DWL-Transcranial Doppler Systems Inc., Sterling, VA) was used to measure simultaneous changes in MCA and PCA BFV (reported as mean flow velocity) in response to: (a) blood pressure changes during a sit-to-stand protocol and (b) end-tidal CO₂ changes (CO₂ Analyzer; Vacumed). The MCA and PCA signals were identified according to the criteria of Aaslid and colleagues (7) and recorded at a depth of 50–65 mm. A Mueller-Moll probe fixation device was used to stabilize the Doppler probes 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 MAP, ECG, and end-tidal CO₂ signals, and stored for later off-line analysis.

Standing protocol.—The active sit-to-stand procedure, which produces immediate orthostatic hypotension without altering the spatial relation between the Doppler probe and the insonated vessels, was developed in our laboratory and previously described in detail (4). After instrumentation, participants sat in a straight-backed chair with their legs elevated at 90° in front of them on a stool. For each of two active stands, participants rested in the sitting position for 5 minutes, then stood upright for 1 minute. The initiation of standing was timed from the moment both feet touched the floor. Data were collected continuously during the final 1 minute of sitting and 1 minute of standing. The autoregulatory response to transient orthostatic hypotension was assessed by determining the absolute and percent changes in cerebrovascular resistance (CVR = MAP/BVF) for each vessel from the sitting position (average of 50 seconds data) to the blood pressure nadir during standing (average of five values). Rate of recovery was calculated from the slope of the recovery of blood flow according to the method of Aaslid and colleagues (8).

CO₂ reactivity protocol.—Changes in MCA and PCA BFV were measured during alterations in end-tidal CO₂ (9) to determine whether differences in regional autoregulation correlated with cerebrovascular reactivity to CO₂ in that vascular territory. In this technique, cerebral BFVs in the MCA and PCA were measured continuously while participants inspired a gas mixture of 5% CO₂, 21% O₂, and balance nitrogen for 2 minutes and then mildly hyperventilated to an end-tidal CO₂ of approximately 25 mmHg for 2 minutes. To determine cerebrovascular reactivity using this technique, percent change in MCA or PCA BFV were plotted against end-tidal CO₂ in response to room air, breathing 5% CO₂, and mild hyperventilation. Cerebrovascular reactivity was measured as the slope of this relationship and expressed as percent change in CBF per mmHg change in end-tidal CO₂.

Data Processing

All data were displayed and digitized in real time at 500 Hz with commercially available data acquisition software (Windaq; Dataq Instruments, Akron, OH). BFV and blood pressure waveforms were resampled at 1 Hz using a MATLAB program (MATHWORKS, Natick, MA). Beat-to-beat R-R interval, MAP, and BFV (reported as mean flow velocity) were determined from the R wave of the ECG and the maximum and minimum of the arterial pressure or BFV waveforms.

Beat-to-beat values for BFV and MAP during the sit-to-stand protocol were averaged across all trials for each individual. CVR was calculated as the ratio of MAP to BFV. To compare group responses, percent change in BFV, CVR, and MAP were calculated as the difference between standing and sitting values, divided by sitting values. Individual percent changes were then averaged to obtain percent changes in BFV, CVR, and MAP for each group.

Statistical Analysis

Group averages in BFV, CVR, and MAP were compared using a Student t test. Significance was set at p < .05. Linear regression was used to compute the slope of the relationship between end-tidal CO₂ and BFV. Data are presented as mean ± standard deviation (SD).

RESULTS

Participant Characteristics

Demographic and baseline data for the younger (n = 13) and older groups (n = 13) are shown in Table 1. Baseline MAP and HR were not significantly different between the two groups. The older participants had lower baseline BFV in the MCA (p < .05).

Hemodynamic Response to Posture Change

Mean MAP and BFV responses in the left MCA and the right PCA during the sit-to-stand protocol for the younger and older groups are shown in Figure 1. This figure shows effective cerebral autoregulation in both vascular territories of the younger and older groups. With the rapid decline in MAP, there is a simultaneous decline in cerebral BFV, which rapidly begins to recover in both vessels at a time when the MAP is still declining.

Hemodynamic responses to standing are summarized in
Table 2. The orthostatic blood pressure decline was significantly higher in the older participants compared to the younger. The older participants also had a smaller increase in HR compared to the younger participants. Despite a larger decline in their MAP, the older group had a very similar decline in BFV in both vascular territories compared to the younger. This decline was caused by a significantly larger reduction in CVR in the MCA and PCA vascular territories of the older participants.

Comparing middle and posterior cerebrovascular territories, we found that there were no statistically significant differences in the CVR and BFV responses to orthostasis in the younger participants. However, in the older participants, there was a larger decline in BFV and a smaller decline in CVR in the PCA as compared to the MCA territory.

The rate of recovery, or rate of autoregulation for the PCA and MCA BFV, was generally higher in the younger than in the older participants, but these differences did not reach statistical significance.

**CO$_2$ Reactivity**

Table 3 shows the values for CO$_2$ reactivity in the PCA and MCA territory for both groups of participants. In the older participants, there were no significant regional differences in vasoreactivity. However, in the younger participants vasoreactivity was significantly higher in the MCA than in the PCA territory.

**DISCUSSION**

To our knowledge, this is the first study comparing cerebral hemodynamics in the PCA and MCA territories of healthy younger and older volunteers. Recently, two studies (10,11) compared MCA and PCA CBF regulation, but the effects of aging were not explored. Rosengarten and Kaps (11) showed that, in healthy younger volunteers (aged 26.7 ± 0.3 years), the PCA BFV decline in response to thigh cuff deflation recovered 900 ms faster than did the MCA response. However, they attributed this accelerated recovery to a smaller initial BFV decline in the PCA, and concluded that cerebral autoregulation in the MCA and PCA territories did not differ. In contrast, Haubrich and colleagues (10) studied 30 older adults (mean age 65 ± 10 years) without...
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Table 3. Vasoreactivity

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<thead>
<tr>
<th>Vasoreactivity</th>
<th>Young</th>
<th>Old</th>
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<tbody>
<tr>
<td>MCA (%/mmHg)</td>
<td>1.5 (0.9)*</td>
<td>0.7 (0.5)</td>
</tr>
<tr>
<td>PCA (%/mmHg)</td>
<td>1.1 (0.8)</td>
<td>0.6 (0.4)</td>
</tr>
</tbody>
</table>

*Significant difference between young and old (p < .02).
Significant differences between MCA and PCA (p < .04).

Note: All values represent mean (standard deviation).

- **Table 3. Vasoreactivity**

  - **Table 3.**

    | Vasoreactivity     | Young     | Old       |
    |--------------------|-----------|-----------|
    | MCA (%/mmHg)       | 1.5 (0.9)*| 0.7 (0.5) |
    | PCA (%/mmHg)       | 1.1 (0.8) | 0.6 (0.4) |

  *Significant difference between young and old (p < .02).
  Significant differences between MCA and PCA (p < .04).

  **Note:** All values represent mean (standard deviation).

- **cerebrovascular disease or dysautonomia. They showed that, in older participants during supine rest and passive tilt, transfer function gains were significantly higher in the MCA than in the PCA territory. They concluded that the PCA territory of older participants permitted greater transmission of arterial blood pressure oscillations into CBF; this finding suggests impaired posterior autoregulation.**

- **Our study demonstrates that healthy aging is associated with a remarkable preservation of cerebral autoregulation. Our older participants had a significantly larger decline in MAP and a smaller increase in HR during postural change, most likely secondary to an impaired baroreflex function (12).**

- **Despite the larger orthostatic stress, there was a significantly higher cerebral vasodilatory response in both vascular territories in the older participants, indicating a preserved autoregulatory response. However, among older participants, BFV declined to a greater extent in the PCA territory compared to the MCA. Although the magnitude of this difference was small and not associated with posterior circulatory symptoms, the PCA circulation may be more vulnerable to hypoperfusion. This finding is supported by Haubrich and colleagues (10), who showed that the PCA territory CBF is more sensitive to beat-to-beat blood pressure variations than the MCA.**

- **The effect of aging on cerebral autoregulation has been the subject of several recent studies. Contrary to animal studies, which have shown age-related alterations in cerebral autoregulation, human studies report preserved cerebral autoregulatory capacity of the MCA with age (4). Our study suggests that, although healthy aging is associated with preserved cerebral autoregulatory capacity, there may be an increased vulnerability of the posterior cerebral circulation to blood pressure fluctuations. This finding may explain the vulnerability of the PCA territory to syncope in older persons.**

- **Finally, we compared CO2 reactivity in the two vascular territories in younger and older participants to determine if there are regional differences in vasoreactivity associated with aging. In the younger participants, MCA vasoreactivity was significantly higher than PCA vasoreactivity. With aging, both the MCA and PCA vasoreactivity declined. Albeit the differences between MCA and PCA vasoreactivity did not reach statistical significance in the older group (p = .07), the lowest vasoreactivity was seen in the PCA territory. Thus, vasomotor responsiveness to alterations in both perfusion pressure and CO2 may be downregulated in the posterior circulation.**

- **It is important to note that the PCA may receive collateral flow from the anterior circulation via the posterior communicating arteries and may therefore be a poor surrogate for the basal artery, which is the main supply to the brain stem. Unfortunately, simultaneous continuous monitoring of the basilar and MCA arteries during the sit-to-stand protocol was not possible using our TCD device. One previous study compared regional cerebral autoregulation and vasoreactivity in the basilar and MCA arteries in healthy younger participants using TCD (13). The study was performed in the supine position with the basilar probe held manually. Autoregulatory and reactivity measures were similar in the basilar artery and the MCA. It is hoped that future technical developments will allow us to extend our study to the basilar artery in healthy older persons and those persons with vascular disease.**

- **Conclusion**

  - **We have shown that healthy aging is associated with overall preserved autoregulation in response to posture change. However, in older persons the PCA territory blood flow may be more vulnerable to hypoperfusion during orthostatic stress. The lower vasoreactivity of the PCA territory may be one possible mechanism for the lower vasodilatory response.**

  **ACKNOWLEDGMENTS**

  - **This work was supported by a generous donation from Mr. and Mrs. Robert Krakoff at the Hebrew Rehabilitation Center for Aged and by grants AG04390, AG08812, and AG05134 from the National Institute on Aging, Bethesda, MD. Dr. Sorond is the recipient of Mentored Clinical Scientist K12 Award (AG00294) from the National Institute on Aging. Dr. Lipsitz holds the Irving and Edyth S. Usen and Family Chair in Geriatric Medicine.**

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  **REFERENCES**


**Received December 23, 2004**
**Accepted February 28, 2005**
**Decision Editor: John E. Morley, MB, BCh**