Elderly Women Regulate Brain Blood Flow Better Than Men Do

Brian M. Deegan, MSc; Farzaneh A. Sorond, MD, PhD; Andrew Galica, BS; Lewis A. Lipsitz, MD; Gearoid O’Laighin, PhD; Jorge M. Serrador, PhD

Background and Purpose—Orthostatic intolerance and falls differ between sexes and change with age. However, it remains unclear what role cerebral autoregulation may play in this response. This study was designed to determine whether cerebral autoregulation, assessed using transcranial Doppler ultrasound, is more effective in elderly females than in males.

Methods—We used transcranial Doppler ultrasound to evaluate cerebral autoregulation in 544 (236 male) subjects older than age 70 years recruited as part of the MOBILIZE Boston study. The MOBILIZE Boston study is a prospective cohort study of a unique set of risk factors for falls in seniors in the Boston area. We assessed CO2 reactivity and transfer function gain, phase, and coherence during 5 minutes of quiet sitting and autoregulatory index during sit-to-stand tests.

Results—Male subjects had significantly lower CO2 reactivity (males, 1.10 ± 0.43; females, 1.32 ± 0.43 cm/s/%CO2; P<0.001) and autoregulatory indices (males, 4.41 ± 2.44; female, 5.32 ± 2.47; P<0.001), higher transfer function gain (males, 1.34 ± 0.49; females, 1.19 ± 0.43; P=0.002), and lower phase (males, 42.7 ± 23.6; females, 49.4 ± 24.9; P=0.002) in the autoregulatory band, implying less effective cerebral autoregulation. However, reduced autoregulation in males was not below the normal range, indicating autoregulation was intact but less effective.

Conclusions—Female subjects were better able to maintain cerebral flow velocities during postural changes and demonstrated better cerebral autoregulation. The mechanisms of sex-based differences in autoregulation remain unclear but may partially explain the higher rates of orthostatic hypotension-related hospitalizations in elderly men. (Stroke. 2011;42:1988-1993.)

Key Words: blood pressure • cerebral autoregulation • cerebral blood flow • sex

Cerebral autoregulation (CA) is an intrinsic mechanism that maintains cerebral blood flow (CBF) relatively constant over a wide range of blood pressures.1 If autoregulatory responses are slow, then the likelihood that transient decreases in blood pressure during postural changes would result in transient cerebral hypoperfusion increases, potentially causing symptoms including dizziness, light-headedness, and syncope.

Orthostatic intolerance is 3- to 4-times higher in young women than in young men.2 Similarly, orthostatic intolerance after space flight also occurs more frequently in women.3 However, in older populations, orthostatic hypotension-related hospitalization rates are higher in men than in women.4 One explanation for these differences could be differences in CA between men and women.

Previous studies have shown higher cerebral flow velocity,5 cerebral vasomotor reactivity,6 and cerebrovascular reactivity7 in females. Gender-related differences in autoregulation also have been observed in adolescent8 and young adult females.9 However, previous data are somewhat conflicting and involve relatively small numbers of subjects (<25). In addition, no work has compared sex differences in autoregulation in older populations.

To address this issue, we analyzed the autoregulatory responses of subjects taking part in the MOBILIZE Boston (Maintenance of Balance, Independent Living, Intellect, and Zest in the Elderly of Boston) study. The Mobilize Boston study is a study of 800 older adults in the Boston area that was designed to improve understanding of how older adults can maintain their health and independence for longer. We hypothesized that CA would be more effective in female subjects when compared to males.

Subjects and Methods

The study sample was taken from the Mobilize Boston study population. In total, 816 subjects (292 male) older than age 70 years were enrolled. Transcranial Doppler testing was completed in 63%
of the sample and partially completed in another 11% of participants. Transcranial Doppler data could not be obtained in some subjects because of the absence of a suitable temporal window to insonate the middle cerebral artery (MCA). Subjects with a history of stroke (N=78; 34 male) were excluded from the study. The Mobilize Boston study was approved by the Institutional Review Board of Hebrew Senior Life and all subjects provided written informed consent.

**Instrumentation**

Each subject was instrumented with a 3-lead ECG and finger-cuff continuous blood pressure monitor (Finometer; FMS Medical Systems) held at heart level with a sling. Cerebral blood flow velocity (CBFV) was measured continuously in the MCA using transcranial Doppler ultrasonography (MultiDop; DWL). Continuous end-tidal CO2 levels were measured by a gas analyzer through a sampling tube attached to a nasal cannula. All physiological signals were digitized at 500 Hz (Windaq) and stored for offline analysis.

**CO2 Reactivity Protocol**

The cerebrovascular response to CO2 was assessed by asking subjects to breathe normally for 2 minutes, inspire a gas mixture of 8% CO2, 21% O2, and balance nitrogen for 2 minutes, and then subjects to breathe normally for 2 minutes, inspire a gas mixture of end-tidal CO2 value. The slope of this relationship was used as an outcome. Data are presented as mean±SD and levels of significance are shown. A greater proportion of female subjects had diabetes (P=0.006). Females had significantly higher ARI values than males and the difference in blood pressure changes between genders was significant (males, 4.41±2.44; females, 5.32±2.46; P=0.001). Changes in heart rate and end-tidal CO2 on standing were not significantly different between male and female subjects.

**Sit-to-Stand Protocol**

For posture change, a sit-to-stand maneuver was performed. Subjects sat with their legs elevated at 90 degrees on a stool for 5 minutes, followed by moving from sit-to-stand for 1 minute. Initiation of stand was considered to be the point at which both feet touched the floor. This was performed twice. Subjects were not included if data quality was considered too poor for analysis.

**Data Processing and Analysis**

Postprocessing was performed using custom-written Matlab scripts. To evaluate beat-to-beat dynamics of mean arterial pressure and CBFV, we calculated the differences between the sitting value (averaged over 50 seconds) and the nadir of blood pressure (average of 5 values surrounding the nadir) in both absolute and percentage change. In addition, we estimated the cerebrovascular resistance (Δmean arterial pressure/CBFV) over the same period. End-tidal CO2 levels were calculated while sitting and 10 to 30 seconds after standing. The average of both sit-to-stand responses for each subject was calculated to produce 1 response per subject.

To quantify autoregulation, we calculated the dynamic autoregulatory index (ARI)\(^\text{10}\) based on the transient changes in CBFV and mean arterial pressure when standing. In addition, we calculated transfer function gain, phase, and coherence on the 5-minute seated period. Subjects with ≥3 ectopic beats per minute were excluded from transfer function analysis.\(^\text{11}\)

To calculate CO2 reactivity, we plotted the CBFV of each beat during the cerebrovascular reactivity test and the corresponding end-tidal CO2 value. The slope of this relationship was used as an index of CO2 reactivity ((cm/s)/mm Hg).

**Statistical Analysis**

The effects of group (male versus female) on CBFV, heart rate, mean arterial pressure, end-tidal CO2, cerebrovascular resistance, ARI, and transfer function indices were assessed by independent samples t tests. Data are presented as mean±SD and levels of P<0.05 are considered statistically significant.

**Subjects**

In total, 544 subjects (236 male) subjects were included in this study. Body mass index and incidence of hypertension, diabetes, and hyperlipidemia were compared between genders (Table 1). Females had higher cholesterol levels (P<0.001) and lower rates of diabetes (P=0.006). CO2 reactivity data were obtained in 383 (164 male) subjects, transfer function analysis was performed in 407 subjects (163 male), and sit-to-stand was performed in 440 subjects (193 male). Of these 440 subjects, 353 subjects (165 males) had data considered suitable for ARI analysis. Remaining subjects were excluded because of inadequate signal quality.

A greater proportion of male subjects had diabetes (P=0.006). We therefore analyzed autoregulatory data for all subjects and subjects without diabetes, because previous studies have shown that CA is impaired in diabetic subjects.\(^\text{12}\)

A higher proportion of females had hyperlipidemia, but a multiple ANOVA analysis found no interaction between gender and hyperlipidemia. Therefore, we do not believe that this difference in hyperlipidemia rates affected the study outcome.

**Sit-to-Stand Protocol**

Figure 1 shows a comparison of male-versus-female sit-to-stand responses (Table 2). Males had a slightly larger decline in mean arterial pressure (P=0.006), and a significantly larger decline in MCA flow velocity (P<0.001). Females had significantly higher ARI values than males (Figure 2), demonstrating that CBFV returned to baseline faster, even considering the difference in blood pressure changes (males, 4.41±2.44; females, 5.32±2.46; P=0.001). Changes in heart rate and end-tidal CO2 on standing were not significantly different between male and female subjects.

Linear regression analysis of baseline sitting CBFV by age showed that females had a significant decrease of ~4.60 cm/s per decade. In contrast, male subjects showed a nonsignificant change of ~1.32 cm/s per decade. This significantly greater decrease found in females (P<0.001) resulted in much higher CBFV values in the younger females, reaching values similar to those of the males by the past decade.

**Transfer Function Response**

Transfer functions were calculated with the subject in the seated position in 3 frequency bands: very low frequency (0.03–0.07 Hz); low frequency (0.07–0.15 Hz); and cardiac frequency surrounding the heart rate (~1 Hz). Previous

<table>
<thead>
<tr>
<th>Table 1. Summary of Subject Characteristics</th>
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<tr>
<td></td>
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<tr>
<td>Age (y)</td>
</tr>
<tr>
<td>BMI</td>
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<tr>
<td>Systolic BP (mm Hg)</td>
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<tr>
<td>Diastolic BP (mm Hg)</td>
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<tr>
<td>Diabetes (%)</td>
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<tr>
<td>Hyperlipidemia (%)</td>
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<tr>
<td>Hypertension (%)</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; BP, blood pressure; N, number of subjects for whom data are available.
research has suggested that gains in the very low frequency range represent autoregulatory processes.\textsuperscript{13}

Males had significantly higher gain (males, 1.34±0.49; females, 1.19±0.43; \(P=0.002\)) and lower phase (males, 42.7±23.6; females, 49.4±24.9; \(P=0.007\)) in the very low frequency band. In contrast, there were no significant differences in the low-frequency band (Figure 3).

**Table 2. Baseline Hemodynamics and Response to Sit-to-Stand Procedure**

<table>
<thead>
<tr>
<th>Metric</th>
<th>Male ((N=193))</th>
<th>Female ((N=247))</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mm Hg)</td>
<td>67.9±13.7</td>
<td>70.4±13.4</td>
<td>0.048</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>63.1±9.6</td>
<td>68.2±10.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CBFV (cm/s)</td>
<td>39.2±10.0</td>
<td>43.1±9.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CVR (mm Hg)/(cm/s)</td>
<td>1.85±0.60</td>
<td>1.73±0.60</td>
<td>0.041</td>
</tr>
<tr>
<td>End-tidal CO(_2) (mm Hg)</td>
<td>35.1±4.5</td>
<td>35.9±3.8</td>
<td>0.044</td>
</tr>
<tr>
<td>DMAP (mm Hg)</td>
<td>−18.2±8.7</td>
<td>−16.0±8.3</td>
<td>0.006</td>
</tr>
<tr>
<td>ΔCBFV (%)</td>
<td>−22.2±13.2</td>
<td>−14.5±10.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ratio of % change</td>
<td>0.746±0.148</td>
<td>0.702±0.970</td>
<td>0.71</td>
</tr>
</tbody>
</table>

\(P=\) male vs female comparison.

CBFV indicates cerebral blood flow velocity; CVR, cerebrovascular resistance; HR, heart rate; MAP, mean arterial pressure; bpm, beats per minute.

To determine the pressure–flow relations within the beat, we examined transfer functions at the cardiac frequency. Male subjects had higher cardiac frequency gains (males, 2.36±0.64; females, 2.04±0.55; \(P<0.001\)).

**CO\(_2\) Reactivity Protocol**

Females had significantly higher CO\(_2\) reactivity slopes (all subjects: males 1.10±0.03 (cm/s)/mm Hg and females 1.32±0.43 (cm/s)/mm Hg; \(P<0.001\); diabetes excluded: males 1.08±0.32 (cm/s)/mm Hg and females 1.31±0.42 (cm/s)/mm Hg). To control for greater baseline CBFV in the females, we also examined the cerebrovascular reactivity calculated from normalized CBFV data, and females also showed significantly greater values (all subjects: males 2.88±0.65%/mm Hg and females 3.15±0.77%/mm Hg; \(P<0.001\); diabetes excluded: males 2.89±0.64 (cm/s)/mm Hg and females 3.21±0.71 (cm/s)/mm Hg).

**Discussion**

The main findings of this study are that, in an older population, females were better able to regulate CBF and demonstrated higher ARI values during a sit-to-stand maneuver and better transfer function CA indices. Females also had higher baseline MCA flow velocities and greater cerebrovascular reactivity to CO\(_2\). Higher rates of diabetes in men did not affect the outcome of this study. Indices of CA were within the normal healthy range for both genders, indicating that CA is not impaired in healthy aging.

A recent epidemiological study showed a higher rate of orthostatic hypotension-related hospitalizations in elderly males.\textsuperscript{4} This could be the result of either greater hypotension in males, resulting in greater cerebral hypoperfusion, or less effective autoregulation, resulting in an inability to compensate for orthostatic blood pressure declines. In fact, our results found that males tended to have larger blood pressure declines during sit-to-stand, as well as lower ARI values, reduced phase shift, and higher gains than females, indicating less effective autoregulation than females. This raises the possibility that reduced autoregulation capacity may be related to this increased incidence of orthostatic hypotension-related hospitalizations in elderly men.

Previous work in young adult females found that MCA transfer function coherence in the low-frequency band was...
lower in females, when tested in the upright position, suggesting better autoregulation.9 Other studies in children have produced conflicting results. No sex differences in either the basilar artery or MCA were found in young children (4–8 years);14 however, in older children (10–16 years), the same group found that females are better able at maintain basilar artery flow when upright whereas males were better at maintaining MCA.8 However, in both these studies, measures of autoregulation were based on steady-state values rather than dynamic changes, as we have reported.

The reasons for improved autoregulation in our female cohort remain unclear. One possibility is that the MCA territory in females was more vasoconstricted. Previous work has demonstrated that autoregulation is improved when the cerebrovascular bed is constricted, such as during hypocapnia,15 and is correlated to cerebrovascular resistance.11 However, females in our study had lower cerebrovascular resistance values than males, indicating their cerebrovascular beds were more dilated and thus autoregulation should have been worse.

Another possibility is that sex hormone levels could have affected the autoregulatory response. This appears to be unlikely because our females were postmenopausal and those using hormone replacement therapy did not significantly differ in response. Previous work has also found no difference in the autoregulatory response to orthostatic stress in premenopausal women when tested at various times throughout the menstrual cycle.16 Thus, it appears unlikely that estrogen levels had an effect on the autoregulatory response.

The relationship between gender and CO₂ cerebrovascular reactivity remains unclear. The Rotterdam study found no difference in cerebrovascular reactivity between males and females older than 65 years, but found lower reactivity in young females.17 Similarly, postmenopausal women younger than age 65 years were found to have lower breath-hold indexes, indicating reduced cerebrovascular reactivity, compared to those of a group of age-matched men.18 In contrast, we found greater cerebrovascular reactive women older than 65 years of age, similar to previous findings in women younger than 65 years,6,7 whereas Vriens et al19 found no significant difference between genders. It remains unclear why these differences exist. One possibility is that methodology issues may underlie the differences. Our technique used 8% CO₂ with 21% O₂, causing increased arterial CO₂ levels without changing arterial oxygen levels. Other studies have used 5% CO₂ with 95% O₂, resulting in hypercapnia but also causing hyperoxia, or with acetazolamide possibly affecting the result. It remains to be determined if methodological issues may explain the contradictory findings.

Regardless, the results of this study, as well as previous work in stroke patients, have found that cerebrovascular reactivity was not correlated to autoregulatory measures.20 Thus, differences in cerebrovascular reactivity likely do not explain differences in cerebral autoregulation between genders.

A potential explanation for the higher MCA flow velocities in females is the possible effect of sex hormone levels. Hormone replacement therapy in postmenopausal women has also been reported to increase CBF,21 as has controlled ovarian stimulation.22 However, higher CBFV has also been shown in prepubital girls14 and in the older population in this study. Because both these groups are known to have lower
levels of estrogen, it appears unlikely that sex hormone differences can explain the differences in MCA flow velocities.

The difference in baseline CBFV between genders also could be explained by differences in MCA vessel diameter. Smaller vessel diameter would lead to increased flow velocity in female subjects, assuming no difference in CBV. Muller et al. reported that MCA vessel diameter was 9.3% larger in male subjects. In contrast, Orlandini et al. reported no significant sex differences in cerebral vessels. Because neither MCA vessel diameter nor absolute MCA flow was measured in this study, we cannot exclude the possibility that differences in global CBF were present. In addition, if anatomic differences explained the higher flow in females, then we would expect that this difference would be unaffected by age. We found that females demonstrated a significant decrease in CBFV with age, consistent with data previously reported by Bakker et al., suggesting that anatomic differences cannot explain the differing CBFV.

Aging is associated with decreased baroreflex function related to vascular stiffening. Because, like the baroreflex, CA is a myogenic response to stretch of the vessel, it would seem logical that CA would be impaired with age. In fact, it has been suggested that impairment in CA associated with aging may contribute to increased rates of syncope in the elderly. However, the results of several studies have shown that dynamic CA is maintained in healthy aging. This may be related to the fact that some data have demonstrated that cerebral vessels may not show the same stiffening effects as peripheral vessels. This is the largest cross-sectional study to date on CA in the elderly, and ARI values for both males and females were similar to those of younger healthy controls in previous studies. This is in contrast to the longitudinal study of Brodie et al. which showed a decline in ARI of 1.1 over 10 years in 10 healthy subjects. Thus, it is possible that our subjects may have had higher ARI values when younger. Regardless, even if there was a decline, indices of autoregulation in this population still remained within the expected range for healthy subjects, further supporting the finding that autoregulation is not impaired in healthy aging.

A limitation of this study is the potential for selection bias, because not all subjects recruited for the MOBILIZE Boston study completed transcranial Doppler analysis. To address this, we compared age, body mass index, and incidences of diabetes, hypertension, and hyperlipidemia for both males and females in the group undergoing transcranial Doppler (N=544) and in the group not undergoing transcranial Doppler (N=221). There were no clinically significant differences between groups. Thus, selection bias seems unlikely but cannot be dismissed completely.

Conclusions
In summary, female subjects were better able to maintain CBFV during postural changes and demonstrated better CA. Females also had higher MCA flow velocities and CO2 cerebrovascular reactivity than males. Finally, females appeared to have greater cerebral vessel compliance. It remains unclear why older females demonstrate improved CA. Future work is needed to examine gender differences in various cerebral arterial beds to better understand these underlying autoregulatory differences.

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Disclosure
None.

References
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