Sex differences in limb vasoconstriction responses to increases in transmural pressures

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Lott ME, Hogeman C, Herr M, Bhagat M, Sinoway LI. Sex differences in limb vasoconstriction responses to increases in transmural pressures. Am J Physiol Heart Circ Physiol 296: H186–H194, 2009. First published November 21, 2008; doi:10.1152/ajpheart.00248.2008.—Women compared with men are more likely to have orthostatic intolerance. The purpose of this study was to examine whether sex affects limb vasconstrictor response to increases in transmural pressure. Brachial and femoral mean blood velocity (MBV) and diameter (Doppler Ultrasound) were measured in 10 women and 10 men as transmural pressure was altered by applying local suction (−25, −50, −75, and −100 mmHg) via pressurized-limb tanks for 1 min to a single arm and leg. With the abrupt application of forearm suction (−75 and −100 mmHg), women compared with men had a greater initial rise in MBV (peak), followed by a quicker dynamic rate of velocity reduction. In the leg, women had a tendency for higher peak MBV but had similar dynamic velocity reductions compared with men. After 60 s of suction, women compared with men had attenuated reductions in brachial flow and conductance (−8.05 ± 1.71 vs. −16.25 ± 1.71 ml/min; −0.12 ± 0.03 vs. −0.20 ± 0.03 ml min−1 mmHg−1; main effect, P < 0.05), as well as attenuated femoral flow and conductance to sustained leg negative pressure at −100 mmHg (P < 0.05). When the data were expressed as percent change, women compared with men continued to have attenuated brachial flow responses (−24 ± 2 vs. −36 ± 2%; main effect, P < 0.05), with a trend toward attenuation at the highest leg pressure (−25 ± 11 vs. −46 ± 4%; P = 0.08). These sex differences remained after normalizing the flow responses by limb volume (percent change). Our findings suggest that young women compared with men have attenuated brachial and femoral vasoconstrictor responses to increases in transmural pressure, which may have implications for the greater incidence of orthostatic intolerance in women.

SYNCOPE, ESPECIALLY DURING postural stress, is more common in women than men (6, 22, 52). Most studies (4, 7, 16, 19, 21, 28, 46, 55, 61, 63), but not all (26), have demonstrated that orthostatic tolerance is impaired in women compared with men. The suggested causes of the reduced orthostatic tolerance in women compared with men include altered central volume adjustments (20, 21) and vasoconstriction responses (56). As human subjects rise from lying or sitting to the standing position, transmural pressure in the levels of the lower limbs rise. Postural stress evokes sympathetic engagement and autoregulatory constrictor responses to the rise in transmural pressure. In contrast to the effect of sex on neurally mediated cardiovascular responses to orthostatic stress, very few studies have examined the impact of sex on autoregulatory constrictor responses. A component of the autoregulatory adjustment is termed the myogenic response, which was first identified by Bayliss in 1902 (15, 38). This response can occur independent of sympathetic and endothelium influences (13, 50).

In vitro animal studies have yielded mixed findings regarding the effects of sex on the myogenic response. Step increases in transmural pressure (i.e., 20 up to 140 mmHg) evoked attenuated myogenic responses in cerebral, mesenteric, and gracilis skeletal muscle arterioles in females compared with males in most (23, 24, 35), but not all, animals (29). Whether there are sex differences in the skeletal muscle myogenic responses to alterations in transmural pressures has not been investigated in human studies.

Our laboratory has characterized the myogenic response in the brachial and femoral artery during changes in transmural pressure using specially designed limb tanks (43). With increasing transmural pressure, the myogenic response has been described by two phases: dynamic [i.e., initial reduction in flow velocity following the transient rise in mean blood velocity (MBV) (peak) after abrupt changes to negative tank pressure] and sustained (i.e., steady-state reductions in flow velocity under continuous negative tank suction) (11, 42, 43).

In this report, we examined constrictor responses in the arm and leg of young, healthy men and women as transmural pressure was raised by limb suction using pressurized-limb tanks. Based on prior animal studies, we hypothesized that women compared with men would display attenuated constrictor responses in the brachial and femoral arteries to increases in transmural pressure. The results of this work support this hypothesis.

METHODS

Study Subjects

Twenty healthy subjects (10 men and 10 women) participated in the study (Table 1). Subjects were nonsmokers, normotensive, and not on any medications. All subjects were free of symptoms and/or history of cardiac, vascular, pulmonary, metabolic, diabetic, or neurological disease. The women were tested 14 ± 2 days (range 2–31 days) into their menstrual cycle, and 3 out of 10 were on oral contraceptives. All subjects were recreationally active, but none was involved in a regular exercise program. The Institutional Review Board of the Milton S. Hershey Medical Center approved the experimental protocol. Each person had the purposes and risks of the protocol explained to him or her before written consent was obtained.

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Table 1. Demographic and anthropometric data

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<th>Men</th>
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<td>Arm volume, ml</td>
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<td>Leg volume, ml</td>
<td>1,087±62</td>
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</table>

Values are means ± SE; n, no. of subjects. BMI, body mass index.

Experimental Measurements

Measurement of heart rate and blood pressure. A standard electrocardiogram was used to monitor heart rate (HR). Systolic and diastolic blood pressures (DBP) were continuously measured using the volume clamp method (Finapres, Ohmeda, Madison, WI), with mean arterial pressure (MAP) calculated from the Finapres waveform. Before testing, Finapres pressure was confirmed by use of an automated sphygmomanometer (Dinamap, Critikon, Tampa, FL). HR and MAP were recorded continuously and collected online at 200 Hz using a PowerLab system (AD Instruments, Castle Hill, Australia).

Measurement of limb volumes and circumference. To measure limb volume, we used a water displacement technique in which the limb (arm or leg) was placed into a cylinder of water and the amount of displaced water was measured [limb volume = (πrd²/4) (h), where h is change in water level with or without the limb, and d is diameter of the test vessel] (27). Circumference of the widest aspect of the lower forearm and calf was measured in centimeters. Changes in limb volume were measured by changes in limb circumferences from baseline (%) during the application of negative pressure with use of a mercury-in-Silastic strain gauge (Hokanson, Bellevue, WA) placed around the largest circumference of the lower forearm and calf (42, 43).

Measurement of MBV. Brachial and femoral MBV were measured on a beat-by-beat basis using a 4-MHz pulsed wave Doppler ultrasound (USN) probe (500M Multigon, Yonkers, NY). This flat probe was securely taped into a fixed position to the skin over the brachial artery ~8–10 cm proximal to the antecubital fossa and over the common femoral artery ~2 cm above the bifurcation. Since these arteries are approximately parallel to the skin surface, the insonation angle with the artery was ~45°. The gate for USN was also set to insonate the total width of the artery diameter. Maximal Doppler frequency shift was obtained with slight manual adjustments of the Doppler probe. MBV was measured continuously and collected online, as noted above. The coefficients of variability for MBV brachial and femoral measurements were 8.9 ± 3.1 and 7.7 ± 1.5%, respectively.

Measurement of limb artery diameters. Brachial and femoral diameters were measured using Doppler USN (12–5 MHz; Advanced Technology Laboratories, model HDI 5000CV, Bothell, WA). The coefficients of variability for MBV brachial and femoral measurements were 2.0 ± 0.2 and 1.2 ± 0.1%, respectively. Blood flow was calculated from diameters and MBV using the following equation: flow (ml/min) = MBV * π * [diameter (cm)/2]² * 60. Conductance was calculated from flow using the following equation: conductance (ml/min⁻¹:mmHg⁻¹) = flow/MAP. In addition, shear rate was calculated from diameter and MBV using the following equation: shear rate (s⁻¹) = MBV/diameter (51).

Experimental Testing

Subjects were instructed to abstain from caffeine and alcohol and to avoid exercise for 24 h before testing. All studies were performed in the morning after a 2-h fast in a quiet, dimly lit, and temperature-controlled room (21–24°C). Subjects were positioned supine and instrumented with ECG electrodes. The subject’s nondominant fore- and ipsilateral leg were inserted into the limb tanks with mercury-in-Silastic strain gauges attached at the widest part of the forearm and calf. On the finger of the dominant hand, a Finapres blood pressure device was attached. Both arms were positioned at heart level. The lower aspect of the nondominant arm was sealed above the elbow, and the lower aspect of the ipsilateral leg was sealed at midtibial level in an airtight pressure tank with neoprene cuffs, creating a snug non-constricting seal. Doppler probes, located outside the tanks, were secured with tape over the brachial and femoral arteries. After a 20-min rest period, baseline measurements were taken.

Increases in transmural pressure were elicited with the application of suction (i.e., negative pressure) to the arm or leg via a pressurized-limb tank in 20 subjects (10 women and 10 men). This method reflects a sustained increase in transmural pressure from ambient transmural pressure (i.e., lowering the limb into a dependent position). Subjects were exposed to four separate levels of negative pressure (−25, −50, −75, and −100 mmHg), with each limb tested separately with diameters and MBV measured during separate trials. A primer trial was performed to ensure that the appropriate pressure was present within the forearm tank. After 1 min at baseline, −25 mmHg of suction were applied within 0.2–0.4 s, and 1 min later the pressure was released. Two trials were done for each pressure, and the responses averaged. A brief rest period (2–3 min) was included between each trial to ensure that blood flow had returned to baseline values. This procedure was repeated using −50, −75, and −100 mmHg, with the sequence of pressure application remaining constant.

Data analysis. The following variables were measured on a beat-by-beat basis: HR, MAP, and MBV. Intraluminal diameters were analyzed at end diastole at the following time periods: baseline, 5–10 s, and 50–60 s after change in tank pressure (8). Trials for each pressure time period were averaged for each individual. To normalize the data for any differences in baseline, the difference in MBV from baseline [Δ = (MBV – MBVbaseline)], as well as percent change [%Δ = (MBV – MBVbaseline)/MBVbaseline * 100] were calculated. Data were also normalized to limb volume (i.e., flow/limb volume). Since there was no difference in resting variables before any change in tank pressure trial, these resting variables were averaged. In addition, since there were no differences between resting flow or flow responses in women on or not on oral contraceptives, all women were included in the analyses. Comparisons between men and women in time series measurements for HR, MAP, MBV, flow, diameter, and conductance were evaluated using a two-way ANOVA for repeated measures. Greenhouse Geisser adjustments for degrees of freedom were used when sphericity assumptions were violated. Post hoc testing using the Tukey method was used when appropriate. A mixed-effect model was used to estimate the correlation coefficient between any two continuous variables having repeated observations per subject (54). To determine whether the correlation coefficient from the mixed-effects model was significantly different from zero, a 95% bootstrapped confidence interval was obtained using 2,500 bootstrapped samples (12). Statistical analyses were performed using SPSS (version 13 for Mac OSX, SPSS, Chicago, IL). Data are presented as means ± SE, and level of significance used was P < 0.05.

RESULTS

Men compared with women were taller, heavier, had a larger body mass index, and had greater limb volumes (Table 1; P < 0.05). Men’s arm and calf circumferences were also larger than the women’s circumferences (27 ± 0 vs. 24 ± 0 cm; 39 ± 1 vs. 36 ± 1 cm; P < 0.05). Men had lower resting HR then women but had similar resting MAP (Table 2). Although women compared with men had greater resting MBV in the
brachial and femoral arteries, men had overall greater resting flow and conductance in these arteries (P < 0.05).

Dynamic Responses to Changes in Limb Tank Pressures

With the application of suction, MBV rose quickly (~2–3 s) and then rapidly fell below baseline values and generally reached a plateau by 20–30 s for all levels of negative pressure (Fig. 1). Women had a greater rise in MBV at the two highest forearm tank pressures (~75 and ~100 mmHg; Fig. 2A, P < 0.05 and P = 0.07, respectively) and also a tendency for a greater rise in MBV with increases in leg tank pressures (Fig. 2E; P = 0.08). When the data were expressed as percent change, these sex differences were no longer evident. In the arm, the timing of this initial peak MBV was delayed in the women compared with the men (2.4 ± 0.2 vs. 1.9 ± 0.2 s; P < 0.05); however, this was not observed in the leg (Fig. 2, C and G). There was no significant change in brachial or femoral diameters at peak MBV compared with baseline diameters in either sex (Fig. 2, B and F). In the arm, women compared with men had a greater rate of dynamic reduction in flow with the highest tank pressures (~75 and ~100 mmHg) (P < 0.05), whereas, in the leg, there were no sex differences in the dynamic rate of MBV reduction (Fig. 2, D and H). When these dynamic responses were normalized by limb volume, additional sex differences were noted. Women compared with men also exhibited a greater rise in leg blood velocity, delayed timing of peak flow in the leg, and a quicker rate of MBV fall (i.e., dynamic phase) in the leg (all main effects, P < 0.05).

Sustained Responses to Changes in Limb Tank Pressures

Sixty seconds after the application of limb suction, MBV and flow fell below baseline levels in the limbs of both sexes (Table 3). Conductance also fell below baseline levels, indicating a vasoconstrictor effect. Brachial and femoral diameters did not significantly change from baseline values with sustained limb suction in either sex. In the arm, women compared with men had attenuated brachial flow vasoconstriction responses to suction (Fig. 3A; main effect, P < 0.05). Women’s brachial conductance responses were also significantly attenuated compared with the men (Fig. 3B, main effect, P < 0.05). When the data were normalized to percent change, these sex differences remained (Fig. 3, C and D). In the leg, women compared with men had attenuated femoral flow and conductance vasoconstriction responses (Fig. 4, A and B, main effect, P < 0.05). Differences between sexes were significant at the highest negative pressure (~100 mmHg) with a trend toward significance for ~25 and ~75 mmHg (P = 0.06 and 0.09, respectively). When these data were expressed as percent change, women had a trend toward attenuated vasoconstriction at the highest pressure (~100 mmHg) for flow and conductance (P = 0.08 and P = 0.09, respectively; Fig. 4, C and D). When data were normalized by body mass index, the findings remained the same (data not shown). When data were normalized by limb volume, sex vasoconstrictor differences also remained (i.e., percent change) (Figs. 5 and 6). Lastly, there was no significant correlation between the influence of peak MBV on the degree of vasoconstriction in men or women across all negative pressures in either limb (data not shown).

With sustained suction using either the arm and leg tanks, HR did not change from baseline levels in either sex (Table 4). MAP and DBP were significantly higher at the greatest forearm tank pressure (~100 mmHg) and higher at the two highest leg tank pressures (~75 and ~100 mmHg), regardless of sex (pressure main effect, P < 0.05). There were no sex differences in HR, MAP, or DBP responses to changes in negative tank pressure. Lastly, there were no sex differences in changes in forearm or calf volume with the sustained suction (arm: 1.2 ± 0.1, 2.1 ± 0.1, 3.2 ± 0.2, and 4.2 ± 0.3% vs. 1.6 ± 0.2, 2.6 ± 0.3, 3.8 ± 0.4, and 4.5 ± 0.4%, women vs. men, for −25, −50, −75, and −100 mmHg, respectively; sex effects = nonsignificant; leg: 0.8 ± 0.1, 1.3 ± 0.2, 1.8 ± 0.2, and 2.5 ± 0.3% vs. 0.8 ± 0.2, 1.7 ± 0.2, 2.2 ± 0.3, and 3.2 ± 0.4%, women vs. men, for −25, −50, −75, and −100 mmHg, respectively; sex effects = nonsignificant).

Potential Vasodilator Influences Opposing Vasoconstriction

To examine the potential contribution of the endothelial influences associated with peak MBV on sustained vasoconstriction between sexes, we calculated shear rate at peak MBV. Women compared with men had significantly higher peak shear rates at the higher tank pressures in the arm (Δ86 ± 8 vs. Δ49 ± 4 and Δ130 ± 12 vs. Δ78 ± 6 s⁻¹ in women vs. men for −75 and −100 mmHg, respectively, P < 0.05) and leg (Δ26 ± 3 vs. Δ15 ± 2 and Δ47 ± 5 vs. Δ27 ± 2 s⁻¹ in women vs. men for −75 and −100 mmHg, respectively, P < 0.05). No

![Fig. 1. A representation of the effects of different levels of suction on mean blood velocity (MBV) in one male subject. With the application of the different levels of suction, MBV rose quickly before rapidly falling below baseline values. Dashed line is the average mean resting MBV before the application of any tank suction.](http://ajpheart.physiology.org/Downloadedfrom)
significant correlations between sustained constrictor responses and peak shear rate with the abrupt application of suction were demonstrated in men or women across all negative pressures in either limb (data not shown).

DISCUSSION

In these studies, we characterized and compared the brachial and femoral MBV responses to increases in transmural pressure in men and women. The main findings of this study were that women compared with men had: 1) a greater initial rise in MBV with the application of limb tank pressure; 2) attenuated brachial vasoconstrictor responses to negative tank pressures (−25 to −100 mmHg); and 3) attenuated femoral vasoconstrictor responses at the highest tank pressure (−100 mmHg).

Most studies (4, 7, 16, 18, 19, 21, 28, 46, 55, 61, 63), but not all (26), have demonstrated that orthostatic tolerance is impaired in women compared with men. The main findings of this study were that women compared with men had 1) a greater initial rise in MBV with the application of limb tank pressure; 2) attenuated brachial vasoconstrictor responses to negative tank pressures (−25 to −100 mmHg); and 3) attenuated femoral vasoconstrictor responses at the highest tank pressure (−100 mmHg).

In the present study, young women compared with young men had attenuated vasoconstrictor responses to varied levels of suction in the brachial artery (−24 ± 2 vs. −36 ± 2%) and at the highest level of suction in the femoral artery (−25 ± 11 vs. −46 ± 4%). This relationship was maintained after taking into consideration limb size differences between men and women. The reasons for the strong sex differences in the arm and only at the highest negative pressure in the leg are not clear. Normally, when an individual stands, intra-arterial pressures increases, due to changes in hydrostatic pressure, to −40 mmHg in the lower arm and to −100 mmHg in lower leg (53). Thus our experimental protocol exposed the arm to suction levels over normal physiological pressure levels observed in the arm with standing. This factor may have amplified the effects of sex noted in the forearm. For the leg tank, our highest suction level approximately matched normal physiological pressure levels observed in the leg with standing. Due to concerns of engaging systemic sympathetic reflexes, we did not use negative pressures >100 mmHg; however, we speculate that women would have exhibited attenuated leg vasoconstrictor responses with higher leg tank pressures.

We examined the influence of peak MBV and peak shear rate on vasoconstriction in the male and female volunteers. Not
surprisingly, women had smaller arm and leg vessel diameters than men. Shear rate, which is based on MBV and diameter, at peak MBV was greater at the higher tank pressures in women compared with men. Since previous studies have shown that smaller vessels experience a larger shear rate to flow-mediated dilation (51), the greater transient increase in women’s shear rate to changes in suction agrees with previous literature. The effects of greater shear rate at higher levels of suction may have been due to greater nitric oxide opposition to the vasoconstrictor response in women compared with men (36); however, at lower levels of suction, we did not find an effect of sex on shear rate, and yet the sex effects on vasoconstriction were still present. These findings suggest that there are likely to be intrinsic differences in autoregulation in women and men.

Autoregulation is a protective process with influences that include myogenic vasoconstriction and vasodilation to changes in transmural pressure across the arteriole vessel wall. Myogenic vasoconstriction helps maintain basal vascular tone (49), and a rise in transmural pressure evokes peripheral vasoconstriction, which may be partially responsible for the increase in vascular resistance with standing or head-up tilt (HUT) (44, 58, 59). In vitro animal studies have suggested that sex can influence myogenic vasoconstrictor responses. In most studies (23, 24, 35, 60, 62), but not all (29), female compared with

### Table 3. Change and percent change in brachial and femoral mean blood velocity and diameters responses to sustained negative tank pressure

<table>
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<tr>
<th>Gender</th>
<th>Tank Pressure (mmHg)</th>
<th>MBV, cm/s</th>
<th>Diameters, %</th>
<th>PC MBV, %</th>
<th>PC Diameters, %</th>
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<td>0.6±0.6</td>
<td>NS</td>
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</tr>
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</table>

Values are means ± SE. Δ, change; PC, percent change; NS, nonsignificant. Men were significantly different from women at specific tank pressure: *P < 0.05, †P = 0.09.

**Fig. 3.** The change and percent change in flow (A and C) and conductance (B and D) under sustained changes in tank pressures (−25, −50, −75, −100 mmHg) in the brachial arteries of men and women.
male animals have demonstrated attenuated vasoconstrictor responses to increases in transmural pressure. This has been seen in cerebral, mesenteric, and skeletal muscle arterioles (23, 24, 35, 60, 62). In our study, we also demonstrated sex differences in vasoconstrictor responses to changes in limb suction in which women compared with men exhibited attenuated brachial and femoral flow responses. Due to the lack of change in our conduit artery’s diameters, the sex differences in our conductance data were likely representative of the changes in the diameters of the downstream resistance vessels to the alterations in transmural pressure.

It cannot be excluded that what we examined was only the effects of sex on the myogenic response. Other local reflexes may be also engaged with posture changes and may contribute to increasing vascular resistance. A combination of myogenic (55%) and venoarteriolar axon reflex (45%) has been suggested to contribute to cutaneous vasoconstriction that occurs during postural changes (48). The local venoarteriolar axon reflex, triggered by an increase in venous pressure, is suggested to occur when vascular transmural pressure is increased from 20 to 40 mmHg (32, 57). In a prior study, men exhibited greater blood flow reductions, as measured by the local xenon washout method, in the skeletal muscle but not in subcutaneous tissue when the leg was placed in a dependent position (1). These authors suggested that sex influenced the axon reflex in skeletal muscle; however, this study did not separate out the potential myogenic contribution to the vasoconstrictor response. In our study, we measured changes in limb circumference during tank suction to be reflective of changes in limb volume (i.e., venous distension). With increasing levels of suction, limb volume linearly increased in both limbs without any sex effects. Thus our findings suggest that the axon reflex may not be the main contributor to the sex differences in vasoconstriction to limb suction that we observed.

Fig. 4. The change and percent change in flow (A and C) and conductance (B and D) under sustained changes in tank pressures (25, 50, 75, 100 mmHg) in the femoral arteries of men and women. *Significant difference between women and men at a specific level of suction.

Fig. 5. The change and percent change in flow (A and C) and conductance (B and D) normalized by limb volume under sustained changes in tank pressures (25, 50, 75, 100 mmHg) in the brachial arteries of men and women.
Sex may influence the other autonomic nervous system indexes that are engaged with standing (33). Women compared with men have been suggested to influence postural cardiac autonomic modulation through attenuation of the sympathetic responses or through augmentation of inhibitory responses (2). In our laboratory, greater muscle sympathetic nerve activity (MSNA) activity has been shown to be associated with increasing levels of negative tank pressure, suggesting that limb vasoconstriction exhibited a combination of sympathetic activation and myogenic vasoconstriction (30-64). Estrogen may also directly inhibit mechanisms of oxygenase products, such as prostaglandins and prostacyclin (3, 23, 24, 35, 62). The specific mechanism by which estrogen affects vascular tone is not completely understood, but likely modulates the vasoconstrictor response through multiple mechanisms, including endothelium-dependent mechanisms, such as the enhancement of nitric oxide release and/or activity (24, 35, 41) and/or other endothelial vasoactive cyclooxygenase products, such as prostaglandins and prostacyclin (3, 23, 34). Estrogen may also directly inhibit mechanisms of vascular smooth muscle contraction through the opening of large-conductance Ca\(^{2+}\) and voltage-activated K\(^+\) channels (30, 64), and altering membrane potential (30, 47, 66) and signaling pathways (e.g., cGMP, protein kinase C, myosin light chain kinase, and Rho kinase), which regulate vascular smooth muscle contraction (40). Although other sex hormones (i.e., progesterone, testosterone) may affect vasoconstriction and

During HUT, MSNA burst frequency (21, 56) and total nerve activity (21) have been shown to increase similarly in the two sexes. When averaged amplitude/burst was examined (56), sex differences were uncovered. Men compared with women had a larger amplitude/burst increase at the highest tilt level (60°). This attenuated MSNA response in women was suggested to be due to a reduced ability to augment sympathetic burst amplitude in response to postural stress (i.e., attenuated autonomic regulation). In the present study, regardless of the limb examined, women had attenuated vasoconstrictor responses with negative pressure. Thus the findings of this study, when viewed in conjunction with a prior MSNA report (56), suggest that, when transmural pressure is increased, women’s attenuated vasoconstriction response is likely due to combined attenuated sympathetic output, along with an attenuated myogenic vasoconstriction, as well as a higher level of shear rate when at higher levels of myogenic engagement. Therefore, with standing, women’s impaired orthostatic tolerance is multifactorial.

The specific reason for women’s attenuated vasoconstriction responses to increases in transmural pressure is unclear. Animal studies suggest estrogen, which has receptors on vascular smooth muscle cells, alters pressure-induced autoregulation (i.e., myogenic) in cerebral, coronary, and skeletal muscle arterioles (5, 23, 25, 35, 62). The specific mechanism by which estrogen affects vascular tone is not completely understood, but likely modulates the vasoconstrictor response through multiple mechanisms, including endothelium-dependent mechanisms, such as the enhancement of nitric oxide release and/or activity (24, 35, 41) and/or other endothelial vasoactive cyclooxygenase products, such as prostaglandins and prostacyclin (3, 23, 34). Estrogen may also directly inhibit mechanisms of vascular smooth muscle contraction through the opening of large-conductance Ca\(^{2+}\) and voltage-activated K\(^+\) channels (30, 64), and altering membrane potential (30, 47, 66) and signaling pathways (e.g., cGMP, protein kinase C, myosin light chain kinase, and Rho kinase), which regulate vascular smooth muscle contraction (40). Although other sex hormones (i.e., progesterone, testosterone) may affect vasoconstriction and

Table 4. Hemodynamic responses during negative tank pressure

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<th>Leg</th>
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<td>Women</td>
<td>Men</td>
</tr>
<tr>
<td>ΔHR, beats/min</td>
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<td></td>
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<td>−25</td>
<td>0.4±0.9</td>
<td>−1.0±0.7</td>
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<tr>
<td>−50</td>
<td>−0.1±0.7</td>
<td>0.2±0.4</td>
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<tr>
<td>−75</td>
<td>−0.7±1.1</td>
<td>−1.8±0.9</td>
</tr>
<tr>
<td>−100</td>
<td>0.2±1.1</td>
<td>2.0±0.7</td>
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<td>ΔMAP, mmHg</td>
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</tr>
<tr>
<td>−25</td>
<td>1.6±1.2</td>
<td>0.5±1.3</td>
</tr>
<tr>
<td>−50</td>
<td>0.8±0.9</td>
<td>1.7±0.8</td>
</tr>
<tr>
<td>−75</td>
<td>2.7±1.8</td>
<td>1.4±1.1</td>
</tr>
<tr>
<td>−100</td>
<td>6.0±2.0</td>
<td>4.4±0.9</td>
</tr>
<tr>
<td>ΔDBP, mmHg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>−25</td>
<td>0.5±0.8</td>
<td>1.5±1.2</td>
</tr>
<tr>
<td>−50</td>
<td>1.4±0.6</td>
<td>1.0±0.7</td>
</tr>
<tr>
<td>−75</td>
<td>4.2±1.5</td>
<td>1.0±0.9</td>
</tr>
<tr>
<td>−100</td>
<td>5.7±1.7</td>
<td>3.4±1.0</td>
</tr>
</tbody>
</table>

Values are means ± SE. DBP, diastolic blood pressure.
calcium influx, estrogen has been noted to be the most effective of these hormones in evoking relaxation of blood vessels in animal studies (9, 10).

**Implications**

The major implication of this study is that the predisposition to orthostatic hypotension seen in women may be due, in part, to attenuated local autoregulatory constrictor responses.

**Limitations to the Study**

Several limitations of the study need to be noted. First, previous studies have shown that different phases of the menstrual cycle can affect reactive hyperemia (31, 39, 65), sympathetic vasoconstriction (17), and sympathetic nerve activity (14). Since our subjects were part of a larger study, we were unable to control for the phase of the menstrual cycle in our female subjects. Sex hormones (i.e., estradiol, progesterone, and testosterone) may have been a potential mechanism for the attenuated vasoconstricter responses observed in the women. Since we did not measure sex hormones in the women, we could not specifically comment on the specific hormone(s) that may be involved with the attenuated myogenic response in women. Lastly, although oral contraceptives may enhance basal nitric oxide production and release (37), oral contraceptives do not appear to affect nitric oxide bioavailability (37), or alter plasma nitric oxide levels (45). In our study, women on oral contraceptives compared with women not on contraceptives had similar resting flow and flow responses to changes in tank suction. The inclusion or exclusion of these women did not alter the main findings of this study. Thus we included all women in the analyses.

**Conclusion**

Our findings suggest that women compared with men have attenuated brachial and femoral constrictor response to increases in transmural pressure. These results may provide attenuated brachial and femoral constrictor response to increases in transmural pressure. These results may provide insights into the mechanisms responsible for sex-related differences in orthostatic tolerance.

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**REFERENCES**


Limb vasoconstriction responses in men and women


