Lack of limb or sex differences in the cutaneous vascular responses to exogenous norepinephrine

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Submitted 30 June 2014; accepted in final form 21 October 2014

Greaney JL, Stanhewicz AE, Kenney WL, Alexander LM. Lack of limb or sex differences in the cutaneous vascular responses to exogenous norepinephrine. J Appl Physiol 117: 1417–1423, 2014. First published October 23, 2014; doi:10.1152/japplphysiol.00575.2014.—The cutaneous circulation is used to examine vascular adrenergic function in clinical populations; however, limited studies have examined whether there are regional limb and sex differences in microvascular adrenergic responsiveness. We hypothesized that cutaneous adrenergic responsiveness would be greater in the leg compared with the arm and that these regional limb differences would be blunted in young women (protocol 1). We further hypothesized that cutaneous vasoconstriction to exogenous norepinephrine (NE) during β-adrenergic receptor antagonism would be augmented in young women (protocol 2). In protocol 1, one microdialysis fiber was placed in the skin of the calf and the ventral forearm in 20 healthy young adults (11 men and 9 women). Laser-Doppler flowmetry was used to measure red blood cell flux in response to graded intradermal microdialysis infusions of NE (10⁻¹² to 10⁻² M). In protocol 2, three microdialysis fibers were placed in the forearm (6 men and 8 women) for the local perfusion of lactated Ringer (control), 5 mM yohimbine (α-adrenergic receptor antagonist), or 2 mM propranolol (β-adrenergic receptor antagonist) during concurrent infusions of NE (10⁻¹² to 10⁻² M). There were no limb or sex differences in cutaneous adrenergic responsiveness (logEC₅₀) to exogenous NE. During α-adrenergic receptor blockade, women had greater exogenous NE-induced cutaneous vasodilatation at the lowest doses of NE (10⁻¹² to 10⁻¹⁰ M). Collectively, these data indicate that there are no limb or sex differences in cutaneous adrenergic responsiveness to exogenous NE; however, young women have a greater β-adrenergic receptor-mediated component of the vascular responsiveness to exogenous NE.

The human cutaneous circulation is increasingly being used to examine mechanisms underlying vascular dysfunction in clinical populations. The cutaneous circulation is reflexively controlled, in part, by an adrenergic vasoconstrictor branch of the sympathetic nervous system and, at rest, is under tonic adrenergic control (16, 18). Studies investigating cutaneous microvascular dysfunction in pathological conditions have revealed dysregulation in adrenergic signaling pathways similar to that which occurs throughout the systemic vasculature (16, 18). Importantly, the cutaneous circulation is on the efferent arm of both thermoregulatory and nonthermoregulatory reflex control (e.g., baroreflex) (2, 8), and deficits in peripheral vasoconstrictor responsiveness to adrenergic stimuli may contribute to a reduced ability to appropriately respond to challenges to the cardiovascular system, such as orthostasis (2, 5, 25, 35, 36).

In muscle, vascular responsiveness to adrenergic stimuli is greater in the legs (24), likely because greater sympathetic tone may be required in the leg vasculature to maintain proper circulatory function. The majority of studies examining cutaneous adrenergic control mechanisms, in health and in disease, have been performed in the forearm microvasculature (27, 33, 36, 39). The only previous investigation of limb-specific differences in cutaneous adrenergic responsiveness demonstrated greater cutaneous vasoconstriction to exogenous norepinephrine (NE) in the legs than in the arms, likely as a result of increased α-adrenergic receptor reactivity (41); however, this study did not account for the potential impact of sex differences in cutaneous vascular responsiveness to exogenous adrenergic stimuli. Importantly, adrenergic sensitivity in the muscle vasculature is less in women than in men (12, 21). In addition, women exhibit greater β-adrenergic-mediated vasodilation compared with men, demonstrated by blunted forearm vasoconstrictor responses to NE (14, 21). Moreover, differential regulation of cutaneous adrenergic responsiveness has been noted in young women with high and low orthostatic tolerance and appears to be modulated by female sex hormones (36). However, potential sex differences in cutaneous adrenergic control are not currently well understood. Therefore, because deficits in cutaneous adrenergic responsiveness have been documented in several clinical populations, including primary aging (33, 39) and essential hypertension (27), understanding potential limb- and sex-related differences in sympathetic function in the cutaneous microcirculation is clinically relevant.

Given this background, as well as the increasingly widespread use of the cutaneous circulation to examine vascular dysfunction in clinical populations, a more thorough understanding of potential limb and sex differences in cutaneous adrenergic responsiveness is warranted. Therefore, the purpose of the present investigation was to examine limb and sex differences in cutaneous microvascular responsiveness to an adrenergic stimulus (exogenous NE). We tested the hypothesis that NE-mediated cutaneous vasoconstriction would be greater in the leg compared with the arm and that these regional differences would be blunted in young women. We further hypothesized that β-adrenergic receptor antagonism would enhance cutaneous vasoconstriction to exogenous NE and that this vasoconstrictor response would be augmented in young women.

METHODS

Subjects. All experimental procedures and protocols were approved by The Pennsylvania State University Institutional Review Board. Verbal and written consent were obtained voluntarily from all subjects before participation. The study conformed to the standards outlined in the Declaration of Helsinki. Twenty young adults (23 ± 1 yr; 11 men and 9 women) participated in the study. Subjects were screened for neurological, cardiovascular, and dermatological diseases and underwent a complete medical screening including a resting 12-lead electrocardiogram, physical examination, and 12-h fasting blood chemis-
try (Quest Diagnostics, Pittsburgh, PA). All subjects were normotensive, nondiabetic, normally active, and not taking over-the-counter or prescription medications or supplements with primary or secondary cardiovascular effects (e.g., statins, antihypertensives, anticoagulants, antidepressants, etc.). Subjects were nonobese (body mass index < 30 kg/m²) and did not use tobacco products.

Women taking hormonal contraceptives were excluded from the study. All women were normally menstruating and were tested during the early follicular phase (days 1–7) of their menstrual cycle. Before all experimental sessions, subjects abstained from caffeinated and alcoholic beverages for 12 h and strenuous physical activity for 24 h.

Protocol 1: cutaneous adrenergic responsiveness. All protocols were performed in a thermoneutral laboratory with the subjects in a supine position, with the experimental arm and leg supported at heart level. With the use of sterile technique and after the skin was temporarily anesthetized with ice (15), one intradermal microdialysis fiber (10 mm, 20 kDa cutoff membrane, MD 2000; Bioanalytical Systems, West Lafayette, IN) was placed in the dermal layer of the ventral forearm and the calf and perfused with lactated Ringer solution (2 μl/min; Bee Hive controller and Baby Bee microinfusion pumps; Bioanalytical Systems) for 60–90 min after placement to allow for the resolution of local hyperemia. NE (Sigma, St. Louis, MO) was mixed just before use and dissolved in lactated Ringer solution with 1 mg/ml (5.7 mM) ascorbic acid (Sigma) as a preservative (28, 33). Prolonged infusion of NE at higher concentrations induces uncoupling and desensitization of G protein receptors (1, 4, 26). Ascorbic acid was therefore added to the NE dilutions to act as a preservative, extending the half-life from 8.5 min to over 180 min (20). Although local ascorbate administration has been shown to inhibit the adrenergic vasoconstrictor response to NE-induced hyperemia in human skin (40), in pilot testing for this study, the perfusion of ascorbic acid alone did not induce a cutaneous vascular response. Therefore, it is unlikely that the addition of ascorbic acid to NE contributed to the observed responses in this study. Solutions were filtered using syringe microfilters (Acrodisc; Pall, Ann Arbor, MI) and wrapped in foil to prevent degradation due to light exposure.

Red blood cell flux, an index of skin blood flow, was measured by laser-Doppler flowmeter probes throughout the protocol. The probes were placed in a local heater (Moor Instruments, Axminster, UK), which was affixed to the skin directly above each microdialysis membrane. Temperature of the local heater was clamped at 33°C for the duration of the protocol to ensure that changes in skin blood flow were due to the exogenous infusion of vasoactive agents. Brachial artery blood pressure was measured on the contralateral arm every 5 min (Cardiocap 5, GE Healthcare) throughout the protocol.

After the recovery period from probe placement, baseline measurements were made for 20 min while lactated Ringer solution was perfused through each microdialysis fiber. Thereafter, increasing doses of NE were continuously infused for 5 min (10⁻¹², 10⁻¹¹, 10⁻¹⁰, 10⁻⁹, 10⁻⁸, 10⁻⁷, 10⁻⁶, 10⁻⁵, 10⁻⁴, 10⁻³, and 10⁻² M), as previously described (39).

Protocol 2: contribution of α- and β-receptors to NE-induced cutaneous vasoconstriction. Perfusion of the lowest doses of NE (10⁻¹³ through 10⁻¹² M) in protocol 1 caused a highly reproducible vasodilation in both the forearm and calf of men and women. Therefore, for an ancillary aim of this study, protocol 2 was developed to begin to probe the relative contribution of α- and β-adrenergic receptors, and potential sex differences, to the cutaneous vascular responses to exogenous NE. For this substudy, we hypothesized that β-adrenergic receptor antagonism would enhance cutaneous vasoconstriction at all concentrations of the NE dose-response protocol and that this vasoconstrictor response would be augmented in young women.

Because there were no limb or sex differences in cutaneous adrenergic responsiveness (see RESULTS), this protocol was performed in the forearm of a subset of men (n = 6; 24 ± 1 yr) and women (n = 8; 23 ± 1 yr) who previously participated in protocol 1. After the skin was temporarily anesthetized with ice (15), three intradermal microdialysis fibers were placed in the ventral forearm skin for the local delivery of l lactated Ringer (control), 2) 5 mM yohimbine (Sigma) for local blockade of α-adrenergic receptors (34), and 3) 2 mM propranolol (Sigma) for local blockade of β-adrenergic receptors (7, 34). Although yohimbine is traditionally employed as a selective α₂-adrenergic receptor antagonist, it antagonizes both α₁- and α₂-adrenergic receptors at the concentration used in this study (13, 30–32). All pharmacological inhibitors were mixed just before use, dissolved in lactated Ringer solution, filtered using syringe microfilters, and wrapped in foil to prevent degradation due to light exposure. Following placement of the fibers, inhibitors were perfused through the fibers (2 μl/min; Bee Hive controller and Baby Bee microinfusion pumps; Bioanalytical Systems) during the resolution of the fiber insertion trauma (~60–90 min).

Similar to protocol 1, temperature of the local heaters was clamped at 33°C throughout the protocol. After the recovery period from probe placement, baseline measurements were made for 20 min while inhibitors or lactated Ringer solution were perfused through each microdialysis fiber. Following baseline, increasing doses of NE were continuously infused for 5 min (10⁻¹², 10⁻¹¹, 10⁻¹⁰, 10⁻⁹, 10⁻⁸, 10⁻⁷, 10⁻⁶, 10⁻⁵, 10⁻⁴, 10⁻³, 10⁻² M), as described above. A 5-min infusion of the inhibitors or lactated Ringer was used between each dose of NE.

Data acquisition and statistical analysis. Data were collected at 40 Hz (Powerlab and LabChart; ADInstruments, Bella Vista, NSW, Australia). Cutaneous vascular conductance (CVC) was calculated as red blood cell flux divided by mean arterial pressure. CVC data were normalized and expressed as a percentage of baseline (%CVCbase; protocol 1) or absolute change from baseline (ΔCVCbase; protocol 2). CVC was averaged over the last minute of each NE dose.

Subject characteristics were compared using unpaired t-tests (SPSS 19.0). For protocol 1, NE doses were transformed to logarithmic concentrations, and CVC was normalized such that baseline CVC = 100% (i.e., pre-NE). Sigmodial dose-response curves with variable slope were generated using four-parameter nonlinear regression modeling (36–38), with constraints set for the top (100) to best fit parameters of the model (Prism v. 5.0, GraphPad, San Diego, CA). Responsiveness to NE was determined by the effective concentration causing 50% of the maximal response (logEC₅₀) and the extent of maximal vasoconstrictor capacity. The differences within anatomical region between sexes were analyzed using an F-test for repeated-measures comparisons (Prism v. 5.0) (36, 37), which takes into account all points over the entire curve as opposed to each specific dose (6). For protocol 2, the primary interest was the vasoconstrictor response at a given concentration of NE, in addition to the maximal NE-induced vasoconstricting capability. Therefore, these data were analyzed using a two-way repeated-measures ANOVA, followed by post hoc testing with Bonferroni corrections when warranted (SPSS 19.0). Results are reported as means ± SE, and the α-level was set at P < 0.05.

RESULTS

NE-induced cutaneous vasoconstriction. Subject characteristics are presented in Table 1. There were no sex differences in body mass index or blood biochemistry. Resting blood pressure was lower in women (P < 0.05). Baseline CVC was not different between sexes or between limbs in protocol 1 (P > 0.05).

NE dose-response curves for each limb in men and women are presented in Fig. 1. There were no differences in cutaneous adrenergic responsiveness to exogenous NE between limbs in either men or women (Table 2 and Fig. 1). There was also no regional limb difference in the maximal vasoconstrictor re-
sponse to exogenous NE in either men or women (Table 2). Furthermore, there were no sex differences in the parameters of the NE dose-response curves (Table 2 and Fig. 1).

**Contribution of α- and β-receptors to NE-induced cutaneous vasoconstriction.** As depicted in Fig. 1, perfusion of the lowest doses of NE (10^{-12} - 10^{-8} M) caused an unexpected, but highly reproducible, vasodilation in both limbs in men and women. Baseline CVC values were different between drug treatments in men and women. Baseline CVC values were different between the NE dose-response curves (Table 2 and Fig. 1).

The primary finding of the current study was that there is no difference in the cutaneous vasconstrictor response to exogenous NE between the arm and leg. In addition, there are no sex differences in exogenous NE-mediated cutaneous vasoconstriction in either limb. It appears both α- and β-adrenergic receptors have an important functional role in the human cutaneous vasculature and differentially mediate the microcirculatory response to exogenous NE. Furthermore, young women have a greater β-adrenergic receptor-mediated component of the vascular responsiveness to low concentrations of exogenous NE. Collectively, these data indicate that there are no limb or sex differences in cutaneous adrenergic responsiveness and further suggest an important role for sex differences in adrenergic receptor subtypes mediating exogenous NE-induced cutaneous vascular responses.

**DISCUSSION**

Regional limb differences in the vascular responses to adrenergic stimuli have been documented in the human skeletal muscle arterial vasculature (24). Specifically, phenylephrine-induced decreases in vascular conductance were greater in the calf compared with the forearm, and the authors speculate that greater adrenergic sensitivity in the legs is a consequence of repeated exposure to both hemodynamic and hydrostatic pressure gradients when upright (24). Because orthostatic stress elicits differential regional vascular responses (10, 11) and given the important role of the cutaneous vasculature in the peripheral vasconstrictor response to orthostatic challenge (2,

![Fig. 1. Group summary data for exogenous norepinephrine (NE)-induced cutaneous vasconstriction in the forearm (○) and calf (△) of men (A) and women (B). There were no regional limb or sex differences in cutaneous adrenergic responsiveness. CVCbase: baseline cutaneous vascular conductance.](image-url)

**Table 1. Subject characteristics**

<table>
<thead>
<tr>
<th>Baseline Characteristic</th>
<th>Men</th>
<th>Women</th>
</tr>
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<tbody>
<tr>
<td>Age, yr</td>
<td>23 ± 1</td>
<td>23 ± 1</td>
</tr>
<tr>
<td>Height, cm</td>
<td>180 ± 3</td>
<td>165 ± 2*</td>
</tr>
<tr>
<td>Mass, kg</td>
<td>79 ± 4</td>
<td>63 ± 3*</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>24.4 ± 1.3</td>
<td>23.4 ± 0.7</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>121 ± 3</td>
<td>108 ± 4*</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>74 ± 2</td>
<td>68 ± 2</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>63 ± 3</td>
<td>59 ± 2</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>5.3 ± 0.1</td>
<td>5.3 ± 0.1</td>
</tr>
<tr>
<td>Fasting total cholesterol, mg/dl</td>
<td>161.1 ± 11.4</td>
<td>187.1 ± 9.6</td>
</tr>
<tr>
<td>Fasting HDL, mg/dl</td>
<td>55.5 ± 4.6</td>
<td>69.3 ± 5.1</td>
</tr>
<tr>
<td>Fasting LDL, mg/dl</td>
<td>88.9 ± 10.1</td>
<td>97.8 ± 6.4</td>
</tr>
<tr>
<td>Fasting triglycerides, mg/dl</td>
<td>83.5 ± 10.5</td>
<td>73.0 ± 7.0</td>
</tr>
<tr>
<td>Basal CVC</td>
<td>0.21 ± 0.02</td>
<td>0.27 ± 0.09</td>
</tr>
<tr>
<td>Forearm</td>
<td>0.25 ± 0.04</td>
<td>0.30 ± 0.07</td>
</tr>
<tr>
<td>Calf</td>
<td></td>
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Values are means ± SE. BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; CVC, cutaneous vascular conductance. *P < 0.05 vs. men.

**Table 2. Modeling parameters for norepinephrine-mediated cutaneous vasoconstriction in the forearm and calf of men and women**

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Forearm</td>
<td>Calf</td>
</tr>
<tr>
<td>Minimum</td>
<td>38.6 ± 9.9</td>
<td>33.8 ± 5.1</td>
</tr>
<tr>
<td>LogEC_{50}</td>
<td>-5.73 ± 0.57</td>
<td>-6.31 ± 0.25</td>
</tr>
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Values are means ± SE.
suggest that this is due to greater through the use of selective adrenergic receptor agonists, soconstrictor response to exogenous NE in the calf and, sponsiveness, the authors report an augmented cutaneous va-

The results of the present study suggest that limb differences in cutaneous vasoconstrictor responses to exogenous NE may not fully account for these previously reported regional differences in microvascular function. As such, further investigation regarding potential limb differences in the contribution of sympathetic neurotransmit-
tors to cutaneous vasodilatory function during thermal hyper-

dilation was observed (10 

Interestingly, there appear to be regional differences in the local vasodilatory responses of the cutaneous vasculature during local skin warming (9, 29). Specifically, the axon reflex, which is dependent on both sensory and sympathetic nerves (22), appears to be lower in the leg compared with the arm (9). NE contributes to this initial vasodilatory response to local heating (17, 19), and the authors of these studies speculate that a blunted initial peak response (i.e., axon reflex) may be suggestive of increased tonic sympathetic vasoconstriction in the lower legs (9). However, the results of the present study suggest that limb differences in cutaneous vasoconstrictor responses to exogenous NE may not fully account for these previously reported regional differences in microvascular function. As such, further investigation regarding potential limb differences in the contribution of sympathetic neurotransmit-
tors to cutaneous vasodilatory function during thermal hyper-

25, 35), it is therefore plausible that cutaneous adrenergic responsiveness may also be greater in the lower leg. However, perhaps surprisingly, we found no evidence for limb differences in the cutaneous vasoconstrictor responses to exogenous NE. Indeed, the sensitivity to adrenergic stimuli, quantified as the logEC50 of the NE dose-response curves, was remarkably similar between the forearm and calf in both men and women. Furthermore, there were no differences in the exogenous NE-induced maximal vasoconstrictor responses between limbs. Taken together, the results of the present study suggest that cutaneous adrenergic responsiveness is similar in the forearm and calf of healthy young adults. This lack of a regional difference in cutaneous adrenergic sensitivity may be due to the low pressure and compliant nature that are characteristic of the human cutaneous circulation. In the only previous study to examine limb-specific differences in cutaneous adrenergic re-

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determination (41) and the present investigation is not clear, methodological differences such as differing NE mixing and dilution techniques, study design (the use of agonists compared with the use of antagonists in the current study), and mathematical modeling and statistical analyses may have contrib-

Antagonism of

Fig. 2. Group summary data for exogenous NE-induced cutaneous vasoconstriction during β-adrenergic receptor antagonism [NE + propranolol (P); A] and during α-adrenergic receptor antagonism [NE + yohimbine (Y); B]. Antagonism of β-receptors enhanced vasoconstriction, whereas antagonism of α-adrenergic receptors blunted NE-induced cutaneous vasoconstriction. *P < 0.05 vs. NE.

Fig. 3. Group summary data for exogenous NE-induced cutaneous vasoconstriction during β-adrenergic (A) and α-adrenergic (B) receptor antagonism in a subset of men (n = 6; ●) and women (n = 8; ○) at the doses of NE during which cutaneous vasodilation was observed (10−12 through 10−7 M). There were no sex differences in the vasoconstrictor response during β-adrenergic receptor blockade; however, during α-adrenergic receptor blockade, women had greater NE-mediated cutaneous vasodilation at the lowest doses of NE (10−12 through 10−10 M) compared with men. *P < 0.05 vs. men; †P = 0.059 vs. men.
This study was also designed to examine potential sex differences in cutaneous adrenergic responsiveness. Importantly, adrenergic sensitivity of the resistance vasculature is less in women compared with men (12, 21). For instance, women have a blunted vasoconstrictor response to brachial artery infusion of phenylephrine compared with men, whereas there were no sex differences in the response to reflex vasoconstriction or to intra-arterial tyramine (12), suggesting sex differences in adrenergic receptor sensitivity/density and not in the responsiveness to neurally mediated stimuli. Sex differences in adrenergic responsiveness are further substantiated by reduced NE-mediated vasoconstriction in the forearm of women compared with men (14, 21). However, to date, limited studies have examined sex differences in the responsiveness of the cutaneous microvasculature to exogenous NE. Our results in protocol 1 demonstrate that exogenous NE-induced cutaneous vasoconstriction was not different between men and women, in either the forearm or the calf. While these findings were perhaps surprising in light of the evidence demonstrating clear sex differences in adrenergic sensitivity in the resistance vasculature (12, 14, 21), the present results instead indicate similar cutaneous vasoconstrictor responsiveness to exogenous NE between sexes. It is important to note that all of the women who participated in the current study were normally menstruating and not using hormonal contraceptives and were tested during the early follicular phase of the menstrual cycle, when female reproductive hormones are at their lowest circulating concentrations. Interestingly, there is evidence that women in the high-hormone phase of oral contraceptives have the same ratio of NE-to-cotransmitter-mediated reflex cutaneous vasoconstriction as men but that women in the low-hormone placebo phase tend to rely almost entirely on NE to effect the same magnitude of vasoconstriction (31). However, when normally menstruating women were tested during the early follicular phase of their menstrual cycle, there was no difference in the magnitude of reflex cutaneous vasoconstriction or the individual contributions of sympathetic cotransmitters compared with men (34), and although methodological differences (i.e., physiological vs. pharmacologically-induced cutaneous vasoconstriction) must be considered, the results of the present investigation extend these previous findings and likewise demonstrate no sex differences in exogenous NE-mediated cutaneous vasoconstriction.

Importantly, the present investigation used a purposefully wide-dosage range of NE in an effort to more precisely detect any limb or sex differences in cutaneous vasoconstriction. The lowest concentrations of NE caused an unexpected, but highly reproducible, dilator response. This consistent early dilator portion of the response, which occurred at NE concentrations that are known to elicit reflex vasoconstriction, is essentially absent from our previously published work using a similar protocol (33). Nevertheless, its consistency and magnitude suggests that a genuine physiological event underlies this response. In addition, because blunted adrenergic sensitivity in women may by explained, in part, by increased sensitivity of β-adrenergic receptors balancing the α-adrenergic vasoconstrictor effect of NE (14, 21), an ancillary protocol was developed to begin to probe the relative contribution of adrenergic receptor subtypes, along with potential sex differences, in this response.

Functional β-adrenergic receptors are present in human skin (7), and when stimulated by NE, cutaneous vasodilation occurs. Therefore, to test the contribution of β-adrenergic receptors to the initial vasodilatory response to NE, the dose-response protocol was repeated during concurrent β-adrenergic receptor blockade in a subset of subjects. Nonspecific β-adrenergic receptor blockade completely abolished the early vasodilation in response to exogenous NE and significantly augmented the vasoconstrictor response, confirming an important role for β-adrenergic receptors in mediating cutaneous vascular responsiveness to adrenergic stimuli. Collectively, these findings suggest that β-adrenergic-mediated vasodilation is present in the human cutaneous vasculature and can be stimulated by administration of physiologically relevant concentrations of exogenous NE (10⁻¹² to 10⁻⁶M). In light of the aforementioned findings (14, 21), it is perhaps surprising that in the present study we did not observe any sex differences in the forearm cutaneous vasoconstrictor response to exogenous NE during β-adrenergic receptor blockade, which we interpret as suggesting that there are no sex differences in the functional role of cutaneous α-adrenergic receptors to this response. However, the significant augmentation in cutaneous vasoconstriction to exogenous NE during propranolol infusion in both men and women suggests that β-adrenergic receptor-mediated buffering of exogenous NE-induced vasoconstriction occurs in the skin microcirculation of both sexes.

Interestingly, despite the fact that α-adrenergic receptor blockade during exogenous NE administration did not appear to entirely recapitulate the early vasodilatory response, there were no statistical differences between NE alone and with concurrent α-adrenergic receptor blockade. Furthermore, α-adrenergic receptor blockade completely prevented vasoconstriction at the much higher pharmacological concentrations of NE, likewise substantiating a crucial role for α-adrenergic receptors in mediating the cutaneous vascular responses to exogenous NE in both men and women. However, during nonselective α-adrenergic receptor antagonism with yohimbine, women had greater exogenous NE-induced cutaneous vasodilation at the lowest physiological doses of NE (10⁻¹² through 10⁻¹⁰ M), suggesting that young women have a greater β-adrenergic component of cutaneous vascular responsiveness to exogenous NE in the forearm compared with young men. These novel findings, which are consistent with those reported using forearm venous occlusion plethysmography (14, 21), further validate the use of the cutaneous circulation as a model with which to study alterations in vascular function in both health and disease.

**Limitations.** It is important to note that nonselective receptor antagonists were used in protocol 2. However, because this protocol was designed only to initially probe the relative contribution of α- and β-adrenergic receptors to the cutaneous vascular responses to exogenous NE, nonspecific antagonists were used. Given the relatively more important role for α₂-adrenergic receptors in the human cutaneous vasculature compared with α₁-adrenergic receptors (3, 23), further studies are necessary to more specifically delineate the contribution of each receptor subtype to NE-induced microvascular responses in both men and women, as well to determine any potential sex differences in the sensitivity of these receptors in the cutaneous vasculature.
Perspectives and significance. In conclusion, the primary novel finding of this study was that there are no limb or sex differences in the cutaneous vascular responses to exogenous NE. These findings were contrary to our initial hypotheses and instead suggest cutaneous adrenergic responsiveness is similar in the forearm and calf of both men and women. Additionally, it appears that both α- and β-adrenergic receptors have an important functional role in mediating the responses of the human cutaneous microvasculature to exogenous NE; however, young women have a greater β-adrenergic component of the cutaneous vascular responsiveness to exogenous NE in the forearm compared with young men. Given the growing use of the cutaneous circulation as a means to probe mechanisms of vascular function in health and in disease, it is important to characterize regional and sex-specific differences in sympathetic control of the cutaneous microvasculature. Collectively, our findings contribute to the growing body of literature characterizing adrenergic function in the human cutaneous vasculature and provide new insights regarding NE-mediated vasoconstriction in the forearm and calf of healthy young men and women.

ACKNOWLEDGMENTS

The time and effort expended by all the volunteer subjects are greatly appreciated. We are grateful for the assistance of Susan Slimak and Jane Pierzga.

GRANTS

This research was supported by National Institutes of Health Grants HL120471-01 (to J. L. Greaney), AG007004-23 (to W. L. Kenney), and HL093-238-04 (to L. M. Alexander).

DISCLOSURES

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

AUTHOR CONTRIBUTIONS


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J Appl Physiol • doi:10.1152/japplphysiol.00575.2014 • www.jappl.org