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Gender related differences in cerebral autoregulation in older healthy subjects

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Abstract— **Cerebral autoregulation is an intrinsic mechanism of the cerebrovasculature that maintains cerebral blood flow relatively constant over a wide range of blood pressures. Recent studies have shown sex differences in cerebral autoregulation in adolescents and young adults. We evaluated cerebral auturegulation in 419 (186 male) subjects over the age of 70 recruited as part of the MOBILIZE Boston study. CO_2 reactivity, transfer function gain and autoregulatory index (ARI) during sit to stand tests were assessed. Female subjects had significantly higher CO_2 reactivity ($p < 0.001$) and vasomotor range ($p<0.001$) as well as ARI indices ($p<0.001$) and lower transfer function gain in the autoregulatory band ($p=0.001$), implying better cerebral autoregulation, than male subjects. The mechanisms of sex based differences in cerebral autoregulation remain unclear, but the results of this study highlight the need for future work to better understand these underlying autoregulatory differences.**

I. INTRODUCTION

Cerebral autoregulation, an intrinsic mechanism of the cerebrovasculature, maintains cerebral blood flow relatively constant over a wide range of blood pressures [1]. Impaired Autoregulation can contribute to the onset of syncope on posture change.

A review of the literature shows that orthostatic intolerance occurs more frequently in women than men. The rate of orthostatic intolerance is three to four times higher in young women than young men [2]. The incidence of post-spaceflight orthostatic intolerance is also higher in women (35%) than in men [3]. One explanation for this sex difference could be difference in cerebral autoregulation.

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Sex related differences in cerebral flow velocity [4, 5], cerebral vasomotor reactivity [6] and cerebrovascular reactivity [7], and cerebral autoregulation in adolescents and young adults [8-10] have been reported. However, the authors are unaware of any data examining gender related differences in older subjects. Also, to date, all studies investigating gender related differences in cerebral autoregulation involved relatively low numbers of subjects (<=24). To address these issues, we analyzed the autoregulatory responses of 419 subjects over the age of 70 that were recruited as part of the MOBILIZE Boston study investigating falls in older people. We hypothesized that cerebral autoregulation would be impaired in female subjects when compared with males.

II. METHODS

A. Subject recruitment

The subjects in this study were recruited as part of the MOBILIZE Boston study investigating falls in older people [11]. A total of 765 subjects over the age of 70 were enrolled in this study. Of the 765 subjects, transcranial Doppler testing was completed in 63% of the sample, and partially completed in another 11% of participants. TCD data could not be obtained in some subjects because of the absence of a suitable temporal window to insonate the middle cerebral artery. In total, TCD testing was successfully completed in 419 subjects.

B. Instrumentation

Each subject was instrumented with a three lead ECG (Collins, TX) to obtain heart rate. Continuous arterial blood pressure measurements were obtained using a Finometer photoplethysmographic system (Finapres Medical Systems, Arnhem, The Netherlands) on a finger and held at heart level with a sling. Cerebral blood flow velocity (CBFV) was measured continuously in the Middle Cerebral Artery (MCA) by placing a 2MHz pulsed flat transcranial Doppler (TCD) probe (MultiDop, DWL) over the right or left temporal bone with the best signal. All physiological signals were digitized at 500Hz by using a commercially available digitizer (Windaq, Dataq Instruments, Columbus, OH) and stored on a computer for offline analysis.

C. CO_2 reactivity protocol

The response to CO_2 was assessed by asking subjects to breath normally for 2 minutes, inspire a gas mixture of 8% CO_2, 21% O_2, and balance nitrogen for 2 minutes and then

mildly hyperventilate to an end-tidal CO_2 of approximately 25 mmHg for 2 minutes. Continuous end-tidal CO_2 levels were measured during the trials by a gas analyzer through a sampling tube attached to a nasal cannula.

D. Sit to stand protocol

For posture change, a sit-to-stand manoeuvre was performed. Subjects sat with their legs elevated at 90 degrees in front of them on a stool. Measurements were obtained continuously during a 5 minute rest in the sitting position, then while standing upright for 1 minute. The initiation of standing was timed from the moment both feet touched the floor. The five minute sitting period was also used to compute the pressure-flow transfer function described below.

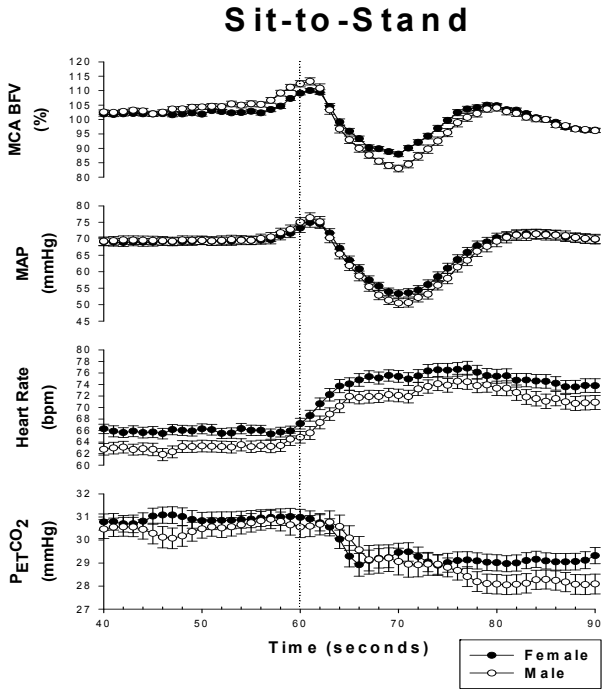

Figure. 1. Normalised middle cerebral artery blood flow velocity (MCA BFV), mean arterial pressure (MAP), heart rate and end tidal CO_2 levels during the 20 seconds prior to and 30 seconds after transition from sitting to standing (at 60 seconds). mmHg = millimetres of mercury, bpm = beats per minute.

E. Data Processing and Analysis

Postprocessing was done using custom-written MATLAB scripts. Beat-to-beat R-R intervals were determined from the R wave of the ECG. Systolic, diastolic, and mean values for blood pressure and CBFV were determined from the associated waveforms.

To evaluate the beat-to-beat dynamics of mean arterial pressure (MAP) and CBFV responses to acute posture changes, we calculated the differences between the baseline sitting value (averaged over a period of 50s) and the value at the nadir of blood pressure (average of 5 values surrounding the nadir) for both mean pressure and velocity for each trial. We also expressed these changes as a percentage of the baseline value. The average of two trials for a group was then computed.

We assessed the autoregulatory response to transient orthostatic hypotension by determining the absolute and percent change in cerebrovascular resistance (CVR) (Δ MAP/CBFV) from sitting (average of 50s) to the nadir of blood pressure during stand (average of 5 points around the nadir). The time to nadir of MAP and CBFV, and the rate of decay of MAP and CBFV were also measured [12]. Furthermore, we determined the dynamic autoregulatory index (ARI) by using the method described by Tiecks et al. [13] to quantify the CBFV response to dynamic changes in MAP.

Coherence and transfer function analyses using the MAP and CBFV signals' autospectra during the 5 minutes of sitting period were also performed. The time series data were decimated to 100Hz to provide equidistant samples. The power spectrum density, based on Welch's algorithm of averaging periodograms was calculated for the filtered signals using a sliding window with a width of 500 points and an overlap of 250 points after detrending and application of a Hanning filter.

To calculate CO_2 reactivity, we plotted the CBFV of each beat during the cerebrovascular reactivity test and the corresponding end-tidal CO_2 value. The slope of this relationship was used as an index of CO_2 reactivity (cm.s-1/%CO_2). Vasomotor Range was calculated as the maximum change in CBFV divided by the maximum change in end tidal CO_2.

F. Statistical Analysis

The effects of posture (sitting vs. standing) or group (male vs. female) on CBFV, heart rate, MAP, end-tidal CO_2, CVR, and transfer function gains were assessed by using a repeated-measures two-way ANOVA, respectively, with a post hoc Bonferroni test for multiple comparisons. Data are presented as mean ± standard deviation, and levels of $P < 0.05$ are considered statistically significant.

III Results

A. Subjects

In total, TCD data was successfully obtained in 419 (186 male) subjects, with the male subjects aged 78.1 ± 5.1 years and females 77.7 ± 5.7 years. The CO_2 reactivity protocol was successfully completed in all 419 subjects. Transfer function analysis was successfully completed in 336 subjects (147 male). Sit to stand data was successfully completed in 271 subjects (129 male).

B. CO_2 reactivity protocol

Females had significantly higher CO_2 reactivity slopes (Males: 1.08 ± 0.35 cms^{-1}/mmHg, Females: 1.32 ± 0.42 cms^{-1}/mmHg, $p < 0.001$) and vasomotor range (Males: 1.16 ± 0.34, Females: 1.45 ± 0.44, $p < 0.001$).

C. Sit to stand protocol

Figure 1 shows a comparison of male versus female responses during sit to stand testing. There was no significant difference in sitting MAP between male and female subjects. Female subjects had significantly higher

sitting MCA flow velocities (Males: 39.1 ± 9.5cms^{-1}, Females: 44.5 ± 9.8cms^{-1}, $p < 0.001$), and lower CVR than male subjects (Males: 1.85 ± 0.59mmHg/cms^{-1}, Females: 1.68 ± 0.52mmHg/cms^{-1}, $p = 0.009$). Females had higher resting heart rates than male subjects (Males: 62.5 ± 9.9bpm, Females: 66.5 ± 9.2bpm, $p = 0.001$). End-tidal CO_2 levels were not significantly different during sitting.

Examining the transition from sitting to standing (Table 1), females had significantly higher ARI values than males ($p < 0.001$). Females had a slightly lower drop in MAP on standing than males ($p = 0.037$) and a lower percentage drop in MCA flow velocity ($p < 0.001$). Also, females had a lower ratio of percentage change in MBV to percentage change in MAP than male subjects ($p = 0.002$). There was no significant difference in ΔHR on standing. Also, the time to reach nadir of MAP and MBFV and rate of decay of MAP and CBFV were not significantly different between the two groups. The drop in end-tidal CO_2 on standing was not significantly different between male and female subjects.

D. Transfer Function Response

To examine the cerebral blood flow response to spontaneous changes in blood pressure, transfer function gains were calculated with the subject in the seated position in three frequency bands: low frequency (0.03– 0.07 Hz); high frequency (0.07– 0.15 Hz), and cardiac frequency surrounding the heart rate (~1 Hz). The low frequency band is thought to reflect cerebral autoregulatory processes [14].

Male subjects had significantly higher gains in the low frequency band than female subjects (Males: 1.38 ± 0.61, Females: 1.24 ± 0.74, $p = 0.001$). Autoregulatory band coherence and phase were not significantly different between groups. There were no significant differences in gain, coherence or phase in the high frequency band between male and female subjects.

To determine the pressure-flow relations within the cardiac cycle, we examined transfer functions in the cardiac frequency. Male subjects had higher cardiac frequency gains (Males: 2.35 ± 0.68, Females: 2.14 ± 1.03, $p < 0.001$). There was also a significant phase lag between male and female subjects (Males: -24.9 ± 4.6 degrees, Females: -45.7 ± 4.1 degrees, $p = 0.001$).

IV Discussion

The main findings of this study are that, in an older population, female subjects have higher baseline MCA flow velocity than male subjects. Female subjects had greater cerebrovascular reactivity to CO_2, and greater vasomotor range than male subjects. Female subjects also demonstrated improved cerebral autoregulation.

The finding that females have higher MCA flow velocities than male subjects is consistent with previous findings in younger populations [4, 5, 8-10]. Higher CO_2 reactivity [7] and greater vasomotor range [6] has also been reported previously.

There are a number of potential explanations for the higher MCA flow velocities in females than in male subjects. One possible explanation is the different sex hormone levels in women and men. Kastrup et al [15] reported that higher cerebral flow velocities and CO_2 vasodilator capacitances in women were diminished by indoethacin. Also, estrogen has been shown to improve vasodilation via enhancement of endothelial nitric oxide synthase in animals [16]. However, higher cerebral flow velocities have been shown in prepubital girls [8], and also in the older population in this study, so it is unlikely that the effects of estrogen alone can explain these findings.

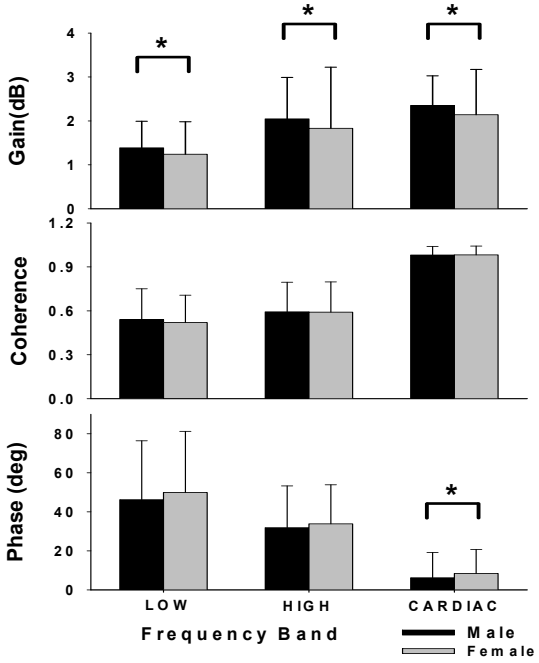

Figure. .2 Male versus female transfer function gain in the low frequency (0.03– 0.07Hz); high frequency (0.07– 0.15Hz), and cardiac (~1Hz) bands

The difference in flow velocities between male and female subjects could also be explained by differences in the diameter of the MCA. Smaller vessel diameter would lead to higher flow velocity in female subjects, assuming similar overall blood flow. However, different studies have shown conflicting results. Muller et al [17] reported that MCA vessel diameter was 9.3% larger in male subjects. Tarasów et al [18] also reported larger MCA diameters in male subjects, but these results were not statistically significant. MCA vessel diameter was not measured in this study, so we cannot confirm this theory.

Females had a significantly larger phase delay in the cardiac frequency than male subjects. The reason for this phase delay is unclear. It may indicate a difference in vessel compliance, or it may reflect differences in downstream resistances between male and female subjects.

In this study, females had significantly higher ARI values, lower transfer function gains in all frequency bands, and a lower ratio of percentage drop in MCA flow velocity to percentage drop in MAP. The reason why female subjects show better CA is unclear. Female subjects did show increased CO_2 cerebrovascular reactivity and vasomotor range. This would suggest that females have more reactive

cerebral vessels than males, which may contribute to the better CA values observed in this study.

TABLE I
HAEMODYNAMIC RESPONSES TO SIT-TO-STAND PROCEDURE

Dependent Variable	Gender	Mean	Std. Error	Sig.
Δ MAP (mmHg)	Male	-20.36	0.60	0.037
	Female	-18.61	0.58	
Δ MCA mean flow velocity (%)	Male	-16.83	0.98	0.000
	Female	-11.10	0.93	
Ratio of % change MBFV to % change MAP	Male	0.58	0.04	0.002
	Female	0.43	0.03	
Δ cerebrovascular resistance (%)	Male	-14.68	1.31	0.177
	Female	-17.14	1.26	
Δ heart rate (bpm)	Male	12.46	0.49	0.914
	Female	12.53	0.47	
Time to reach nadir of blood pressure (s)	Male	12.02	0.25	0.277
	Female	11.65	0.24	
Time to reach nadir of blood velocity (s)	Male	8.18	0.26	0.907
	Female	8.22	0.24	
Δ End-tidal CO_2 (mmHg)	Male	1.75	0.19	0.37
	Female	2.00	0.21	
Autoregulation Index	Male	4.08	0.20	0.000
	Female	5.08	0.19	

In contrast with previous studies, females showed higher ARI values in the MCA in females. Previous studies have shown higher ARI values in the basilar artery in females, but lower ARIs in the MCA [9], or no difference in ARIs in the MCA [8]. Wang et al [10] showed higher transfer function coherence in the low frequency band in females while supine, but lower coherence while upright, whereas the female subjects in this study showed lower coherence while sitting. The reasons for the differences between this study and previous work in this area are unclear. One main difference between this study and previous work is that this study has examined CA in an older population. Also, this study involved much larger numbers of subjects than previous studies. The clinical significance of the findings of this study remains unclear, and it is still uncertain why females are more likely to demonstrate orthostatic intolerance or develop post-spaceflight orthostatic issues.

V CONCLUSION

In summary, female subjects have higher MCA flow velocities, CO_2 cerebrovascular reactivity and vasomotor range than males. Females also showed better CA than male subjects in response to sit-to-stand testing and showed lower pressure to cerebral flow transfer function gain than male subjects. The reasons for these differences remain unclear, but are possibly due to more reactive vessels in female subjects. Other potential factors include vessel diameter, sex hormone levels, cerebral metabolic rate, but none of these theories have been confirmed. Future work is needed to examine gender differences in various cerebral arterial beds to better understand these underlying autoregulatory differences.

VI REFERENCES

[1] O. B. Paulson, S. Strandgaard, and L. Edvinsson, "Cerebral autoregulation," *Cerebrovasc Brain Metab Rev,* vol. 2, pp. 161-92, 1990.

[2] R. Schondorf, J. Benoit, and R. Stein, "Cerebral autoregulation in orthostatic intolerance," *Ann N Y Acad Sci,* vol. 940, pp. 514-26., 2001.

[3] J. M. Fritsch-Yelle, P. A. Whitson, R. L. Bondar, and T. E. Brown, "Subnormal norepinephrine release relates to presyncope in astronauts after spaceflight," *J Appl Physiol,* vol. 81, pp. 2134-41, 1996.

[4] R. G. Ackerstaff, R. W. Keunen, W. van Pelt, A. D. Montauban van Swijndregt, and T. Stijnen, "Influence of biological factors on changes in mean cerebral blood flow velocity in normal ageing: a transcranial Doppler study," *Neurol Res,* vol. 12, pp. 187-91, Sep 1990.

[5] M. Marinoni, A. Ginanneschi, D. Inzitari, S. Mugnai, and L. Amaducci, "Sex-related differences in human cerebral hemodynamics," *Acta Neurol Scand,* vol. 97, pp. 324-7, May 1998.

[6] R. Karnik, A. Valentin, W. B. Winkler, N. Khaffaf, P. Donath, and J. Slany, "Sex-related differences in acetazolamide-induced cerebral vasomotor reactivity," *Stroke J1 - Publication Type Clinical Trial Clinical Trial, Phase Ii Journal Article,* vol. 27, pp. 56-58, // 1996.

[7] A. Kastrup, C. Thomas, C. Hartmann, and M. Schabet, "Sex dependency of cerebrovascular CO2 reactivity in normal subjects," *Stroke,* vol. 28, pp. 2353-2356, // 1997.

[8] N. Tontisirin, S. L. Muangman, P. Suz, C. Pihoker, D. Fisk, A. Moore, A. M. Lam, and M. S. Vavilala, "Early childhood gender differences in anterior and posterior cerebral blood flow velocity and autoregulation," *Pediatrics,* vol. 119, pp. e610-5, Mar 2007.

[9] M. S. Vavilala, M. S. Kincaid, S. L. Muangman, P. Suz, I. Rozet, and A. M. Lam, "Gender differences in cerebral blood flow velocity and autoregulation between the anterior and posterior circulations in healthy children," *Pediatr Res,* vol. 58, pp. 574-8, Sep 2005.

[10] X. Wang, S. Krishnamurthy, J. Evans, D. Bhakta, L. Justice, E. Bruce, and A. Patwardhan, "Transfer function analysis of gender-related differences in cerebral autoregulation," *Biomed Sci Instrum,* vol. 41, pp. 48-53, 2005.

[11] S. G. Leveille, D. P. Kiel, R. N. Jones, A. Roman, M. T. Hannan, F. A. Sorond, H. G. Kang, E. J. Samelson, M. Gagnon, M. Freeman, and L. A. Lipsitz, "The MOBILIZE Boston Study: design and methods of a prospective cohort study of novel risk factors for falls in an older population," *BMC Geriatr,* vol. 8, p. 16, 2008.

[12] B. M. Deegan, M. O'Connor, D. Lyons, and O. L. G, "Development and evaluation of new blood pressure and heart rate signal analysis techniques to assess orthostatic hypotension and its subtypes," *Physiol Meas,* vol. 28, pp. N87-102, Nov 2007.

[13] F. P. Tiecks, A. M. Lam, R. Aaslid, and D. W. Newell, "Comparison of static and dynamic cerebral autoregulation measurements," *Stroke,* vol. 26, pp. 1014-9, // 1995.

[14] R. Zhang, J. H. Zuckerman, C. A. Giller, and B. D. Levine, "Transfer function analysis of dynamic cerebral autoregulation in humans," *Am J Physiol,* vol. 274, pp. H233-41, 1998.

[15] A. Kastrup, V. Happe, C. Hartmann, and M. Schabet, "Gender-related effects of indomethacin on cerebrovascular CO2 reactivity," *J Neurol Sci,* vol. 162, pp. 127-32, Jan 15 1999.

[16] K. L. Chambliss and P. W. Shaul, "Estrogen modulation of endothelial nitric oxide synthase," *Endocr Rev,* vol. 23, pp. 665-86, Oct 2002.

[17] H. R. Muller, C. Brunholzl, E. W. Radu, and M. Buser, "Sex and side differences of cerebral arterial caliber," *Neuroradiology,* vol. 33, pp. 212-6, 1991.

[18] E. Tarasow, A. Abdulwahed Saleh Ali, A. Lewszuk, and J. Walecki, "Measurements of the middle cerebral artery in digital subtraction angiography and MR angiography," *Med Sci Monit,* vol. 13 Suppl 1, pp. 65-72, May 2007.