Hemodynamics and brain blood flow during posture change in younger women and postmenopausal women compared with age-matched men

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Edgell H, Robertson AD, Hughson RL. Hemodynamics and brain blood flow during posture change in younger women and postmenopausal women compared with age-matched men. J Appl Physiol 112: 1482–1493, 2012. First published February 23, 2012; doi:10.1152/japplphysiol.01204.2011.—Increased incidence of orthostatic hypotension and presyncopal symptoms in young women could be related to hormonal factors that might be isolated by comparing cardiovascular and cerebrovascular responses to postural change in young and older men and women. Seven young women, 11 young men, 10 older women (>1 yr postmenopausal, no hormone therapy), and 9 older men participated in a supine-to-sit-to-stand test while measuring systemic hemodynamics, end-tidal PCO2, and blood flow velocity of the middle cerebral artery (MCA). Women had a greater reduction in stroke volume index compared with age-matched men (change from supine to standing: young women: −22.9 ± 1.6 ml/m2; young men: −14.4 ± 2.4 ml/m2; older women: −17.4 ± 3.3 ml/m2; older men: −13.8 ± 2.2 ml/m2). This was accompanied by offsetting changes in heart rate, particularly in young women, resulting in no age or sex differences in cardiac output index. Mean arterial pressure (MAP) was higher in older subjects and increased with movement to upright postures. Younger men and women had higher forearm vascular resistance that increased progressively in the upright posture compared with older men and women. There was no difference between sexes or ages in total peripheral resistance index. Women had higher MCA velocity, but both sexes had reduced MCA velocity while upright, which was a function of reduced blood pressure at the MCA and a significant reduction in end-tidal PCO2. The reductions in stroke volume index suggested impaired venous return in women, but augmented responses of heart rate and forearm vascular resistance protected MAP in younger women. Overall, these results showed significant sex and age-related differences, but compensatory mechanisms preserved MAP and MCA velocity in young women.

ORTHOSTATIC HYPOTENSION (a condition that sometimes leads to fainting) is an important and sometimes dangerous condition that particularly affects young women during daily life, as reflected by admission to emergency rooms (51). It has been speculated that female sex hormones might modulate reflex neural or vascular properties, resulting in the greater incidence of orthostatic hypotension in young women (5, 14, 15, 52, 69). An additional indication of impaired orthostatic responses in women includes the observation that women have a greater propensity towards postural orthostatic tachycardia syndrome (18, 60).

Contrary to observations for young women, clinical evidence supports the concept that orthostatic hypotension occurs less frequently in women ages 40–60 yr (many of whom could be postmenopausal) (51). Investigations of men and women from 23–77 yr of age indicated that the heart rate response to tilt was reduced with aging, but vascular responses appeared to be enhanced to protect against low blood pressure (17, 32). A study that focused on postmenopausal women also reported a reduction in arterial baroreflex responsiveness and heart rate control characterized by greater sympathetic and reduced parasympathetic modulation (33). Another investigation revealed that, during lower body negative pressure (LBNP), postmenopausal women had higher systolic (SBP) and mean arterial blood pressures (MAP) with an attenuated increase in heart rate compared with premenopausal women (21). Furthermore, this study found that, after estrogen replacement therapy, postmenopausal women had lower SBP, diastolic blood pressure (DBP), and MAP at rest and during LBNP (21).

Several hypotheses in the literature have attempted to explain the greater incidence of orthostatic hypotension in women compared with men, including greater splanchic blood flow (70), lower sympathetic output (23), or reduced cardiac filling, leading to an inability to maintain sufficient cardiac output (14). It is also possible that regulation of brain blood flow could affect orthostatic tolerance, as women have a greater cerebrovascular reactivity to changes in carbon dioxide (29) (i.e., cerebrovascular vasodilatory response to higher arterial CO2), yet better autoregulatory responses than men (8) (i.e., the brain’s inherent ability to control flow over a wide range of perfusion pressures). Higher cerebrovascular reactivity to carbon dioxide and better autoregulatory responses in elderly women were also observed compared with that in elderly men (>70 yr old) (9); however, cerebrovascular reactivity was reported to be reduced in postmenopausal compared with younger women (39).

The present study extensively investigated the cerebrovascular and cardiovascular responses of younger and older women and men in different postures (supine, sitting, and standing). While the effect of age or sex on cerebral blood flow has been investigated previously, this study was designed to concurrently observe both systemic and cerebral hemodynamic changes in younger and older men and women during orthostatic stress, while considering the effects of both cerebral perfusion pressure and CO2 on brain blood flow. We investigated the effects of both cerebral perfusion pressure and end-tidal PCO2 (PETCO2), since the latter might overestimate changes in arterial PCO2, and the reduction of PETCO2 with posture change might not fully explain lower brain blood flow in upright posture (25, 53). It was designed to investigate both the sexually dimorphic responses to orthostatic stress and the effects of female sex hormones by comparing pre- and postmenopausal women to each other and to age-matched men. This complicated design was then simplified into three hypo-
es. Due to similar decreases in $P_{ET\text{CO}_2}$ during orthostatic stress between sexes (as observed by Ref. 68) and greater reactivity to CO$_2$ in women, our primary hypothesis is that there will be a greater reduction in cerebral blood flow in upright postures in young women compared with young men. Furthermore, CO$_2$ reactivity decreases with age in women to a level equal with that of age-matched men (28). Therefore, we also hypothesize that cerebral blood flow will not be different between postmenopausal women and age-matched men in different postures. Despite previous observations that there is reduced cardiac filling and stroke volume index in young women during orthostatic stress, there was no difference in the MAP response to orthostatic stress between sexes (16). Therefore, our third hypothesis is that any differences in cerebral blood flow between sexes are not simply due to changes in MAP.

**MATERIALS AND METHODS**

**Participant description.** Thirty-seven men and women participated: 7 young women (25.9 ± 1.1 yr; body mass index (BMI): 25.2 ± 2.1 kg/m$^2$), 11 young men (24.5 ± 1.2 yr; BMI: 25.3 ± 0.9 kg/m$^2$), 10 older women (57.2 ± 1.7 yr, range: 50–67 yr; BMI: 23.9 ± 1.5 kg/m$^2$), and 9 older men (57.0 ± 1.4 yr, range: 50–62 yr; BMI: 26.5 ± 1.1 kg/m$^2$). The group of young women all participated from days 8–11 of the menstrual cycle and were all taking cyclic-OC (Tricyclen-lo or Tricyclen, Janssen-Ortho, Toronto, ON, Canada; 0.180 mg norgestimate and 0.025–0.035 mg ethinyl estradiol). The older women were each postmenopausal (i.e., cessation of menstruation) for at least 1 yr (6.2 ± 1.3 yr; range: 2–15 yr) and were not taking hormone replacement therapy (HRT). Testing younger postmenopausal women allowed for the examination of the loss of cycling endogenous female sex hormones after menopause, while minimizing the effects of aging. According to a brief health questionnaire, all participants were free of cardiovascular disease. Participants were asked to refrain from exhaustive exercise and alcohol for 24 h before testing and from caffeinated beverages for 12 h before testing. All testing was performed in the morning. All participants gave written, informed consent, in accordance with the Office of Research Ethics at the University of Waterloo, which approved this study.

**Imaging.** Cross-sectional area of the aortic ring and brachial artery were obtained in the supine position with ultrasound imaging (Micro-maxx, Sonosite, Bothell, WA) using a HFL38 transducer (6–13 MHz; brachial artery) or a P17 transducer (1–5 MHz; aorta). The aortic ring diameter (36) and brachial artery diameter do not change during orthostatic stress (56). Thus the supine value was used throughout the test.

**Systemic beat-by-beat measurements.** Continuous estimates of arterial blood pressure were measured using finger-cuff plethysmography (Finometer Pro; Finapres Medical Systems, Arnhem, The Netherlands), and heart rate was measured from the R-R interval of the electrocardiogram (Colin Pilot, Colin Medical Instruments, San Antonio, TX). SBP and DBP were normalized to a standard arm cuff measurement. Mean blood flow velocity of the outer envelope to capture peak central velocity from just above the aortic root (Eriksen and Walloe) and the mean of the intensity weighted mean from the parabolic profile in the brachial artery (i.e., the velocity time integral over an R-R interval) were recorded using 2- and 4-MHz probes, respectively (Neurovision Transcranial Doppler System Model 500M, Multigon Industries, Yonkers, NY). At least 1 min of beat-by-beat data were averaged for each steady-state posture. All signals were output at 1,000 Hz from a PowerLab (ADInstruments, Colorado Springs, CO) and recorded onto a computer running Chart 5.5.1 for future analysis.

Using the baseline velocity of the aorta, stroke volume was determined with the calculation $SV (ml) = \text{velocity} \times (\pi \times \text{radius}^2) \times R-R$ interval. Cardiac output was determined by multiplying heart rate by stroke volume. Cardiac output quantification by Doppler ultrasound has been shown to have good correlation with thermodilution (10, 38) and magnetic resonance imaging (65). Jansen et al. (26) suggest that the Modelflow estimate of cardiac output should be calibrated to another measurement of cardiac output. Therefore, our measurement of cardiac output using Doppler ultrasound (13) was used to normalize the Modelflow estimated cardiac output from the Finometer. Total peripheral resistance was calculated as MAP divided by cardiac output. Brachial arterial flow was determined from the cross-sectional area of the brachial artery and the blood velocity [brachial flow (ml/min) = velocity × (π × radius$^2$) × 60]. Brachial vascular resistance was used as an index of limb vascular resistance and calculated as MAP divided by flow. Cardiac output and stroke volume were normalized to body surface area, and brachial vascular flow was normalized to arm volume. Blood pressure at the middle cerebral artery (BP$_{MCA}$) was calculated as BP$_{MCA}$ = MAP – (distance in cm from heart to MCA × 0.735 mmHg/cmH$_2$O).

**Transcranial Doppler.** Mean blood flow velocity from the middle cerebral artery (MCA) was recorded using a 2-MHz probe and a Neurovision Transcranial Doppler System (model 500M, Multigon Industries, Yonkers, NY), positioned at the temporal window and held in place by an adjustable headband (i.e., the velocity time integral over an R-R interval). At least 1 min of beat-by-beat data were averaged for each steady-state posture. The MCA was identified using previously described criteria (1). Technical difficulties in acquiring a valid ultrasound signal through the temporal window varied the sample size (valid sample sizes: $n = 7$ for young women, $n = 11$ for young men, $n = 8$ for older women, and $n = 9$ for older men).

**Cerebrovascular resistance index (CVRi).** This was calculated by dividing cerebral perfusion pressure by mean MCA velocity. The resistance index (RI) was calculated as systolic MCA velocity – diastolic MCA velocity/systolic MCA velocity. The pulsatility index (PI) was calculated as systolic MCA velocity – diastolic velocity/mean MCA velocity.

**$P_{ET\text{CO}_2}$** Breath-by-breath CO$_2$ was sampled through a nasal cannula and analyzed by infrared spectroscopy (Colin Pilot, Colin Medical Instruments, San Antonio, TX). End-tidal values were used as an indicator of arterial pressure of CO$_2$.

**Posture change protocol.** While supine, participants were instrumented with ultrasound probes (transcranial, brachial, and aorta), ECG electrodes, nasal cannula, and continuous finger arterial blood pressure. Following a 5-min period for baseline measurements, the participants moved into a seated position on the side of the bed with minimal physical assistance from a researcher to avoid displacement of the transcranial Doppler probe and finger cuff. A chair back was placed behind them for their comfort and relaxation during a 5-min period of data collection. The participants stood up and could hold a pole to support themselves while measurements were made for an additional 5-min period. They were asked to stand still during the protocol. The participants were asked to sit down immediately if systolic pressure fell to <70 mmHg or at any time the participant experienced nausea, dizziness, or light-headedness. One young woman could not maintain the standing posture for 5 min due to low systolic pressure.

Measurements of brachial vascular resistance, heart rate, stroke volume index, cardiac output index, MAP, total peripheral RI, and MCA velocity were averaged after 2 min of each posture. Measurements of $P_{ET\text{CO}_2}$ were averaged for the 3rd and 4th min of each posture. Postural transition data for MAP, cardiac output index, stroke volume index, heart rate, total peripheral RI, and MCA velocity were taken at the time of the nadir of MAP during active sitting or standing. We expected immediate and transient reductions in MAP, stroke volume index, total peripheral RI, and MCA velocity with increases in cardiac output index and heart rate, as observed by Wieling et al. (72) and Sorond et al. (58).
Design and statistical analysis. This study was designed to examine the effects of sex and age on the cardiovascular responses to different postures. Statistical analysis of both steady-state and transitional data was completed using a three-way ANOVA with one repeated measure (posture). Factors were sex, age, and posture (see Figs. 1–3 and 5). Statistical analysis of the relationships between MCA blood flow velocity and PETCO₂ and MCA blood flow velocity and BPₘₐₛₐ, were completed using two-way ANOVA. Factors were sex and age (see Fig. 4). Statistical analysis of the change in heart rate from supine to standing was completed using one-way ANOVA. The factor was sex. Statistical analysis of the difference in stroke volume index between older and younger women at the transition to standing was completed using one-way ANOVA. The factor was age. These last two comparisons are found at the end of RESULTS). Analysis was completed using SAS 9.1.3 analysis software (Cary, NC). Results are expressed as means ± SE. *P values < 0.05 are indicated as significant, and P values < 0.10 are noted. Significant main effects and significant interaction effects are identified on each graph.

RESULTS

Main effects of posture. Changing posture from supine to sitting to standing resulted in increased heart rate (P < 0.0001; Fig. 1A), decreased stroke volume index (P < 0.0001; Fig. 1B), and decreased cardiac output index (P < 0.0001; Fig. 1C). There were also decreases in MCA velocity (P < 0.0001; Fig. 2A) and increased MAP (P = 0.004; Fig. 2B). Systolic MCA velocity and diastolic MCA velocity decreased with changing postures. These changes are reflected in the changes of CVRᵢ, RI, and PI (P < 0.05; Table 1). Posture did not affect respiration rate (P = 0.209; data not shown), but PETCO₂ decreased with movement to upright postures (P < 0.0001; Fig. 2C). Total peripheral RI (P < 0.0001; Fig. 3A) and brachial vascular resistance (P < 0.0001; Fig. 3B) both increased with movement to upright posture. Comparing the supine to the standing position, the percent change in MCA velocity per change in PETCO₂ was calculated (young men: 3.46 ± 0.55%/Torr; young women: 3.41 ± 0.55%/Torr; older men: 2.25 ± 2.61%/Torr; older women: 3.43 ± 1.22%/Torr; sex effect P = 0.811; age effect P = 0.790; interaction effect P = 0.785; data calculated from Fig. 4). Comparing the supine to the standing position, the percent change in MCA velocity per change in BPₘₐₛₐ was calculated (young men: 0.82 ± 0.15%/mmHg; young women: 0.98 ± 0.19%/mmHg; older men: 1.22 ± 0.35%/mmHg; older women: 0.50 ± 0.27%/mmHg; sex effect P = 0.339; age effect P = 0.705; interaction effect P = 0.111; data calculated from Fig. 4). Cardiovascular responses during the transitions were sampled at the point of nadir in the arterial blood pressure response and are expressed as a change from the previous steady-state posture. There were no significant main effects of posture during the postural transitions (i.e., the transition to sitting vs. the transition to standing) in heart rate (P = 0.935; Fig. 5A), stroke volume index (P = 0.427; Fig. 5B), cardiac output index (P = 0.898; Fig. 5C), MCA velocity (P = 0.530; Fig. 6A), MAP (P = 0.116; Fig. 6B), or total peripheral RI (P = 0.374; Fig. 6C). The CVRᵢ decreased more during the

Fig. 1. Heart rate (A), stroke volume index (B), and cardiac output index (C) while supine, sitting, and standing in younger and older men (open bars) and women (shaded bars). Values are means ± SE. *Statistical significance with P < 0.05, except where noted (for more details on significance level, see text): Sex indicates a significant main effect of sex; Posture indicates a significant main effect of posture; (Posture × Age) indicates a significant interaction effect between posture and age (i.e., the younger groups had a greater increase of heart rate than the older groups); (Posture × Sex) indicates a significant interaction effect between posture and sex (i.e., women had a greater increase of heart rate and a greater decrease of stroke volume index than men); (Posture × Sex × Age) indicates a significant interaction effect between posture, sex, and age (i.e., young women had a greater increase of heart rate than all other groups).
Posture; (Posture significant main effect of age; Posture indicates a significant main effect of sex; Age indicates a significant main effect of sex; Age indicates a significant main effect of age; there was a smaller fall in PETCO2 in the older groups).

there was a smaller fall in PETCO2 in the older groups).

However, there was higher CVRi in older participants (Table 1). There were no significant sex differences in MAP (Fig. 1), or cardiac output index (P = 0.038; Fig. 2B), PETCO2 (P = 0.770; Fig. 2C), or respiration rate (P = 0.226; data not shown). There were no sex differences in total peripheral RI (P = 0.158; Fig. 3A), or brachial vascular resistance (P = 0.684; Fig. 3B). There were no significant sex differences in the slope of the relationship between MCA velocity and PETCO2 (P = 0.484; Fig. 4, left). There were no significant sex differences in the slope of the relationship between MCA velocity and BPMCA (P = 0.729; Fig. 4, right). There were no effects of sex on the change in heart rate (P = 0.999; Fig. 5A) seen at posture transition. Women had a greater reduction (young group) or a smaller increase (older group) in stroke volume index during posture transition (P = 0.006; Fig. 5B) and also exhibited a smaller increase in cardiac output index (P = 0.003; Fig. 5C). There were no effects of sex on the change in MCA velocity (P = 0.585; Fig. 6A) or MAP (P = 0.801; Fig. 6B). Women had a smaller reduction in total peripheral RI (P = 0.032; Fig. 6C). Women had a smaller increase of PI (P = 0.040) and tended to have a smaller increase of RI (P = 0.057) during postural transitions (Table 2).

Main effects of age. There was no main effect of age on heart rate (P = 0.121; Fig. 1A), stroke volume index (P = 0.204; Fig. 1B), or cardiac output index (P = 0.583; Fig. 1C). There was no effect of age on MCA velocity (P = 0.303; Fig. 2A); however, there was higher CVRi in older participants (P = 0.034; Table 1). MAP was higher in the older participants (P = 0.038; Fig. 2B), and the older participants tended to have lower PETCO2 (P = 0.062; Fig. 2C). There was no effect of age on respiration rate (P = 0.258; data not shown). There was no effect of age on total peripheral RI (P = 0.994; Fig. 3A), while brachial vascular resistance was reduced with age (P = 0.0003; Fig. 3B). There were no significant age differences in the slope of the relationship between MCA velocity and PETCO2 (P = 0.673; Fig. 4, left). There was a significant effect of age on the slope of the relationship between MCA velocity and BPMCA (P = 0.004; Fig. 4, right). Older participants had smaller increases in heart rate (P < 0.0001; Fig. 5A) with higher stroke volume index (P = 0.003; Fig. 5B) in response to posture transitions. There was no effect of age on cardiac output index during posture transitions (P = 0.545; Fig. 5C), yet older participants tended to have a smaller decrease in MCA velocity during posture transition (P = 0.056; Fig. 6A). There are no main effects of age on the MAP response (P = 0.861; Fig. 6B), nor the total peripheral RI response (P = 0.526; Fig. 6C) to posture transitions. During the postural transitions, diastolic MCA velocity decreases more in younger participants (P = 0.028) leading to larger increases of RI (P = 0.009) and PI (P = 0.004; Table 2).

Interaction effects. Women had a greater increase of heart rate with posture change (P = 0.0006; posture × sex; Fig. 1A). The increase in heart rate seen with posture change was attenuated with age (posture × age; P < 0.0001; Fig. 1A),...
particularly in women (posture × sex × age; $P = 0.050$; Fig. 1A). The decrease in stroke volume index seen with changing postures was greater in women (posture × sex; $P = 0.031$; Fig. 1B). In response to posture change, the older population increased MAP ($P = 0.028$; posture × age; Fig. 2A). There was a smaller fall in $\text{PETCO}_2$, due to posture change in the older group (posture × age; $P = 0.030$; Fig. 2C). Age attenuated the increase of brachial vascular resistance seen at standing (posture × age; $P = <0.0001$; Fig. 3C). Compared with the transition to sitting, the transition to standing resulted in a greater heart rate response in the younger group and a smaller heart rate response in the older group (posture × age; $P < 0.0001$; Fig. 5A). In the younger group, the same fall in MAP was seen in both the sit and stand transitions, but there was a smaller fall in pressure during the stand transition in the older group (posture × age; $P = 0.028$; Fig. 6B). There is a (posture × age) effect for systolic MCA velocity ($P = 0.045$, Table 1; $P = 0.038$, Table 2).

The change in heart rate from supine to standing was greater in young women compared with young men (young women: $-22.9 \pm 1.6 \text{ ml/m}^2$; young men: $-14.4 \pm 2.4 \text{ ml/m}^2$; $P = 0.009$; data not shown), with no significant difference when comparing the older groups (change from supine to standing: older women: $-17.4 \pm 3.3 \text{ ml/m}^2$; older men: $-13.8 \pm 2.2 \text{ ml/m}^2$; $P = 0.385$; data not shown). Young women had a greater decrease of stroke volume index at the transition to standing compared with older women (young women: $-7.0 \pm 4.2 \text{ ml/m}^2$; older women: $+2.4 \pm 1.8 \text{ ml/m}^2$; posture × age effect; $P = 0.017$; data not shown).

**DISCUSSION**

The present study investigated the cardio- and cerebrovascular responses to the everyday orthostatic challenge of moving from supine to seated and standing postures. We hypothesized that young women would have lower cerebral blood flow velocity with orthostatic stress, yet we did not find evidence of this. We also hypothesized that older women would have similar cerebral blood flow velocity compared with older men, which we did observe. Our results confirm previous findings that young women do respond to an orthostatic challenge with indications of greater cardiovascular stress compared with not only young men, but also with older, postmenopausal women. The significantly greater decline of stroke volume index in women on moving from supine to sitting to standing postures was met by significantly greater increases in heart rate in women, with an exaggerated response in young women. This led to an equal decrease in cardiac output index in all groups after movement to upright posture. During the transition to the seated or standing posture, the augmented heart rate response in women was not observed. This led to lower stroke volume index and cardiac output index in women during the postural transition. The mean MCA velocity decreased with movement to upright posture, but pre- and postmenopausal women had significantly higher mean MCA velocity than age-matched men. Decreases in calculated cerebral perfusion pressure and $\text{PETCO}_2$ were observed with movement to sitting and standing postures. This supports our last hypothesis that changes in MCA velocity are not simply due to changes in arterial pressure alone. $\text{PETCO}_2$ values were lower in the older subjects, but the decrease with posture change was not as great as in the younger subjects.

**Methodological considerations.** Young women were recruited on *days 8–11* of the menstrual cycle and were taking cyclic types of oral contraceptives. Therefore, all of the young women in this study would have moderate to high levels of estrogen analog, with low levels of progesterone analog. Carter et al. (4) recently reported that there were no cardiovascular or sympathetic repercussions of taking oral contraceptives in young women; thus we anticipated no difference in the cardiovascular responses of women taking oral contraceptives compared with normally cycling women.

Considering that the postmenopausal women had not cycled for at least 1 yr, they would have had low levels of estrogen with low levels of progesterone. These older women were not on any HRT. By comparing the younger women who had moderate to high estrogen and low progesterone to older noncycling women in this study, we effectively investigated the effects of moderate levels of circulating estrogen and age. By comparing the younger men to older men in this study, we effectively investigated the effects of age alone.

**Systemic hemodynamics.** In all participants, the adaptations that occurred in the steady-state seated and standing postures...
included increasing heart rate, decreasing stroke volume index, decreasing cardiac output index, and increasing total peripheral RI. This has been observed previously with standing in younger and older populations (6). These cardiovascular responses occurred to increase MAP and maintain cerebral perfusion pressure during the orthostatic stress. Women had a greater increase of heart rate during steady-state orthostatic stress. There have been many animal studies that indicate that estrogen supplementation enhances baroreceptor function in ovariectomized female animals (12, 22, 41); however, it has been shown that women have less sensitive baroreceptors than men (3, 63). Therefore, the greater increase in heart rate is not likely due to differences in cardiovagal baroreflex gain, which would result in a smaller increase of heart rate. Therefore, we propose that the greater increase of heart rate with orthostatic stress was likely due to a lower stroke volume index. This was particularly evident in the younger women. Our results correspond with those of Convertino (5), who previously observed a greater fall in cardiac output with LBNP (i.e., a simulated orthostatic stress) in women, and those of Fu et al. (14), who previously observed a greater increase in heart rate with a greater decrease in stroke volume index with LBNP in women.

During the postural transitions, we observed a smaller increase of cardiac output index with lower stroke volume in women of both age groups compared with men. This is despite a reduction in MAP similar to men. This was likely the result of the absence of a compensatory increase of heart rate (in contrast to the steady state) and attenuated venous return. This could be a key observation for why there are higher rates of orthostatic hypotension in young women and could have been a consequence of the effects of estrogen on the circulation. Estrogen is well known to affect the endothelium to cause greater vasodilation in vascular beds (reviewed in Ref. 40). For example, it has previously been shown that a group of postmenopausal women taking HRT had higher resting femoral blood flow (and shear stress) than postmenopausal women who were not taking HRT (42). The postmenopausal women studied in this investigation were young (57.2 ± 1.7 yr old) and were only required to be menopausal for 1 yr for entry into the study (the mean duration postmenopause was 6.2 ± 1.3 yr). Therefore, some postmenopausal participants could have higher estrogen than others, considering the results of Rannevik et al. (50), who showed gradually declining estrogen levels for 3 years after menopause. However, estrogen levels would still be significantly lower than those seen in the younger women due to the marked decrease Rannevik et al. observed after 6 mo of menopause. If present, residual follicular-derived estrogen could lead to greater peripheral blood pooling and to a lower venous return.

Tanaka et al. (62) and Sprangers et al. (59) also observed a decrease of total peripheral RI and MAP during postural transitions due to vasodilation and movement of blood to the lower body. The decrease of total peripheral RI was greater in men and could be due to greater leg muscle mass (55) and/or a greater number of dilated vessels. Since the drop in total peripheral resistance was attenuated in women during active postural change, blood pooling in other vascular beds, such as the splanchnia, could be leading to the reduced venous return observed during orthostatic stress. Other researchers have indeed shown that women have lower splanchnic vasoconstrictor reserve (i.e., greater splanchnic blood pooling) during an orthostatic stress compared with men (27, 70). While there was no difference between sexes or ages in total peripheral RI response to different postures, the brachial vascular resistance response was attenuated in older participants. This, along with the greater increase of heart rate in the older groups during postural transition, could be a result of a less sensitive arterial baroreflex with age (7, 49, 61), or perhaps increased vascular resistance in other areas in the older participants, including the splanchnic vascular bed. Wicklein et al. (71) found lower portal vein flow in elderly participants compared with younger participants. There is very little known about splanchnic blood flow with age, sex, and orthostatic stress. We suggest that, if postmenopausal women have lower splanchnic blood pooling compared with young women during an orthostatic stress, this would contribute to the preserved stroke volume. Our suggestion is supported by previous observations that leg vein diameter, compliance, and capacitance do not change with age in women during an orthostatic stress (31, 34). Older men have
lower leg venous compliance and capacitance during LBNP (44), which is consistent with our observations that they experience a higher stroke volume and cardiac output, likely due to better venous return.

In comparison to the postmenopausal women during postural transition, young women had a similar decrease in total peripheral RI, yet stroke volume index was lower. These results imply that venous return is better maintained during a postural change after menopause. We suggest that this could be due to reduced splanchnic pooling with age (71). Compared with the age-matched men, postmenopausal women displayed a smaller fall in total peripheral RI during the transitions, with a smaller increase in stroke volume index and cardiac output index. All of these results indicate that venous return is higher after menopause, but it still does not equate to that seen in age-matched men. No venous return-related sex differences during orthostatic stress have yet been observed in older populations, outlining the importance of our study.

Brain blood flow velocity. We observed higher mean MCA velocity in women (due to both higher systolic and higher
**Fig. 5.** Change in heart rate (A), stroke volume (B), and cardiac output (C) at the nadir of mean arterial pressure during the transition between positions in younger and older men (open bars) and women (shaded bars). Values are means ± SE. *Statistical significance with \( P < 0.05 \) (for more details on significance level, see text): Age indicates a significant main effect of age; Sex indicates a significant main effect of sex; (Posture × Age) indicates a significant interaction effect between posture and age (i.e., there was a smaller increase of heart rate during standing compared with sitting in the older groups, whereas there was a larger increase of heart rate during standing compared with sitting in the younger groups).

**Fig. 6.** Change in MCA velocity (A), mean arterial pressure (B), and total peripheral resistance (C) at the nadir of mean arterial pressure at the time of transition between positions in younger and older men (open bars) and women (shaded bars). Values are means ± SE. *Statistical significance with \( P < 0.05 \) (for more details on significance level, see text): Sex indicates a significant main effect of sex; (Posture × Age) indicates a significant interaction effect between posture and age (i.e., there was a smaller decrease of mean arterial pressure during standing compared with sitting in the older groups, whereas there was a greater decrease of mean arterial pressure during standing compared with sitting in the younger groups).
diastolic MCA velocity) compared with men, which has been well documented (9, 43, 64, 67). It has also previously been shown that premenopausal women have greater resting brain blood flow compared with age-matched men (despite a smaller brain mass) (19, 20). This could be a result of the vasodilatory effects of estrogen on the cerebrovascular endothelium (47). Previously, MCA diameter was shown to be constant during simulated orthostatic stress (54); thus any change in blood flow velocity reflects a parallel change in flow. Due to the higher incidence of orthostatic hypotension and syncope known to exist in women, we expected that women would experience a greater fall in brain blood flow during orthostatic stress. Contrary to this hypothesis, no sexually dimorphic differences in the response to sitting or standing were observed.

In this study, there were no differences in baseline MCA velocity due to age. There was, however, higher CVRi with age, which likely reflects the higher MAP, considering that there were no age effects on either systolic or diastolic MCA velocity. As expected due to intact cerebral autoregulation with age (66), there were no changes in the response of mean MCA velocity to sitting and standing with age; however, with more erect posture, systolic MCA velocity decreased more in the younger groups. Many researchers have observed lower MCA velocity in participants over 70 yr old (35, 48, 57), and Sorond et al. (57) observed a greater decrease in MCA velocity in participants over 70 yr old during standing. Contrary to the results of Sorond et al. (57), we observed an attenuated loss of mean and diastolic MCA velocity during the transitions to sitting and standing with age. This difference could be due to the younger age of our “older” participants. Muller et al. (43) found that, in both men and women, there were no changes in the diameter of the MCA with age. Therefore, if the artery diameter does not change with age, it can be assumed that the changes in the MCA velocity truly reflect changes in brain blood flow with aging. The attenuated loss of brain blood flow during transition in the older groups could be due to the observed greater cardiac output index and stroke volume index preserving brain blood flow.

Carbon dioxide has long been known to cause vasodilation of the cerebral arteries (25, 28, 46, 53), while cerebral autoregulation can control brain blood flow over a range of changing perfusion pressure (9, 24, 35, 57). In the present study, the transitions from supine to sitting to standing intentionally manipulated BP<sub>MCA</sub>, but simultaneous changes in PET<sub>CO2</sub> with postural change complicated the interpretation of the MCA velocity response. As expected with orthostatic stress, we observed decreasing mean, systolic, and diastolic MCA velocity. The decrease in systolic MCA velocity corresponded to the decrease in stroke volume, and the decrease in diastolic MCA velocity correlates with the increase of total peripheral resistance that was observed. (Lower diastolic velocity implies downstream vasoconstriction, which would increase cerebral resistance.) However, we observed a decrease in cerebral resistance indexes (RI and PI) with standing (in the younger groups), implying vasodilation and/or a decrease in systolic MCA velocity, which we observed. Higher arterial CO<sub>2</sub> (as estimated by PET<sub>CO2</sub>) could cause vasodilation of downstream cerebral arterioles, yet we observed decreasing PET<sub>CO2</sub> with posture change. Therefore, cerebral autoregulation likely plays an important role.

The slope relating MCA velocity to BP<sub>MCA</sub> was significantly smaller in older compared with younger subjects (Fig. 4, right), with no difference between men and women. This would imply that cerebral autoregulation may be improved with age and would indicate that cerebral blood flow is preserved over a wider range of perfusion pressure. However, previous research has found no difference in the autoregulatory index as a function of age (46, 57). These past studies were done in participants ~10 yr older, which could account for the difference. Our results describing a smaller change in MCA velocity relative to the change in BP<sub>MCA</sub> in the older subjects should be viewed with caution, since the PET<sub>CO2</sub> was not constant over the body positions. A siphon effect of the jugular and cerebral veins has been proposed, which would prevent cerebral vein collapse and, therefore, increase or maintain cerebral flow (45). However, evidence has shown that cerebrovascular resistance indexes change proportionally with changes in cerebral perfusion pressure (2, 24).

We found that PET<sub>CO2</sub> decreased with age, and there was a smaller decrease of PET<sub>CO2</sub> with standing (which may have been due to the lower baseline). In this study, we did not find any difference in respiratory rate with age, but we do not have data for CO<sub>2</sub> output to allow us to assess whether the lower PET<sub>CO2</sub> in the older subjects was simply a reflection of relative

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### Table 2. Changes in cerebral vascular resistance indexes during the mean arterial pressure nadir in the transition to different postures

<table>
<thead>
<tr>
<th></th>
<th>CVRi†</th>
<th>MCA Systolic</th>
<th>MCA Diastolic‡</th>
<th>Resistance Index‡</th>
<th>Pulsatility Index*‡</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Young women</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transition to sitting</td>
<td>-0.37 ± 0.07</td>
<td>-4.6 ± 7.0</td>
<td>-15.6 ± 5.2</td>
<td>0.11 ± 0.04</td>
<td>0.40 ± 0.13</td>
</tr>
<tr>
<td>Transition to standing</td>
<td>-0.17 ± 0.03</td>
<td>-4.1 ± 4.1§</td>
<td>-16.7 ± 4.0</td>
<td>0.15 ± 0.04</td>
<td>0.50 ± 0.14</td>
</tr>
<tr>
<td><strong>Young men</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transition to sitting</td>
<td>-0.51 ± 0.08</td>
<td>-6.4 ± 5.7</td>
<td>-14.2 ± 4.1</td>
<td>0.12 ± 0.03</td>
<td>0.47 ± 0.15</td>
</tr>
<tr>
<td>Transition to standing</td>
<td>-0.23 ± 0.06</td>
<td>9.7 ± 3.5§</td>
<td>-15.2 ± 2.5</td>
<td>0.20 ± 0.03</td>
<td>0.72 ± 0.10</td>
</tr>
<tr>
<td><strong>Older women</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Transition to sitting</td>
<td>0.38 ± 0.08</td>
<td>2.1 ± 1.8</td>
<td>-6.2 ± 3.7</td>
<td>0.06 ± 0.04</td>
<td>0.19 ± 0.14</td>
</tr>
<tr>
<td>Transition to standing</td>
<td>0.17 ± 0.11</td>
<td>-7.1 ± 4.6</td>
<td>-6.1 ± 2.9</td>
<td>0.03 ± 0.02</td>
<td>0.09 ± 0.04</td>
</tr>
<tr>
<td><strong>Older men</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transition to sitting</td>
<td>-0.59 ± 0.19</td>
<td>-4.9 ± 5.9</td>
<td>-10.7 ± 5.1</td>
<td>0.10 ± 0.03</td>
<td>0.30 ± 0.10</td>
</tr>
<tr>
<td>Transition to standing</td>
<td>-0.21 ± 0.07</td>
<td>-2.2 ± 3.4</td>
<td>-9.4 ± 4.0</td>
<td>0.10 ± 0.03</td>
<td>0.37 ± 0.12</td>
</tr>
</tbody>
</table>

Values are means ± SE. †There was a main age effect for diastolic MCA velocity, resistance index, and pulsatility index (P < 0.03). ‡There was a main sex effect for pulsatility index (P = 0.040). §There was a main posture effect for CVRi (P = 0.0002). ‡There is a posture × age effect for systolic MCA velocity (P = 0.038).
hyperventilation, or possibly an alteration in acid-base balance (11). Lower PETCO2 and MCA velocity (mean, systolic, and diastolic) were observed with sitting and standing, consistent with previous observations (25, 53). This reduction of PETCO2 could be a consequence of reduced venous return with standing, especially in light of maintained alveolar ventilation (25). Previous investigations of the sit-to-stand component of the maneuver in young and older subjects did not include changes in PETCO2 in the model (57); however, spontaneous fluctuations in PETCO2 do impact the MCA velocity (46). During the spontaneous fluctuations in PETCO2, in the present study, there were no significant differences in the slopes for the relationship between MCA velocity and PETCO2, as a function of sex or age, nor were there any group differences in the percent change of MCA velocity per percent change in PETCO2 from supine to standing. Under conditions in which body posture was maintained, a greater sensitivity to CO2 has been observed in women than men (9, 29), yet, after the age of 50 yr, cerebrovascular reactivity to CO2 is not different between men and women (28). This is not evident from our results, which measured spontaneous changes in PETCO2. Further investigation is required to determine the interaction between posture, CO2, and MCA velocity.

Perspectives and significance. The present study showed that young women had a higher heart rate during steady-state standing, and that all women had a lower stroke volume index during standing (transitional and steady state) compared with age-matched men. Importantly, we have noted that, where young women increase heart rate higher than all other groups during standing, this heart rate response is attenuated during the postural transition when women had lower stroke volume and cardiac output. After menopause, women had lower heart rates during standing compared with younger women, but still higher than age-matched men. Despite the reduction of stroke volume in women with orthostatic stress, the MCA velocity response suggested that they were not at a greater risk for cerebral hypoperfusion. This was not anticipated, considering the higher incidence of orthostatic hypotension known to exist in women. Our data suggest that both PETCO2 and BPmCA play a role in controlling brain blood flow changes with posture, and that the role of BPmCA is lessened with age. It would, therefore, be prudent to investigate CO2 reactivity in younger and older men and women to manipulated concentrations of inhaled CO2 rather than spontaneous changes to determine whether there are indeed sexually dimorphic and age-related differences affecting brain blood flow. These future studies might help to explain the greater incidence of orthostatic hypotension in women, if there is indeed an observable sexually dimorphic difference. Furthermore, if sex differences in the relative contributions of BPmCA or PETCO2 to brain blood flow exist, this might establish the conditions for a greater incidence of stroke in men (30, 37, 73).

This study investigated women aged 50+ yr who were not taking any hormonal replacement and compared their responses to those of younger women to determine the effects of age and female sex hormones on the cardiovascular system. This study would benefit from the investigation of a group of postmenopausal women taking HRT, since age would not be a confounding variable. This study would also benefit from a description of splanchnic blood flow during standing. If splanchnic blood flow is indeed greater in the premenopausal women during an orthostatic stress compared with men and postmenopausal women, this could help to explain the reduced venous return.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

H.E., A.D.R., and R.L.H. conception and design of research; H.E. and A.D.R. performed experiments; H.E. analyzed data; H.E. and R.L.H. interpreted results of experiments; H.E. prepared figures; H.E. drafted manuscript; H.E., A.D.R., and R.L.H. edited and revised manuscript; H.E. and R.L.H. approved final version of manuscript.

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