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Does local heating-induced nitric oxide production attenuate vasoconstrictor responsiveness to lower body negative pressure in human skin?

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Low DA, Shibasaki M, Davis SL, Keller DM, Crandall CG. Does local heating-induced nitric oxide production attenuate vasoconstrictor responsiveness to lower body negative pressure in human skin? *J Appl Physiol* 102: 1839–1843, 2007. First published February 1, 2007; doi:10.1152/jappphysiol.01181.2006.—We tested the hypothesis that local heating-induced nitric oxide (NO) production attenuates cutaneous vasoconstrictor responsiveness. Eleven subjects (6 men, 5 women) had four microdialysis membranes placed in forearm skin. Two membranes were perfused with 10 mM of *N*^G-nitro-L-arginine (L-NAME) and two with Ringer solution (control), and all sites were locally heated to 34°C. Subjects then underwent 5 min of 60-mmHg lower body negative pressure (LBNP). Two sites (a control and an L-NAME site) were then heated to 39°C, while the other two sites were heated to 42°C. At the L-NAME sites, skin blood flow was elevated using 0.75–2 mg/ml of adenosine in the perfusate solution (Adn + L-NAME) to a similar level relative to control sites. Subjects then underwent another 5 min of 60-mmHg LBNP. At 34°C, cutaneous vascular conductance (CVC) decreased (Δ) similarly at both control and L-NAME sites during LBNP ($\Delta 7.9 \pm 3.0$ and $\Delta 3.4 \pm 0.8\%$ maximum, respectively; $P > 0.05$). The reduction in CVC to LBNP was also similar between control and Adn + L-NAME sites at 39°C (control $\Delta 11.4 \pm 2.5$ vs. Adn + L-NAME $\Delta 7.9 \pm 2.0\%$ maximum; $P > 0.05$) and 42°C (control $\Delta 1.9 \pm 2.7$ vs. Adn + L-NAME $\Delta 4.2 \pm 2.7\%$ maximum; $P > 0.05$). However, the decrease in CVC at 42°C, regardless of site, was smaller than at 39°C ($P < 0.05$). These results do not support the hypothesis that local heating-induced NO production attenuates cutaneous vasoconstrictor responsiveness during high levels of LBNP. However, elevated local temperature, per se, attenuates cutaneous vasoconstrictor responsiveness to LBNP, presumably through non-nitric oxide mechanisms.

skin blood flow; nitric oxide; orthostatic stress; cutaneous microdialysis

HEAT STRESS SIGNIFICANTLY reduces orthostatic tolerance in humans (13, 25). Exposure to hyperthermic conditions leads to pronounced increases in skin blood flow, with up to ~50% of cardiac output distributed to the cutaneous circulation (17). Therefore, adequate control of cutaneous vasculature is of primary importance for the maintenance of arterial blood pressure during combined heat and orthostatic stress (8, 18, 20). Sustained local or “direct” heating of skin, such as that which occurs during passive heat exposure, increases cutaneous blood flow due to a direct effect of heat on the skin through nonneural mechanisms (7). Local heating impairs α -adrenergic cutaneous vasoconstrictor responsiveness to exogenous norepinephrine administration (24) and attenuates the reduction in cutaneous vascular conductance (CVC), compared with non-

locally heated conditions, during moderate levels of lower body negative pressure (LBNP) (6). Impaired cutaneous vasoconstrictor responsiveness associated with local heating may be an important component of previously observed heat-induced reductions in orthostatic tolerance in humans (13, 25).

Nitric oxide (NO) is a potent vasodilator that is predominantly responsible for sustained cutaneous vasodilation during local heating (9, 16). Recent work from our laboratory has shown that exogenous NO inhibits sympathetically mediated cutaneous vasoconstriction in response to whole body cold stress (4). Together, these findings suggest that local heating-induced NO production could be responsible for reduced cutaneous vasoconstrictor responsiveness during stimuli such as orthostatic stress. However, in our laboratory’s previous study (4), NO concentrations were increased via exogenous administration of sodium nitroprusside, and it is possible that the concentrations of NO delivered to the skin were higher than what might occur via endogenous release of NO. To that end, it remains unknown whether endogenous NO production associated with local heating attenuates reductions in skin blood flow to vasoconstrictor stimuli. Therefore, the aim of this study was to test the hypothesis that local heating-induced NO production attenuates cutaneous vasoconstrictor responsiveness in human skin. This objective was accomplished by examining cutaneous vasoconstrictor responses during LBNP at locally heated sites with and without NO synthase inhibition.

METHODS

Subjects

Eleven subjects (6 men, 5 women) participated in this study (means \pm SD; age 30 ± 5 yr, height 1.78 ± 0.08 m, weight 74.8 ± 7.8 kg). Subjects were healthy and free from cardiovascular, metabolic, and neurological diseases. Subjects refrained from alcohol and exercise for 24 h and from caffeine for 12 h before the study. Institutional approved written, informed consent was obtained from all participants before enrolling in the study.

Measurements

Each subject was dressed in a two-piece water-perfused tube-lined suit (Med-Eng, Ottawa, Canada) that permitted the control of skin temperature by changing the temperature of the water perfusing the suit. The suit covered the entire body surface with the exception of the hands, face, feet, and one forearm. Mean skin temperature was measured via the electrical average of six thermocouples attached to the skin on the lateral gastrocnemius, anterior quadriceps, lower and upper back, abdomen, and upper chest (19). Heart rate was obtained from an electrocardiogram (HP Patient Monitor, Agilent, Santa Clara,

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CA) interfaced with a cardiometer (CWE, Moore, PA). Intermittent arterial blood pressure was measured from the brachial artery by electrophygmomanometry (SunTech Raleigh, NC). Mean arterial pressure (MAP) was calculated as one-third pulse pressure plus diastolic pressure. Continuous beat-by-beat arterial blood pressure was also recorded using a Finapres device (Finapres, Ohmeda, Louisville, CA). Skin blood flow was measured from the forearm that was not exposed to the tube-lined suit using integrated multifiber laser-Doppler flowmetry (Perimed, North Royalton, OH) which samples from a larger area of skin relative to single-fiber probes. An index of CVC was calculated from the ratio of laser-Doppler flux to MAP. Forearm CVC was expressed as a percentage of maximal cutaneous vasodilation as determined following local administration of 50 mM sodium nitroprusside (SNP) (9) following the completion of all experimental procedures.

Protocol

All experiments were performed in a temperature-controlled laboratory ($26 \pm 1^\circ\text{C}$) in the morning or early afternoon at least 2-h postprandial. After instrumentation, the subject entered the LBNP device. The two-piece water-perfused suit permitted the waist seal of the LBNP device to be sealed directly (at the level of the iliac crest) to the skin, thereby effectively eliminating air leakage at this seal and associated cooling (23). Water at 34°C was perfused through the suit throughout the protocol. The LBNP device was attached to a vacuum source capable of rapidly reducing pressure within the box, controlled with a variable autotransformer. The pressure difference inside the LBNP box and atmosphere was measured with a digital manometer (Sper Scientific, Scottsdale, AZ). Four microdialysis probes were placed in the dermal space of dorsal forearm skin, with each probe positioned at least 2 cm apart. The depth of probe placement was not identified, although similar procedures report a depth of 0.3–1.0 mm (9). The membrane window for each probe was 10 mm. The probes were placed by piercing a 25-gauge needle in the dermal space and then having the needle exit 20–25 mm away from the point of entry. The microdialysis probe was inserted through the lumen of the needle. The needle was then withdrawn, leaving the probe in place. After placement, the probes were perfused with Ringer solution at a rate of 2 $\mu\text{l}/\text{min}$. Heating elements (3-cm-diameter; Perimed, North Royalton, OH) were positioned over each membrane to control local skin temperature. Location of the placement of the heating elements was aided through the use of markings on the polyimide tubing that indicated the center of the membrane portion of the microdialysis probe. Each heating element housed an integrating laser-Doppler flow probe (PF413, Perimed) such that skin blood flow (PF4000, Perimed) was assessed from the same location directly over the microdialysis membrane.

An outline of the experimental protocol is illustrated in Table 1. At least 90 min after microdialysis membrane placement, during which the associated hyperemic response had subsided, local skin temperature at all sites was clamped at 34°C for ~ 15 min. An NO synthase inhibitor [10 mM of N^G -nitro-L-arginine (L-NAME)] was then perfused through two of the microdialysis membranes. The other two membranes continued to be perfused with Ringer solution. After

stable skin blood flow had been established (at least 10 min), the subject was exposed to 60 mmHg of LBNP for 5 min or until the onset of presyncopal symptoms. After a recovery period of ~ 5 min, local temperature was increased to 39°C at one L-NAME and at one control site. The local temperature at the other two sites (one L-NAME and one control site) was increased to 42°C . The location of the sites heated to 39 and 42°C were randomly selected. After the initial axon reflex associated with an increase in local temperature had subsided (~ 15 min), adenosine combined with 10 mM L-NAME was perfused through both membranes that had previously received L-NAME only. This procedure was used to increase skin blood flow at the L-NAME treated sites, predominantly via a non-NO mechanism, to similar levels relative to the control site, given the effects of NO synthase inhibition in attenuating cutaneous vasodilation during local heating (9, 16). Typical doses of adenosine ranged from 0.75 to 2.0 mg/ml. Ringer solution continued to be perfused through the adjacent control sites. Once a plateau in vasodilation at all sites was evident (~ 15 min), the aforementioned LBNP protocol was repeated. After a recovery period of ~ 5 min, while the skin continued to be locally heated, 50 mM SNP were perfused through all membranes for at least 10 min for the determination of maximal cutaneous vasodilation (9).

Data Analysis

Data were sampled at 50 Hz via a data-acquisition system (Biopac System, Santa Barbara, CA). Sixty seconds of data before LBNP (pre-LBNP baseline) and the last 30 s of the 5 min of LBNP were averaged and analyzed using a statistical software package (SigmaStat 3.01, Chicago, IL). If a subject became presyncopal, then last 30 s of LBNP were used for data analysis. The mean skin temperature, blood pressure, and heart rate at baseline and at the end of both LBNP tests were evaluated using a two-way repeated-measures ANOVA (LBNP order and time). Differences in CVC before LBNP between control and L-NAME-treated sites, when local temperature was clamped at 34°C , were evaluated using a paired *t*-test. The magnitude of the subsequent reduction in CVC due to LBNP between these sites was compared using a paired *t*-test. When local temperature was clamped at 39 and 42°C , pre-LBNP CVC and the reduction in CVC due to LBNP were both analyzed via a two-way ANOVA (local temperature and site). All values are reported as means \pm SE. *P* values of <0.05 were considered statistically significant.

RESULTS

Hemodynamic and Mean Skin Temperature Responses to LBNP

Hemodynamic responses to LBNP are presented in Table 2. There was no difference in blood pressure ($F_{1,10} = 1.80$, $P > 0.05$), heart rate ($F_{1,10} = 0.91$, $P > 0.05$), or mean skin temperature ($F_{1,10} = 2.74$, $P > 0.05$) between the first and second LBNP tests. Therefore, averaged data from these LBNP tests are presented in Table 2. Blood pressure significantly reduced during LBNP (-10 ± 1 mmHg; $F_{1,10} = 50.47$, $P <$

Table 1. Schematic illustration of study protocol

Site No.	Local Heating (15 min), $^\circ\text{C}$	Drug Administration (10 min)			Local Heating (15 min), $^\circ\text{C}$	Adn Administration (15 min)			
1	34	Ringer			39	Ringer			
2	34	L-NAME	60-mmHg	Recovery	39	Adn + L-NAME	60-mmHg	Recovery	50 mM SNP
3	34	Ringer	LBNP	(5 min)	42	Ringer	LBNP	(5 min)	administration
4	34	L-NAME	(5 min)		42	Adn+L-NAME	(5 min)		(10 min)

LBNP, lower body negative pressure; Adn, adenosine; SNP, sodium nitroprusside; L-NAME, N^G -nitro-L-arginine.

Table 2. Combined hemodynamic and thermoregulatory responses at baseline before and during both LBNP challenges

	Baseline	-60 mmHg
BP, mmHg	80 ± 2	74 ± 2*
HR, beats/min	60 ± 3	96 ± 5*
T _{sk} , °C	35.4 ± 0.1	35.1 ± 0.1*

Values are means ± SE. BP, blood pressure; HR, heart rate; T_{sk}, mean skin temperature. *P < 0.05 vs. baseline.

0.001), whereas heart rate significantly increased (34 ± 4 beats/min; F_{1,10} = 80.52, P < 0.001). Mean skin temperature showed a very small reduction during LBNP (-0.47 ± 0.08°C; F_{1,9} = 31.75, P < 0.001). One subject became presyncopal during the first LBNP test. For this subject, the second LBNP test was stopped at the same time relative to when the first LBNP was stopped. Two other subjects became presyncopal during their second LBNP test.

Cutaneous Vasoconstrictor Responses to LBNP

Normothermic local temperature. Before LBNP, when local temperature was 34°C, baseline CVC was similar at the control and L-NAME sites (26.6 ± 4.7 vs. 19.8 ± 1.8% maximum; t₁₁ = -1.49, P > 0.05; see Fig. 1). During 60-mmHg LBNP, there was a significant decrease in CVC (F_{1,10} = 9.87, P < 0.01; Fig. 2) at both the control and L-NAME sites (-7.9 ± 3.0 and -3.4 ± 0.8% maximum, respectively) with no difference between these sites (T₁₁ = 1.33, P > 0.05). These changes corresponded to relative decreases in CVC of 20.3 ± 4.7 and 16.6 ± 4.0% for the control and L-NAME sites, respectively, with no difference between these sites (T₁₁ = 0.86, P > 0.05; Fig. 3).

Local heating. Local heating to 39°C increased CVC at the control site to 74.5 ± 4.5% maximum, whereas the combination of 39°C local heating with L-NAME plus adenosine

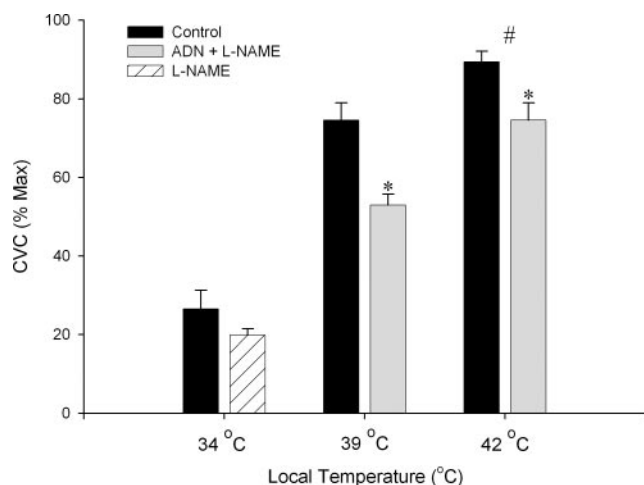


Fig. 1. Mean (± SE) pre-lower body negative pressure cutaneous vascular conductance [CVC; expressed as a percentage of maximum (% max)] at control and N^G-nitro-L-arginine (L-NAME) sites at local temperatures of 34, 39, and 42°C. Adenosine (Adn) was added to the L-NAME perfusion solution at local temperatures of 39 and 42°C in an attempt to match the increase in CVC achieved during local heating at the control site. *P < 0.05 vs. control. #P < 0.05 vs. local temperature of 39°C.

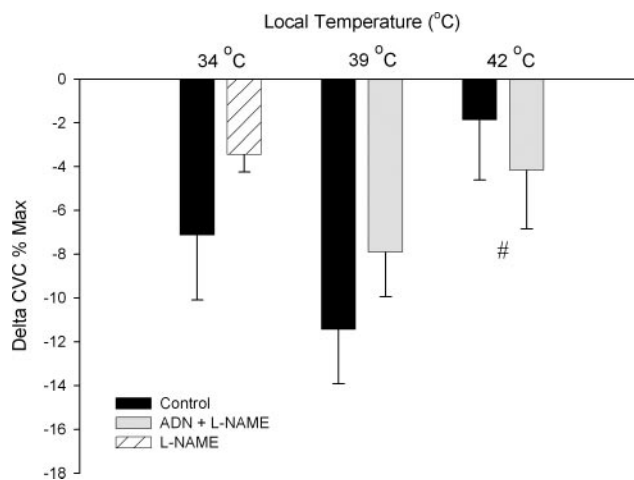


Fig. 2. Mean (± SE) decrease (delta) in CVC (expressed as % max) during LBNP at each local temperature and each site. #P < 0.05 vs. local temperature of 39°C.

increased CVC to 53.0 ± 2.8% maximum (F_{1,42} = 34.28, P < 0.001 vs. Control site; see Fig. 1). Local heating to 42°C at the control site increased CVC to 89.4 ± 2.7% max, while the combination of 42°C local heating with L-NAME plus adenosine increased CVC to 66.3 ± 5.0% max (F_{1,42} = 34.28, P < 0.001 vs. control site; see Fig. 1). As expected CVC was higher at a local temperature of 42°C relative to 39°C, regardless of site (F_{1,42} = 13.69, P < 0.001).

The decrease in CVC during 39°C local heating at the control site (11.4 ± 2.5% maximum) was not different relative to at the L-NAME plus adenosine site (7.9 ± 2.0% maximum; F_{1,42} = 0.06, P > 0.05; Fig. 2). These changes in CVC corresponded to relative decreases in CVC of 15.8 ± 3.9 and 15.2 ± 4.2% at the control and L-NAME plus adenosine sites, respectively (F_{1,42} = 0.12, P > 0.05; see Fig. 3). LBNP, at sites locally heated to 42°C, decreased CVC to a similar extent at the control and L-NAME plus adenosine sites (1.9 ± 2.7 and 4.2 ± 2.7% maximum, respectively; F_{1,42} = 0.06, P > 0.05; Fig. 2). These decreases in CVC represented a relative decrease in CVC of 2.4 ± 3.2 and 5.7 ± 3.4% at the control and

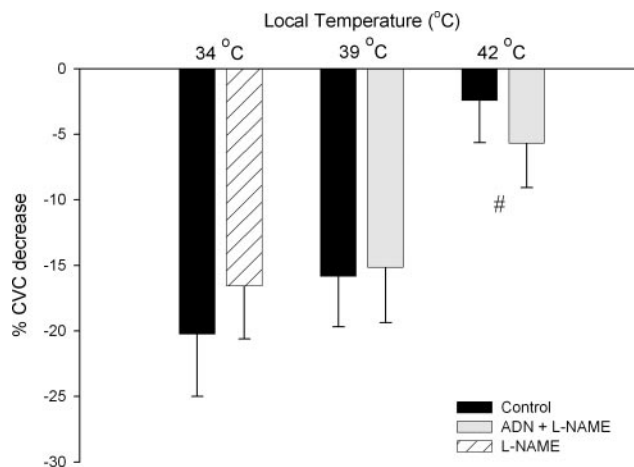


Fig. 3. Mean (±SE) relative decrease in CVC (expressed as a percent decrease) during LBNP at each site and local temperature. #P < 0.05 vs. local temperature of 39°C.

L-NAME plus adenosine sites, respectively ($F_{1,42} = 0.12$, $P > 0.05$; see Fig. 3). The decrease in CVC to LBNP at sites heated to 42°C (regardless of site) was significantly lower than at sites heated to 39°C ($F_{1,42} = 7.10$, $P < 0.05$). Similarly, the relative (i.e., percent) decrease in CVC at sites heated to 42°C (regardless of site) was significantly lower than the percent decrease in CVC at sites heated to 39°C ($F_{1,42} = 9.53$, $P < 0.005$).

DISCUSSION

The aim of this study was to test the hypothesis that local heating induced NO production attenuates cutaneous vasoconstrictor responsiveness in humans. This objective was accomplished by examining cutaneous vasoconstrictor responses during LBNP at locally heated sites with and without NO synthase inhibition. Specifically, cutaneous vasoconstrictor responses at control sites and sites where NO synthase was inhibited were evaluated during 60-mmHg LBNP when local skin temperature was clamped at 34, 39, and 42°C. The primary finding of this study was that regardless of the presence or absence of NO, the reduction in CVC (expressed as either a percent change in maximal CVC or as a percent change in CVC from pre-LBNP baseline) to LBNP was similar at all local temperatures. A secondary finding was that the cutaneous vasoconstrictor response to LBNP was significantly reduced at the highest local temperature (42°C) relative to a lower local temperature (39°C), regardless of whether NO was present, indicating that a high local temperature inhibits cutaneous vasoconstrictor responsiveness through non-NO mechanisms.

Previously, our laboratory has shown that local surface heating to temperatures of 37°C and above reduced cutaneous α -adrenergic vasoconstrictor responsiveness to increasing doses of exogenous norepinephrine locally administered with cutaneous microdialysis (24). In addition, local heating reduces the relative decrease in skin blood flow during moderate levels of LBNP compared with nonheated conditions (6). A reduced cutaneous vasoconstrictor responsiveness with local heating may be an important component of reductions in orthostatic tolerance in heat-stressed humans (13, 25). Sustained cutaneous vasodilation during local surface heating is predominantly mediated by increases in NO (9, 16). Therefore, reduced cutaneous vasoconstrictor responsiveness during local heating may be due to local heating-induced production of NO. To this end, our laboratory has recently demonstrated that exogenous NO, locally administered via cutaneous microdialysis sufficient to increase CVC to similar levels obtained during local heating in the present study, inhibited sympathetically mediated cutaneous vasoconstriction (4). Possible mechanisms through which NO could attenuate vasoconstriction of the cutaneous circulation include presynaptic inhibition of norepinephrine release from sympathetic vasoconstrictor nerves (2, 5), postsynaptic inhibition of α -adrenergic receptors (11, 26), and/or deactivating and thereby reducing the bioavailability of norepinephrine (11). Before the present study however, it was unknown whether endogenous NO production associated with local heating is capable of attenuating reductions in CVC to vasoconstrictor stimuli.

In the present study, cutaneous vasoconstrictor responsiveness to high levels of LBNP at locally heated sites was not different at NO (control) and non-NO (L-NAME plus adenosine) sites. These findings do not support the hypothesis that

local heating induced endogenous production of NO attenuates vasoconstrictor responses to orthostatic stress. A number of reasons may explain differences in findings between the present study and our laboratory's prior observations of reduced vasoconstrictor responses to exogenous NO administration (4). Foremost is the possibility that endogenous concentrations of NO via local heating are likely different than concentrations achieved via exogenous administration of the NO donor sodium nitroprusside, despite similar magnitudes of increase in CVC between exogenous NO administration relative to local heating. This hypothesis would dictate that endogenous cutaneous NO concentrations achieved during local heating (3, 10, 16) are not sufficient to attenuate the effects of the cutaneous vasoconstrictor system.

Interestingly, in the present study, the reduction in CVC was significantly attenuated, regardless of the site (i.e., control or L-NAME plus adenosine), at a local temperature of 42°C compared with 39°C. This observation is consistent with our laboratory's prior findings (24), and it further demonstrates that a high local temperature per se reduces vasoconstrictor responsiveness to an orthostatic stress. Similarly, vasoconstrictor responsiveness to electrical stimulation and exogenous norepinephrine administration is attenuated in canine cutaneous, saphenous, and mesenteric veins, when these vessels were heated from 37 to 41–43°C (similar to those used in this study) (1, 22). In additional experiments, these authors showed that the mechanism for the reduced vasoconstriction at higher local temperatures was due a selective inhibition of the postjunctional α_2 -adrenoreceptors rather than reduced norepinephrine release (1, 21). Similar observations have also been found in heated rat vessels (12, 14). The present observation that heating to 42°C reduced vasoconstrictor responses to LBNP similarly at the control and the L-NAME plus adenosine-treated sites strongly suggests the local heating induced impairment of cutaneous vasoconstriction is unlikely to be NO dependent. The mechanism by which local heating attenuates human cutaneous vasoconstrictor responsiveness warrants further examination.

Study Limitations

Previous studies have investigated the effects of local heating on cutaneous vasoconstrictor responsiveness to exogenous norepinephrine administration (24) and LBNP (6). However, in those studies, locally heated sites were compared with non-locally heated sites, and thus both preperturbation CVC and local temperature were different between sites. The experimental design of the present study intended to match CVC achieved with local heating with CVC at sites where local heating-induced vasodilation was blunted or abolished by L-NAME via coadministration with adenosine. Although absolute maximal CVC was not different between control and adenosine + L-NAME sites regardless of local temperature, because of heterogeneity of skin blood flow responses we did not know until after all procedures were completed whether we had successfully matched normalized CVC between control and L-NAME-treated sites. Despite our attempts, CVC at the control sites during local heating were significantly greater than CVC at the L-NAME plus adenosine-treated sites. These differences in pre-LBNP CVCs during local heating could potentially impact the interpretation of the findings given that a

higher CVC (at the control site) would theoretically allow for a greater reserve for reductions in CVC during LBNP. Arguing against these possibilities are the observed similar relative (i.e., percent) reductions in CVC between control and L-NAME plus adenosine-treated sites. If these relatively minor differences in pre-LBNP CVCs were sufficient to alter vasoconstrictor responsiveness to LBNP, then it would be expected that the percent change from pre-LBNP baseline would be accentuated at the site where NO synthase was inhibited.

Five of the 11 subjects in this study were women, and the timing of data collection for these subjects was not controlled. Given that gender and menstrual cycle phase can affect skin blood flow responses to orthostatic stress (15), these two factors could have affected the reductions in CVC during LBNP in the present study. However, subjects served as his or her own control, given that the difference in responses between the control and L-NAME-treated site on the same arm was the primary variable of interest. Nevertheless, to address a potential bias caused by the menstrual cycle and gender, we closely inspected each female subject's data and found that all female subjects responded in a homogeneous manner and that those responses were similar to that observed in male subjects.

In conclusion, the presence or absence of NO did not affect the reduction in CVC (expressed either as an absolute change in CVC or as a percent change in maximal CVC) to 60-mmHg LBNP regardless of local temperature. However, the cutaneous vasoconstrictor response to LBNP was significantly reduced at the highest local temperature (42°C), regardless of whether NO was present. These results do not support the hypothesis that local heating induced NO production attenuates cutaneous α -adrenergic vasoconstrictor responsiveness, although a high local temperature per se can attenuate cutaneous vasoconstrictor responsiveness through non-NO mechanisms.

GRANTS

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