



*Original Research*

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## **Effect of Sex and Menstrual Cycle on Skin Sensory Nerve Contribution to Local Heating**

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### ABSTRACT

*International Journal of Exercise Science 12(2): 1265-1279, 2019.* The purpose of this study was to determine sex differences in the contribution of sensory nerves to rapid cutaneous thermal hyperemia. Healthy young females ( $n = 15$ , tested during both the early follicular (EF) and the mid-luteal (ML) phase of the menstrual cycle) and males ( $n = 15$ ) had a 4 cm<sup>2</sup> area of skin on one forearm and one leg treated with a eutectic mixture of local anesthetic (EMLA). EMLA sites, along with corresponding control sites, were instrumented with laser Doppler flowmetry probes and local skin heaters. Baseline (33 °C), rapid and sustained vasodilation (42 °C), and maximal vasodilation (44 °C) skin blood flow data were obtained and expressed as a percentage of maximal cutaneous vascular conductance (%CVCmax). Contribution of sensory nerve involvement was determined by comparing the EMLA site to its matched control site utilizing the formula  $[(\% \text{CVCmax control} - \% \text{CVCmax treatment}) / \% \text{CVCmax control}] \times 100$ . The contribution of sensory nerves to rapid cutaneous thermal hyperemia in the forearm was  $24 \pm 18$  %CVCmax in males,  $41 \pm 17$  %CVCmax in ML females ( $p = 0.02$  vs. males), and  $35 \pm 17$  %CVCmax in EF females ( $p > 0.05$  vs. males). In the leg, the contribution of sensory nerves was  $16 \pm 15$  %CVCmax in males,  $34 \pm 17$  %CVCmax for ML females ( $p = 0.02$  vs. males), and  $28 \pm 21$  %CVCmax in EF females ( $p > 0.05$  vs. males). ML females exhibited a greater contribution of sensory nerves to rapid cutaneous thermal hyperemia in the forearm and leg, possibly attributed to elevated reproductive hormones during the ML phase.

KEY WORDS: Adrenergic, thermal stimulus, vascular response

### INTRODUCTION

Cutaneous sensory nerves can detect and respond to a variety of stimuli including touch (33), pressure (18), warmth (14), cold (4), and pruritus (34). When a localized warm stimulus is detected, unmyelinated warmth-sensing afferent C fibers release vasodilatory neuropeptides such as substance P and calcitonin gene-related peptide (12) to rapidly increase blood flow to the skin. If the localized warm stimulus persists, skin blood flow will transiently decrease to a nadir before slowly rising again to a nitric oxide-dependent sustained vasodilation (25).

Although chemical (3) contributors respond to the rapid initial vasodilation that begins immediately after local warming have been identified, the response is largely dependent on sensory nerves (19).

Local warming of the skin can be utilized to assess microvascular reactivity, and mechanistic investigations into the various components of the cutaneous thermal hyperemic response can bring to light underlying vascular dysfunction (29). Previously it was determined that diabetic individuals exhibited a significantly higher (~58%) sensory thermal threshold and significantly lower (~58%) rapid initial cutaneous vasodilation in the dorsum of the hand during local heating compared to healthy controls (36). Thus, our understanding of the mechanisms that lead to microvascular dysfunction in aging, in different sexes, and in people with various clinical conditions is imperative (22) for developing appropriate preventive measures such as aerobic exercise training (37) and amino acid supplementation (27), or treatment therapies such as resistance exercise training (9) or pharmaceuticals (5).

Numerous vascular control mechanisms differ according to sex (21, 24, 35). Sex-specific factors that drive these differences include reproductive hormones, (17) sympathetic tone, (15) and baroreflex sensitivity (26). Thus, investigations into the integrated physiological response to day-to-day perturbations such as thermal stress, and long-term stressors like aging and disease need to be individualized so that the influence of sex does not confound research findings. As such, the mechanisms of cutaneous vascular control that differ between sexes should be investigated to further our understanding of how microvascular reactivity is impacted by sex-specific factors.

Although sensory nerve-mediated cutaneous vasodilation has been studied extensively in healthy (20, 37) and diseased populations (10), no study has exclusively attempted to discern if there are sex-related differences in the mechanisms of the initial rapid cutaneous vasodilation response to local heating. Therefore, in this study, we aimed to determine if there were sex-related differences in the contribution of sensory nerves to the initial rapid cutaneous thermal hyperemia via pharmacologically blocking sensory nerves and monitoring skin blood flow with laser-Doppler flowmetry (LDF) in females and males. Based on the known influence of female reproductive hormones on systemic hemodynamics (16), we hypothesized that there would be significant, sex-related differences in the contribution of sensory nerves to rapid cutaneous thermal hyperemia only when females were in the mid-luteal phase of the menstrual cycle, when estrogen and progesterone are elevated.

## **METHODS**

### *Participants*

Ethical approval for human subjects research was obtained from the Ball State University Institutional Review Board and conformed to the guidelines set forth by the Declaration of Helsinki. Additionally, this research was carried out in accordance to the ethical standards of the International Journal of Exercise Science (32). All participants were informed of the

experimental procedures and risks of the study before participating. Verbal and written informed consent were obtained from each participant.

Participant characteristics are provided in Table 1. A minimum of 15 male and 15 female participants was determined by conducting a power analysis using nQuery (version 3.0) (Statistical Solutions, Cork, Ireland) and using standard deviation variations from our laboratory's previous work in skin blood flow (8, 21). Thirty total participants were required to identify a statistical difference (power = 0.80, alpha = 0.05). All participants were required to be healthy, without signs or symptoms of disease determined via self-report on a health history questionnaire, and between the ages of 18 and 40 years. Since hormone phases in human females have been shown to affect skin blood flow (7, 21) female participants were tested once during the early follicular (EF) phase of the menstrual cycle, when reproductive hormones are at their lowest, and once during the mid-luteal (ML) phase of the menstrual cycle, when reproductive hormones are elevated. The EF was separated from the ML by collecting data within six days from the start of menstruation as reported by self-report (28).

**Table 1.** Participant resting data and demographic and anthropometric characteristics.

| Characteristics  | Male        | Female        |
|--|-------------|---------------|
| Age (yrs)  | 23 ± 2      | 23 ± 4        |
| Resting HR (bpm)   | 56 ± 11     | 64 ± 12       |
| Resting MAP (mm Hg)  | 101 ± 9     | 97 ± 13       |
| Height (cm)  | 178.7 ± 7.4 | 162.5 ± 7.3 * |
| Weight (kg)  | 87 ± 14.1   | 67.3 ± 12.6 * |
| Body Composition (% Fat)   | 19.5 ± 10.7 | 29.8 ± 9.5 *  |
| VO <sub>2</sub> max (ml · kg <sup>-1</sup> · min <sup>-1</sup> ) | 44.5 ± 8.9  | 39.3 ± 7.0    |

Values presented as mean ± SD. Yrs = years; HR = heart rate; bpm = beats per minute; MAP = mean arterial blood pressure; mm Hg = millimeter of mercury; cm = centimeter; kg = kilogram; % fat = percent fat; ml · kg<sup>-1</sup> · min<sup>-1</sup> = milliliters per kilogram per minute. \* =  $p < 0.05$

### Protocol

**Session One:** Participants were instructed to arrive at the laboratory after a three hour fast, well hydrated, having not consumed alcohol or caffeine for 24 hours, and to not have used tobacco or performed vigorous exercise for 24 hours prior. After completing the health history questionnaire and providing informed consent, height and weight were measured using a standard stadiometer and scale (Health o meter; McCook, IL). Then, each participant completed a body composition analysis via air displacement plethysmography (BOD POD®, COSMED; Rome, Italy), according to manufacturer instructions. Finally, VO<sub>2</sub>max was measured using a ramped cycle ergometer protocol and indirect calorimeter (Parvo Medics; Sandy, UT). During the exercise test, participants were instrumented with a telemetric heart rate monitor (Polar Electro Inc.; Bethpage, NY), a nose clip and two-way valve breathing mouthpiece (Hans Rudolph, Inc.; Shawnee, KS). The exercise intensity started at 50 watts and increased by 23 watts per minute, in a continuous ramp of .38 watts per s, until volitional exhaustion was achieved, the participant requested to stop, or the test became unsafe for any reason.

**Session Two:** On a separate occasion occurring a minimum of 48 hours following session one, each participant underwent an experimental skin blood flow assessment. Female participants

completed this trial twice – once during the EF phase and once during the ML phase of the menstrual cycle. Participants were instructed to arrive at the laboratory at 07:00 having fasted for a minimum of two hours (permitted to drink water ad libitum) and having refrained from caffeine, tobacco, alcohol, and vigorous exercise for at least 24 hours prior. All data collection took place in a  $23 \pm 0.5$  °C climate-controlled room. Each participant was acclimated to the room temperature for 90 minutes prior to data collection.

Each participant rested in the supine position on an adjustable table for instrumentation, where they remained for the duration of the study. Four sites (two control; two treatment), at least five centimeters apart, two on one forearm and two on one leg were selected. These sites were free from major skin anomalies, such as moles or scars, and care was taken to prevent selecting sites that were located above superficial, prominent veins. Cutaneous sensory nerve function was blocked by applying 2.5 g of EMLA cream (2.5% lidocaine & 2.5% prilocaine; AstraZeneca; Wilmington, DE) over a 4 cm<sup>2</sup> area in one of the two selected skin sites on one forearm and one leg (20, 37). The sites were covered with an occlusive dressing for one hour. The first application of EMLA cream was then wiped from the skin and a second application of the cream and a corresponding dressing were applied for an additional 30 minutes. After the second application of EMLA cream was wiped clear, sensory nerve blockade was verified by lightly pricking and brushing the sites with a hypodermic needle (37). Once confirmation of sensory nerve blockade was completed, with local heating discs (Perimed AB; Järfälla-Stockholm, Sweden) and LDF probes (Perimed AB; Järfälla-Stockholm, Sweden) were placed on the participant. The heating discs were placed over the four predetermined sites on the left side of the body and then taped in place. The LDF probes were then placed in the aperture in the center of the heating discs. Additionally, an oscillometric blood pressure cuff (BpTRU Medical Devices; Coquitlam, BC, Canada) was placed on the right arm opposite to the skin blood flow assessment.

Once local skin sensory nerve blockade was achieved in one forearm and one leg, resting HR was taken via automated blood pressure cuff, and skin blood flow data collection began at time zero. Blood pressure measurements were recorded every five minutes thereafter throughout the study. MAP was calculated for each five-minute section and used to determine CVC. Then, the local heating discs were set to 33 °C (thermoneutral) and held constant for 10 minutes following confirmation that local skin blood flow responses were stable (20). After baseline skin blood flow measurements were complete, the rapid initial vasodilation phase of the cutaneous hyperemic response to local heating was initiated by increasing local skin temperature from 33 °C to 42 °C at a rate of  $1 \text{ °C} \cdot 20 \text{ s}^{-1}$  (19). Once all sites were at 42 °C, this local skin temperature was maintained for 35 minutes, thereby producing the sustained vasodilation phase of the thermal hyperemic response (20). Upon completion of the sustained vasodilation phase, maximal cutaneous vasodilation was induced by increasing the local skin temperature from 42 to 44 °C at a rate of  $1 \text{ °C} \cdot 5 \text{ s}^{-1}$  (19). This temperature was then held for 20 minutes (20). After the maximal vasodilation phase, the experiment was complete and all instruments were removed from the participant.

The data from the local skin heating and LDF units were collected via PowerLab (ADInstruments – North America; Colorado Springs, CO) and displayed on a personal

computer screen via the LabChart software (ADInstruments – North America; Colorado Springs, CO). The skin blood flow LDF data, in mV, were obtained for each site by selecting stable 30 s sections (the middle of the initial response to the beginning of the nadir) from the rapid thermal hyperemia skin blood flow tracing for each testing site; in addition, 5 min sections of skin blood flow data were captured from the thermoneutral baseline and sustained and maximal vasodilation phases. Cutaneous vascular conductance (CVC), was then determined by dividing the LDF data (in mV) by mean arterial blood pressure (mm Hg). Furthermore, since differences in the heterogeneity of cutaneous blood vessels are numerous between participants, all CVC data were expressed and analyzed as a percentage of maximum obtained through maximal cutaneous vasodilation (23), where  $\%CVC_{max} = CVC \text{ (during the evaluated period)} / CVC \text{ (at maximal vasodilation)}$ . The percentage contribution of sensory nerves to rapid initial cutaneous vasodilation from the heat stimulus was calculated by comparing the experimental site for each limb to its accompanying control site utilizing the formula  $[(\% CVC_{max} \text{ control} - \% CVC_{max} \text{ treatment}) / \% CVC_{max} \text{ control}] \times 100$  (20).

### *Statistical Analysis*

All data were processed using the SPSS software v.22 (SPSS, Inc., Chicago, IL) and statistical significance was set at  $p < .05$ . CVC data were normally distributed as indicated by the Kolmogorov-Smirnov goodness of fit test. Text and illustrative results are reported as mean  $\pm$  standard deviation. Paired t-statistics were used to compare data during phases of the menstrual cycle in women, and independent samples t-statistics were used to compare women to men. One-way analysis of variance (ANOVA) was utilized to detect differences in CVC among treatment sites for all groups during the thermoneutral, rapid vasodilation, and sustained vasodilation phases of the heating protocol. One-way ANOVA was also employed to analyze the CVC data for the contribution of sensory nerves to rapid cutaneous thermal hyperemia. A Bonferroni post hoc analysis was performed when indicated by the ANOVA significance.

## **RESULTS**

While age and relative  $VO_{2max}$  were similar between male and female participants, male participants were significantly taller and heavier than the female participants (see Table 1). Additionally, females exhibited higher body fat percentages than men.

**Skin Blood Flow Responses:** Forearm and leg  $\%CVC_{max}$  data for each time point and group can be found in Table 2. Representative tracings of the skin blood flow response at baseline and during local heating, showing the rapid initial vasodilation, nadir, and sustained vasodilation phases of the thermal hyperemic response, from two female participants (one for each phase of the menstrual cycle studied) and one male participant, are provided within Figure 1.

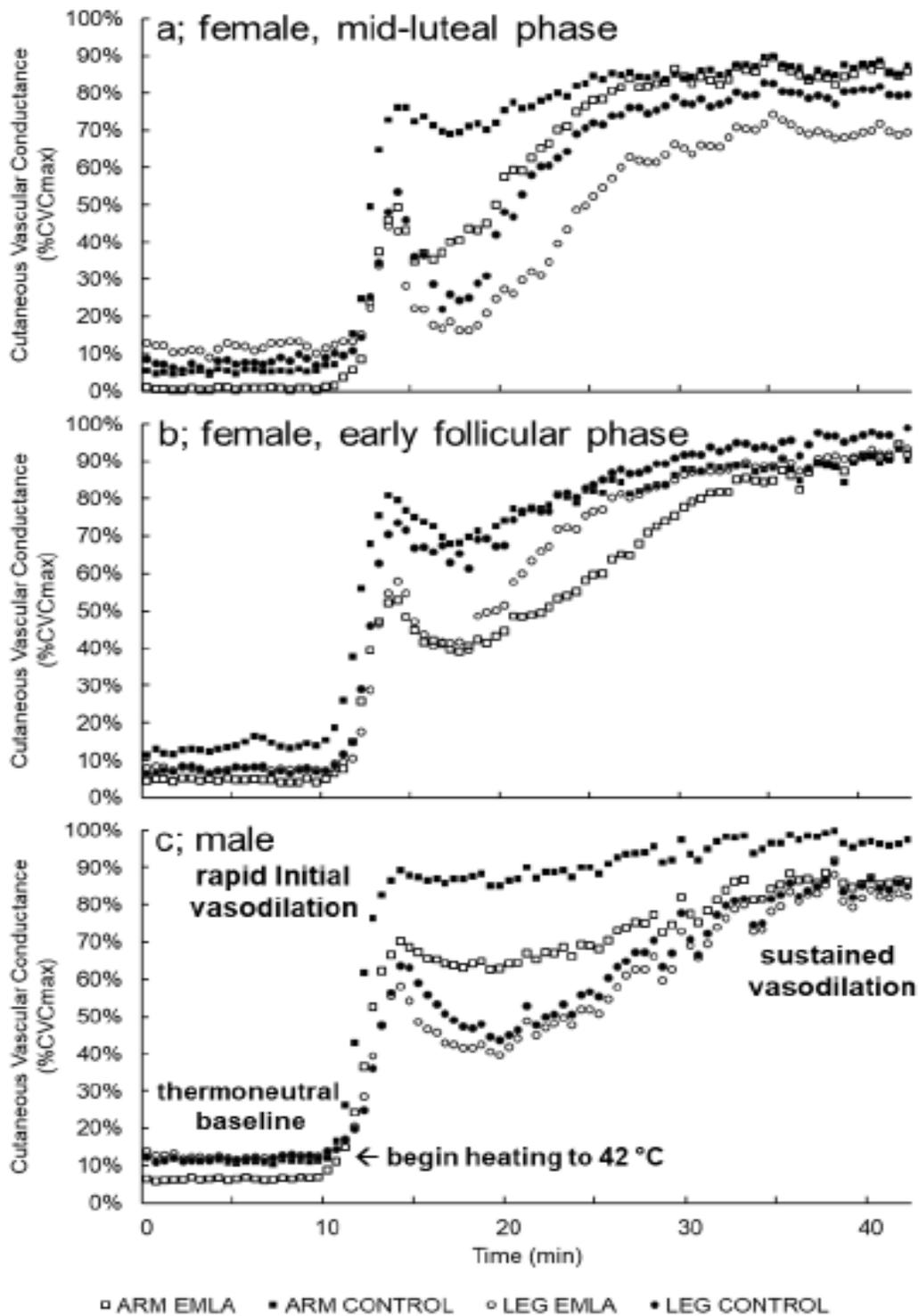
**Baseline Skin Blood Flow:** Baseline skin blood flow in the forearm EMLA sites was significantly lower than in the forearm control sites in all groups (Figure 2a); however, this effect was not observed between the EMLA and control sites of the leg in any group (Figure 2b). The EMLA-treated leg sites in males ( $11 \pm 4 \%CVC_{max}$ ) exhibited significantly greater vasodilation at baseline than did the EMLA-treated legs sites of mid-luteal females ( $7 \pm 2 \%CVC_{max}$ ;  $p = .036$ ;

Figure 2b). Additionally, baseline skin blood flow in the leg control sites of male participants ( $11 \pm 6$  %CVCmax) was significantly greater than in the leg control sites of the early follicular ( $6 \pm 2$  %CVCmax;  $p = .004$ ) and mid-luteal ( $7 \pm 2$  %CVCmax;  $p = .013$ ) female participants (Figure 2b).

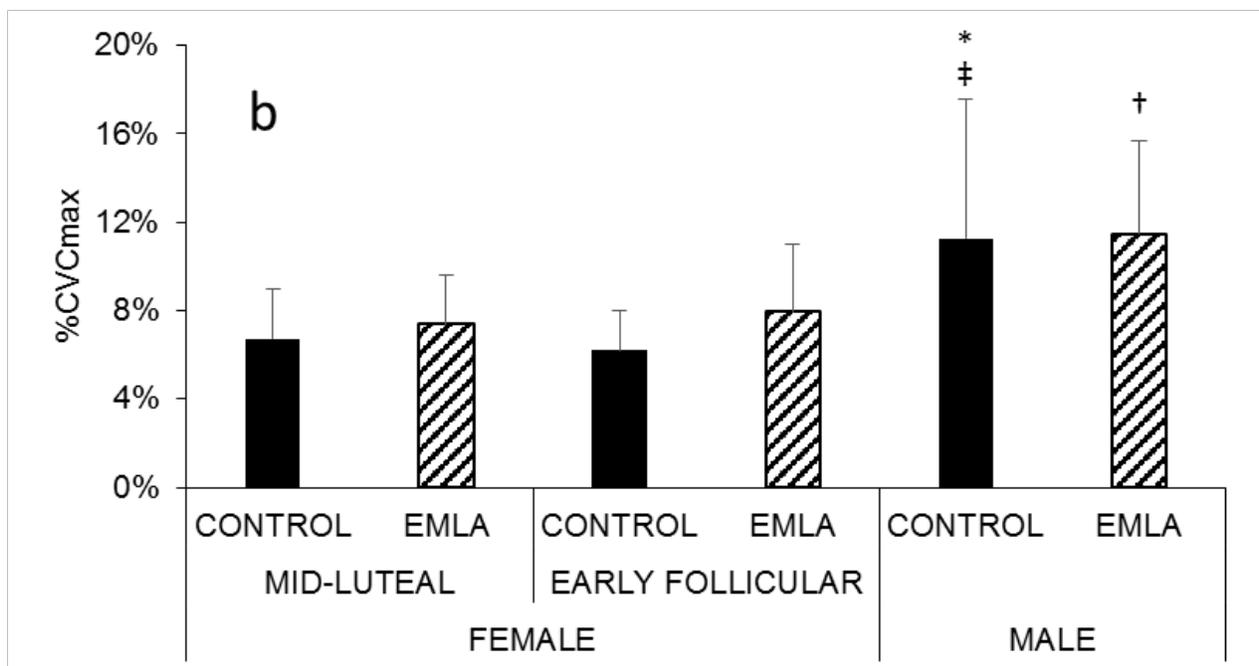
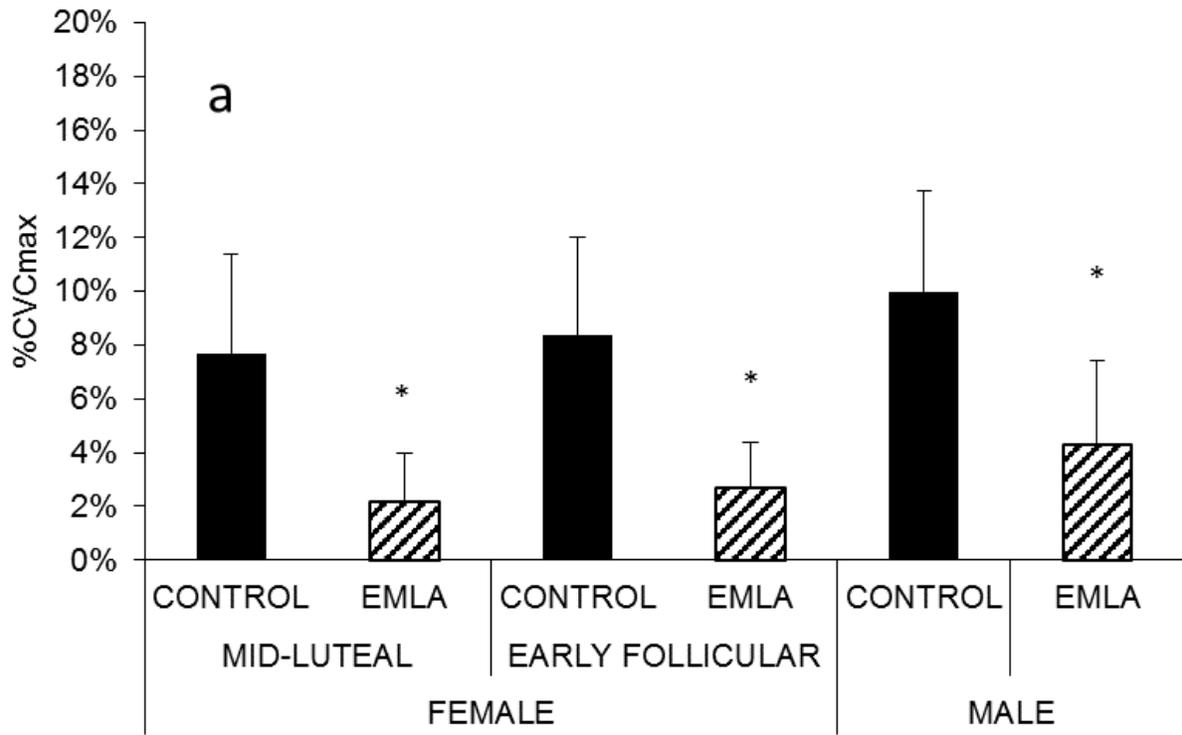
**Table 2.** Percent Maximal Cutaneous Vascular Conductance Values

| Limb and Time Point               | Sex    | Phase            | Treatment | %CVC    | SD     |
|-----------------------------------|--------|------------------|-----------|---------|--------|
| Forearm<br>Baseline               | FEMALE | MID-LUTEAL       | CONTROL   | 7.66%   | 3.70%  |
|                                   |        |                  | EMLA      | 2.18%*  | 1.81%  |
|                                   |        | EARLY FOLLICULAR | CONTROL   | 8.36%   | 3.66%  |
|                                   |        |                  | EMLA      | 2.68%*  | 1.70%  |
|                                   | MALE   |                  | CONTROL   | 9.98%   | 3.77%  |
|                                   |        |                  | EMLA      | 4.28%*  | 3.15%  |
| Leg<br>Baseline                   | FEMALE | MID-LUTEAL       | CONTROL   | 6.72%   | 2.28%  |
|                                   |        |                  | EMLA      | 7.40%   | 2.19%  |
|                                   |        | EARLY FOLLICULAR | CONTROL   | 6.20%   | 1.76%  |
|                                   |        |                  | EMLA      | 7.93%   | 3.06%  |
|                                   | MALE   |                  | CONTROL   | 11.25%  | 6.29%  |
|                                   |        |                  | EMLA      | 11.45%  | 4.21%  |
| Forearm<br>Rapid Initial Response | FEMALE | MID-LUTEAL       | CONTROL   | 74.32%  | 9.09%  |
|                                   |        |                  | EMLA      | 49.72%* | 18.59% |
|                                   |        | EARLY FOLLICULAR | CONTROL   | 78.16%  | 5.85%  |
|                                   |        |                  | EMLA      | 52.66%* | 16.35% |
|                                   | MALE   |                  | CONTROL   | 74.90%  | 10.07% |
|                                   |        |                  | EMLA      | 58.36%* | 17.00% |
| Leg<br>Rapid Initial Response     | FEMALE | MID-LUTEAL       | CONTROL   | 66.33%  | 14.53% |
|                                   |        |                  | EMLA      | 45.10%* | 14.73% |
|                                   |        | EARLY FOLLICULAR | CONTROL   | 64.50%  | 10.97% |
|                                   |        |                  | EMLA      | 50.10%  | 21.52% |
|                                   | MALE   |                  | CONTROL   | 63.65%  | 10.06% |
|                                   |        |                  | EMLA      | 53.71%  | 9.44%  |
| Forearm<br>Sustained Response     | FEMALE | MID-LUTEAL       | CONTROL   | 87.89%  | 8.82%  |
|                                   |        |                  | EMLA      | 87.55%  | 8.04%  |
|                                   |        | EARLY FOLLICULAR | CONTROL   | 90.24%  | 3.62%  |
|                                   |        |                  | EMLA      | 88.32%  | 5.73%  |
|                                   | MALE   |                  | CONTROL   | 87.51%  | 6.40%  |
|                                   |        |                  | EMLA      | 84.24%  | 5.90%  |

Phase = phase of the menstrual cycle; %CVC = Percentage of maximal cutaneous vascular conductance; \* indicates that  $p < 0.05$  when compared to control sites.

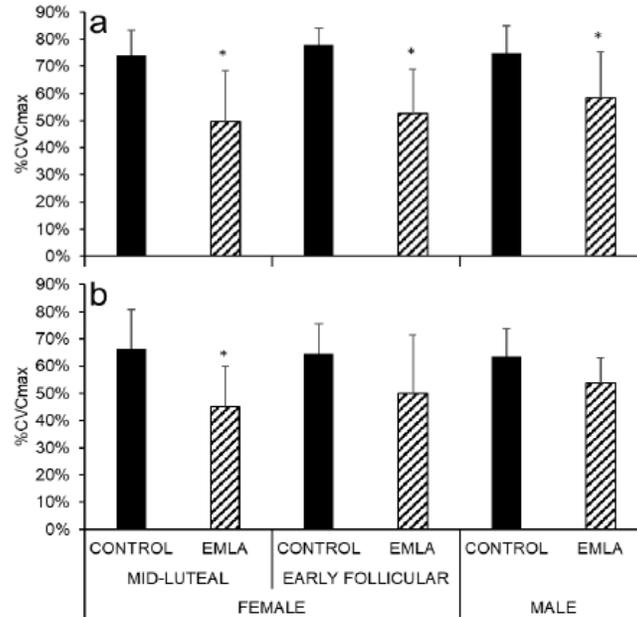


**Figure 1.** Representative skin blood flow tracings from one female in the mid-luteal phase (a), one female in the early follicular phase (b), and one male (c) showing the thermoneutral baseline, rapid cutaneous thermal hyperemia, and sustained vasodilation phases of local heating.



**Figure 2.** Baseline (thermoneutral, 33 °C) skin blood flow in the forearm (a) for EMLA and control sites for all participants. \*  $p < 0.05$  vs control. Baseline (thermoneutral, 33 °C) skin blood flow in the leg (b) for EMLA and control sites in all participants. †  $p < 0.05$  vs control site in mid-luteal females. ‡  $p < 0.05$  vs control site in early follicular females. \*  $p < 0.05$  vs control site in mid-luteal females.

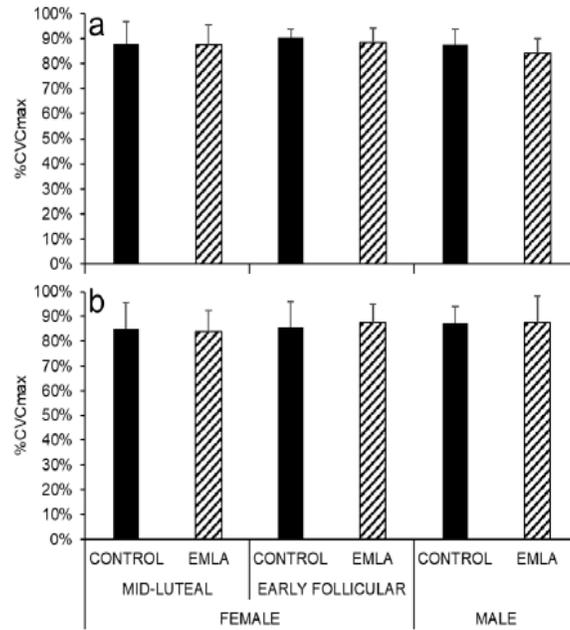
**Rapid Initial Vasodilation:** During the rapid initial vasodilation phase of the skin blood flow response to local heating, skin blood flow was significantly reduced in the EMLA-treated forearm sites in all groups when compared to the respective forearm control sites ( $p < .0001$  for early follicular and mid-luteal phases;  $p = .017$  for males). (Figure 3a). However, in the leg, only mid-luteal females exhibited a significant skin blood flow reduction in the EMLA-treated sites as compared to control ( $p = .001$ ; Figure 3b).



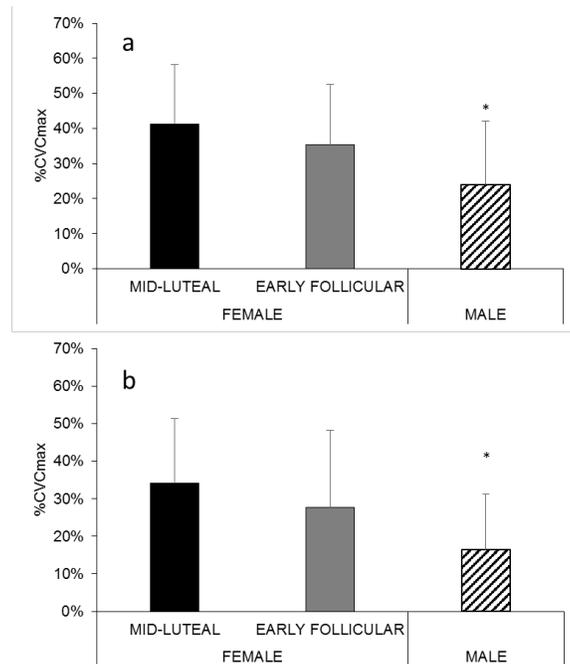
**Figure 3.** Rapid initial forearm (a) and leg (b) skin vasodilation during local heating for EMLA and control sites in all participants. \*  $p < .05$  vs control.

**Sustained Vasodilation:** The sustained vasodilation phase of the skin blood flow response to local heating elicited comparable responses in the EMLA-treated and control sites of the forearm (Figure 4a) and the leg (Figure 4b) for all groups.

**Sensory Nerves and Rapid Cutaneous Vasodilation:** The contribution of sensory nerves to rapid cutaneous thermal hyperemia in the forearm (Figure 5a) of mid-luteal females ( $41 \pm 17$  %CVCmax), but not early follicular females ( $35 \pm 17$  %CVCmax), was significantly higher than males ( $24 \pm 18$  %CVCmax;  $p = .036$  vs mid-luteal females). This trend was also observed in the leg (Figure 5b), where, mid-luteal females ( $34 \pm 17$  %CVCmax), but not early follicular females ( $28 \pm 21$  %CVCmax), exhibited a significantly greater contribution of sensory nerves than males ( $16 \pm 15$  %CVCmax) during the rapid initial vasodilation phase of the thermal hyperemic response ( $p = .026$  for mid-luteal females vs males).



**Figure 4.** Sustained cutaneous vasodilation during local heating in the forearm (a) and leg (b) EMLA and control sites in all participants.



**Figure 5.** The contribution of sensory nerves to rapid cutaneous thermal hyperemia in the forearm (a) and leg (b) of all participants. \*  $p < .05$  vs mid-luteal females.

## DISCUSSION

The purpose of this study was to determine possible sex differences in the contribution of sensory nerves in response to a local heat stimulus. We observed greater contribution of sensory nerves to rapid cutaneous thermal hyperemia in female participants who were in the mid-luteal phase of the menstrual cycle as compared to men. However, these sex differences were not detected when female participants were assessed during the early follicular phase of the menstrual cycle. Furthermore, there were no detectable differences in the contribution of sensory nerves to the sustained hyperemic response between the two hormone phases of the female participants.

The results of this study indicate that the contribution of sensory nerves to rapid cutaneous thermal hyperemia is not uniform across the sexes. In order to control for the influence of sex hormones on cutaneous blood flow mechanisms, previous studies have tested female participants during the early follicular phase (within six days from the start of menstruation) of the menstrual cycle, when estrogen and progesterone are at their lowest levels. However, females are only in this phase for approximately 25% of their reproductive lives, and this method fails to properly represent physiological responses during the remainder of the menstrual cycle (6). Therefore, in this study, we also tested female participants during the mid-luteal phase to examine the potential influence of high levels of progesterone and relatively elevated levels of estrogen. Our findings did not support the notion that sensory nerve involvement during rapid cutaneous thermal hyperemia is modulated by reproductive hormone differences throughout the menstrual cycle.

The absolute magnitude of the initial (2) and sustained (7) cutaneous vasodilation provoked by a local heat stimulus has been shown to be significantly augmented by elevated estrogen and progesterone levels. However, no study until now has investigated the relative contribution of sensory nerves and the potential effect of sex hormones on rapid cutaneous thermal hyperemia. Moderately high levels of estrogen and near-maximal levels of progesterone have been observed during the mid-luteal phase of the menstrual cycle and may have had an influence on the sex differences in this study. Calcitonin gene-related peptide (1) and substance P (13) are potent vasodilating agents, thought to be released in an axon reflex fashion from local sensory nerves within the skin when subjected to a local thermal stimulus (38). Estrogen and/or progesterone administration has been shown to increase substance P and calcitonin gene-related peptide synthesis in sensory neurons (11, 30, 31). Therefore, it is possible that elevated sex hormones in the females who were in the mid-luteal phase of the menstrual cycle in our study stimulated increased substance P and calcitonin gene-related peptide production and release from sensory nerves, thereby explaining the augmented contribution of sensory nerves to the rapid thermal hyperemic response.

Local control of skin blood flow aids in the maintenance of a myriad of homeostatic mechanisms within the body (10). Due to the importance of sensory nerves in maintaining local cutaneous homeostasis (39) and the preponderance of evidence for sex- and reproductive hormone-related differences in local skin blood flow control (7, 21, 35), the findings of this study provide unique

insight into sensory nerve-mediated skin blood flow responses between sexes and between two reproductive hormone phases in female participants. A possible explanation for the sex differences detected in this study could rest in the contribution of nitric oxide (NO) to the rapid thermal hyperemic response in the skin. Previous researchers have determined that females exhibited less dependence on nitric oxide for sustained cutaneous vasodilation during local heating (35). Thus, the male participants in our study may have achieved the same absolute level of rapid cutaneous vasodilation during local heating by relying more heavily on NO-dependent mechanisms rather than sensory nerves, but this remains to be directly tested.

Limitations of this study include a relatively small sample size, and the fact that serum concentrations of reproductive hormones were not measured. Although we tested participants during the self-reported early follicular and mid-luteal phases of the menstrual cycle, we cannot confirm circulating levels of estrogen or progesterone. Approximately half of the female participants were taking oral contraceptive medication, which artificially alters hormonal balances. We cannot exclude the possibility that this may have skewed some of the reported observations. Future research is recommended to more clearly elucidate the influence of various contraceptive methods on thermoregulation.

The present study suggests women who are in the mid-luteal phase of the menstrual cycle exhibit a greater contribution of sensory nerves to the thermal hyperemic response than males. However, there were no differences detected between females who were in the early follicular phase of the menstrual cycle and males. It is theorized that the mechanism underlying these observations are related to calcitonin gene-related peptide (11, 30) and substance P (31) synthesis in sensory neurons. Given that women have a higher prevalence rate of rare vascular skin conditions (e.g. Erythromelalgia and Raynaud's phenomenon), where sensory dysfunction plays a role, these results may be valuable for improving our understanding of the pathophysiology of such conditions. Future mechanistic skin blood flow studies should consider sex differences in the contribution of sensory nerves during rapid cutaneous thermal hyperemia. The sensory nerve-mediated rapid increase in skin blood flow seen during a local thermal perturbation is part of the integrated response to maintain local tissue homeostasis. Females in the mid-luteal phase of the menstrual cycle, where estrogen and progesterone are elevated, exhibited augmented sensory nerve involvement during rapid cutaneous thermal hyperemia when compared to females in the early follicular phase of the menstrual cycle (low levels estrogen and progesterone) and males. Thus, our data indicate that the mechanisms by which males and females regulate local skin temperature differs, but only when females are in the mid-luteal phase of the menstrual cycle.

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