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Sex differences in forearm vasoconstrictor response to voluntary apnea

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Patel HM, Heffernan MJ, Ross AJ, Muller MD. Sex differences in forearm vasoconstrictor response to voluntary apnea. Am J Physiol Heart Circ Physiol 306: H309–H316, 2014. First published December 6, 2013; doi:10.1152/ajpheart.00746.2013.—Clinical evidence indicates that obstructive sleep apnea is more common and more severe in men compared with women. Sex differences in the vasoconstrictor response to hypoxygenia-induced sympathetic activation might contribute to this clinical observation. In the current laboratory study, we determined sex differences in the acute physiological responses to maximal voluntary end-expiratory apnea (MVEEA) during wakefulness in healthy young men and women (26 ± 1 yr) as well as healthy older men and women (64 ± 2 yr). Mean arterial pressure (MAP), heart rate (HR), brachial artery blood flow velocity (BBFV, Doppler ultrasound), and cutaneous vascular conductance (CVC, laser Doppler flowmetry) were measured, and changes in physiological parameters from baseline were compared between groups. The breath-hold duration and oxygen-saturation nadir were similar between groups. In response to MVEEA, young women had significantly less forearm vasoconstriction compared with young men (ΔBBFV: 2 ± 7 vs. −25 ± 6% and ΔCVC: −5 ± 4 vs. −31 ± 4%), whereas ΔMAP (12 ± 2 vs. 16 ± 3 mmHg) and ΔHR (4 ± 2 vs. 6 ± 3 bpm) were comparable between groups. The attenuated forearm vasoconstriction in young women was not observed in postmenopausal women (ΔBBFV: −21 ± 5%). We concluded that young women have blunted forearm vasoconstriction in response to MVEEA compared with young men, and this effect is not evident in older postmenopausal women. These data suggest that female sex hormones dampen neurogenic vasoconstriction in response to apnea-induced hypoxemia.

sympathetic nervous system; blood flow; hypoxia; vascular resistance; chemoreflex

NUMEROUS POPULATION-BASED STUDIES have demonstrated that obstructive sleep apnea (OSA) is more common in men than women (41, 54, 69). Furthermore, this difference is magnified in the clinical setting with estimates of the male:female ratio as high as 8:1 (55). The exact mechanisms underlying the apparent sex differences are unclear, but prior studies have suggested that upper airway anatomy, body fat distribution, reproductive hormones, and neurovascular control might all contribute to the higher prevalence of OSA in men (41, 44, 51). With regard to neurovascular control, it has been established that both obstructive apnea during sleep (39, 60, 72) and voluntary apnea during wakefulness (19, 22, 34, 40, 62) lead to a reduction in arterial oxygen saturation (SaO₂), a rise in muscle sympathetic nerve activity (MSNA), reduced limb blood flow, and a transient rise in arterial blood pressure (BP). Whether there are sex differences in these acute physiological responses to voluntary apnea have not been evaluated. In fact, most previous apnea studies have only enrolled male participants (19, 39, 40, 46, 62, 72) or studied only a few women (25, 59, 60). Understanding the physiological responses to apnea is clinically valuable because heightened vasoconstriction and elevated BP are thought to be primary stimuli for adverse cardiovascular events (e.g., sudden cardiac death) in patients with OSA (15, 42).

The purpose of the present investigation was to determine whether young women have attenuated forearm vasoconstriction in response to maximal voluntary end-expiratory apnea (MVEEA) compared with age-matched men. We hypothesized that acute reductions in brachial artery blood flow velocity (BBFV, Doppler ultrasound) and cutaneous vascular conductance (CVC, laser Doppler flowmetry) would be blunted in young women compared with young men (i.e., less vasoconstriction at similar levels of hypoxemia). We also enrolled groups of older men and postmenopausal older women to test the hypothesis that forearm vasoconstrictor response to MVEEA would be augmented in older women compared with young women. To determine whether the observed sex differences in forearm vasoconstriction were unique to MVEEA or were generalizable to another sympathoexcitatory stimulus that raises BP, participants also underwent the cold pressor test. The present data indicate that young women have blunted vasoconstriction in both forearm skeletal muscle and the cutaneous circulation in response to MVEEA compared with young men; this effect is not evident in older postmenopausal women.

MATERIALS AND METHODS

Participants. All study protocols were approved in advance by the Institutional Review Board of the Penn State Milton S. Hershey Medical Center and conformed to the Declaration of Helsinki. A total of 9 young men, 10 young (premenopausal) women, 9 older men, and 8 older (postmenopausal) women participated and provided written informed consent (Table 1). All young women were eumenorrheic and were studied in the early follicular phase (days 1–4) of the menstrual cycle, which is when both estradiol and progesterone levels are lowest in women (5, 45, 61). Six of the ten young women were using a combined estrogen and progestin for contraceptive purposes. None of the older women were taking hormone replacement therapy. It is important to note that serum estrogen is markedly greater in young women compared with young men (35); estrogen levels in older women (55–80 yr) are not different than older men. The young men were taller and heavier than the young women and also had a higher

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**Table 1. Anthropometric and baseline hemodynamic characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Young Men</th>
<th>Young Women</th>
<th>Older Women</th>
<th>Older Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>9</td>
<td>10</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Age, yr</td>
<td>27 ± 1</td>
<td>26 ± 1</td>
<td>64 ± 2†</td>
<td>66 ± 3‡</td>
</tr>
<tr>
<td>Height, cm</td>
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<td>166 ± 3*</td>
<td>163 ± 4</td>
<td>179 ± 2</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>80.8 ± 2.4</td>
<td>64.5 ± 3.7*</td>
<td>67.0 ± 1.9</td>
<td>81.7 ± 3.0</td>
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<tr>
<td>BMI</td>
<td>25.2 ± 0.3</td>
<td>23.1 ± 0.8*</td>
<td>25.3 ± 1.9</td>
<td>25.5 ± 0.8</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>110 ± 2</td>
<td>107 ± 1</td>
<td>119 ± 2‡</td>
<td>118 ± 2‡</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>67 ± 1</td>
<td>65 ± 2</td>
<td>73 ± 3‡</td>
<td>77 ± 2‡</td>
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<td>MAP, mmHg</td>
<td>81 ± 1</td>
<td>78 ± 2</td>
<td>87 ± 3‡</td>
<td>90 ± 2‡</td>
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<td>HR, beats/min</td>
<td>64 ± 2</td>
<td>61 ± 2</td>
<td>63 ± 5</td>
<td>59 ± 3</td>
</tr>
</tbody>
</table>

Values are means ± SE. *Significant difference from young men, †significant difference from young women, ‡significant difference from young men.

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; HR, heart rate.

...bined with a previous report (40) suggest that changes in velocity attributable to MVEEA are proportional to changes in absolute blood flow because diameter does not change.

**MVEEA procedures.** Participants were familiarized to the MVEEA procedure by performing a practice trial to ensure they held their breath in expiration without performing Valsalva and Müller maneuvers, consistent with prior reports (18, 40, 46, 56). After baseline cardiovascular parameters were obtained (~3 min), participants were then asked using standard wording to perform an MVEEA in room air (21% oxygen), "Whenever you are ready, please perform a breath hold. Keep your body relaxed and hold your breath as long as you can, only breathe when you have to." HR, mean arterial pressure (MAP), SatO₂, BBFV, and skin blood flow flux were recorded continuously. Three separate apnea parameters were used during offline analysis: 1) an average of seconds 12–15 of MVEEA (i.e., cessation of lung inflation but only modest hypoxemia), 2) an average of the three cardiac cycles immediately before inspiration (i.e., the "asphyxic break point"), and 3) an average of the three cardiac cycles immediately after inspiration (i.e., usually coinciding with the lowest observed SatO₂). These time points were chosen based on previously published studies from this laboratory (53) and others (39, 40, 56).

Because expired gases were not measured in this study, the onset of inspiration and expiration was quantified by offline inspection of the pneumograph tracing. Two separate MVEEA trials were conducted for each subject (separated by 3 to 5 min), and an average is reported.

**Cold pressor test procedures.** Seven young men, seven young women, seven older men, and seven older (postmenopausal) women underwent the cold pressor test after completing the MVEEA trials. The cold pressor test was chosen because it is a sympathoexcitatory stimulus that raises BP without altering arterial blood gases (i.e., it does not activate the arterial chemoreflex) (38, 65). Participants placed their left hand up to the styloid process into 1°C water, and the hand remained submerged for 2 min. Only HR, MAP, and skin blood flow flux (right ventral forearm) were measured during the cold pressor test. Data from the last 20 s of immersion were used as the peak physiological response. Thermal sensation (0 = neutral/no sensation of cold and 11 = unbearable cold) and pain perception (0 = no pain and 10 = unbearable pain) were obtained immediately after the hand was removed from the water (17, 21).

**Data collection and statistical analysis.** Data were collected at 200 Hz by a PowerLab (ADInstruments) and were analyzed offline. The three forearm skin blood flow sites were averaged, and CVC was calculated as skin blood flow flux/MAP and then expressed as a percent change from baseline, which is a common method of data presentation for CVC (49, 50, 64). To compare BBFV and CVC in the same units, percent change was also calculated for BBFV. Changes in HR and MAP from baseline were determined in absolute physiological units. As stated above, the MVEEA data were analyzed at three distinct time points: 1) an average of seconds 12–15, 2) an average of the three cardiac cycles immediately before inspiration, and 3) an average of the three cardiac cycles immediately after inspiration. In this report, these time points are called “15 s of apnea”, “last three apnea”, and “first three inhale,” respectively.

All statistical analyses were conducted using IBM SPSS 21.0, and graphics were produced using Microsoft Excel and Adobe Illustrator CS5. Baseline anthropometric and hemodynamic parameters were determined with independent sample t-tests (Table 1). Physiological responses to MVEEA and the cold pressor tests were also compared between groups with independent sample t-tests. Bivariate correlations were conducted to relate CVC and BBFV responses, and intraclaus correlations were used to determine test-retest reliability in the combined group of participants (comparing the first apnea performed to the second apnea performed). Significance was set at P < 0.05, and data are presented as means ± SE throughout.
RESULTS

**MVEEA: young men vs. young women.** MVEEA duration was not different between young men (26 $\pm$ 3 s) and young women (23 $\pm$ 1 s, $P = 0.262$). Similarly, the $SaO_2$ nadir was not different between young men (91 $\pm$ 1%) and young women (93 $\pm$ 1%, $P = 0.188$). As shown in Fig. 1, the $\Delta MAP$ and $\Delta HR$ were comparable between groups at the three separate time points. However, young women had significantly less $\Delta BBFV$ (i.e., less vasoconstriction) compared with young men at all time points ($P = 0.033, 0.018,$ and $0.019$, respectively). Young women also had a blunted $\Delta CVC$ (i.e., less vasoconstriction) during the last three cardiac cycles of apnea ($P = 0.029$) and the first three cardiac cycles of inhalation ($P = 0.048$) compared with young men. Representative recordings of MVEEA are included for one young man (Fig. 2) and one young woman (Fig. 3). In a secondary analysis, there were no significant differences in the physiological responses to MVEEA between young women using hormonal contraceptives ($n = 6$) and those not using hormonal contraceptives ($n = 4$).

In three young men and three young women, we measured brachial artery diameter in response to MVEEA (instead of measuring BBFV). Expectedly, men had larger brachial artery size at rest ($P < 0.001$). However, MVEEA did not influence brachial artery diameter in either men (from 3.7 $\pm$ 0.1 mm at rest to 3.6 $\pm$ 0.2 mm at peak) or women (from 3.0 $\pm$ 0.1 mm at rest to 3.1 $\pm$ 0.1 mm at peak). The percent change in diameter was also not different between men ($-1.7 \pm 0.8\%$) and women (1.0 $\pm$ 1.5%, $P = 0.191$). Thus the sex differences in BBFV (Fig. 1) are likely indicative of changes in absolute blood flow because brachial diameter was unchanged in response to MVEEA.

**MVEEA: young women vs. older women.** When comparing the young women to the older postmenopausal women, we found that there were no difference in breath-hold duration (28 $\pm$ 3 s, $P = 0.183$) or $SaO_2$ nadir (94 $\pm$ 1%, $P = 0.749$). As shown in Fig. 4, the older women had an augmented $\Delta MAP$ during the last three cardiac cycles of apnea ($P = 0.009$), but $\Delta HR$ was not statistically different at any time point. The $\Delta BBFV$ was larger in the older women (i.e., more vasoconstriction) compared with the young women at 15 s of apnea ($P = 0.026$), last three cardiac cycles of apnea ($P = 0.027$), and first three cardiac cycles of inhalation ($P = 0.027$). Importantly, the forearm vasoconstrictor response to MVEEA in older women was remarkably similar to that observed in young men (i.e., both groups were expected to have low levels of female reproductive hormones).

**MVEEA: older men vs. older women.** MVEEA duration was not different between older men (29 $\pm$ 3 s) and older women (28 $\pm$ 3 s, $P = 0.483$). Similarly, the $SaO_2$ nadir was not different between older men (91 $\pm$ 2%) and older women (93 $\pm$ 1%, $P = 0.156$). As shown in Fig. 4, the physiological responses to MVEEA were not different between older men and older women.

**MVEEA: correlations.** In addition to reporting mean data (above), we also used intraclass correlations to determine test-retest reliability in physiological response to MVEEA (comparing the first MVEEA to the second MVEEA). The breath-hold duration (Cronbach’s $\alpha = 0.905, P < 0.001$) and $SaO_2$ nadir (Cronbach’s $\alpha = 0.943, P < 0.001$) both demonstrated high test-retest reliability, which indicates a similar
level of hypoxemia within the same individual for different apnea trials. The ΔMAP at 15 s of apnea (Cronbach’s α = 0.837, P < 0.001), last three apnea (Cronbach’s α = 0.867, P < 0.001), and first three inhale (Cronbach’s α = 0.888, P < 0.001) demonstrated moderate to strong test-retest reliability. In a similar way, the ΔHR at 15 s of apnea (Cronbach’s α = 0.812, P < 0.001), last three apnea (Cronbach’s α = 0.901, P < 0.001), and first three inhale (Cronbach’s α = 0.918, P < 0.001) also demonstrated moderate to strong test-retest reliability. When analyzing ΔBBFV, we found that test-retest reliability was high at all time points (15 s of apnea: Cronbach’s α = 0.820, last three apnea: Cronbach’s α = 0.893, all P < 0.001). In a similar way, test-retest reliability was moderate to high for CVC (Cronbach’s α = 0.787, 0.766, and 0.771, respectively, all P < 0.001). Thus individuals with greater forearm vasoconstrictor responses for the first trial also had greater forearm vasoconstrictor responses during the second trial.

We conducted additional correlation analysis to determine the relationships between BBFV and CVC in response to MVEEA in the combined group of participants. During the last three cardiac cycles before inspiration, CVC and BBFV were positively related (R = 0.633, P = 0.001), and, during the first three cardiac cycle of inhalation, this relationship was also evident (R = 0.527, P = 0.008). Thus individuals with greater skeletal muscle vasoconstriction also had greater cutaneous vasoconstriction.

**Cold pressor test.** As displayed in Table 2, immersion of the hand into 1°C water for 2 min increased MAP (P = 0.329) and HR (P = 0.869) to similar levels in young men and young women. However, young women exhibited cutaneous vasodilation, whereas young men had cutaneous vasoconstriction, and this comparison was statistically significant (P = 0.034). Older women had similar ΔMAP (P = 0.411) and ΔHR (P = 0.869) in response to the cold pressor test compared with young women. In contrast to the vasodilation observed in young women, older women experienced a modest cutaneous vasoconstriction (P = 0.034) such that CVC was comparable to young men. As shown in Table 2, ratings of hand pain and cold sensation were comparable in all groups.

**DISCUSSION**

In this study, we examined the acute physiological responses to MVEEA in healthy women and men. Along with HR and MAP, we measured forearm skeletal muscle blood flow velocity and cutaneous blood flow flux to MVEEA in young men, young women, older men, and postmenopausal older women.

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**Fig. 2.** Representative recording of arterial blood pressure (BP), BBFV, respiratory movement (Pneumo), arterial oxygen saturation (SaO2), and skin blood flow flux in one young man during baseline and during MVEEA. In young male participants, MVEEA (as indicated by lack of respiration on Pneumo) elicited a strong pressor response with a decrease in BBFV, SaO2, and skin blood flow flux.

**Fig. 3.** Representative recording of arterial BP, BBFV, Pneumo, SaO2, and skin blood flow flux in one young woman during baseline and during MVEEA. In young female participants, the apnea-induced hypoxemia elicited a moderate pressor response along with a minimal change in BBFV and skin blood flow flux.
The major findings are that young women have blunted apnea-induced forearm vasoconstriction compared with young men, and this response is lost in older postmenopausal women. These findings are novel because previous apnea studies have either excluded female participants altogether (19, 39, 40, 46, 62, 72) or have combined men and women into one group for data analysis (25, 32, 34, 56, 59, 60). Importantly, none of these cited studies measured forearm blood flow. The present data provide evidence that sex modifies the vascular response to apnea-induced hypoxemia in healthy humans and might also stimulate future work in patients with OSA.

Both obstructive apnea during sleep and MVEEA during wakefulness activate the sympathetic nervous system (19, 26, 32, 40, 60). Specifically, Greaney et al. (18) observed a 51% increase in MSNA in response to MVEEA, Hardy et al. (19) noted a 94% increase in MSNA, and Leuenberger et al. (40) documented a ~200% increase in MSNA in response to this same stimulus. The rise in MSNA and the resulting peripheral vasoconstriction are due to the combined effects of hypoxemia, hypercapnia, and cessation of lung inflation (46, 56, 59). With respect to sympathetically mediated vasoconstriction, Leuenberger et al. (40) demonstrated an 11% decrease in femoral artery blood flow in response to MVEEA as measured via Doppler ultrasound. In the present study, we observed a 20–30% decrease in BBFV in young men (depending on the time point), indicating forearm vasoconstriction (Figs. 1 and 4). We further the literature by demonstrating that young women have a blunted forearm vasoconstriction in response to MVEEA compared with young men. Because the apnea duration and \( \text{Sa}_\text{O}_2 \) nadir were similar between groups, we suspect that afferent input to the chemoreflex is comparable between healthy young men and women. The observed sex difference in efferent responses (i.e., forearm blood flow) could be due to 1) reduced sympathetic outflow (i.e., MSNA), 2) impaired synthesis and/or release of norepinephrine and cotransmitters, 3) attenuated \( \alpha \)-adrenergic responsiveness, 4) enhanced vasodilation due to activation of \( \beta \)-adrenergic receptors, nitric oxide, adenosine, and/or estrogen (all of which would dampen the chemoreflex-mediated vasoconstrictor signal), or 5) a combination of the aforementioned effects (4, 16, 36, 66). This process is undoubtedly complex and warrants further study to pharmacodissect the observed sex differences.

Reflex control of the cutaneous circulation is tightly regulated by the sympathetic nervous system (6, 30). Previous studies have demonstrated that cutaneous vasoconstriction occurs in response to voluntary apnea (1, 2, 28, 33). However,
each of these cited studies had fundamental limitations, such as not maintaining mean skin temperature at a constant level (28), performing apnea during exercise (2), not allowing values to return to baseline (1), and the use of plethysmographic methods (33). In the present study, we determined the reflex cutaneous vascular responses to MVEEA (i.e., a nonthermal stimulus) under rigorously controlled laboratory conditions. The present data demonstrate clear sex differences in CVC during the last three cardiac cycles of apnea and also the first three cardiac cycles of inspiration (Figs. 1, 2, and 3). These findings are consistent with a study by Feger and Braune (12), which revealed sex differences in skin blood flow responses to inspiratory gasp. However, a short-duration inspiratory gasp is unlikely to elicit a reduction in SaO2, and rather exerts its cutaneous effects via involvement of lung-stretch receptors. Indeed, a recent publication by Seitz et al. (56) demonstrated that inspiratory apnea causes a brief sympathetic inhibition unrelated to chemoreceptor reflex mechanism. Given that cutaneous vasoconstriction is aimed at oxygen redistribution (1), these findings suggest men may be better suited to redistribute blood flow toward vital organs, such as the brain and heart during hypoxemia (29, 52). Thus cutaneous vasoconstriction during MVPEA teleologically makes sense.

OSA is not only more prevalent in men, but disordered breathing during sleep is also more common among postmenopausal women compared with premenopausal women with estimates ranging from 4% to 22% (57). Hence, we studied eight postmenopausal women and nine men of similar age to determine whether cutaneous and forearm skeletal muscle blood flow responses to MVEEA are different. Herein, we demonstrate postmenopausal women have an augmented pressor response to voluntary apnea as well as augmented forearm vasoconstriction compared with young women (Fig. 4). The most likely mechanism is that estrogen exerts direct vascular effects by inducing vasodilation through increased vascular nitric oxide production in young women (63). Although MVEEA is an intense stimulus for peripheral vasoconstriction, it may be counterbalanced by the vasodilatory effects of estrogen, resulting in minimal to no net change in BBFV in young women. In postmenopausal women, the vasodilatory effects of estrogen are less, allowing a more complete expression of vasoconstriction, as indicated in Fig. 4. Because we studied young women in the early follicular phase of the menstrual cycle (i.e., when serum sex hormones are lowest albeit still higher than levels in young men), the ability of progesterone to inhibit the vasodilatory effects of estrogen was likely low. Indeed, α-adrenergic responsiveness is lower in the early follicular phase compared with the midluteal phase (14), and this is consistent with a recent study showing that progesterone enhances cutaneous vasoconstriction in response to norepinephrine (66). Beyond the effects of female sex hormones on the vasculature, there is mounting evidence in humans and animal models that estradiol is sympathoinhibitory and progestosterone is sympathoexcitatory (5). Taken together, the present data support the concept that young women have markedly different forearm vascular responses to MVEEA compared with either young men (Fig. 1) or older women (Fig. 4).

In addition to the observed sex differences detailed above, our correlation data provide two interesting findings that may inform future studies. First, ΔCVC and ΔBBFV were correlated such that larger cutaneous vasoconstriction was associated with larger skeletal muscle vasoconstriction. This may indicate that either CVC or BBFV is a valuable measurement to be used in future MVEEA studies despite the fact that skin and muscle blood flow are not controlled identically (6). Second, physiological responses to MVEEA are reproducible in subsequent trials. This might suggest that physiological responses to MVEEA measured in a laboratory setting (e.g., MAP, HR, BBFV, CVC) could translate into predictable hemodynamic outcomes during obstructive apnea during sleep. This speculation warrants further study.

A subset of participants also underwent the cold pressor test to evaluate whether the observed sex differences with apnea were attributable to a generalized inability of young women to vasoconstrict the forearm in responses to sympathetic stressors or whether sex differences were unique to MVEEA. The present data suggest that young women also have a blunted vasoconstrictor response to the cold pressor test. Indeed, young men and women had similar MAP and HR responses, but women had a smaller reduction in CVC compared with young men (and also compared with older women). It is thought that the reflex cutaneous vasoconstriction in response to the cold pressor test is mediated by α-adrenergic receptors (13), but vasoconstriction is not universally observed (8). With respect to sex differences, a previous study found that young women had an attenuated increase in BP and MSNA to isometric handgrip exercise compared with men (11). Other studies reported sex differences in the MSNA responses to orthostatic stress (58, 68). However, prior studies did not find sex differences in MSNA responses to the cold pressor test, but these studies did not measure skin blood flow (27, 31). Because MSNA is positively correlated to total peripheral resistance in young men, but not in young women (20), it is likely that there are also sex differences in the transduction of sympathetic nerve activity to cutaneous vasoconstriction as well. It is also possible that the myogenic response is different between young men and young women, such that a given stretch of a blood vessel results in an attenuated net vasoconstrictor response in women (43). This concept remains to be experimentally tested in human skin.

Recently, polysomnography studies have confirmed epidemiological findings that OSA is, not only more common, but also more severe in men than women (51). Our data suggest that differences in clinical expression of OSA may be in part related to altered vascular responses to apnea-induced hypoxemia. There is convincing evidence that OSA is associated with an increased risk of ischemic heart disease (37), myocardial infarction (24), stroke (10), arrhythmia (15), and mortality (3). The strongest evidence supports an independent causal link between OSA and arterial hypertension (70). The cyclical rise in BP during sleep is believed to result from apnea-induced peripheral vasoconstriction mediated by repetitive activation of the sympathetic nervous system (40). MVEEA similarly activates the sympathetic nervous system to induce peripheral vasoconstriction and a transient rise in BP (32, 34, 62). Considering that there are sex differences in many aspects of BP control (71), we believe that future studies should enroll both men and women with OSA to examine the underlying mechanisms and potential therapeutic targets.

Limitations. In the present study, we did not measure serum estrogen or progesterone. However, we studied young women in the early follicular phase (days 1–4), which is the point at
which estrogen and progesterone are lowest (5, 45, 61). Because sex differences in vascular responses to MVEEA were not observed in older women (i.e., a group of women expected to have low levels of female sex hormones), it is reasonable to suspect that female sex hormones had an effect in vivo. Some of the young women were using hormonal contraception, but the physiological responses to MVEEA were not significantly different compared with women who were not using hormonal contraception. In consideration that hormonal contraceptives have differing mechanisms of action (e.g., androgenic vs. antiandrogenic), this area of research is indeed complex. A previous study found that postmenopausal women undergoing hormone replacement therapy \((n = 907)\) had a lower prevalence of sleep-disordered breathing compared with women not taking hormone replacement \((n = 1,945)\) (57). An interesting follow-up study would be to evaluate whether vascular responses to apnea are influenced by hormone replacement therapy. It is important to note that MVEEA is not a true OSA per se because it does not involve arousal from sleep or upper airway collapse (i.e., both of which may engage the sympathetic nervous system) (7, 9, 48). However, we believe there is similar underlying physiology between MVEEA and OSA, allowing us to make useful comparisons between men and women (25).

**Conclusions.** The present data indicate that young (premenopausal) women have blunted forearm vasoconstriction in response to MVEEA compared with young men. This presumably favorable characteristic of young women is lost in postmenopausal older women. Thus sex can have a profound effect on vascular responses to sympathetic stress in healthy humans. Whether these effects are also present in patients with OSA requires further study.

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**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the authors.

**AUTHOR CONTRIBUTIONS**


**REFERENCES**
