Sex differences in sympathetic neural and limb vascular reactivity to mental stress in humans

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Yang H, Drummer TD, Carter JR. Sex differences in sympathetic neural and limb vascular reactivity to mental stress in humans. Am J Physiol Heart Circ Physiol 304: H436–H443, 2013. First published November 30, 2012; doi:10.1152/ajpheart.00688.2012.—Mental stress elicits a robust and consistent forearm vasodilation, but vascular reactivity in the calf remains inconsistent. It has been reported that calf vascular responses to MS may be sex dependent. Muscle sympathetic nerve activity (MSNA) is an important contributor to calf blood flow (CBF), yet the relations between sex, limb blood flow, and MSNA reactivity to mental stress have not been explored. We hypothesized that mental stress would elicit more dramatic vasodilation of the limbs in women and that this might be explained by reduced MSNA reactivity and/or blunted sympathetic vascular transduction. We measured heart rate (HR), mean arterial pressure (MAP), CBF, calf vascular conductance (CVC), forearm blood flow (FFB), forearm vascular conductance (FVC), and MSNA concurrently in 18 men (age: 23 ± 2 yr) and 16 women (age: 24 ± 2 yr) during 5 min of supine baseline and 5 min of mental stress. Mental stress elicited similar increases in MAP (Δ10 ± 1 vs. Δ11 ± 1 mmHg), HR (Δ16 ± 2 vs. Δ17 ± 2 beats/min), FBF (Δ61 ± 16% vs. Δ53 ± 15%), and FVC (Δ62 ± 13% vs. Δ65 ± 13%) in men and women, respectively. In contrast, CBF (Δ16 ± 8% vs. Δ37 ± 9%, P = 0.036) and CVC (Δ4 ± 7% vs. Δ24 ± 8%, P = 0.036) responses were exaggerated in women compared with men. Changes in FVC were significantly correlated with changes in CVC in women (r = 0.681, P = 0.004) but not in men. MSNA reactivity to mental stress was not different between men and women; however, changes in CVC were negatively correlated with increases of MSNA in men (r = -0.411, P = 0.045) but not in women. In conclusion, our data suggest different patterns of calf vascular reactivity to mental stress in men and women that might relate, in part, to altered vascular transduction of MSNA.

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Since the classic work of Barcroft and Edholm (4), vasodilation of the human skeletal muscle has been recognized as an important contributor to “vasovagal” syncope. Barcroft and Edholm (4) reported a paradoxical forearm vasodilation during syncope, at a time when both heart rate (HR) and blood pressure dropped precipitously. In subsequent years, this forearm vasodilatory response was also observed during acute mental stress (3, 5), suggesting that limb vascular responses might contribute to emotionally induced syncope. Recent evidence suggests that altered limb vascular responsiveness to mental stress may also play an important role in the pathogenesis of hypertension. Specifically, it has been reported that forearm vasodilatory responses to mental stress are blunted in hypertensive (8) and prehypertensive (46, 48) humans. Thus, investigations of limb vascular responsiveness to mental stress are clinically relevant.

While numerous studies have verified a consistent vasodilation of the forearm during mental stress, calf vascular reactivity to mental stress remains controversial. Some studies (5, 31, 35, 37) have reported calf vasodilation during mental stress, whereas others (12, 30, 45) have reported no change. Interestingly, sympathetic neural responsiveness to mental stress also remains inconsistent (13). Mental stress has been shown to increase (1, 7, 14, 30, 35, 51), decrease (19, 40), or not change (10, 12, 52) muscle sympathetic nerve activity (MSNA) when recorded from the peroneal nerve in the leg. Halliwill et al. (25) demonstrated that forearm vasodilation during mental stress was significantly correlated with decreases in forearm MSNA. However, Carter et al. (12) reported a significant forearm vasodilation during mental stress that was not associated with decreases in forearm MSNA, suggesting that mental stress forearm vasodilation is not necessarily dependent on MSNA withdrawal. In fact, studies have suggested that circulating epinephrine (34, 38, 39) and nitric oxide (9, 20, 34) also contribute to forearm vasodilation during mental stress. To date, very few studies have focused on the relations between calf blood flow (CBF) and MSNA responsiveness to mental stress, presumably due to the inconsistencies in both neural and vascular reactivity.

In recent years, several studies (16, 18, 27, 28, 47) have demonstrated that sex (i.e., male vs. female) can influence sympathetic neural and vascular control in humans. Germena (39) and mental stress, Butt et al. (6) reported sex differences in calf vascular reactivity to mental stress. Specifically, females demonstrated a significantly greater calf vasodilation than males, and males demonstrated a greater calf vasoconstriction than females. More recently, Hogarth et al. (32) demonstrated an inverse correlation between resting CBF and resting MSNA in men but not in women. These investigators (32) also reported significantly blunted increases in calf vascular resistance in women during cold pressor and isometric handgrip despite similar MSNA responses to these stressors in both sexes. Thus, it appears that women tend to have a blunted transduction of MSNA into vasomotor tone at rest and during certain sympathetic excitatory maneuvers. Given these findings (6, 32), sex-related differences might help explain reported inconsistencies regarding calf vascular responsiveness to mental stress.

The purpose of the present study was to determine the influence of sex on limb vascular and MSNA reactivity to mental stress. We hypothesized that 1) women would demonstrate an augmented vasodilation during mental stress in the forearm and calf compared with men and 2) MSNA reactivity...
to mental stress and/or the vascular transduction of the MSNA reactivity would be augmented in men compared with women.

**METHODS**

**Subjects**

Thirty-four healthy subjects (18 men and 16 women) participated in this study. Subject characteristics are shown in Table 1. Exclusion criteria included smoking, hypertension, diabetes, autonomic dysfunction, asthma, and other cardiovascular diseases. Female subjects were not taking oral contraceptives, reported regular menstrual cycles (range: 26–30 days), and were tested throughout the menstrual cycle. A covariance analysis using days after menstruation onset as a control variable indicated that phase of menstruation did not significantly influence the presented results. Participants were studied retrospectively from two recent studies (11, 15); subjects with concurrent and complete recordings of MSNA, CBF, and/or forearm blood flow (FBF) throughout the resting supine baseline and mental stress trial were included for analysis. The testing procedures were explained to all subjects before written informed consent was obtained. This experimental design of this study was approved by the Institutional Review Board of Michigan Technological University.

**Experimental Design**

Participants arrived to the laboratory after abstaining from exercise, alcohol, and caffeine for at least 12 h. After 5 min of quiet rest, three seated blood pressure recordings were obtained with an automated sphygmomanometer. Subjects were then instrumented for the autonomic function test in which HR, beat-to-beat arterial blood pressure via finger plethysmography (detailed below), FBF, CBF, and MSNA were simultaneously recorded. After at least 5 min of nonrecorded rest, three consecutive supine blood pressures were taken with the automated sphygmomanometer. After the supine blood pressure recordings, a mental stress trial, which consisted of 5 min of supine baseline and 5 min of mental stress, was conducted. Mental arithmetic was used to elicit mental stress. Briefly, subjects continuously subtracted the number 6 or 7 from a two- or three-digit number verbally and were encouraged by an investigator to subtract as quickly as possible. Immediately after the mental stress protocol, subjects were asked to report a rating of perceived stress on a scale of 1–4, where 4 = maximal stress.

**Measurements**

**Microneurography.** Multifiber recordings of MSNA were recorded by inserting a tungsten microelectrode (Frederick Haer, Bowdoinham, ME) into the common peroneal nerve of the right leg (i.e., located in the popliteal region of the knee or at the base of the fibular head of the lower leg). A reference electrode was inserted subcutaneously 2–3 cm from the microneurography electrode. Both electrodes were connected to a differential preamplifier and then to an amplifier (total gain of 80,000), where the nerve signal was band-pass filtered (700–2,000 Hz) and integrated at a time constant of 0.1 s to obtain a mean voltage display of the nerve activity. Quality recordings of MSNA were determined by spontaneous, pulse synchronous bursts that increased during end-expiratory apnea and remained unchanged during auditory stimulation or stroking of the skin.

**Blood pressure and HR.** Seated and supine resting arterial blood pressures were measured three consecutive times (separated by ~1-min intervals) using an automated sphygmomanometer (Omron HEM-907XL, Omron Health Care) with the average of the three readings calculated to provide a resting value. Beat-to-beat arterial blood pressure was recorded continuously throughout the baseline and mental stress trial to track changes using the Finometer (Finapres Medical Systems, Amsterdam, The Netherlands). Supine resting arterial blood pressures obtained from automated sphygmomanometer immediately preceding the baseline were used to calibrate the Finometer to calculate calf vascular conductance (CVC) and forearm vascular conductance (FVC). Arterial blood pressures are expressed as systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP). HR was recorded continuously via a three-lead electrocardiogram.

**Venous occlusion plethysmography.** Limb blood flows were measured via venous occlusion plethysmography (EC6, D. E. Hokanson, Bellevue, WA). Briefly, mercury-in-silastic strain gauges were placed around the subject’s forearm and calf at the point of greatest circumference to measure changes in FBF and CBF during the study. Cuffs were placed around the subject’s left wrist and upper arm and left ankle and upper thigh. Both the forearm and calf were placed above the heart level during venous occlusion plethysmography. The occluding cuff placed on the wrist and ankle were inflated to 220 mmHg, whereas the upper arm and thigh cuffs were inflated to 60 mmHg for 8 s and deflated for 7 s (i.e., 15-s blood flow intervals). CVC and FVC were calculated as the respective limb blood flow divided by MAP. All change (Δ) values expressed in the tables and figures were 5-min average changes during mental stress. Due to limb movement artifacts during the mental stress trial, FBF was not available in two women; thus, n = 14 for FBF and FVC in women.

**Data Analysis**

Data were recorded using WinDaq/Pro data-acquisition software (DATAQ Instruments, Akron, OH) and imported and analyzed in the WinCRPS software program (Absolute Aliens, Turku, Finland). R waves from the electrocardiogram were detected and marked in the time series. Integrated bursts of MSNA recordings were detected on the basis of amplitude using a signal-to-noise ratio of 3:1, within a

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<th>Table 1. Subject characteristics and baseline values</th>
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<td>Variable</td>
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<td>Body mass index, kg/m²</td>
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<td>Calf blood flow, ml·100 ml tissue⁻¹·min⁻¹</td>
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<td>Calf vascular conductance, 100·ml·100 ml tissue⁻¹·min⁻¹·mmHg⁻¹</td>
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Values are means ± SE; n = 18 men and 16 women except for forearm vascular measurements, where n = 18 men and n = 14 women. HR, heart rate; MAP, mean arterial pressure; MSNA, muscle sympathetic nerve activity. *Significantly different between men and women (P < 0.05).
0.5-s search window centered on a 1.3-s expected burst peak latency after the previous R wave. The average area of the bursts occurring during baseline of each subject was normalized to a mean value of 100, which allows for the assessment of burst area (i.e., strength). This is a necessary procedure because the neurogram is highly dependent on the electrode location within the peroneal nerve in multunit recordings. As such, burst area is normalized during baseline so changes in total MSNA can be meaningfully compared during mental stress between men and women. MSNA was expressed as burst frequency (bursts/min), burst incidence (bursts/100 heart beats), and change in total MSNA (changes of the normalized burst areas/min compared with baseline).

**Statistical Analysis**

All data were analyzed statistically using commercial software (IBM SPSS Statistics 20.0, SPSS, New York, NY). Subject characteristics as well as neural and hemodynamic baseline values were compared in men and women using independent t-tests. To compare mental stress responses between sexes, we used repeated-measures ANOVA with time (i.e., baseline vs. mental stress) as the within-factor variable and sex (male vs. female) as the between-factor variable. Pearson correlations were used to probe for the relationships between FBF, FVC, CBF, CVC, HR, and MSNA responses to mental stress. Results are expressed as means ± SE, and a significance level of P < 0.05 was used.

**RESULTS**

Table 1 shows subject characteristics, baseline hemodynamic activity, and sympathetic neural activity. Age, body mass index, HR, DBP, MAP, and MSNA were not different between men and women. Men demonstrated higher SBP, FBF, and FVC compared with women. Baseline CBF and CVC were not different between sexes.

Table 2 shows hemodynamic and neural responses to mental stress. HR and MAP significantly increased in both groups, and these increases were not statistically different between sexes. MSNA increased in both men and women when expressed as burst frequency and total MSNA. The increases in burst frequency, burst incidence, and total MSNA were similar between sexes (time × sex, P = 0.147, P = 0.208, and P = 0.495, respectively). Ratings of perceived stress during the mental stress trial were not different between men and women (Table 2).

Figure 1 shows limb vascular reactivity to mental stress in men and women. FBF and FVC were significantly increased in both men (Δ81 ± 16% and Δ62 ± 13%, respectively, P < 0.05) and women (Δ83 ± 15% and Δ65 ± 13%, respectively, P < 0.05), and these increases were not different between sexes (time × sex, P > 0.05). In contrast, calf vascular responses were different between men and women. Specifically, CBF and CVC significantly increased in women (Δ37 ± 9% and Δ24 ± 8%, respectively, P < 0.05) but not in men (Δ16 ± 8% and Δ4 ± 7%, respectively; time × sex, P < 0.04 for both CBF and CVC). When expressed as changes in absolute values, limb vascular responses were consistent with the percent change data. Specifically, FVC significantly increased in both men (Δ1.6 ± 0.3 100·ml·100 ml tissue⁻¹·min⁻¹·mmHg⁻¹, P < 0.05) and women (Δ1.3 ± 0.3 100·ml·100 ml tissue⁻¹·min⁻¹·mmHg⁻¹, P < 0.05), and these responses were not different between sexes (time × sex, P > 0.05). Likewise, similar to the percent change data, CVC significantly increased in women (Δ0.5 ± 0.2 100·ml·100 ml tissue⁻¹·min⁻¹·mmHg⁻¹, P < 0.05) but not in men (Δ0.1 ± 0.1 100·ml·100 ml tissue⁻¹·min⁻¹·mmHg⁻¹, P > 0.05; time × sex, P = 0.04).

Bivariate Pearson correlations were used to examine individual reproducibility between limbs (i.e., forearm vs. calf). The results shown in Fig. 2 demonstrate the significant positive correlation between FVC and CVC responses to mental stress in women (percent change: r = 0.681, P = 0.004; absolute change: r = 0.785, P = 0.001) but not in men (percent change: r = 0.296, P = 0.116; absolute change: r = 0.324, P = 0.095). In contrast, men demonstrated a modest but significant negative correlation between CVC and MSNA responses (percent change: r = −0.411, P = 0.045; absolute change: r = −0.448, P = 0.032), but this relation was not observed in women (percent change: r = −0.013, P = 0.316; absolute change: r = 0.025, P = 0.427), as shown in Fig. 3.

Finally, recent work by Pike et al. (43) revealed a strong correlation between forearm vasodilation and HR to mental stress. Thus, we examined the correlations between HR and limb vascular conductance responses during mental stress. Figure 4 shows positive correlations between FVC and HR as well as CVC and HR in both men (r = 0.441, P = 0.034; and r = 0.476, P = 0.023, respectively) and women (r = 0.555, P = 0.020; and r = 0.507, P = 0.023, respectively). When FVC and CVC were expressed as absolute values, these positive correlations remained significant between FVC and HR as well as CVC and HR in men (r = 0.568, P = 0.007; and r = 0.526, P = 0.013, respectively) and women (r = 0.708, P = 0.001; and r = 0.642, P = 0.004, respectively).

**DISCUSSION**

The present study investigated the influence of sex on limb vascular responses to mental stress as well as the neural-mediated mechanisms underlying the vascular reactivity. We reported three new findings. First, calf vascular responses to mental stress were sex dependent. Specifically, women demonstrated greater calf vasodilation, which was tightly correlated with their forearm vascular response. In contrast, men demonstrated divergent forearm and calf vascular responses to mental stress, with the majority of male subjects showing forearm vasodilation with no change (or even vasoconstriction) of the calf. Second, we found a significant inverse relationship between changes of CVC and changes of MSNA in men but not in women. These findings suggest sex differences in the transduction of sympathetic nerve activity to vascular tone. Finally, changes of HR were strongly correlated with changes in both FVC and CVC during mental stress in both men and women.
These findings support and extend recent work by Pike et al. (43). Collectively, the present data provide new evidence showing that sympathetic neural and limb vascular reactivity to mental stress are sex dependent in humans. While mental stress consistently elicits forearm vasodilation, calf vascular reactivity to mental stress remains controversial. Mental stress can elicit vasoconstriction (6), vasodilation (5, 6, 31, 35, 37), or no change (12, 30, 45) in the muscular bed of the

![Fig. 1. Percent changes (Δ) in forearm blood flow (FBF), forearm vascular conductance (FVC), calf blood flow (CBF), and calf vascular conductance (CVC) during mental stress. Mental stress elicited similar increases in FBF and FVC in men and women. In contrast, increases in CBF and CVC during mental stress were observed in women (time × sex interactions, \( P < 0.05 \)) but not in men. *\( P < 0.05 \) vs. baseline values. NS, not significant.](image)

![Fig. 2. Scatterplots depicting changes in FVC and CVC in men and women. Changes in FVC were correlated with CVC in women but not in men.](image)
calf. Butt et al. (6) reported a greater calf vasodilatation in women and a greater calf vasoconstriction in men during mental stress. They speculated that there was greater β2-receptor density in the calf vascular bed in women and greater α-receptor density in men (6). More recently, Hogarth et al. (32) demonstrated smaller increases in calf vascular resistance to sympatoexcitatory tests (i.e., cold pressor and isometric handgrip) in women compared with men, but...
the mechanisms responsible for this apparent sex difference were not identified.

Our data demonstrate significantly greater calf vasodilation during mental stress in women compared with men, thus supporting the work of Butt et al. (6). We extended this concept in two critical ways. First, we demonstrated that the relations between forearm and calf vascular responses to mental stress are sex dependent; despite remarkably similar forearm vasodilation during mental stress, only women demonstrated a parallel vasodilation of the calf. To our knowledge, this is the first evidence to suggest a decoupling of limb vascular responses to mental stress that is dependent on sex (i.e., decoupling in men). Second, our data provide insights into a potential mechanism for this sex difference. Specifically, calf vascular reactivity was modestly, but significantly, correlated to MSNA reactivity in men but not in women. This finding is consistent with Hogarth et al. (32) and suggests that the transduction of MSNA into vascular tone may be different between sexes during mental stress. In other words, our data suggest men may be more sensitive to the vasoconstricting action of MSNA during mental stress. Because the vascular responsiveness to mental stress is important for both cardiovascular disease (24, 49, 54) and orthostatic hypotension (3, 5, 37, 44), the reported sex differences of this study could be critical in the development of sex-specific therapeutic strategies aimed at reducing the risk of these cardiovascular conditions.

Other studies support the concept of sex differences in MSNA-vascular coupling. For example, Charkoudian et al. (17) demonstrated that resting MSNA is positively correlated to resting total peripheral resistance and inversely correlated to resting cardiac output in men. Interestingly, the relationship between resting MSNA and total peripheral resistance is not observed in women (27). It has been suggested that the altered neural-vascular coupling between sexes may be related to adrenergic receptor sensitivity/density (28). Specifically, women appear to have less α-adrenergic receptor support of resting blood pressure (47) and lower α-adrenergic receptor sensitivity to norepinephrine (23, 36). Moreover, evidence exists to suggest enhanced β-adrenergic receptor-mediated dilatation in young women as an important factor uncoupling MSNA from vasoconstriction in young women (26, 36). Thus, if sex differences in vascular transduction of MSNA during mental stress exist, as suggested by the present data, they may exist due to differences in α/β-adrenergic receptor sensitivity/density; this was beyond the scope of the present study, but it could be established in future work.

An alternative interpretation would be that non-neural mechanisms may help explain the reported sex differences in limb vascular reactivity to mental stress. Both nitric oxide (9, 20, 34, 43) and circulating epinephrine (34, 38, 39) are known contributors to the forearm vasodilation during mental stress. Unfortunately, their influence in calf vascular reactivity is less established. Evidence suggests that estrogen, but not testosterone, increases nitric oxide synthesis and release from the vascular endothelium (2, 29, 42, 50). Estrogens have been reported to increase β2-adrenergic-mediated vasodilation (22), partially through a nitric oxide-related mechanism (9, 21, 33). In contrast, McCredie et al. (41) reported that testosterone supplementation impaired vascular reactivity in females by reducing vascular responses to nitric oxide. Thus, women may have a greater endothelium-dependent vasodilatory capacity than men due to more circulating estrogen and reduced testosterone. The present study did not measure any indexes of nitric oxide levels or bioavailability, nor did we measure circulating epinephrine.

The present study revealed some significant relations between HR and vascular reactivity to mental stress that extends recent work by our laboratory and others. Pike et al. (43) and a recent study from our laboratory (53) have reported a striking correlation between HR and FVC responses to mental stress. However, these previous studies (43, 53) did not examine the relations between CVC and HR. In present study, we reported not only a strong correlation between HR and FVC but also a strong correlation between HR and CVC responses to mental stress in men and women. These findings support the findings of Pike et al. (43), who put forth the concept that increased shear stress (via increased HR and the presumable release of nitric oxide from the endothelium) might contribute to limb blood flow regulation during mental stress. In the present study, HR responses to mental stress were significantly correlated with the CVC response to mental stress in both sexes. It is tempting to speculate that the similar relations between HR and limb vascular reactivity to mental stress indicate similar nitric oxide responses, thus lending further support to a sex difference in sympathetic vascular transduction, but we are cautious not to overinterpret our data. This once again underscores the need to further explore the influence of sex on nitric oxide responsiveness to mental stress.

We limited our MSNA-vascular interpretations to the lower leg because it remains unclear if MSNA responses to mental stress are parallel in the upper and lower extremity. Anderson et al. (1) reported that mental stress increased MSNA in the leg but not in the arm. Halliwill et al. (25) later demonstrated mental stress decreased forearm MSNA, but leg MSNA was not recorded. More recently, a study from our laboratory (12) simultaneously recorded MSNA from both the forearm and leg and reported similar MSNA responsiveness between limbs. Thus, at the present time, it remains unclear if the microelectrode location (i.e., leg vs. forearm) influences MSNA reactivity to mental stress; thus, we limit our discussion of sympathetic vascular transduction to the calf because the present study examined peroneal MSNA.

In conclusion, mental stress induces similar forearm vasodilation between men and women. In contrast, calf vascular reactivity to mental stress is different between sexes. This sex difference in calf vascular reactivity may be due, in part, to an augmented vasomotor transduction of MSNA in men during mental stress. Such information may be important in developing sex-specific therapies to lower the risk for cardiovascular diseases associated with vascular dysfunction during mental stress. Moreover, our findings suggest a need to better understand the potential role of sex in nitric oxide responsiveness to mental stress.

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DISCLOSURES

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


REFERENCES


